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Cost-effectiveness of Cancer Nanotechnology - deel 1

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Abstract

Cancer is a class of diseases in which abnormal cells divide without control and are able to invade other tissues and organs through the blood stream and lymphatic system, which is called metastasis. Cancer belongs to the top three causes of death worldwide. It affects people at all ages with the risk for most types increasing with age. On the one hand, malignant phenotypes can be caused by internal factors, such as inherited mutations, hormones, immune conditions, and mutations from the metabolism. These cancers are, thus, due to genetics. On the other hand, the disease can be induced by environmental factors or a bad lifestyle, for instance, chemicals, radiation, and infectious organisms, the use of tobacco, alcohol, and lack of physical activity. Environmental factors can cause abnormalities in the genetic material of cells. While some cancers can be prevented through an adapted lifestyle, others can not be prevented.

Since the 1950s great strides have been made in cancer treatment. This is particularly true for early detected, localized malignancies. Nevertheless, still more than half of cancer patients do not respond to therapy or progress to the metastatic stage. The low effectiveness of current chemotherapeutic treatments is, however, not due to the efficacy of the drug itself, but to the ineffective delivery of those agents to the cancerous regions. After the intravenous administration, drugs encounter some biological barriers that have a negative impact on the particles' ability to reach the target cells at desired

concentrations. Striking is the declaration that only 1-10 out of 100.000 drug molecules are able to reach their parenchymal targets. Consequently, many healthy cells will be irreversibly damaged causing patient suffering and this at the expense of therapeutic action. This, in turn, causes a decreased therapeutic index. There is, thus, an urgent need to find an effective and safe cure for cancer. To that end, thousands of nanodevices are currently being studied. By combining nanodevices with different drugs and targeting moieties, scientists hope to find novel therapies. The promise of nanotechnology is to find a way to combat cancer with novel, personalized treatments. The National Cancer Institute (NCI) defines nanotechnology as: "the field of research that deals with the engineering and creation of things from materials that are less than 100 nanometers (one-billionth of a meter) in size, especially single atoms or molecules. It is being studied in the detection, diagnosis, and treatment of cancer." The promise of nanotechnology is to find the right combination of therapeutics and targeting moieties to attack diseased cells without or with minimal side-effects. Nanotechnology can be used in different fields: prevention and control, early detection and proteomics, imaging, multifunctional and targeted therapeutics, pain management, therapeutic monitors, and finally, tissue engineering.

Spiraling costs are a major concern for health administrators allocating limited resources. Rising health care costs are, on the one hand, due to a growing and ageing population. On the other hand, new therapies, like nanotherapeutics, typically entail high acquisition costs that may be offset and justified, however, by increased effectiveness, reduced toxicities and a better quality of life. The increasing demand – and costs – for health care services coupled with constant

or even decreasing national resources, led to an increased interest in the economic analyses of medical interventions. The challenge is to adopt new therapeutics and medical technologies while maintaining the standard quality of care and staying within the constraints of a predetermined health care budget.

The available cost-effectiveness studies of nanotechnological cancer therapies have some serious methodological flaws. Typically, the results are not quality-adjusted. Since therapies affect both the length and quality of life, this might lead to ineffective choices. Moreover, only direct medical costs are taken into account, neglecting indirect costs that impose a significant economic burden on patients and society. This might lead to wrong policy conclusions at the expense of patients and society. It is, thus, crucial to develop a cost-effectiveness taxonomy comprising all direct and indirect costs and adjusting effectiveness outcomes with quality of life estimates. Only then, cost-effectiveness analysis is helpful to making efficient choices in healthcare.

Developing a framework for cost calculation starts with the identification of all possible relevant costs in function of a given perspective, preferably that of society, i.e. all relevant costs are considered regardless of who they incur. Cost analysis comprises the costs related to treatment itself, but also resource uses associated with the therapies' downstream events. Identifying, measuring, and valuing resources is, however, not easy. A new drug may cause fewer or less severe adverse events, require less monitoring efforts, or may not require hospitalizations. Consequently, savings may offset the higher acquisition cost.

A cost framework should include all relevant costs, direct and indirect, of treatment, the management of adverse events, and recurrent disease. Relevant direct costs are drug (study drug and pre-treatment), administration (in- and outpatient visits), expected administration (e.g. drug administration at home), and monitoring (diagnosis and follow-up) costs, and expected costs of after care (psychological assistance, rehabilitation, palliation, additional therapies). Lost production of patients and relatives, transportation costs, expected costs related to caregivers, visiting costs, interests forgone on funeral expenses due to a premature death, and administration costs of health insurances can not be directly attributed to a specific treatment. These are the tangible indirect costs of cancer. Moreover, intangible indirect costs, which are the emotional costs of pain, suffering and reduced quality of life, are conceptualized into quality-of-life estimates. As more CEAs are pursued, it will become a lot easier to compare different treatments in terms of their cost-effectiveness.

The taxonomy is used to calculate the cost-effectiveness of conventional and nanotechnology-based treatments for recurrent or progressive ovarian cancer. Ovarian cancer is the most prevalent cause of death due to gynecological malignancy. Second-line chemotherapeutic agents not only show limited tumor activity, but may also result in adverse events of increasing severity. Costs to manage adverse events tend to be high. A comprehensive cost-effectiveness analysis (CEA) was pursued, taking into account all direct and indirect costs of cancer. Effectiveness outcomes were taken from a recent phase III clinical trial carried out in Italy comparing gemcitabine (GEM) versus PEGylated liposomal doxorubicin (PLD) for recurrent or progressive ovarian cancer. A hundred fifty three patients were, therefore, enrolled and randomly assigned to PLD (n = 76)

and GEM (n = 77). The robustness of the model was tested by Monte Carlo resampling. Total average direct costs per patient were estimated at €4.723,83 in the PLD treatment group, compared to €6.517,08 for patients treated with GEM. The higher acquisition cost of PLD was, thus, significantly offset by other direct costs related to conventional therapy (GEM). Moreover, tangible indirect costs were also higher in the GEM patients group, namely €2.233,43 per patient compared to €2.083,84 for patients treated with PLD. The intangible indirect costs monetizing pain and suffering were also included by using quality of life estimates. Liposome therapy saved 2.017,065 quality-adjusted weeks compared with only 1.453,945 for conventional treatment. The CEA shows that PLD is more cost-effective than GEM. The cost-effectiveness ratio of PLD is €247,60 per quality-adjusted week (€12.875,20/QALY) compared to €439,33 (€22.845,16/QALY) for GEM. The CEA, thus, suggests that the nanotechnology-based cancer agent PLD is more cost-effective than GEM, and thus helps saving scarce health resources. Although its acquisition cost is significantly higher, this cost difference is more than offset by other direct and indirect costs.

However, most drug candidates fail in the drug development cycle. High attrition rates are mainly due to three obstacles: safety, efficacy, and economics. Because the cost of failure rises with duration, unsuccessful drugs have to be abandoned as early as possible in the development process. An important venue to avoid waste of scarce resources is cost-effectiveness analysis, which should be pursued in the early stages of the drug development cycle. To that end, an algorithm estimating the sales revenues required to recover costs and earn a reasonable profit to be successful is developed. For 2010, sales revenues should be at least US$9.902 million. To break even, 247.550 quality-adjusted life years

should, therefore, be saved. Clinical researchers have to demonstrate that it is possible to save this number of quality-adjusted life years. If not, the new medicine is not cost-effective and further development should be abandoned.

Pursuing cost-effectiveness analysis in an early stage is crucial when investing scarce health care resources. However, this could be particularly important for nanotherapeutics as well as target-based agents. Since these therapies will probably be very effective but also have very high acquisition costs, it will be crucial to demonstrate their cost-effectiveness. If not, these new therapeutics could be considered as not cost-effective due to their high acquisition cost. Consequently, cures to treat life-threatening diseases could be lost.

Over the next 10 to 20 years, new nanotechnologies may revolutionize science, technology and society. But if medical nanotechnology wants to realize its full potential, some major legal and economic impediments blocking a genuine breakthrough have to be removed. The future of nanomedicines is undermined by lack of financial profitability, consumer distrust, ineffective regulation of new and generic products, weak patent protection and insurance market failure. Its success, in turn, requires a whole set of countervailing measures and actions. Success requires more investments induced by cost-effectiveness analyses and business plans based on clinical data, public education based on nanotoxicology studies, smart regulatory reform in the areas of testing, market entry and liability, effective and strategic patenting, patent dispute prevention and resolution, and innovative insurance policies.

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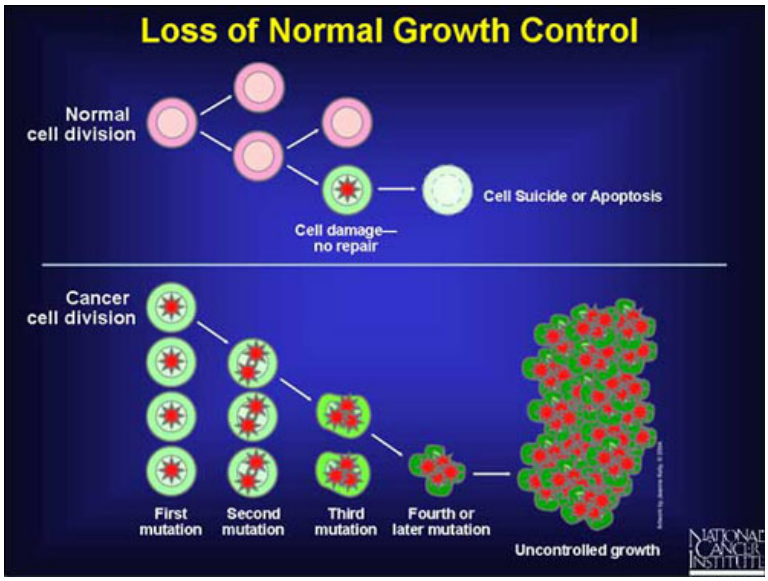
Chapter 1: Introduction

1.1 Problem statement

Cancer is a class of diseases in which abnormal cells divide without control and are able to invade other tissues and organs through the blood stream and lymphatic system, which is called metastasis. Today, more than hundred different types of cancer are known. Most cancers are named for the organ or type of cell in which they start. To understand cancer, however, it is helpful to know what happens when normal cells become malignant. The body consists of many cells. These cells grow and divide in a controlled way to produce more cells as they are needed to keep the body healthy. When cells are old or damaged, they die and are replaced by new ones. Unfortunately, sometimes this process goes wrong. The cell's genetic material or DNA can become damaged or changed. This, in turn, produces mutations that affect normal cell growth and division. In this case, old or damaged cells do not die and new cells are not produced. The extra cells may form a mass of tissue called a tumor. This mechanism is represented in figure 1.1.

Fig. 1.1: Loss of normal growth control



Source: National Cancer Institute; URL:

http://www.cancer.gov/cancertopics/what-is-cancer

Cancer belongs to the top three causes of death worldwide.[1] Table 1.1 shows the world-leading causes of death in 2001. For 2007, it was estimated that there would be over 12 million new cases of cancer and 7.6 million of cancer-related deaths. This figure is expected to rise to 27 million respectively 17.5 million by 2050. The main reason for this increase is the growing and ageing population.

Table 1.1: Leading causes of death worldwide in 2001 (in thousands)

	Rank	**Death**	**Share**
Heart diseases	1	11.004	19,6
Malignant neoplasms	2	7.021	12,5
Cerebrovascular diseases	3	5.390	9,6
Lower respiratory infections	4	3.753	6,7
Chronic obstructive pulmonary disease	5	2.676	4,8
HIV/AIDS	6	2.574	4,6
Perinatal conditions	7	2.522	4,5
Diarrhoeal diseases	8	1.783	3,2
Tuberculosis	9	1.606	2,9
Road traffic accidents	10	1.108	2,0
Malaria	11	1.208	2,1
Diabetes mellitus	12	960	1,7
Suicide	13	875	1,6
Cirrhosis of the liver	14	771	1,4
Measles	15	763	1,4
All causes		56.242	100,0

Source: American Cancer Society; URL:

http://www.cancer.org/downloads/STT/Global_Facts_and_Figures_2007_rev2.pdf

Cancer affects people at all ages with the risk for most types increasing with age. On the one hand, malignant phenotypes can be caused by internal factors, such as inherited mutations, hormones, immune conditions, and mutations from the metabolism. These cancers are, thus, due to genetics. On the other hand, the disease can be induced by environmental factors or a bad lifestyle, for instance, chemicals, radiation, and infectious organisms, the use of tobacco, alcohol, and lack of physical activity. Environmental factors can cause abnormalities in the genetic material of cells. Some cancers can, however, be prevented through an adapted lifestyle. This, in turn, can be attained by educational policies, encouraging people to adapt healthy types of behavior and discourage unhealthy ones. It is estimated that, in this way, half of the cancers could be prevented. Unfortunately, the other fifty percent of cancers can not be prevented in any way. These malignancies are caused by gene mutations. Some of these gene mutations are passed from parent to child and are, thus, present at birth. In this case, the genes are present in all cells of the body.

Until the nineteenth century, cancer was incurable. The first efforts to find a cure for neoplastic disease go back to the 1940-1950s, when the use of nitrogen mustard, which slows the proliferation of cancerous cells, was introduced.[2,3] Radiation therapy for local disease was only introduced in the 1960s.[3] It did not take a long time to realize that a more systemic approach was needed to treat metastatic disease. The real fight against cancer began in 1971 with the approval of the National Cancer Act. It permitted the Cancer Chemotherapy National Service Center (CCNSC) to increase its efforts on cancer research.[4] After more than 35 years, however, the mortality rate of metastatic disease has not significantly improved.[3]

In metastatic disease, conventional chemotherapy has almost no curative potential but is used to maximize quality of life for as long as possible. The drugs used in conventional chemotherapy are cytotoxic, i.e. they destroy cells. After intravenous administration, the free molecules encounter some biological barriers (epithelial and endothelial barriers, immune system, interstitial fluid pressures, and multiple drug resistance) present in the body. Therefore, drug molecules have little chance to reach the target cells in the desired concentrations. They circulate throughout the body in the bloodstream, attacking both cancerous and healthy cells. Although cytotoxic agents are carefully controlled in both dosage and frequency, lots of healthy cells are destroyed.[5,6] This causes some severe systemic side-effects in cancer patients. Consequently, they experience a poor quality of life.[7] New therapies have thus to be developed, which (1) increase the efficacy of the treatment and (2) improve the quality of life.

A technology that could give rise to important opportunities to overcome some challenges related to current chemotherapy regimens is cancer nanotechnology.[6,7,8,9] The National Cancer Institute (NCI) defines it as: "the field of research that deals with the engineering and creation of things from materials that are less than 100 nanometers (one-billionth of a meter) in size, especially single atoms or molecules. It is being studied in the detection, diagnosis, and treatment of cancer." The promise of nanotechnology is to find the right combination of therapeutics and targeting moieties to attack diseased cells without or with minimal side-effects. To that end, the National Cancer Institute invests an extra of US$4.2 billion to accelerate the development of molecular oncology, nanotechnology, and bioinformatics. The focus is on creating new, personalized medicines for diagnostic and therapeutic purposes.

1.2 Motivation

Spiraling costs are a major concern for health administrators allocating limited resources.[10] Rising health care costs are, on the one hand, due to a growing and ageing population. On the other hand, new therapies typically entail high acquisition costs that may be offset and justified, however, by increased effectiveness, reduced toxicities and a better quality of life. The increasing demand – and costs – for health care services coupled with constant or even decreasing national resources, led to an increased interest in the economic analyses of medical interventions.[11] The challenge is to adopt new therapeutics and medical technologies while maintaining the standard quality of care and staying within the constraints of a predetermined health care budget.[12]

Cancer-associated morbidity and mortality cause enormous economic burdens on patients, their families, and on society.[13] Moreover, a high number of individuals are affected by the disease. Consequently, total costs of cancer are significant. Therefore, it is crucial to invest scarce resources in a therapy that has the lowest cost for a given effect.

Allocating resources is, thus, not only about costs. Both costs and effects have to be considered. There are different methods of economic evaluation: cost-effectiveness analysis (CEA), cost-benefit analysis (CBA), and cost-utility analysis (CUA). Cost-effectiveness analysis compares the costs and effects of two or more health care interventions. CEA is helpful in demonstrating that the cost per additional health effect is worth paying for. Therefore, it allows policy-makers to efficiently allocate scarce resources and maximize health effects at the lowest

cost. Its main disadvantage is that cost-effectiveness ratios can only be compared among options with a similar objective. Cost-benefit analysis evaluates treatment regimens by comparing their costs and benefits. Benefits are expressed in monetary terms. The therapy with the highest benefit-cost ratio is chosen for implementation. An important advantage of this method is that many programs with widely disparate objectives can be compared. Finally, cost-utility analysis compares the costs and utility of treatments. Utility expresses the satisfaction derived by individuals from one or more outcomes. The health care intervention which attains a given level of utility at the lowest cost is chosen. The method's main advantage is that a large number of outcomes can be included in the evaluation. However, results are often difficult to reproduce among different evaluators. This is due to the numerous and often conflicting methodologies used to estimate utility weights.[14]

Since health effects are difficult to express in monetary terms, cost-effectiveness analysis is the most interesting method for economic evaluation in the health care sector. Cost-effectiveness studies are extremely valuable in allocating scarce resources. First, resource utilization for any given outcome is minimized. Second, by considering costs and effects, resources can be used more efficiently. Finally, it permits to free up resources and redirect them to other, more cost-effective initiatives.[14]

Despite cost-effectiveness analysis is a valuable tool in allocating scarce resources; inaccuracy is highly likely to lead to inefficient choices. Current cost-effectiveness studies comparing conventional therapies with new nanotechnology-based treatments are found to be incomplete, neglecting indirect costs and

quality-adjusted life years. This might lead to wrong policy conclusions at the expense of patients and society. Therefore, it is crucial to develop a generic cost-effectiveness model comprising all relevant direct and indirect costs and adjusting effectiveness outcomes with quality of life estimates. Only then, cost-effectiveness analysis is helpful to making efficient choices in health care.

1.3 Contributions

The objective of this dissertation is to develop a generic cost-effectiveness model comprising all relevant direct and indirect costs and adjusting effectiveness outcomes with quality of life estimates. Since cancer patients' length but also, and even more so, quality of life is affected, it is crucial to adjust effectiveness outcomes with quality of life estimates. Moreover, costs are calculated from a social perspective instead of the more common hospital perspective. Consequently, comparing different studies will become a lot easier.

Then, the generic model will be used to assess the cost-effectiveness of gemcitabine versus PEGylated liposomal doxorubicin for recurrent or progressive ovarian cancer. Results will also be compared with the more common methodology, i.e. cost calculation from a hospital perspective. With this model, I will investigate on the cost per health effect of a new nanoparticulate-based therapy and if the additional cost is worth paying for. Objective CEA may also facilitate strategic collaborations between small and medium sized enterprises (SMEs) and skeptical large companies.

1.4 Overview

Chapter 2 presents an introduction of cancer nanotechnology. It discusses the problems related to conventional chemotherapy (freely injected molecules) and how nanotechnology could possibly overcome these problems. The chapter also presents the roadblocks that have still to be surmounted. Moreover, first, second, and third generation nanotherapeutics are shortly reviewed. The promise of nanotechnology is to find the right combination of therapeutic agents and targeting moieties to combat cancer with no or minimal adverse events.

Chapter 3 discusses related work. It assesses the quality of cost-effectiveness analyses of nanotechnological cancer therapies. The objective is to present the knowledge gaps found in current studies. Eighteen major studies are, therefore, screened.

Chapter 4 discusses some important concepts of health economics and nanotechnology.

Chapter 5 presents a method for pursuing cost-effectiveness analysis in the early stages of the drug development cycle. To that end, an algorithm estimating the sales revenues required to recover costs and earn a reasonable profit is developed. Consequently, it is possible to estimate the cost per quality-adjusted life year for a specific future nanotherapeutic. If the new nanomedicine costs more than a predetermined threshold value of US$40.000 per quality-adjusted life year, it is considered not cost-effective. Further development and commercialization should be abandoned.

Chapter 6 presents a generic cost-effectiveness model comprising all possible direct and indirect costs of cancer and cancer care as well as quality of life. The objective is to eliminate the methodological heterogeneity and deficiencies found in current studies. The chapter puts a strong emphasis on the cost model. It presents the formulas for cost calculation.

In chapter 7 the costs and cost-effectiveness of gemcitabine versus PEGylated liposomal doxorubicin are calculated from a social perspective. Cost calculation includes all relevant direct and indirect costs of cancer and cancer care. Also intangible indirect costs, i.e. the costs of pain and suffering, or non-financial costs are considered. Non-financial costs are included in the quality of life estimates. Cost-effectiveness is expressed as the cost per quality-adjusted week. Furthermore, results are compared with the more common approach, i.e. from a hospital perspective. A literature search indicates that it is the first study that compares costs from a social perspective.

Chapter 8 discusses the obstacles to successful commercialization of nanomedicines. Moreover, some important remedies are presented. If medical nanotechnology wants to realize its full potential, the impediments blocking serious steps forward have to be removed. This chapter provides a scientific evidence based policy agenda for the future economic growth and survival of nanomedicines.

Finally, chapter 9 concludes this dissertation with some general conclusions. Furthermore, an outlook of future perspectives is presented.

Chapter 2: On Cancer Nanotechnology

This chapter is based on the article "On cancer nanotechnology" found in *Rita Bosetti and Lode Vereeck. On Cancer Nanotechnology. Key Engineering Materials 2010; 441, volume: Advanced Bioceramics for Nanomedicine and Tissue Engineering:307–32. Trans Tech Publishing Inc.*

2.1. Introduction

Billions of dollars are spent on cancer research each year. The U.S. National Cancer Institute (NCI), which is part of the National Institutes of Health and the U.S. Department of Health and Human Services, is the principal agency for cancer research in the U.S. and coordinates the National Cancer Program. The NCI has invested, on average, US$4.86 billion a year during the last three years and US$4.81 billion a year over the past six years. Billions of dollars invested on intense cancer research in the last decades has led to outstanding results in laboratories. Unfortunately, this has not been translated in even distantly comparable advances in the clinical setting. This is due to the inability of therapeutic agents to reach target cells with minimal or without adverse events. Current technologies thus fail to selectively reach the target locations. Stated otherwise, very few molecules reach the desired cells.[6] Consequently, patients

experience a lot of side-effects and a poor quality of life.[5,6,7] Cancer continues to be one of the major causes of death worldwide.[1]

To increase the efficacy of therapeutics and diagnostics, two important objectives should be fulfilled simultaneously: (1) the targeting selectivity has to be enhanced; and (2) particles should be able to overcome the biological barriers and reach the desired sites. In an ideal scenario, a system should be able to detect and destroy clusters of cells in the very early stages of the transformation towards the malignant stage.[6]

Before such a system can be developed, important challenges must be solved. First, suitable early markers of malignant phenotypes have to be identified. Furthermore, the use of biomarkers requires a thorough understanding of their evolution in time. Second, a technology for the biomarker-targeted delivery of multiple therapeutic agents, which, simultaneously, should be able to pass the biological barriers (cell membranes, immune system, blood-brain barrier), has to be developed. Nanotechnology is considered as an important technology that could give rise to significant opportunities to meet these challenges.[6]

This chapter gives an overview of some problems related to oncology. Furthermore, it tries to explain how these problems could possibly be solved by using nanoparticulate-based approaches. Then, first, second, and third generation nanotechnologies are shortly reviewed. The final paragraph offers the conclusions.

2.2. Unmet medical needs in oncology

Since the 1950s great strides have been made in cancer treatment. This is particularly true for early detected, localized malignancies. Nevertheless, still more than half of cancer patients do not respond to therapy or progress to the metastatic stage.[3] The low effectiveness of current chemotherapeutic treatments is, however, not due to the efficacy of the drug itself, but to the ineffective delivery of those agents to the cancerous regions, i.e. regions characterized by an abnormal growth of tissue. After the intravenous administration, drugs encounter some biological barriers that have a negative impact on the particles' ability to reach the target cells at desired concentrations. Striking is the declaration that only 1-10 out of 100.000 drug molecules are able to reach their parenchymal targets.[5,6,8] Consequently, many healthy cells will be irreversibly damaged causing patient suffering and this at the expense of therapeutic action.[7] This, in turn, causes a decreased therapeutic index, which is the ratio between the toxic dose and the therapeutic dose of a drug and is used as a safety measure. The biological barriers are discussed in more detail below. Another limitation is that drug molecules can be highly toxic.[5,6] In spite of their extraordinary efficacy, they can not be used in their free form. There is, thus, an urgent need to find an effective and safe cure for cancer. To that end, thousands of nanodevices are currently being studied. By combining nanodevices with different drugs and targeting moieties, scientists hope to find novel therapies. The promise of nanotechnology is to find a way to combat cancer with novel, personalized treatments, which are also called theranostics.[6]

In an ideal scenario, precancerous cells would be detected as early as possible by non-invasive methods. With such a system, the biology of the host would be determined by analyzing simple body fluids like saliva or blood.[6] Unfortunately, it remains an illusion to think about a system that effectively detects precancerous and neoplastic lesions. Current cancer imaging technologies, such as Magnetic Resonance Imaging (MRI), Computed Tomography (CT), X-rays, ultrasonography, and radionuclide scanning have a spatial resolution that is too weak to make an early detection based on lesion anatomy possible. The objective of nanotechnology-based contrast agents is to detect smaller and earlier-stage neoplastic cells. They are currently tested as possible and promising candidates of molecularly or physically targeted contrast agents for all clinical imaging modalities. By identifying molecular expressions of neoplasms and their microenvironment, they should be able to provide an improved anatomical definition for lesions.[6]

2.2.1. Endothelial and epithelial barriers

A very challenging barrier to overcome is the blood brain barrier (BBB), which is a network that consists of vascular cellular structures that are mainly represented by tight junctions between endothelial cells. The BBB plays a significant role in cell trafficking via the central nervous system.[15,16,17] It includes enzymes, receptors, transporters and efflux pumps. Access of molecules and particles to the brain regions is controlled and limited by the BBB. Once particles overcome the BBB, they are rapidly distributed to the whole brain. This is due to the large vascular density in brain regions.[17]

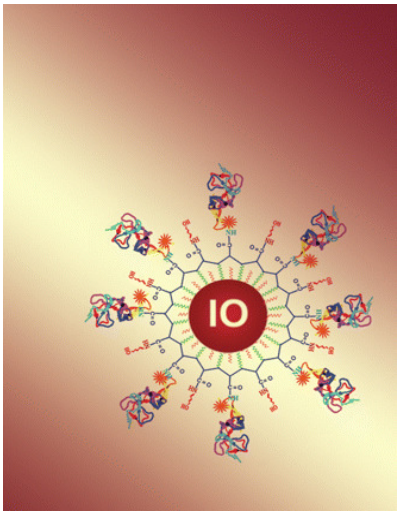
When particles try to access brain tissues, they are opsonized, i.e. the rendering of bacteria and other foreign particles subject to phagocytosis, and cleared from the blood stream by the macrophages. It has been shown that only small, lipid-soluble and electrically neutral particles with a molecular weight up to 500 Da are able to penetrate the BBB. Particles are transported to the brain tissues through passive diffusion. Since free molecules used in chemotherapy are too large to pass through the membrane pores, they can not be transported by passive diffusion. Consequently, they have little chance to gain access to the BBB and, therefore, to the brain.[18]

Nanotechnology can solve this problem. Coating the particles with polyethylene glycol (PEG), polysorbate, or other polymers and surfactants, reduce the chance of opsonization.[18,19,20] Other factors that determine if a particle passes the BBB are the particle's size, material composition, and structure of the particle. Gao and Jiang (2006) showed that drug delivery in both brain tissue and cerebrospinal fluids (bodily fluids that occupy the subarachnoid space and ventricular system around and inside the brain) was improved by using particles with a size of 70nm. Moreover, by mimicking the molecules that have access to the brain, nanoparticles can have a rapid access to brain tissues. This is, however, only possible if particles are modified with the right moieties.[21]

Iron oxide nanoparticles are able to pass the BBB and reach the neoplastic tissues.[1,5,22] Malignant cells can only be reached, however, when the administration of iron oxide nanoparticles and the application of an external magnetic field occur simultaneously.[23] Magnetic targeting is possible because of the 'magnetic responsiveness' of the iron oxide core. Moreover, iron oxide

nanoparticles can also be used as a MRI contrast agent. Therefore, it is possible to map cancer lesions during treatment, diagnostics, and surgery.[5]

Fig 2.1: Iron oxide nanoparticle



Source: Woodruff Health Science Center

Finally, epithelial barriers hinder particles in reaching the desired locations. Because penetration enhancers open the tight junctions for a limited period of time, the co-delivery of therapeutic agents and penetration enhancers could possibly bypass this obstacle without endangering patients' health.[5]

2.2.2. Sequestration by the reticulo-endothelial system

Freely injected molecules do not survive for a long time. Clearance from the blood stream is due to the uptake and sequestration of particles by the

phagocytic cells of the immune system.[24,25] With a phagocytic activity of approximately 80%, the liver is the main organ through which particles are cleared.[26] The reticulo-endothelial system (RES), which includes the phagocytic cells, is an essential part of the human immune system. To attain a significant therapeutic effect, particles have to stay in the blood stream for a sufficiently long time.[15] This is not possible with conventional chemotherapy.[24,25]

Surface modification with polymers can significantly prolong the circulation time of nanoparticles. Polyethylene glycol (PEG), is frequently chosen for this purpose because of the following properties: (1) it is a flexible and water-soluble molecule that can be end-functionalized for chemical modification; (2) possibility to attain co-polymerization with other polymers; (3) it has controllable mechanical properties and degradation rates; and (4) shows minimal toxicity and immune response and it is biocompatible.[6,17] Due to the stealth effect caused by PEGylation, particles are less easily recognized and captured by the RES. Consequently, they can stay a much longer time into circulation and reach their target locations more easily.[6,17]

2.2.3. Interstitial fluid pressure

When comparing healthy and cancerous cells, significantly higher interstitial fluid pressures, exerted by the free interstitial fluid, are found in solid tumors. This phenomenon, which is caused by the abnormal tumor vasculature that develops from angiogenesis, results in a poor uptake and distribution of macromolecular agents. In normal cells, the hydrostatic and osmotic pressures

of capillary vasculature determine the net fluid movement across capillaries. In malignant cells, however, the hydrostatic pressures increase, which is due to growing lesions.[5] Increased interstitial fluid pressure (IFP) plays a crucial role in disease progression and drug resistance.[27]

The efficient uptake of drugs in neoplastic tissues is hampered by increased interstitial pressures. This results in a rapid removal of therapeutic agents from the neoplasms. Moreover, cancerous cells are exposed to a lesser extent to therapeutic agents than is the case for healthy ones which, in turn, reduces the therapeutics' efficacy while increasing the toxicities.[3]

The inverse relationship between IFP and drug uptake was shown by animal studies. It has been demonstrated that reducing the IFP leads to an improved drug uptake.[27] Due to the importance of IFP in effective drug delivery, a solution for this problem has to be found. According to Heldin et al. (2004), there are some effective treatments available. These are VEGF (vascular endothelial growth factor)-, PDGF (platelet-derived growth factor)-, and TGFβ (transforming growth factor beta)-inhibitors, TNFα (tumor necrosis alpha), and PGE_1 (Prostaglandin E_1). In spite of the existence of these treatments, efforts to decrease IFP in tumor tissues remain a formidable challenge. This is because healthy cells must remain unaffected.[28]

2.2.4. Multiple drug resistance

A last obstacle is the phenomenon of multiple drug resistance (MDR), which causes an organism to resist specific drugs.[15] It causes a decreased therapeutic efficacy and increased patient suffering. When cells are exposed to a cytotoxic agent, they will not only develop resistance to that particular molecule but also to a broad range of therapeutics with different targets. This is not different for neoplastic cells.[18,29]

The efflux pump P-glycoprotein and the multi-drug resistance-associated protein (MDRP) contribute to multiple drug resistance. While, on the one hand, the P-glycoprotein plays a significant role in eliminating therapeutic agents from the blood stream, on the other hand, the membrane protein MDRP protects tumor cells from injected cytotoxic agents.[18] These two players affect the effectiveness of cancer agents, and lead to a poor prognosis.[18,29]

According to Ozben (2006), the overexpression of cell-membrane transporters is the leading cause of multiple drug resistance. Since cytotoxic drugs are pumped away from cancerous cells, the intracellular concentration of drugs in neoplastic cells is lowered. Consequently, the anti-tumor activity is hindered.[29]

Recent studies showed that spherical particles with a size of 50-100nm are the worst possible geometries for drug delivery.[6] This is bad news because almost all particles that have been developed have these characteristics. Since spherical particles tend to stay in the center of the capillaries, their extravasation through the fenestrations is adversely impacted and their ability

to recognize molecular markers limited.[30] Optimization of margination, extravasation, firm adhesion to the vascular endothelia, and control of phagocytic uptake can be attained by the development of non-spherical particles with the optimal characteristics. Consequently, a dramatic increase in therapeutic index can be attained.[30]

2.3. The history and future of cancer nanotechnology

The National Cancer Institute in the U.S. defines nanotechnology as: "The field of research that deals with the engineering and creation of things from materials that are less than 100 nanometers (one-billionth of a meter) in size, especially single atoms or molecules. Nanotechnology is being studied in the detection, diagnosis, and treatment of cancer".

Due to the small dimensions of nanoparticles, they can be manufactured with very large surface areas. The larger the surface area of nanomaterials, the larger the surface that is available for interactions with the molecules around them.[31] Consequently, nanomaterials have physico-chemical properties that are completely different than those of their bulk counterparts'. Furthermore, it is possible to obtain multiple bioactive functions in a very small space. This is possible through modification of the nanoparticles, so-called conjugation, which can be easily attained.[9,32,33]

The promise of nanoscience as a whole and nanotechnology in particular in the medical world rests on some challenges. One of those challenges has to do with scientists' ability to manipulate the behavior of a group of cells or even only a single cell of neoplastic tissue by using engineered nanoparticles. The latter interact specifically with receptors, specific organelle locations, and nuclear compartments, which are themselves part of individual cells that have nanoscale dimensions.

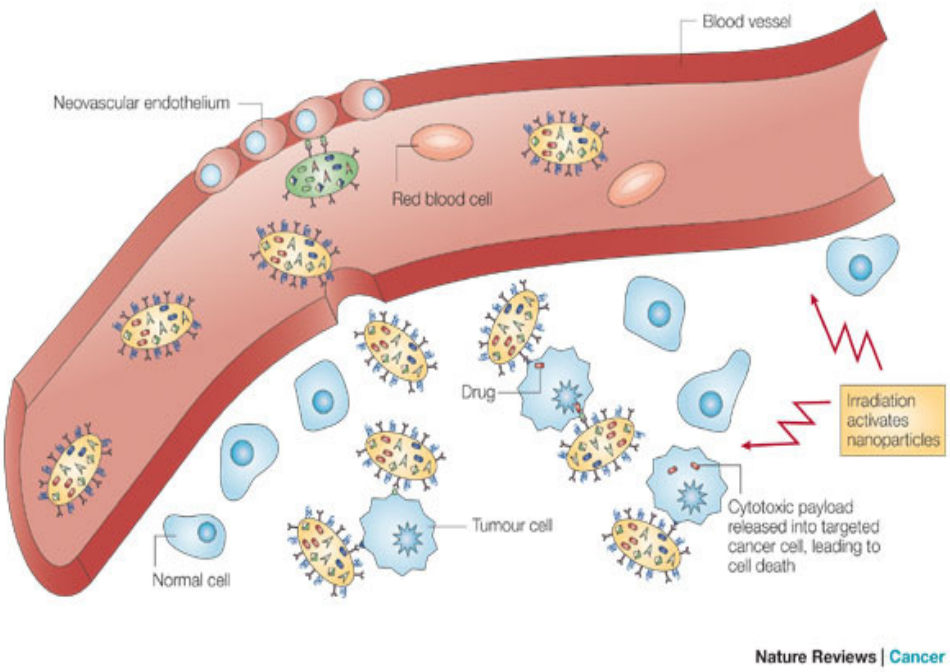
Nanoparticles are expected to attain drug localization at target sites. Moreover, they are able to bypass the biological barriers between the point of administration and the target cells. This is referred to as targeting.[6]

2.3.1. First generation nanotechnologies

A nanoparticle that consists of a biologically active agent is defined as a first generation nanodevice.[6] To avoid a premature clearance, most devices also consist of a stealthing layer. By escaping the vascular network through the fenestrations that are present on tumor-associated neovascular endothelia, first generation nanodevices localize preferentially at tumor sites. Moreover, in general, there is a lack of effective lymphatic drainage in the malignant tissue. This makes the angiogenic vessels hyperpermeable. Due to these 'defects' in tumor microvasculature, first generation nanodevices provide a larger tumor localization and accumulation than the free drug. This working mechanism is known as the Enhanced Permeability and Retention Effect or EPR-Effect.[6,15,34]

Due to this effect, it is possible to attain a several-fold rise in drug concentration in neoplastic tissues.[3]

Fig 2.2: EPR-Effect



Source: Mauro Ferrari (2005)

The simplest and most used form of first generation nanovectors are liposomes, which are artificial microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers.[15] In 1996 the Food and Drug Administration (FDA) approved liposomally formulated doxorubicin for use against Kaposi's Sarcoma. Liposomes are considered the archetype nanovector drug delivery

system. They are used already for more than ten years in the clinic for breast, ovarian, and AIDS-related cancer.[3,6] This type of nanocarrier encapsulates the therapeutic agent within the core of the liposome.[15,35]

Fig 2.3: Liposome

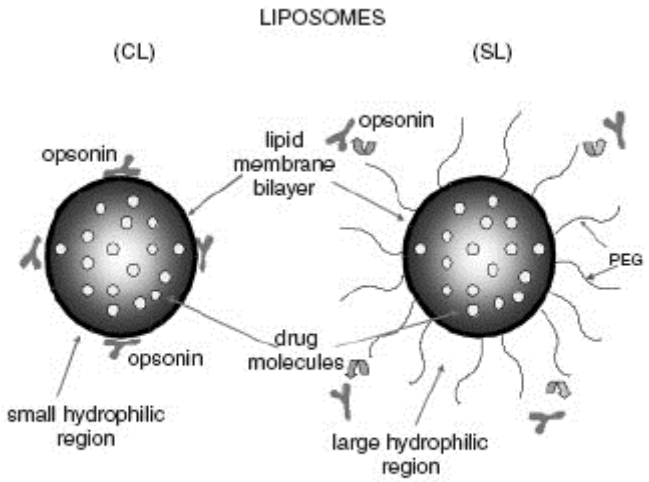


Figure 1 - Conventional liposomes (CL) and sterically stabilized (Stealth®) liposomes (SL).

Source: Di Paolo et al. (2008)

Liposomal doxorubicin (Myocet®) and liposomal daunorubicin (DaunoXome®) are used in the clinic as a treatment for breast and ovarian cancer. Despite they reduce cardiovascular toxicities, which are generally associated with the administration of anthracyclines, they have a short half-life of approximately 2-4 hours.[36] To be effective, however, it is crucial that particles stay in the blood

stream for a sufficiently long time.[15] Longevity in the blood can be achieved by PEGylation. Currently, Doxil® (U.S.) and Caelyx® (Europe) are used in the treatment of breast and ovarian cancer and Kaposi's sarcoma. They have an increased half-life of 55 hours.[36,37]

Table 2.1: First generation nanotechnologies used in the clinic

Composition	Trade name	Company	Indication
Liposomal amphotericin B	Abelcet®	Enzon	Fungal infections
Liposomal amphotericin B	AmBisome®	Gilead Sciences	Fungal and protozoal infections
Liposomal daunorubicin	DaunoXome®	Gilead Sciences	HIV-related Kaposi's sarcoma
Liposomal doxorubicin	Myocet®	Zeneus	Combination therapy with cyclophosphamide in metastatic breast cancer
Liposomal-PEG doxorubicin	Doxil®/ Caelyx®	Ortho Biotech, Schering-Plough	HIV-related Kaposi's sarcoma, metastatic breast cancer, metastatic ovarian cancer
Methoxy-PEG poly (lactide)taxol	Genexol-PM	Samyang	Metastatic breast cancer
PEG-GCSF	Neulasta®	Amgen	Neutropenia associated with cancer chemotherapy
PEG-L-asparaginase	Oncaspar®	Enzon	Acute lymphoblastic leukemia
Albumin-bound paclitaxel	Abraxane	Abraxis BioScience, AstraZeneca	Metastatic breast cancer

Source: Zhang et al. (2008)[38]

Liposomal vincristine (OncoTCS) has been approved for the treatment of relapsed aggressive non-Hodgkin's lymphoma. Furthermore, liposomal therapies are used in the treatment of cancer-related fungal infections. Liposomal amphotericin B and amphicilin have been approved by the FDA for this

purpose.[6] A completely different nanoparticle-based therapy used to treat metastatic breast cancer is albumin-bound paclitaxel or Abraxane. Because paclitaxel molecules are encapsulated in an albumin shell, toxicities are reduced and standard steroidal, anti-inflammatory pre-treatment is not necessary. Moreover, greater taxane (a type of drug that blocks cell growth by stopping cell division or mitosis) dosages can be administered.[6] The last category of first generation nanodevices are polymeric nanoparticles. These particles are in the form of polymer-protein conjugates. Currently, they are used in the clinic either as cancer therapeutics or as adjuvant chemotherapy.[39] Drug molecules can be physically entrapped or covalently bond to the particle.[35] Therapies using these nanoparticles (their trade names are presented between brackets) are clinically used for hepatocellular carcinoma (Zinostatin® and Stimalmer®), the prevention of chemotherapy-induced neutropenia (Neulasta®) and acute lymphoblastic leukemia (Oncaspar®).[39] The last agent is intended to deplete asparaginase, which is crucial in reducing tumor growth. A major limitation of this treatment is that it can produce an anaphylactic shock, which can be fatal, and other hypersensitivity reactions.[39]

Few studies were able to show that first generation nanotherapies reduce some important side-effects. Despite this amelioration, their efficacy is not yet satisfying.[12,40,41] Another problem is that the fenestrations present on tumor microvasculature change over time and some cancers do not show fenestrations at all. Therefore, the EPR-effect is not always an effective working mechanism. To overcome these limitations, second generation devices were developed, which are currently tested in clinical trials.

2.3.2. Second generation nanotechnologies

Second generation, or multifunctional nanodevices, possess different functionalities on individual particles.[6] By attaching different moieties on the particle's surface, multifunctionality can be attained. In an ideal scenario, the functions of targeting, imaging, diagnosis, and treatment are being combined.[24,25] Moreover, multifunctionality may offer new approaches to monitor a drug's pharmacodynamics and pharmacokinetics in real time.

1. Circulation time

To have a significant therapeutic effect and reach the desired locations at desired concentrations, particles have to stay in the blood stream for a sufficiently long time.[15] Longevity in the blood is usually attained by modifying the particles' surface with PEG or other synthetic polymers.[24,25,36] Because these modifications lead to fewer interactions of blood components with the particles' surface, the binding of plasma proteins with the modified particles is reduced. Consequently, immediate opsonization is prevented. It follows that, circulation time increases.[24,25]

2. Targeting

Second generation nanodevices can attain a higher therapeutic index by focusing drug delivery to target cells, which is known as active targeting. Drug delivery to selected cells is only possible due to the overexpression of some receptors or markers that are present on neoplastic cells. Receptor-mediated endocytosis underlies active targeting of nanodevices, which consists in delivering drugs to target sites by the use of site-specific ligands or targeting moieties.[24,25,42]

Few molecules have been studied and proposed as targeting ligands. Targeting moieties must have a high specificity and affinity for receptor cells. Furthermore, endocytosis must be caused in an efficient way. Finally, they have to be biodegradable.[15,43] First, monoclonal antibodies and antibody-fragments are proposed as targeting ligands. Antibodies, which are part of the immune system, are called monoclonal because they belong to a single cell type.[44] In spite of the molecules' good stability and excellent specificity, they have a large hydrodynamic diameter, which makes the diffusion into cancerous cells difficult. Recently, advances have led to the development of antibody-fragments. While these molecules show the same specificity as antibodies, they cause a reduced immune response. Moreover, a disulfide bond can be used to stabilize them and can be produced more economically. These properties make them good candidates for both diagnosis and therapy.[34,45] Second, peptides could be interesting because they seem to be far more stable than antibodies. Furthermore, they have a higher binding affinity, which is due to their higher rigidity and to an improved interaction with the cell membrane.[34] Other

attractive ligands are the small molecules which are able to translocate through the plasma membrane, i.e. a semipermeable membrane that encloses the cytoplasm of a cell. Consequently, they can interact with the receptors that are present on diseased cells.[46] Moreover, different small molecules can be functionalized on the surface of one particle, they have a low cost, and they can be easily conjugated with other drugs.[34] A recently developed antibody is the nanobody. It combines the advantages of conventional antibodies with the attractive properties of small molecules. Like antibodies, they have a high targeting specificity, a high affinity for their target and a low toxicity. Moreover, like small molecules, they can inhibit enzymes and readily access receptor clefts. Furthermore, these particles have an extreme stability and are easy to manufacture. Finally, a promising type of ligands are the aptamers or nucleic acid ligands which are (modified) DNA or RNA oligonucleotides with unique targeting properties.[47] They have the advantage of exhibiting an extremely high affinity and specificity for receptor cells while being also small, non-immunogenic, easy to isolate and they can be produced very economically.[47]

An important problem associated with targeting moieties is that they are, in general, shorter than PEG molecules. Consequently, they tend to be hidden inside the PEG shield, which decreases their targeting efficiency. This hindrance can, however, be solved by attaching the targeting ligands at the distal end of the PEG arm.[24,25]

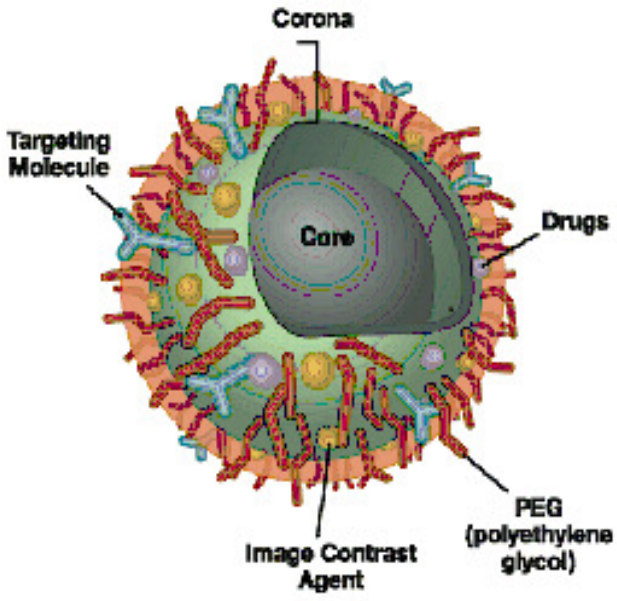
3. Triggered release

Nanovectors can be stimulated and activated internally by binding molecules that are sensitive to the tumor microenvironment on their surface. The lower pH-value and higher temperature that characterizes tumors have been used to develop pH- and temperature-sensitive nanodevices. Due to the presence of pH- and temperature-sensitive bonds on the particle's surface, it remains inactive upon encountering a lower pH or higher temperature. On that precise moment, the nanodevice releases its load and the therapeutic agents can reach the desired locations.[15,24,25] As an example, pH-sensitive polymers will swell, degrade and release therapeutic agents when detecting the acidic environment of cancerous regions. Another strategy used to release the therapeutic load in the desired locations involves the injection of nanoparticles that can be triggered by external stimuli, for example near-infrared light.

4. Imaging

Nanodevices should be modified with contrast agents. Because irradiation signals are absorbed significantly better by nanoscale particles, small cancer lesions can be enhanced sufficiently to make an earlier diagnosis possible. Another advantage of nanoparticles is that a drug's pharmacodynamics, pharmacokinetics, its biodistribution, and its desired as well as adverse effects can be monitored in real-time.[24,25]

Fig 2.4: Multifunctional nanoparticle



Source: McNeil (2010)

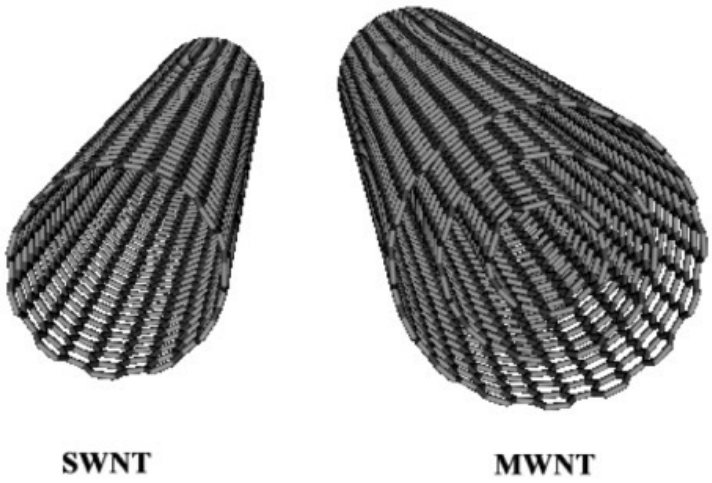
As discussed above, individual functions can be easily attained. The objective is, however, to have two or more functions simultaneously on the surface of the same nanoparticle, which would significantly enhance the efficacy of therapeutic and diagnostic protocols. This, in turn, requires the attachment of different moieties simultaneously on the particle's surface. To provide the desired combination of properties, the moieties have to function in a specific and coordinated way, which remains a challenge for current devices.[24,25]

In the literature, hundreds of multifunctional nanodevices have been described. Since it is impossible to review all the devices in the rapidly-evolving field of nanomedicine, only the most relevant ones are shortly discussed.

1. Carbon nanotubes

Carbon nanotubes (CNTs) are tubular nanodevices that consist of carbon atoms, and can be single-walled (SWCNTs) or multiwalled (MWCNTs).[48,49] While SWCNTs consist of only one graphene layer, MWCNTs have multiple layers.[49] These devices attracted scientists' attention because of their remarkable physicochemical properties. The most important property is their high aspect ratio.[48] According to Decuzzi (2006), the strength of adhesion to the cell membrane rises with the aspect ratio. Stated otherwise, these particles are far more effective in adhering than spherical particles. Consequently, nanotubes can have a larger volume for a given adhesive strength.[42] Moreover, they are extremely light, have a high mechanical strength, high thermal conductivity and a very high surface area. An important phenomenon observed in nanotubes is their ability to cross cell membranes through the nanoneedle mechanism. They are, thus, able to penetrate the cell membrane and arrive into the cells' nucleus.[49,50] Although this mechanism is not completely understood yet, it provides an interesting and efficient way for drug delivery.[50]

Fig 2.5: Carbon nanotubes



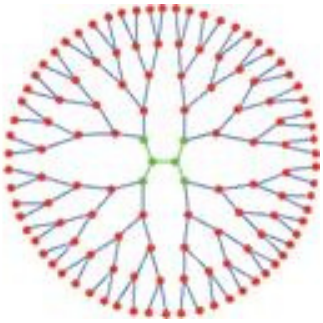
Source: Institut de Biologie Moléculaire et Cellulaire

While, on the one hand, the CNTs' surface can be functionalized with various moieties, on the other hand, they can also serve as nanocarriers. Therefore, they are attractive tools for therapy, diagnosis and imaging.[49] An important problem associated with nanotubes is their possible toxicities on the long term. On the short term, however, they are easily excreted by the kidneys, which encourage their further development.[49]

2. Dendrimers

Dendrimers are highly branched synthetic polymers consisting of a central core and an internal region.[51] Because of their properties, they are considered attractive drug delivery systems: (1) are multi-valent and water-soluble; (2) have a monodisperse size and a void space that can serve as a drug carrier; (3) can be triggered by a decreased pH-value; (4) functionalization with a wide array of terminal groups can occur; and (5) it seems that P-gp (P-glycoprotein) efflux transporters are not affecting them.[33,34,35,52] Since efflux pumps hamper an efficient drug delivery, dendrimers are extremely interesting systems.[52] Moreover, dendrimers can be modified with different moieties. Therefore, they are able to provide biomolecular recognition, imaging contrast, and cytotoxicity.

Fig 2.6: Dendrimer



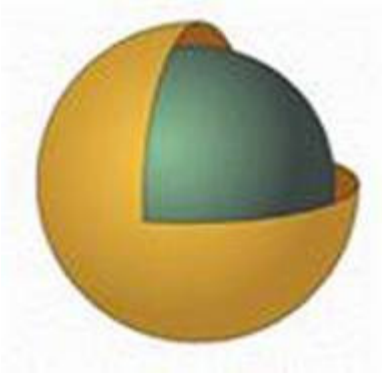
Source: Hedden (2008)

Recent efforts resulted in the development of a multipurpose dendrimer, which targets diseased cells via the folate receptors. They are known as PAMAM dendrimers (Methotrexate-containing polyamidoamine).[52] Since the multiple terminal groups present on PAMAM dendrimers can be chemically modified, these devices can be used either as targeted MRI contrast agents, as delivery vehicles for therapeutics, or both.[33,35]

3. Nanoshells

Nanoshells consist of a dielectric core that is surrounded by a metal shell, which is usually made of gold. The particles' emission spectra range from infrared to UV. By modifying the core and shell thickness, nanoshells can be optimized to absorb light of a specific wavelength. They can, thus, be optically tuned. In turn, this is useful in the destruction of solid tumors using nanoshell-assisted photothermal therapy. The gold nanoshells are activated by near-infrared light, which is harmless while it penetrates deeply into tissues. When targeting the particles with near-infrared light, they heat up to 55–70°C which results in the thermal ablation of the surrounding cancer tissues.[8] Even tumors that can not be removed surgically can be destroyed in a minimally-invasive way. Another attractive property of nanoshells is their high loading efficiency.[34]

Fig. 2.7: Gold nanoshell



Source: National Institute of Standards & Technology (NIST)

Nanoshells can carry different agents on their surface. Therefore, they can be used for both imaging and therapy. Furthermore, it is possible to attain a controlled drug release. Finally, the surface of nanoshells can be easily modified. Therefore, they can be used as a targeting tool.[34]

4. Biological particles

Multifunctional polymeric nanoparticles or nanoplatforms make a combination of targeted delivery and controlled release possible. These devices could be interesting in oncology, were cytotoxic drugs are delivered to cancerous cells over an extended period of time. This is possible through one of the following mechanisms: (1) a constant amount for a long period of time; (2) a cyclic release for an extended period; or (3) it can be internally triggered by the tumor microenvironment or by an externally applied stimulus. Consequently, the

drug's efficacy is enhanced while surrounding non-cancerous tissues remain unaffected.[34] A critical step in the development of these devices is finding the right targeting moiety that recognizes tumor-specific antigens.

Nanoplatforms are characterized by two important properties. First, they can carry two or more agents simultaneously. Second, these devices are able to penetrate the blood-brain barrier. Therefore, it becomes possible to detect and diagnose brain cancer in a minimally invasive way.[18,53]

5. Ceramic nanoparticles

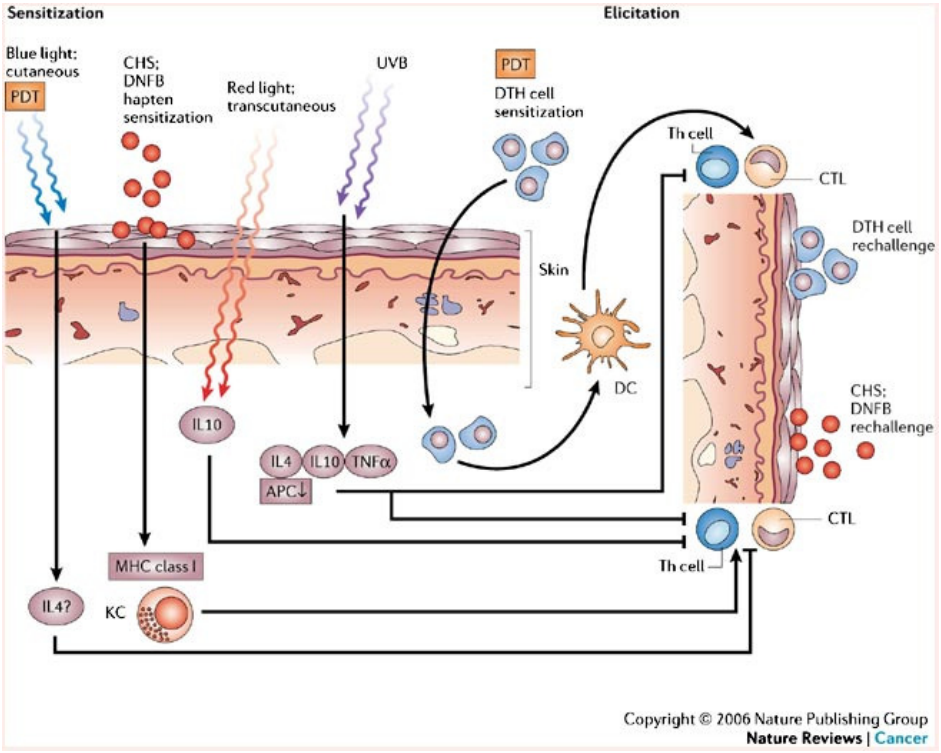
Ceramic nanoparticles are inorganic and have porous characteristics. Since these particles can be easily engineered with the desired properties (size, shape and porosity), the use of porous ceramic-based nanoparticles as drug delivery vehicles has great potential in future cancer therapies.[51] Furthermore, ceramic nanoparticles are extremely useful in the encapsulation of bio-active agents. Scientists discovered their potential application as a delivery system for photosensitizing agents. The unique properties of ceramic-based nanoparticles have paved the way for two important medical applications.

First, ceramic nanoparticles can be used in photodynamic therapy, which has emerged as an attractive treatment to destroy selective cancers. This therapy uses photosensitizing agents in combination with a light source. Since malignant cells tend to absorb higher concentrations of photosensitizing drugs than normal cells, these particles localize and accumulate preferentially in tumor regions.

Therefore, malignant cells are more sensitive to light. Light-sensitive agents are inactive until they are triggered through an externally applied stimulus, e.g. irradiation with a certain wavelength. Consequently, neoplastic cells are destroyed in a minimally invasive way, whereby healthy cells remain almost unaffected. Even if healthy cells are damaged, they heal after therapy.[54]

Most photosensitizing agents are highly hydrophobic. Therefore, to deliver the drug to the desired locations, photosensitizing drugs are encapsulated in a nanocarrier. Because ceramic nanoparticles can be engineered in the desired size, shape and porosity, they are extremely suitable for this application. Moreover, they have other attractive properties: (1) functionalization with targeting moieties is possible; (2) they are extremely small; and (3) are biocompatible. Because the particles' size does not exceed 50nm, they are able to escape the body's immune system. In turn, a longer circulation time can be attained.[54]

Fig 2.8: Photodynamic therapy



Source: Castano et al. (2006)

The importance of ceramic-based nanoparticles as a drug delivery system in photodynamic therapy has been demonstrated by Roy et al. (2003). In their study, they used silica-based nanoparticles that entrapped a water-insoluble photosensitizing cancer drug. In turn, these nanoparticles were synthesized in the core of a micelle. Due to the porosity of ceramic nanoparticles, irradiation of the photosensitizing agent with light of a specific wavelength causes the generation of singlet oxygen. Roy et al. (2003) demonstrated that the

nanoparticles were internalized by the cytosol of malignant cells and were subsequently destroyed.[55]

Second, ceramic nanoparticles can be used in gene therapy. Body-owned genes can be used to treat diseases because they can either express or interfere with the synthesis process of a protein in the cell. By replacing the defective genes by normal genes, the gene function is restored and diseased cells eliminated.[56]

An important limitation in gene therapy is, however, that genes undergo a rapid enzymatic degradation in human plasma. To overcome this, genes are encapsulated in a delivery system. Ceramic nanoparticles seem to be particularly suitable for this purpose.[22]

Tan et al. (2007) showed that ceramic-based nanoparticles made of silica could be used in the delivery of genes to the spleen. The authors demonstrated that those particles cause a potent immune response which, in turn, destroys malignant cells. To find the most favorable surface modification for these particles, the authors carried out a series of experiments. They conclude that silica particles should be modified with protamine sulfate because this protein leads to the most favorable physical properties for effective gene delivery systems. This delivery system has also been tested in an animal model using mice and the authors were able to show that these particles did cause a significant immune response and, consequently, tumor growth was hindered.[57]

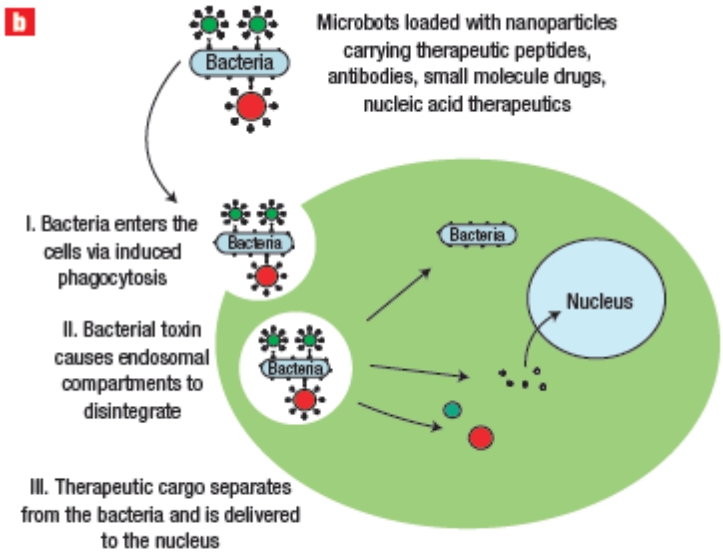
2.3.3. Third generation nanotechnologies

Individual nanoparticles represent attractive and promising candidates in the applications of drug delivery. However, the biological barriers in the body prevent nanoparticles from localizing at target sites at desirable concentrations. Because biological barriers are sequential in nature, the chance for a particle to arrive in the target cells is the product of the individual probabilities of overcoming each single barrier. The chance of bypassing all those barriers and arrive and accumulate in the desired sites is thus very small even for nanoparticles. Because biological barriers are sequential in nature, the delivery of drugs might be favored by a drug delivery system that consists of multiple stages. Multi-stage delivery systems comprise of a first stage carrier that consists of nanoparticles and is directed to the desired sites. Once arrived at the target sites, second stage nanoparticles are released with different time-release profiles. Eventually, the nanoparticles degrade into elementary, biologically benign components. Third generation nanodevices, thus, consist of multiple nano-components. Each component is designed to achieve a specific task while having the common objective of target-specific drug delivery. Due to their excellent properties, third generation nanodevices open new frontiers in drug delivery.

Very few multi-stage delivery systems have been described in the literature so far. Microbots to deliver DNA and therapeutic agents were developed by Akin et al. (2007). These delivery systems are composed of nanoparticles that are loaded with contrast or DNA agents and are carried by Listeria monocytogenes, which are the first stage carriers. Listeria monocytogenes are bacterial strains

that are able to penetrate in solid organ tumors to which drug molecules have a very limited accessibility. Moreover, they can be internalized by mammalian cells. The authors demonstrated that microbots incubated with cells were internalized and that second stage nanoparticles were released and transferred into the nucleus. They argue that this kind of system has an extraordinary potential for nonviral gene delivery but also for proteins, small molecules and synthetic objects.[58]

Fig. 2.9: Microbots



Source: Akin et al. (2007)

A second class of multi-stage delivery systems, a network of bacteriophages and gold nanoparticles, was developed by Souza et al. (2005). The phages, which are the first stage carriers, are engineered in such a way that each phage displays a peptide. Furthermore, these systems are biocompatible, have a low cost and a high-yield production. Moreover, they eliminate the challenges associated with the development of cell/peptide detection tools.[59]

These systems can be used as biological sensors as well as cell-targeting agents. Because of the properties of the gold nanoparticles, they can also be used as targeting tools and as signal reporter for the following applications: (1) fluorescence and dark-field-microscopy; and (2) near-infrared surface-enhanced Raman-scattering spectroscopy. These methods can, however, not be used in vivo. According to the authors, these systems are an important opportunity of multifunctional integration within a single entity.[59]

Bacterial magnetic particles (BMPs)-PEI (polyethylenimine), were developed by Xiang et al. (2007). While PEI is considered a very effective gene carrier, it is also very toxic. To overcome these toxicities, bacterial magnetic nanoparticles (BMPs) are used as gene carriers. PEI is coated on the surface of the BMPs. Advantages of these systems are that they exhibit a high transfection efficiency while having low toxicities. The authors conclude that these systems are an attractive and promising way for gene therapy.[60]

Steinfield et al. (2006) developed a multi-stage delivery system that exploits human immune cells or T lymphocytes as a first stage carrier. T lymphocytes are important in the destruction of malignant cells. Moreover, their sequestration and elimination from the blood stream can be avoided.[61]

The authors claim that this completely autonomous working system is able to detect and destroy malignant cells (also metastasis). Furthermore, they have a high specificity and localized drug delivery is possible. Moreover, the patient is protected against new tumor formation, which is due to the development of memory T-cells. This multi-stage delivery system promises to be an efficient method that could deliver a combination of immune therapy and chemotherapeutic agents.[61]

Finally, a multi-stage delivery system that uses a nanoporous silicon microparticle as a first stage carrier has been developed by Tasciotti et al. (2008). The microparticles are, in turn, loaded with second-stage nanoparticles which can be loaded with therapeutic agents, contrast agents, or both.[62] Therefore, it is possible to optimize endocytosis.

Due to the engineering processing applied in the design of the first stage silicon particles, the overall objective of this third generation nanosystem is to take into account the different barriers and to locate and release therapeutics in target cells. The silicon carriers are biodegradable and biocompatible. Future designs will functionalize the silicon carriers with targeting ligands and penetration enhancers, with the objective of further increasing the efficiency of drug delivery.[62]

2.4. Conclusions

There are still important unmet medical needs in the field of oncology. Cancer nanotechnology could give rise to important opportunities to solve some of these unmet medical needs. There are, however, still significant roadblocks that have to be surmounted. The promise of cancer nanotechnology is to find the right combination of therapeutic agents and targeting moieties, avoiding the biological barriers, and to combat cancer without or with minimal adverse events.

Chapter 3: Assessing the need for quality-adjusted cost-effectiveness studies of nanotechnological cancer therapies

3.1. Introduction

The spiraling costs of healthcare are a worldwide cause of concern, especially for policy-makers and public health administrators allocating limited resources. New therapies like nanotechnological cancer treatments typically entail high acquisition costs and are, thus, major cost drivers. Their use might be justified, however, by their superior cost-effectiveness due to an increased efficacy, reduced toxicities, less adverse events, and a better quality of life. Health consumers are increasingly interested to receive unconventional therapies, like nanotherapeutics, to complement or replace traditional practices.[63] Since national resources are scarce, they have to be allocated in efficient ways. Responsible use of limited health care resources requires a thorough understanding of the cost-effectiveness of new therapies. Hailed as a major breakthrough in medicine, cancer nanotechnology is no exception.[64] The purpose of this chapter is to assess the quality of cost-effectiveness studies of nanotechnological cancer therapies. It finds that the existing analyses are incomplete, neglecting indirect costs and quality-adjusted health.

Nanomedicine is an emerging class of therapeutics that takes advantage of materials on the nanometer scale. Scaling down the size of materials to the molecular level, radically alters and improves their physico-chemical properties. Due to their nanoscale size, nanoparticles are able to interact at the cellular level. Nanotherapeutics are, thus, based on small molecule chemistry. They have the ability to deliver drug molecules to specific regions or tissues, and even into target cells.[7] The use of these nanotechnological optimized drug delivery systems makes it possible to modify the pharmacokinetics and biodistribution of the drug molecule. Nanotherapeutics could, thus, significantly improve efficacy, patients' quality of life, as well as reduce societal and economic costs associated with health care.

The first nanotechnology-based cancer products on the market were liposomes. These are artificial, microscopic vesicles consisting of an aqueous core enclosed in one or more phospholipid layers. Liposomes encapsulate the therapeutic agents within their core. Doxil® and DaunoXome® were approved in 1996 by the Food and Drug Administration (FDA) for use against Kaposi Sarcoma. They are frequently used in the clinic for breast, ovarian, and AIDS-related cancer.

Cost-effectiveness analysis (CEA) is an economic tool that compares the costs and effects of different health care interventions. It is helpful in demonstrating that the cost per additional health effect is worth paying for. CEA allows an efficient allocation of scarce resources and maximizes health effects at the lowest cost.

Cost, effectiveness, adverse events, and quality of life are four crucial factors that should be considered when pursuing cost-effectiveness analyses.[12] Costs included in the analysis depend on the perspective from which cost-effectiveness should be assessed. While the hospital perspective includes all costs incurred by the hospital,

the social perspective includes all relevant costs, i.e. regardless of who bears them. The acquisition cost of novel nanotherapeutics is significantly higher than conventional ones. Although the acquisition cost is a crucial aspect in economic analysis, its significance is relatively small compared to other cost components that are often neglected. For instance, the management of therapy-related side-effects can entail huge economic costs. More adverse events increase total costs since more effort to cure side-effects is required.[40,41,65,66,67,68,69,79] Moreover, it will lead to higher economic output losses. Production loss is an important component, among others, of the indirect costs. While a direct cost can be directly related to a specific therapy, an indirect one can not. Indirect costs should not be ignored when conducting cost-effectiveness studies in cancer care.

Novel therapies are expected to improve efficacy. The parameters that have to be evaluated are: overall survival rates, progression-free survival rates, and response rates (partial and complete). Significant differences between therapies can be detected by statistical tests.[70] Since therapies affect both the length and quality of life, if possible, effectiveness outcomes should be adjusted with the quality of life estimates. If not, the results of cost-effectiveness analyses could be quite misleading. In turn, this might lead to inefficient choices. Quality of life is measured by using questionnaires like the EORTC QoL-30 (European Organization for Research and Treatment of Cancer Quality of Life questionnaire), FACT-O (Functional Assessment of Cancer Therapy – Ovarian) or SF-36 (Short Form 36), among many others. They are submitted to patients and health care experts. Quality-adjusted life years are calculated by multiplying length of life with quality of life estimates.

CEA uses a ratio where the denominator represents the health effects of a specific health care intervention, while the numerator expresses the cost of obtaining these benefits. The resulting cost-effectiveness ratio (CER) is interpreted as the cost to obtain a single unit of effectiveness. The smaller the cost-effectiveness ratio, the smaller the cost for a given effect. The therapy with the smallest cost-effectiveness ratio is, thus, the most cost-effective one and has to be chosen to save resources.

A problem related to CEA is the dynamic nature of predetermined circumstances. They can seldom be regarded as the right conditions in all possible situations. Therefore, analysis is repeated under different conditions. This is done by pursuing uncertainty analysis, which investigates the extent to which outcomes are sensitive to changing parameters. First, costs and effects are estimated for a base case scenario. To account for the uncertainty involved, cost-effectiveness is recalculated under different scenarios. If a therapy remains the most cost-effective one over the whole range of values, the model can be considered as robust. That treatment dominates the other one. However, it is highly likely that more parameters change simultaneously. Therefore, it is interesting to pursue multi-way sensitivity analysis instead of one-way sensitivity analysis, whereby one parameter is changing, ceteris paribus, every time analysis is carried out. Other methods as for example Monte Carlo sampling can also be used to assess the uncertainty involved.

Prices of new biomedical products are typically perceived as too high since their pricing mechanism is poorly understood. The development of new drugs and biomedical technologies requires not only the necessary technological expertise, but also major financial investments with a relatively small chance of success. Furthermore, new effective biomedical devices are thoroughly tested to fulfill strict safety standards before being implemented in clinical practice. Indeed, most

research efforts do not lead to marketable products. It follows that, the costs of successfully developing and launching new biomedical devices are significant.[71] Investing in research and development is not only risky, but also time-consuming. Longer development durations increase the risk that a competitor introduces a similar product sooner. While the return on R&D is potentially high, it comprises both the risk and costs of unsuccessful research projects.[71,72,73]

Therefore, companies and research groups are given an incentive to develop new medical devices by means of patents. Due to patent protection, the innovator receives a monopoly position for a determined period of time, usually 20 years. The additional revenues generated by patent protection are meant to recover the huge costs that were incurred by discovering and developing the innovation and to provide a risk premium.[74] Firms that successfully launch a new biomedical product into the market are likely to have invested in other promising applications that never made it. Obviously, the costs of unsuccessful projects have to be recouped by the product that does reach the market. Hence, the pharmaceutical industry is dependent of some high-revenue products to restore its profitability.[75] Without patent protection, the incentive to invest in research and development would be significantly weakened.[74]

The purpose of the patent system is, thus, to encourage innovation. By impeding competitors to copy new ideas, patents guarantee sufficient revenues to the innovator. That way, these firms can at least recover the costs that were incurred by developing the innovation.[74]

During patent protection, the innovator is the sole producer of the protected biomedical device meeting the whole market demand. Therefore, the demand for the innovator's product equals the whole market demand. Since the demand curve has a negative slope, the monopolist is faced with a trade-off between the price and quantity demanded. To maximize profits, the monopolist chooses an output level that equals marginal cost to marginal revenue. Once that condition is fulfilled, no additional profit can be generated. The market power of a monopolist, c.q. patent holder is, however, not unlimited. Setting unreasonable high prices may lead to the withdrawal of relatively more patients than the increase in average revenue, which, in turn, leads to the loss of profit. It is in the private interest of the monopolist to set the prices correctly.

Patent protection is, thus, a legal instrument to help innovators recoup their investments and make a reasonable profit. After patent expiration, competing companies can produce the medicine as well. Generic manufacturers can market their products at lower prices because they do not incur the costs of R&D or marketing.[76,77]

Finally, patients are often not well informed about new drugs and therapies that may be more expensive but also more effective. In spite of their high cost, it is wrong to withhold this information from patients. Patients have the right to be informed of all available therapies.[78] However, some medical doctors do not inform their patients and some governments practically forbid patients to pay out-of-pocket for the medical care they desire – with possibly fatal consequences.[79]

The purpose of this chapter is to assess the quality of recent studies on the cost-effectiveness of nanotechnological cancer treatments. Since nanotherapeutics have a very high acquisition cost, it is important to consider all other relevant direct and indirect costs of therapy. For instance, ignoring indirect costs, leads to an underestimation of costs of some conventional therapies that seem more prone to adverse effects. If CEA is not pursued correctly, it could result in misleading results. Therefore, it is crucial to assess the quality of current CEAs of nanotechnology-based therapies. The databases and search terms that were used are described in appendix. Most of the analyses have been carried out in the U.S. and Europe, but some evaluations have been carried out in other parts of the world and are included as well. The next section presents the analyses by cancer type. Furthermore, results are reviewed. Then, the quality of these cost-effectiveness analyses is discussed. It is stated for which cancers the use of liposomal therapies is economically sound and for which cancers, at this moment, it is more cost-effective to use conventional treatment. Moreover, the shortcomings of available studies and the knowledge gaps are discussed. Finally, the last paragraph offers the conclusions.

3.2. Cost-effectiveness studies classified by cancer type

This paragraph reviews and discusses cost-effectiveness studies for the treatment of ovarian, breast, AIDS-related and non-nasopharyngeal head and neck cancer, cancer-related infections, hematological diseases, and aggressive non-Hodgkin's lymphoma. The results and conclusions are briefly explained and the shortcomings of these studies are discussed.

3.2.1. Ovarian cancer

Several studies comparing the cost-effectiveness between conventional and nanotechnology-based treatments have been pursued for ovarian cancer. Women whose cancer is not responding (platinum-resistant) or relapsing (platinum-sensitive) after initial treatment with first-line therapies (initial treatment used to reduce cancer), have to proceed to second-line therapies (treatment that is given when first-line therapy does not work or stops working). Unfortunately, there are only a few second-line therapies with acceptable efficacy. Moreover, they cause various adverse events with different grades of severity which raise the total cost of cancer care.[12] Therefore, there is a critical need for new classes of cancer agents. The advantage of PEGylated liposomal doxorubicin is its increased half-life of approximately 55 hours, which may improve the specificity of delivery to target sites while decreasing the absorption by normal tissues leading to reduced toxicities, with the only exception of palmar-plantar erythrodysesthesia (PPE) and stomatitis.[12,40]

Three studies, pursued by Smith et al., Capri and Cattaneo, and Ojeda et al., compared conventional therapy using topotecan with PEGylated liposomal doxorubicin (PLD).[12,40,41] Based on the original (short-term) results of the trial conducted by Gordon et al., who reported that differences in clinical results between topotecan and PLD are not statistically significant, the authors of the three studies conclude that the efficacy of both therapies is equivalent.[12,40,41,70] Assuming that PEGylated liposomal doxorubicin is at least as effective as topotecan, it is sufficient to pursue a cost-minimization analysis.[69] Unfortunately, the authors considered only the direct medical costs. Although the acquisition cost

of the liposomal variant is significantly higher, this initial cost is often offset by the costs of adverse events. With an equivalent efficacy as topotecan but lower total costs, the authors conclude in favor of liposomal therapy.[12,40,41]

Although the authors of the three studies assumed an equivalent efficacy between topotecan and PLD, Smith et al. noticed that the response rate of PLD is twice as high as topotecan's (12,3% versus 6,5%) in platinum-refractory patients.[12] With the exception of PPE and stomatitis, PLD causes also less severe toxicities. Moreover, Main et al. noted that a significant increase in progression-free survival and overall survival was achieved when a subgroup analysis on platinum-sensitive patients in the PLD group was carried out. Therefore, an equal effectiveness between both therapy regimens can not be assumed and the use of a cost-minimization analysis is thus debatable.[69] The same conclusion is reached by Forbes et al., who stated that the incidence of adverse events differ between PLD and topotecan. Consequently, equivalence in terms of quality-adjusted life years can not be established. Furthermore, the different toxicity profiles urge for the adjustment of outcomes with quality of life estimates.[66] According to Smith et al., liposomal therapy requires also a less frequent treatment (28 days instead of 21) and also fewer dosages per cycle (1 versus 5).[12] The savings that can be obtained by using liposomal therapy instead of topotecan varies between US$2.909 (U.K.) and US$12.325 (U.S.). Cost savings with PLD were achieved under all scenarios.[12,40,41]

In terms of incremental cost-effectiveness ratio (ICER), PLD is superior to topotecan.[69] This is in accordance with the conclusions of Smith et al., Capri and Cattaneo, and Ojeda et al.[12,40,41] Main et al. found the ICER of PLD compared to

paclitaxel to be £7.033 per additional QALY in the overall patient population, £5.777 in the platinum-sensitive population, and £9.555 in the platinum-resistant population.[69] It has to be noted, however, that important cost categories were not included. Since topotecan is being administered over 5 days in comparison with 1 day for PLD, it is highly likely that the inclusion of these costs will further widen the cost gap between topotecan and PLD.[69]

Main et al. also pointed out that cost calculation of adverse events was different in the three studies.[69] To avoid double counting, Smith et al. made an important assumption. In instances where patients experienced two or more grade 3 and 4 adverse events in the same cycle, the most severe one was selected.[12] Consequently, underestimation of the cost of managing adverse events is likely to occur. Capri and Cattaneo and Ojeda et al., on the contrary, included also hospitalizations as a consequence of grade 1 and 2 side-effects. Furthermore, patients could have more than one hospitalization per cycle.[40,41] As a result, these authors did not take into account the possibility that patients may already have been hospitalized for another adverse event in the same period. This creates a risk of double counting and overestimation of costs.[69] Despite the differences in costs of side-effects, the cost savings that are achieved by using PEGylated liposomal doxorubicin instead of topotecan are similar in the three studies.

Another important shortcoming is that the effectiveness has not been quantified in terms of QALYs. To facilitate a direct comparison of the relative cost-effectiveness of all relevant comparators and to include QALYs, Main et al. developed a new analytic model, in which they evaluated overall survival in two important periods in time: the progression-free period and the period from progression to death.[69]

Further, the overall survival is being quality-adjusted using utility weights for the two periods. According to the authors, it is possible to incorporate all the evidence from different trials simultaneously using a mixed treatment comparison or MTC model. By using this model, it is possible to identify the most cost-effective therapy.[69]

3.2.2. Kaposi's Sarcoma

In the treatment of AIDS-related Kaposi's Sarcoma, liposomal therapies are nowadays frequently used. Because the disease is not curable, the objective is to give patients a safe and efficacious palliation therapy in order to reduce the symptoms and improve the quality of remaining life.[80]

Studies comparing liposomal treatments present similar conclusions. First, the response rate in patients treated with liposomal therapies (PEGylated liposomal doxorubicin (PLD) and liposomal daunorubicin (DNX)) was equivalent and even slightly superior to conventional therapy. Therefore, the authors conclude in favor of the liposomal treatments, though PLD showed a higher efficacy than DNX.[65,80,81] Furthermore, the studies present the cost-effectiveness of the different therapies in terms of the 'average cost per responder' where a 'responder' is defined as a patient that responds partially or fully to therapy.[65,80,81]

The studies conducted by Bennett et al. and Hjortsberg et al. were carried out in developed countries (U.S. and Sweden).[65,81] Since conventional therapy has already been replaced in these countries by liposomal therapies, conventional

treatment is not considered. While, on the one hand, liposomal formulations seem to be more effective and less toxic, they have, on the other hand, a high acquisition cost. Therefore, they are a less attractive option in resource-limited countries. For this reason, a third study that was carried out in a developing country (Brazil), considers also conventional treatment next to two liposomal therapies.[80]

To asses the treatments' effectiveness, the three studies make use of two randomized controlled trials pursued in the U.S. Both PLD (Caelyx®) and DNX (DaunoXome®) where compared to conventional treatment in two separate clinical trials.[65,80,81] It should be noted that administration costs differ between the trials. In the PLD trial conducted by Stewart et al. (1997), the treatment cycle was 3 weeks. The median response was reported to be 142 days for patients treated with PLD and 175 days for the DNX treatment arm. According to Hjortsberg et al., however, 'response' in this clinical trial was defined in a different way. Therefore, it is highly likely that the duration of response for PLD is underestimated.[65] In the PLD trial conducted by Northfelt et al. (1998), on the contrary, the treatment cycle was only 2 weeks. The median duration of response was 90 days in the PLD treatment arm and 175 days for patients treated with DNX. This may also have resulted in different findings between the studies in developed and developing countries. An important limitation is that both liposomal therapies have never been compared in the same trial, which would lead to more accurate results and a more correct comparison.

The use of PLD leads to a significantly higher response rate than DNX. In developed countries, the response rate is 59% for PLD and 25% for DNX, while it is reported to be 46% respectively 25% in the developing country.[65,80,81] The discrepancy between PLD and DNX might be explained by the dosages of PLD that are higher compared to DNX. Moreover, the two liposomal variants are composed in a different way. Finally, hospitals have less experience with DNX.[65] The difference in response rate of PLD found by Vanni et al. can be explained by the authors' choice of choosing another clinical trial for PLD.[80] They used the trial pursued by Northfelt et al. (1998) while Bennett et al. and Hjortsberg et al. based their findings on the trial carried out by Stewart et al. (1997).

The studies pursued in developed countries found that PLD has a more favorable cost-effectiveness ratio compared to DNX. This ranges between US$8.871 in Sweden and US$11.976 in the U.S. for PLD and respectively US$18.340 and US$26.483 for DNX.[65,81] In Brazil, PLD is also found to be far more cost-effective than DNX with a cost per responder of US$10.272 versus US$16.263. This study also compares conventional therapy that has a cost of US$1.260 per responder.[80] Sensitivity analyses confirm these results.[65,80,81]

Despite the higher effectiveness and lower toxicity of liposomal therapies, it does make economic sense to choose conventional treatment in resource-limited countries. Vanni et al. remark that 'cost per responder' is not ideal as cost-effectiveness outcome because it does not reflect patients' health, disability, or quality of life.[80] Since AIDS-related Kaposi's sarcoma is not curable, these factors are of particular importance. Introducing the concept of quality of life may alter these results because of the lower toxicity of liposomal agents.[80]

Table 3.1 summarizes the most important cost-effectiveness studies performed until now. It clearly shows that cost definitions differ widely making any comparison between studies virtually impossible. Moreover, from a health economic perspective, cost definitions are incomplete and QALYs rarely used. It follows that the cost-effectiveness of nanotechnology-based cancer therapies has not been conclusively determined yet.

Table 3.1: Overview of cost-effectiveness analyses of nanotechnological therapies

Authors	Country	Cancer type	Treatment	Variable	Cost-effectiveness	Year of prices	Cost definition
Capri and Cattaneo (2003)[40]	Italy	Ovarian Cancer	PLD	Total cost per patient	€8.812/patient	2002	Acquisition costs, administration costs, and costs of adverse events
			Topotecan	Total cost per patient	€15.788/patient	2002	
Ojeda et al. (2003)[41]	Spain	Ovarian cancer	PLD	Total cost per patient	€9.614,72/patient	2001	Acquisition costs, administration costs, and costs of adverse events
			Topotecan	Total cost per patient	€11.824,69/patient	2001	
Smith et al. (2002)[12]	U.K. and U.S.	Ovarian cancer	PLD	Total cost per patient	Treatment with topotecan was US$12.325/patient higher in the U.S. and US$2.909/patient	1999/ 2000	Acquisition costs, administration costs, and costs of adverse events
			Topotecan	Total cost per patient		1999/ 2000	

					higher in the U.K.		
Forbes et al. (2002)[66]	Meta-analysis	Ovarian cancer					
Main et al. (2006)[69]	Meta-analysis	Ovarian cancer					
Bennett et al. (1998)[81]	U.S.	Kaposi's Sarcoma	PLD	Average cost per responder	US$11.976/responder	N.A.	N.A.
			DNX	Average cost per responder	US$26.483/responder	N.A	
			Standard	Not assessed	/	/	
Hjortsberg et al. (1999)[65]	Sweden	Kaposi's Sarcoma	PLD	Average cost per responder	US$8.871/responder	1998	Drug costs per cycle, administration costs per cycle and cost of colony-stimulating factors (CSF) [treatment adverse events, neutropenia]
			DNX	Average cost per responder	US$18.340/responder	1998	

			Standard	Not assessed	/	/	
Vanni et al. (2006)[80]	Brazil	Kaposi's Sarcoma	PLD	Average cost per responder	US$10.272/responder	2004	Drug costs, drug administration costs, costs of CSF
			DNX	Average cost per responder	US$16.263/responder	2004	
			Standard	Average cost per responder	US$1.268/responder	2004	
Gradishar et al. (2004)[67]	U.S.	Breast cancer	Nanoparticle albumin-bound paclitaxel	Total cost per responder	US$30.692,49/ responder	N.A.	Utilization and costs considered were those associated with pre-treatment medications, drug administration, management of toxicities, and treatment failure
				Total cost per course	US$10.128,52/course		
			Cremophor-based paclitaxel	Total cost per responder	US$72.790,16/ responder	N.A.	
				Total cost per course	US$13.830,13/course		

Porter and Rifkin (2007)[88]	U.S.	Multiple myeloma	DVd (treatment with PLD) VAd (standard treatment	Total treatment cost per patient Total treatment cost per patient	US$34.442/patient US$35.846/patient	2004 2004	Drug acquisition costs, cost of administration, tests, transfusions, concomitant medication, and hospitalization cost management adverse events
Fountzilas et al. (2006)[89]	Greece	Non-naso-pharyngeal cancer	PLD with paclitaxel Gemcitabine with paclitaxel	Total treatment cost per patient Total treatment cost per patient	€11.068/patient €7.419€/patient	N.A N.A.	N.A.
Al-Badriyeh et al. (2008)[86]	Australia	Cancer-related infections	Liposomal amphotericin B	Cost differences	Liposomal amphotericin B costs 1.422 australian dollar less per patient	N.A.	N.A.

			Voriconazole	Cost differences			
Bruynesteyn et al. (2007)[84]	U.K.	Cancer-related infections	Liposomal amphotericin B	Cost differences	Caspofungin costs £2.033 less and adds an additional 0,40 QALYs	N.A.	N.A.
			Caspofungin	Cost differences			
Cagnoni et al. (2000)[82]	U.S.	Cancer-related infections	Liposomal amphotericin B	Break-even cost-effective price	US$72-US$87/50mg For all patients	1996	Hospital length of stay and costs from the first dose of study medication to the time of hospital discharge
			Amphotericin B		US$83-US$112/50mg in allogeneic bone marrow transplant patients	1996	

Cornely et al. (2008)[87]	Germany	Cancer-related infections	Liposomal amphotericin B	Treatment-associated cost per patient	US$49.216/patient	N.A.	N.A.
			Micafungin	Treatment-associated cost per patient	US$43.243/patient	N.A.	
Motzkat et al. (2003)[83]	Germany	Cancer-related infections	Liposomal amphotericin B	Direct cost per successfully treated patient	€23.737,85/ patient	N.A.	N.A.
				Effectiveness-adjusted costs/patient	€14.556,93/ patient	N.A.	
			Amphotericin B	Direct cost per successfully	€12.488,11/ patient	N.A.	

				treated patient Effectiveness-adjusted costs/patient	€12.488,11/ patient	N.A.	
Stam et al. (2008)[85]	Italy	Cancer-related infections	Liposomal amphotericin B	Total treatment cost per patient	€11.821/patient	2007	The direct medical costs included were first- and second-line antifungal drug costs, costs because of adverse events, and the cost of hospital stay
			Caspofungin	Total treatment cost per patient	€8.351/patient and an extra 0,25 QALYs	2007	
Limat et al. (2005)[68]	U.S.	Aggressive non-Hodgkin's lymphoma	Dexrazoxane	Total costs per patient 40-year old 60-year old	€155,99/patient €69,31/patient	N.A.	Direct medical costs of cardioprotection and the treatment of heart failure per live year saved.

			Liposome-encapsulated doxorubicin	Total costs per patient 40-year old 60-year old	 €46.449,82/ patient €229,40/patient	N.A.	

3.2.3. Cancer-related infections

Treatment of malignant phenotypes may lead to cancer-related infections. To eliminate the severe and frequent adverse events, liposomal agents have been developed. Liposomal and conventional amphotericin B were compared by Cagnoni et al. and Motzkat et al.[82,83] Cagnoni et al. found an equivalent aggregate efficacy, but the liposomal agent was far more effective in the treatment of invasive fungal infections.[82] Furthermore, it leads to decreased infusion-related toxicities and causes fewer and less severe side-effects. This was certainly the case for patients who developed nephrotoxicity. Moreover, the authors estimate the break-even points beyond which liposomal therapy is cost-effective. Sensitivity analyses of the cost of study drugs revealed that total hospital costs for patients treated with liposomal amphotericin B would be the same as that for conventional treatment at an acquisition cost of US$72 per 50mg for all patients and US$83 per 50mg for allogeneic bone marrow transplant (BMT) patients. The sensitivity analysis carried out on the basis of frequency of nephrotoxicity, on the contrary, shows that the liposomal agent would be cost-effective at an acquisition cost equal or less than US$87 per 50mg for all patients and US$112 per 50mg for allogeneic BMT patients. The authors argue that both the acquisition cost and dosing requirements of liposomal therapy are significantly higher. This is also the case for hospital costs.[82] Given that the cost of liposomal amphotericin B is US$188,40 per 50mg, compared with US$16,60 for the conventional agent, Cagnoni et al. conclude that the use of liposomal amphotericin B is, for the moment, not yet cost-effective.[82] It is important to note, however, that nephrotoxicity does not only cause costly adverse events, it also affects the quality of life which should be considered to produce unbiased results.

Motzkat et al. used the rate of patients who were successfully treated as an efficacy parameter.[83] Costs were estimated from a hospital perspective. Furthermore, they were effectiveness-adjusted. The authors found the direct cost to be €23.737,85 for the liposomal agent versus €12.480,11 for the conventional one. The cost-effectiveness ratio was €14.556,93 respectively €12.488,11. Sensitivity studies confirmed the dominance of conventional amphotericin B for a broad range of values.[83] Both, Motzkat et al. and Cagnoni et al. consider only the hospital costs without taking into account other direct and indirect costs and quality of life estimates.

In a U.K.-based study, Bruynesteyn et al. compared caspofungin with liposomal amphotericin B and showed that caspofungin costs £2.033 less than liposomal therapy while adding 0,40 QALYs.[84] Analysis was performed using a decision-tree.[84] Stam et al. compared the same agents for patients with neutropenic fever in Italy.[85] These authors also used a decision-tree as evaluation method. The variables were: success in terms of resolution of fever, resolution of baseline infection, absence of breakthrough infection, survival, and quality of lives saved.[85] Although the chance of experiencing a successful outcome was similar between both treatment regimens (35%), mortality among patients treated with caspofungin was lower (7%) than for liposomal amphotericin B (11%). Furthermore, treatment with the liposomal agent saves only an extra 0,25 QALYs compared with 0,35 QALYs with caspofungin.[85] Despite the adjustments, the authors of both studies conclude that liposomal treatment is not cost-effective yet.

Al-Badriyeh et al. investigated the cost-effectiveness of liposomal amphotericin B versus voriconazole in the treatment of febrile neutropenia in Australia.[86] The main outcomes of the study were: success, breakthrough fungal infections, persistent baseline fungal infection, persistent fever, premature discontinuation and death. With a net cost saving of 1.422 Australian dollars and a higher efficacy, the study concludes in favor of liposomal amphotericin B. When investigating on the cost per death prevented and the cost of successful treatment, a similar conclusion was reached. Uncertainty studies confirmed liposomal amphotericin B as the most cost-effective agent in 99,80% of cases.[86]

Finally, Cornely et al. compared liposomal amphotericin B and micafungin for the treatment of candidaemia and invasive candidiasis in Germany.[87] Effectiveness was based on the percentage of patients, alive at the end of the study, achieving clinical and mycological response after initial therapy. The authors also estimated the total treatment-related costs over the study period. They state that 52,90% of patients were successfully treated with micafungin versus 49,10% for liposome therapy. Furthermore, this last agent has a treatment cost of €49.216 per patient versus €43.243 for micafungin. Despite micafungin, at this moment, seems to be more cost-effective in the base case scenario, it can not be considered as robust by probabilistic sensitivity analysis.[87] Moreover, the results were not quality-adjusted, which is likely to distort the results.

3.2.4. Hematological disease

Porter and Rifkin compared PEGylated liposomal doxorubicin (PLD) and conventional doxorubicin for the treatment of multiple myeloma.[88] They found that PLD leads to increased tumor exposure, less cardiac toxicities, less myelosuppression and less alopecia. Furthermore, a 1-hour infusion every month is required instead of a 96-hour infusion when using conventional doxorubicin. However, according to the authors, an equivalent efficacy can be deduced from the fact that, on the one hand, the objective response rates were equivalent in both treatment arms while, on the other hand, there is no significant difference in progression-free survival and overall survival in both patient groups. Despite an equivalent efficacy, significantly more grade 3 and 4 adverse events (neutropenia and sepsis) and heart failure are occurring in the conventional treatment arm.[88] Consequently, adjusting the results with quality of life would have widened the gap between therapy regimens.

Costs were estimated from a hospital perspective. While the acquisition cost of liposomal therapy is higher, less hospital days are required (4,75 days versus 14,4) which leads to lower hospitalization costs. Furthermore, liposome therapy reduces the drug administration time (1,3 days versus 5,2 days per cycle). Therefore, drug administration costs are significantly lower.[88] Total costs per patient were estimated at €35.846 for conventional treatment, which is only slightly higher to the €34.442 for the liposomal therapy. With an equivalent effectiveness and similar costs, the liposomal treatment should be favored because of the better toxicity profile and fewer side-effects.[88] Finally, the authors state that the decreased hospitalization and administration costs in the liposomal

treatment arm more than offset the disparity in drug acquisition costs between both therapies.

3.2.5. Advanced non-nasopharyngeal head and neck cancer

Fountzilas et al. compared conventional cisplatin-based therapy with a combination of paclitaxel with gemcitabine and paclitaxel with PEGylated liposomal doxorubicin (PLD).[89] Those two new therapies were compared with conventional treatment in two separate clinical trials. PLD has been developed to increase the anti-tumor activity and drug delivery, but the authors found this agent to reduce adverse events as well. Based on the overall response rate, the time to progression and survival, the authors found an equivalent efficacy between both combination therapies and the conventional one. Despite their similar efficacy, the authors note that the quality of life should be taken into account in future analysis.[89]

Assuming an equivalent efficacy, the authors concentrated on total treatment costs. For paclitaxel and gemcitabine, it was estimated at €7.419 compared to €11.068 for paclitaxel and PLD. The cost difference was mainly attributed to the difference in chemotherapy costs which, according to the authors, make up 95% of treatment cost. They conclude that as long as the acquisition cost of gemcitabine remains significantly lower than that of PLD, the therapy combining paclitaxel and gemcitabine is the most cost-effective one.[89]

3.2.6. Aggressive non-Hodgkin's lymphoma

Non-Hodgkin's lymphoma is the name of a collective group of cancers arising from white blood cells (lymphocytes). Aggressive non-Hodgkin's lymphoma is a particularly fast growing form of this malignant disease. Fortunately, the disease responds relatively well to therapy. Limat et al. compared two novel therapies to treat aggressive non-Hodgkin's lymphoma, dexrazoxane and liposome-encapsulated doxorubicin.[68] Based on the outcome of life expectancy, both treatments were found to be equivalent. Although the primary objective of the study was to asses the cost-effectiveness of cardioprotective strategies, the results were not quality-adjusted.[68] Costs were estimated from a hospital perspective and included the costs of cardioprotection and the costs for treating heart failure per life year saved. They were estimated for two patient groups of respectively 40 and 60 years old.[68]

In the liposomal treatment arm, costs are estimated at €229,40 per 60-year old patient and €46.449,82 per 40-year old patient. For dexrazoxane, they were estimated at €69,31 respectively €155,99. Stated otherwise, dexrazoxane costs €46.293,83 less for a 40-year old patient and €160,09 for a 60-year old one, compared with liposome-encapsulated doxorubicin. Therefore, the liposome agent is not cost-effective yet. This is due to higher costs and an equivalent efficacy.[68] The authors argue that more studies are required to verify these results.

3.2.7. Breast cancer

In developed countries, breast cancer is the most frequently found malignancy in women. A nanotechnological variant of paclitaxel has been developed for treating metastatic breast cancer. Albumin-bound paclitaxel (nab-paclitaxel), with the trade name 'Abraxane', is a solvent-free form of paclitaxel, leading to a safer therapy without the need of standard steroidal, anti-inflammatory pre-treatment.[90]

Gradishar et al. compared nab-paclitaxel and conventional paclitaxel.[67] Nab-paclitaxel, having a shorter infusion time, higher response rate, longer time to disease progression for second-line treatment, and longer median survival, results in a higher efficacy than conventional therapy.[67] To estimate the costs, the authors included the cost of pre-treatment, drug administration, management of adverse events, and costs of treatment failure. Since the acquisition cost was not yet available, it was not included. Therefore, the authors estimated the total cost per course and total cost per responder.[67]

Total cost per course was estimated at US$10.128,52 for nab-paclitaxel and US$13.830,13 for conventional therapy. Furthermore, the total cost per responder was found to be US$30.692,49 respectively US$72.790,16.[67] Although the acquisition cost was not included, the authors emphasize that nab-paclitaxel is both more effective and less costly than conventional agents and should, thus, be preferred in the treatment of metastatic breast cancer.[67]

3.3. Discussion

The objective of this chapter was to explore the existing studies on the cost-effectiveness of liposomal treatments in clinical use today. From a cost-effectiveness perspective, it is interesting to use liposomal treatment for ovarian and breast cancer and multiple myeloma. In spite of their higher acquisition cost, liposomal agents may help save resources due to a higher (or equivalent) efficacy and lower total costs that are due to fewer and less severe adverse events. It is important to note, however, that cost-studies based on the information of one country are difficult to use by policy-makers in another country.[12] Liposomal therapies for cancer-related infections and aggressive Non-Hodgkin's lymphoma are, on the contrary, not cost-effective yet. This is due to higher costs and slightly inferior (or equivalent) efficacy compared to conventional treatment.

In general, the acquisition cost of liposomal agents is significantly higher than their conventional counterparts'. However, with the exception of palmar-plantar erythrodysesthesia and stomatitis, the use of liposomal therapies gives rise to fewer side-effects, both in number and severity. Mutatis mutandis, the costs for the management of these toxicity-related adverse events are significantly higher for the conventional treatment regimen. Therefore, it is crucial to consider all costs to obtain a relevant cost analysis.

An important drawback of the cost-effectiveness analyses discussed in this chapter is that the results are not quality-adjusted. Very few authors calculate the cost per QALY. Since cancer affects both length and quality of life, it is important to adjust the effectiveness results with quality of life estimates. Since some cancers are not

curable, the sole objective of treatment is sometimes only to provide safe and effective palliation, i.e. to reduce the symptoms and attain a better quality of remaining life.[80] Consequently, it is crucial to estimate the cost per QALY. Another flaw is that most studies consider only the direct hospital costs instead of the total social costs.

The available existing cost-effectiveness analyses reveal some important knowledge gaps: (1) most studies do not include QALYs and, therefore, tend to underestimate the cost-effectiveness of nanotechnology-based therapies; and (2) indirect costs are virtually ignored in all cost-effectiveness studies, leading to an underestimation of costs of conventional treatments that are more prone to side-effects. It is, thus, crucial to include QALYs and indirect costs into cost-effectiveness analysis. Since cancer treatments not only affect the length but even more so the quality of life and since indirect costs are substantial, the results of cost-effectiveness analyses are unreliable, if not misleading. It follows that there is an urgent need for economic research on cancer therapies including both QALYs and indirect costs.

3.4. Conclusions

Most nations face rising health care costs due to an ageing population and new more expensive therapies with limited resources. Therefore, it is crucial to have a clear understanding of the cost-effectiveness of public health expenditures. Cost-effectiveness analysis is a valuable tool in allocating limited resources but inaccuracy is highly likely to lead to inefficient choices. Current cost-effectiveness

analyses comparing conventional treatments with new nanoparticulate-based therapeutics are found to be incomplete neglecting indirect costs and quality-adjusted life years. This might lead to wrong policy conclusions at the expense of patients and society. It is crucial to develop a generic cost-effectiveness model comprising all direct and indirect costs and adjusting effectiveness results with quality of life estimates. Only then, cost-effectiveness analysis is helpful to making efficient choices in healthcare.

Appendix: Literature search

The electronic databases "Pubmed", "Scopus" and "Web of Science" were searched. This search was pursued in May 2008 and provided us with the available cost-effectiveness studies on liposomal and other nanotechnological cancer therapies. The following keywords were used: cost-effectiveness AND cancer AND one of the following: nano*, liposome*, liposom*, nab-paclitaxel, Abraxane, Myocet®, DaunoXome®, OncoTCS, Doxil®, Caelyx®, Zinostatin®, Stimalmer®, Oncospar®.

No date limits were applied to the searches. The searches aimed to retrieve published studies. There were no limits applied by study design. The literature search retrieved 16 articles and 2 meta-analyses. All but two articles and both meta-analyses were relevant and thus included.

Full paper texts of any titles/abstracts that were considered relevant were included. The relevance of each study was assessed according to the following criteria: only phase III trials were included. Furthermore, only studies based upon a randomized controlled trial were included. Only full economic evaluations that compared two or more treatment regimens and considered both costs and effects were considered. Animal studies, phase I and II studies were excluded from the analysis. Moreover, non-systematic reviews, effectiveness studies, general background reports, case reports, commentaries, cohort studies, and long term follow-up studies were excluded from analysis. Studies which were reported in abstract form only, and where no further information was available, were excluded. Foreign language papers were also excluded.

In January 2009 another search was performed. Next to the original search terms, the following terms were also used:

- Cost-effectiveness AND ovarian cancer AND one of the following: liposomal doxorubicin, Doxil®, Caelyx®, liposom*, nano*
- Cost-effectiveness AND Kaposi's Sarcoma AND one of the following: liposomal daunorubicin, DaunoXome®, liposomal doxorubicin, Doxil®, Caelyx®, liposome*, nano*
- Cost-effectiveness AND cancer-related infections AND one of the following: liposomal amphotericin B, Abelcet®, AmBisome®, caspofungin, liposom*, nano*
- Cost-effectiveness AND hematological disease or multiple myeloma AND one of the following: liposom*, nano*

- Cost-effectiveness AND nasopharyngeal head and neck cancer AND one of the following: liposom*, nano*, liposomal doxorubicin, PLD, gemcitabine
- Cost-effectiveness AND aggressive non-Hodgkin's lymphoma AND one of the following: liposom*, nano*
- Cost-effectiveness AND breast cancer AND one of the following: liposomal doxorubicin, Myocet®, Doxil®, Caelyx®, Genexil-PM, albumin-bound paclitaxel, nab-paclitaxel, Abraxane, liposom*, nano*
- Cost-effectiveness AND acute lymphoblastic leukemia AND liposom*, nano*, Oncospar®

Chapter 4: Literature review: Health economics and nanotechnology

The Office of Technology Assessment defines medical technology as: "The techniques, drugs, devices, and medical and surgical procedures used in health care, and the organizational and supportive systems within which such are provided".

The objective of health technology assessment is to assist public health administrators and give them valid and timely information about the general value of a particular medical application under consideration. Technology assessment occurs primarily through scientific testing. Scientific testing is indispensable to determine the extent to which, and under what conditions, the implementation of a specific technology reaches the desired and intended effects while it does not involve unreasonable risk of harm.[91]

Technology assessment tries to give an answer on three main questions[92]:

- Does it work?: this question tries to give an answer on the effectiveness of a new medical technology. Effectiveness studies give information on how much better a new technology is. It takes, thus, both benefits and adverse events into account.
- At what cost?: it is important to consider the whole cost of care of different alternatives. This is, however, not always an easy task. A first problem is encountered when savings are at the marginal rather than

average cost. Second, sometimes savings are found in other budgets. Third, resources may be used for other purposes. Consequently, these savings could lead to an overall increase in cost. Finally, cost analysis frequently uses data from trials that may not reflect those in routine care.

- Is it worth it?: effects and costs are compared. The therapy that results in the largest effects for a given cost is the preferred health care intervention.

The production of health is an important issue for health care administrators. There are a large number of beneficial health care interventions but, unfortunately, society can not afford them all. Therefore, public health administrators have to make difficult decisions.[93]

A medical technology goes through different stages during its life-cycle. The first stage is the basic research stage. Here, new knowledge about the biological mechanisms underlying the normal functioning of the human body and its malfunctions in disease is produced. This basic research is then used in a second stage, the applied research and development stage. The outcomes of this stage are the creation of new solutions to problems in the prevention and treatment of a specific disease. In the next phase or the clinical investigation and testing phase, new medical technologies are tested in human subjects. This stage includes a range of tests from first human use that goes as far as large–scale clinical trials and demonstration projects to show the new medical technology's efficacy and safety. The last phase is pursued when the new technology appears to be of value. When this is the case, the new technology will be used by clinicians and patients

will ask for it. This process is known as diffusion. It has to be noted that a new technology evolves. This is because new patient groups become eligible and additional applications are found.[94]

The decision to introduce a new medical technology is interwoven with the decision on its optimal diffusion pattern. Due to budgetary pressures, health care administrators have to be more rational and selective in their decision-making. Important to note is, however, that a technology should not only be assessed on its safety but also on its efficacy and costs.[91,94] A technology's cost-effectiveness is calculated to measure the extent to which it can reach a specific objective with minimal resource use.[91] Three important conditions have to be fulfilled when evaluating a new technology[94]:

- Effectiveness: a new medical intervention has to show some ability to beneficially alter the natural course of a clearly defined condition or set of conditions.
- Cost: if two or more interventions have an almost equivalent effectiveness, the one with the lowest cost should be preferred.
- Acceptability and equity: an important condition for a cost-effective technology to be of value for society is that it has to be socially acceptable and equally accessible to all relevant subgroups of society into which it is being introduced.

The assessment of a new technology typically occurs through three stages [91]:

- Identification: of a new technology or a technology about which too little is known. This could be the case for a new technology or an existing technology considered for a new or expanded area of application.
- Analysis: here the technology is tested on humans. The effects, costs and social and ethical benefits have to be considered. The prerequisites for testing are, however, that the technology's objective and assessment of criteria are clearly defined in advance. This, in turn, provides the base for choosing the right indicators, measurement instruments and research design.
- Synthesis: of all the accumulated knowledge about the technology. This is the basis for a comprehensive assessment.

The study of the cost-effectiveness of a new medical application is based on the results of a previously pursued effectiveness study. Effectiveness studies demonstrate if new treatments obtain improvements in health state. Consequently, cost-effectiveness studies can only be as good as the underlying effectiveness study.[94] Benefits of a new technology are, however, not confined to the individuals cured for a specific disease. Most individuals benefit from the return to health of relatives, friends, and even individuals they do not know. As far as possible all those benefits should be considered in cost-effectiveness analysis.[95] Before beginning a cost-effectiveness study, all relevant costs and effects should be listed.[95]

Effectiveness studies can be pursued in different ways. These are: experimental studies, quasi-experimental studies and observational studies.[92] The main difference between these methods is in their answer to the attributability problem. This means that the observed differences between the outcomes of alternative policies can be attributed with any confidence to the policies themselves.[94] However, there exists no standardized method to define for deciding what is 'good' and what and how much is 'better'. To this end, statistical principles to demarcate which effects are statistically significant have been developed, but no comparable clinical principles have been developed to indicate what is significant therapeutically.[9] However, a new medical technology that does not fulfil some pre-determined standards of efficacy and safety should by no means be included in the medical armamentarium.[91]

When assessing a new technology's effectiveness, outcome measures to assess length of life are frequently included. Since in health care quality of life is frequently affected, if possible, it should be included.[96] Moreover, empirical studies showed that health gains are important to the general public.[97] Quality-adjusted life years (QALYs) represent the benefit given by a specific health care intervention. The relationship between QALY scores and social value gives information about the relative social valuations of medical interventions within and across different patient arms and are defined on an interval scale. This relationship is the only thing that matters when pursuing economic evaluations.[97] Quality weights are added to reflect the desirability of living in a particular health status that goes from perfect health, which is weighted as 1 and death which is weighted as 0.[93,98] Once quality weights have been assessed, they have to be

multiplied by the time spent in a particular health status. This product is expressed as the total number of QALYs.[93]

To assess patients' quality of life, different methods are available but the time-trade-off method and the standard gamble are the most important ones.[92,96] These methods have, however, some drawbacks. The methods' main disadvantage is that the individuals' responses to the choices that they are asked to make in interviews about hypothetical situations may not reflect the choices they would make in real situations. Another shortcoming is that most outcomes reflect the move from a position of a good health to worse health states. If health is subject to the law of diminishing marginal utility and if the results of earlier situations are used in later situations, bias could arise. Furthermore, outcomes are affected by the expected duration of the health status. A final drawback is that quality-adjusted life years are possibly not measuring all benefits.[96]

Quality of life is a multifunctional concept. It comprises aspects of organ functioning, the ability to do physical activity, their social role in society, and their feeling of general well-being. Because quality of life is multifunctional, it is also very difficult to measure because every single health component has to be measured. Like stated previously, there are two important methods for measuring QALYs[96]:

- Time-trade-off (TTO): the question asked when using this method is: suppose you had a disease that would leave you in health state X for T years if left without treatment. The only available treatment is free and would cure you perfectly. However, it would shorten your life span to t years. The life span is then varied until the interviewed individual is

indifferent between the alternatives 'treatment' and 'no treatment'.[96] This method is the most used one to estimate QALYs. There are, however, some shortcomings. Firstly, results could be influenced by the way the question is asked. Secondly, the time frame for the trade is important. Thirdly, the health status of the time sacrificed, and when it is supposed to take place, could possibly influence the willingness to trade with time. Fourthly, the health status of family members may influence the trade. Due to these problems, it is extremely difficult to know whether differences in quality of life weights are due to the individuals' characteristics or to characteristics of the TTO methodology.[98]

- Standard gamble method: the following question is asked: assume that you had a disease that would leave you permanently in state H without treatment. The only treatment is free and would cure you perfectly with probability x, but leads with probability y to your immediate death. Now, probability x is varied until the individual is indifferent between the alternatives 'treatment' and 'no treatment'. The resulting x*(H) is interpreted as the relative weight with which to weight status H.[96]
- Questionnaires: different tools to estimate an individual's preference for a specific health status have been developed. These are generic health-state classification methods. They link information from general questionnaires with preferences for health states derived separately from the community.[93]

Important to note is, however, that preferences between patients and non-patients differ. Patients tend to place a higher value on their health states. The discrepancy between the values placed on a specific health condition by patients and non-patients is that the former adapt in order to accommodate their limitations and alter their objectives and expectations.[93] Incorporating preferences into economic analysis is one of the most challenging issues. The use of QALYs is also subject to some important criticisms.[93] Firstly, the use of QALYs assumes a constant proportional tradeoff between length of life and health status. This means that an individual is prepared to give up some constant amount of years of life to achieve a specific improvement in quality, independent from the number of years that remains to that individual. Secondly, there is concern whether QALY estimates really represent the society's preferences for rationing. Furthermore, due to the different methods of estimating individuals' preferences, the comparability between studies is probably compromised.[93,98] Until now, however, no acceptable alternative to QALYs has been found. The main challenge is to find valid measurement methods for QALYs.[93]

Due to the increasing reliance upon economic evaluations to invest in a specific health care intervention, a growing interest in methods for the monetary valuation of preferences has been experienced.[99] Giving a monetary value to human life is not an easy task and is subject to a lot of controversy. There are, however, two important methods to value human life. These are the human-capital-approach and willingness-to-pay. The human-capital-approach values life by measuring the individual's financial losses. Value of life is, thus, equal to the individual's future income losses. This is called gross human capital. This method's primary shortcoming is that retired individuals, who do not contribute to production, have

a value of zero. Another drawback is that the method does not consider the pleasure of living. This method has, thus, serious economic and ethical drawbacks. The willingness-to-pay (WTP), on the contrary, considers the individual's maximization of expected utility.[96,100] To that end, the monetary value of a marginal reduction of the death risk corresponds to the individual's marginal rate of substitution between his wealth and his probability of survival.[96] This approach is used primarily in two situations: on the one hand to provide the benefit-measure in a partial economic evaluation when a new intervention is considered and, on the other hand, to compare relative values of alternatives when different interventions are competing for the same scarce resources.[101] However, one unique WTP per QALY is not enough to adequately reflect social preferences.[97] There are two methods to measure an individual's willingness-to pay: questionnaires or observing his behaviour.[96,100,102] Both methods have some drawbacks. In the first method a hypothetical question is presented to individuals. When constructing such questionnaires, two points are of particular importance. Firstly, the researchers must choose the relevant dimensions and items that are included in the questionnaire. Secondly, the relative weights to each health state described in the questionnaire have to be attached.[103] However, the assumption used in the questionnaires is such that the conversion of time in 'ill health' to time in 'full health' is linearly related to the time spent in the state of ill health. Questionnaires are, thus, based on a specific preference pattern. Stated otherwise, an individual can be an expected utility maximizer without following this particular assumption. This is very restrictive and may fail to reveal the person's true preferences. When using the second method, one is never sure that the individuals know exactly what the relevant risks are. Furthermore, there are no other motives for the individuals' observed behavior.[96]

Like stated previously, different kinds of designs can be used to assess a technology's effectiveness. These are: randomized experiments, non-randomized experiments, and non-experiments. In randomized experiments subjects are assigned randomly to each treatment. In this kind of trials patients are randomized between a standard and a new treatment. The objective is to test if the new treatment can be accepted or not. This is done through the use of statistical tests. If the null hypothesis is accepted, the new therapy is adopted.[104] Firstly, randomization avoids systematic sources of error. Furthermore, in the long run, it attains a balance between the comparison groups regarding prognostic factors that are important for the outcomes. Finally, randomization provides a basis for statistical inference. In non-randomized experiments, on the contrary, comparisons are based on non-equivalent patient arms. Therefore, differences wrongly attributed to the treatment could possibly arise.[11] The main disadvantage of randomized controlled trials is their higher cost. In non-experiment or observational studies, researchers have no opportunity to influence the outcomes.

However, more often than not, empirical evidence from clinical trials is not enough to make a rigorous assessment of all relevant direct and indirect costs possible. To that end, mathematical modelling is frequently used to predict how the use of a specific technology affects medical outcomes. These mathematical techniques are decision modelling, state transition modelling, discrete event modelling, and survival modelling. Mathematical modelling is important and ranges from the translation of surrogate to final outcomes, the adjustment of outcomes with prognostic factors, the extrapolation of final outcomes beyond trial durations and informing the design and prioritization of future research.[92]

When pursuing cost analysis, opportunity costs are considered. This implies that the input of resources in one specific activity could have been invested in another intervention. The amount of benefit foregone by not investing in a particular health care intervention becomes the measure of cost for the activity that is undertaken. Furthermore, cost analysis is based on marginal costs. This means that only the change in the use of resources under different alternatives is relevant.[94,95,105] Moreover, not only resources for which money has to be paid are considered. Working and leisure time are both important. Also resources used in self-medication, transport to hospital, home adaptation and volunteer work have to be accounted for in cost analysis. If not, there is a risk of underestimating total costs.[106] Although these activities do not involve cash transactions, they represent a cost for society.[95]

Because future costs and effects are less valuable than costs and effects occurring now, they have to be discounted. Future costs and effects are less valuable because individuals generally prefer present effects. This is due to individuals' dislike for waiting or because incomes rise over time and hence, future effects accrue to a better-off population.

The objective of cost-effectiveness analysis (CEA) is to provide a guide for choosing among different health care interventions and choose the option with the best possible outcomes given the available and limited resources.[107,108] CEAs are very useful because they permit to represent the costs and effects of different alternatives in a single conceptual framework, and this over an extended period of time. It is important to emphasize, however, that the limitations of such models have to be understood completely when interpreting the results. This is

particularly true when assessing these results within the full cultural, sociological, political and economic context.[109] The use of cost-effectiveness data has permitted to health care administrators to compare the costs of different types of health interventions.[11] Economic evaluations give an idea if a new health care intervention creates value for money.[110] They provide useful information to support health care administrators in their decisions.[65] The importance of cost-effectiveness studies is emphasized due to the high costs of health care.[81] On the one hand, it is highly likely that the important advances in molecular biology will lead to the development and introduction of new and expensive technologies.[111] On the other hand, the demand of health care rises due to a growing and ageing population. This last aspect has far-reaching implications for health care delivery.[112]

Accurate economic analysis considers effectiveness, costs, toxicities, and quality of life. The objective is to adopt new health technologies while maintaining quality care and staying within a pre-determined health care budget.[12] The main problem when pursuing cost-effectiveness analysis is that the researcher is confronted with the dynamic nature of the world. This requires a built-in flexibility to cope with possible changes in the variables considered in the study.[94] The external conditions under which analysis is pursued can be described, but can seldom be regarded as the right conditions in all situations. Therefore, testing must be repeated under different conditions.[91] Here, sensitivity analysis comes into play. This kind of analysis investigates the extent to which outcomes are sensitive to specific variables.[40,92,94] Other methods as for example Monte Carlo sampling, can also be used to assess the uncertainty involved.[92]

Economic data differ from country to country and their stability changes over time. Therefore, conclusions based on the information of a specific country may not be used in other parts of the world. International differences in health care delivery should always be considered.[12,80,106] Moreover, not only the hospital and drug costs may change over time, but the introduction of new technologies may cause changes in practice with shifts towards or away from in-patient care and resultant variant in cost. Therefore, costs of different approaches where analysis is carried out in different times can not be compared. It follows that, economic analysis is only useful if pursued rigorously and if enough attention is given to possible problems and pitfalls which may invalidate the conclusions.[11] The cost-effectiveness of alternative health care interventions can also be represented by plotting an efficiency curve. The options lying inside the efficiency curve are inefficient because there exist options that are either less costly or more effective.[106]

In cost-effectiveness analysis, there are, thus, four possible outcomes. When an intervention decreases total costs while increasing effectiveness, that technology dominates the other one. If, on the contrary, effectiveness decreases while increasing costs, the intervention is not cost-effective. When a technology increases costs while increasing also effectiveness, cost-effectiveness analysis becomes an important tool to assess which intervention is the most interesting one.[113] The same is true when a new therapy has lower costs but also lower effectiveness. Thus, when costs and effectiveness move in the same direction, cost-effectiveness analysis has to be pursued. A health care intervention is cost-effective if it yields an additional benefit worth the additional cost. These interventions provide more value for money.[89] Until today, no single, standardized

format to pursue and report cost-effectiveness analyses has been developed.[113] It is, however, important to note that a model never perfectly reflects reality.[85]

Ethical questions do always arise when testing new medical technologies on human subjects. The Declaration of Helsinki is based on three important ethical principles. These are: doing what is good or beneficence, showing respect for persons, and justice. The concept of beneficence means that it is important to do 'what does not harm'. Research on humans can not be legitimately pursued unless the importance of the objective is in proportion to the risks of the project. Respect for persons means that human subjects enrolled in a clinical trial have to be informed of the aims, methods, anticipated benefits and potential risks of a specific technology. Furthermore, individuals can not be forced to participate in a clinical trial against their will. A last ethical principle is the one on justice. It is related to the assessment of effects and risks and their distribution among different groups. Moreover, the Declaration of Helsinki states that the design of a clinical trial should be clearly defined in an experimental protocol and supervised by an independent committee for consideration, comment and guidance.[91,105,114]

There are three major decisions of any health care system:

- How much to spend on health care: consumer demands for health care seem to be distorted. This is due to excess health coverage that results from tax subsidies for the purchase of health insurance and by the lack of information on which to base their choices. These distortions cause the provisions of too many or too few of specific health care services.
- How to best produce medical services: health services should be provided at the lowest cost. An efficient provision of health services and

the containment of rapidly increasing health expenses are important to health care administrators.

- The distribution of health services: the third important decision is how health services should be redistributed among different patient groups and by what mechanisms. Redistribution could be achieved by programs giving additional benefits to one group of patients while adding costs to the other groups.

The delivery of health care can differ considerably between countries. Health services can be provided for free to everyone or it can be distributed based on individuals' willingness-to-pay. This last phenomenon is called consumer sovereignty. This is based on two value judgments. On the one hand, should consumers determine the amount they would like to spend on health care? On the other hand, it is important to determine the method and size of subsidy that has to be extended to individuals with low incomes and whose health services is below what society believes it should be.[115]

Some countries chose to give their citizens the right to health. In these cases, governments tend to be directly responsible for the provision of medical services. In other cases, individuals are responsible for their own health. There is, thus, great variation in the organization of health care. In a certain sense, this is surprising because the relationship between physicians and patients forms the cornerstone of all health care systems. It is always expected that physicians do what is the best for their patients. In real situations, however, physicians frequently pursue their own personal objectives. The so-called principal-agent relationship between physicians (agent) and patient (principal) is thus not without

conflict. Other possible organizations of health are national health services and private insurances. National health services represent the intermediate solution between public and private health care. Individuals who want to have free choice of physician must pay the full cost. Private insurers are under competitive pressures to pass savings achieved to the insured. The form of health care delivery has much to do with the choice of principal-agent relationships that are designed to complement the basic physician-patient relationship.[96]

It has to be noted, however, that the market of health care is different from other markets. This is due to consumers' lack of information on their diagnosis and methods of treatments and their consequent need to rely on physicians. Furthermore, there is an uncertainty about illness, treatment outcomes and provider competence. These factors give rise to a greater demand for consumer protection. Another difference of health care markets is that society is more concerned with the redistribution issue and that everybody has access to health care.[115]

According to Grossman, individuals demand health care for two main reasons. Firstly, fewer sick days make individuals feel better. It is, thus, a consumption commodity. Secondly, the individual's health state determines the amount of available time for both market and non-market activities. Therefore, health care is an investment commodity. The demand of health care varies according to a set of patient and physician factors. The patient demands a treatment and this demand depends from the number, type or quality of treatments. The patient, thus, initiates this demand. Consequently, the physician combines different inputs to give the patient a satisfying treatment. The patient's demand is determined by the

incidence of disease, a set of cultural-demographic factors and, finally, economic factors. The degree of choice is dependent from two factors. These are knowledge and availability of substitutes. This is true for both patients and physicians.[115]

The last decade, the development of new nanotechnologies for imaging, diagnosis and treatment of cancer has skyrocketed. Furthermore, with the advent of suitable technological platforms, multidimensional measurement of biological processes has become feasible.[6,116] New technologies may decrease toxicity by avoiding unnecessary therapy in patients and in individuals in which therapy would not respond. A therapy's efficacy could be maximized by selecting for treatment those individuals who would experience the maximal benefit. Although a lot of technologies and markers have been developed successfully in the laboratory setting, only a handful has moved into clinical practice.[6,117]

There is an increasing demand for the evaluation of diagnostic tests. This evaluation does, however, differ from the evaluation of treatments. This is because new methods of diagnosis result in intermediate results without influencing health outcomes directly. The method to pursue the assessment of a new diagnostic test is the following: evaluation should start with an overview of the diagnostic test's capabilities in the laboratory setting. The second step is then to determine which the new method's place is in the clinical pathway. Subsequently, evidence on the diagnostic accuracy is synthesized according to its place in the clinical pathway. Furthermore, the test's impact on the patient is assessed. The final step is to carry out cost-effectiveness analysis and to assess societal consequences.[118]

Finally, the global market for innovative pharmaceuticals and medical devices has increased to one of the most significant sectors for government healthcare spending. Since more medicines and technologies are re-shaped by nano and gene technology – and priced accordingly - its influence on public policy is expected to increase exponentially. The European Medicines Agency Guidelines on Risk Management Systems for Medicinal Products for Human Use is responsible for medicines' and medical devices' safety and efficacy. It has to be noted that a distinction between medicines and medical devices has to be made. Medicines, in turn, can be subdivided depending on whether they are available to the general public or by physician prescription, have synthetic or biologic components, are patented or generic, or are complementary – outside the traditional medical evidence base – in nature. Medical devices, on the contrary, are defined differently by different agencies. It refers to any instrument or apparatus that is made to be used in the prevention, diagnosis, monitoring and treatment of disease. Moreover, it could be intended to affect the structure or function of the human anatomy.[119]

In 1959 Richard Feynman stated that: "There's plenty of room at the bottom" in which he stated: "I leave to your imagination the improvement of the design to take full advantage of the properties of things on a small scale". The recent developments, which are now already having an impact on modern medicine, confirmed his statement.[120]

The physical and chemical properties of a specific material can be largely improved as size is down-scaled to small clusters of atoms.[5,9,34,121] These are mechanical, thermal, electrical, magnetic, and light emission properties.[120] These new materials are changing the foundations of diagnosis, imaging, monitoring and

treatment. To be ideal as an injected nanotherapeutic, it has to travel through the vasculature, reach the target cells at full concentration without reaching healthy cells and, thus, causing minimal or no side-effects.[5] Unfortunately, this is not the case even not for the best current technologies. This is due to the biological barriers or the natural defences of the body.[5,8]

Nanotechnology finds applications in every branch of medicine. This is because they are able to deliver therapeutic agents in the optimum dosage range, frequently resulting in an increased therapeutic index.[34] The major areas in which nanotechnologies can be used are:

- Prevention and control: Health care systems are primarily based on reactive approaches which mean that diseases are cured once they occurred. The main problem with this kind of approaches is that it leaves some marks on the individuals concerned. Damages occurred and, although, individuals are cured, their bodies suffer traumas due to the diseases and treatment. Therefore, it is better to prevent than to cure. Furthermore, studies proved that prevention is more cost-effective than treatment. The use of vaccines to prevent problematic diseases is becoming an important area of investigation that is being positively impacted by the development of nanoparticles. Vaccines based on nanoparticles offer a platform to enhance the in vivo potency of the next generation vaccines.[51] The influence of vaccines on human health could be enormous. Like stated by vaccinologist Stanley Plotkin: "The impact of vaccination on the health of the world's peoples is hard to exaggerate. With the exception of safe water, no other modality, not even antibiotics, has had such a major effect on mortality reduction and

population growth".[122] The development of new vaccines dictates the need for additional delivery vehicles as well as new adjuvants. In most cases, the antigen itself is relatively weakly immunogenic. It follows that, adjuvants are needed to enhance the immune response. These adjuvants can also be added in the vaccines to guide the type of immune response generated. This is particularly true for cancer vaccines.[122] There are, however, different challenges that have to be solved. Firstly, the adjuvant or delivery vehicle has to stimulate humoral, cellular and mucosal immune responses. Secondly, less invasive approaches for the administration of vaccines have to be developed.[122]

- Early detection and proteomics: The difference between death and survival can come down to the very early detection of a life-threatening disease. Nanoparticulate-based technologies could possibly overcome the limitations found in current detection methods and, thus, advance the diagnosis and treatment of such a disease. The solution could lie in the development of 'smart' platforms for the simultaneous mass analysis of cancer-related markers. Early detection is important in cancer because it leads to the largest probability of success.[120,123,124] Biomolecular sensors with the ability to multiplex massively are being developed. Multiplexing means that the devices are able to detect a large number of different molecular species at the same time. This delivers enormous advantages over standard immunohistological methods.[22,124] These devices are developed for serum and tissue proteomics-based cancer diagnostics, prognostics and therapeutic efficacy monitoring.[9,39,121,123,] Promising technologies are bio-bar code

assays, cantilevers and nanowires. Bio-bar codes can amplify and detect nucleic acids and proteins. It uses two particles: a microparticle with a recognition agent and a nanoparticle also with a recognition agent, and that can sandwich the target with the microparticle. Its most significant impact is expected to be on protein marker—based diagnostics.[123,124,125] Cantilevers exist of a large number of beams that deflect when the molecules under consideration bind. Moreover, their working mechanism is based on biomolecular binding events that deflect the nanocantilevers. This results in a change in their resonating frequencies.[6,121,123,125,126] Likewise, nanowires yield highly multiplexed and real-time detectors of simultaneous molecular binding events. These devices report changes in their conductance that are generated by molecular binding events on their surface.[6,123,126] Also the proteomic analysis of human plasma for the early detection of malignant diseases is receiving more attention.[127] These methods could lead to the recognition and characterization of very early and even pre-symptomatic detection of diseases. Unfortunately, early detection is useless without effective treatment.[9]

- Imaging: Imaging allows the observation of the effects of disease and damage to the patient's body. Current techniques limit imaging possibilities to specific tissues. Nanotechnology could change this by the creation of new imaging contrast agents which can efficiently light-up the desired tissues. These agents comprise a targeting molecule, which binds specifically to the diseased regions and an imaging molecule, which can be detected by MRI or other imaging techniques. Recent developments have stimulated the emergence of molecular imaging.

This field focuses on the visualization or imaging of biological events and processes in the human body and other living organisms.[15] Nanoparticles can serve as a technology enabler that can leverage the increasing discovery of new disease markers into powerful imaging agents.[121] Targeted contrast agents improve the resolution of cancer to a single cell. For instance, quantum dots have important characteristics: excellent photostability, and photobleaching does not occur, i.e. the emission of fluorescent light over a long time without a rapid decline in emission. Individual quantum dots can be linked to specific diseases and can, thus, be detected simultaneously by spectroscopy. According to Iga et al. (2007) quantum dots could be used in sentinel lymph node mapping which is the mapping of the first tumor draining lymph node, as a diagnostic tool, as treatment option and as live cell labelling. Also non-invasive surgeries are possible with the use of multicolor in vivo imaging. Without the use of quantum dots this is not possible.[128] Their use is, however, limited by the toxicities of the heavy-metal core, long-term in vivo stability and metabolic elimination from the body.[1] It has to be noted, that the modifications of quantum dots may limit their toxicity in response to UV radiation.[116,128] It will, however, be extremely difficult to replace the toxic core of the quantum dots without losing the interesting properties. The engineering of quantum dots is still in its infancy.[128] Furthermore, supermagnetic nanoparticles have been developed as MRI contrast agents and bismuth-based nanoparticles used as contrast agents for CT scans.[15,116,124] Bismuth-particles have

[1] References: 1,7,15,22,116,120,121,125,128,129

also some toxic effects. Moreover, biologically targeted contrast agents are being developed for cancer imaging with MRI.[116]

- Multifunctional and targeted therapeutics: In the past decade, multifunctional therapeutic devices that can control the release of cancer agents and to optimally deliver medications have been developed. Liposomes were the first nanotechnology-based therapeutics to reach FDA-approval. They were able to show the way towards the revolutionary advances that medicine can expect in the following years and decades. Today, many new nanotechnologies have joined liposomes. They all have their characteristics, strengths and weaknesses. However, the utilization of nanoparticles for the delivery of therapeutic molecules in vivo has led to dramatic ameliorations in the efficacy of different therapies.[2] These are polymer-based platforms[3], dendrimers[4], gold nanoshells[5], semiconductor nano-crystals[5,143,144,145], carbon-60 fullerenes, biologically derived nano-constructs[5,36,146,147,148], silicon- and silica-based nanosystems[5,149,150], superparamagnetic nanoparticulates[5,36,116,151,152] and carbon nanotubes. Nanotubes have a very high surface area.[48,50] The studies pursued by Decuzzi found that the adhesive strength of a particle increases with the aspect ratio for any given value. Oblate particles can, thus, have larger volumes than spherical particles with the same probability of adhesion. Non-spherical particles can, thus, carry a larger number of therapeutic molecules or contrast agents. Consequently, the therapeutic efficacy or imaging resolution is increased. However, the aspect ratio can not be increased

[2] References: 34,35,39,51,116,121,126,130
[3] References: 5,24,35,36,39,51,125,131,132,133,134,135
[4] References: 1,5,34,35,36,39,51,52,125,135,136,137,138
[5] References: 1,5,34,36,116,139,140,141,142

infinitely. This is because particles have to circulate in the smallest capillaries without blocking or altering the blood flow. This knowledge could result in the optimal design of particles for the intravascular delivery of therapeutic and contrast agents.[42] Spherical nanoparticles have the worst possible size and shape from both hemorheological properties and endothelial delivery. The good news is, however, that nanoparticles possess the right properties to reduce death and suffering. The study conducted by Gratton et al. (2008) discusses a new technique that allows the production of monodisperse, shape-specific particles from an extensive array of organic precursors. This technique is called the PRINT technique (Particle Replication In Non—wetting Templates). It takes advantage of the unique features of elastomeric molds comprised of a low surface energy perfluoropolyether network.[130] The great successes of targeted therapies depend on the expression of the targeted molecules. These molecules can also be used as cancer-specific biomarkers. In an ideal scenario, the construction of multifunctional nanoparticles is based on an appropriate combination of therapeutic agents and targeting ligands. The choice of these agents is based on accurate biological information within the tumor environment with imaging agents attached on the particles' surface.[15]

- Pain management: Pain plays a significant role in cancer patients. These patients frequently experience breakthrough cancer pain. These are episodes of intense pain that occur with a large frequency. Recently, new solutions to this problem have been found. These are implantable drug delivery devices, transdermal and transmucosal patches.[153]

- Tissue engineering: Nanotechnology can be used to produce better artificial veins, arteries and heart valves. Furthermore, probably it will also be possible to develop a scaffold for growing patches of heart tissue to repair damage from heart attacks, and grow artificial muscle in the earliest stages.[1,7,120,154] These kinds of implants could lead to a decreased rate of implant rejections, better regulation of adhesive properties, improved adherence of cells and decreased biofouling of implanted devices. This area is, however, still in its infancy.[120]
- Therapeutic monitors: To observe some clinical response that indicates therapeutic effect, clinicians have to wait some weeks or even months. Furthermore, drug development initiatives suffer from the lag between the start of treatment and the first observations of efficacy. In vivo cell death or apoptosis can be monitored with the help of nanoparticles. This could lead to near-immediate proof that a therapeutic agent is having the desired effects. Moreover, it could also be used to provide early indications that a therapy is reaching its target. Nanoparticles could attain this goal by attaching both therapeutic agents and contrast agents to the nanoparticles' surface.[116,121]

The ideal nanoparticle would be the one that is capable of detecting neoplastic cells, pinpointing and visualizing their exact location and kill malignant cells without or with minimal adverse events. Furthermore, such a nanosystem should also be able to report back that its payload actually reached the target cells.[15]

There are different ways for nanoparticles to enter target cells. However, receptor-mediated endocytosis is the most effective mechanism for the uptake of nanoparticles. Endocytosis is used to define the process used by cells to give access to extracellular organisms. Endocytosis is being made possible by binding ligands to the particles' surface that bind to countermolecules or receptors expressed on the cells' membrane. Decorating the particle's surface with a too large number of ligands slows endocytosis. Design maps allow scientists to predict if the particle would adhere or not to targeted vasculature and if the particles would be internalized or not.[155] Increased repulsive interactions between particle and cell, however, make endocytosis more difficult and even impossible. Attractive, non-specific interactions, on the contrary, favor particle endocytosis. Other parameters that influence endocytosis are: the binding energy and bond elasticity factors, which have the largest influence, the density, length and type of surface polymeric linkers decorating the particle and its bulk dielectric properties.[155]

Nanotechnology can, thus, possibly overcome challenges associated with current treatments. Unfortunately, very little is known about nanotoxicology. This refers to the biokinetic assessment of engineered nanostructured particles and nanodevices.[156,157] The strength of nanoparticles lies in their small size but is also one of the main factors that might endanger human health.[1,7,48,124,138,157] The important routes of exposure are: skin, respiratory tract, and gastro-intestinal tract.[156,157] Therefore, further nanotoxicology studies are necessary to assure the population's safety.[48] These could be studies in vivo, imaging studies, functional studies, mechanisms of tissue uptake and tissue clearance. The objective of those studies is to better understand the biokinetics and toxicity profiles of

nanomaterials in animals. Moreover, legal and intellectual property issues, new regulatory requirements and how to implement them, scalability, the ability to cost-effectively produce nanoparticles on a large scale and societal impacts have to be assessed. Providing answers on these important questions will undoubtedly lead to a more rational design of optimized nanoparticlulate-based treatments that have an enhanced selectivity, efficacy and safety.[15] The government should play an important role in this task together with academia and commercial organizations.[7,156,158] This last aspect is crucial in promoting medical nanotechnology.[156]

Chapter 5: Economic evaluation and drug discovery: Cost-effectiveness analysis in the early stages of the drug development cycle

5.1. Introduction

The twentieth century has been characterized by extraordinary progress in the pharmaceutical industry.[159] Significant improvements in the treatment of diseases while maintaining quality of life have been attained.[159,160] The discovery and development process of new drugs is, however, lengthy, costly, and time-consuming.[160–163] The magnitude of drug development costs is heavily dependent on the proportion of drugs that fail in the clinical testing phase and are abandoned without obtaining market approval.[160,161,164]

The pharmaceutical industry faces issues of high attrition rates and long development periods. In turn, this causes high drug development costs. Success rates, are dependent on drug characteristics, company size and the firm's strategic behavior.[161,165,166] Attrition occurs during all stages of the drug development cycle. However, a vast majority of compounds fail in full clinical development. Even after human testing, approximately 25% of drug candidates fail, while the full cost of drug discovery and development is incurred.

The failure rate for new drug molecules is, thus, very high. While in the early stages of the development process this is mainly due to an inadequate therapeutic index, in late-stage clinical development, economic reasons take the lead. To reduce attrition and costs, it is crucial to develop a clear research and development (R&D) strategy. Firstly, to reduce attrition due to a lack of efficacy (30%) and safety (30%), time and resources could be saved by assessing safety and efficacy simultaneously. Probability of success should be assessed already in the discovery phase. In turn, this requires a methodological change in toxicology research.[167] According to Ulrich and Friend (2002), it has to be more amenable to the pace of the discovery team. Furthermore, it should be integrated into the discovery phase rather than following it. Kola and Landis (2004) argue that more predictive animal models and experimental medicine paradigms should be developed. Finally, they state that proof-of-concept clinical trials should be carried out in the early phases of the drug development cycle.[168] Secondly, late-stage attrition can be avoided by pursuing cost-effectiveness analysis (CEA) early in the development cycle. Since only cost-effective drugs will make their way to the market, CEA could be helpful in demonstrating that additional health effects are worth paying for. It allows the most efficient allocation of scarce resources and maximizes health effects at the lowest cost.

The chapter is structured as follows. The next paragraph discusses the R&D costs before launching a new medicine. Then, an algorithm is developed estimating the sales revenues required to recover costs and earning a reasonable profit to be successful. Furthermore, a method for early stage CEA is presented. The last paragraph summarizes the conclusions.

5.2. Drug development costs

Drug development requires large investments in human resources and technological expertise next to financial resources. The cost of drug development was estimated by DiMasi and colleagues (2003), following their previous study pursued in 1991 and an earlier analysis by Hansen in 1979.[6] Both the cost of successful and unsuccessful drug candidates were included. Furthermore, R&D expenditures were capitalized to the point of marketing approval or abandonment of research. In their last study, average out-of-pocket costs were estimated at an average of US$403 million per successfully launched product while total capitalized costs were expected to reach US$802 million in real terms of 2000. Half of total development cost was, thus, due to time costs. The latter have to be included because new drug approvals require R&D investments made many years before. Ignoring them would result in inaccurate estimates. Moreover, expenditures were capitalized at an appropriate discount rate, which is the expected return foregone by shareholders not investing in an equally risky portfolio of financial securities. The cost per approved new drug was then found by dividing the capitalized cost per successfully launched product by the overall success rate. It represents the full resource cost needed, on average, to discover and develop a new drug to the point of approval. Finally, DiMasi et al. (2003) pursued uncertainty analyses and

[6] DiMasi et al. (2003) based their study on 68 randomly selected new drugs that were obtained from a survey of ten multinational pharmaceutical companies. The survey included both foreign and US-owned companies. The sample was taken from a Tufts Center for the Study of Drug Development (CSDD) database of investigational compounds. The distribution of investigational drugs across therapeutic classes for the ten survey firms was found to be very close to the distribution for all drugs in the database. Also the probability that the average drug will get to each phase was calculated by using the CSDD database. By multiplying the estimated average amount spent in each phase by the probability of success, the expected cost of developing a successful drug was found. Finally, the authors used the CSDD database to estimate the average development periods for each step in the drug development cycle. The latter were then used to estimate time costs or the opportunity cost of developing a new drug. The authors used a real discount rate of 11%, which is an average company cost-of-capital.

concluded that in 95% of cases, total costs were estimated between US$684 and US$936 million while in 90% of cases they were estimated between US$705 and US$917 million. R&D costs are rising rapidly, which is due to the high and increasing cost of clinical trials.[160] Development costs have tripled over the last decade and are still rising.[160,161] DiMasi and colleagues stated that their results can be viewed as supportive, but not as conclusive.[160]

The estimates of DiMasi and colleagues (1991) have been used by the Congressional Budget Office (CBO) and the Office of Technology Assessment (OTA).[160] The latter organization argued that the results of this study provide a reasonably accurate picture of R&D development costs. The Boston Consulting Group also tried to estimate the development cost of a new successful drug, which was estimated at US$880 million.[169] Finally, Adams and Brantner replicated the study of DiMasi et al. (2003).[7] They estimated the development cost per approved new drug at US$868 million.[166]

The studies pursued by DiMasi and colleagues have, however, led to some controversy. Relman and Angell (2002) criticized this study for including capitalized costs in the estimate. This is, however, economically correct and accepted because opportunity costs need to be included.[159] Moreover, they argued that the study fails to consider the R&D expenses that are deductible from a

[7] Adams and Brantner (2006) estimated the drug development cost the same way as DiMasi et al. (2003) but they used data from the publicly available Pharmaprojects database. They note that these data may be less accurate then the CSDD database. Pharmacoprojects data are collected by vendors (PJB publications). The latter are based on press releases, academic presentations, and other public information about drugs in development. The authors are convinced that these data are not biased. The sample of new drugs used in the study pursued by Adams and Brantner (2006) includes information on 3.181 compounds. The data sample used by DiMasi and colleagues included only 538 compounds. Adams and Brantner (2006) also used a discount rate of 11%. Because the Pharmacoprojects database did not include information on when a phase was finished, the authors assumed that the end date was equal to the start date of the next phase.

manufacturer's tax base. They claimed that the development cost was overestimated.[170] Light and Warburton also questioned the usefulness of the study carried out by DiMasi et al. (2003). Firstly, they argued that the cost data were proprietary and confidential. Therefore, it is not known how each company collected the data and what was included as research costs. According to the authors, the internal validity of the study is undermined. Secondly, they were convinced that the sample of surveyed companies used by DiMasi et al. (2003) was too small and non-random. Finally, the authors argued that the drug development cost was presented without deducting government subsidies.[171] However, a subsidy is a cost for society. These arguments were repudiated by DiMasi and colleagues.[172]

When adding R&D costs after approval, total development cost rose to approximately US$900 million in real terms of 2000.[160] Unsuccessful projects have, thus, to be abandoned as soon as possible. Faster failure and shorter duration, ceteris paribus, could lower the development cost of drug research projects significantly.[160,161,167]

5.3. Estimating the sales revenues required to recover costs and earn a reasonable profit to be successful

Since the cost of failure rises with development duration, companies are forced to abandon unsuccessful drugs as soon as possible. Uneconomic drugs are usually abandoned in late-stage research. An important venue to avoid waste of scarce resources and maximize therapeutic value for patients is economic evaluation,

which should be pursued in the early phases of the drug development process. Cost-effectiveness analysis (CEA) is an economic tool that compares the costs and effects of different health care interventions. Because, eventually, only cost-effective drugs will make their way to the market, CEA is helpful in demonstrating that the cost per additional health effect is worth paying for. It allows an efficient allocation of scarce resources and maximizes health effects at the lowest cost.

The costs incurred by a pharmaceutical company are R&D costs before and after approval, production, and marketing costs. Moreover, companies have a return on investment that equals a percentage of total costs. Total cost augmented with a profit margin equals the acquisition cost of the medicine multiplied by the quantity sold, or sales revenues. Sales revenues required to recover costs and earn a reasonable profit to be successful can be found by solving the following equation.

$$\mathbf{PQ_t = RD_{at} + RD_{pt} + PC_t + MC_t + \Pi_t(RD_{at} + RD_{pt} + MC_t + PC)}$$

where PQ_t: sales revenues in year t

RD_{at}: ex ante R&D cost in year t

RD_{pt}: ex post R&D cost in year t

PC_t: production cost in year t

MC_t: marketing cost in year t

Π_t: return on investment in year t

5.3.1. Ex ante R&D development costs

DiMasi and colleagues (2003) estimated average total R&D development cost per successful medicine at US$802 million in real terms of 2000. Contrary to the critics, the methodology is well-described and, according to the OTA, results are reasonably accurate. Hansen (1979) estimated ex ante R&D spending at US$54 million in 1976.[173,174] They rose to US$231 million in 1987.[175] Because calculation was based on a similar methodology, the results of the studies can be easily compared.[160] During the period 1976-1987, the average yearly growth rate equalled 12,88%.[8] Costs rose at a rate of 9,30%, on average, per year during the period 1987-2000.[9] When considering the whole period 1976-2000, R&D costs, which conceal the potential differences between companies, increased from US$54 million to US$802 million. This translates into an average annual growth rate of 11,40%.[10] According to Munos (2009), since the 1950s inflation has been around 3,70% a year.[176] The average growth rate of R&D expenditures has to be corrected for inflation, and one can infer that average real ex ante R&D spending has been growing at 7,43% annually.[11] It equals a doubling of R&D costs every 9,67 years. Extrapolation results in an ex ante R&D cost of US$1.642 million in 2010.[12]

[8] (231-54)/54 = 3,278 → annual growth rate during period 1976-1987 = $\sqrt[12]{4,278}$ = 12,88%
[9] (802-231)/231 = 2,472 → annual growth rate during period 1987-2000 = $\sqrt[14]{3,472}$ = 9,30%
[10] (802-54)/54 = 13,852 → annual growth rate during period 1976-2000 = $\sqrt[25]{14,852}$ = 11,40%
[11] R&D expenditures rise also with an inflation rate which is found to be around 3,7% annually since the 1950s.[24] R&D growth rate has thus to be corrected for inflation → 1.1140/1.0370 = 1,07425 or 7,43% per year.
[12] $(1.0743)^{10}$ * US$802 million = US$1.642 million

The real ex ante R&D development cost per successful medicine in a specific year (2010+t) can be estimated by

$$\mathbf{RD_{at} = (1{,}0743)^{t} * US\$1.642\ million}$$

t = number of years since 2010

5.3.2. Ex post R&D development costs

A pharmaceutical company also incurs further R&D development costs after approval. Additional costs could be incurred for phase IV trials that might be required by the regulatory agency, to gain approval in foreign markets, or for additional label claims for new indications.[176] Expected future costs are based on an average real growth rate of 7,43% annually. DiMasi and colleagues (2003) estimated ex post R&D expenses at US$98 million in real terms of 2000. Extrapolation results in a cost of US$200 million in 2010.[13] Future real ex post R&D costs per successful medicine in a specific year (2010+t) can thus be estimated as follows

$$\mathbf{RD_{pt} = (1{,}0743)^{t} * US\$200\ million}$$

t = number of years since 2010

[13] $(1.0743)^{10}$ * US$98 million = US$200 million

5.3.3. Product manufacturing costs

Product manufacturing costs are part of a pharmaceutical company's total expenses. Barton and Emanuel (2005) found that manufacturing costs for the ten largest and multinational pharmaceutical firms equal 29,40% of sales revenues.[177] This can be reformulated as $0{,}294PQ_t$. Once manufacturing plants are operational, the variable cost of manufacturing drugs is very low. Hence, bringing the first unit of a medicine to market is associated with extremely high costs, while the incremental manufacturing cost of producing one additional unit is small.[178]

$$\mathbf{PC_t = 0.294 * PQ_t}$$

t = number of years since 2010

5.3.4. Marketing costs

The largest costs incurred when commercializing a new successful medicine are marketing costs.[179] These costs comprise communication, direct-to-consumer advertising as well as the costs of packaging and distribution. Gagnon and Lexchin (2008) stated that almost twice the amount of ex ante R&D costs is spent on marketing activities. In 2004, total expenditures for all promotional activities were estimated at US$57,5 billion, whereas only US$31,5 billion were spent on R&D. The authors are convinced that their estimate is robust and relevant because it is not based on extrapolations from companies' annual reports but on proprietary databases.[179] Gagnon and Lexchin (2008) argued that the pharmaceutical industry

has evolved from an innovative and research-driven business to a marketing-driven one.[179] There is, however, little information about trends in spending of pharmaceutical companies on promotional activities in recent years.[180] According to Donohue et al. (2007), real spending on marketing in the pharmaceutical industry grew at an average annual rate of 10,60%.

R&D costs per successfully launched medicine equal US$1.642 million in 2010. The relationship between marketing and R&D costs, in 2004, is expressed as 57,5/31,5. Since marketing and R&D costs grow at different rates, the ratio above has to be multiplied with a correction factor: 1,1906[14]. The marketing cost per successfully launched drug in 2010, thus, equals US$3.568 million[15]

The real marketing cost per successful medicine in a specific year (2010+t) can thus be estimated as follows

$$\mathbf{MC_t = (57,5/31,5) * (1,0295)^t * US\$3.568\ million}$$

t = years since 2010

[14] $(1.1060/1,0743)^t = (1,0295)^6$
[15] US$1.642 million * (57,5/31,5) * 1,1906

5.3.5. Return on investment

Despite the high risks that pharmaceutical companies face, they also enjoy higher profits than any other industry. In 1999, drug companies had a profit margin of 18,60% of sales revenues.[181] In 2002, the top ten US pharmaceutical companies had a median profit margin of 17% compared with 3,10% in other businesses.[182] Bloor and Maynard (1997) argued that in the UK, profit margins vary between 17–21%, making it one of the most profitable sectors.[183] Therefore, a median profit margin of 19% of sales revenues is assumed, which stimulates an efficient and competitive development and supply of therapeutics worldwide.

$$\Pi_t = 0{,}19[1.642(1{,}0743)^t + 200(1{,}0743)^t + 3.568(1{,}1060)^t + 0{,}294.PQ_t]$$

t = years since 2010

5.3.6. An algorithm estimating the sales revenues required to recover costs and earn a reasonable profit

The sales revenues required to recover costs and earn a reasonable profit to be successful can be found by solving the following equation.

$$PQ_t = 1.642(1,0743)^t + 200(1,0743)^t + 3.568(1,106)^t + 0,294.PQ + 0,19[1.642(1,0743)^t + 200(1,0743)^t + 3.568(1,1060)^t + 0,294.PQ]$$

$$PQ_t = 2.525,61(1,0743)^t + 307,63(1,0743)^t + 5.488,05(1,106)^t + 0,292[1.642(1,0743)^t + 200(1,0743)^t + 3.568(1,1060)^t]$$

t = years since 2010

For 2010: $0,706PQ_1 = 1.642(1,0743)^0 + 200(1,0743)^0 + 3.568(1,106)^0 + 0,19[1.642(1,0743)^0 + 200(1,0743)^0 + 3.568(1,106)^0 + 0,294.PQ]$

$$PQ_0 = US\$9.902 \text{ million}$$

Cost-effectiveness outcomes in se do not allow health administrators to draw conclusions. Therefore, they are compared with a reference value, i.e. a threshold value above which the new drug is considered not cost-effective. Although the threshold value of the cost per quality-adjusted life year (cost/QALY) is a much discussed topic, a universal threshold value has not been established. In the United States, US$50.000/QALY is frequently cited as an acceptable cost/QALY. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) does not have a 'hard' decision rule. New technologies with an incremental cost-effectiveness ratio (ICER) between £20.000-£30.000/QALY (US$31.600-US$47.400 per QALY – 1,00GBP = 1,58USD) are usually accepted. This range of acceptable cost-effectiveness ratios seems to be independent of type of disease.[13,92]

While health economists should give a rough estimate of sales revenues required to be successful, clinical researchers should provide an estimate of how many QALYs the new drug could save during its entire lifecycle. For 2010, costs were estimated at US$9.902 million. Assuming a median threshold value of US$40.000/QALY, at least 247.550 quality-adjusted life years should be saved to break-even. If the new therapeutic does not save a sufficient number of quality-adjusted life years to break even, it should not be developed further.

5.4. Conclusions

Since the cost of failure rises with duration, cost-effectiveness analysis should be pursued early in the drug development cycle. To that end, a formula to estimate sales revenues required to recover costs and earn a reasonable profit to be successful has been developed. A median threshold value of US$40.000/QALY is considered as cost-effective. Consequently, it is possible to establish how many quality-adjusted life years the therapeutic has to save during its entire lifecycle. At this point, clinical researchers have to demonstrate that it is possible to save that number of QALYs. If not, the drug is not cost-effective, and further development should be abandoned.

Pursuing cost-effectiveness analysis in an early stage could, however, be particularly important for nanotherapeutics as well as target-based agents. Since these therapies will probably be very effective but also have very high acquisition costs, it will be crucial to demonstrate their cost-effectiveness. If not, these new

therapeutics could be considered as not cost-effective due to their high acquisition cost. Consequently, cures to treat life-threatening diseases could be lost.

Chapter 6: Improving health care decision-making through a comprehensive cost-effectiveness taxonomy

6.1. Introduction

In developed countries, cancer accounts for a major burden of mortality and morbidity.[13] In spite of the existence of several effective cancer prevention and screening interventions, the number of new cancer cases will increase from an estimated 10 million cases in 2000 to an estimated of 15 million in 2020.[184] On the one hand, cancer-associated morbidity and mortality cause enormous economic burdens on patients, their families, and on society.[13] Moreover, a high number of individuals are affected by the disease. Consequently, total costs of cancer are significant. On the other hand, national resources are scarce. Therefore, they have to be allocated in efficient ways. In turn, this requires a clear understanding of the cost-effectiveness of new treatments. Cost-effectiveness analysis (CEA) compares the costs and effects of two or more health care interventions. It provides the opportunity to compare alternative therapies, considering both their costs and effects. It allows policy-makers to efficiently allocate scarce resources and maximize health effects at the lowest cost. Hence, it could demonstrate that the cost per additional health effect is worth paying for. Cost-effectiveness studies, thus, address questions whether health care interventions represent value for money. The additional cost for a more effective treatment has to be reasonable

and justifiable in relation to its effects.[89] CEAs represent the costs and effects of a treatment in a single conceptual framework. Therefore, they are extremely useful in guiding policy decisions. In recent years, economic evaluation became more important in the decision to include new treatments into clinical practice.

New nanomedicines – and associated high costs – raised questions about their availability for unrestricted use. Therefore, the area of nanotherapeutics is particularly suitable for economic evaluation.[13] Results of cost-effectiveness studies can, however, be challenging to compare, which is due to: (1) parameter assumptions may vary among study perspectives; (2) uncertainty in effectiveness and cost outcomes that possibly varies among settings; and (3) studies may be pursued using a different perspective. A common problem encountered in CEA is the use of inappropriate patient populations. Furthermore, the omission of relevant comparators, the exclusion of important costs and effects, and the use of inappropriate health economic outcomes severely limits the interpretation of results.[185] Therefore, cost-effectiveness studies should be carried out using a specific methodology, which makes results more comparable.

Since it is difficult to place a monetary value on health effects, cost-effectiveness analysis is the preferred method in the health care sector. Economic evaluation starts with a thorough assessment of effects. Then, a rigorous cost analysis is carried out. Because health care interventions impact patients and society, costs should be calculated from a social perspective. Not only private costs are considered but also the broader social costs.

The objective of this chapter is to describe a cost-effectiveness taxonomy that will play a major role in the economic assessment of tomorrow's nanotechnology-based cancer therapies. The chapter is structured as follows. The next paragraph discusses the methodology used to develop the cost-effectiveness taxonomy. Then, a detailed overview of the cost model is presented. Finally, the last paragraph offers the conclusions.

6.2. Methodology

6.2.1. Current cost-effectiveness studies: Drawbacks

Several studies comparing conventional and nanotechnology-based therapies have been pursued. When investigating the existing literature, it is possible to conclude that there is a significant degree of methodological heterogeneity. Moreover, different conceptual deficiencies are found in these studies. Cancer remains a significant cause of morbidity and mortality, which results in high indirect costs for patients and society. In spite of their significance, they are virtually ignored in current studies, leading to an underestimation of costs of conventional therapies. Current studies assess costs from a hospital perspective. Consequently, only direct medical costs are taken into consideration.[16]

Another important shortcoming of current cost-effectiveness studies is that the results are almost never quality-adjusted. Very few authors calculate the cost per quality-adjusted life year (QALY). Since cancer affects length but also, and even

[16] References: 12,40,41,65,66,67,68,69,80,81,82,83,84,85,86,87,88,89

more so, quality of life, it is crucial to adjust the effectiveness outcomes with quality of life estimates. Moreover, some cancers are not curable. Therefore, the sole objective of treatment is to provide safe and effective palliation, i.e. to reduce the symptoms and attain a better quality of remaining life. Consequently, cost-effectiveness should be estimated as the cost per QALY.[17]

Finally, some authors assume an equivalent effectiveness between treatments by considering only survival data - progression-free survival and overall survival. When looking at toxicity profiles, however, treatments are completely different. Different toxicity profiles urge for the adjustment of results with quality of life estimates. It is, thus, not sufficient to base equivalence in effectiveness solely on survival data.[18]

Current costs-effectiveness studies are, thus, incomplete. This might lead to wrong policy conclusions at the expense of patients and society. Moreover, cost definitions differ widely among studies, making any comparison among studies virtually impossible. Therefore, it is crucial to develop a cost-effectiveness taxonomy that includes all relevant direct and indirect costs and considers patients' quality of life. As more CEAs are pursued, it will become a lot easier to compare different treatment regimens in terms of their cost-effectiveness. To that end, it is crucial to have high-quality studies.[13] Only then, cost-effectiveness analysis is helpful in making efficient choices in health care.

[17] References: 12,40,41,65,66,67,68,69,80,81,82,83,86,87,88,89
[18] References: 12,40,41,66,67,68,69,80,83,86,87,88,89

6.2.2. Generic effectiveness model

Clinical trials are carried out to allow safety and efficacy data to be collected for specific health care interventions. They take place after satisfactory information has been gathered on the quality of the non-clinical safety. Before conducting effectiveness studies, it is crucial to attain approval by the ethical committee of the country in which the trial takes place. Clinical studies assess the effectiveness of a specific treatment in a well-defined patient population by using a sensitive clinical outcome indicator.[13] The effects of treatment are usually assessed by randomized controlled trials, which are the most rigorous way to establish cause-and-effect relationships between therapy and outcome. As these trials adjust for known and unknown variables, they ensure that preconceived views can not bias the assessment of outcomes.[186,187]

The use of specific effectiveness parameters depends on what is being measured. Outcomes could be disease-specific, which have the disadvantage that results can not be compared to analyses with other outcomes. This problem can be solved when the denominator is expressed as a standard measure.[93,188] Effectiveness outcomes are presented in table 6.1. They could consider only length of life, such as life years gained (YLG,) but also a combination of mortality and morbidity could be used. Healthy life years gained (HYLG), disability-adjusted life years (DALY), and quality-adjusted life years (QALY) are common practice for this purpose. While HYLG is the simplest outcome measure that takes account of both length of life and morbidity, QALY is more complex by considering patients' valuations of quality of life. The latter is the most suitable since it enables inter-technology comparisons across studies.[105]

Before assessing the effects, it is important to distinguish between different types of effects. Firstly, it is possible to distinguish between direct and indirect effects. Direct effects are directly attributable to a specific health care intervention. Indirect effects, on the contrary, are not. In most cases, indirect effects are not considered in economic evaluation because they are coming into play in the future. Consequently, due to discounting effects, their impact diminishes. Moreover, they are difficult to observe.

Secondly, intended and non-intended effects can be distinguished. Intended effects are effects that were meant to occur because of the treatment. Unintended effects are effects that exist because of the intervention but that were not meant to be caused. These effects can be both direct and indirect.

Costs and effects can, however, not be used interchangeably. Effects exist because of a health care project, while costs have to be made to execute a specific project. When pursuing cost-effectiveness analysis, it is crucial to explain which effects are considered and which are not. Sometimes, specific effects are not considered because calculation would be to complex. However, all the observed effects have to be described, even if they are not considered further in the analysis.

Clinical studies require a group of patients treated with conventional treatment or the control group, which is compared with another patient group that receives a new treatment or the treatment group. Both groups have to be equivalent from the beginning, the only difference between both groups being the treatment they receive. In case of non-equivalence, this is referred to as selection bias.

Differences in effectiveness, wrongly attributed to the treatment, may arise. This kind of bias can be avoided by using randomized experiments.[14] Randomization is a procedure in which the assignment of a subject to a specific therapy is decided by chance. Therefore, it is not possible to influence the outcomes and, consequently, bias will be avoided.

Despite randomization remains the only method of treatment assignment that assures strong evidence about the comparability of therapies, it does not guarantee their equivalence. Bias can arise when differences between patient groups do not only exist because of differences in treatment or therapeutic strategy, but in other significant and maybe unrecognized ways. On the one hand, a possible source of bias may exist because of the investigator's desire to show the superiority of the new treatment whereby he unintentionally ignores some adverse events occurring to the treatment group. On the other hand, bias may also arise because of the patient. If the patient is aware of the treatment he receives, he can possibly anticipate some positive or negative effects. Bias could, thus, result in an underestimation or overestimation of a specific health effect. These sources of bias can be avoided by blinding the investigator or patient (blinded study) or both (double blinded study). Blinded randomized controlled studies are, thus, preferred when carrying out cost-effectiveness analyses.[189]

<u>* Years of life gained (YLG)</u>

Years of Life Gained (YLG) considers only mortality. Although cancer patients experience cancer-related morbidity; this outcome measure ignores it completely.

It is calculated by comparing the difference between age of premature death and normal life expectancy. The numbers of years of life gained by a specific treatment are then summed. The method's main advantage is its ease of calculation. Moreover, overall survival is an unambiguous measure of clinical benefit, which is directly relevant to economic evaluation. Years of Life Gained has also some important drawbacks. Firstly, each additional year of life gained is treated equally. Secondly, the true survival benefit of a specific treatment compared to another one relates to the area between two survival curves, or the mean survival benefit.[190] Finally, for treatments with a high morbidity, the use of YLG as an outcome measure may mislead the results.

* Healthy Years of Life Gained (HYLG)

Healthy Years of Life Gained (HYLG) is the simplest of alternatives presenting a combination of morbidity and mortality. HYLG sums the years of life saved that results from using a specific treatment, and the years of life that will no longer be affected by morbidity, with weights applied to the latter to make them comparable with healthy years saved. In a next step, disability weights have to be estimated. Consequently, a year of morbidity saved is converted into the equivalent of a year gained. Important to note is, however, that disability weights have to be constant over the life of the health care intervention. To attain these constant weights, researchers base their results on a self-perceived question which aims to measure the extent of any limitations because of a health problem that may have affected respondents as regards activities they usually do. The drawback of this outcome measure is that the varying degrees of the disability's severity are not considered.

* Disability-Adjusted Life Years (DALY)

In comparison with HYLG, Disability-Adjusted Life Years (DALY) adds another level of complexity. It is a unit for measuring the health lost because of a specific disease, and is estimated by calculating the future life years free of disability that are lost because of a premature death or disability occurring in a specific year.[187] There is, however, a drawback. In view of society's preference, when basing the findings on productivity of those affected, than saving the lives of individuals of working age are creating a higher social gain than saving the lives of older and very young patients. A year lived with a disability is calculated as one minus the weight related with that particular disability, which measures the remaining degree of health.

* Quality-Adjusted Life Years (QALY)

A full assessment of the outcomes of cancer therapy involves a consideration of its impact not only on length of life but also on its quality. Quality of life is a multidimensional concept that includes physical, social, and psychological functioning. It is estimated as the number of years of live gained adjusted with the quality of these years. By using QALYs, it is possible to weight the life years gained in different states of health using the valuation by persons affected, in a way that they can be compared with each other. It is, thus, possible to derive the value of changes of health states from the value of a statistical life.[190] This is particularly true in the case of palliative care or when administering toxic therapeutic agents while yielding a modest survival benefit. Since QALYs

incorporate length and quality of life, this effectiveness outcome measure is particularly suitable when dealing with decisions involving tradeoffs between length and quality of life, which frequently arise in cancer care. Quality of life is measured in such a way that the product of length and quality of life has a meaningful relationship between both aspects. For instance, the patient is indifferent between 1 year at quality x and 4 months at quality 3x. These measures, which are called utilities, are defined as the quantitative measure of the strength and an individual's preference for a particular health status. They are measured on a scale of 0 to 1, where 0 represents death while 1 represents perfect health.[187] Finally, QALYs are calculated by multiplying length of life with quality of life estimates.[13]

QALYs capture the gains from both prolongation and improved quality of life in one single effectiveness outcome. Moreover, the value of preferences that individuals place on different health outcomes is incorporated in this effectiveness measure. In spite of the advantages related to the use of QALYs, they have also some shortcomings. Firstly, the use of QALYs assumes a constant proportional tradeoff between length of life and health condition. This means that individuals are prepared to give up some constant proportion of their remaining years of life in order to attain a specific improvement in health condition, without considering the number of years that remain.[93] Secondly, QALYs depend on the time when the questionnaires are given. This could influence the results. When time profiles of toxic events as a consequence of treatment or recovery durations following therapy are very different, quality of life may be hard to interpret. Thirdly, there is concern whether QALY estimates really represent society's preferences for rationing. Furthermore, due to the different methods of estimating individuals'

preferences, the comparability between studies is probably compromised. Moreover, according to Tappenden et al. (2006), censoring the quality of life data may not be random. The authors call this informative censoring. Therefore, completion rates are not independent of the quality of life of patients, and the results of the extremely ill patients may not be presented within the results of analysis. These non-random outcomes can possibly bias the Health-Related Quality of Life (HRQoL) results.[185] Finally, preferences between patients and non-patients differ.[93]

Table 6.1: Effectiveness outcomes: Advantages and disadvantages

Outcome measure	Advantages	Disadvantages
Life Years Gained (LYG) → The number of life years gained by using a specific treatment are summed → Morbidity is completely neglected	• Easy to calculate • Is an unambiguous outcome measure • Directly relevant to economic evaluation	• Only length of life is considered • Each additional year is treated as equal • True survival benefit relates to the area between two survival curves • For diseases with high morbidity it might lead to misleading results
Healthy Life Years Gained (HYLG) → Sums the years of life saved that results from using a specific treatment and the years of life that will no longer be affected by morbidity with weights applied to the latter to make them comparable with healthy years saved	• Simplest alternative considering both length of life and morbidity	• Does not consider the varying degrees of severity of the disability

Disability-Adjusted Life Years (DALY) → Calculates the future life years free of disability that are lost because of a premature death or disability occurring in a specific year → Is calculated as 1 minus the weight related with a particular disability, which measures the remaining degree of health	• Adds another level of complexity	• Creates a higher social gain for individuals working, thus discriminating the very young and older individuals
Quality-Adjusted Life Years (QALY) → Considers mortality and quality of life → Estimated as the number of years gained adjusted with the quality of these years → They are measured on a scale of 0 to 1, where 0 represents death and 1 perfect health	• A multidimensional concept • Particularly suitable when dealing with decisions involving tradeoffs between length of life and quality of life	• Constant proportional tradeoffs • Results depend on the time when the questionnaires are given • There is concern whether QALY estimates really represent the society's preferences for rationing • Due to the different methods of estimating individual's preferences, the comparability between studies is probably compromised • Censoring quality of life data might not be random • Preferences between patients and non-

→ Are calculated by multiplying length of life with quality of life estimates		patients differ

Since in cancer, patients' length of life but also, and even more so, quality of life is affected, QALY is the preferred outcome measure.[92] Future research should, however, focus on finding novel and valid measurement methods for QALYs.[93]

Finally, effects occurring in the future are less valuable than those occurring now. The problem is that they do not all occur at the same point in time. These differences in timing are most obvious, however, in the comparison of preventive treatments with their main alternative. The most widely accepted and used method to incorporate the time preference notion into economic evaluation is the process of discounting future effects to their present values. This methodology multiplies the value of effects occurring in the future year by a weighting factor. To that end, they can be compared as if they all occurred at the same point in time.[95] Discounting future costs and effects is important to reflect inherent uncertainty about the future and preferences for timing of consumption. The formula to discount future effects is

Present value: $E/(1+r)^{t-1}$

Where E: effect occurring in the future

r: discount rate

t: number of years in the future the effect will occur

Not discounting future costs and effects may mislead the results. The percentage of discount rate is, however, debatable. This is made more difficult because discounting the effects of a health care intervention might possibly underestimate interventions for which benefits appear long after the costs have been paid.[14,190,192] The impact of the discount rate is presented in table 6.2.

Table 6.2: Impact of discount rate

Years until effect	**Discount rate**			
	0%	2%	5%	10%
1	1	1	1	1
2	1	1.02	1.05	1.1
5	1	1.082	1.216	1.464
10	1	1.195	1.551	2.358

If costs and effects are occurring far in the future, than the magnitude of discount rate has not a large impact on the outcome.

6.2.3 Cost taxonomy

Developing a framework for cost calculation starts with the identification of all possible relevant costs in function of a given perspective, preferably that of society.[13] It should be questioned how these costs could be collected. In a next step, their magnitude, which differs substantially from charges, should be

assessed. Finally, the cost per unit and volumina should be multiplied.[13] Cost analyses pursued from a social perspective comprise the costs related to treatment itself, but also resource uses associated with the therapies' downstream events. Identifying, measuring, and valuing resources is, however, not easy.[187] A new drug may cause fewer or less severe adverse events, require less monitoring efforts, or may not require hospitalizations for intravenous administration. Consequently, savings may offset the higher acquisition cost.[92] Cost estimates included in the model should, therefore, relate upon the number of cycles and mean dose of drug. Furthermore, it should consider patients who are withdrawn from treatment. Moreover, administration costs, resources used to manage side-effects, and indirect costs should be considered.[185] Finally, to estimate the total real cost of therapy, costs related to resource use beyond the scope of the trial should be included.[185]

The framework includes all relevant costs, both direct and indirect, of treatment, the management of adverse events, and recurrent disease. Relevant direct costs are drug, administration, expected administration, monitoring costs, and the expected costs of cancer after care. These costs are directly attributable to a specific treatment. Lost production for patients and relatives, transportation costs, expected costs for caregivers, visiting costs for relatives and friends, the interests forgone on funeral expenses due to a premature death, and administration costs of health insurance can, on the contrary, not be directly attributed to a specific therapy. Moreover, intangible indirect costs, which are the emotional costs for pain, suffering and a reduced quality of life, have to be considered. These are the non-financial costs related to treatment.

Costs associated with treatment and the management of adverse events are calculated by using the same methodology. A problem that could arise is that two or more adverse events occur in the same cycle. This creates a risk of double counting and overestimation of total costs. Therefore, in instances were this scenario occurs, the most severe side-effect is selected. The rationale behind this methodology is that a patient cured for a severe adverse event is automatically cured for a less severe one. While this methodology causes a slight underestimation of costs, it is, however, limited. Moreover, each grade of each adverse event requires a different treatment plan. Therefore, costs are estimated for each side-effect separately. Finally, cost per patient is attained by summing the cost of each adverse event that was experienced by that patient.

The magnitude of economic burden is heavily dependent on the patient's final health status. Consequently, costs should be calculated separately for patients' that died, remained disabled, and recovered fully. When costs are based on an expected percentage of individuals involved, they are called expected costs.

The cost taxonomy discussed further in this chapter, has been developed in line with a social perspective. Some direct hospital costs are estimated using daily costs. In doing this, caution is needed. There is a risk of double counting. This can, however, be avoided by using the methods explained in the next section. Moreover, costs vary by hospital and condition. Therefore, cost components included in the administration and monitoring costs have to be defined for each case study separately.

Other important costs are the expected costs related to disease recurrence. They are based on an expected percentage of patients relapsing. Because different therapies could lead to a difference in relapses, which is particularly true for future nanotherapeutics, the costs of disease recurrence have to be included.

The numerator of the cost-effectiveness ratio represents total costs incurred when using a specific treatment regimen. Cost calculation is, however, based on marginal costs or costs that are different between health care interventions. This chapter discusses all the possible costs that could be relevant in cost analysis. Costs that differ between treatment regimens – and are, thus, relevant to consider – depend from case to case. Moreover, careful assessment of costs related to adverse events is required. When side-effects and cancer treatment occur simultaneously, there is a risk of double counting. For instance, lost production has to be included only once.

Finally, like effects, costs occurring in the future have to be discounted to their present values. The following formula is, therefore, used:

Present value: $C/(1+r)^{t-1}$

With: C = cost occurring in the future

r = the discount rate

t = number of years in the future the cost is occurring

In spite of the importance of cost-effectiveness analysis when allocating scarce resources, additional criteria such as affordability, distributional impacts and equity considerations, capacity to deliver treatments, and public preferences can often be more influential.[187]

6.2.4 Cost-effectiveness taxonomy

Once the costs and effects of the alternative treatments are known, their cost-effectiveness can be calculated. CEA uses a ratio where the denominator represents the health effects of a specific health care intervention, while the numerator expresses the cost of obtaining these benefits. The denominator may be expressed in different ways. However, since cancer affects patients' length but also, and even more so, quality of life, the number of quality-adjusted life years is the preferred outcome measure. Moreover, it enables inter-technology comparisons among studies.

The resulting cost-effectiveness ratio (CER) is interpreted as the cost to obtain a single unit of effectiveness.[14] The smaller the cost-effectiveness ratio, the smaller the cost for a given effect. The therapy with the smallest cost-effectiveness ratio is, thus, the most cost-effective one and has to be chosen to save resources.

A problem related to CEA is the dynamic nature of predetermined circumstances.[95] They can seldom be regarded as the right conditions in all possible situations. Therefore, analysis is repeated under different conditions.[91] This is done by

pursuing uncertainty analysis, which investigates the extent to which outcomes are sensitive to changing parameters.[40,92,187]

Firstly, costs and effects are estimated for a base case scenario. To account for the uncertainty involved, cost-effectiveness is recalculated under different scenarios. This is done by carrying out the next steps: (1) identify the parameters that reflect the greatest degree of uncertainty; and (2) identify a range over which the parameters under consideration may vary. The baseline values lay in the middle of these ranges.[14] Secondly, cost-effectiveness is recalculated for the other values. If a therapy remains the most cost-effective one over the whole range of values, the model can be considered as robust. However, it is highly likely that more parameters change simultaneously. Therefore, it is interesting to pursue multi-way sensitivity analysis instead of one-way sensitivity analysis, whereby one parameter is changing, ceteris paribus, every time analysis is carried out. Other methods as for example Monte Carlo sampling, can also be used to assess the uncertainty involved.[92]

However, economic data differ among countries and their stability changes over time. Therefore, conclusions based on the information of one country can not be used in another country. International differences in health care delivery should always be considered.[12,80,106] Moreover, not only drug and hospital costs change over time, the introduction of new technologies may also cause changes in practice with shifts towards or away from in-patient care and resultant change in cost. Therefore, the cost of different approaches where analysis is carried out in different periods can not be compared. It follows that, economic analysis is only

useful if pursued rigorously, and if enough attention is given to possible problems and pitfalls which may invalidate the conclusions.[11]

The use of cost-effectiveness ratios as an economic evaluation method implicitly assumes that the scale of the alternatives is the same. If not, the results could be misleading. In the case of cancer treatment, as in the major part of cases, the scale of different options is the same and this problem can, thus, be ignored.[14]

Finally, it is important to note that a cost-effectiveness analysis of a new health care intervention is based on the results of a previously pursued effectiveness study. Effectiveness studies demonstrate if new treatments obtain improvements in health state. Consequently, cost-effectiveness studies can only be as good as the underlying clinical study.[94]

6.3. A detailed overview of the comprehensive cost taxonomy

This section gives a complete overview of the costs that could be relevant in cancer care. Two types of costs can be distinguished, direct and indirect costs. While direct costs are directly attributable to a specific treatment, indirect costs are not. These costs are described for cancer treatment and the management of adverse events. Furthermore, calculation methods are presented. Tables 6.3 and 6.4 give an overview of the appropriate formulas. Since costs differ significantly between patient groups, they are subdivided in fatal, disabled, and fully recovered.

6.3.1. Direct costs

The incidence of malignant diseases has become a major healthcare issue. In addition to being associated with serious economic and emotional problems for patients and their family, cancer therapy imposes significant economic consequences on nations' healthcare systems. Direct costs of cancer and cancer care include: drug, administration, expected administration, and monitoring costs. Moreover, it includes the expected costs for after care. Direct healthcare costs represent the value of resources used to diagnose and treat diseases and the resulting adverse events.

a) Drug costs

Cancer drugs account for a significant share of total health care expenditure for cancer. New therapies are often expensive and thus leading contributors to the increase in overall health care spending. High acquisition costs are, thus, a major concern for policy-makers and health administrators allocating limited public funds. The use of new therapeutics might be justified, however, by their superior effectiveness.

There are two possibilities to allocate drug costs. While, on the one hand, they could include only the cost of therapeutic agents, on the other hand, they may also comprise the cost related to their administration. The latter includes personnel costs and costs of materials, devices, and equipment such as needles. Finally, it includes the use of a common room where all cancer patients receive

cancer therapy. If these administration costs are included in drug costs, they have to be subtracted from total administration costs. If not, double counting and overestimation of costs could occur. It is interesting to consider drug costs separately from other direct medical costs because they can differ significantly between conventional and nanotechnology-based therapeutics. In turn, it will be easier to attribute cost differences between therapies.

The calculation of drug costs depend on three important parameters: (1) the acquisition cost; (2) the dosage required every time treatment is given; and (3) the number of times per cycle that therapy is administered. In general, conventional therapy needs more infusions than nanoparticulate-based treatments. The exact numerical values depend, however, on the treatment under consideration. Drug costs are calculated by multiplying the previously mentioned parameters. Costs are calculated per patient.

Drug cost for cancer drugs per cycle per patient = acquisition cost per dose * number of doses * frequency

Total cost for cancer drugs per patient = Cost per cycle * number of cycles

OR

Total cost for cancer drugs per patient = Exact cumulative dose * acquisition cost per dose

Treatment cost per cycle multiplied by the number of cycles is, however, only an approximation of total treatment costs. Drug costs are based on a constant drug dose per administration. Unfortunately, drug dosages are not always the same. They may differ between cycles. By using the exact cumulative drug dose, on the contrary, the exact cost of treatment can be calculated. Therefore, if the exact cumulative drug dose is available, it has to be used to calculate total treatment cost.

Furthermore, according to international guidelines and to limit allergic reactions related to the administration of cancer agents, standard steroidal, anti-inflammatory pre-treatment is given. Pre-treatment drug costs are calculated analogously to the cost of cancer drugs:

Cost for pre-treatment per cycle per patient = acquisition cost per dosage * dosage * frequency

Total cost for pre-treatment per patient = Cost per cycle * number of cycles

Like stated previously, it could be interesting to include the administration costs related to therapy in the drug costs. This is, however, only possible if hospitals use a rule of thumb to allocate part of total administration costs solely to the administration of cancer drugs. When such a rule of thumb does not exist than, it is not possible to include this part of administration costs in total drug costs.

Finally, adverse events are frequently experienced by cancer patients. These side-effects are treated with different drugs, depending on the type and severity. Therefore, drug costs have to be calculated for each side-effect and each cure separately. Cost per patient is attained by summing the drug costs of all adverse events experienced in a specific cycle.

Cost for drugs to treat adverse events per patient per cycle = $\sum^{\{1\ldots x\}}_{cure}\sum^{\{1\ldots y\}}_{adverse\ event}$ [acquisition cost per dosage * number of dosages * frequency]

Drug costs have to be calculated for the treatment period but, if necessary, also in the period thereafter.

b) Administration costs

Administration expenses are the costs incurred for drug administration and therapy. They comprise the costs of in- and outpatient visits for both cancer treatment and the management of therapy-related adverse events. Hospital costs account for a large share of total spending for cancer care. The quality and cost of health care can vary by hospital and condition. Consequently, to avoid double counting and overestimation of costs, the cost components included in the daily hospital cost have to be defined every time analysis is carried out.

Administration costs comprise the costs related to hospital stay and outpatient visits. Cancer therapy and the treatment of adverse events often require hospitalization. Sometimes, day hospitalization suffices. To calculate total administration costs, the daily cost is multiplied by the number of in- or outpatient visits.

Administration costs for the management of adverse events are estimated in the same way, though costs have to be calculated for each adverse event and each cure separately. The hospital cost per patient related to the management of adverse events is attained by summing the hospital costs associated with all adverse events experienced during the chemotherapy period.

Cost of hospital stay per cycle for cancer therapy per patient = [(cost per hospital day – drug costs) * number of hospital days]

Total costs for hospital stay for cancer therapy per patient = (cost per cycle * number of cycles)

Cost of hospital stay per cycle for the treatment of a specific adverse event per patient = $\sum^{\{1...x\}}_{\text{cure}} \sum^{\{1...y\}}_{\text{adverse event}}$ [(cost per hospital day – drug-related costs) * number of hospital days]

Cost of outpatient visits per cycle for the treatment of a specific adverse event per patient = $\sum^{\{1...x\}}_{\text{cure}} \sum^{\{1...y\}}_{\text{adverse event}}$ [(cost per outpatient day – drug-related costs) * number of outpatient days]

Cost for an outpatient visit per cycle for cancer therapy per patient = [(cost per outpatient day – drug costs) * number of outpatient days]

Total cost for outpatient visits for cancer therapy= (cost per cycle * number of cycles)

Both, hospitalization costs and the costs for outpatient visits consist of a cost for using the facilities during day care. This is the cost for using a common room by all cancer patients simultaneously during therapy. Furthermore, they comprise personnel costs; costs for materials, devices, and equipment; and drug costs (with the exception of cancer drugs). Finally, they also include the cost for renting a room (including a cleaning fee) and a cost for food and beverages. The latter includes also a fee for preparing adapted alimentation. The differences between the costs of in- and outpatient visits are mostly sustained by the cost of drugs and invasive procedures.

Since drug costs are part of administration costs but already considered in a separate cost category, they have to be subtracted from total administration costs. If not, double counting and overestimation of total costs will occur. If administration costs related to drug infusion are already included in drug costs, they are also subtracted.

c) Expected drug administration costs

Some medications may be administered only by a nurse or practitioner. Home medication allows a person the freedom to spend less time in the hospital. Nurses manage nursing care for residents with cancer. They perform difficult procedures such as administering intravenous fluids. Nurses are qualified and selected to ensure the highest standards of quality care provision for private nursing. The costs of these caregivers have, thus, to be considered and are based on the average hourly wage of private nurses. However, some injections may also be performed by relatives. In this case, private nurses are not needed. Therefore, nursing costs are expected costs.

Expected drug administration costs for cancer treatment per patient:

(Average hourly wage of a nurse * time needed for drug administration) * expected number of patients needing private nurses

Expected drug administration costs for a specific adverse event:

$\sum^{\{1...x\}}_{\text{adverse events}}$ [(average hourly wage of a nurse * time needed for administration) * expected number of patients needing private nurses for specific adverse event]

d) Monitoring costs

Monitoring costs are the costs related to the diagnosis and detection of disease, but also to follow-up disease progression. Tests to detect cancer depend on the disease that is being suspected. It can be physical exams, imaging (MRI, CT, X-rays, ultrasonography, and radionuclide scanning), and biopsy (needle and surgical biopsy). Moreover, blood, urine, pathology, and other tests related to specific cancers can be used. The costs related to different types of tests in different phases of cancer care are included in the category of monitoring costs. These tests are diagnostic tests, follow-up tests and, finally, additional medical and home visits.

Monitoring costs are calculated as the cost of a specific test multiplied by the number of tests. Since costs differ among tests, monitoring costs have to be calculated for each test separately. Monitoring costs comprise of personnel costs; and costs for materials, devices, and equipment. The cost per patient is attained by summing all the monitoring costs incurred by that patient. This is the case for cancer treatment as well as for adverse events.

Cost of diagnostic tests for cancer per patient = $\sum^{\{1...x\}}{}_{test}$ (cost per specific diagnostic test * number of diagnostic tests)

Cost of follow-up tests for cancer per patient = $\sum^{\{1...x\}}{}_{test}$ (cost per specific follow-up test * number of follow-up tests)

Cost of diagnostic tests for a specific adverse event per patient = $\sum^{\{1...x\}}_{test}\sum^{\{1...y\}}_{adverse\ event}$ (cost for a specific diagnostic test * number of diagnostic tests)

Cost of follow-up tests for a specific adverse event per patient = $\sum^{\{1...x\}}_{test}\sum^{\{1...y\}}_{adverse\ event}$ (cost for a specific follow-up test * number of follow-up tests)

Sometimes additional home or medical visits are required. Costs are estimated by multiplying the average cost of a visit by the average number of visits needed. The average cost per visit includes the physician's fee and cost for materials, devices, and equipment. The average cost for a home visit includes an additional transportation cost. Since it is extremely difficult to know the exact number of additional medical and home visits, costs are based on an expected number of patients needing additional visits. Therefore, these costs are expected costs. In the management of adverse events, additional visits are estimated for each adverse event separately. Again, cost per patient is attained by summing all visits that were required.

Expected cost for medical visits for cancer = [(average cost for a medical visit * average number of visits needed) * expected number of patients needing additional medical visits]

Expected cost for home visits for cancer = [(average cost of a home visit * average number of home visits) * expected number of patients needing additional home visits]

Expected cost for medical visits for a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse event}}$[(average cost for a medical visit * average number of visits) * expected percentage of patients needing additional medical visits

Expected cost for home visits for a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse event}}$[(average cost for a home visit * average number of visits) * expected percentage of patients needing additional home visits]

e) Expected costs for cancer after care

Costs associated with cancer after care, which is often needed, can be enormous economic burdens on patients, their families and on society. Costs associated with after care are incurred after the patient left the hospital but still needs some additional assistance. These are the costs related to rehabilitation, palliative care, additional therapies, wigs, and also for psychological assistance.

Firstly, cancer rehabilitation helps a person with cancer obtain the best physical, social, psychological, and work-related functioning during and after cancer treatment. The objective of rehabilitation is to help patients regain control over many aspects of their lives and remain as independent and productive as possible. Rehabilitation can be valuable to anyone with cancer and those recovering from

cancer therapy. Many cancer centers and hospitals offer a variety of cancer rehabilitation services to their patients, or are willing to help them identify local resources to assist with rehabilitation. Patients and family members are encouraged to be active, informed partners in the rehabilitation process and seek out the services they need.

Therefore, physical therapists may be needed. This kind of therapist helps patients to restore mobility and physical functioning while preventing further disability. This service may be particularly important for individuals who have lost muscle tone because of prolonged bed rest, or cachexia (an adverse event of cancer treatment characterized with muscle wastage).

Rehabilitation costs are based on the average cost of a rehabilitation session. It comprises the cost associated with the use of materials, devices, and equipment. Furthermore, it includes the therapist's fee. Since it is difficult to know exactly how many individuals need some kind of after care, calculations are based on an expected percentage of patients needing some additional care. Therefore, costs for cancer after care are expected costs, both for cancer treatment and the management of adverse events. The duration of rehabilitation depends on the patient's disability grade.

Expected total cost for rehabilitation for cancer = $\sum^{\{1...x\}}_{\text{type of rehabilitation}}$ [(average cost for a rehabilitation session * average number of rehabilitation sessions that are needed) * expected percentage of patients that need rehabilitation after disease]

Expected total cost for rehabilitation for a specific adverse event = $\sum^{\{1...x\}}_{\text{type of rehabilitation}} \sum^{\{1...y\}}_{\text{adverse event}}$ [(average cost for a rehabilitation session * average number of sessions) * expected percentage of patients needing rehabilitation after having experienced a specific adverse event]

Secondly, physical activity can reduce the risk of certain cancers, improve quality of life, and is helpful for reducing stress in individuals living with cancer. Physical activity can also influence cancer recurrence and survival. Just 30 minutes of moderate activity a day, five days a week, can have a positive impact on people's health. This is the same for patients treated with different treatments. Since these costs do not differ between therapies, they are not considered in economic evaluation.

Thirdly, it is common for cancer patients to experience stress, depression and anxiety during and after cancer treatment. Many patients find it helpful to talk about their feelings with family and friends, other patients but also to health professionals, and counsellors or therapists. Being part of a support group can provide another outlet for patients to share their fears and feelings. Relaxation exercises, like guided imagery (a technique in which the person focuses on positive images in the patient's mind) and slow rhythmic breathing, can also help

to ease negative thoughts and feelings. Reaching out to others by participating in volunteer activities can patients help feel stronger and in more control. However, patients who continue to experience emotional distress (extreme mental or physical pain or suffering) should ask their doctor to refer them to someone who can help determine what may be causing or contributing to their distress and how to deal with it.

Not only during therapy but also once treatment has finished patients could encounter some emotional problems. Patients may expect life to return to the way it was before being diagnosed with cancer. It can take some time to recover. Patients could have permanent scars on their body and even mild but permanent impairments. Consequently, cancer survivors may not be able to do daily things as before disease. Even emotional scars could arise. Patients could have the idea that people see them differently or may even view themselves in a different way. For these patients, psychological assistance could give some release. Furthermore, couples counselling, genetic counselling, fertility/sexual counselling, nutrition counselling, and occupational or vocational therapy could be helpful. Costs depend on the type of assistance that is needed.

Psychologists and psychiatrists work to address the emotional, psychological, and behavioral needs of cancer patients and their families. These may be longstanding or have resulted from the illness and consequences of treatments. Mental health professionals can help patients process their experience and find ways of coping with changes in their lives. Costs related to psychological assistance are calculated analogously to the previously described rehabilitation costs.

Expected cost for psychological assistance for cancer = $\sum^{\{1...x\}}_{\text{type of assistance}}$ [(average cost of a psychological session * average number of sessions) * expected percentage of patients needing psychological assistance]

Expected cost for psychological assistance for a specific adverse event = $\sum^{\{1...x\}}_{\text{type of assistance}} \sum^{\{1...y\}}_{\text{adverse event}}$ [(average cost of a psychological session * average number of sessions) * expected percentage of patients needing psychological assistance]

The session's average cost comprises of the psychologist's or psychiatrist's fee. Cancer patients are frequently infested by an enormous mental strain due to cancer and the effects of therapy, which are sometimes even more severe than those of the disease itself. Researchers in the U.S. estimate that at least one third of all cancer patients suffer from fear and depression and need psychotherapy.[194]

Fourthly, some patients will also need additional therapies. Cancer treatment can cause severe impairments. Cancer treatment can lead to, for instance, nephrotoxicity and cardiac toxicities which, in turn, could lead to renal, respectively heart failure. These impairments need some additional care. The costs associated with these additional therapies have to be considered in cost analysis. The cost for a therapy includes the personnel costs, costs for used materials, devices, and equipment and, if necessary, drug costs. Furthermore, since treatment depends on the impairment concerned, costs are calculated for each type of additional therapy separately.

Expected costs for additional therapies for cancer = $\sum^{\{1...x\}}_{\text{type of therapy}}$ [(cost per treatment * average number of treatments needed) * expected percentage of patients needing a specific additional treatment]

Expected cost for additional therapies for a specific adverse event = $\sum^{\{1...x\}}_{\text{type of therapy}}\sum^{\{1...y\}}_{\text{adverse event}}$ [(cost per treatment * average number of treatments needed) * expected percentage of patients needing a specific additional treatment]

A potential side-effect of cancer treatment is hair loss or alopecia. It follows that, costs related to wigs are only incurred in case of this adverse event. This cost includes the average cost of a wig. Hair loss may occur throughout the body, including the head, face, arms, legs, underarms, and pubic area. The hair may fall out entirely, gradually, or in sections. In some cases, the hair will simply become thin, sometimes even unnoticeably, and may become duller and dryer. Losing hair can be a psychologically and emotionally challenging experience, and can affect an individual's self-image and quality of life. However, the hair loss is usually temporary, and the hair will grow back. Hair loss occurs because the hair follicles responsible for hair growth are damaged by cancer therapy.

Hair loss due to cancer therapy is not preventable or treatable with stimulants, solutions, or special shampoos. Therefore, it is crucial learning to deal with hair loss before it occurs. It can help an individual to better adjust to this change in physical appearance. Moreover, talking about feelings with a counsellor, someone with a similar experience, family member, or friend may also provide comfort.

Furthermore, the use of a wig can help patients cope with the psychological distress associated with hair loss.

Expected cost associated with the use of wigs in case of alopecia = average cost of a wig * expected percentage of those patients needing a wig

Finally, some patients need palliation. Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychological and spiritual.

Palliation does not mean useless, his exact definition comes from the Latin word pallium and means protection. Palliative care, which appeared about 30 years ago in England, is the global care and multidisciplinary approach to patients' suffering from a disease that no longer responds to specific treatments and whose death is a direct result. In palliative pain control, other symptoms and psychological problems, social and spiritual, are of paramount importance. The World Health Organisation (WHO) defines palliative care as 'the active total care of the patient's body, mind and spirit, which also involves giving support to the family'. The purpose of palliation is to improve patients' quality of remaining life and of their families. Palliative care patients are turning to the terminal stage of any chronic illness, and palliative care is designed to give the patient the highest possible quality of life, respecting his wishes, helping him to better enjoy the terminal phase of illness, and accompany him to a dignified death. The terminal is a

condition no longer reversible with treatments, within a few weeks or months; it evolves into the death of the patient and is characterized by a progressive loss of autonomy, the emergence of physical symptoms such as pain and psychological interventions involving the family and social relationships.

Patients could receive palliative care in their homes. Home assistance of terminally ill patients is, however, an overwhelming challenge for health and social resources. Despite palliative home care is becoming more attractive, the hospital remains a major contributor to health care costs for terminally ill cancer patients.[195]

Palliative care is typically provided by a team that includes palliative care doctors, nurses and social workers. In this case, patients remain in the hospital to receive the best possible care. The average daily cost for palliative care includes personnel costs; costs for used materials, devices, and equipment; cost for renting a room including a cleaning fee and a fee for food and beverages, and finally, painkilling drugs.

Expected cost for palliative care for cancer = $\sum^{\{home,\ hospital\}}_{type\ palliation}$ [(average daily cost for palliative care * average number of days spend in the palliative care facility) * expected percentage of patients needing palliative care due to cancer]

Expected cost for palliative care for a specific adverse event = $\sum^{\{home,\ hospital\}}_{type\ palliation} \sum^{\{1\ldots x\}}_{adverse\ event}$ [(average daily cost for palliative care * average number of days spend in the palliative care facility) * expected percentage of patients needing palliative care due to a specific adverse event]

6.3.2. Indirect costs

Indirect costs are not directly accountable to a specific treatment regimen. They come from the loss of resources – the time and productivity lost or foregone by the patient, family, friends, and others from employment, volunteer activities, leisure and housekeeping. Psychosocial or intangible indirect costs come from the reduced quality of life from disability, suffering and pain which force undesirable changes in lifestyle such as economic dependence, social isolation, changes or loss of job opportunities or changed conditions of living. Because indirect costs inevitably influence al programs, they should never be ignored. In spite of their importance, tangible and intangible indirect costs are completely neglected in current cost-effectiveness studies. Tangible indirect costs are: lost production of patients and relatives, expected costs associated to caregivers during disease, transportation costs for patients, visiting costs for relatives and friends, and administration costs for social insurance. Moreover, the interests forgone on funeral expenses due to a premature death can also be indirectly attributed to a specific treatment. Intangible indirect costs or non-financial costs, on the contrary, are the emotional costs for pain, suffering and the loss of quality of life. This section discusses the indirect costs of cancer and cancer care that should be included in economic evaluation. Also the methods to estimate those costs are explained.

a) Lost production

The most important of tangible indirect costs is lost production. On the one hand, it includes the loss of economic output due to days off work, or morbidity costs. On the other hand, it also includes mortality costs, which are the costs associated with a premature death. Furthermore, next to lost production, cancer also incurs hidden costs. These are costs for health insurance, and non-medical expenses such as transportation, child or elder care and housekeeping assistance. These costs are discussed next in this chapter.

The magnitude of economic output losses depend on: (1) the average age of patients; (2) the magnitude of lost income; and (3) the degree of disability. This cost taxonomy considers the lost production due to a premature death, to disability, and to disease. The expected lost production of patients' relatives is considered as well. The cost of lost production is based on the wage cost of a fully employed employee.

Lost production = average wage cost * average number of hours/days/years the individual can not contribute to production

In case of a premature death and permanent disability, lost production has to be discounted for future years. Furthermore, it is important to emphasize that lost production differs significantly among patients that died, remained disabled, and were fully recovered. Therefore, lost production has to be estimated for each of these patient groups separately.

** Lost production due to a premature death*

Cancer patients that died prematurely as a consequence of disease or a specific adverse event incur significant mortality costs. The value of mortality costs is the value of lifetime earnings lost by individuals that died prematurely. This value has to be discounted to the present value. Parameters that have to be considered when estimating the lost production of patients that died prematurely are:

- Patients' average age: this depends on the disease under consideration.
- Average age to which individuals have to work: this age can differ from the official retirement age and also among males and females. Furthermore, these ages can possibly differ between countries.
- The average value of production that an individual realizes per year: this value varies from year to year. To correct for this varying value, it is necessary to consider the evolution in Gross Domestic Product (GDP) per capita. Total production lost has to be discounted to attain its present value.

Economic output losses due to a premature death as a consequence of cancer

= [(retirement age – age at death) * yearly value of production * adjustment for evolution in GDP/capita] * non-survival rate due to cancer / $(1+r)^{t-1}$

Economic output losses due to a premature death as a consequence of a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse event}}$ [(retirement age – age at death) * yearly value of production * adjustment for evolution in GDP/capita] * non-survival rate due to a specific adverse event / $(1+r)^{t-1}$

Lost production has to be estimated for each adverse event separately. Lost income of relatives is not considered in analysis. Although relatives could have sacrificed some income to assist the patients during disease before their premature death, calculation would be too complex and is, thus, not considered.

** Lost production due to disability*

Cancer and therapy-related adverse events can cause some disabilities which can be reversible or even permanent. Consequently, patients may stop working. Lost production is calculated analogously as described for patients that died prematurely. The only difference is that for both treatment and adverse events, economic output losses due to disability are based on an expected percentage of patients remaining disabled and stop working. Lost production is again estimated for each adverse event separately. Moreover, relatives may give up work to assist their disabled relative. Costs are based on an expected percentage of relatives giving up their job.

Expected economic output losses due to disability as a consequence of cancer = {[(retirement age – age at disability) * yearly value of production * adjustment for evolution GDP/capita] * expected percentage of patients remaining disabled as a consequence of cancer} / $(1+r)^{t-1}$

Expected output losses due to disability as a consequence of a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse event}}$ {[(retirement age – age at disability) * yearly value of production * adjustment for evolution GDP/capita] * expected percentage of patients remaining disabled} / $(1+r)^{t-1}$

Expected economic output losses of relatives due to disability as a consequence of cancer = {[(retirement age – age when the relative stops working) * yearly value of production * adjustment for evolution GDP/capita] * expected percentage of relatives giving up work due to a disabled relative as a consequence of cancer} / $(1+r)^{t-1}$

Expected output losses of relatives due to disability as a consequence of a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse event}}$ {[(retirement age – age when relative stops working) * yearly value of production * adjustment for evolution GDP/capita] * expected percentage of relatives giving up work due disabled patients due to a specific adverse event} / $(1+r)^{t-1}$

While, on the one hand, patients may stop working due to a permanent disability, on the other hand, patients may change work intensity, intentionally or unintentionally. For instance, the cancer survivor may intentionally choose to work

only part-time. However, patients may also become less productive due to disease. Costs related to a decreased productivity are incurred by society. It is, however, very difficult to estimate people's diminished productivity. Therefore, it is not considered in economic evaluation.

Occupational or vocational therapy could be interesting for cancer survivors. Before returning to their jobs, some cancer patients may require vocational therapy. It is often used in combination with a structured rehabilitation program and is designed to enable the disabled individual to resume productive employment. Individuals who have experienced changes in their mental or physical function due to illness may require such vocational therapy to allow them to return to work. Vocational therapy works with patients and their new physical or mental status to find an appropriate occupational match. It involves an assessment phase where the patient's skills and attitudes are evaluated through tests, which is an integral part of therapy. These tests may take several forms and are used to assess an individual's general intelligence level, his or her attitudes, interests, and work skills. Following completion of the assessment phase, a list of goals is developed and the requirements of specific jobs are assessed. Finally, a determination is made as to whether the individual has the attitude and skills necessary for a particular job of interest or whether additional training is required. If additional training is required, the vocational therapist helps determine the types of training necessary. Costs related to this type of therapy are included in the expected costs of cancer after care.

** Lost production during disease*

Individuals under treatment are not expected to work during the whole treatment period. This assumption holds for both the treatment period for cancer and adverse events. The average number of days patients do not contribute to production have to be considered. Caution is, however, needed. If adverse events are experienced during cancer treatment, lost production is incurred only once. Moreover, some relatives choose to assist patients. Consequently, they do not contribute to production. This lost production has to be considered as well to attain accurate cost analysis. Again, it is based on an expected percentage of relatives that are placed on a leave for the whole treatment period to assist patients.

Economic output losses due to treatment of cancer = average number of days lost * daily value of production

Economic output losses due to the treatment of a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse event}}$ (average number of days lost * daily value of production)

Expected output losses due to cancer treatment for relatives = average number of days lost * daily value of production * expected percentage of relatives assisting the patient

Expected output losses due to treatment of adverse events for relatives = $\sum^{\{1...x\}}_{\text{adverse event}}$ (average number of days lost * daily value of production * expected percentage of relatives assisting the patient)

** Lost production during follow-up*

Once treatment is finished, patients need follow-up visits to monitor disease progression. Although they start working again; they still loose time to see their oncologist. Calculation of lost production is based on the lost time caused by these visits, which is calculated by summing the average waiting time, average time spent with the oncologist, and average time on the road.

Lost production due to follow-up cancer = lost time * average hourly value of production

Lost production due to follow-up for a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse event}}$ (lost time * average hourly value of production)

Concerning lost production it is important to mention the following implications. Firstly, lost production depends on the average age of individuals. This means that older individuals do not incur costs for lost production. This is discriminatory because the elderly, who already tend to have lower earnings and higher consumptions of medical care, receive lower priority in the delivery of health care. Generally, older individuals have higher levels of morbidity and mortality. Cost-effectiveness analysis, which puts strong emphasis on the potential of a treatment option to add years of life with a higher quality, may tend to direct resources in the opposite direction of these older individuals.[107] Despite the discrimination of older individuals, this approach is usually used to assess the indirect costs of lost production and will, thus, also be used in this cost taxonomy. Secondly,

unemployment is not considered. In cost-effectiveness analysis, it is important to know what the potential lost production is or, stated otherwise, what the value of an employee for the economy is. This approach values individuals working at home in the same way as individuals working on the labor market. Finally, and like stated previously, the average value of production is not constant in time. Therefore, the evolution in real GDP per capita has to be estimated and will be used to adjust the value of production.

b) Transportation costs

Patients incur transportation costs when going to the hospital or oncology center. The cost of driving does not only include the cost of gas but also car maintenance. This includes tune-ups, oil and tires, as well as costs for insurance, registration, and parking. Transportation costs can be divided in two categories: (1) operating costs; and (2) ownership costs. Operating costs are variable costs and may change depending on where patients live, how they drive, how much they drive and what is spent on service and repairs. Ownership costs, on the contrary, are fixed costs such as insurance, license fees, registration fees, taxes, finance, and depreciation. Fixed costs may differ among vehicles and place, but they change little with the amount and type of driving. Transportation costs are based on an all-inclusive cost per kilometer.

Transportation costs are estimated for patients only. Patients incur transportation costs when going to the hospital for: 1) during disease for drug administration; 2) during follow-up visits; 3) for the management of adverse events; and 4) for cancer after care.

Costs for car usage for cancer = average cost per km * average number of km's

Costs for car usage for the management of a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse events}}$ [average cost per km * average number of km's]

c) Expected costs of caregivers

Home care consists of a range of professional health care and supportive services delivered in the home to a person with cancer who requires assistance with daily activities. Home care can make an enormous difference at times of stress, such as the period following surgery or during recovery from a lengthy hospitalization, or those in need of longer-term care. Care provided in the home allows a person the freedom to spend less time in the hospital. Home care can be appropriate for patients with cancer who are actively receiving treatment or rehabilitation services, or those who need help with daily activities such as bathing, cooking or cleaning. A cancer caregiver is a person who provides care for someone with cancer. Full-time caregivers could be family members, such as spouse or child or may be a trained home health aid that provides regular or respite care.

For some cancer patients some help in the household, and maybe also in taking care of children may be needed. A home health aide is a person that provides personal care services by helping patients with activities of daily living, such as bathing, using the toilet, and moving around. Patient attendants are persons that provide personal care services and perform light household tasks, such as cooking, laundry, and basic cleaning. Finally, independent providers are home care personnel who are privately employed by the client. The client is responsible for hiring, supervising, and paying caregivers. Independent workers can be recommended by a social worker or hospital discharge planner, or they can be found through advertisements. Paid caregivers are, thus, all persons coming from outside the family nucleus to help the cancer patients. Caregivers'-associated costs have to be included in cost analyses. Costs related to relatives assisting the patients are already included in the economic output losses. Finally, it is important to note that it is extremely difficult to know how many patients will rely upon caregivers. It follows that costs are expected costs. This is true for both cancer treatment and the management of adverse events.

Expected costs related to health aides due to cancer = (average hourly wage * average number of hours a health aide is needed) * expected percentage of cancer patients needing a health aide

Expected costs related to health aides due to a specific adverse event = $\sum^{\{1\ldots x\}}_{\text{adverse events}}$ [(average hourly wage * average number of hours a health aide is needed) * expected percentage of patients needing a health aide]

Expected costs related to personnel due to cancer = $\sum^{\{\text{patient attendants, independent providers}\}}_{\text{kind of personal}}$ [(average hourly wage * average number of hours personnel is needed) * expected percentage of cancer patients needing personnel]

Expected costs related to personnel due to a specific adverse event = $\sum^{\{1\ldots x\}}_{\text{adverse events}} \sum^{\{\text{patient attendants, independent providers}\}}_{\text{kind of personal}}$ [(average hourly wage * average number of hours personnel is needed) * expected percentage of patients needing personnel]

The assumption that is used in this calculation is that patients only need help during the treatment period.

d) Visiting costs

Patients' relatives and friends incur costs when visiting the patients. These are traveling costs and costs for presents. They are related to the hospitalization period only. These costs are dependent from: (1) average number of hospitalization days; (2) the number of times a day the patient is visited; and (3) the amount per visit. Visiting costs are calculated for each adverse event separately.

Visiting costs due to cancer therapy per patient = number of hospitalization days * average number of times the patient is visited per day * amount per visit

Visiting costs due to a specific adverse event per patient = $\sum^{\{1\ldots x\}}_{\text{adverse event}}$ (number of hospitalization days * average number of times the patient is visited per day * amount per visit)

e) Forgone interests on funeral expenses

Patients that died as a consequence of disease incur an additional cost due to a premature death. This is the cost associated with the funeral expenses and has to be interpreted as the forgone interest on the amount of funeral expense for the number of years the patient lives less than normal life expectancy. This cost is, thus, based on the difference between normal life expectancy and age of premature death. It is important to note that there exists a difference in life expectations between males and females.

To estimate these costs three parameters have to be known: (1) the average age of patients; (2) total number of years lost (mortality tables); and (3) average funeral expense. This last parameter depends on the number of interments and cremations. Furthermore, the forgone interest on funeral expenses depends on the interest rate. Finally, forgone interests have to be discounted for their present values.

Since each adverse event has another mortality rate, the forgone interest on funeral expenses has to be calculated for each adverse event separately.

Forgone interests on funeral expenses due to cancer for n years of premature death per patient = [(funeral expense * interest rate)^{1} / (1 + discount rate)^{0}] + … + [(funeral expense * interest rate)^{n} / (1 + discount rate)$^{n-1}$]

Forgone interests on funeral expenses due to a specific adverse event per patient = $\sum^{\{1\ldots x\}}_{\text{adverse events}}$ [[(funeral expense * interest rate)^{1} / (1 + discount rate)^{0}] + … + [(funeral expense * interest rate)^{n} / (1 + discount rate)$^{n-1}$]]

f) Administrative costs for social insurance

Universal health care systems vary according to the extent of government involvement in providing care and/or health insurance. In some countries, such as the U.K., Spain, Italy and the Nordic countries, the government has a high degree of involvement in the commissioning or delivery of health care services, and access is based on residence rights not on the purchase of insurance. Others have a much more pluralistic delivery system based on obligatory health with contributory insurance rates related to salaries or income, and usually funded by employers and beneficiaries jointly. Sometimes the health funds are derived from a mixture of insurance premiums and government taxes. These insurance based systems tend to have a higher proportion of private medical providers obtaining reimbursement, often at heavily regulated rates, through mutual or publicly owned medical insurers. A few countries such as the Netherlands and Switzerland

operate via privately owned but heavily regulated private insurers. The compulsory system of central and Eastern Europe typically fail to provide truly universal coverage, leaving up to 3% of their population without coverage. They often operate as two-tier systems and also fail to guarantee fee reimbursement.

Universal health care in most countries has been achieved by a mixed model of funding. General taxation revenue is the primary source of funding, but in many countries it is supplemented by specific levies, which may be charged to the individual and/or an employer, or with the option of private payments for services beyond that covered by the public system.

In treatment, each patient uses its own personal insurance. Costs are estimated by looking at total administrative costs of insurance companies. This amount is then divided by the number of patients needing treatment for cancer, and is defined as a cost for social insurance per patient. Finally, administration costs of social insurance have to be estimated for each adverse event separately. The reimbursements of direct costs should not be included in order to avoid double counting.

Administration costs for cancer treatment = (% of patients with private insurance + % of patients with public insurance)/number of patients

Administration costs for the management of a specific adverse event = $\sum^{\{1...x\}}_{\text{adverse events}}$ [(% of patients with private insurance + % of patients with public insurance)/number of patients experiencing a specific adverse event]

g) Non-financial costs

Cancer patients incur costs that can not easily be quantified in monetary terms. These intangible costs are extremely difficult to measure but crucial to consider. Since patients incur serious emotional costs, they can not be ignored in cost calculation. These costs represent the burden of pain, suffering, and loss in quality of life. Pain is among the most common and feared symptoms of cancer. According to the Cancer Information Network, between 30% and 50% of cancer patients experience pain and approximately 70% experience severe pain at some point during the course of their disease Since these intangible costs affect health and well-being, they are conceptualized in the quality of life estimates of cancer patients. In turn, these estimates are used to calculate the quality-adjusted survival that reflects both morbidity and mortality. Non-financial costs can easily extent to patients' relatives who could experience a decreased quality of life due to lower standards of living as a result of emotional distress and depression.

The direct and indirect costs that were discussed in this chapter have to be estimated for the treatment itself, for recurrent disease, and for the management of adverse events. The costs related to recurrent disease are defined as expected costs. This is because cost calculation is based on an expected percentage of patients relapsing and experiencing adverse events.

Table 6.3: Cost taxonomy of cancer treatment

	Fatal	Disabled	Fully recovered
Direct costs related to cancer treatment			
Drug costs			
Drugs	Acquisition cost per dosage * number of dosages every time drug is given * frequency OR (if available) Exact cumulative drug dose * acquisition cost per dose		
Pre-treatment	Acquisition cost per dosage * number of dosages every time drug is given * frequency		

Total drug costs	Cost of cancer drug + cost of pre-treatment		
Administration costs			
Hospitalization (inpatient visits)	(cost per hospital day – drug-related costs) * number of hospital days		
Outpatient visits	(cost per outpatient day – drug-related costs) * number of outpatient days		
Total administration costs	Cost for hospitalization + cost for outpatient visits		
Monitoring costs			
Tests for diagnosis	$\Sigma^{\{1...x\}}_{test}$(cost for a specific test * number of different tests)		
Tests for follow-up	$\Sigma^{\{1...x\}}_{test}$(cost for a specific test * number of different tests)		

Expected costs for additional medical visits	(Average cost for a medical visit * average number of visits) *expected percentage of patients needing additional medical visits		
Expected costs for additional home visits	(Average cost for a home visit * average number of visits) * expected percentage of patients needing additional home visits		
Total monitoring costs	Cost for diagnostic tests + cost for follow-up tests + expected cost for medical visits + expected cost for home visits		
Expected administration costs	(average hourly wage for a private nurse * time needed for drug administration) * expected number of patients needing a private nurse		
Expected costs for after care			

Expected costs for rehabilitation	/	(average cost for a rehabilitation session * average number of sessions) * expected percentage of patients needing rehabilitation after disease	/
Expected costs for psychological assistance	$\Sigma^{\{1...x\}}_{\text{type of assistance}}$ [(average cost of a session of psychological assistance * average number of sessions) * expected percentage of patients needing specific psychotherapy]		
Expected costs for additional therapies	$\Sigma^{\{1...x\}}_{\text{type of therapy}}$ [(average cost of a therapy * average number of therapies needed) * expected percentage of patients needing a specific therapy]		
Expected costs for palliation	$\Sigma^{\{\text{home,hospital}\}}_{\text{palliation}}$ [(average cost of a day of palliation * average number	/	/

	of days) * expected percentage of patients needing palliation]		
Total expected costs For after care	$\Sigma^{\{1...x\}}_{\text{type of assistance}}$ [Expected cost for psychological assistance] + $\Sigma^{\{1...x\}}_{\text{type of therapy}}$ [expected cost for additional therapies] + $\Sigma^{\{\text{home,hospital}\}}_{\text{palliation}}$ [expected cost for palliation]	Expected cost for rehabilitation + $\Sigma^{\{1...x\}}_{\text{type of assistance}}$ [expected cost for psychological assistance] + $\Sigma^{\{1...x\}}_{\text{type of therapy}}$ [expected cost for additional therapies]	$\Sigma^{\{1...x\}}_{\text{type of assistance}}$ [Expected cost for psychological assistance] + $\Sigma^{\{1...x\}}_{\text{type of therapy}}$ [expected cost for additional therapies]
Indirect costs related to cancer treatment			
Lost production of patients			

Lost production due to a premature death	{[(retirement age – age at death due to cancer) * yearly value of production adjustment for evolution in GDP/capita] * non-survival rate due cancer}/ $(1+r)^{t-1}$		
Expected lost production due to disability		{[(retirement age – age at disability due to cancer) * yearly value of production * adjustment for evolution GDP/capita] * expected percentage of patients remaining disabled due to cancer}/$(1+r)^{t-1}$	
Lost production during treatment	[Average number of days lost * daily value of production]		

Lost production during follow-up	[Total average time lost * average hourly cost]		
Total production loss	(lost production due to a premature death) + (lost production due to treatment) + (lost production due to follow-up)	(expected lost production due to disability) + (lost production due to treatment) + (lost production due to follow-up)	(lost production due to treatment) + (lost production due to follow-up)
Expected lost production of relatives			
Expected lost production due to disability	/	{[(retirement age – average age when giving up work) * yearly value of production * adjustment for evolution GDP/capita] * expected Percentage of relatives giving up work due to patients	/

		remaining disabled due to cancer}/$(1+r)^{t-1}$	
Expected lost production due to treatment	[(Average number of days lost due to the patient's treatment * daily value of production) * expected percentage of relatives giving up work temporarily]		
Total expected lost Production of relatives	(expected lost production of relatives due to treatment)	(expected lost production of relatives due to patients' disability) + (expected lost production of relatives due to treatment)	(expected lost production of relatives due to treatment)
Expected costs related to caregivers			
Expected costs related to home health aides	[(average hourly wage * average number of hours such personnel is needed) * expected percentage of patients needing this kind of help]		

Expected costs related to household help	$\sum^{\{\text{patient attendants, independent providers}\}}_{\text{kind of personnel}}$ [(average hourly wage * average number of hours such personnel is needed) * expected percentage of patients needing this kind of help]		
Total expected costs related to caregivers	(expected cost for home health aides) + $\sum^{\{\text{patient attendants, independent providers}\}}_{\text{kind of personnel}}$(expected cost related to household help)		
Transportation costs	[cost per km * average number of km's]		
Visiting costs	Cost per visit * number of hospital days * number of visits per day		
Total interests forgone on funeral expenses	[(funeral expense * interest rate)^{1} / (1 + discount rate)^{0}] + … + [(funeral expense *		

	interest rate)^{n} / (1 + discount rate)$^{n-1}$]		
Costs for social insurance	[(administration cost for public health * % of patients using public health) + (administration cost of private health * % of patients using private health)] / total number of patients		
Non-financial costs	Included in quality of life estimates (QALYs)		

Table 6.4: Cost taxonomy of cancer-related adverse events

Adverse events			
	Fatal	**Disabled**	**Fully recovered**
Direct costs related to the management of adverse events			
Drug costs			
Drugs	$\sum^{\{1...x\}}_{\text{adverse event}} \sum^{\{1...4\}}_{\text{grade of severity}}$ [Acquisition cost per dosage * number of dosages every time drug is given * frequency]		
Pre-treatment	/		
Total drug costs	$\sum^{\{1...x\}}_{\text{adverse event}} \sum^{\{1...4\}}_{\text{grade of severity}}$ (cost of drug to treat a specific adverse event)		
Administration costs			

Hospitalization costs (inpatient visits)	$\sum^{\{1...x\}}_{\text{adverse event}} \sum^{\{1...4\}}_{\text{grade of severity}}$ [(cost per hospital day – drug-related costs) * number of hospital days]
Outpatient visits	$\sum^{\{1...x\}}_{\text{adverse event}} \sum^{\{1...4\}}_{\text{grade of severity}}$ [(cost per outpatient day – drug-related costs) * number of outpatient days]
<u>Total administration costs</u>	$\sum^{\{1...x\}}_{\text{adverse event}} \sum^{\{1...4\}}_{\text{grade of severity}}$ (Cost for hospitalization) + $\sum^{\{1...x\}}_{\text{adverse event}} \sum^{\{1...4\}}_{\text{grade of severity}}$ (cost for outpatient visits)
<u>Monitoring costs</u>	
Costs for tests	$\sum^{\{1...x\}}_{\text{test}} \sum^{\{1...y\}}_{\text{adverse event}}$ (cost for a specific test * number of different tests)
Tests for follow-up	$\sum^{\{1...x\}}_{\text{test}} \sum^{\{1...y\}}_{\text{adverse event}}$ (cost for a specific test * number of different tests)
Expected additional medical visits	$\sum^{\{1...x\}}_{\text{adverse event}}$ [(Average cost for a medical visit * number of visits) * expected percentage of

	patients needing additional medical visits]		
Expected additional home visits	$\sum^{\{1...x\}}_{\text{adverse event}}$ [(Average cost for a home visit * number of visits) * expected percentage of patients needing additional home visits]		
Total monitoring costs	$\sum^{\{1...x\}}_{\text{test}}\sum^{\{1...y\}}_{\text{adverse event}}$ (cost for diagnostic tests) + $\sum^{\{1...x\}}_{\text{test}}\sum^{\{1...y\}}_{\text{adverse event}}$ (cost for follow-up tests) + $\sum^{\{1...x\}}_{\text{adverse event}}$ (cost for medical visits) + $\sum^{\{1...x\}}_{\text{adverse event}}$ (cost for home visits)		
Expected administration costs	$\sum^{\{1...x\}}_{\text{adverse event}}$ [(average hourly wage of private nurses * time needed to administer the drug) * expected number of patients needing private nurses for a specific adverse event		
Expected costs for after care			

Expected costs for rehabilitation	/	$\Sigma^{\{1...x\}}_{\text{adverse event}}$ [(average cost for a rehabilitation session * average number of sessions) * expected percentage of patients needing rehabilitation after disease]	/
Expected costs for psychological assistance	$\Sigma^{\{1...x\}}_{\text{type of assistance}}\Sigma^{\{1...y\}}_{\text{adverse event}}$ [(average cost of a session of psychological assistance * average number of sessions) * expected percentage of patients needing specific psychotherapy]		
Expected costs for additional therapies	$\Sigma^{\{1...x\}}_{\text{type of therapy}}\Sigma^{\{1...y\}}_{\text{adverse event}}$ [(average cost of a therapy * average number of therapies needed) * expected percentage of patients needing a specific therapy]		

Expected costs for palliation	$\sum^{\{home, hospital\}}_{type\ palliation}$ $\sum^{\{1...x\}}_{adverse\ event}$ [(average cost for a day of palliation * average number of days) * expected percentage of patients needing palliation	/	/
Expected wig costs	(average cost of a wig * expected number of patient needing a wig		
Total expected costs For after care	$\sum^{\{1...x\}}_{type\ of\ assistance}$ $\sum^{\{1...y\}}_{adverse\ event}$ (expected cost for psychological assistance) + $\sum^{\{1...x\}}_{type\ of\ therapy}$ $\sum^{\{1...y\}}_{adverse\ event}$ (expected cost for additional therapies) + (expected cost	$\sum^{\{1...x\}}_{adverse\ even\ event}$ (expected cost of rehabilitation) + $\sum^{\{1...x\}}_{type\ of\ assistance}$ $\sum^{\{1...y\}}_{adverse\ event}$ (expected cost for psychological assistance) + $\sum^{\{1...x\}}_{type\ of\ therapy}$ $\sum^{\{1...y\}}_{adverse\ event}$ (expected cost	$\sum^{\{1...x\}}_{type\ of\ assistance}$ $\sum^{\{1...y\}}_{adverse\ event}$ (expected cost for psychological assistance) + $\sum^{\{1...x\}}_{type\ of\ therapy}$ $\sum^{\{1...y\}}_{adverse\ event}$ (expected cost for additional therapies) + (expected cost for wigs)

	for wigs)+ $\sum^{\{home, hospital\}}_{type\ palliation}$ $\sum^{\{1...x\}}_{adverse\ event}$ (expected cost for palliation)	for additional therapies) + expected cost for wigs	
Indirect costs related to the management adverse events			
Lost production for patients			
Lost production due to a premature death	$\sum^{\{1...x\}}_{adverse\ event}$ {[(retirement age – age at death due to a specific adverse event) * yearly value of production * adjustment for evolution in	/	/

	GDP/capita] * non-survival rate due to a specific adverse event}/$(1+r)^{t-1}$		
Expected lost production due to disability	/	$\sum^{\{1...x\}}_{\text{adverse event}}$ {[(retirement age - age at disability due to a specific adverse event) * yearly value of production * adjustment for evolution GDP/capita] * expected percentage of patients remaining disabled due to a specific adverse event}/ $(1+r)^{t-1}$	/
Lost production during treatment	$\sum^{\{1...x\}}_{\text{adverse event}}$[Average number of days lost due to treatment of specific adverse event * daily value of production]		

Lost production due to follow-up	$\sum^{\{1...x\}}_{\text{adverse event}}$ [Total average time lost * average hourly cost]		
Total lost production	$\sum^{\{1...x\}}_{\text{adverse event}}$ (lost production due to a premature death) + $\sum^{\{1...x\}}_{\text{adverse event}}$ (lost production due to treatment) $\sum^{\{1...x\}}_{\text{adverse event}}$ (lost production due to follow-up)	$\sum^{\{1...x\}}_{\text{adverse event}}$ (expected lost production due to disability) + $\sum^{\{1...x\}}_{\text{adverse event}}$ (lost production due to treatment) + $\sum^{\{1...x\}}_{\text{adverse event}}$ (lost production due to follow-up)	$\sum^{\{1...x\}}_{\text{adverse event}}$ (lost production due to treatment) + $\sum^{\{1...x\}}_{\text{adverse event}}$ (lost production due to follow-up)
Expected lost production of relatives			
Expected lost production due to disability		$\sum^{\{1...x\}}_{\text{adverse event}}$ {[(retirement age – average age when giving up work) * yearly value of production *	

	/	adjustment for evolution GDP/capita] * expected percentage of relatives giving up work due to patients remaining disabled due to specific adverse event}/$(1+r)^{t-1}$	/
Expected lost production due to treatment	$\sum^{\{1...x\}}_{\text{adverse event}}$[(Average number of days lost due to the patients' treatment of a specific adverse event * daily value of production) * expected percentage of relatives giving up work temporarily]		
Total lost production of relatives	$\sum^{\{1...x\}}_{\text{adverse event}}$ (expected lost production of relatives due to treatment)	$\sum^{\{1...x\}}_{\text{adverse event}}$ (expected lost production of relatives due to patients' disability) + $\sum^{\{1...x\}}_{\text{adverse event}}$ (expected lost production of relatives due to treatment)	$\sum^{\{1...x\}}_{\text{adverse event}}$ (expected lost production of relatives due to treatment)

Expected costs related to caregivers			
Expected costs related to home health aides	$\sum^{\{1...x\}}_{\text{adverse event}}$ [(average hourly wage * average number of hours such personnel is needed) * expected percentage of patients needing this kind of help]		
Expected costs related to household helps	$\sum^{\{1...x\}}_{\text{adverse event}} \sum^{\{\text{patient attendants, independent providers}\}}_{\text{kind of personnel}}$ [(average hourly wage * average number of hours such personnel is needed) * expected percentage of patients needing this kind of help]		
Total expected costs related to caregivers	$\sum^{\{1...x\}}_{\text{adverse event}}$ (expected cost for home health aides) + $\sum^{\{1...x\}}_{\text{adverse event}} \sum^{\{\text{patient attendants, independent providers}\}}_{\text{kind of personnel}}$ (expected cost related to household helps)		

Transportation costs	$\sum^{\{1...x\}}_{\text{adverse event}}$ [cost per km * average number of km's]		
Visiting costs	$\sum^{\{1...x\}}_{\text{adverse event}}$ (cost per visit * number of hospital days)* average number of visits per day)		
Expected forgone interests on funeral expenses	$\sum^{\{1...x\}}_{\text{adverse events}}$ [[(funeral expense * interest rate)^1 / (1 + discount rate)^0] + … + [(funeral expense * interest rate)^n / (1 + discount rate)$^{n-1}$]	/	/

Costs for social insurance	$\sum^{\{1...x\}}_{\text{adverse event}}$ [(administration cost for public health * % of patients using public health) + (administration cost of private health * % of patients using private health)] / total number of patients
Non-financial costs	Included in quality of life estimates (QALYs)

6.4. Conclusions

Cancer affects millions of individuals worldwide. Therefore, the economic burden related to cancer and cancer care is potentially very high. Because nations' resources are limited, it is crucial to invest them in cost-effective health care interventions. To that end, cost-effectiveness analyses have to be pursued. A limitation of cost-effectiveness studies is that inaccuracy could induce ineffective choices. In this chapter, a comprehensive cost taxonomy, including all relevant direct and indirect costs, has been developed. The importance of such a complete model increases with the introduction of new generation nanomedicines and target-based agents. Since these therapies will probably be very effective but also have very high acquisition costs, it will be crucial to demonstrate their cost-effectiveness by including all relevant direct and indirect costs as well quality of life estimates. Finally, it is important to emphasize that daily costs – and the cost components they include – used when calculating direct costs differ from hospital to hospital. Consequently, they have to be defined every time cost analysis is pursued.

Appendix: Costs

a) Drug costs

This cost category includes the costs of the drug itself but could also include all other costs related to drug administration. This cost includes the costs for

materials, devices, and equipment to administer the drug. Moreover, it includes also the personnel costs incurred when administering therapeutics.

b) Administration costs

Hospital costs:

- Costs for renting the room (including a cleaning fee)
- Costs for stay during days of therapy (common room for all cancer patients receiving therapy)
- Personnel costs
- Costs for materials, devices, and equipment
- Costs for food and beverages (diet programs)
- Drug costs

Costs for outpatient visits:

- Cost for stay during the day (common room for all cancer patients receiving therapy)
- Room during day care
- Personnel costs
- Costs for materials, devices, and equipment
- Drug costs
- Costs for food and beverages

c) Monitoring costs

Diagnostic tests:

- Personnel costs
- Costs for materials, devices, and equipment
- Drug costs

Tests to monitor disease progression:

- Personnel costs
- Drug costs
- Costs for materials, devices, and equipment

Tests for follow-up

- Personnel costs
- Drug costs
- Costs for materials, devices, and equipment

Medical visits:

- Physician cost
- Costs for materials, devices, and equipment

Home visits:

- Physician costs
- Costs for materials, devices, and equipment
- Transportation cost

d) Cancer after care

Rehabilitation:

- Personnel costs,
- Costs for materials, devices, and equipment

Palliative care:

- Costs for renting the room (including a cleaning fee)
- Personnel costs
- Drug costs
- Costs for materials, devices, and equipment
- Costs for food and beverages

Psychological assistance:

- Psychologist or psychiatrist's fee
- Drug costs

Chapter 7: Cost and cost-effectiveness analysis of conventional versus nanotechnology-based cancer therapies. A case study of gemcitabine versus PEGylated liposomal doxorubicin for the treatment of recurrent or progressive ovarian cancer

7.1. Introduction

Successful commercialization of new nanotherapeutics starts with a business plan that convinces private investors or third party payers. Since only cost-effective drugs will make their way to the market, cost-effectiveness analysis (CEA) is helpful in demonstrating that the cost per additional health effect is worth paying for. CEA compares the costs and effects of two or more health care interventions. It allows health administrators to efficiently allocate scarce resources and maximize health effects at the lowest cost.

Costs, effectiveness, adverse events, and quality of life are four crucial factors that should be taken into account when pursuing cost-effectiveness analyses. The challenge is to adopt new therapies that enhance quality of life while staying within the constraints of a predetermined health care budget.[12] To make

economic evaluation possible, clinical data are needed. Unfortunately, the scarcity of clinical data is a major impediment for any serious CEA of nanomedicines. Rendering the necessary data available is an absolute precondition for the success of economic studies and, in turn, nanotherapeutics. Cost-effectiveness studies should also be carried out as early as possible, preferably in the pre-clinical phase, to avoid the waste of scarce resources and maximize the therapeutic value for patients. To that end, governments should invest in making available clinical data of high quality.

The clinical trial pursued by Ferrandina et al. (2008), compares PEGylated liposomal doxorubicin (a first generation nanotherapeutic) and gemcitabine (conventional therapy) in the treatment of recurrent or progressive ovarian cancer. Ovarian cancer is the most prevalent cause of death due to gynecological malignancy.[196] Since the disease remains asymptomatic for a long period, women usually already have advanced stage disease when diagnosed. Therefore, prognosis is poor, with a 5-years survival rate of 25–30% in metastatic disease.[197] Since prolongation of survival and palliation of symptoms remain the most realistic objectives of salvage therapy, special attention has to be given to quality of remaining life.[196]

Unfortunately, conventional chemotherapeutic agents used in the salvage setting are likely to result in adverse events with different grades of severity while showing a limited tumor activity and efficacy. Consequently, the cost for the management of adverse events is high.[3] Therefore, there is a critical need for new classes of cancer agents and to establish the cost-effectiveness balance also in terms of preservation of quality of life (QoL) issues within the currently

available salvage chemotherapeutic agents. In this context, topotecan, gemcitabine (GEM), and PEGylated liposomal doxorubicin (PLD) have been shown to be active in the salvage treatment of ovarian cancer.[198,199] In particular, topotecan and GEM are mainly endowed with hematological toxicity, while PLD, due to its unique pharmacokinetic properties, shows reduced toxicity with mucositis and hand-and-foot syndrome, especially at the recommended dose of 50 mg/m².[196,198,199] However, very few studies have addressed whether liposome-based therapies are also cost-effective.[196]

Recently, a phase III randomized multicenter trial that compared GEM (Gemzar, Eli Lilly, Indianapolis, IN) with PLD (Caelyx®, Schering-Plough, New York, NY) demonstrated that GEM is not superior to PLD in patients relapsing after first-line treatment within 12 months from the completion of treatment. PLD proved to be more manageable than GEM and more advantageous in terms of toxicity and preservation of QoL.[11] In particular, the lower rates of mucositis and skin toxicity seen with PLD were likely related to the use of PLD at the dose of 40 mg/m², already shown in several phase II studies to be equally effective but less toxic than the conventional dose.[196] The acquisition cost per dose is, however, significantly higher for the liposomal agent (€335,54/20mg vs. €28,58/200mg). When solely considering the acquisition cost per quality-adjusted week (QALW), liposomal therapy is significantly less cost-effective than conventional treatment (€100,45/QALW vs. €73,79/QALW). However, the question is whether this assertion still holds when all direct and indirect costs of cancer treatment are considered.

This chapter is structured as follows. First, it assesses the costs and cost-effectiveness of two alternative cancer treatments, GEM and PLD, used in a recent phase III clinical trial. Then, the results are compared with the methodology used by other authors, i.e. cost calculation from a hospital perspective. Finally, the last paragraph offers the conclusions.

7.2. Methods

A comprehensive cost model to assess the cost-effectiveness of alternative cancer therapies was developed. The effectiveness study compares PLD and GEM for women with epithelial ovarian carcinoma recurring within 12 months after one first-line platinum/paclitaxel containing regimen. Model outcomes include quality-adjusted survival and total cost of cancer treatment. The performance of the treatments is measured by the cost-effectiveness ratio, defined as total cost of cancer divided by its clinical benefit (quality-adjusted survival). In the model, a social perspective taking into account all direct and indirect costs of cancer was adopted. An interest rate of 2% was used and time preference was incorporated by discounting future cash flows by 4% annually. Finally, the reliability of the data set was tested by Monte Carlo resampling. The results derived from 1.000 resamples were used to estimate the probability that a similar study would yield a cost-saving result.

7.2.1. Patient population

Between January 2003 and January 2007, hundred fifty three patients were enrolled in a randomized multicenter controlled trial of PEGylated liposomal doxorubicin (n = 76) versus gemcitabine (n = 77) for recurrent or progressive ovarian cancer. Six patients in the treatment arm (GEM) and four patients in the control arm (PLD) refused therapy, leaving 71 respectively 72 patients available for analysis. The patient groups were well balanced for clinicopathologic characteristics (table 7.1). While outcome evaluators were blinded, physicians and patients were not. Patients were at least 18 years old and had measurable or assessable ovarian cancer according to Response Evaluation Criteria in Solid Tumors, and experienced recurrence or treatment failure with first-line paclitaxel/platinum chemotherapy. Additional inclusion criteria were patients' bone marrow function (platelets ≥ 100.000/μL, hemoglobin ≥ 9 g/dL, and absolute neutrophil count (ANC) ≥ 1.500 cells/μL), renal function (serum creatinine ≤ 1.5 mg/dL), liver function (AST ≤ 1.5 x the upper limit of normal, alkaline phosphatase ≤ 1.5 x the upper limit of normal, and bilirubin ≤ upper limit of normal), and cardiac function (left ventricular ejection fraction ≥ 50% or the institutional normal), Eastern Cooperative Oncology Group performance status of 0 to 2, and no prior malignancies, with the exception of curatively treated basal cell carcinoma, squamous cell carcinoma of the skin, or carcinoma-in-situ of the cervix. Patients were not enrolled if they were pregnant or breast-feeding, had a life expectancy of less than three months, had a history of cardiac disease that met the New York State Heart Association classification of class II or higher, or had an uncontrolled systemic infection. Furthermore, patients were excluded if they had received an investigational agent within 30 days of the first

dose of study drug, prior PLD/GEM, or chemotherapy within 30 days of the first dose of study drug.[196]

Table 7.1: Patient characteristics at initial diagnosis and at time of recurrence

Number of patients		
Characteristic	**PLD**	**GEM**
Number of patients enrolled	76	77
FIGO stage		
I-II	4	3
III	49	51
IV	23	23
Histotype		
Serous	64	59
Undifferentiated	2	4
Clear cell	4	6
Endometrioid	3	5
Mucinous	2	1
Mixed	1	2
Residual tumor at first surgery		
Optimal (< 1cm)	27	23
Suboptimal (> 1cm)	49	54
Grade		
1-2	12	15
3	50	48
4	14	14
At recurrence		
Age, years		
Median	63	63
Range	28-80	39-79

Performance status	33	38
0	39	33
1	4	6
2		
Platinum-free interval	43	43
≤ 6 months	33	34
7-12 months		
CA-125 level, U/mL	165	243
Median	4-3.280	3-3.970
Range		
Site of recurrence	24	25
Intra-abdominal	6	8
Lymph nodes	12	8
Pelvis	34	36
Mixed		

Source: Ferrandina et al. (2008)[196]

7.2.2. Data source

Effectiveness is based on a phase III multicenter, randomized study comparing PLD and GEM in women with epithelial ovarian carcinoma relapsing within 12 months after completion of first-line platinum/paclitaxel-based therapy. The primary endpoint of the study was the assessment of time to progression (TTP) in GEM-treated versus PLD-treated patients. Secondary endpoints were the assessment of overall survival (OS), response rate, safety/toxicity, and QoL.[196]

All participating hospitals were required to obtain protocol approval by an ethical committee. The Gynecologic Oncology Unit of the Catholic University Sacred Heart of Rome registered and assigned patients as well as established the data management procedures. Before random assignment in a 1:1 fashion, patients were stratified (institution, PFI interval, and initial stage of disease). Treatment began immediately after assignment.[196]

Patients in the control group were treated with PLD (Caelyx®; Schering-Plough; New York, NY). They received 40 mg/m² via a 1-hour intravenous (i.v.) infusion every 28 days. The experimental group received GEM (Gemzar, Eli Lilly, Indianapolis, IN), which was administered at 1,000 mg/m² as a 30-minute i.v. infusion on days 1, 8, and 15 of a 28-day cycle. Patients were given premedication with methylpredisolone (20 mg intravenous) and this always 30 minutes before drug infusion. Physicians were allowed to adjust the dose of the study drug for evidence of toxicity.[196]

Assessment of response was performed according to the RECIST criteria (a voluntary, international standard, based on measurable disease, i.e. the presence of at least one measurable lesion, every 2 cycles. Safety analysis was performed on all patients with blood cell counts performed at 7,14,21 days from chemotherapy infusion, and serum chemistry assayed at day 14. Therefore, three visits were required during the treatment cycle in which the toxicity was experienced.

Patients were followed up with transvaginal (TV) ultrasound and CA-125 serum evaluation every three months, plus a thorax/abdomen CT scan every six months for the following two years after the completion of treatment. Then, for the subsequent two years, TV ultrasound and CA-125 serum evaluation were performed every 6 months and a thorax/abdomen CT scan annually.

Disease progression, serious or intolerable adverse events precluding further treatment, inability to tolerate study drug despite dose modification, or patient's decision to withdraw participation caused the temporarily suspension or even the discontinuation of treatment with either therapy regimen.[196]

The study also evaluated the quality of life of patients, which was done within 2 weeks before enrollment and before each treatment cycle. Quality of life was assessed by using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30.[196]

7.2.3. Resource utilization

In the PLD patient group 12.077mg of liposome agent was administered during the whole treatment period, whereas 750.800mg of conventional agent was used for patients treated with GEM. PEGylated liposomal doxorubicin requires one administration per cycle compared with three for gemcitabine. The standard care of chemotherapy administration includes one outpatient visit per drug infusion.[196] This translates into three outpatient visits per GEM cycle compared to only one per PLD cycle.

Resources to treat therapy-related adverse events were different between the GEM and PLD treatment arm. Fourteen adverse events were assessed: leukopenia, neutropenia, anemia, thrombocytopenia, anorexia, nausea, vomiting, diarrhea, mucositis, alopecia, fatigue, PPE, and hepatic and neurological toxicity. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria. Sixteen patients (22%) in the GEM treatment arm and five patients (7%) treated with PLD experienced grade 3 and 4 neutropenia (P = 0.007). Furthermore, there was a trend towards a more frequent use of granulocyte colony-stimulating factor (G-CSF) in patients receiving GEM. Three administrations of G-CSF (once per week during three weeks), and three outpatient visits, were required to treat grade 4 leukopenia and neutropenia. The proportion of grade 3 and 4 anemia was not significantly different between the two treatment regimens, whereas grade 3 and 4 thrombocytopenia was more frequently observed in patients treated with GEM, with 4 patients (6%) versus no patients in the PLD treatment arm. Statistical significance was, however, not reached (P = 0.058). In the GEM treatment arm, a slightly higher percentage of patients (14%) received red blood cell (RBC) transfusion compared with patients treated with PLD (4%) (P = 0.038). Grade 4 anemia and thrombocytopenia, which require RBC respectively platelet transfusion, need one outpatient visit. Five percent of patients treated with PLD required growth factor support compared with fourteen percent of patients treated with GEM. The percentage of patients requiring erythropoietin (EPO) did not differ significantly between the two treatment regimens: 7% in GEM-treated patients compared with 4% in the PLD treatment arm (P = 0.58). EPO was administered in case of grade 2/3 anemia and grade 1/2/3 thrombocytopenia. Grade 3 and 4 gastro intestinal toxicity (nausea, vomiting, and diarrhea) was modest and not significantly

different between the two treatments. Grade 3/4 nausea/vomiting were treated with 5-HT3 antagonists while the therapy for grade 3/4 diarrhea consisted of probiotic therapy. Moderate and severe PPE, on the contrary, was more frequently observed in the PLD-treatment arm (4 patients or 6%) compared with patients treated with GEM (no patients) (P = 0.061).[196] Table 7.2 presents the resource costs.

Table 7.2: Resource costs

PEGylated Liposomal Doxorubicin (20 mg)	€335,54
Gemcitabine (200 mg)	€28,58
Pre-treatment – Corticosteroids (40 mg)	€10,00
G-CSF - Granulokine 30 (per cycle)	€381,15
EPO (per cycle)	€1.600,00
RBC transfusion (per transfusion)	€153,00
Platelets transfusion (per transfusion)	€438,00
Glutathione (per cycle)	€44,31
5-HT3 (per cycle)	€39,00
Probiotic therapy	€31,50
Mouthwash Mycostatin (per bottle)	€6,34
Inpatient visit (per day)	€450,00
Outpatient visit (per day)	€350,00
Blood analysis (per test)	€30,00
Average cost of a funeral*	€5.610,28
Transportation cost (per km)**	€0,35
Private nurse (per hour)***	€24,30

Costs attained in collaboration with the Catholic University Sacred Heart in Italy
*Average quoted prices in Italy
**Automobile Club Italia
***Bellanger and Or (2008)[200]

7.2.4. Clinical efficacy

Ferrandina et al. (2008) calculated the required sample size assuming that a median TTP of 12 weeks from the beginning of drug administration would be observed in the PLD patient group. Hundred forty seven patients were required to detect an improvement with GEM in median TTP to 19 weeks, which corresponds to a hazard ratio (HR) of progression of 0.63, based on a two-sided log-rank test at an error α = 0,05 and a power of 80%. Interim analysis was not planned. Efficacy was based on the intent-to-treat principle. Response rates were compared by the use of an unadjusted normal approximation for the difference of two binomial proportions. Furthermore 95% confidence intervals (CI) were evaluated. TTP was estimated from the first day of study drug administration to the point of disease progression or the date last seen. To compute medians and life-tables, the product-limit estimate of the Kaplan-Meier method was used. Furthermore, they were analyzed using the log-rank test. Moreover, the Cox proportional hazards model was used to evaluate the effect of therapy after adjusting for other variables. Finally, changes in quality of life from baseline were compared by the Wilcoxon signed rank sum test.[196]

Multivariate analyses including age, CA-125 levels, performance status, and progression-free interval (PFI) duration were done for both TTP and OS. On the one hand, for TTP, higher CA-125 levels (> 500 U/mL; $x^2 = 6.0$; HR = 1.5; 95% CI, 1.0–1.9: P = 0.013) at recurrence and a shorter duration of PFI (< 6 months; $x^2 = 10.7$; HR = 1.9; 95% CI, 1.5–2.4; P = 0.001) at study entry maintained their independent negative prognostic value. On the other hand, for OS, high CA-125 levels at recurrence ($x^2 = 5.0$; HR = 1.3; 95% CI, 1.0–1.4; P = 0.025), a

shorter duration of PFI (x^2 = 9.9; HR = 1.6; 95% CI, 1.4–2.4; P = 0.001), and a performance status of more than 0 (x^2 = 10.1; HR = 1.9; 95% CI, 1.1–2.1; P = 0.001) were independently associated with a poorer prognosis. The treatment difference was no longer significant for either TTP (x^2 = 2.5; HR = 0.9; 95% CI, 0.8–1.0; P = 0.102) or OS (x^2 = 1.9; HR = 0.9; 95% CI, 0.7–1.2; P = 0.158).[196]

Although there were no statistical significant differences in the frequency of patients requiring dose modifications in the GEM and PLD treatment arm, GEM-treated patients required more dose delays. Also a higher percentage of patients receiving GEM had to discontinue treatment compared with patients receiving PLD, though statistical significance was not reached (P = 0,114).[196]

Response was assessed in 133 patients (70 patients in the PLD-treatment arm versus 63 patients treated with GEM). Analysis showed a lower rate of objective response in patients relapsing within 6 months versus patients with a PFI of 7 to 12 months (15% versus 31%, respectively while statistical significance was reached (P = 0,032)). In the PLD treatment arm, 3 complete and 8 partial responses were assessed with an overall response of 16%. Furthermore, 30 patients (43%) experienced stabilization of disease. For the patient group treated with GEM, 3 complete and 15 partial responses were attained and an overall response rate of 29%, while 27 patients (43%) experienced stabilization of disease. Overall response was not significantly different between both therapies (P = 0.066). Moreover, a subgroup analysis of patients with measurable disease was pursued. This analysis showed similar results (P = 0.221). Also the percentage of overall clinical benefit between the GEM and PLD treatment arm (58% and 71%, respectively) was not significantly different (P = 0.085).[196]

As of June 2007, 95 patients (62%) died as a consequence of disease while 134 patients (88%) experienced disease progression. The median follow-up time was 39 weeks (3 to 215 weeks). After this time period, no statistically significant difference in time to response (TTR) was found (16 weeks in the PLD treatment arm versus 20 weeks in patients treated with GEM; P = 0.441). The median overall survival time was, however, higher for patients treated with PLD (56 weeks) compared with patients treated with GEM (51 weeks). No difference was found in TTP curves according to treatment allocation in the two treatment groups. When assessing the overall survival, no difference was found between patients treated with GEM and PLD in the subgroup with a PFI of less than 6 months. In the subgroup of patients with a PFI of 7 to 12 months, on the contrary, a better survival favoring PLD was found (P = 0.013).[196]

Furthermore, patients' quality of life was assessed. Hundred twenty one patients (79%) completed the quality of life questionnaire before starting therapy and at least one post-baseline questionnaire. At baseline, the differences in QoL were not statistically significant between patients of both treatment arms. After the first and second post-baseline assessment, however, significantly higher QoL scores were found in patients treated with PLD. This was particularly true for physical and emotional functioning among the five functional scales and in fatigue among the symptom items.[196] Consequently, equivalence can not be assumed.

Gemcitabine was thus shown to be not superior to PEGylated liposomal doxorubicin in terms of TTP in patients relapsing after first-line treatment within 6 months or between 7 and 12 months. Although no long-term follow-up was

done, these data are unlikely to change because only 12,4% of individuals were censored at time of analysis. It was demonstrated that PLD is more manageable than GEM, which is due to negligible hematological toxicities and low rates of mucositis and skin toxicity.[196]

7.3. Cost analysis from a social perspective

The rising cost of health care is a worldwide cause of great concern, especially for health administrators and policy-makers allocating scarce resources. Responsible use of limited resources requires a clear understanding of the cost-effectiveness of therapies. Cost-effectiveness analysis assists decision makers in weighing the costs of treatments against their health effects. It leads to a more effective use of resources. Costs and effects are evaluated with the objective to improve health while minimizing resource use.

Cost calculation starts with the quantification of all costs.[13] The whole cost of care, with and without the new drug, is taken into account.[92] Correct cost analysis is crucial for success in any organization and for each product, from the smallest product to the largest multinational company. Since it provides key information for planning and controlling, cost analysis helps making better decisions. Therefore, it is essential to include all relevant direct and indirect costs of cancer and cancer care.

Costs associated with direct medical resources (i.e., drug, administration, and monitoring costs) are based on the clinical protocols of the Catholic University Sacred Heart in Italy. Data was provided by the Medical Direction Staff of the Catholic University Sacred Heart. The exact cumulative dosage of the study drug, and drugs to treat therapy-related adverse events were taken from the clinical trial. Table 7.3 presents all relevant direct and indirect costs of cancer treatment and the management of adverse events.

Total cost for administering cancer drugs includes the cost of the study drug, pre-treatment, and outpatient visits are required for each drug infusion. Both PLD and GEM treatments do not require inpatient visits. The study also includes other direct costs: expected administration costs (drug administration at home), monitoring costs (diagnosis and follow-up), and expected costs for after care (psychological assistance, rehabilitation, additional therapies, palliation, wigs). Moreover, both tangible and intangible indirect costs are included: expected production loss for patients and relatives, expected costs of caregivers, transportation costs, visiting costs (relatives and friends), the interest forgone on funeral expenses, non-financial costs, and administration costs of health insurance. These costs are considered for both treatment and the management of adverse events. Lost production is based on the average hourly wage for women regardless of unemployment or household production since the cost of lost production remains the same for all categories. It has to be noted that the average value of production is not constant in time. Therefore, evolution in gross domestic product (GDP) per capita is used to adjust the value of production. Transportation costs are based on an all-inclusive cost per kilometer. These costs are incurred when patients go to the hospital for drug administration, monitoring

visits, and for cancer after care. Costs related to caregivers are based on an average hourly wage. It is assumed that caregivers are only needed during treatment. Visiting costs are only incurred during hospitalization. The opportunity cost of an early funeral is based on the average quoted prices in Italy and depends on the number of interments and cremations. Estimates of indirect costs are based on the findings of the published literature. Finally, non-financial costs represent the burden of pain, suffering, and loss of quality of life. These costs are conceptualized in the quality of life estimates.

Table 7.3: Direct and indirect costs of cancer treatment and therapy-related adverse events

DIRECT COSTS
Drug costs
Study drug
Pre-treatment
Administration costs
Inpatient visits
Outpatient visits
Expected administration costs
Nursing costs
Monitoring costs
Diagnosis
Follow-up

Expected costs for after care
Psychological assistance
Rehabilitation
Palliation
Additional therapies
Wigs (in case of alopecia)
INDIRECT COSTS
Expected costs for caregivers
Home health aide
Patient attendant
Transportation costs
Lost production
Patients
Relatives
Visiting costs
Forgone interests on funeral expenses
Non-financial costs
Administration costs of insurance

Finally, statistical analyses are performed on cost data. Descriptive statistics are presented as percentages for discrete variables and means, standard deviations, and 95% confidence intervals for continuous variables. Costs are nonparametric, and differences are tested with the Mann-Whitney test. Two-sided P values of 0,05 or less are considered statistically significant. Finally, the reliability of the

data set is tested by Monte Carlo resampling. The results derived from 1.000 resamples are used to estimate the probability that a similar study would yield a cost-saving result. All statistical analyses were performed with the use of the software SPSS.[19]

7.3.1. Direct costs

The incidence of malignant diseases has become a major healthcare issue. In addition to being associated with serious economic and emotional problems for patients and their family, cancer therapy imposes significant economic

[19] Since many statistical tests require a normal distribution, it is crucial to check for normality. A normal distribution is a statistical distribution in which data are represented graphically by a symmetrical bell-shaped curve, with the highest frequency in the middle and smaller frequencies towards the edges. Although no real data sets follow the normal distribution exactly, many kinds of data follow a distribution that is approximately Gaussian.

There are several ways to assess the normality of a distribution:

- The simplest method of assessing normality is by producing a histogram. The most important things to look at, are the symmetry and the peak of the histogram. A normal distribution should be represented by a bell-shaped curve. A histogram with a non-symmetrical distribution has a long tail.
- Another method of assessing the normality of a distribution is by producing the normal probability plot, P-P, or Q-Q plot. For a normal distribution, the probability plot should show a linear relationship. Normality can be assumed if values fall more or less in a straight line.
- Finally, it is also possible to use the Shapiro-Wilk or Kolmogorov-Smirnov test. These tests determine whether one distribution (data set) is significantly different from another (normal distribution) and produce a numerical answer. Here, the significance value has to be checked. The convention is that a value larger than 0,05 indicates normality. A value less or equal to 0,05 is, thus, considered as good evidence that the data set is not normally distributed. Since these tests can produce misleading results, graphical plots should always be pursued as well.

Moreover, it is important to determine if a cost difference is statistically significant or not. In statistics, a result is called significant if it is unlikely to have occurred by chance. If the obtained P value is small, then it can be concluded either the null hypothesis is false or an unusual event has occurred. If normality can be assumed, the t-test can be used. Normality is rejected if data are skewed. A convenient way to handle the problem of positive skewed data (right skewed) is to transform the data into a data set which has a near-normal distribution. Otherwise, the Mann-Whitney test can be used, which is an alternative to the t-test. It is a nonparametric test that is used to compare two population means that come from the same population. This test is also used to verify whether two population means are equal or not. If the P-value is less than 0,05 it can be concluded that the difference was not caused by chance.

consequences on nations' healthcare systems. Direct costs of cancer and cancer care include two broad components: direct medical costs (drug, administration, expected administration, and monitoring costs), and expected costs for cancer after care. Direct healthcare costs represent the value of resources used to diagnose and treat diseases and the resulting adverse events.

a) Drug costs

Cancer drugs account for a significant share of total health care expenditure for cancer. New therapies are often expensive and thus leading contributors to the increase in overall health care spending. Some analysts of the Congressional Budget Office are convinced that the availability of expensive new therapies fuel health care spending not only because of development costs but also because they create a higher consumer demand. Moreover, caring for the growing and ageing population increased total health care costs. However, experts agree that the influence of the ageing population on health expenditure is minimal. High acquisition costs are, thus, a major concern for policy-makers and health administrators allocating limited public funds. The use of new therapeutics might be justified, however, by their superior effectiveness.

There are two ways to allocate drug costs. While, on the one hand, drug costs could include only the cost of the therapeutic agents themselves, on the other hand, they could also comprise the costs related to drug administration. These are personnel costs, and costs of materials, equipment, and devices related to

drug infusion. It is, however, rather uncommon that hospitals use a rule of thumb to allocate these costs.

In this case study, drug costs include only the cost of therapeutic agents. Since hospitals have different policies to allocate their costs, cost components included in a specific cost category have to be defined for each case study separately. This is important to avoid double counting and, thus, overestimation of costs. Drug costs have to be calculated for: (1) cancer drugs; (2) pre-treatment; and (3) drugs to treat adverse events.

** Cancer drugs*

Data provided by the Medical Direction Staff of the Catholic University Sacred Heart indicate that gemcitabine (Gemzar, Eli Lilly, Indianapolis, IN) is currently administered at a treatment dosage of 1000 mg/m². A single vial containing 200 mg of drug costs €28,58. PEGylated liposomal doxorubicin (Caelyx®; Schering-Plough; New York, NY), on the contrary, is administered at a dosage ranging from 35–50 mg/m². A single vial containing 20 mg of drug costs €335,54.

It is common practice to calculate the drug cost per cycle. Total costs are attained by multiplying the cost per cycle by the number of cycles received. Since the clinical trial registered the exact cumulative dose in mg during the whole chemotherapy period for each patient, it is used to calculate the exact total drug cost. Drug cost per patient is calculated by multiplying exact cumulative drug dosage and price per dosage. The cost to administer the drug is not included in

this cost; it will be included in the administration costs further in the chapter. The same methodology is used to calculate the drug costs related to pre-treatment and to manage adverse events.

Total drug costs of PLD amount to €202.617,08. This is almost twice as high as the cost of GEM which is €107.289,32. This translates into an average drug cost per patient of €2.814,13 respectively €1.511,11 and an average drug cost per patient per cycle of €667,14 for PLD compared to €387,69 for GEM.

However, drug cost per patient per cycle differs not only between treatment arms but also within patient groups. Treatment is, thus, not the only variable that causes a difference in drug costs per cycle. Since drug cost per cycle could be dependent on different explanatory variables, multiple regression analysis is pursued. The purpose is to learn more about the relationship between drug cost per cycle and several independent variables. There are several variables that are likely to affect drug cost per cycle: progression-free interval, overall survival, CA-125 level at recurrence, time to response, duration of response, dose modifications, and discontinuation of treatment. It is interesting to see whether and how these variables relate to the drug cost per cycle. Therefore, a multiple regression analysis was performed.

Several multiple regression analyses were performed before attaining the definitive regression model. Initially, all independent variables were entered in the model. Multiple regression was performed using the enter method. The model was simplified by discarding the explanatory variables that did not contribute to explain the variability in the dependent variable. At each iteration, the least

significant explanatory variable was removed and regression was re-calculated. This procedure was repeated until only significant independent variables remained in the model. In the end, two variables were significant: treatment and treatment discontinuation (fig 7.1 in appendix 1).

Figure 7.1 gives the unstandardized and standardized beta coefficients of the final simplified model. While the unstandardized coefficients are used in the prediction and interpretation of results, the standardized coefficients are a measure of the contribution of each variable to the model.[20] Figure 7.1 indicates that treatment (PLD or GEM) and discontinuation of treatment are the independent variables with the largest impact on drug cost per cycle.

Moreover, the figure shows the tolerance values. These are a measure of the correlation between the explanatory variables and can vary between 0 and 1.[21] The tolerance values in figure 7.1 show that the remaining variables are not correlated with each other. The same is concluded when looking at the VIF, which is another measure of collinearity (it is the reciprocal of tolerance) in which a large value indicates a strong relationship between independent variables.

It is also important to test for interaction effects. Interaction effects represent the combined effects of independent variables on the dependent variable. When an interaction effect is present, the impact of one variable depends on the level

[20] A large value indicates that a unit change in this explanatory variable has a large effect on the dependent variable. The t and P values (sig) give a rough indication of each independent variable. A big absolute t value and small P value suggest that an independent variable is having a large impact on the dependent variable.

[21] The closer to zero the tolerance value is for a specific independent variable, the stronger the relationship between this and the other independent variables

of the other variable. This could have important implications for the interpretation of statistical models.[22] To test for interaction, a product term was constructed and included in multiple regression. If the test is significant, the two independent variables have an interactive effect on the dependent variable. However, before constructing the product term, the independent variables had to be centered. That is, for each independent variable the mean had to be subtracted from each participant's score on that variable. The interaction term was then constructed from the centered variables by multiplying them together. The model was tested using the centered main effects and the constructed interaction terms.[23] Firstly, interaction effects are calculated for the complete model. Secondly, interaction effects are recalculated by discarding the least significant interaction effect from the model. The final model contains only relevant interaction effects (fig. 7.2 in appendix 1)

The model summary of the final regression model (figure 7.3 in appendix 1) shows an adjusted R square of 0,652. This value predicts that 65,20% of variance in the drug cost per cycle is caused by the variables in the model. Stated otherwise, 34,80% of variance in the drug cost per cycle is caused by something else. That the model is significant can also be concluded from the ANOVA test (figure 7.4 in appendix 1).

[22] Multiple regression can be used to estimate and test interaction effects when the explanatory variables are either categorical or continuous.

[23] Centering the independent variables does not change their relationship to the dependent variable, but will reduce the collinearity between the main effects and the interaction terms.

Using the enter-method a significant model emerged ($F_{2,134}$ = 128,607; P < 0,005; adjusted R^2 = 0,652). The following are significant explanatory variables (the other independent variables were not significant in this model):

- Treatment (beta = -0,745; P < 0,0005)
- Discontinuation of treatment (beta = -0,174; P = 0,007)

However, caution must be exercised when interpreting the coefficients of individual variables in the presence of interaction effects. Adding interaction terms drastically changes the interpretation of all of the coefficients. Although only treatment and discontinuation of treatment are significant main effects in explaining the difference in drug cost per cycle within treatment arms, the excluded variables have interactive effects on drug cost per cycle. This means that the main effects do not collectively explain all of the influence of the independent variables on the dependent variable.

** Pre-treatment*

According to international guidelines, pre-treatment drugs have to be administered before each drug infusion. In the clinical trial, these are Corticosteroids and are administered for the prevention of allergic reactions. The cost of these procedures is €10. This is for a 40mg dose of Corticosteroids. Twenty mg of pre-treatment (intravenous) drug is given 30 minutes before each drug infusion. This translates into a cost of €5 per drug infusion. Since GEM is administered 3 times per cycle, also pre-treatment in this patient group is given 3 times. PLD, on the contrary, is administered only once per cycle. Pre-treatment

costs per patient per cycle are, thus, €5 in the PLD arm compared to €15 for patients treated with GEM. Total costs of pre-treatment drugs amount to €1.505 respectively €4.125. This translates into an average drug cost of €20,34 per patient treated with PLD compared to €58,10 per patient in the GEM arm.

The cost of pre-treatment per cycle, thus, differs between treatment arms. Since GEM requires more drug infusions per cycle, treatment is the only variable that causes a difference between patient groups. The difference in pre-treatment cost between treatment arms is statistically significant ($P < 0,0005$).

** Total costs related to cancer drugs*

Total cost of cancer drugs includes both the cost of the chemotherapeutic agents and the cost of pre-treatment drugs. When considering total costs related to both chemotherapeutic agents, total drug costs amount to €204.122,08 in the PLD treatment arm and €111.414,32 in the GEM patient group. This translates into an average cost per patient of €2.958,29 respectively €1.614,70. The cost per patient per cycle is, thus, estimated at €672,14 for patients treated with PLD compared to €402,69 in the GEM treatment arm ($P < 0,0005$). Drug costs are, thus, significantly higher in the PLD treatment arm. This finding is in accordance with the studies that have been carried out sofar and were discussed in chapter 3.

** Drugs to treat adverse events*

Cancer treatment causes several adverse events with different grades of severity. In the clinical trial pursued by Ferrandina et al. (2008), the following side-effects were observed and evaluated: white blood cell (WBC), neutrophils, hemoglobin, platelets, cutaneous, neurological, hepatic, and asthenia toxicity. Furthermore, anorexia, nausea, vomiting, diarrhea, mucositis, and alopecia were also caused by cancer therapy. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria. The severities of these side-effects range from grade 1 (mild) to grade 4 (life-threatening). Since each adverse event needs a different treatment, costs have to be calculated for each adverse event separately.

The frequency of each of the adverse events experienced by the patients enrolled in the clinical trial is represented in table 7.4. Before looking at the frequencies, it is important to have some additional information about the different toxicities. Therefore, this section discusses the problem and possible treatments for each grade of each adverse event. Data about which treatments patients received as well as the cost of each drug was provided by Ferrandina, director of the department Gynecologic Oncology, and by the Medical Direction Staff of the Catholic University Sacred Heart. Drug costs do, however, not include the cost associated to day hospitalization. Neither the costs related to the diagnosis nor follow-up of adverse events are included. Costs other than drug costs are calculated separately and are included in the 'administration costs' respectively 'monitoring costs'.

The most relevant adverse events are hematological toxicities (WBC, neutrophils, hemoglobin, and platelets toxicity). In fact, according to international guidelines, patients experiencing a severe reduction of blood count levels, after chemotherapy administration, are candidate to receive a support treatment with erythropoietin (EPO) or granulocyte-colony stimulating factor (G-CSF). For these reasons, the trial conducted by Ferrandina et al. (2008) was designed in such a way that growth factor support (granulocyte colony-stimulating factor) was allowed in subsequent cycles for any patient with grade 4 neutropenia lasting more than 5 days or febrile neutropenia. In case of hemoglobin less than 9g/dL, erythropoietin or RBC transfusion was allowed at the physician's discretion. The growth factor support includes three administrations per cycle of G-CSF (Granulokine 30), which has a cost of €127,05 per administration. Erythropoietin support includes weekly EPO administrations during the whole chemotherapy cycle in which a severe hemoglobin reduction was experienced. The cost of a single administration is €400. From a strictly technical point of view, considering that the duration of a chemotherapy cycle is 28 days, if during a cycle EPO support was required, it was administered 4 times (once per week). According to the protocol used in the clinical trial conducted by Ferrandina (2008), growth factor support was required in 14% of GEM-treated patients compared with 5% of patients treated with PLD. EPO was required in 7% of patients treated with GEM compared with 4% of patients in the PLD arm.

It is important to note that white blood cells (WBC) and neutrophils are related to one another. Neutrophils serve as a major defense of the body against acute bacterial and certain fungal infections. They usually constitute about 45–75% of all white blood cells in the blood stream. When the neutrophil count falls below

500 cells per microliter, there is a large increase in the risk of infection. Without the key defense provided by neutrophils, patients have problems controlling infections and are at an increased risk of dying from an infection. The use of chemotherapy can destroy neutrophils faster than they are produced. A decreased value of neutrophils is called neutropenia. The treatment of neutropenia depends on its cause and severity. Sometimes the bone marrow recovers by itself without treatment. Patients with mild neutropenia generally have no symptoms and may not need treatment. Neutropenia can lead to infection because the bodies lack the means to fight invading organisms. When infections are developed, patients are usually hospitalized and immediately given strong antibiotics. To avoid strong infections, neutropenia has to be treated. Grade 1, 2, and 3 toxicities are usually not treated. Grade 4 toxicity, on the contrary, is treated by the administration of colony stimulating factors. This stimulates the production of white blood cells. Growth factors are synthetic versions of substances involved in stimulating red and white blood cell production. However, physicians exercise caution when prescribing these medications for patients with tumors that involve the bone marrow, because growth factors might stimulate malignant cell growth. The same treatment is used when treating white blood cell toxicity or leukopenia. In general, grade 4 toxicity requires also day hospitalization. Febrile neutropenia refers to having a fever while the white blood cell count is low. Fever indicates the presence of infection, which, in most cases, originates from germs and bacteria that resides in the intestine or skin. Febrile neutropenia is a medical emergency and must be dealt with immediately. Hours and minutes are critical.

Hemoglobin toxicity is also known as anemia. This is a strong decrease in red blood cells. Blood count tests are carried out to confirm the diagnosis of anemia. A complete blood count determines the number, size, volume, and hemoglobin content of red blood cells. If anemia is found, than it will already be treated from grade 2 toxicity or when the blood count is below 9.0 g/dL. Grade 2 and 3 toxicities are treated with EPOs. Grade 4 toxicity requires day hospitalization and RBC transfusion. Likewise, grade 1, 2 and 3 platelets toxicities or thrombocytopenia are treated with EPOs. In case of grade 4 toxicity, a platelets transfusion and day hospitalization are required. A RBC transfusion costs €153 while a platelets transfusion costs €438.

Cancer treatment may also cause some gastric toxicities. These are nausea, vomiting, and diarrhea. Nausea and vomiting are recognized as two separate and distinct conditions. Nausea is the subjective, unpleasant feeling or urge to vomit, which may or may not result in vomiting. Vomiting is the forceful expelling of the contents of the stomach and intestines through the mouth. To some, nausea is a more distressing symptom than vomiting. Chemotherapy-induced nausea and vomiting continues to afflict cancer patients to a great extent. An estimated 60–80% of patients receiving chemotherapy experience some level of nausea and vomiting. In some cases, grade 3/4 nausea and vomiting require hospitalization. Another gastric toxicity is diarrhea. When chemotherapy affects the cells lining the intestine, it can cause diarrhea (watery or loose stools). To treat grade 1/2 diarrhea, patients have to do diets to prevent or treat dehydratation and nutrition deficiencies. In case of severe diarrhea, a medicine to control the diarrhea is prescribed. This is the case with grade 3/4 toxicities. If diarrhea persists, intravenous fluids to replace the water and nutrients that were lost may be

needed. In these cases hospitalization is required. In this case study, there is a general agreement that only patients experiencing grade 3/4 nausea/vomiting should be treated. At this purpose, they were prescribed 5-HT3 antagonists (ondansetron, ganinsetron, palonosetron), one tablet per day for three days. The average cost for such a tablet is €13. Hospitalization was, however, not required. The 5-HT3 or serotonin antagonist constitutes the most effective treatment for cancer-related nausea and vomiting thus far and represents today's standard of care. These agents are designed to impede one or more of the signals that cause nausea and vomiting. 5-HT3 antagonists work both centrally and peripherally to inhibit the binding of this serotonin to the 5-HT3 receptor, thereby preventing acute nausea and vomiting associated with emetogenic chemotherapy or radiation. Owing to its longer half-life and its higher binding affinity for the 5-HT3 receptor, the newest 5-HT3 antagonist, Aloxi® (palonosetron), maintains a longer duration of action. Hence, it prevents the nausea and vomiting that occurs during the two to five days following treatment. Patients experiencing grade 3/4 diarrhea are prescribed probiotic therapy at a dosage of two vials three times per day for seven days. A single vial has a cost of €0,75. Also in this case, hospitalization is not required. Probiotic therapy is used to restore and replace the normal flora.

Tumor growth is associated with profound metabolic and neurochemical alterations, which can lead to the onset of the anorexia-cachexia syndrome. Anorexia, the loss of appetite and weight, is a common symptom in individuals with cancer. It may occur early in the disease or later, when the tumor grows and spreads. Some patients may have anorexia when they are diagnosed with cancer. Almost all patients who have widespread cancer will develop anorexia. It

is the most common cause of malnutrition in cancer patients. In certain types of cancer, there is an increased basal metabolic rate and increased total energy expenditure. This means that more energy (calories) is required to maintain current weight and lean body mass. Anorexia can also be a consequence of nausea and vomiting, which causes loss of appetite. Furthermore, cachexia can occur in cancer patients. It is a wastage syndrome that causes weakness and a loss of weight, fat, and muscle. Anorexia and cachexia can occur simultaneously. These conditions can, in turn, lead to fatigue, depression, loss of some normal functions, intolerance to treatment, and ultimately a poorer survival. Cancer-related anorexia-cachexia is highly prevalent and has a large impact on morbidity and mortality. Moreover, it affects patients' quality of life. However, its clinical relevance is frequently overlooked. The optimal therapeutic approach to deal with these adverse events should be based on changes in dietary habits, achieved via nutritional counseling. Nutrition therapy can help cancer patients get the nutrients needed to maintain body weight and strength, prevent body tissue from breaking down, rebuild tissue, and fight infection. Cancer patients frequently require a high-energy diet to prevent weight loss. Furthermore, they may also need a diet that is high in protein to prevent muscle wastage. Nutrition recommendations for cancer patients are designed to help patients cope with the effects of cancer and cancer treatment. In some cases, pharmacologic agents are given to complement diets. The most common therapeutic agents administered are appetite stimulants. There are three primary agents used to increase appetite: corticosteroids, progestational agents, and serotonin antagonists. These agents have, however, not proven to increase patients' quality of life. However, loss of appetite is psychologically and emotionally distressing to patients and caregivers and appetite stimulants seem to relieve some of the distress.[201] In the clinical

trial pursued by Ferrandina et al. (2008), three patients experienced mild anorexia. These patients were not treated. Only a change in dietary habits was advised.

Cancer-related fatigue (CRF) has not to be confused with tiredness. Tiredness happens to everyone. It is an expected feeling after certain activities or at the end of the day. Fatigue, on the contrary, is a lack of energy; an unusual of excessive whole-body tiredness not relieved by sleep. It can be acute (lasting a month or less) or chronic (lasting from one month to six months or longer). Fatigue can prevent a person from functioning normally and impacts a person's quality of life. CRF or asthenia toxicity is one of the most common adverse events of cancer therapy. It is experienced by 14% to 96% of cancer patients. Fatigue is complex and has biological, psychological, and behavioral causes. It is difficult to describe and cancer patients may express it in different ways, such as saying they feel tired, weak, exhausted, weary, worn-out, heavy, or slow. Fatigue can be described as a condition that causes distress and decreased ability to function due to a lack of energy. This cancer-related adverse event can become a very important issue in the life of cancer patients. It may affect how the individual feels about him- or herself, his or her daily activities, family care and relationships with others, and whether he or she continues with cancer therapy. Patients receiving cancer treatment may miss work or school, withdraw from friends, need more sleep and, in some cases, may not be able to think clearly or perform any physical activities because of fatigue. It is not predictable by cancer type, treatment, or stage of disease. Unfortunately, there are no treatments to combat fatigue. The best thing to do for cancer patients is to evaluate their energy level.

Chemotherapy consists of the administration of drugs that destroy rapidly reproducing cancer cells. Neoplastic cells are some of the most rapidly reproducing cells in the body but other normal cells, such as hair follicles, which contribute to the formulation of hair shaft and nails, are also rapidly reproducing. Cytotoxic agents preferentially destroy cancer cells but, unfortunately, also affect normal cells and hair follicles. This causes hair loss or alopecia, which frequently affects cancer patients. It is a transient but often psychologically devastating consequence of cancer chemotherapy. For some patients, the emotional trauma may be so severe as to lead to discontinuing or refusing treatment that might otherwise be beneficial. It is the most common side-effect of cancer treatment and often is the most distressing to the patient's self-image. It occurs 7–10 days after treatment and continues to progress over 2–3 months. Alopecia can be caused in two ways: (1) anagen effluvium, which is the most common cause and refers to the toxic effects on rapidly dividing hair cells; and (2) telogen effluvium, which refers to increased shedding of normal hair cells. Alopecia is often temporary and resolves after therapy is finished. However, some drugs can cause permanent hair loss. Unfortunately, there are no therapies to treat cancer-related alopecia. The only solution to feel more self-confident could be the use of wigs.

Neurological toxicities are rather rare but in some cases they can occur. These complications of cancer therapy may result from direct toxic effects on the nervous system, or indirectly from drug-induced metabolic derangements or cerebrovascular disorders. Their recognition is important because of potential confusion with metastatic disease, paraneoplastic syndromes or comorbid neurological disorders that do not require dose reduction or discontinuation. If the neurological disorder is caused by chemotherapy, discontinuation of the

offending agent may prevent irreversible injury. These can be sudden blindness, correctable and not correctable deafness, severe headaches and even suicidal intentions, cerebral necrosis, coma, and paralysis. However, grade 3/4 toxicities are seldom experienced. In this case study, five patients in the PLD treatment arm and one patient treated with GEM experienced grade 1 neurological toxicities. These patients were, however, not treated.

Skin rashes are frequently caused by chemotherapy. However, only grade 4 toxicity usually requires hospitalization. An important skin rash is acral erythema or palmar-plantar erythrodysesthesia (PPE) or hand-foot syndrome. It manifests as painful erythema (redness of the skin) of the palms and soles, with or without bullae (large blisters). These symptoms can be preceded by dysesthesia (altered sensation of the skin). The pain from this rash may be so severe that daily activities are limited. If recognized early, the usual course of PPE is desquamation (shedding of the outer layers of the skin) followed by re-epithelialization (re-growth of the outer layers of the skin). Since no standard therapy is currently available, the patients enrolled in the clinical trial were suggested to use moisturizers.

Mucositis or stomatitis is the painful inflammation and ulceration of the mucous membranes lining the digestive tract. It can occur anywhere along the gastro intestinal tract but oral mucositis refers to the particular inflammation and ulceration that occurs in the mouth. Oral mucositis is a common and often debilitating complication of cancer treatment. For grade 1/2 toxicity, the treatment is mainly supportive. Oral hygiene and mouthwashes are the mainstay of treatment. Mouthwashes can soothe the pain and keep food particles clear so

as to avoid infection. Patients are also encouraged to drink plenty of liquids, at least three liters a day and avoid alcohol. Citrus fruits, alcohol, and foods that are hot are all known to aggravate mucositis lesions and have, thus, to be avoided. Grade 4 toxicity, in some cases, requires hospitalization. In the clinical trial, only anti-fungal mouthwashes were prescribed. Currently, medical doctors give the mouthwash called Mycostatin, which has a cost of €6,34 for a single bottle.

Finally, liver damage could occur. When liver damage is caused by chemicals, it is called hepatotoxicity. It can be mild or severe, with severe hepatotoxicity resulting in possible hepatitis or inflammation of the liver. Liver damage is serious but treatable. Chemotherapy drugs may cause liver damage because they are toxins and they place added stress on the liver's filtering function. The liver removes toxins and chemicals from the blood stream and changes them into products that can be readily removed through the bile or urine. If toxins accumulate faster than the liver can process them, liver damage will result. There are many tests that may be used to diagnose liver damage. The most common one is a simple blood test. The primary approach is to discontinue any medications that are processed through the liver. Furthermore, medications that help reduce the symptoms of liver damage may be prescribed. Ferrandina stated that treatment is only required for grade 3/4 hepatic toxicity. She currently recommends a three days therapy with intramuscular injection of glutathione which costs €14,77 for each single vial.

Table 7.4: Frequency of adverse events, according to severity

Adverse event	PLD number (%) (% of all) of events	GEM number (%) (% of all) of event
WBC toxicity (leukopenia)		
Grade		
1	12 (41,38%) (2,77%)	8 (20,51%) (1,85%)
2	11 (37,93%) (2,54%)	14 (35,90%) (3,23%)
3	5 (17,24%) (1,15%)	13 (33,33%) (3,00%)
4	1 (3,45%) (0,23%)	4 (10,26%) (0,92%)
Total	**29 (100%)**	**39 (100%)**
Total of all events	**29 (6,69%)**	**39 (9,00%)**
Neutrophils toxicity (neutropenia)		
Grade		
1	12 (42,86%) (2,77%)	8 (21,05%) (1,85%)
2	11 (39,29%) (2,54%)	14 (36,84%) (3,23%)
3	4 (14,29%)(0,92%)	12 (31,58%) (2,77%)
4	1 (3,57%) (0,23%)	4 (10,53%) (0,92%)
Total	**28 (100%)**	**38 (100%)**
Total of all events	**28 (6,46%)**	**38 (8,78%)**
Hemoglobin toxicity (anemia)		
Grade		
1	15 (50%) (3,46%)	23 (56,10%) (5,31%)
2	12 (40%) (2,77%)	13 (31,71%) (3,00%)
3	3 (10%) (0,69%)	4 (9,76%) (0,92%)
4	0 (0%) (0%)	1 (2,44%) (0,23%)
Total	**30 (100%)**	**41 (100%)**
Total of all events	**30 (6,92%)**	**41 (9,46%)**
Platelets toxicity (thrombocytopenia)		
Grade		
1	3 (60%) (0,69%)	8 (34,78%) (1,85%)
2	2 (40%) (0,46%)	8 (34,78) (1,85%)
3	0 (0%) (0%)	3 (13,04) (0,69%)
4	0 (0%) (0%)	4 (17,39) (0,92%)
Total	**5 (100%)**	**23 (100%)**
Total of all events	**5 (1,15%)**	**23 (5,31%)**

Cutaneous toxicity (PPE)		
Grade		
1	8 (50%) (1,85%)	0 (0%) (0%)
2	4 (25%) (0,92%)	0 (0%) (0%)
3	3 (18,75%) (0,69%)	0 (0%) (0%)
4	1 (6,25%) (0,23%)	0 (0%) (0%)
Total	**16 (100%)**	**0 (0%)**
Total of all events	**16 (3,69%)**	**0 (0%)**
Neurological toxicity		
Grade		
1	5 (100%) (1,15%)	1 (100%) (0,23%)
2	0 (0%) (0%)	0 (0%) (0%)
3	0 (0%) (0%)	0 (0%) (0%)
4	0 (0%) (0%)	0 (0%) (0%)
Total	**5 (100%)**	**1 (100%)**
Total of all events	**5 (1,15%)**	**1 (0,23%)**
Hepatic toxicity (liver)		
Grade		
1	3 (60%) (0,69%)	8 (53,33%) (1,85%)
2	1 (20%) (0,23%)	4 (26,67%) (0,92%)
3	1 (20%) (0,23%)	2 (13,33%) (0,46%)
4	0 (0%) (0%)	1 (6,67%) (0,23%)
Total	**5 (100%)**	**15 (100%)**
Total of all events	**5 (1,15%)**	**15 (3,46%)**
Asthenia toxicity (fatigue)		
Grade		
1	1 (16,67%) (0,23%)	2 (33,33%) (0,46%)
2	3 (50%) (0,69%)	1 (16,67%)(0,23%)
3	2 (33,33%) (0,46%)	3 (50%) (0,69%)
4	0 (0%) (0%)	0 (0%) (0%)
Total	**6 (100%)**	**6 (100%)**
Total of all events	**6 (1,38%)**	**6 (1,38%)**

Anorexia		
Grade		
1	1 (50%) (0,23%)	0 (0%) (0%)
2	1 (50%) (0,23%)	1 (100%) (0,23%)
3	0 (0%) (0%)	0 (0%) (0%)
4	0 (0%) (0%)	0 (0%) (0%)
Total	**2 (100%)**	**1 (100%)**
Total of all events	**2 (0,46%)**	**1 (0,23%)**
Nausea		
Grade		
1	13 (56,52%) (3,00%)	16 (61,54%) (3,70%)
2	7 (30,43%) (1,62%)	9 (34,62%) (2,08%)
3	3 (13,04) (0,69%)	1 (3,85%) (0,23%)
4	0 (0%) (0%)	0 (0%) (0%)
Total	**23 (100%)**	**26 (100%)**
Total of all events	**23 (5,31%)**	**26 (6,01%)**
Vomiting		
Grade		
1	13 (56,52%) (3,00%)	17 (62,96%) (3,93%)
2	7 (30,43%) (1,62%)	9 (33,33%) (2,08%)
3	3 (13,04%) (0,69%)	1 (3,70) (0,23%)
4	0 (0%) (0%)	0 (0%) (0%)
Total	**23 (100%)**	**27 (100%)**
Total of all events	**23 (5,31%)**	**27 (6,24%)**
Diarrhea		
Grade		
1	3 (60%) (0,69%)	5 (71,43%) (1,15%)
2	1 (20%) (0,23%)	1 (14,29%) (0,23%)
3	1 (20%) (0,23%)	1 (14,29%) (0,23%)
4	0 (0%) (0%)	0 (0%) (0%)
Total	**5 (100%)**	**7 (100%)**
Total of all events	**5 (1,15%)**	**7 (1,61%)**

Mucositis (stomatitis)		
Grade		
1	12 (66,67%) (2,77%)	3 (42,86%) (0,69%)
2	5 (27,78%) (1,15%)	2 (28,57%) (0,46%)
3	1 (5,56%) (0,23)	2 (28,57%) (0,46%)
4	0 (0%) (0%)	0 (0%) (0%)
Total	**18 (100%)**	**7 (100%)**
Total of all events	**18 (4,15%)**	**7 (1,61%)**
Alopecia (baldness)		
Grade		
1	2 (66,67%) (0,46%)	4 (100%) (0,92%)
2	1 (33,33%) (0,23%)	0 (0%) (0%)
3	0 (0%) (0%)	0 (0%) (0%)
4	0 (0%) (0%)	0 (0%) (0%)
Total	**3 (100%)**	**4 (100%)**
Total of all events	**3 (0,69%)**	**4 (0,92%)**
Data missing	7	8
No toxicities	9	5

Source: Ferrandina et al. (2008) and own calculations

Grade 1 = light; grade 2 = moderate; grade 3 = serious; grade 4 = life threatening

Table 7.5: Common toxicity criteria

	Toxicity	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
Blood/bone marrow	WBC	>= 4.0	3.0-3.9	2.0-2.9	1.0-1.9	<1.0
	Platelets	WNL	75.0-normal	50.0-74.9	25.0-49.9	<25.0
	Hemoglobin	WNL	10.0-normal	8.0-10.0	6.5-7.9	<6.5
Gastro-intestinal	Nausea	None	Able to eat/ reasonable intake	Intake significantly decreased but can eat	No significant intake	/
	Vomiting	None	Episode in 24 hours	2-5 episodes in 24 hours	6-10 episodes in 24 hours	10 episodes in 24 hours or requiring parenteral support

	Diarrhea	None	Increase of 2-3 stools per day over pre-Rx	Increase 4-6 stools per day, or nocturnal stools, or moderate cramping	Increase of 7-9 stools per day or incontinence or severe cramping	Increase of >= 10 stools per day or grossly bloody diarrhea, or need for parenteral support
Stomatitis	Stomatitis	None	Painless ulcers, erythema or mild soreness	Painful erythema, edema or ulcers but can eat	Painful erythema, edema or ulcers and cannot eat	Requires parenteral or enteral support
Liver	Liver	No change from baseline	/	/	Precoma	Hepatic coma

Alopecia	Alopecia	No loss	Mild hair loss	Pronounced or total hair loss	/	/
Anorexia	Weight loss	<5.0%	5.0-9.9%	10.0-19.9%	>= 20%	/
Cutaneous	Skin	None or no change	Scattered macular or papular eruption or erythema that is asymptomatic	Scattered macular or popular eruption or erythema with pruritis or other associated symptoms	Generalized symptomatic macular, popular or vesicular eruption	Exfoliative dermatitis or ulcerating dermatitis

Neurological	Neurological/ sensory	None	Mild pares-thesias/ loss of deep tendon reflexes	Mild or moderate objective sensory loss/moderate paresthesias	Severe objective sensory loss or paresthesias that interfere with function	/
	Neurological/ motor	None or no change	Subjective weakness / no objective findings	Mild objective weakness without significant impairment of function	Objective weakness with impairment of function	Paralysis
	Neurological/ cortical	None	Mild somnolence or agitation	Moderate somnolence or agitation	Severe Somnolence, agitation, confusion, disorientation or hallucinations	Coma, seizures, toxic paralysis

	Neurological/ cerebellar	None	Slight incoordination /dys- diadokinesis	Intention tremor, dysmetria, slurred speech, nystagmus	Locomotor ataxia	Cerebellar necrosis
	Neurological/ mood	No change	Mild anxiety or depression	Moderate anxiety or depression	Severe anxiety or depression	Suicidal ideation
	Neurological/ headache	None	Mild	Moderate or severe but transient	Unrelenting and severe	/
	Neurological/ constipation	None or no Change	Mild	Moderate	Severe	Lleus>96hours

	Neurological/ hearing	None or no change	Asymptomatic/ hearing loss on audiometry only	Tinnitus	Hearing loss interfering with function but correctable with hearing aid	Deafness not correctable
	Neurological/ vision	None or no change	/	/	Symptomatic subtotal loss of vision	Blindness

Source: Radiation Therapy Oncology group

Table 7.6: Resource utilization adverse events

Adverse event	Grade	Visits	Tests	Drugs	Cost
WBC toxicity	1,2,3	/	Blood count and	/	/
(leukopenia)	4	1	chemistry evaluation	G-CSF administered 3 times/cycle	€381,15
Neutrophils	1,2,3	/	Blood count and	/	/
(neutropenia)	4	1	chemistry evaluation	G-CSF administered 3 times/cycle	€381,15
Hemoglobin toxicity	1	/	Blood count and	/	/
(anemia)	2,3	/	chemistry evaluation	EPO administered 4 times/cycle	€1.600
	4	1		RBC transfusion	€153
Platelets toxicity	1,2,3	/	Blood count and	EPO administered 4 times/cycle	€1.600
(thrombocytopenia)	4	1	chemistry evaluation	Platelets transfusion	€438

Cutaneous toxicity (palmar-plantar erythrodysesthesia or PPE)	1,2,3,4	/	No tests available	/	/
Neurological toxicity	1,2,3,4	/	No tests Available	/	/
Hepatic toxicity (liver)	1,2 3,4	/ /	Blood count and chemistry evaluation	/ a three days therapy with intramuscular injection of glutathione	/ €44,31
Asthenia toxicity (fatigue)	1,2,3,4	/	No tests available	/	/
Anorexia	1,2,3,4	/	No tests available	/	/

Nausea	1,2 3,4	/ /	No tests available	/ 5-HT3 antagonist: 1 tablet per day for 3 days	/ €39
Vomiting	1,2 3,4	/ /	No tests available	/ 5-HT3 antagonist: 1 tablet per day for 3 days	/ €39
Diarrhea	1,2 3,4	/ /	No tests available	/ Probiotic therapy: 2 vials three times a day for 7 days	/ €31,50
Mucositis (stomatitis)	1,2,3,4	/	No tests available	Mouthwash	€6,34
Alopecia (baldness)	1,2,3,4	/	No tests available	/	/

Because grade 4 leukopenia and neutropenia could have occurred simultaneously, they were considered only once. This is important to avoid double counting and overestimation of costs. This was also the case for grade 2,3 anemia and grade 1,2,3 thrombocytopenia and for grade 3,4 nausea and vomiting

Hematological toxicities are expensive to treat. Therapies that cause fewer and less severe hematological toxicities could save health care resources. Drug costs related to the treatment of therapy-related adverse events are calculated per patient. They are attained by summing the drug costs incurred for each adverse event that was experienced during the whole treatment period. Since grade 4 neutropenia and leukopenia as well as grade 1/2/3 anemia and thrombocytopenia could have occurred during the same chemotherapy cycle and because they require the same treatment, they are considered only once. This is important to avoid double counting and, thus, overestimation of costs. This was also the case with nausea and vomiting.

Managing adverse events in the PLD treatment arm costs €27.855,42 compared with €53.494,07 in the GEM patient group, which is almost twice as high as in the PLD arm. This translates into a cost of €403,70 per patient respectively €775,28. Statistical significance is, however, not reached (P = 0,062). An important drawback of the clinical trial pursued by Ferrandina et al. (2008) is that the treatment-related adverse events were not registered per cycle. Only the worst case per side-effect during the whole treatment period was registered. Consequently, the costs related to the management of adverse events are likely to be underestimated. In an ideal scenario, all adverse events per cycle would have been registered. If all adverse events during the whole treatment period had been registered, it is highly likely that the cost gap between GEM and PLD would have significantly widened.

b) Administration costs

Administration expenses are the costs incurred for drug administration and therapy. They comprise the costs of in- and outpatient visits for both cancer treatment and the management of therapy-related adverse events. Hospital costs account for a large share of total spending for cancer care. The quality and cost of health care can vary by hospital and condition. Consequently, to avoid double counting and overestimation of costs, the cost components included in the daily hospital cost have to be defined every time analysis is carried out.

In general, the differences between the costs for day clinic and one day of hospitalization are mostly sustained by the costs of drugs, invasive procedures, etc. In particular, in the field of chemotherapy administration, it is reasonable to assume that the cost for one day of hospitalization is the sum of the cost of an in- or outpatient visit and GEM/PLD costs.

Both gemcitabine and PEGylated liposomal doxorubicin require hospitalization but can easily be administered in an outpatient setting. Sometimes, however, on the basis of patients' performance status (a measure of how well a patient is able to perform ordinary tasks and carry out daily activities), or single institution policies, therapy is administered as a two days hospitalization regimen. The patients enrolled in the clinical trial were administered cancer therapy in an outpatient setting. It is interesting to consider that GEM is currently administered with the following schedule: day 1-8-15 every 28 days, whereas for PLD the administration schedule is: day 1 every 28 days. Stated otherwise, only one infusion (one administration) is required to complete a PLD cycle, whereas three

infusions (three administrations are required, one infusion weekly for the first three weeks) to complete a GEM cycle.

** Inpatient visits (hospitalization with overnight stay)*

Data provided by the Medical Direction Staff of the Catholic University Sacred Heart indicate that the cost of hospitalization amounts to €450 per day. It includes the costs of staff wages, materials, equipment, and devices, room renting, room cleaning, food and beverages, use of a common room for all cancer patients receiving cancer therapy, as well as drug costs except for gemcitabine and PEGylated liposomal doxorubicin. Drug costs other than the cost of chemotherapeutic agents have, thus, to be subtracted to avoid double counting and overestimation of costs.

Since both treatment and the management of therapy-related adverse events were administered in an outpatient setting, administration costs for inpatient visits were not incurred.

** Outpatient visits (without overnight stay)*

Data provided by the Medical Direction Staff of the Catholic University Sacred Heart indicate that the cost of an outpatient visit amounts to €350 per day. It includes personnel costs, materials, equipment, and devices, room renting during day care, room cleaning, food and beverages, the use of a common room for all

cancer patients receiving cancer therapy, as well as drug costs except for gemcitabine and PEGylated liposomal doxorubicin. Drug costs other than the cost of chemotherapeutic agents have, thus, to be subtracted to avoid double counting and overestimation of costs.

Therapy

Gemcitabine is administered on days 1, 8, and 15 of a 28-day cycle. The standard care of chemotherapy administration includes one outpatient visit per drug infusion. This translates into three outpatient visits per GEM cycle. PEGylated liposomal doxorubicin, on the contrary, requires only one administration per cycle of 28 days. Patients, thus, need only one outpatient visit per cycle.

In the field of chemotherapy, it is reasonable to assume that the cost of a day of hospitalization is the sum of the cost of one outpatient visit and GEM/PLD costs. Therefore, to avoid double counting, the costs of pre-treatment drugs have to be subtracted from the total cost of outpatient visits.

Administration costs are calculated per patient as total number of visits needed multiplied by the cost per outpatient visit. Number of visits needed depend of the number of cycles received. Finally, total pre-treatment costs are subtracted to avoid double counting.

Total administration costs are €103.845 for patients treated with PLD, whereas they are €284.625 in the GEM treatment arm. Average drug costs per patient per cycle are estimated at €672,14 for PLD and €402,69 for GEM, which include both the cost of the chemotherapeutic agents and the cost of pre-treatment. Hospital costs per cycle, on the contrary, are €345 respectively €1.035 ($P < 0.0005$). Administration costs related to drug infusion vary with treatment and are significantly higher for patients treated with GEM. When considering both drug and hospital costs, PLD costs €1.017,14 per cycle, whereas GEM costs €1.437,69. In spite of the significantly higher acquisition cost of liposomal therapy, this discrepancy is more than offset by the higher hospital costs related to GEM. It is highly likely that the inclusion of other relevant direct and indirect costs will further widen the cost gap between PLD and GEM.

Adverse events

Grade 4 hematological toxicities (WBC, neutrophils, hemoglobin, and platelets toxicity) are treated in an outpatient setting. Therapy for grade 4 WBC and neutrophils toxicity is based upon the use of granulocyte-colony stimulating factor, which is a glycoprotein, growth factor, or cytokine, produced by a number of different tissues to stimulate the bone marrow to produce granulocytes and stem cells. The costs of these substances are not included in the cost for day care. Therefore, they are not subtracted. The same applies for the treatment of grade 4 platelets and hemoglobin toxicity, which require platelets respectively RBC transfusions.

Three administrations of G-CSF (once per week during three weeks) are required to treat grade 4 WBC and neutrophils toxicity. This, in turn, requires three outpatient visits. RBC and platelets transfusions, on the contrary, require only one outpatient visit per transfusion.

Costs are calculated per patient by multiplying the total number of visits needed by the cost per outpatient visit. Since WBC and neutrophils toxicity could occur during the same chemotherapy cycle, administration costs are included only once. This is important to avoid double counting and, thus, overestimation of costs.

The average drug cost to treat adverse events per patient is estimated at €403,70 in the PLD treatment arm, compared to €775,28 for patients treated with GEM. Total administration costs amount to €1.050 in the PLD treatment group compared with €4.900 in the GEM arm. This translates into an average administration cost per patient of €15,22 respectively €71,02 (P = 0,052). Average drug and administration costs related to the management of adverse events per patient are, thus, €418,92 in the PLD treatment arm and €846,30 for patients treated with GEM. The costs for the management of adverse events are, thus, lower in the PLD treatment group, though statistical significance is not reached. If the trial had registered all adverse events during the whole treatment period, it is highly likely that the cost gap between treatment arms would have significantly widened.

c) Expected administration costs

Some drug administrations require the intervention of a nurse or practitioner. Home assistance allows the patient to spend less time in the hospital. For instance, the injection of erythropoietin (EPO) for the treatment of chemotherapy-related hematological toxicities requires the expertise of a nurse.

In the clinical trial, the incidence of grade 1, 2, and 3 platelets toxicity; grade 2/3 hemoglobin toxicity; and grade 3/4 hepatic toxicity is different between treatment arms. Treatment of hemoglobin and platelets toxicity requires four injections of EPO (once per week during the four weeks in the treatment cycle that the adverse event occurred), whereas the treatment of hepatic toxicity requires three injections of glutathione. Usually, nurses administer the drugs at the patients' home. Costs are based on the average wage cost of a registered nurse in Italy, which costs €24,30 per hour.[200] Nurses need approximately 15 minutes to visit the patient and administer treatment. It follows that, per injection, a cost of €6,075 is incurred.

Since hemoglobin and platelets toxicity could have occurred during the same chemotherapy cycle, and because they require the same treatment, they are included only once. This is important to avoid double counting. Total expected nursing costs amount to €431,33 in the PLD treatment group compared to €832,29 in the GEM patient arm. Average expected nursing costs are, thus, €6,25 per patient respectively €12,06. Expected nursing costs are significantly higher in the patient group treated with conventional therapy (P = 0,008). If all adverse events had been registered for all chemotherapy cycles, it is highly likely

that the expected nursing costs between both treatment arms would have significantly widened.

d) Monitoring costs

Cancer is initially recognized either because signs or symptoms appear or through screening. Neither of these lead to a definitive diagnosis, which usually requires the opinion of a pathologist. Women with suspected ovarian cancer are investigated with different tests. Furthermore, there are different tests to monitor patients with a history of ovarian cancer. Monitoring costs are the costs related to diagnosis and detection of disease, but also to follow-up disease progression. Costs include the personnel costs, and costs for materials, equipment, and devices.

Cancer may be suspected for a variety of reasons. Different imaging methods, such as computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, and ultrasound studies, can confirm whether a pelvic mass is present. These tests can, however, not confirm if the mass is malignant. The definitive diagnosis of ovarian malignancy is confirmed by histological examination of the cancerous tissue by a pathologist. Laparoscopies and biopsies are usually carried out. Laparoscopy uses a thin, lighted tube through which a specialist can look at the ovaries and other pelvic organs and tissues in the area around the bile duct. The tube is inserted through a small incision in the lower abdomen and sends the images of the pelvis and abdomen to a video monitor. These kinds of tests provide a view of organs that can help plan surgery or other treatments and can

help specialists confirm the stage of the cancer. Biopsies, on the contrary, are the only way to determine for certain if a growth is malignant. A sample of the mass is removed and examined under a microscope. Diagnosis serves to indicate the type of cell that is proliferating, its histological grade, genetic abnormalities, and other features of the tumor. This information is used to evaluate the prognosis of the patient and to choose the best treatment.

Moreover, follow-up care visits are required to monitor disease progression. It involves regular medical check-ups that include a review of a patient's medical history and a physical exam. A key purpose of follow-up care is to check for recurrence or metastasis. To monitor disease progression specialists make use of tumor markers, which can be extremely useful in epithelial ovarian cancer follow-up. This test, which uses the CA-125, basically measures a microscopic substance produced by the tumor, which breaks off and circulates in the blood stream. It is, however, not elevated in every patient with ovarian malignancy, and can be falsely elevated in individuals who have no diagnosis of ovarian cancer. Therefore, it is not an ideal screening test for ovarian malignancy. However, when ovarian cancer is definitely diagnosed by other tests and the CA-125 is elevated at the initial diagnosis, levels can be followed as a rough measure of treatment effect. In general, for the best possible prognosis, it should drop to normal (less than 35) within three cycles of therapy. In cases of low elevation, it may not be a good marker to gauge treatment results. There are also other tumor markers which may be used but, despite its limitations, the CA-125 is the most reliable in ovarian cancer. It can be concluded that, if the CA-125 was elevated at the beginning of therapy, if it decreases, the treatment should continue. If it continues to rise or stuck at a certain level, it may be time to re-

evaluate options. Follow-up care visits may also be helpful for identifying and addressing treatment-related problems a patient may have, or checking for problems that continue or can arise after treatment ends. However, follow-up is individualized based on the type of cancer, the type of treatment received, and the person's overall health, including possible cancer-related problems. Data about monitoring efforts – and costs – were provided by Ferrandina, director of the department Gynecologic Oncology of the academic hospital of the Catholic University Sacred Heart.

* Diagnosis

Cancer

The final diagnosis of ovarian cancer is performed at the definitive histopathological examination after primary surgery. Moreover, thorax/abdomen CT scan and pelvic ultrasound are the tests routinely performed before surgery in symptomatic patients at the first medical examination in order to pose the clinical suspicion of ovarian malignancy. Individuals treated with GEM and PLD receive the same tests to diagnose ovarian cancer. It follows that there are no cost differences between both treatment arms. Therefore, monitoring costs to diagnose ovarian cancer are not considered further.

Adverse events

Hematological toxicities (leukopenia, neutropenia, anemia, and thrombocytopenia) and hepatic toxicity are diagnosed by laboratory analyses consisting of blood count and chemistry evaluation. These tests are pursued always on every patient and they represent for physicians the adverse events diagnostic tool. White and red blood cell counts are counts of the actual number of white or red blood cells per volume of blood. Both decreases and increases can point to abnormal conditions. Hemoglobin, on the contrary, measures the amount of oxygen-carrying proteins in the blood. Finally, the platelet count is the number of platelets in a given volume of blood. Both increases and decreases can point to abnormal conditions of excess bleeding or clotting. Mean platelet volume (MPV) is a machine-calculated measurement of the average size of platelets. New platelets are larger, and an increased MPV occurs when increased numbers of platelets are being produced. MPV gives information about platelet production in the bone marrow.

For other adverse events there are no tests to diagnose a possible toxicity. In those cases, clinical examination represents the cornerstone for diagnosis and grading. Although adverse events differ in number and severity between treatment arms, blood analysis and chemistry evaluation is pursued on every patient. It follows that the average cost to diagnose treatment-related side-effects is equivalent between treatment arms. Consequently, monitoring costs to diagnose treatment-related adverse events are not considered further.

** Follow-up tests to monitor disease progression*

Cancer

Patients diagnosed with ovarian cancer are recommended transvaginal (TV) ultrasound and CA-125 serum evaluation every 3 months plus thorax/abdomen CT scan every 6 months for the first two years after the completion of primary treatment (surgery plus chemotherapy). Transvaginal ultrasound is used to examine the reproductive organs (womb, fallopian tubes and ovaries) in women. Then, for the subsequent two years, TV ultrasound and CA-125 assessment are performed every 6 months and thorax/abdomen CT scan annually. After 5 years from the completion of primary treatment further follow-up evaluation is not recommended. The previously described tests are recommended after primary treatment as well as after treatment for recurrent ovarian cancer. No differences exist between the GEM and PLD group. Since there will be no cost differences between both patient groups, costs to monitor disease progression are not considered further.

Adverse events

Only patients experiencing hematological and hepatic toxicities are monitored for follow-up. Follow-up visits consist of blood analysis and chemistry evaluation. Since these tests are only performed on patients diagnosed with a specific hematological or hepatic toxicity, monitoring costs could differ between treatments arms. Consequently, these costs have to be considered in cost

analysis. Follow-up visits are carried out every week during the treatment cycle in which the toxicity was experienced. The first week of each cycle every patient is tested for toxicity. Follow-up visits, thus, begin in week 2 to week 4. Stated otherwise, three follow-up visits are needed. A single test has a cost of €30. Monitoring costs to follow up therapy-related adverse events are calculated as total number of tests needed multiplied with the cost of a single blood test. Because different hematological and hepatic toxicities could have been experienced during the same treatment cycle, follow-up costs are included only once.

Total monitoring costs to follow-up adverse events amount to €5.580 in the GEM treatment arm compared with €4.140 in the PLD patient group. This translates into an average follow-up cost per patient of €80,70 respectively €60,88 (P = 0,002). The use of PLD, thus, saves €19,82 of resources per patient. The problem encountered here is again that only the worst case toxicity during the whole treatment period has been registered. Therefore, total costs to follow-up a specific toxicity are probably largely underestimated. If the trial had registered all adverse events per cycle, it is highly likely that the cost difference of follow-up visits between PLD and GEM had significantly widened.

e) Expected costs for cancer after care

During and after cancer treatment patients may need some additional care. Firstly, it is common for cancer patients to experience stress, depression and anxiety during and after cancer treatment. Each patient's experience with a

malignant disease is different, and the feelings, emotions and fear that these patients have are unique. The values the patients grew up with may affect how they think about and deal with the disease. Some people may feel they have to be strong and protect their friends and family. Others seek support from loved ones or turn to their faith to help them cope. Still others seek psychological assistance while others do not feel comfortable with this idea. Also worrying about the cancer coming back is an important reason of fear. This is especially true during the first year after therapy. For some patients the fear is so strong that they no longer enjoy life, sleep or eat well, or even go to follow-up visits. As time goes by, however, many survivors report that they think about their disease less often. Moreover, angry, tense, or sadness may be experienced after treatment. Usually, these feelings go away or lessen over time. For some patients, however, these emotions can become more severe. The painful feelings do not get any better, and they get in the way of daily life. These people may have a medical condition called depression. For these patients psychological assistance could give some release.

Secondly, patients could be reversibly or permanently disabled. These patients probably need rehabilitation. Cancer rehabilitation helps a patient with cancer obtain the best physical, social, psychological, and work-related functioning during and after cancer therapy. The main objective of rehabilitation is to help patients regain control over many aspects of their lives and remain as independent and productive as possible. Rehabilitation can be valuable to anyone with cancer and those recovering from cancer therapy. Cancer rehabilitation depends on many factors including type of tumor; organs affected; treatment methods such as chemotherapy, radiation therapy or surgery; and individual

capabilities and support systems. The rehabilitation team will develop an individualized program with the patient in order to address the patient's functional limitations and concerns, and achieve his or her personal objectives.

Thirdly, patients diagnosed with advanced ovarian cancer have a poor prognosis. Therefore, a large percentage of patients need palliative care. The purpose for these patients is to have the best possible quality of remaining life. In Italy, patients can be assisted in a hospital but also in their home. Home assistance of terminally ill patients is, however, an overwhelming challenge for health and social resources. Assistance is made possible due to donations. Oncology hospitals at home offer not only health care given in a traditional hospital, but also the comfort coming from assisting the patients in their environment, surrounded by their family. Although palliative home care is becoming more attractive, the hospital remains a major contributor to health care costs for terminally ill cancer patients.

Since effectiveness outcomes are similar between both treatments, no difference in the number of patients needing psychological assistance, rehabilitation, or palliation is assumed. Costs are, thus, assumed to be equal in both treatments arms. Therefore, these costs are not considered further.

The patients enrolled in the clinical trial did not require additional treatments after therapy. Finally, mild alopecia was experienced by three patients in the PLD treatment arm and four patients treated with GEM. Consequently, the costs related to the use of a wig do not differ between both treatment regimens and are, thus, not considered further.

7.3.2. Indirect costs

A diagnosis of cancer can be a major blow for the individual and family budget and strongly influences the earning capacity of those who fall ill and are called, often for months, to invest time and resources in psycho-physical treatments.

Measuring this type of loss is difficult and few, so far, have ventured. The latest example comes from a group of Canadian researchers, who interviewed 459 women. Patients were asked to explore how their financial condition had changed. In the relevant year, they did not work for seven and a half months, on average, while income was reduced by 58%. Any compensation, such as insurance, sick-leave, vacation, and pension funds, was considered. Approximately 15% of patients had received no income during that year.

The most disadvantaged women live far away from the center of care, have invasive disease, and need chemotherapy. Furthermore, the women can count on a limited social support and are usually surrounded by a small number of people able to provide practical assistance and moral support. According to Sophie Lauzier, who led the working group from Canada, the problem of absence from work and loss of income should be openly discussed before the start of therapy. This may be particularly useful for women at risk of losing income, such as part-time employees and the self-employed. Lauzier argues that a greater awareness could prepare these patients to consider al sources of financial compensation available. This would make an efficient use of social and financial resources possible which, in turn, could help them negotiate about work reorganization.

It is, however, very difficult to retrieve data. The study entitled 'Caring about women and cancer' evaluated a sample of 2000 Italian patients. The results were published in the European Journal of Cancer in 1999. More than a third of them reported a reduction of salary. Furthermore, 7% lost their job.

Moreover, a survey on relatives of patients treated at the Department of Oncohematology at the Policlinico Umberto I in Rome, has registered heavy economic losses. Twenty two percent of carers have left their job, while 13 percent was placed on a leave. At the end of the month, this resulted in a loss from several hundreds up to 1.200 euros. According to Francesco Schittulli, manager of the Department of Breast Surgical Oncology Institute of Bari and chairman of the Italian League for the Fight Against Cancer, the problem is due to a lack of organized support service. Cancer treatment may involve postoperative chemotherapy and radiation therapy sessions, exams and repeated visits for years (and not always well justified by the clinical point of view). Consequently, patients could experience additional stress, and money worries. A reflection is shared by Azzurra, a woman who had a diagnosis of breast cancer eight years and thousands of miles ago. After surgery, she had to face chemotherapy and radiation therapy, 33 sessions, each time 45 miles away from home. Furthermore, she had to go to a lot of visits, inspections, and, unfortunately, a relapse and new appointments. She worked with her husband in the family company. Since her husband accompanied her every time, he was absent from work and lost his income. Especially at the beginning, no one thinks of the economic side, the patient just wants to be cured. But when therapies take years, it makes the difference. Also Elizabetta Iannelli, vice president of the Italian cancer patients (AIMaC), states that the problems that arise in work and

social life are caused by long treatments. Returning to work after treatment may be problematic. Informed patients can, however, do several things to lighten the burden on themselves and their family. For instance, few people know that patients and family members who assist patients have periods of special leave, up to two years. Furthermore, patients have the right to go from full time to part-time. It is, thus, crucial that patients are well-informed of which rights they have in the labor market, to manage absences, reduce losses and to avoid being pushed to the margins of society. Unfortunately, this is not always the case.

Indirect costs of cancer are not directly accountable to a specific treatment regimen. They come from the loss of resources – the time and productivity lost or foregone by the patient, family, friends, and others from employment, volunteer activities, leisure and housekeeping. Furthermore, psychosocial or intangible indirect costs come from the reduced quality of life from disability, suffering and pain which force undesirable changes in lifestyle such as economic dependence, social isolation, changes or loss of job opportunities or changed conditions of living. Because indirect costs inevitably influence al programs, they should never be ignored. Despite the importance of tangible and intangible indirect costs, they are completely neglected in current cost-effectiveness studies. Indirect costs are: lost production for patients and relatives, costs related to caregivers, transportation costs, visiting costs, forgone interests on funeral expenses, non-financial costs, and administration costs for social insurance.

a) Production loss

Cancer is one of the major causes of mortality and morbidity worldwide. This results in time and productivity lost by patients and their relatives. Morbidity costs estimate the value of losses in productivity for diseased individuals. Stated otherwise, these are the losses due to temporary absence from work, and short and long term disabilities. Mortality costs, on the contrary, represent the present value of future income losses due to a premature death. Furthermore, lost production includes the value of informal care, i.e. the productivity loss of relatives caring for the patients. Economic output losses are based on the average wage cost of a fully employed employee. Although productivity losses are significant, they are seldom considered in health economic analyses. Due to a lack of methodology and scarcity of reliable data, the full impact of mortality, disability, and disease has almost never been evaluated. Consequently, studies fail to appreciate the full cost of disease.

Lost production is the value that every working individual contributes to the economy. It is the labor cost of every employee. In other words, it is the employers' costs for every employee. Economic output loss depends on the average age and income of patients. Once lost production is known, it has to be adjusted for the future by discounting future production losses. Since economic output losses are equal for all categories, both productivity losses of paid and unpaid work have to be considered.

Finally, it is important to note that decreased health conditions have an impact on economic growth by decreasing worker productivity. Since cancer survivors could suffer from a weakened physical and mental ability, it is possible that these workers produce less with a given amount of inputs. Although the impact of decreased labor productivity could be significant, it is difficult to consider in cost analysis.

The individuals enrolled in the clinical trial have an average age of 63 years. Since in Italy retirement age for the female population is set at 60 years, these individuals do not incur productivity losses. Therefore, costs of lost production equal zero. Finally, there is no reason to assume a difference in the percentage of relatives assisting the patients between both treatment arms. Consequently, economic output losses of relatives are not considered.

b) Expected costs related to caregivers

Cancer diagnosis and treatment can be very stressful for patients and their families. Patients have to cope with the emotional and physical demands of the experience. Providing care to cancer patients is a challenging and stressful task. Therefore, they often feel more comfortable and secure when being cared by professional collaborators in their home. Consequently, patients do not have to be separated from their relatives, friends, and familiar surroundings. Home care helps patients achieve this desire. It consists of a range of professional health care and supportive services delivered in the home to a person with cancer who requires assistance with daily activities. Services provided by caregivers may

include access to medical equipment, physical therapists, and social workers. Furthermore, caregivers could help with meal preparation, personal hygiene, and delivery of medication. Home care can make an enormous difference at times of stress, such as the period following surgery or during recovery from a lengthy hospitalization, or for those in need of longer-term care. Care provided in the home allows a patient the freedom to spend less time in the hospital. It also offers relief and peace of mind to caregivers caring for a family member who is in the home or in a different location.

Caregivers are, thus, all paid and unpaid individuals who help a diseased individual with his or her daily activities. Unpaid caregivers are family members. Relatives may take time off work to assist the cancer patient. Although this informal care is given free of charge, there is an economic cost because the time spent with caring can not be directed to other activities, for instance paid work, volunteer activities, or leisure. These costs are, however, not included here but in the lost production of relatives. Paid caregivers, on the contrary, are companions, personal care aides, and home health aides. These caregivers are trained to meet a variety of special health care requirements. It is assumed that caregivers are only needed during the treatment period.

Since effectiveness outcomes are similar between both treatments, there is no reason to assume a difference in the number of patients that need home assistance. Costs are, thus, assumed to be equivalent in both treatments arms. This is also the case for the management of adverse events.

c) Transportation costs

Patients incur costs when going to the hospital for treatment or visits. Transportation cost is an indirect expense for cancer patients that comprises more than only fuel costs. To understand and estimate these costs the right training and tools are required. Transportation costs in Italy are attained by looking at the tables prepared by the ACI (Automobile Club d'Italia). The validity of these tables is recognized by all business organizations in Italy. Costs are expressed as an all-inclusive cost per kilometer, and are the direct expenses incurred for the use of a vehicle, referred to some standard values of annual mileage. Annual mileage affects the operating costs that consist of various cost items. The all-inclusive cost per kilometer is used to calculate the transportation cost of patients cured for cancer and treatment-related adverse events.

The items included in the all-inclusive cost per kilometer are as follows:

- Share capital depreciation calculated on the 'maximum service of the vehicle' in kilometer – this variable varies according to the displacement and the power of the vehicle, and includes the purchase price and the cost of going 'on the road' minus the residual value considered equal to 20% of the purchase price.
- Accrued interest on investment (prime rate plus two percentage points).
- Insurance
- Ownership tax
- Fuel costs according to the approval of the individual vehicle, mediating between the different methods of measurement and 'worse'

consumption by 10% to take into account the performance degradation.

- Tires.
- Repair and maintenance on the basis of market prices for parts and labor.

The indirect costs of driving, such as accidents (government-paid cleanup, lost economic activity, etc.); state and local construction; improvements and repair; state and local highway maintenance and operations; waste disposal (highway cleanup, tire and oil removal); air pollution damage (health costs, trees, materials, etc.); external resource consumption costs (economic trade and natural resource use); road noise (property value decrease and abatement); CO_2 reduction (motor vehicles only); water pollution and hydrologic impacts; transportation diversity and equity; barrier effects on pedestrians and bicycles; land use impact costs; roadway land value; and congestion costs are not included in the cost per kilometer.

To find the transportation cost incurred by cancer patients enrolled in the clinical trial, the total number of kilometers has to be multiplied by the cost per kilometer. The cost per kilometer is based on an average car, running on diesel. In Italy, this kind of car has an all-inclusive cost per kilometer of €0,35 (automobile club d'Italia). This cost has to be multiplied by the average distance to a hospital or oncology center that treats cancers of the female reproductive system. Average distance in Italy is estimated at 12,74 km (or 25,48 km per visit). See appendix 3 for more details. Finally, the cost per visit has to be multiplied by the total number of visits.

Transportation costs are incurred every time the patient has to go to the hospital for treatment or a visit. Costs are, thus, incurred when going to the hospital for cancer treatment, treatment of chemotherapy-related adverse events, and to diagnose and follow-up cancer and side-effects. Since diagnosis of cancer and adverse events do not differ between treatment arms, these transportation costs are not considered. This is also the case for the follow-up of malignant disease.

Total transportation costs are estimated at €9.087,40 in the GEM treatment group compared to €3.816,47 for patients treated with PLD. This translates into an average transportation cost of €36,26 per GEM cycle, which is significantly higher than the cost of €15,26 in the PLD treatment group (P < 0,0005).

d) Visiting costs

Visiting costs are incurred when visiting a hospitalized patient. They include a transportation cost and a present for the patient. Since treatment of cancer and adverse events was administered in an outpatient setting, no visiting costs are incurred.

e) Forgone interest on funeral expenses

The costs of funeral arrangements vary greatly, depending on the funeral home and on the type of service and merchandise that is chosen. For instance, if the selected service involves viewing the remains, the funeral home may require

embalming and preparation of the body, which can be very expensive. Furthermore, there is a tremendous range in the price of caskets, depending on style, type of wood, lining, etc. Moreover, tariffs vary from city to city. Therefore, average quoted prices are used. The least expensive type of funeral service is direct burial or direct cremation. Depending on the preferences of the family or the deceased, the cremated remains can be scattered, or placed in an urn or mausoleum.

The costs that have to be considered are not the funeral expenses but the forgone interests on the amount of funeral expenses for the years that an individual dies before normal life expectancy. A first variable that has to be known is, thus, the average cost of a funeral. This depends on the number of interments and cremations. Like stated previously, funeral expenses may vary greatly from city to city. To that end, average quoted prices are used. Furthermore, the percentage of interments and cremations has to be known. Once the average cost of both types of funerals and also the percentage of individuals that choose for each type of funeral are known, the average cost of a funeral can be estimated. The calculation of this cost can be found in tables 7.7 and 7.8.

Table 7.7: Interment and cremation costs

Interment costs	**Cost in euro**
Various services (transports with funeral car, documents for the entombment, embellish the corpse, closing the coffin, etc.)	1.000
Coffin and accessories	1.000
Garlands	150
Pillow	160
Flowers for coffin	150
Dead pictures	75
Death letters	300
Priest	100
Tomb	1.413,18
Concession	1.250
Cemetery taxes	200
Cremation costs	**Costs in euro**
Coffin	500
Urn	440
Cremation	440
Various services	1.000
Garlands	150
Flowers for coffin	150
Dead pictures	75
Death letters	300
Priest	100
Memorial	398,62
Concession	425
Cemetery tax	200

Scattering of ashes	**Costs in euro**
Cremation costs (coffin, urn, cremation, various services, flowers for coffin)	3.005
Dead pictures ,death letters, priest)	150
In cemetery	300

Various sources[24]

In 2007, the number of cremations in Italy was 58.554 while the number of deaths amounted to 570.601. It follows that, approximately 10,30% of death individuals were cremated in that year. It is highly likely that the total number of cremations in Italy will rise and reach a total of around 30% in 2050. Of the total number of cremations, 20% requested the scattering of ashes. It follows that 2,06% of the ashes are scattered. In Italy, the scattering of ashes in the sea is rather exceptional. Therefore, it is not considered. The phenomenon of cremation is, however, growing rapidly, with a larger frequency in the north. The minimum and maximum values for 2050 are estimated to range between 25% and 35%. Among the reasons for this increase, increased secularization and lower costs compared to interment.

[24] http://www.cremazione.it/index_Page6081.htm;

http://www.codacons.it/articolo.asp?idInfo=117055;

http://www.comune.chiavari.ge.it/documenti/showdoc.aspx?idDoc=350

Table 7.8: Total average cost of a funeral

Interment	5.798,18 (89,70%)
Cremation	4.178,62 (8,24%)
Cremation with scattering in cemetery	3.155 (2,06%)
Cremation with scattering in sea	3.305 (nil)
Average	5.610,28

Next to the average cost of a funeral, which is €5.610,28, it is important to find out how many years an individual dies prematurely. This can be deduced from the mortality tables in Italy. When the age of death and the normal life expectancy are both known, the forgone interest on the funeral expenses can be estimated. Mortality tables are represented in table 7.9. This table gives the mortality table of both men and women and on average. It is obvious that in the case of ovarian cancer only the mortality table of women is of interest. The other data are presented for informative purposes.

Table 7.9: Life expectancy in Italy, per age (2007)

Number of years until death				Number of years until death			
Age	Average	Men	Women	Age	Average	Men	Women
1	80,64	77,97	83,31	59	24,81	22,73	26,88
2	79,66	76,99	82,32	60	23,94	21,89	25,98
3	78,67	76,00	81,33	61	23,07	21,06	25,08
4	77,86	75,01	80,34	62	22,22	20,24	24,19
5	76,69	74,02	79,35	63	21,37	19,44	23,30
6	75,70	73,03	78,36	64	20,54	18,64	22,43
7	74,71	72,04	77,37	65	19,72	17,87	21,56
8	73,71	71,05	76,37	66	18,90	17,10	20,70
9	72,72	70,05	75,38	67	18,10	16,34	19,85
10	71,72	69,06	74,38	68	17,30	15,59	19,00
11	70,73	68,06	73,39	69	16,51	14,85	18,16
12	69,73	67,07	72,39	70	15,72	14,12	17,32
13	68,74	66,08	71,40	71	14,95	13,40	16,50
14	67,75	65,09	70,41	72	14,20	12,71	15,69
15	66,76	64,10	69,42	73	13,46	12,03	14,89
16	65,78	63,12	68,43	74	12,74	11,38	14,10
17	64,80	62,15	67,44	75	12,04	10,74	13,33
18	63,82	61,18	66,45	76	11,36	10,13	12,58
19	62,84	60,21	65,46	77	10,69	9.53	11,85
20	61,86	59,24	64,48	78	10,05	8,96	11,14
21	60,89	58,28	63,49	79	9,42	8,40	10,44
22	59,91	57,32	62,50	80	8,83	7,87	9,78
23	58,94	56,36	61,51	81	8,25	7,37	9,13
24	57,97	55,40	60,53	82	7,71	6,89	8,52
25	56,99	54,44	59,54	83	7,19	6,44	7,93
26	56,02	53,48	58,55	84	6,69	6,00	7,37

27	55,04	52,52	57,56	85	6,23	5,61	6,85
28	54,07	51,56	56,57	86	5,79	5,22	6,35
29	53,10	50,60	55,59	87	5,34	4,82	5,86
30	52,12	49,63	54,60	88	4,91	4,44	5,38
31	51,15	48,67	53,62	89	4,51	4,09	4,93
32	50,17	47,71	52,63	90	4,19	3,81	4,56
33	49,20	46,74	51,65	91	3,93	3,60	4,25
34	48,22	45,78	50,66	92	3,71	3,44	3,98
35	47,25	44,82	49,68	93	3,52	3,30	3,73
36	46,28	43,85	48,70	94	3,30	3,13	3,47
37	45,31	42,89	47,72	95	3,09	2,95	3,23
38	44,34	41,93	46,74	96	2,89	2,77	3,00
39	43,38	40,98	45,77	97	2,71	2,61	2,80
40	42,41	40,02	44,79	98	2,51	2,43	2,59
41	41,45	39,07	43,82	99	2,31	2,24	2,37
42	40,49	38,12	42,85	100	2,10	2,04	2,15
43	39,53	37,17	41,89	101	1,90	1,85	1,95
44	38,58	36,23	40,93	102	1,75	1,70	1,79
45	37,63	35,29	39,96	103	1,61	1,57	1,65
46	36,68	34,35	39,00	104	1,49	1,45	1,53
47	35,74	33,42	38,05	105	1,38	1,34	1,41
48	34,80	32,49	37,10	106	1,28	1,24	1,31
49	33,86	31,57	36,15	107	1,19	1,15	1,22
50	32,93	30,65	35,20	108	1,11	1,08	1,14
51	32,01	29,75	34,26	109	1,04	1,01	1,06
52	31,08	28,84	33,32	110	0,98	0,95	1,00
53	30,17	27,94	32,39	111	0,92	0,89	0,94
54	29,26	27,05	31,46	112	0,87	0,84	0,89
55	28,35	26,17	30,53	113	0,82	0,80	0,84

56	27,45	25,29	29,61	114	0,78	0,76	0,80
57	26,56	24,43	28,69	115	0,75	0,73	0,76
58	25,68	23,57	27,78	116	0,72	0,70	0,73

Source: Istat, available on http://demo.istat.it/unitav/index.html?lingua=ita

The years stated in table 7.9 represent the number of years that an individual dies prematurely. These numbers have to be considered when calculating the forgone interest on funeral expenses. To that end, an interest rate of 2% and a discount rate of 4% are used. Resources could be invested in other projects. The alternative is to invest these resources in government bonds which are currently leading to an interest rate of 2%. Furthermore, there is a time preference to use resources. Individuals prefer to use resources now instead of in the future. To account for this preference, a discount rate of 4% annually is being used. Table 7.10 shows the discounted forgone interest due to a premature death. A detailed overview of calculation can be found in appendix 2 of this chapter.

Table 7.10: Discounted forgone interest on funeral expenses due to premature death

Age death patient	NPV of total forgone interests for women dying prematurely	Age death patient	NPV of total forgone interests for women dying prematurely
1 year	4.670,04	51 year	2.819,70
2 year	4.647,21	52 year	2.760,58
3 year	4.623,93	53 year	2.700,30
4 year	4.600,20	54 year	2.638,84
5 year	4.576,00	55 year	2.576,17
6 year	4.551,33	56 year	2.512,28
7 year	4.526,17	57 year	2.447,14
8 year	4.500,52	58 year	2.380,72
9 year	4.474,37	59 year	2.312,99
10 year	4.447,70	60 year	2.243,93
11 year	4.420,51	61 year	2.243,93
12 year	4.392,79	62 year	2.173,52
13 year	4.364,52	63 year	2.101,73
14 year	4.335,70	64 year	2.028,53
15 year	4.306,31	65 year	1.953,90
16 year	4.276,35	66 year	1.877,81
17 year	4.245,80	67 year	1.800,22
18 year	4.214,65	68 year	1.800,22
19 year	4.182,89	69 year	1.721,11
20 year	4.150,51	70 year	1.640,45
21 year	4.117,49	71 year	1.558,22
22 year	4.083,83	72 year	1.474,37
23 year	4.049,51	73 year	1.388,87
24 year	4.014,51	74 year	1.388,87

25 year	3.978,83	75 year	1.301,70
26 year	3.942,45	76 year	1.212,82
27 year	3.905,35	77 year	1.122,20
28 year	3.867,53	78 year	1.122,20
29 year	3.828,96	79 year	1.029,80
30 year	3.789,64	80 year	935,58
31 year	3.749,55	81 year	935,58
32 year	3.708,67	82 year	839,52
33 year	3.666,99	83 year	741,57
34 year	3.624,49	84 year	741,57
35 year	3.581,16	85 year	641,71
36 year	3.536,98	86 year	641,71
37 year	3.491,93	87 year	539,89
38 year	3.446,00	88 year	539,89
39 year	3.399,17	89 year	436,07
40 year	3.351,42	90 year	436,07
41 year	3.302,74	91 year	436,07
42 year	3.253,51	92 year	330,22
43 year	3.202,90	93 year	330,22
44 year	3.151,29	94 year	330,22
45 year	3.098,67	95 year	330,22
46 year	3.098,67	96 year	330,22
47 year	3.045,02	97 year	222,26
48 year	2.990,32	98 year	222,26
49 year	2.934,55	99 year	222,26
50 year	2.877,68	100 year	222,26

Table 7.10 indicates that the forgone interest decreases with the individuals' age. This is a direct consequence from the fact that less years are lost when patients' have a higher age. Furthermore, the discount rate is higher than the interest rate. This also leads to a decreasing forgone interest with higher ages.

Median age at recurrence is 63 years for both treatment groups, while median overall survival favored patients treated with PLD. OS was 56 weeks in the PLD patient group compared with 51 weeks in the GEM treatment arm (P = 0,048). Age at death is, thus, 64 years for patients treated with PLD compared with 63 years for GEM-treated patients. Forgone interest amount to €2.028,53 respectively €2.101,73.

f) Non-financial costs

In cost-effectiveness analysis, the intangible or psychosocial costs, i.e. emotional distress, the cost of pain and suffering from disease and its treatment, the reduced quality of life and resulting lifestyle changes, can be significant. Since these intangible costs affect health and well-being, they are conceptualized in the quality of life estimates of cancer patients. In turn, these estimates are used to calculate the quality-adjusted survival that reflects both morbidity and mortality. However, a reduction in intangible costs does not free up resources that could be used to produce other goods or services. Therefore, it is difficult to estimate their impact. Non-financial costs can easily extent to patients' relatives who could experience a decreased quality of life due to lower standards of living as a result

of emotional distress and depression. These costs are, however, not considered in cost analysis.

g) Administration costs for health insurance

According to the World Health Organisation (WHO), in 2000, Italy had the world's second overall best health care system in the world, coming after France. This was in respect to health status, fairness in financial contribution, and responsiveness to people's expectations of the health system. In 1978 Italy adopted a tax-funded universal health care system called 'National Health Service' which in Italian is called 'Servizio Sanitario Nazionale' or SSN. It was modelled on the British system. The SSN covers general practice (distinct between adult and pedriatic practice), outpatient and inpatient treatment, and the cost of most, but not all, drugs and sanitary ware. The government sets fundamental levels of care, called 'Livelli Essenziali di Assistenza' or LEA, which cover all necessary treatments, which the state must guarantee to all for free or for a 'ticket', a share of the costs. The public system has also the duty of prevention at place of work and in the general environment. A private sector also exists, with a minority role in medicine. To avoid the high costs related to private health, private health insurance is necessary. With a private insurance, it is possible to freely choose a doctor or specialist, and treatments at private hospitals, thus, avoiding the long queues just to get an appointment for medical specialists. Private hospitals in Italy have the best accommodations.

Since the differences in administration costs between both patient arms are nil, they are not considered further in cost analysis. Nevertheless, it is important to list this cost since it could be significantly different.

7.3.3. Overview of direct and indirect costs

Table 7.11: Direct costs of cancer treatment and the management of adverse events

	PLD	GEM
Drug costs		
Study drug (P < 0,0005)	€202.617,08 €2.814,13/patient €667,14/patient/cycle	€107.289,32 €1.511,11/patient €387,69/patient/cycle
Pre-treatment (P < 0,0005)	€1.505 €20,34/patient €5/patient/cycle	€4.125 €58,11/patient €15/patient/cycle
Drugs to treat adverse events (P = 0,062)	€27.855,42 €403,70/patient	€53.494,07 €775,28/patient
Administration costs		
Inpatient visits for treatment	/	/
Outpatient visits for treatment (P < 0,0005)	€103.845 €1.403,31/patient	€284.625 €4.008,80/patient

	€345/patient/cycle	€1.035/patient/cycle
Inpatient visits for adverse events	/	/
Outpatient visits for adverse events (P = 0,052)	€1.050 €15,22/patient	€4.900 €71,02/patient
Expected administration cost		
Expected nursing costs (P = 0,008)	€431,33 €6,25/patient	€832,29 €12,06/patient
Monitoring costs		
Diagnosis of cancer	=	=
Follow-up of cancer	=	=
Diagnosis of adverse events	=	=
Follow-up of adverse events (P = 0,002)	€4.140 €60,88/patient	€5.580 €80,70/patient
Costs for after care		
Psychological assistance – cancer	=	=
Psychological assistance – adverse events	=	=
Rehabilitation – cancer	=	=
Rehabilitation – adverse events	=	=
Palliative care – cancer	=	=
Palliative care – adverse events	=	=

Additional therapy – cancer	/	/
Additional therapy – adverse events	/	/
Wigs	=	=
Total direct costs	**€341.443,83**	**€460.845,68**

Table 7.12: Indirect costs of cancer treatment and the management of adverse events

	PLD	**GEM**
Lost production		
Patients	/	/
Relatives	=	=
Cost for caregivers	=	=
Transportation costs (P < 0,0005)	€3.816,47 €55,31/patient	€9.087,40 €131,70/patient
Visiting costs	/	/
Forgone interests on funeral expenses (P = 0,048)	€154.168,28 €2.028,53/patients	€168.833,21 €2.101,73/patient
Non-financial losses	Included in QALYs	Included in QALYs
Administration costs of insurance	=	=
Total indirect costs	**€157.984,75**	**€177.920,61**

7.4. Results

Cost-effectiveness analysis (CEA) is a form of economic evaluation that compares the costs and effects of two or more health care interventions. It is a technique for selecting among competing treatments wherever resources are limited. Since in the health care sector it may be inappropriate to monetize health effects, cost-effectiveness studies are the most suitable form of economic evaluation. The objective of these kinds of studies is to help decision-makers in health care priority setting. Typically, CEA uses a ratio where the denominator represents the health effects of a specific health care intervention, while the numerator expresses the cost of obtaining these benefits. The denominator may be expressed in different ways. However, since cancer affects patients' length but also, and even more so, quality of life, the number of quality-adjusted life years (QALYs) is the preferred outcome measure. Moreover, it enables inter-technology comparisons among studies. The cost-effectiveness ratio has to be interpreted as the cost per acquired quality-adjusted life week.

7.4.1. Quality-adjusted survival

Quality-adjusted survival per patient is calculated by multiplying overall survival with quality of life estimates. To estimate the quality of life, 121 patients completed the QoL questionnaire at baseline and at least one post-baseline questionnaire. Before treatment, the difference in quality of life was not statistically different between patients of both treatment arms. In post-baseline assessments, however, significantly higher QoL scores were found in patients

treated with PLD.[196] Since quality of life is only assessed during treatment, the quality of life after chemotherapy is based on the last quality of life estimate.

Salvage therapy increased survival by 1.453,945 to 2.017,065 quality-adjusted weeks, depending on the treatment received. Quality-adjusted survival was higher for patients treated with liposome therapy, though statistical significance was not reached (P = 0,331).

7.4.2. Costs and cost-effectiveness

Average drug costs for cancer therapy per patient per cycle are estimated at €402,69 for GEM compared with €672,14 for PLD (P < 0,0005). This cost includes both the cost of study drug and pre-treatment. The higher drug costs associated with liposome therapy are due to its acquisition cost (€335,54/20mg vs. €28,58/200mg). When only taking drug costs into account conventional therapy seems to be far more cost-effective than the nanotechnology-based alternative (€73,79/QALW vs. €100,45/QALW). However, due to fewer and less severe hematological toxicities in the PLD treatment arm, drug costs related to the management of adverse events are estimated at €403,70 per patient in the PLD patient group and €775,28 in the GEM arm (P = 0,062). Statistical significance is, however, not reached. When considering drug costs related to cancer treatment and the therapies' downstreaming events, conventional treatment remains similarly cost-effective as liposome therapy (€113,42/QALW vs. €115/QALW).

Moreover, hospitalization costs are as high as €1.035 per patient per cycle in the GEM treatment arm, whereas they are only €345 for patients treated with PLD ($P < 0,0005$). Differences in administration costs are due to dosing frequency (1 versus 3 times per cycle of 28 days for PLD respectively GEM). Administration costs related to the management of adverse events are also lower in the PLD treatment arm. They are estimated at €15,22 compared to €71,02 for patients treated with GEM ($P = 0,062$). When considering drug and administration costs, liposome therapy becomes significantly more cost-effective than conventional treatment (€167,01/QALW vs. €312,55/QALW).

Expected administration costs differ between patient arms. Expected nursing costs are estimated at €431,33 for patients treated with PLD compared with €832,29 in the GEM treatment group ($P = 0,008$). The inclusion of this cost slightly widens the gap between conventional and nanotechnology-based cancer therapeutics (€167,23/QALW vs. €313,12/QALW)

Monitoring costs to diagnose ovarian cancer and adverse events as well as those to follow-up ovarian malignancy are equal in both treatment arms. Therefore, they are not considered further. The cost to follow-up therapy-related adverse events is €80,70 for patients treated with GEM. They are significantly higher than in the PLD treatment arm, which are estimated at €60,88 ($P = 0,002$). This strengthens the cost-effectiveness of PLD (€169,28/QALW vs. €316,96/QALW).

There is no reason to assume a difference in the number of patients needing after care (psychological assistance, rehabilitation, additional therapies, and palliation) between patient groups.

Since patients are at retirement age, there is no lost production in terms of GDP. Furthermore, there is no reason to assume a difference in the number of relatives caring between treatment groups. This is also the case for the administration costs of health insurance.

The effectiveness between GEM and PLD treated patients is found to be equivalent. Consequently, there is no reason to assume a difference in patients needing caregivers between both patient groups. The cost of caregivers is equivalent between both arms and is ,thus, not considered in cost analysis.

Transportation costs differ between patient arms. They are significantly higher for patients treated with GEM. They are estimated at €9.087,40 whereas they amount to €3.816,47 for patients in the PLD treatment arm ($P < 0,0005$). Furthermore, visiting costs are not incurred because hospitalizations with overnight stays are not required.

The forgone interest on funeral expenses was different between treatment groups. Time preference was incorporated by discounting future interests (2%) by 4% annually. Forgone interests are estimated at €154.168,28 in the PLD treatment arm, while it is higher for patients treated with GEM, €168.833,21.

Finally, the intangible indirect costs monetizing pain, suffering, and reduced quality of life, or non-financial costs, are included in the quality of life estimates.

Average indirect costs per patient are, thus, estimated at €2.083,84 for patients treated with PLD and €2.233,43 in the GEM patient group. The inclusion of tangible indirect costs further widens the gap between the conventional and the nanotherapeutic, in favor of the latter (€247,60/QALW vs. €439,33/QALW).

The CEA shows that PLD is more cost-effective than GEM. The cost-effectiveness ratio of PLD is €247,60 per quality-adjusted week (€12.875,20/QALY) compared to €439,33 (€22.845,16/QALY) for GEM. The study, thus, suggests that the nanotechnology-based cancer agent PLD is more cost-effective than GEM, and thus helps saving scarce health care resources. Although its acquisition cost is significantly higher, this cost difference is more than offset by other direct and indirect costs.

7.5. Cost and cost-effectiveness analysis from a hospital perspective

This section recalculates the costs and cost-effectiveness of gemcitabine and PEGylated liposomal doxorubicin for the treatment of advanced ovarian cancer from a hospital perspective, i.e. only direct hospital costs are considered. Total cost comprises drug, administration, and monitoring costs related to cancer treatment and the management of chemotherapy-related adverse events.

Table 7.13: Direct hospital costs

Drug costs
Cancer drugs
Pre-treatment
Drugs to treat adverse events
Administration costs
Inpatient visits
Outpatient visits
Monitoring cost
Diagnosis
Follow-up

Direct hospital costs were calculated in section 7.3. Drug costs for cancer therapy, which include both the cost of chemotherapeutic agents and pre-treatment, are estimated at €672,14 per patient per cycle in the PLD treatment arm, whereas they amount to €402,69 in the GEM patient group. Chemotherapy costs are, thus, significantly higher for liposomal therapy. Drug costs related to the management of adverse events are, on the contrary, lower in the PLD treatment group. They are estimated at €403,70 per patient compared with €775,28 for patients treated with GEM, though statistical significance is not reached.

Hospitalization is not required. Cancer and adverse events are treated in an outpatient setting. Administration costs are €345 per patient per cycle in the PLD treatment group, whereas they are €1.035 in the patient group treated with GEM. Hospital costs are, thus, significantly higher in the GEM treatment group.

Likewise, administration costs associated with the management of adverse events are higher for patients treated with GEM, namely €71,02 per patient compared to €15,22 for PLD. These costs are, however, not statistically significant. When considering drug and administration costs, liposome therapy is more cost-effective than the conventional one.

Finally, monitoring costs to follow-up adverse events amount to €60,88 per patient treated with liposomal therapy. Monitoring costs in the GEM treatment arm are €80,70 per patient and are, thus, significantly higher.

Total direct hospital costs related to cancer therapy are, thus, €1.017,14 per patient per cycle in the PLD treatment arm, whereas they amount to €1.437,69 for patients treated with GEM. The direct hospital costs associated to the management of adverse events are estimated at €479,80 respectively €927,00.

An important drawback found in current cost-effectiveness studies is that effectiveness outcomes are almost never adjusted with quality of life estimates. Since cancer affects length but also, and even more so, quality of life, it is crucial to adjust effectiveness outcomes with quality of life estimates. Moreover, quality of life estimates incorporate the non-financial costs of pain, suffering and reduced quality of life of cancer patients. Therefore, quality of life could have a large impact on the cost-effectiveness of cancer therapies. Tables 7.14 and 7.15 give the cost-effectiveness of gemcitabine and PEGylated liposomal doxorubicin with and without considering quality of life.

Table 7.14: Cost-effectiveness of both treatments without considering patients' quality of life

Treatment	Cost (1)	Effectiveness (2)	Cost-effectiveness (3) = (1)/(2)
GEM	€460.013,41	2.999 weeks	€153,39/week
PLD	€341.012,50	3.612 week	€94,41/week

Table 7.15: Cost-effectiveness of both treatments adjusted with patients' quality of life

Treatment	Cost (1)	Effectiveness (2)	Cost-effectiveness (3) = (1)/(2)
GEM	€460.013,41	1.453,945 QALWs	€316,40/QALW
PLD	€341.012,50	2.017,065/QALW	€169,06/QALW

Tables 7.14 and 7.15 indicate that adjusting effectiveness outcomes with quality of life estimates has a large impact on cost-effectiveness outcomes. When adjusting effectiveness outcomes with quality of life estimates, the cost-effectiveness of GEM increases from €153,39 per week to €316,40. The cost-effectiveness ratio, thus, increases with 106,27%. The cost-effectiveness ratio of PLD increases from €94,41 to €169,06. This translates into an increase of only 79,07%. When considering all direct and indirect costs of cancer, the cost-

effectiveness ratio of GEM increases further from €316,40 to €439,33 (+38,85%), while the CER of PLD rises from €169,06 to €247,60 (+46,45%).

Liposomal therapy remains the most cost-effective treatment regimen under all scenarios. However, adjusting the effectiveness outcomes with quality of life estimates gives a more accurate estimate because it incorporates the non-financial costs of cancer and treatment. Including all costs results in better estimates. Despite its high acquisition cost, more accurate results favor liposomal therapy. Considering only direct hospital costs penalizes more expensive but also more effective and less toxic nanotechnology-based therapies. Consequently, it is important to calculate the cost-effectiveness of cancer therapies from a social perspective, including all relevant direct and indirect costs and adjusting effectiveness outcomes with quality of life estimates. Only then, cost-effectiveness studies can lead to effective choices in health care.

7.6. Uncertainty analyses

The reliability of the data set is tested by Monte Carlo resampling.[25] The results derived from 1000 resamples are then divided by 1000 to estimate the probability that a similar study would yield a cost-saving result. Monte Carlo analysis, thus, results in the number of cases that we have absolute confidence that a study like the one carried out would find PEGylated liposomal doxorubicin

[25] Bootstrapping is used to assess whether the distribution of characters has been influenced by stochastic effects. Datasets are generated by randomly sampling the original character matrix to create new matrices of the same size as the original.

to be cost saving compared to Gemcitabine. The software to perform Monte Carlo analysis was not available.

7.7 Discussion

Spiraling health care costs are a major concern for health administrators allocating scarce resources. Therefore, difficult allocation decisions have to be made. Responsible use of limited resources requires a clear understanding of the cost-effectiveness of health practices. The objective of cost-effectiveness analyses is to aid in resources allocation decisions. Economic evaluation is distinct but complementary to epidemiological approaches to the assessment of disease burden. It addresses policy issues concerning the consequences of disease. Economic assessments provide useful information to decision-makers and health administrators about the overall magnitude of economic losses and their distribution across a number of cost drivers. However, to serve as a basis for setting priorities and allocating resources, economic analyses must be based upon effectiveness studies. Consequently, it is possible to identify strategies able to reduce health care costs.

When investigating the existing literature, it is possible to conclude that there is a significant degree of methodological heterogeneity. Moreover, a lot of conceptual deficiencies are found in current studies. In light of these problems, this chapter calculates costs and cost-effectiveness from a social perspective. To provide the overall cost of cancer, direct and indirect costs are summed. Cost-effectiveness studies can provide important arguments for investments in a

specific health care intervention. However, such analysis should always be pursued in a credible and scientific way. CEA aims at setting priorities among different health care interventions. In turn, this requires information on costs and effects of these interventions.

The treatment of advanced ovarian cancer is a significant and costly problem. Ovarian cancer is the most prevalent cause of death due to gynecological malignancy. Because the disease remains asymptomatic for a long period, women usually already have advanced stage disease when diagnosed. Therefore, prognosis is poor, with a 5-years survival rate of 25–30% in metastatic disease.[196] Since ovarian malignancy is rarely curable, prolongation of life while preserving quality of life is the most realistic objective.[196,202] Decisions concerning incurable diseases are often difficult. Furthermore, cost is usually not the most pressing concern. The decision of a new health practice hinges upon an objective calculation of effectiveness and associated cost.[203] Therefore, treatments that are less toxic, more tolerable, and economically viable are required.

The study evaluated the health economic effects and consequences of PEGylated liposomal doxorubicin and gemcitabine. PLD was associated with significantly lower resource utilization than GEM. Direct and indirect cost savings associated with PLD are primarily achieved through a less frequent treatment plan, less hospital visits, and fewer and less severe hematological toxicities. Base case analysis, thus, demonstrates that the use of PEGylated Liposomal Doxorubicin improves the effectiveness, costs, and cost-effectiveness compared with gemcitabine. The superior cost-effectiveness of PLD is the result of fewer direct and indirect costs (with the exception of acquisition cost) and high quality of life

estimates. Liposome therapy (first generation nanotechnology-based cancer agent) provides the best balance between clinical efficacy, safety, and costs.

In spite of the importance of CEA, it serves only as an input to decision-making.[204] Economic data differ among countries and their stability changes over time. Therefore, conclusions based on the information of one country can not be used in another one. International differences in health care delivery should always be considered. Moreover, not only drug and hospital costs change over time, the introduction of new technologies may also cause changes in medical practices in inpatient care and consequent costs.[12]

The strength of the model is the comprehensive cost taxonomy including all relevant direct and indirect costs. Furthermore, intangible indirect costs that monetize pain, suffering, and a reduced quality of life are conceptualized in the quality of life estimates. One drawback of the clinical trial, however, is that therapy-related adverse events were not registered per cycle. Only the worst case per side-effect during the entire chemotherapy period was registered. Consequently, the costs related to the management of adverse events are likely to be underestimated. In an ideal scenario, all side-effects during the whole chemotherapy period would have been registered.

It is crucial to emphasize the importance of cost-effectiveness studies for future generation nanotechnology-based cancer therapies, as well as target-based agents. Since these treatments will probably be very effective but also have very high acquisition costs, it will be crucial to demonstrate their cost-effectiveness by including all relevant direct and indirect costs as well as quality of life estimates.

However, it is extremely difficult to retrieve clinical data. The scarcity of clinical data is a major impediment for any serious cost-effectiveness study. Up to now, health economics studies do not cover many innovations coming from nanoparticle-based therapeutics. Rendering the necessary data available is an absolute precondition for the success of economic studies and, in turn, nanomedicines. To that end, governments should invest resources in making more easily available clinical data of high quality. This is a fundamental step in promoting new drugs and medical technologies.

7.8 Conclusions

The current study evaluated the health economic effects and consequences of PEGylated liposomal doxorubicin versus gemicitabine. The liposomal agent was associated with significantly lower health-care resource utilization. The current trial indicates that both treatments have a similar efficacy. However, the liposomal agent is associated with fewer and less severe adverse events and a better quality of life after therapy. It was demonstrated that PLD has a more favorable cost-effectiveness profile. In spite of the significantly higher acquisition cost of the liposomal agent, this discrepancy is more than offset by other direct and indirect costs of cancer. Different from previous studies addressing this problem, this study estimates costs from a social perspective rather than considering only treatment-related costs.

Appendix 1: Statistical output

Drug costs to treat ovarian cancer: Multiple regression model

Fig. 7.1: Coefficients – Final model

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	Collinearity Statistics	
		B	Std. Error	Beta			Tolerance	VIF
1	(Constant)	923,493	27,473		33,615	,000		
	1 = PLD 2 = GEM	-253,850	17,908	-,745	-14,175	,000	,924	1,082
	0 = no discontinuation 1 = discontinuation	-92,247	27,880	-,174	-3,3 09	,001	,924	1,082

a. Dependent Variable: Drugcostpercyle

Fig. 7.2: Interaction effects – Final model

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			Correlations			Collinearity Statistics	
		B	Std. Error	Beta	t	Sig.	Zero-order	Partial	Part	Tolerance	VIF
1	(Constant)	853,713	37,329		22,870	,000					
	1 = PLD 2 = GEM	-222,283	22,322	-,801	-9,958	,000	-,902	-,905	-,710	,786	1,272
	CenteredCA	,021	,016	,099	1,331	,197	-,154	,273	,095	,926	1,080
	Centereddurat	,070	,904	,008	,077	,939	,099	,016	,006	,475	2,104
	CenteredOS	,068	,302	,023	,224	,825	,193	,048	,016	,465	2,152
	0 = no discontinuation 1 = discontinuation	-94,862	26,245	-,287	-3,614	,002	-,609	-,610	-,258	,806	1,241
2	(Constant)	910,469	21,784		41,795	,000					
	1 = PLD 2 = GEM	-231,299	11,302	-,834	-20,466	,000	-,902	-,985	-,643	,595	1,679
	CenteredCA	,332	,059	1,561	5,657	,000	-,154	,843	,178	,013	77,019

Centereddurat	2,741	1,130	,314	2,425	,031	,099	,558	,076	,059	16,932
CenteredOS	-,701	,173	-,243	-4,052	,001	,193	-,747	-,127	,276	3,626
0 = no discontinuation 1 = discontinuation	-139,223	17,647	-,422	-7,889	,000	-,609	-,910	-,248	,346	2,890
centeredPFI_duration	-,096	,023	-,240	-4,127	,001	,365	-,753	-,130	,292	3,420
centeredCA125_TTR	,050	,008	1,324	5,908	,000	,005	,854	,186	,020	50,799
centeredCA125_duration	,015	,003	1,066	4,441	,001	-,058	,776	,140	,017	58,308
centeredCA125_PFS	-,020	,003	-1,885	-6,269	,000	-,202	-,867	-,197	,011	91,478
centeredCA125_OS	,001	,001	,279	2,645	,020	-,159	,591	,083	,089	11,268
centeredTTR_duration	-1,441	,196	-1,289	-7,351	,000	,017	-,898	-,231	,032	31,090
centeredduration_OS	,101	,016	,976	6,211	,000	,126	,865	,195	,040	24,977
centeredduration_PFS	-,192	,050	-,874	-3,822	,002	-,001	-,727	-,120	,019	52,902
centeredTTR_PFS	,780	,109	1,760	7,149	,000	-,036	,893	,225	,016	61,345

a. Dependent Variable: Drugcostpercyle

Fig. 7.3: Model summary

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	,811[a]	,657	,652	100,75154

a. Predictors: (Constant), 0 = no discontinuation 1 = discontinuation, 1 = PLD 2 = GEM

Fig. 7.4: Anova

ANOVA[b]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	2610942,163	2	1305471,082	128,607	,000[a]
	Residual	1360216,917	134	10150,873		
	Total	3971159,080	136			

a. Predictors: (Constant), 0 = no discontinuation 1 = discontinuation, 1 = PLD 2 = GEM

b. Dependent Variable: Drugcostpercyle

Pre-treatment costs for cancer therapy

Normality test

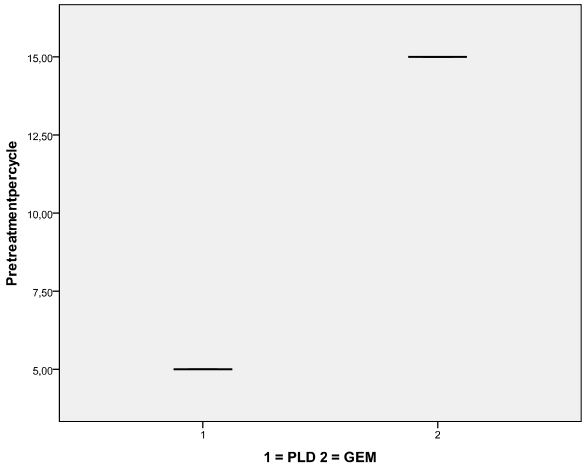
Fig. 7.5: Case processing summary of pre-treatment costs

Case Processing Summary

	1 = PLD 2 = GEM	Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
Pretreatment per cycle	dimension1 1	76	100,0%	0	,0%	76	100,0%
	2	77	100,0%	0	,0%	77	100,0%

Histogram

Fig. 7.6: Histogram of pre-treatment costs



The histogram indicates that pre-treatment costs are not normally distributed. The histogram does not present a symmetrical distribution. Therefore, the Mann-Whitney test is used to test for significance.

Test of significance: Mann-Whitney test

Fig. 7.7: Mann-Whitney test for pre-treatment costs for cancer therapy

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Pretreatmentpercycle is the same across categories of 1 = PLD 2 = GEM.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

The result suggests that there is a statistically significant difference between the distributions of pre-treatment costs among treatment arms. Since P < 0,0005 the data does provide statistically significant evidence of a difference in pre-treatment costs between both treatment arms.

Drug cost to treat adverse events

Normality tests

Fig. 7.8: Case processing summary of drug costs to treat adverse events

Case Processing Summary

1 = PLD 2 = GEM		Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
Cost AEs	dimension1 1	69	90,8%	7	9,2%	76	100,0%
	2	69	89,6%	8	10,4%	77	100,0%

Fig. 7.9: Descriptive statistics for drug costs to treat adverse events

Descriptives

	1 = PLD 2 = GEM			Statistic	Std. Error
CostAEs	1	Mean		403,7017	84,99761
		95% Confidence Interval for Mean	Lower Bound	234,0916	
			Upper Bound	573,3118	
		5% Trimmed Mean		352,6528	
		Median		,0000	
		Variance		498497,002	
		Std. Deviation		706,04320	
		Minimum		,00	
		Maximum		1987,49	
		Range		1987,49	
		Interquartile Range		822,16	
		Skewness		1,220	,289
		Kurtosis		-,494	,570
	2	Mean		775,2764	100,10954
		95% Confidence Interval for Mean	Lower Bound	575,5109	

	Mean	Upper Bound	975,0418	
	5% Trimmed Mean		750,8954	
	Median		31,5000	
	Variance		691512,444	
	Std. Deviation		831,57227	
	Minimum		,00	
	Maximum		2038,00	
	Range		2038,00	
	Interquartile Range		1600,00	
	Skewness		,177	,289
	Kurtosis		-1,958	,570

Fig 7.10: Tests of normality for drug costs to treat adverse events

Tests of Normality

	1 = PLD 2 = GEM	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
CostAEs	dimension 1	,448	69	,000	,555	69	,000
	1 2	,334	69	,000	,693	69	,000

a. Lilliefors Significance Correction

Histogram

Fig. 7.11: Histogram for the distribution of drug costs to treat adverse events related to PLD

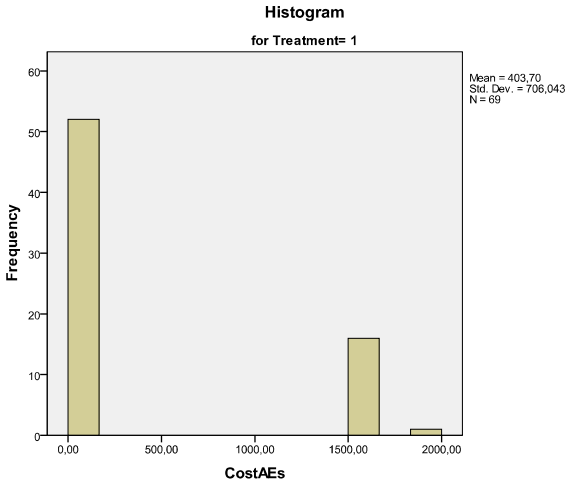
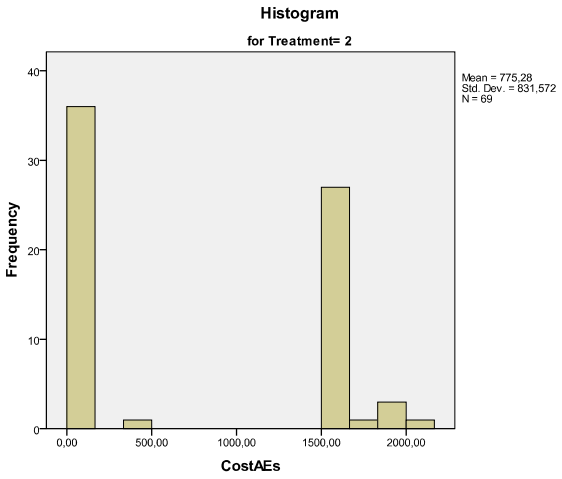


Fig 7.12: Histogram for the distribution of drug costs to treat adverse events for GEM



Q-Q plot

Fig. 7.13: Q-Q plot for the distribution of drug costs to treat adverse events for PLD

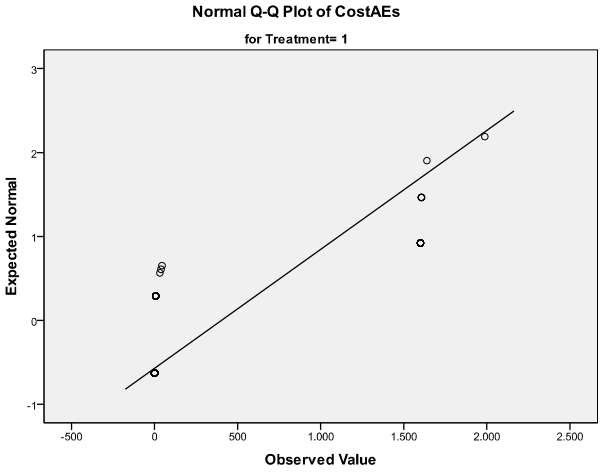
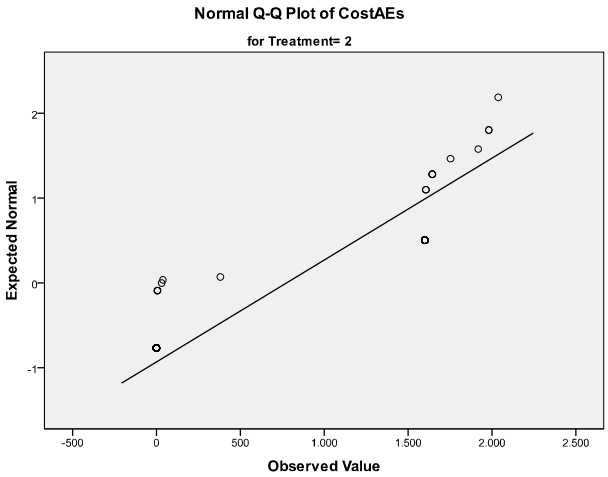


Fig. 7.14: Q-Q plot for the distribution of drug costs to treat adverse events for GEM



The Kolmogorov-Smirnov test indicates that drug costs to treat adverse events are not normally distributed (0,000 < 0,05). This result is confirmed by the histograms and Q-Q plots for both treatment regimens. The histograms do not present a symmetrical distribution. Also the Q-Q plots for both treatments do not show linear relationships between the observed values and the expected values from a normal distribution. Therefore, the Mann-Whitney test is used to test for significance.

Test of significance: Mann-Whitney test

Fig 7.15: Mann-Whitney test for costs to treat adverse events

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of CostAEs is the same across categories of 1 = PLD 2 = GEM.	Independent-Samples Mann-Whitney U Test	.062	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

The result suggests that there is no statistically significant difference between the distributions of drug costs to treat adverse events among treatment arms. Since P > 0,05 the data does provide a not statistically significant evidence of a difference in the drug costs to treat adverse events between both treatment arms.

Outpatient visits for cancer treatment

Normality tests

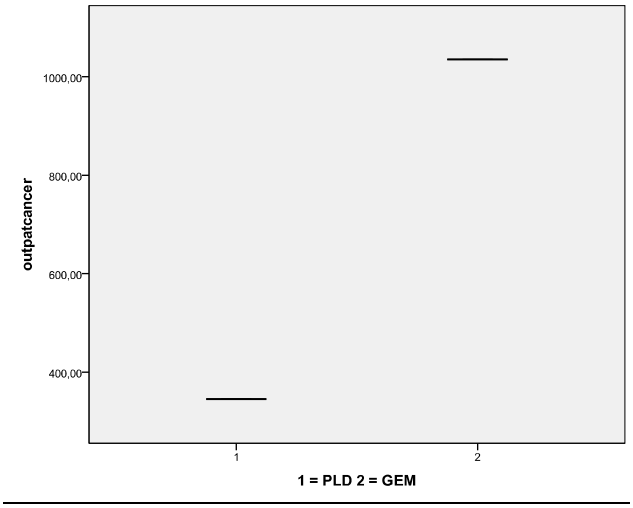
Fig. 7.16: Case processing summary for outpatient visits for cancer

Case Processing Summary

1 = PLD 2 = GEM		Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
Outpat cancer	dimension1 1	76	100,0%	0	,0%	76	100,0%
	2	77	100,0%	0	,0%	77	100,0%

Histogram

Fig. 7.17: Histogram for outpatient visit costs for cancer treatment



The histogram indicates that costs for outpatient visits are not normally distributed. The histogram does not present a symmetrical distribution. Therefore, the Mann-Whitney test is used to test for significance.

Test of significance: Mann-Whitney test

Fig. 7.18: Mann-Whitney test for outpatient visit costs related to cancer treatment

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of outpatcancer is the same across categories of 1 = PLD 2 = GEM.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

The result suggests that there is a statistically significant difference between the distributions of outpatient visit costs related to cancer treatment among treatment arms. Since P < 0,05 the data does provide statistically significant evidence of a difference in the outpatient costs between both treatment arms.

Outpatient visits for the treatment of chemotherapy-related adverse events

Normality tests

Fig. 7.19: Case processing summary of outpatient visit costs related to the management of adverse events

Case Processing Summary

	1 = PLD 2 = GEM	Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
outpatadverse	dimension 1	70	92,1%	6	7,9%	76	100,0%
	1 2	69	89,6%	8	10,4%	77	100,0%

Fig. 7.20: Descriptive statistics of outpatient visit costs related to the management of adverse events

Descriptives

	1 = PLD 2 = GEM			Statistic	Std. Error
outpatadverse	1	Mean		15,0000	15,00000
		95% Confidence Interval for Mean	Lower Bound	-14,9242	
			Upper Bound	44,9242	
		5% Trimmed Mean		,0000	
		Median		,0000	
		Variance		15750,000	
		Std. Deviation		125,49900	
		Minimum		,00	
		Maximum		1050,00	
		Range		1050,00	
		Interquartile Range		,00	
		Skewness		8,367	,287
		Kurtosis		70,000	,566
	2	Mean		71,0145	30,29772

	95% Confidence Interval for Mean	Lower Bound	10,5563	
		Upper Bound	131,4726	
	5% Trimmed Mean		20,5717	
	Median		,0000	
	Variance		63338,662	
	Std. Deviation		251,67173	
	Minimum		,00	
	Maximum		1050,00	
	Range		1050,00	
	Interquartile Range		,00	
	Skewness		3,586	,289
	Kurtosis		11,629	,570

Fig. 7.21: Test of normality for outpatient visit costs related to the management of adverse events

Tests of Normality

	1 = PLD 2 = GEM	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
outpatadverse	dimension 1	,533	70	,000	,098	70	,000
	1 2	,524	69	,000	,300	69	,000

a. Lilliefors Significance Correction

Histogram

Fig. 7.22: Histogram for the distribution of outpatient visit costs related to the management of adverse events for PLD

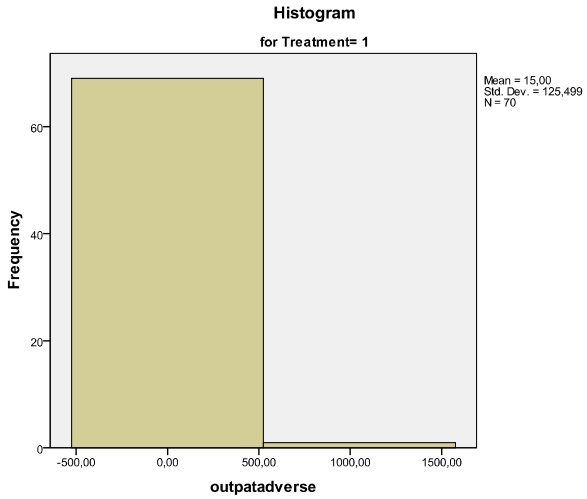
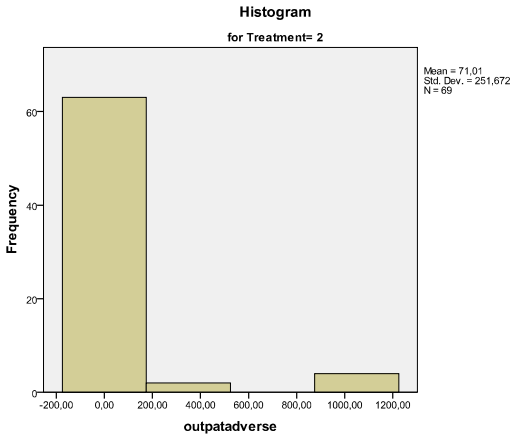


Fig. 7.23: Histogram for the distribution of outpatient visit costs related to the management of adverse events for GEM



Q-Q plot

Fig. 7.24: Q-Q plot for the outpatient visit costs related to the management of adverse events for PLD

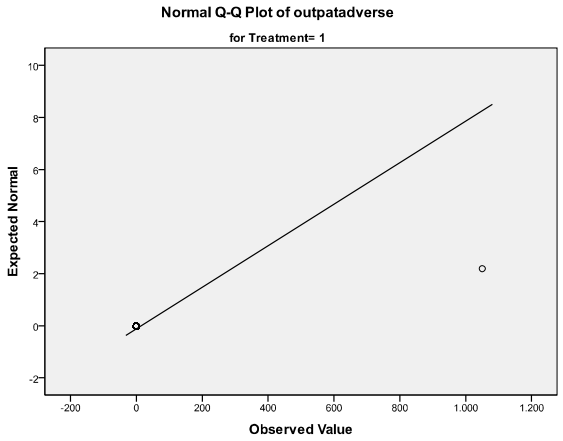
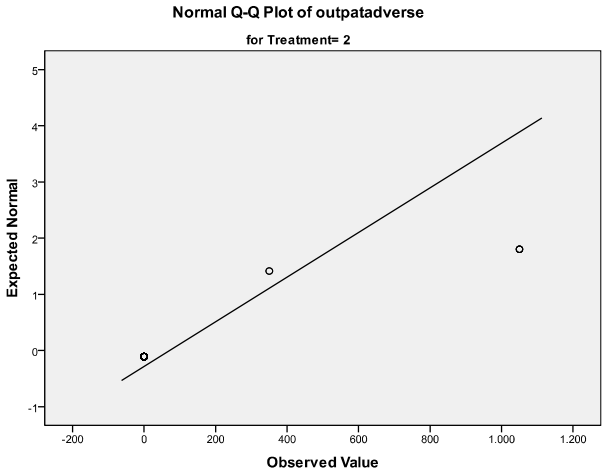


Fig. 7.25: Q-Q plot for outpatient visit costs related to the management of adverse events for GEM



The Kolmogorov-Smirnov test indicates that the outpatient visit costs related to the management of adverse events are not normally distributed (0,000 < 0,05). This result is confirmed by the histograms and Q-Q plots for both treatment regimens. The histograms do not present a symmetrical distribution. Also the Q-Q plots for both treatments do not show linear relationships between the observed values and the expected values from a normal distribution. Therefore, the Mann-Whitney test is used to test for significance.

Test of significance: Mann-Whitney test

Fig. 7.26: Mann-Whitney test for the outpatient visit costs related to the management of adverse events

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of outpatadverse is the same across categories of 1 = PLD 2 = GEM.	Independent-Samples Mann-Whitney U Test	.052	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

The result suggests that there is no statistically significant difference between the distributions of outpatient visit costs related to the management of adverse events among treatment arms. Since P > 0,05 the data does provide a not statistically significant evidence of a difference in the outpatient visit costs between both treatment arms.

Costs to follow-up adverse events

Normality tests

Fig. 7.27: Case processing summary for costs to follow-up adverse events

Case Processing Summary

	1 = PLD 2 = GEM	Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
FollowupAEs	dimension 1	68	89,5%	8	10,5%	76	100,0%
	1 2	69	89,6%	8	10,4%	77	100,0%

Fig. 7.28: Descriptive statistics for costs to follow-up adverse events

Descriptives

	1 = PLD 2 = GEM			Statistic	Std. Error
FollowupAEs	1	Mean		60,8824	5,14383
		95% Confidence Interval for Mean	Lower Bound	50,6152	
			Upper Bound	71,1495	
		5% Trimmed Mean		62,6471	
		Median		90,0000	
		Variance		1799,210	
		Std. Deviation		42,41709	
		Minimum		,00	
		Maximum		90,00	
		Range		90,00	
		Interquartile Range		90,00	
		Skewness		-,772	,291
		Kurtosis		-1,448	,574
	2	Mean		80,8696	3,29522
		95% Confidence Interval for Mean	Lower Bound	74,2941	

	Mean	Upper Bound	87,4451	
	5% Trimmed Mean		84,8551	
	Median		90,0000	
	Variance		749,233	
	Std. Deviation		27,37212	
	Minimum		,00	
	Maximum		90,00	
	Range		90,00	
	Interquartile Range		,00	
	Skewness		-2,699	,289
	Kurtosis		5,442	,570

Fig.7.29: Tests of normality for costs to follow-up adverse events

Tests of Normality

	1 = PLD 2 = GEM	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
FollowupAEs	dimension 1 1	,430	68	,000	,590	68	,000
	2	,529	69	,000	,346	69	,000

a. Lilliefors Significance Correction

Histogram

Fig. 7.30: Histogram for costs to follow-up adverse events for PLD

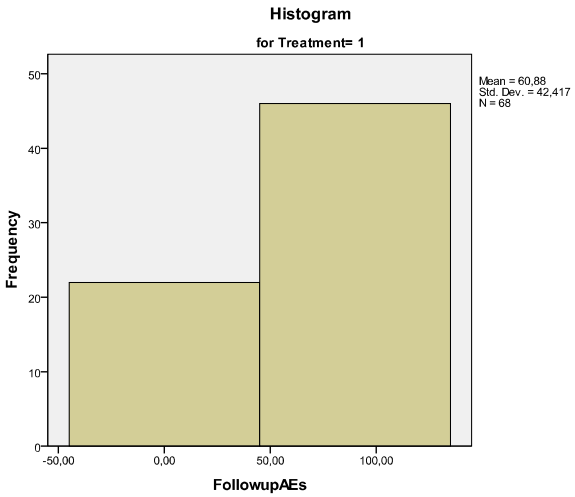
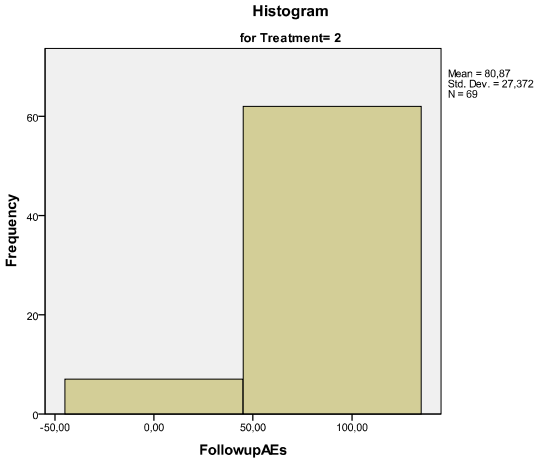


Fig. 7.31: Histogram for costs to follow-up adverse events for GEM



Q-Q plot

Fig. 7.32: Q-Q plot for the costs to follow-up adverse events for PLD

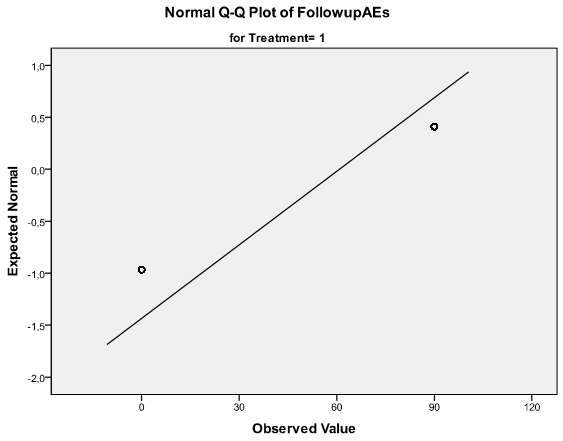
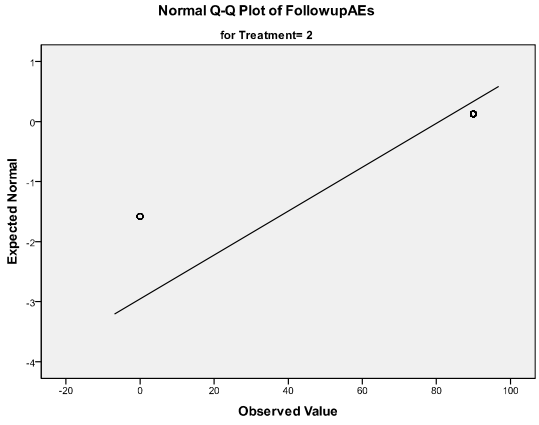


Fig. 7.33: Q-Q plot for the costs to follow-up adverse events for GEM



The Kolmogorov-Smirnov test indicates that the costs to follow-up adverse events are not normally distributed (0,000 < 0,005). This result is confirmed by the histograms and Q-Q plots for both treatment regimens. The histograms do not present a symmetrical distribution. Also the Q-Q plots for both treatments do not show linear relationships between the observed values and the expected values from a normal distribution. Therefore, the Mann-Whitney test is used to test for significance.

Test of significance: Mann-Whitney tests

Fig.7.34: Mann-Whitney test for the costs to follow-up adverse events

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of FollowupAEs is the same across categories of 1 = PLD 2 = GEM.	Independent-Samples Mann-Whitney U Test	.002	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

The result suggests that there is a statistically significant difference between the distributions of costs to follow-up related adverse events among treatment arms. Since P < 0,05 the data does provide a statistically significant evidence of a difference in the follow-up costs between both treatment arms.

Transportation costs

Normality tests

Fig. 7.35: Case processing summary for transportation costs

Case Processing Summary

	1 = PLD 2 = GEM	Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
Transportationcost	dimension 1	69	90,8%	7	9,2%	76	100,0%
	1 2	69	89,6%	8	10,4%	77	100,0%

Fig. 7.36: Descriptive statistics for transportation costs

Descriptives

	1 = PLD 2 = GEM			Statistic	Std. Error
Transportationcost	1	Mean		15,2630	,77554
		95% Confidence Interval for Mean	Lower Bound	13,7155	
			Upper Bound	16,8106	
		5% Trimmed Mean		14,7910	
		Median		13,3800	
		Variance		41,501	
		Std. Deviation		6,44212	
		Minimum		8,92	
		Maximum		35,67	
		Range		26,75	
		Interquartile Range		13,38	
		Skewness		,993	,289
		Kurtosis		,892	,570
	2	Mean		35,9675	,88458
		95% Confidence Interval for	Lower Bound	34,2024	

	Mean	Upper Bound	37,7327	
	5% Trimmed Mean		35,3616	
	Median		33,5100	
	Variance		53,991	
	Std. Deviation		7,34789	
	Minimum		26,74	
	Maximum		62,43	
	Range		35,69	
	Interquartile Range		8,92	
	Skewness		1,470	,289
	Kurtosis		2,564	,570

Fig. 7.37: Tests of normality for transportation costs

Tests of Normality

	1 = PLD 2 = GEM	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
Transportationcost	dimension 1	,171	69	,000	,830	69	,000
	1 2	,199	69	,000	,848	69	,000

a. Lilliefors Significance Correction

Histogram

Fig. 7.38: Histogram of transportation costs for PLD

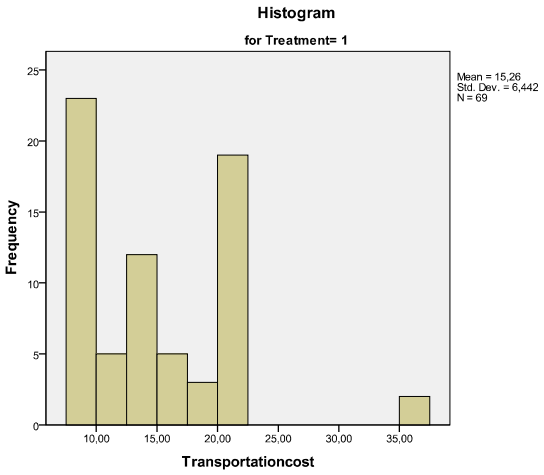
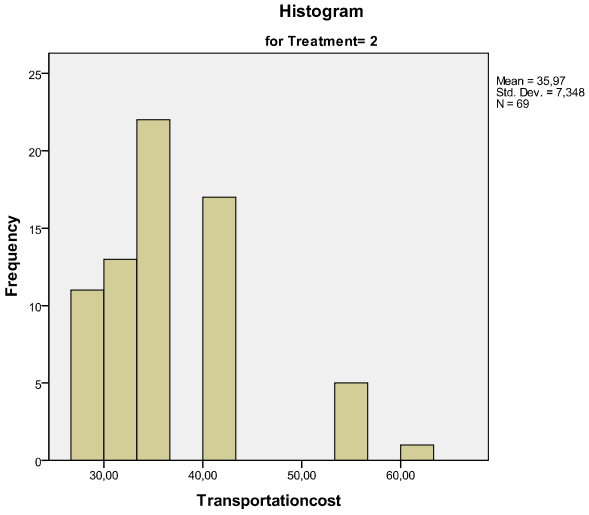


Fig. 7.39: Histogram of transportation costs for GEM



Q-Q plot

Fig. 7.40: Q-Q plot of transportation costs for PLD

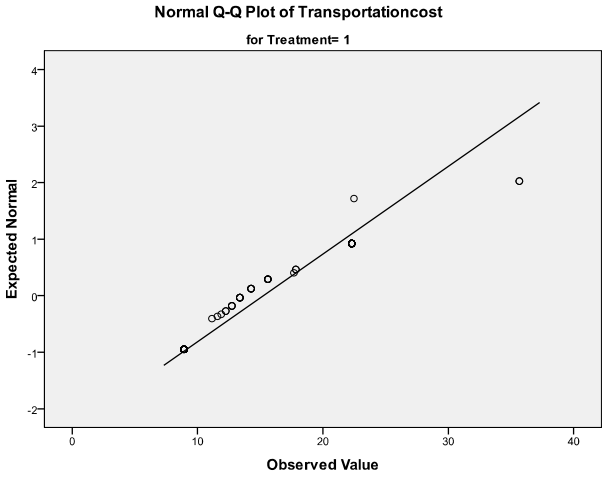
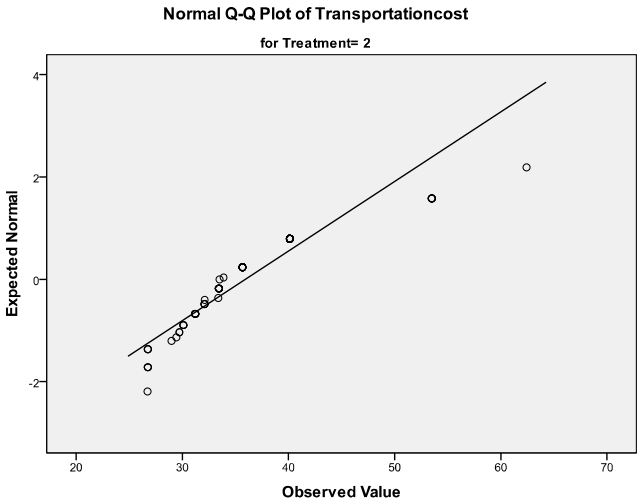


Fig. 7.41: Q-Q plot of transportation costs for GEM



The Kolmogorov-Smirnov test indicates that transportation costs are not normally distributed (0,000 < 0,005). This result is confirmed by the histograms and Q-Q plots for both treatment regimens. The histograms do not present a symmetrical distribution, they both have a long tail towards the right. Also the Q-Q plots for both treatments do not show linear relationships between the observed values and the expected values from a normal distribution. Therefore, the Mann-Whitney test is used to test for significance.

Test of significance: Mann-Whitney test

Fig. 7.42: Mann-Whitney test for transportation costs

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Transportationcost is the same across categories of 1 = PLD 2 = GEM.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

The result suggests that there is a statistically significant difference between the distributions of transportation costs among treatment arms. Since P < 0,05 the data does provide statistically significant evidence of a difference in the transportation costs between both treatment arms.

Expected nursing costs

Normality test

Fig. 7.43: Case processing summary of expected nursing costs related to the management of adverse events

Case Processing Summary

	1 = PLD 2 = GEM	Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
NursingAE	1	69	90,8%	7	9,2%	76	100,0%
	2	69	89,6%	8	10,4%	77	100,0%

Fig.7.44: Descriptive statistics of expected nursing costs related to the management of adverse events

Descriptives

	1 = PLD 2 = GEM			Statistic	Std. Error
NursingAE	1	Mean		6,2512	1,27892
		95% Confidence Interval for Mean	Lower Bound	3,6991	
			Upper Bound	8,8032	
		5% Trimmed Mean		5,5957	
		Median		,0000	
		Variance		112,858	
		Std. Deviation		10,62347	
		Minimum		,00	
		Maximum		24,30	
		Range		24,30	
		Interquartile Range		21,27	
		Skewness		1,127	,289

		Kurtosis	-,738	,570
	2	Mean	12,0622	1,63295
		95% Confidence Interval for Mean	Lower Bound	8,8037
			Upper Bound	15,3207
		5% Trimmed Mean	11,1717	
		Median	,0000	
		Variance	183,991	
		Std. Deviation	13,56433	
		Minimum	,00	
		Maximum	42,53	
		Range	42,53	
		Interquartile Range	24,30	
		Skewness	,443	,289
		Kurtosis	-1,230	,570

Fig.7.45: Tests of normality for expected nursing costs related to the management of adverse events

Tests of Normality

	1 = PLD 2 = GEM	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
NursingAE	1	,461	69	,000	,552	69	,000
	2	,349	69	,000	,710	69	,000

a. Lilliefors Significance Correction

Histogram

Fig. 7.46: Histogram of the distribution of expected nursing costs related to PLD

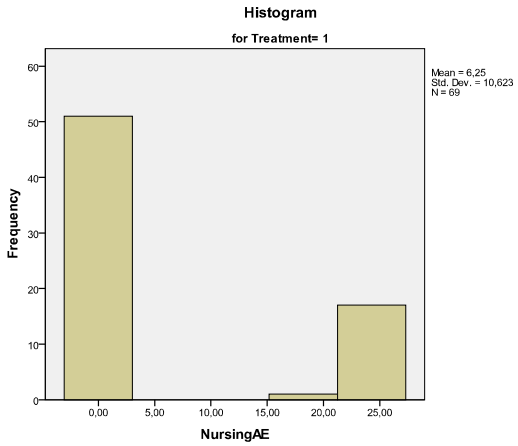
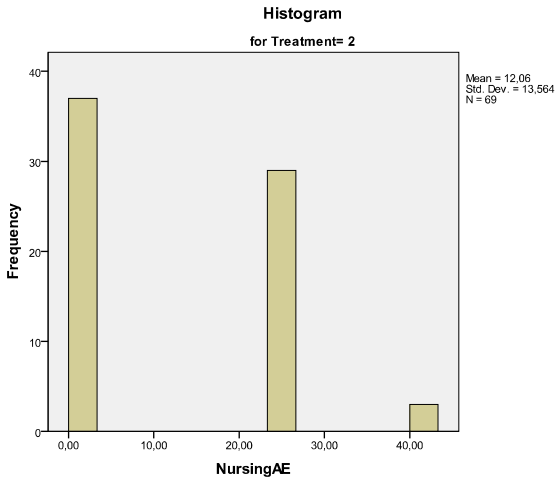


Fig. 7.47: Histogram of the distribution of expected nursing costs related to GEM



Q-Q plots

Fig. 7.48: Q-Q plot of expected nursing costs related to PLD

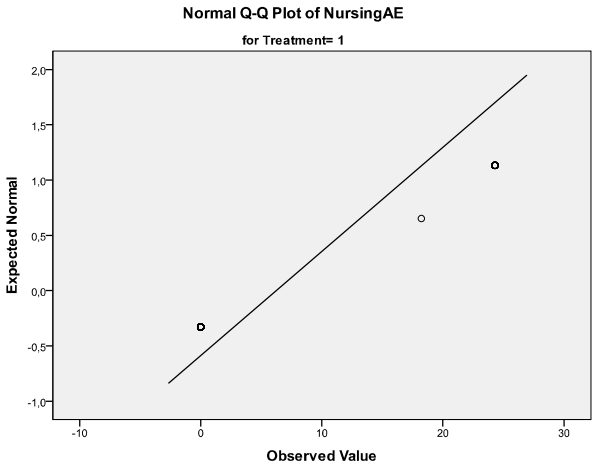
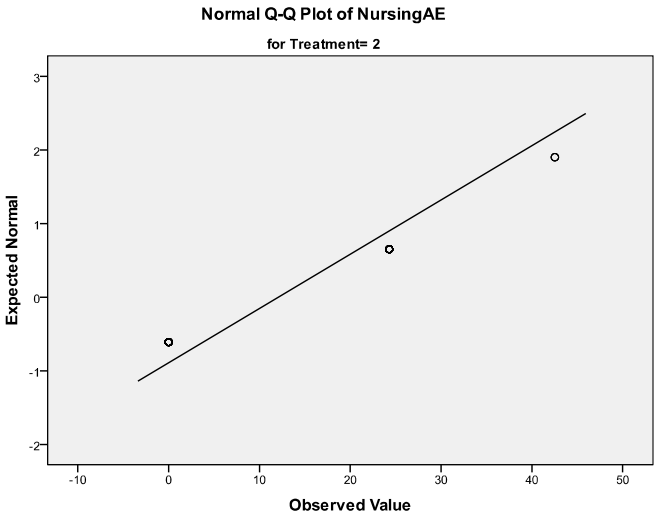


Fig. 7.49: Q-Q plot of expected nursing costs related to GEM



The Kolmogorov-Smirnov test indicates that expected nursing costs are not normally distributed (0,000 < 0,005). This result is confirmed by the histograms and Q-Q plots for both treatment regimens. The histograms do not present a symmetrical distribution, they both have a long tail towards the right. Also the Q-Q plots for both treatments do not show linear relationships between the observed values and the expected values from a normal distribution. Therefore, the Mann-Whitney test is used to test for significance.

Test of significance: Mann-Whitney test

Fig. 7.50: Mann-Whitney test of expected nursing costs

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of NursingAE is the same across categories of 1 = PLD 2 = GEM.	Independent-Samples Mann-Whitney U Test	.008	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

The result suggests that there is a statistically significant difference between the distributions of expected nursing costs among treatment arms. Since P < 0,05 the data does provide statistically significant evidence of a difference in the expected nursing costs between both treatment arms.

Quality-adjusted survival

Normality tests

Fig. 7.51: Case processing summary of quality-adjusted survival

Case Processing Summary

1 = PLD 2 = GEM		Cases					
		Valid		Missing		Total	
		N	Percent	N	Percent	N	Percent
AdjustedOS	1	64	84,2%	12	15,8%	76	100,0%
	2	61	79,2%	16	20,8%	77	100,0%

Fig 7.52: Descriptive statistics of quality-adjusted survival

Descriptives

	1 = PLD 2 = GEM			Statistic	Std. Error
AdjustedOS	1	Mean		31,51352	3,722078
		95% Confidence Interval for Mean	Lower Bound	24,07554	
			Upper Bound	38,95149	
		5% Trimmed Mean		28,93516	
		Median		20,43200	
		Variance		886,647	
		Std. Deviation		29,776621	
		Minimum		,501	
		Maximum		122,015	
		Range		121,514	
		Interquartile Range		34,505	
		Skewness		1,348	,299
		Kurtosis		,993	,590
	2	Mean		23,83516	2,389499
		95% Confidence Interval for	Lower Bound	19,05545	

	Mean	Upper Bound	28,61487	
	5% Trimmed Mean		22,87046	
	Median		17,35800	
	Variance		348,292	
	Std. Deviation		18,662583	
	Minimum		1,837	
	Maximum		64,028	
	Range		62,191	
	Interquartile Range		30,809	
	Skewness		,670	,306
	Kurtosis		-,849	,604

Fig. 7.53: Tests of normality for quality-adjusted survival

Tests of Normality

	1 = PLD 2 = GEM	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
		Statistic	df	Sig.	Statistic	df	Sig.
AdjustedOS	1	,165	64	,000	,831	64	,000
	2	,151	61	,001	,891	61	,000

a. Lilliefors Significance Correction

Histograms

Fig. 7.54: Histogram distribution of quality-adjusted survival related to PLD

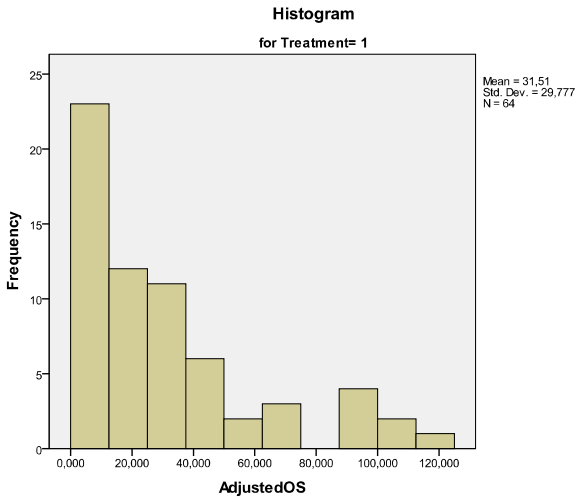
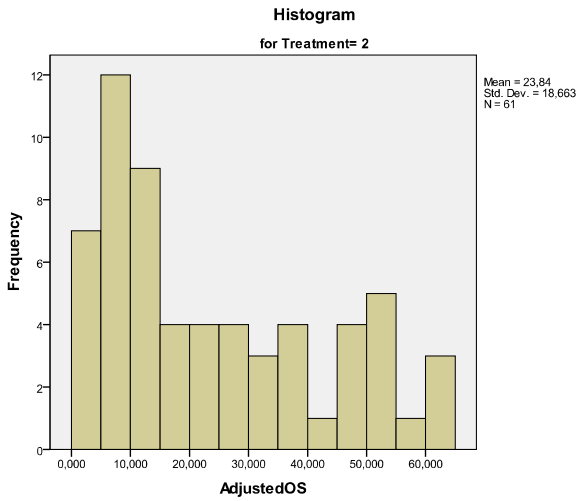


Fig 7.55: Histogram distribution of quality-adjusted survival related To GEM



Q-Q plots

Fig. 7.56: Q-Q plot of quality-adjusted survival related to PLD

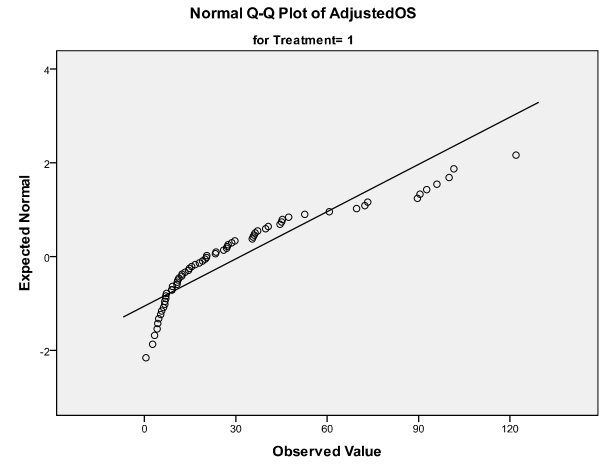
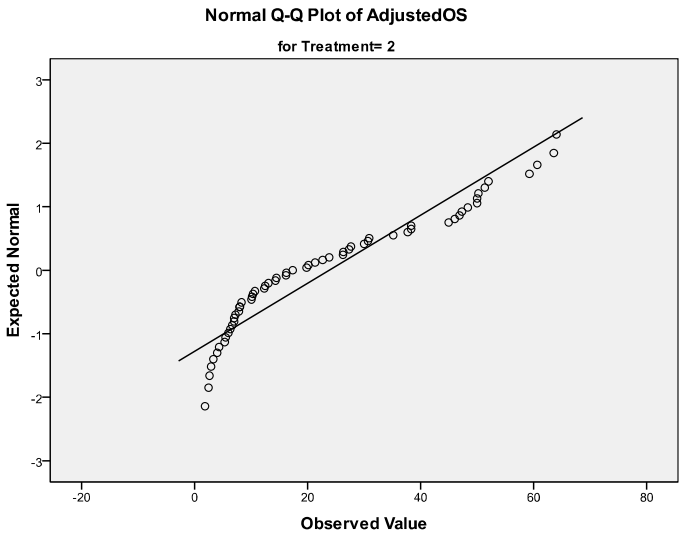


Fig 7.57: Q-Q plot of quality-adjusted survival related to GEM



The Kolmogorov-Smirnov test indicates that quality-adjusted survival is not normally distributed (0,000 < 0,005). This result is confirmed by the histograms and Q-Q plots for both treatment regimens. The histograms do not present a symmetrical distribution, they both have a long tail towards the right. Also the Q-Q plots for both treatments do not show linear relationships between the observed values and the expected values from a normal distribution. Therefore, the Mann-Whitney test is used to test for significance.

Test of significance: Mann-Whitney test

Fig. 7.58: Mann-Whitney test for quality-adjusted survival

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of AdjustedOS is the same across categories of 1 = PLD 2 = GEM.	Independent-Samples Mann-Whitney U Test	.331	Retain the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

The result suggests that there is no statistically significant difference between the distributions of quality—adjusted survival among treatment arms. Since P > 0,05 the data does not provide statistically significant evidence of a difference in quality-adjusted survival between both treatment arms.

Appendix 2: Forgone interests on funeral expenses

Forgone interests on funeral expenses are based on an interest rate of 2% and discounted at 4% annually (funeral expense: €5.610,28).

Table 7.16: Forgone interests on funeral expenses due to a premature death

	Yearly interest	NPV of yearly interest	NPV of total interests
1	112,21	112,21	112,21
2	114,45	110,05	222,26
3	116,74	107,93	330,22
4	119,07	105,85	436,07
5	121,46	103,82	539,89
6	123,88	101,82	641,71
7	126,36	99,86	741,57
8	128,89	97,95	839,52
9	131,47	96,06	935,58
10	134,10	94,22	1029,80
11	136,78	92,40	1122,20
12	139,51	90,62	1212,82
13	142,30	88,88	1301,70
14	145,15	87,17	1388,87
15	148,05	85,50	1474,37
16	151,01	83,85	1558,22
17	154,03	82,23	1640,45
18	157,11	80,66	1721,11
19	160,26	79,11	1800,22

20	163,46	77,59	1877,81
21	166,73	76,09	1953,90
22	170,07	74,63	2028,53
23	173,47	73,20	2101,73
24	176,94	71,79	2173,52
25	180,48	70,41	2243,93
26	184,09	69,06	2312,99
27	187,77	67,73	2380,72
28	191,52	66,42	2447,14
29	195,35	65,14	2512,28
30	199,26	63,89	2576,17
31	203,25	62,67	2638,84
32	207,31	61,46	2700,30
33	211,46	60,28	2760,58
34	215,69	59,12	2819,70
35	220,00	57,98	2877,68
36	224,40	56,87	2934,55
37	228,89	55,77	2990,32
38	233,47	54,70	3045,02
39	138,13	53,65	3098,67
40	242,90	52,62	3151,29
41	247,76	51,61	3202,90
42	252,71	50,61	3253,51
43	257,76	49,64	3302,74
44	262,92	48,68	3351,42
45	268,18	47,75	3399,17
46	273,54	46,83	3446,00
47	279,01	45,93	3491,93
48	284,59	45,05	3536,98

49	290,28	44,18	3581,16
50	296,09	43,33	3624,49
51	302,01	42,50	3666,99
52	308,05	41,68	3708,67
53	314,21	40,88	3749,55
54	320,50	40,09	3789,64
55	326,91	39,32	3828,96
56	333,45	38,57	3867,53
57	340,11	37,82	3905,35
58	346,92	37,10	3942,45
59	353,86	36,38	3978,83
60	360,93	35,68	4014,51
61	368,15	35,00	4049,51
62	375,51	34,32	4083,83
63	383,02	33,66	4117,49
64	390,68	33,02	4150,51
65	398,50	32,38	4182,89
66	406,47	31,76	4214,65
67	414,60	31,15	4245,80
68	422,89	30,55	4276,35
69	431,35	29,96	4306,31
70	439,98	29,39	4335,70
71	448,77	28,82	4364,52
72	457,75	28,27	4392,79
73	466,90	27,72	4420,51
74	476,24	27,19	4447,70
75	485,77	26,67	4474,37
76	495,48	26,15	4500,52
77	505,39	25,65	4526,17

78	515,50	25,16	4551,33
79	525,81	24,67	4576,00
80	536,33	24,20	4600,20
81	547,05	23,73	4623,93
82	557,99	23,28	4647,21
83	569,15	22,83	4670,04
84	580,54	22,39	4692,43
85	592,15	21,96	4714,39
86	603,99	21,54	4735,93
87	616,07	21,12	4757,05
88	628,39	20,72	4777,77
89	640,96	20,32	4798,09
90	653,78	19,93	4818,02
91	666,85	19,54	4837,50
92	680,19	19,17	4856,67
93	693,80	18,80	4875,47
94	707,67	18,44	4893,91
95	721,82	18,08	4911,99
96	736,26	17,74	4929,73
97	750,99	17,40	4947,13
98	766,00	17,06	4984,19
99	781,33	16,73	4980,92
100	796,95	16,41	4997,33

Appendix 3: Estimating the average distance to an oncology center (hospitals and centers that treat cancers of the female reproductive system) in Italy

The objective of this appendix is to estimate the average distance to a hospital or oncology center in Italy that treats cancers of the female reproductive system. To that end, all facilities were plotted on a map. This was done for each region separately. Consequently, it was possible to estimate the average distance per region. Since some regions are more densely populated than others, average distance per region was adjusted with an importance weight. The latter was calculated as population region divided by population Italy, which has 60.494.632 residents (updated in July 2010). Finally, the average distance was calculated as the sum of the average adjusted distances of all regions (Σ average adjusted distance in all regions). It is important to note that the average distance in major cities is significantly less than in the region overall. Since it was too complex to consider the many hospitals in the major cities, they were considered as one hospital.

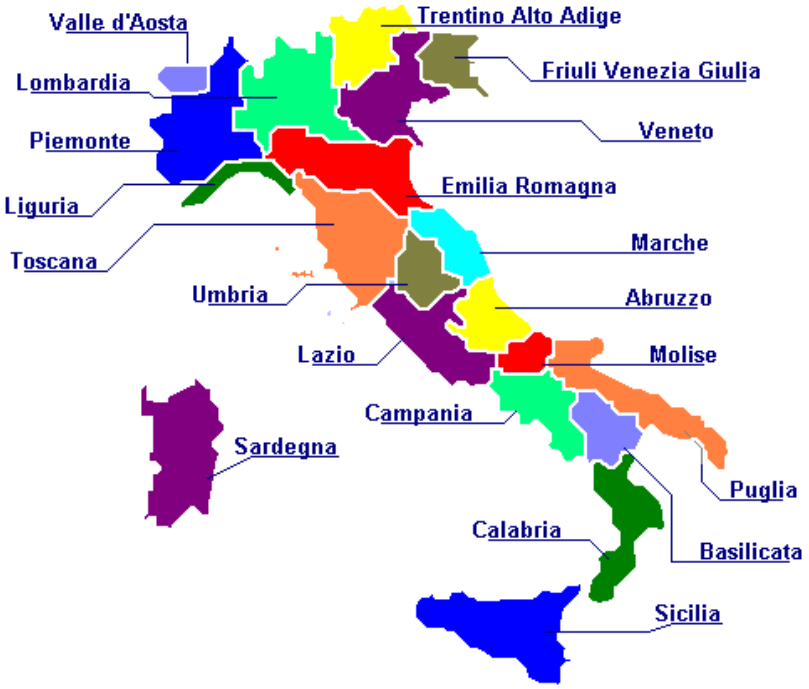
To estimate the average distance per region, the following procedure was used. Per region, the oncology centers were plotted on a map. Average distance for a region was then estimated. The objective was to cover the whole region without or with minimal overlap. Then, the radius was measured. By taking into account the scale of the map, it was possible to transform the radius into the distance around the hospital. This procedure was repeated for all centers. Finally, to attain the average distance to a hospital in a region, all the kilometers were summed and divided by the number of centers on the map.

Tables 7.17 – 7.37 present the names of all hospitals involved in cancer treatment of the female reproductive system. Hospitals and oncology centers are sorted according to their experience (number of hospitalizations and surgeries performed in one year), and Medicare on the basis of the index, a parameter developed in the United States, which permits evaluation of the complexity of the overall work of a hospital.

Information included in tables 7.17 – 7.37:

- **Hospitalizations and day care:** the column "hospitalization", i.e. stay that lasts at least for one night, contains the total number of patients admitted during 2008 at each hospital. However, the same patient may have been counted several times if she has undergone several hospitalizations during the year in the same hospital. The column "day care" contains the total number of admissions that lasts for only one day.
- **Surgeries:** the column "surgeries" contains the total number of surgeries performed in 2008.
- **Medicare weight**: the Medicare weight takes into account a number of factors that describe the use of resources needed to treat the patient, equipment, drugs, medical, and paramedical personnel, and so on. This index was developed as a benchmark for reimbursement by insurance companies, and is interpreted as a sign of "expensive" for admission (more weight equals more expensive).

Fig. 7.59: The 20 Italian regions



Valle d'Aosta

Table 7.17: Oncology centers in region Valle d'Aosta

Hospital	Hospitalization	Day care	Surgeries	Medicare Weight
Ospedale Regionale "Umberto Parini" Aosta	51	43	31	50
Total	**51**	**43**	**31**	**50**

Source: Il Corriere della Sera, available on: http://www.corriere.it/sportello-cancro/db/mdc/valledaosta/2008/mdc13completo.shtml

Fig. 7.60: Valle d'Aosta

Average distance to oncology center: 39,91 km

Population: 127.836

Area: 3.263 km²

Importance weight: 127.836/60.494.632 = 0,00211

Piemonte

Table 7.18: Oncology centers in region Piemonte

Hospital	Hospitali-zation	Day clinic	Surgeries	Medicare Weight
Azienda ospedaliera Ospedale infantile Regina Margherita e Ospedale Sant' Anna – Torino	349	350	516	467
Ospedale Mauriziano Umberto I di Torino e istituto per la ricerca e la cura del cancro di Candiolo	144	234	161	238
Azienda ospedaliera – Universitaria "Maggiore della Carita" – Novara	134	63	152	212
Ospedale Cardinal Massaia	119	77	100	149
Azienda ospedaliera Santa Croce a Carle – Cuneo	92	63	117	139
Azienda ospedaliera SS. Antonio Biagio e Cesare Arrigo – Alessandria	92	66	85	129
Ospedali ASL to 5 – Chieri Moncalieri – Carmagnola	73	45	83	118
Azienda sanitaria Ospedaliera San Giovanni Battista (Molinette) – Torino	69	11	42	106
Ospedale civile Edoardo Agnelli – Pinerolo	57	58	42	88
Ospedale degli infermi – Biella	63	29	51	86
Presidio sanitario Gradenigo - Torino	67	37	10	81
Ospedale evangelico Valdese di Torino	41	48	81	78
Presidi ospedalieri riuniti ASL no –	53	43	53	72

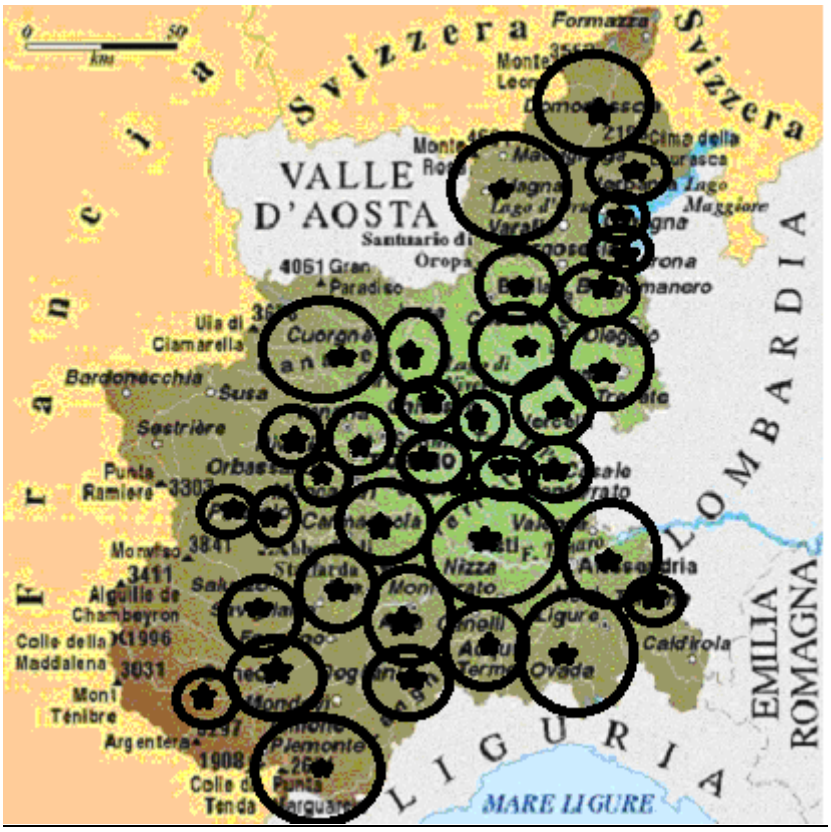
Borgomanero				
Ospedale integrato ASL – Vercelli	50	40	39	71
Ospedali riuniti ASL al – Novi Ligure – Acqui Terme – Ovada	56	48	69	71
Presidio ospedaliero Alba – Bra	42	25	35	64
Ospedale degli infermi – Rivoli	40	48	64	62
Ospedale unico plurisede ASL vco – Pallanza – Domodossola	44	51	46	60
Presidio sanitario ospedale Cottolengo – Torino	48	5	24	59
Presidio riunito di Ivrea – Cuorgne' – Castellamonte	46	74	59	54
Ospedale Martini – Torino	30	14	32	53
Azienda sanitaria Ospedaliera San Luigi Gonzaga – Orbassana	27	23	32	43
Ospedale Santo Spirito – Casale Monferrato	32	22	31	39
Presidio riunito di Cirie' – Lanzo Torinese	30	12	28	39
Ospedale Maria Vittoria – Torino	30	3	24	37
Torino nord emergenza – San Giovanno Bosco – Torino	25	13	10	37
Presidio ospedaliero Saluzzo – Savigliano	30	69	80	35
Ospedale di Mondovi' – Ceva	24	12	25	31
Ospedale SS. Antonio e Margherita – Tortona	19	18	25	27
Presidio di Chivasso	18	20	19	26

Clinica Santa Rita – Vercelli	24	0	22	25
Pro infantia spa ospedale Koelliker – Torino	14	10	20	22
Villa Maria Pia hospital – Torino	9	0	9	11
Casa di cura sedes Sapientiae – Torino	10	0	5	10
Casa di cura Cellini – Torino	6	0	6	9
Casa di cura e riposo San Luca – Pecetto Torinese	7	2	6	8
Casa di cura Villa Iris – Pianezza	6	0	0	7
Villa Ida – Lanzo Torinese	3	0	0	3
Casa di cura l'eremo di Miazzina – Cambiasca	3	0	0	3
Casa di cura Villa Grazia – San Carlo Canavese	3	0	0	3
Azienda ospedaliera C.T.O – Torino	2	0	1	3
Villa la Bertalazona – San Maurizio Canavese	3	0	0	2
Istituto Climatico di Robilante	3	0	0	2
Casa di cura I Cedri – Fara Novarese	1	0	1	2
Casa di cura San Giuseppe – Asti	2	0	0	2
Clinica San Carlo di Arona	1	0	0	1
Istituto clinico Salus – Alessandria	1	0	0	1
Casa di cura Villa Igea – Acqui Terme	1	0	0	1
Nuova casa di cura citta' di Alessandria SRL	1	0	0	1
Centro ortopedico di Quadrante spa – Ospedale Madonna del popolo di Omegna	1	0	0	1

Casa di cura Sant' Anna – Casale Monferrato	1	1	2	1
Casa di cura Villa Adriana – Arignano	1	0	0	1
Promea S.P.A. – Torino	0	5	5	0
Total	**2.047**	**1.639**	**2.212**	**2893**

Source: Il Corriere della Sera, available on: http://www.corriere.it/sportello-cancro/db/mdc/piemonte/2008/mdc13.shtml

Fig. 7.61: Piemonte



Average distance to oncology center: 12,61 km

Population: 4.450.359

Area: 25.402 km²

Importance weight: 4.450.359/60.494.632 = 0,07357

Liguria

Table 7.19: Oncology centers in region Liguria

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Azienda ospedaliera Universitaria "San Martino" – Genova	157	49	166	233
Azienda sanitaria Locale 1 imperiese – Imperia – Sanremo - Bordighera	121	77	138	151
E.O. Ospedali Galliera - Genova	87	42	67	119
Presidio ospedaliero Asl4 Chiavarese – Lavagna – Sestri Levante – Santa Margherita Ligure	66	31	50	96
Ospedale Sant' Andrea – La Spezia	65	53	70	93
Istituto nazionale per la ricerca sul Cancro – Genova	56	54	95	84
Ospedale San Paolo - Savona	47	28	49	56
Presidio ospedaliero Villa scassi – Genova	31	20	43	45

Ospedale San Carlo - Genova	19	5	17	28
Ospedale Evangelico Internazionale – Genova	19	13	21	27
Ospedale San Bartolomeo – Sarzana	16	0	13	21
Ospedale Santa Corona – Pietra Ligure	16	3	8	20
Ospedale Santa Maria della Misericordia – Albenga	11	7	3	14
Istituto Giannina Gaslini – Genova	5	4	5	7
Presidio ospedaliero Genova Nord Pontedecimo – Gallino	3	2	0	4
Casa di cura Alma Mater – La Spezia	1	0	1	2
Ospedale Sant' Antonio – Recco	1	0	0	1
Ospedale San Giuseppe – Cairo Montenotte	0	1	0	0
Total	**838**	**475**	**864**	**1.145**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/liguria/2008/mdc13.shtml

Fig. 7.62: Liguria

Average distance to oncology center: 24,16 km

Population: 1.615.951

Area: 5.416 km²

Importance weight: 1.615.951/60.494.632 = 0,02671

Lombardia

Table 7.20: Oncology centers in region Lombardia

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Istituto Europeo di Oncologia – IEO – Milano	877	4	641	1.164
Azienda ospedaliera San Gerardo – Monza	441	277	382	710
Fondazione I.R.C.C.S. Istituto Nazionale dei Tumori – Milano	389	132	412	612
Ospedali Civili di Brescia	340	405	266	462
Istituto scientifico universitario San Raffaele – Milano	376	63	119	432
Ospedale Filippo del Ponte – Varese	195	180	150	306
Azienda ospedaliera ospedali riuniti di Bergamo	167	34	134	245
Presidio ospedaliero di Busto Arsizio	191	25	65	243
Fondazione I.R.C.C.S. Ca' Granda ospedale Maggiore policlinico – Milano	173	237	226	242
Azienda ospedaliera ospedale Niguarda Ca' Granda – Milano	162	11	97	211
Fondazione I.R.C.C.S. policlinico San Matteo – Pavia	135	80	152	184
Ospedale Sant' Anna – Como	120	44	80	174
Ospedale Alessandro Manzoni – Azienda ospedaliera Ospedale di Lecco	116	144	116	163
Istituto clinico Humanitas I.R.C.C.S. – Rozzano	94	41	109	159

Azienda ospedaliera Carlo Poma – Mantova	113	22	73	152
Azienda ospedaliera "Istituti Ospedalieri" di Cremona	93	34	78	143
Ospedale civile di Voghera	93	18	66	118
Ospedale di Legnano e Cuggiono	78	56	91	108
Presidio ospedaliero Vittorio Emanuele III di Carate Brianza	60	61	75	100
Azienda ospedaliera di Desio e Vimercate presidio ospedaliero di Desio	68	15	61	97
Ospedale Maggiore di Lodi	74	41	49	97
Ospedale "Oglio Po" – Casalmaggiore	62	23	59	96
Ospedale Treviglio-Caravaggio – Treviglio	57	9	61	94
Congregazione suore infermiere dell' Addolorata – ospedale Valduce – Como	68	39	65	93
Ospedale Sant' Antonio Abate – Gallarate	62	8	47	91
Fondazione Poliambulanza – istituto ospedaliero – Brescia	57	35	77	90
Ospedale Edoardo Bassini – Cinisello Balsamo	63	17	54	90
Ospedale Maggiore – Crema	59	38	55	83
Presidio ospedaliero di Vimercate	53	84	69	83
Ospedale civile di Vigevano	73	3	36	79
Azienda ospedaliera ospedale San Carlo Borromeo – Milano	58	39	49	78
Ospedale Sant' Orsola Fatebenefratelli – Brescia	53	10	51	73
Azienda ospedaliera della Valtellina	46	25	39	72

e della Valchiavenna – Sondrio				
Istituto clinico Beato Matteo – Vigevano	46	19	38	70
Ospedale Bolognini – Seriate	39	21	58	62
Casa di cura San Pio X – Milano	40	10	38	60
Ospedale San Giuseppe – Gruppo Multimedica – Milano	43	6	37	59
Ospedale Arnaboldi – Broni	47	5	36	57
Azienda ospedaliera – Polo Universitario "Luigi Sacco" – Milano	41	43	41	56
Ospedale "Carlo Ondoli" – Angera	39	19	35	56
Ospedale di Cantu' – Como	41	5	37	53
Presidio ospedaliero di Manerbio	44	11	48	53
Ospedale San Paolo – Polo Universitario – Milano	37	49	41	52
Ospedale G. Fornaroli – Magenta	34	45	31	51
Ospedale di circolo – Rho	31	14	23	50
Presidio ospedaliero Macedonio Melloni – Milano	47	32	68	50
Ospedale di circolo – Merate	44	3	34	50
I.R.C.C.S. Fondazione Salvatore Maugeri – Pavia	41	13	3	47
Ospedale di circolo presidio Ospedaliero di Vizzolo Predabissi	40	15	27	47
Policlinico San Marco S.R.L. – Presidio di Ponte San Pietro	35	21	55	46
Ospedale di Vallecamonica – Esine e Edolo	31	3	23	44
Ospedale civile di Iseo	33	23	38	42
Azienda ospedaliera Desenzano del	29	28	52	39

Garda del presidio di Desenzano/Lonato				
Ospedale Sacra Famiglia – Fatebenefratelli - Erba	28	3	27	37
Ospedale Guido Salvini – Garbagnate Milanese	24	3	19	37
Ospedale Pesenti Fenaroli – Alzano Lombardo	24	25	44	37
Ospedale Citta' di Sesto San Giovanni	22	6	18	36
Ospedale di Gavardo	27	7	31	35
Ospedale Mellino Mellini – Chiari	23	2	22	34
Ospedale civico di Codogno	24	4	22	34
Istituto clinico citta' di Brescia	25	26	47	33
Ospedale Medaglia oro Antonio Locatelli – Priario	23	8	25	33
Policlinico San Marco – Osio Sotto	21	14	26	32
Ospedale dei bambini Vittore Buzzi – Istituti clinici di prefezionamento (ICP) – Milano	27	4	28	31
Ospedale di circolo e fondazione Macchi – Polo universitario Varese	25	0	11	31
Istituto clinico Sant' Anna – Brescia	26	13	32	31
Ospedale di Saronno	32	21	19	29
Ospedale civile "Destra Secchia" – Pieve di Coriano	19	3	19	29
Ospedale F.M. Passi – Calcinate	21	0	21	29
Presidio ospedaliero del Verbano – Luino e Cittiglio	27	16	40	28
Istituti clinici Zucchi – Monza	23	0	23	26

Istituto clinico Citta' Studi SPA – Milano	20	8	26	26
I.R.C.C.S. Multimedica – Sesto San Giovanni	17	0	17	25
Ospedale Moriggia Pelascini – Gravedona	20	27	20	25
Ospedale civile di Asola	16	8	12	24
Ospedale civico – Casalpusterlengo	21	23	0	21
Presidio ospedaliero di Giussano Ospedale Carlo Borella	19	1	2	21
Ospedale Caduti Bollatesi – Bollate	19	7	22	21
Ospedale di Gardone Val Trompia	15	0	8	20
Presidio ospedaliero Melzo Santa Maria delle Stelle – Melzo	11	7	15	18
Azienda ospedaliera Fatebenefratelli E Oftalmico – Milano	14	5	1	17
I.R.C.C.S. Policlinico San Donato – San Donato Milanese	15	0	0	15
Casa di cura La Madonnina – Milano	9	4	12	15
Azienda ospedaliera della Valtellina e della Valchiavenna – Sondalo	11	19	7	12
Casa di cura Ambrosiana – Cesano Boscone	9	0	7	11
Casa di cura "Giovanni Battista Mangioni" – Lecco	12	13	12	11
Casa di cura La Qiuete – Varese	13	0	0	9
Casa di cura San Carlo/Istituto Auxologico Italiano – Milano	5	0	5	9
Multimedica Castellanza	8	5	3	9
Istituti clinici Zucchi – Carate Brianza	7	0	0	9

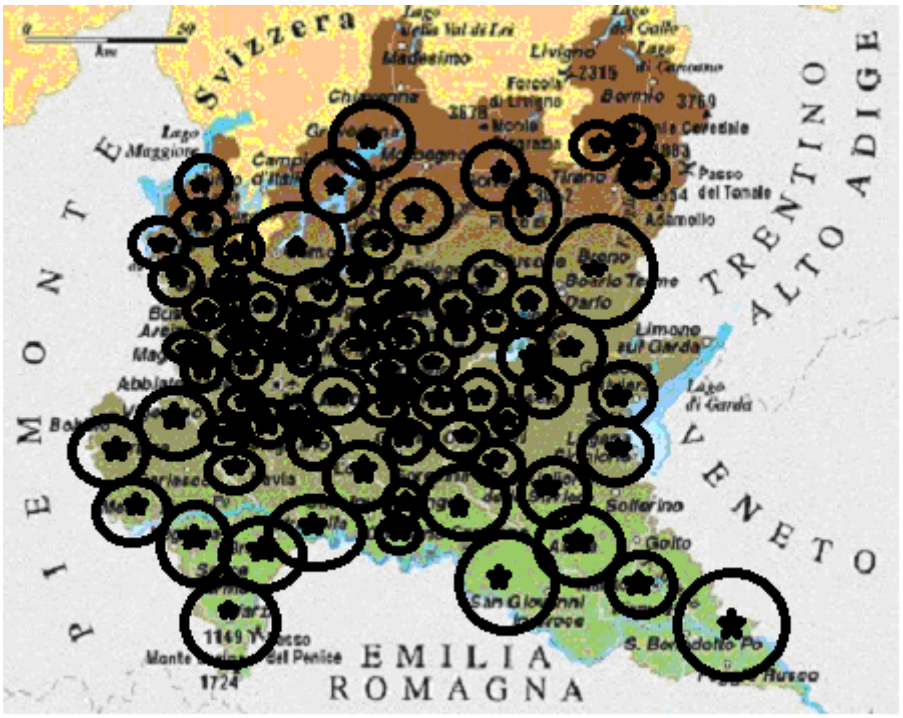
Casa di cura Igea S.P.A. – Milano	5	2	2	8
Ospedale civile di San Giovanni Bianco	7	6	8	8
Casa di cura Ancelle della Carita' – Cremona	6	0	0	8
Ospedale "San Pellegrino" di Castiglione delle Stiviere S.R.L.	5	3	4	7
Cliniche Gavazzeni SPA – Bergamo	4	0	3	7
Ospedale asilo Vittoria – Mortara	5	0	1	7
Azienda ospedaliera della Valtellina e Valchiavenna – Chiavenna	6	4	9	7
Casa di cura Citta' di Pavia	4	0	4	6
Casa di cura San Camillo – Milano	5	0	5	6
Presidio ospedaliero L.A. Galmarini – Tradate	5	4	2	6
Casa di cura San Camillo – Cremona	5	2	6	6
Istituto clinico San Siro – Milano	3	0	2	5
Presidio ospedaliero Ambrogio Uboldo – Cernusco sul Naviglio	3	1	2	4
Casa di cura Citta' di Milano – Milano	3	2	5	4
Casa di cura San Francesco –Bergamo	3	0	0	4
Ospedale civile di Montichiari	3	0	0	4
Ospedale civile SS. Annunziata – Varzi	2	0	1	4
Ospedale Sola Forni Gazzaniga – Stradella	2	0	1	4
Ospedale Serbelloni – Gorgonzola	3	3	0	4
Ospedale SS. Trinita' – Romano di Lombardia	2	23	25	3
Ospedale Crotta Oltrocchi – Vaprio d' Adda	3	0	0	3

Casa di cura San Clemente – Mantova	2	1	1	3
Casa di cura Figlie di San Camillo – Cremona	2	0	1	3
Ospedale "A. Bellini" – Somma Lombardo	2	0	0	3
Ospedale di Erba Renaldi – Menaggio	2	0	0	3
Ospedale "Delmati" – Sant' Angelo Lodigiano	2	0	0	3
Policlinico di Monza	1	0	1	2
Ospedale Bambini – Brescia	1	0	1	2
Casa di cura San Raffaele Turro – Milano	1	0	1	2
Casa di cura Beato Palazzolo – Milano	2	0	0	2
Casa di cura San Camillo – Brescia	2	0	0	2
Istituto clinico Sant' Ambrogio – Milano	2	2	0	2
Humanitas Mater Domini – Castellanza	1	0	0	1
Istituto clinico Villa Aprica – Como	1	1	0	1
Casa di cura Lecco "Beato L. Talamoni" – Lecco	1	0	0	1
Azienda ospedaliera della Valtellina e Valchiavenna – Morbengo	1	0	0	1
Ospedale circolo "C. Cantu" – Abbiategrasso	1	0	0	1
Clinica San Carlo – Casa di cura privata Polispecialistica SPA – Paderno Dugnano	1	0	0	1
Ospedale SS. Capitanio e Gerosa – Lovere	1	0	0	1
Ospedale Tribanti Pavoni di Orzinuovi	1	0	0	1
Ospedale di circolo Carlo Mira – Casorate Primo	1	0	0	1
Istituto clinico San Rocco SPA – Ome	1	0	0	1

Casa di cura San Donato – Osio Sotto	1	0	0	1
Fondaziona I.R.C.C.S. istituto Neurologico Carlo Besta – Milano	1	0	0	1
Ospedale civile di Mede	1	1	1	1
I.R.C.C.S. Fondazione istituto Neurologico C. Mondino – Pavia	1	0	0	1
Ospedale di Mariano Comense – Como	0	5	5	0
Total	**6.667**	**2.98**	**5.601**	**9.248**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/lombardia/2008/mdc13.shtml

Fig. 7.63: Lombardia



Average distance to oncology center: 7,5 km

Population: 9.866.104

Area: 23.863 km²

Importance weight: 9.866.104/60.494.632 = 0,16309

Emilia Romagna

Table 7.21: Oncology centers in region Emilia Romagna

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Azienda ospedaliera-universitaria di Bologna Policlinico Sant' Orsola – Malpighi – Bologna	454	219	532	738
Presidio ospedaliero Bellaria – Maggiore di Bologna	217	44	136	274
Azienda ospedaliera universitaria Arcispedale Sant' Anna – Ferrara	195	41	121	242
Azienda ospedaliera-universitaria Policlinico di Modena	156	43	108	231
Arcispedale Santa Maria Nuova – Reggio Emilia	130	92	158	198
Azienda ospedaliera-universitaria di Parma	115	144	105	171
Presidio ospedaliero "Guglielmo da Saliceto" - Piacenza	114	62	114	159
Ospedale Maurizio Bufalini – Cesena	111	14	104	123
Ospedale degli Infermi – Rimini	77	32	55	113
Ospedale Santa Maria delle Croci – Ravenna	68	21	67	103

Ospedale Ramazzini – Carpi	68	62	57	93
Casa di cura Citta' di Parma S.P.A – Parma	53	35	68	90
Ospedale di Fidenza a San Secondo Parmense	50	33	68	82
Ospedale Morgagni-Pierantoni – Forli'	44	2	40	72
Ospedale Umberto I – Lugo	47	8	45	71
Ospedale degli Infermi – Faenza	50	13	44	71
Ospedale di Bentivoglio	58	25	57	68
Ospedale di Sassuolo SPA	50	28	55	64
Santa Maria della Scaletta – Imola	37	5	32	48
Ospedale del Delta – Lagosanto	32	15	25	45
Ospedale Santa Maria Bianca – Mirandola	26	10	25	45
Ospedale Cervesi – Cattolica	30	31	53	44
Ospedale civile di Guastalla	30	57	51	44
Ospedale Sant' Anna – Castelnovo ne' Monti	28	43	38	41
Ospedale Ercole Franchini – Montecchio Emilia	31	28	46	41
Casa di cura Madre Fortunata Toniolo – Bologna	28	0	15	36
Ospedale Mazzolani Vandini – Argenta	25	29	32	34
Ospedale Santissima Annunziata – Cento	18	12	18	25
Ospedale Costa – Porretta Terme	17	3	15	21
Presidio Val d' Arda – Fiorenzuola d' Arda	19	14	21	20
Villa Erbosa – Bologna	19	2	9	20
Ospedale di Budrio	12	2	12	16
I.R.S.T. Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori – Meldola	15	5	0	16
Casa di cura San Lorenzino – Cesena	12	7	17	16

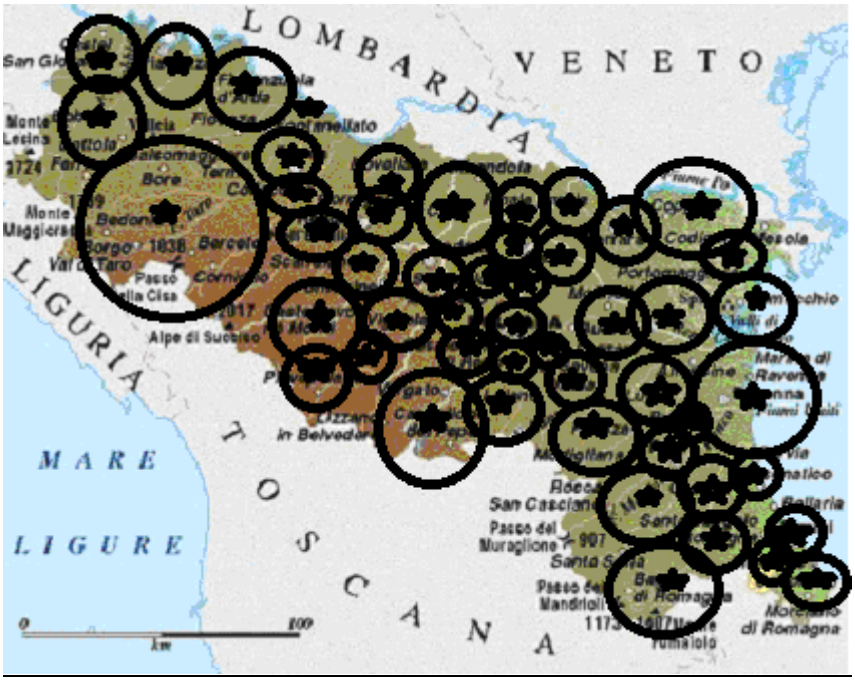
Casa di cura Villa Maria – Rimini	14	6	11	15
Ospedale di Pavullo	13	15	23	14
Ospedale privato accreditato Villa Regina – Bologna	12	0	12	14
Ospedale di Vignola	9	9	4	13
Ospedale Ceccarini – Riccione	6	0	5	11
Casa di cura Malatesta Novello – Cesena	9	0	5	11
Casa di cura Piccole Figlie – Parma	10	26	28	10
Ospedale di San Giovanni in Persiceto	8	11	10	10
Santa Maria – Borgo Val di Taro	10	13	15	9
Ospedale Cesare Magati – Scandiano	9	19	14	8
Nuovo ospedale civile Sant' Agostino Estense – Modena	7	1	1	8
Ospedale privato accreditato Nigrisoli – Bologna	6	1	3	8
Ospedale San Giuseppe – Copparo	7	0	0	8
Ospedale privato Villa Serena – Forli'	5	0	3	7
Ospedale privato accreditato Villa Chiara – Casalecchio di Reno	5	5	8	7
Casa di cura Villa Verde – Reggio Emilia	6	0	0	7
San Pier Damiano Hospital – Faenza	5	0	5	7
Casa di cura Piacenza - Piacenza	5	0	1	7
Casa di cura Salus – Ferrara	7	0	0	7
Ospedale civile di Castel San Pietro Terme	5	0	0	6
Presidio ospedaliero della Val Tidone – Castel San Giovanni	4	6	1	6
Ospedale Fratelli Borselli di Bondeno	4	0	0	6
Ospedale privato Domus Nova – Ravenna	4	2	1	5

Ospedale civile di Vergato	3	11	0	4
Ospedale Giovanni Battista Simiani – Loiano	3	0	0	4
Casa di cura Prof. Nobili – Castiglione dei Pepoli	3	0	0	4
Ospedale San Camillo – Comacchio	4	0	0	4
Ospedale privato S. Viola – Bologna	4	0	0	4
Hesperia Hospital Modena S.R.L. – Modena	3	1	4	4
Clinica Quisisana – Ferrara	3	0	0	3
Ospedale Regina Margherita – Castelfranco Emilia	2	2	1	3
Ospedale civile San Sebastiano – Correggio	2	0	0	3
Ospedale Genesio Marconi – Cesenatico	2	0	0	3
Ospedale Franchini – Santarcangelo di Romagna	2	0	0	3
Ospedale privato accreditato Villa Laura – Bologna	4	0	0	2
Casa di cura San Francesco – Ravenna	2	0	0	2
Ospedale Piero Angioloni – San Piero in Bagno	1	0	0	1
Casa di cura S. Antonino - Piacenza	1	0	0	1
Casa di cura Villa Pineta – Pavullo nel Frignano	1	0	0	1
Casa di cura Villalba – Bologna	2	0	0	1
Maria Cecilia Hospital SPA – Cotignola	1	0	0	1
Poliambulatorio Chirurgico Modenese – Modena	0	5	5	0
Ospedale Don Giuseppe Dossetti – Bazzano	0	1	1	0
Presidio ospedaliero di Bobbio	0	2	0	0

Total	**2.649**	**1.317**	**2.504**	**3.724**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/emiliaromagna/2008/mdc13.shtml

Fig. 7.64: Emilia Romagna



Average distance to oncology center: 11,06 km

Population: 4.417.113

Area: 22.446 km²

Importance weight: 4.417.113/60.494.632 = 0,07302

Trentino – Alto Adige

Trentino

Table 7.22: Oncology centers in Trentino

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Ospedale di Trento	270	102	129	317
Ospedale di Rovereto	46	49	74	71
Ospedale San Camillo - Trento	31	7	32	45
Ospedale III Novembre – Tione di Trento	11	14	12	13
Ospedale Alto Garda e Ledro – Arco	9	18	7	12
Ospedale civile di Cles	7	16	18	9
Ospedale di Fiemme – Cavalese	8	21	14	9
Casa di cura Villa Bianca SPA – Trento	4	0	0	4
Ospedale San Lorenzo – Borgo Valsugana	3	1	2	2
Casa di cura Sacra Famiglia – Arco	2	0	0	1
Total	**391**	**228**	**288**	**482**

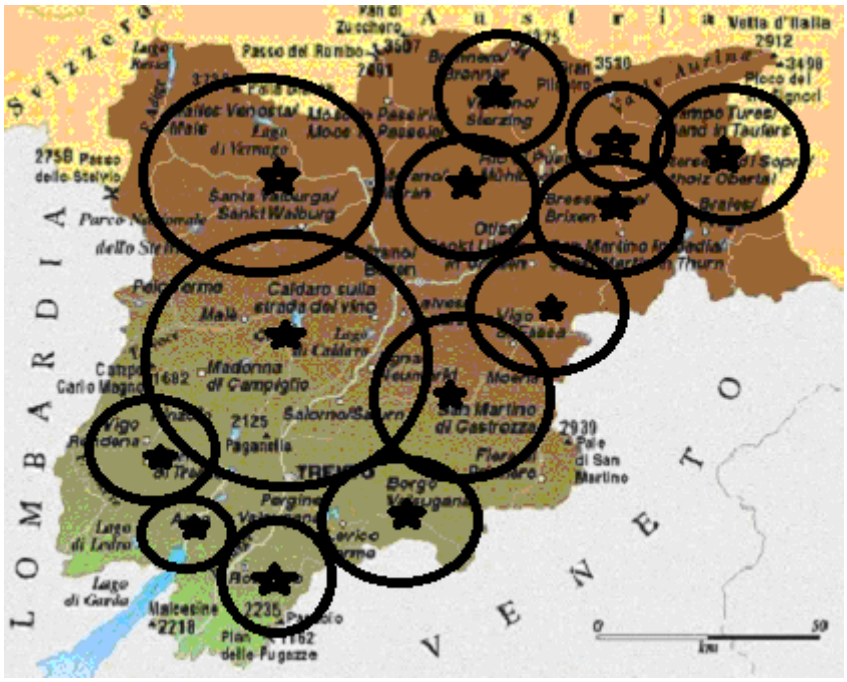
Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/trento/2008/mdc13.shtml

Table 7.23: Oncology centers in Alto Adige

Hospital	Hospital-ization	Day care	Surgeries	Medicare Weight
Comprensorio sanitario di Bolzano	101	56	82	141
Ospedale Franz Tappeiner – Merano	49	44	34	64
Ospedale di Brunico	30	23	40	45
Ospedale di Bressanone	22	31	34	31
Ospedale di San Candido	14	2	13	17
Comprensorio sanitario Meran – Ospedale di Silandro	12	6	13	14
Casa di cura Santa Maria – Bolzano	11	4	9	12
Ospedale di Vipiteno	13	11	21	11
Casa di cura Fonte San Martino – Merano	3	0	0	2
Casa di cura Villa Sant' Anna – Merano	1	0	0	1
Fondazione Sarentino	1	0	0	1
Total	**257**	**177**	**246**	**339**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/bolzano/2008/mdc13.shtml

Fig. 7.65: Trentino - Alto Adige



Average distance to oncology center: 16,25 km

Population: 1.033.943

Area: 13.607 km²

Importance weight: 1.033.943/60.494.632 = 0,0171

Veneto

Table 7.24: Oncology centers in region Veneto

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Azienda ospedaliera universitaria Integrata di Verona	209	77	191	319
Azienda ospedaliera di Padova	178	51	174	274
Ospedale San Maria di Ca' Foncello – Treviso	120	22	90	181
Ospedale di Cittadella	73	31	97	142
Ospedale dell' Angelo – Mestre – Venezia	85	20	83	130
Casa di cura Abano Terme	71	5	74	126
Ospedale Sacro Cuore e Don Calabria – Negrar	68	48	113	118
Presidio ospedaliero di Vicenza	70	1	51	109
Ospedale Boldrini – Thiene	68	35	93	106
Ospedale San Giacomo Apostolo – Castelfranco Veneto	72	14	44	103
Presidio ospedaliero di Monselice	63	10	52	96
Ospedale Santa Maria della Misericordia – Rovigo	53	45	60	91
Ospedale di Mirano	60	10	54	91
Ospedale di Dolo	54	17	43	78
Ospedale Santa Maria del Prato – Feltre	45	13	53	75
Presidio ospedaliero di Conegliano	52	4	36	73
Ospedale di Camposampiero	53	23	53	72
Ospedale San Bassiano – Bassano del Grappa	49	25	46	72

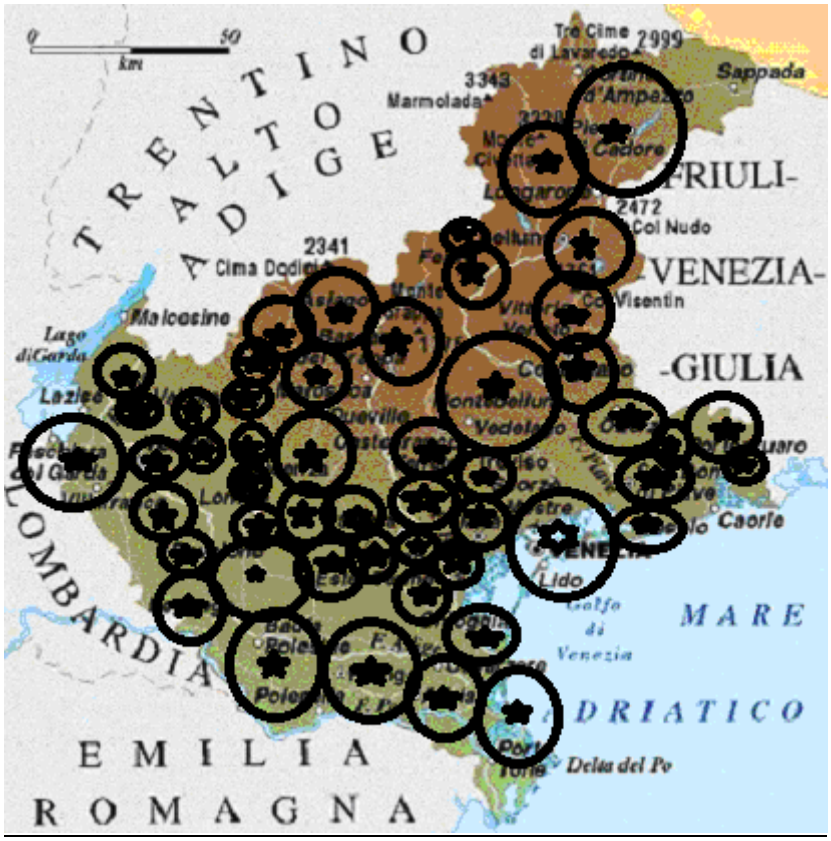
Istituto oncologico Veneto – I.R.C.C.S. – Padova	65	2	0	66
Ospedale San Martino di Belluno	36	22	50	57
Ospedale Villa Salus – Mestre – Venezia	39	7	42	57
Presidio ospedaliero di San Dona' di Piave	39	11	30	49
Ospedale Mater Salutis di Legnano	36	44	25	48
Ospedale Immacolata Concezione – Piove di Sacco	37	72	59	47
Casa di cura Dott. Pederzoli SPA – Peschiera del Garda	30	32	58	46
Ospedale Girolamo Fracastoro – San Bonifacio	30	28	46	45
Ospedale Orlandi – Bussolengo	29	44	60	44
Ospedale di Montebelluna	25	8	20	44
Ospedale generale di zona San Camillo – Treviso	27	32	56	43
Ospedale San Luca – Trecenta	23	23	39	42
Ospedale Santa Maria Regina degli Angeli – Azienda ULSS19 – Adria	36	11	26	42
Casa di cura Villa Berica – Vicenza	23	19	39	42
Presidio ospedaliero di Portogruaro San Tommaso dei Battuti	29	7	25	39
Ospedale di Chioggia	33	4	20	39
Ospedale di Arzignano	30	9	37	38
Ospedale civile di Venezia SS. Giovanni e Paolo - Venezia	29	6	14	34
Ospedale di Valdagno	22	9	25	33
Ospedale Pietro Milani – Noventa Vicentina	16	3	17	29

Ospedale de Lellis – Schio	15	3	5	23
Ospedale Don Calabria – Negrar	20	1	0	23
Presidio ospedaliero di Vittorio Veneto	15	15	20	20
Ospedale Pompeo Tomitano di Oderzo	17	12	14	18
Casa di cura policlinico San Marco SPA – Mestre – Venezia	15	0	0	18
Ospedale Sant' Antonio – Padova	10	1	1	13
Ospedale di Isola della Scala	10	4	9	12
Casa di cura Madonna della Salute – Porto Viro	8	0	4	12
Presidio ospedaliero de Gironcoli – Conegliano	8	1	0	10
Presidio ospedaliero di Jesolo	7	0	1	10
Casa di cura "Sileno e Anna Rizzola" SPA – San Dona' di Piave	7	0	2	9
Presidio ospedaliero di Este	7	19	11	8
Ospedale di Noale	7	8	1	8
Casa di cura Citta' di Rovigo	5	2	0	6
Ospedale San Biagio – Bovolone	5	0	0	6
Ospedale di Lonigo	4	0	0	5
Ospedale di Agordo	3	0	1	5
Ospedale di Pieve di Cadore	4	0	1	5
Casa di cura Giovanni XXIII – Monastier di Treviso	4	0	0	4
Casa di cura Eretenia – Vicenza	2	5	7	3
Casa di cura Morgagni – Padova	3	0	3	3
Ospedale di Marzana	2	0	0	3
Casa di cura Diaz – Padova	1	0	1	2

Ospedale di Asiago	2	0	2	2
Ospedale di Motta di Livenza	1	0	0	1
Presidio ospedaliero di Montagna	1	0	0	1
Casa di cura Villa Maria – Padova	1	0	0	1
Total	**2.261**	**915**	**2.178**	**3.369**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/veneto/2008/mdc13.shtml

Fig. 7.66: Veneto



Average distance to oncology center: 7,94 km

Population: 4.928.671

Area: 18.399 km²

Importance weight: 4.928.671/60.494.632 = 0,08147

Friuli Venezia Giulia

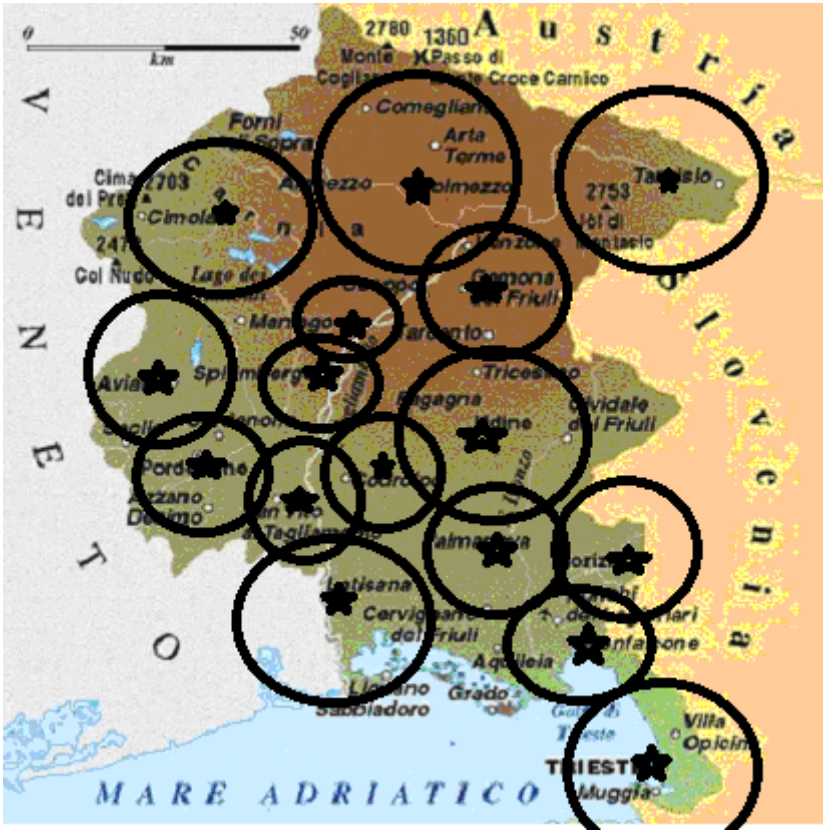
Table 7.25: Oncology centers in region Friuli Venezia Giulia

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Centro di riferimento oncologico – Aviano	408	145	244	525
Azienda ospedaliera-universitaria Santa Maria della Misericordia – Udine	113	39	76	143
Istituto di ricovero e cura a carattere Scientifico materno-infantile – Burlo – Garofolo – Trieste	66	8	60	101
Azienda ospedaliera Santa Maria degli Angeli – Pordenone	75	1	47	89
Ospedale Sant' Antonio – San Daniele del Friuli	47	78	100	71
Azienda ospedaliera-universitaria Ospedali riuniti di Trieste	45	3	10	56
Nuovo presidio ospedaliero di Gorizia	37	23	49	55
Ospedale civile di Latisana	34	11	28	52
Ospedale civile San Antonio Abate – Tolmezzo	40	0	25	44
Ospedale San Polo – Monfalcone	30	2	22	31

Ospedale Santa Maria dei Battuti – San Vito al Tagliamento	21	10	24	28
Presidio ospedaliero di Palmanova	21	9	23	28
Casa di cura San Giorgio S.P.A. – Pordenone	15	6	15	23
Casa di cura Citta' di Udine	15	9	24	21
Casa di cura Sanatorio Triestino – Trieste	12	10	20	15
Ospedale civile San Michele – Gemona del Friuli	8	1	1	10
Policlinico Triestino S.P.A. – Casa di cura Salus – Trieste	5	2	5	6
Ospedale San Giovanni dei Battuti – Spilimbergo	4	0	0	4
Total	**996**	**357**	**773**	**1.302**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/friuli/2008/mdc13.shtml

Fig. 7.67: Friuli Venezia Giulia



Average distance to oncology center: 13,93 km

Population: 1.234.679

Area: 7.844 km²

Importance weight: 1.234.679/60.494.632 = 0,02041

Toscana

Table 7.26: Oncology centers in region Toscana

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Azienda ospedaliera-universitaria Careggi – Firenze	373	77	255	471
Azienda ospedaliera-universitaria Pisana – Pisa	318	64	230	436
Nuovo ospedale San Giuseppe – Empoli	109	26	62	182
Azienda ospedaliera-universitaria Senese – Siena	98	12	62	135
Ospedale Santa Maria Annunziata – Bagno a Ripoli	90	14	72	118
Presidio ospedaliero dell' Apuane di Massa e Carrara	88	28	85	110
Ospedale del Ceppo – Pistoia	72	10	72	103
Ospedale civile – Livorno	68	4	35	103
Ospedale Misericordia e Dolce – Prato	77	10	53	99
Ospedale San Donato – Arezzo	66	31	57	98
Ospedale Versilia – Lido di Camaiore	58	21	71	90
Presidio ospedaliero provinciale Misericordia – Grosseto	62	10	56	89
Ospedale Fiorentino – Firenze	55	109	104	85
Ospedale "Felice Lotti" – Pontedera	44	0	24	55
Ospedale SS. Cosma e Damiano – Pescia	35	5	35	50
Monoblocco ospedaliera Alta Val D' Elsa – Poggibonsi	36	11	28	49

Azienda USL 8 Arezzo – Ospedale Santa Maria alla Gruccia - Montevarchi	37	7	26	49
Presidio ospedaliero Campo di Marte – Lucca	32	23	20	40
Nuovo ospedale del Mugello – Borgo San Lorenzo	27	5	25	39
Presidio ospedaliero Valle del Serchio – Castelnuovo Garfagnana e Barga	25	16	15	29
Presidio ospedaliero Villamarina – Piombino	17	9	17	23
Ospedali riuniti Valdichiana Senese – Montepulciano	12	2	9	20
Ospedale del Casentino – Bibbiena	13	9	20	19
Presidio ospedaliero Orbetello Colline Dell' Albegna – Orbetello	12	1	8	19
Presidio ospedaliero della Lunigiana – Pontremoli e Fivizzano	12	4	7	11
Casa di cura Villa Donatello – Firenze	10	1	10	11
Ospedale Santa Margherita – Zona Valdichiana – Cortona	6	2	5	10
Ospedale Amiata Senese – Abbadia San Salvatore	7	1	2	9
Casa di cura Ulivella – Firenze	7	0	0	9
Presidio ospedaliero Colline Metallifere (Sant' Andrea) – Massa Marittima	6	13	13	8
Casa di cura Santa Chiara – Firenze	4	0	4	8
Casa di cura Santa Zita – Lucca	5	0	1	8
Ospedale Santa Maria Maddalena –	7	0	3	7

Volterra				
Presidio ospedaliero Cecina	6	7	5	7
Azienda ospedaliera-universitaria Anna Meyer – Firenze	4	2	3	7
Casa di cura San Camillo – Forte dei Marmi	3	5	2	6
Presidio ospedaliero di Portoferraio	4	5	3	5
Casa di cura Villa Tirrena – Livorno	3	7	9	5
Casa di cura Poggio Sereno – Fiesole	6	0	0	4
Casa di cura Valdisieve SAS – Pelago	3	0	3	4
Casa di cura Poggio del Sole – Arezzo	2	0	2	3
Casa di cura M.D. Barbantini – Lucca	1	0	1	2
Centro oncologico Fiorentino – Sesto Fiorentino	1	1	2	2
Casa di cura Villa Cherubini – Firenze	2	0	0	2
Casa di cura Villa delle Terme – Impruneta	2	0	0	2
Casa di cura Leonardo - Vinci	2	3	5	2
Casa di cura Il Pergolino – Firenze	1	0	0	1
Ospedale civile di Castel del Piano	1	0	0	1
Casa di cura privata San Rossore – Pisa	1	0	1	1
San Giuseppe Hospital – Arezzo	1	0	1	1
Casa di cura della Misericordia – Cascina	1	0	0	1
Ospedale zona Valtiberina – Sansepolcro	1	0	0	1
Casa di cura Villa Fiorita – Prato	0	4	4	0
Casa di cura Suore dell' Addolorata – Pisa	0	2	2	0
Total	**1.933**	**561**	**1.529**	**2.645**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/toscana/2008/mdc13.shtml

Fig. 7.68: Toscana

Average distance to oncology center: 13,27 km

Population: 3.734.355

Area: 22.994 km²

Importance weight: 3.734.355/60.494.632 = 0,06173

Umbria

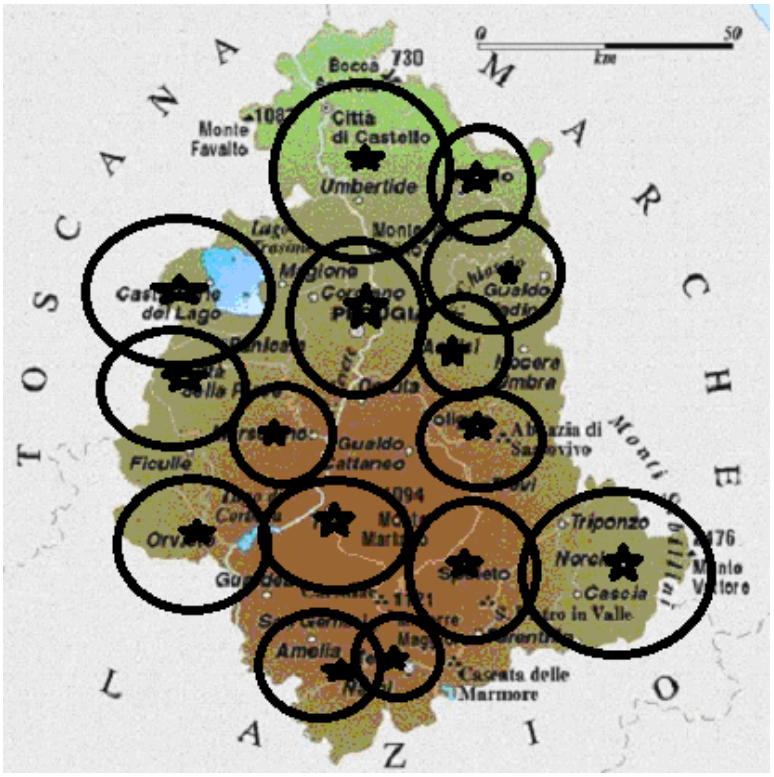
Table 7.27: Oncology centers in region Umbria

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Ospedale Santa Maria della Misericordia – Perugia	107	108	136	147
Azienda ospedaliera Santa Maria – Terni	80	68	84	130
Ospedale nuovo San Giovanni Battista – Foligno	57	50	74	86
Presidio ospedaliero Alto Tevere – Citta' di Castello e Umbertide	53	3	22	63
Ospedale civile San Matteo degli Infermi – Spoleto	41	28	46	63
Ospedale di Assisi	16	4	16	23
Presidio ospedaliero di Narni - Amelia	23	20	25	22
Ospedale Santa Maria della Stella – Orvieto	22	9	11	22
Ospedale di Marsciano	16	4	16	20
Presidio ospedaliero Alto Chiascio – Gubbio	12	3	12	16
Stabilimento ospedaliero di Castiglione del Lago	13	14	22	16
Casa di cura Liotti SPA – Perugia	5	4	9	8
Stabilimento ospedaliero di Todi	7	1	2	8
Ospedale civile di Norcia	8	1	0	6
Ospedale Beato Giacomo Villa – Citta' della Pieve	3	0	0	4
Casa di cura Villa Aurora SPA – Foligno	1	1	2	2
Casa di cura Porta Sole – Perugia	2	1	3	2

Total	**466**	**319**	**480**	**637**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/umbria/2008/mdc13.shtml

Fig. 7.69: Umbria



Average distance to oncology center: 13,80 km

Population: 904.904

Area: 8.456 km²

Importance weight: 904.904/60.494.632 = 0,01496

Marche

Table 7.28: Oncology centers in region Marche

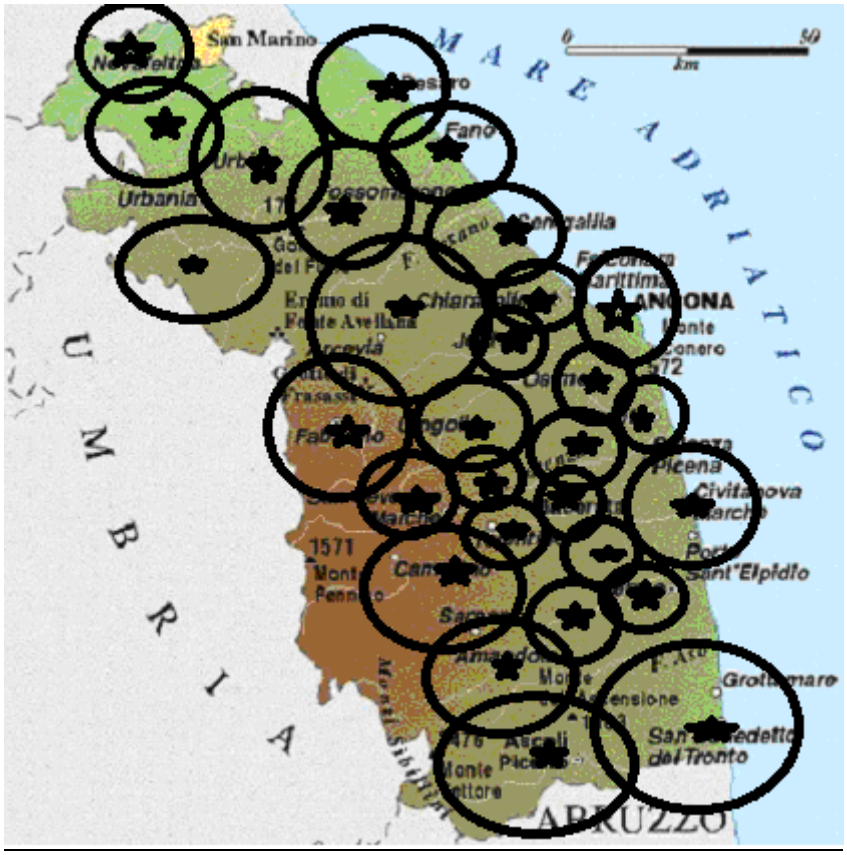
Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Presidio ospedaliero G. Salesi – Ancona	86	25	92	112
Azienda ospedaliera San Salvatore – Pesaro	62	38	43	96
Ospedale Santa Croce – Fano	78	28	20	89
Azienda ospedaliera-universitaria Umberto I - Ancona	66	18	13	86
Ospedale Santa Maria della Misericordia – Urbino	50	28	43	75
Presidio ospedaliero di Macerata	49	80	36	72
Ospedale Principe di Piemonte – Senigallia	45	60	46	65
Presidio ospedaliero Mazzoni – Ascoli Piceno	41	32	60	64
Ospedale Murri – Jesi	45	16	34	58
Ospedale Bartolomeo Eustacchio – San Severino Marche	35	12	29	53
Ospedale Egles Profili – Fabriano	34	10	31	41
Presidio ospedaliero Madonna del Soccorso – San Benedetto del Tronto	28	52	33	40
Ospedale A. Murri – Fermo	29	34	16	34
Ospedale civile di Civitanova Marche	24	10	24	28
Casa di cura privata Villa Anna –	13	2	11	19

San Benedetto del Tronto				
Ospedale SS. Benvenuto e Rocco – Osimo	13	7	17	15
Ospedale di Recanati	11	5	9	13
Casa di cura privata Stella Maris SRL - San Benedetto del Tronto	7	0	7	10
Casa di cura Villa dei Pini – Civitanova Marche	8	0	3	8
Casa di cura Villa Igea – Ancona	7	0	7	7
S. Maria della Pieta' - Camerino	3	2	3	7
Casa di cura Villa Serena – Jesi	6	0	4	7
Ospedale di Pergola	4	0	3	6
Ospedale Sacra Famiglia – Novafeltria	6	5	9	5
Presidio ospedaliero – Amandola	5	0	0	5
Ospedale civile di Fossombrone	3	0	0	4
Ospedale Lanciarini - Sassocorvaro	2	2	2	3
Presidio di Tolentino	2	0	1	2
Casa di cura San Marco – Ascoli Piceno	2	0	0	2
Inrca – Istituto di Ricovero a Carattere Scientifico – Ancona	2	0	0	2
Presidio ospedaliero di comunita' – Chiaravalle	1	1	0	1
Santa casa di Loreto	1	0	0	1
Ospedale di Cingoli	1	0	0	1
Presidio di Treia	1	0	0	1
Ospedale di Montegiorgio	1	0	0	1

Ospedale di Sant' Elpidio a Mare	1	0	0	1
Inrca – Istituto di Ricovero e Cura a Carattere Scientifico – Fermo	1	0	0	1
Total	**773**	**467**	**596**	**1.036**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/marche/2008/mdc13.shtml

Fig. 7.70: Marche



Average distance to oncology center: 12,32 km

Population: 1.560.785

Area: 9.366 km²

Importance weight: 1.560.785/60.494.632 = 0,02580

Abruzzo

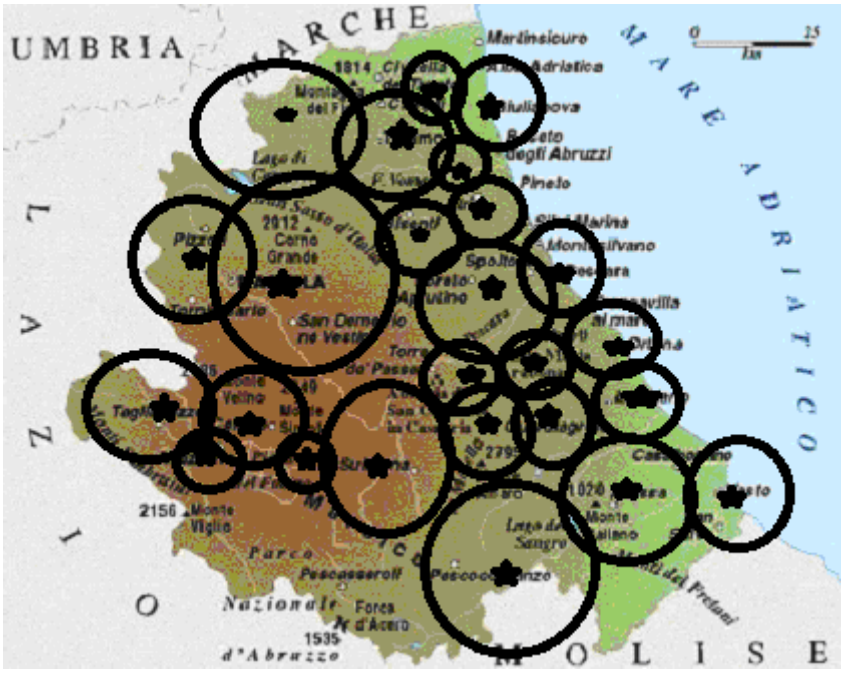
Table 7.29: Oncology centers in region Abruzzo

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Ospedale Spirito Santo – Pescara	133	99	72	170
Ospedale San Salvatore – L'Aquila	97	80	99	120
Ospedale clinicizzato SS. Annunziata – Chieti	59	95	79	89
Ospedale civile Giuseppe Mazzini – Teramo	58	34	30	59
Ospedale civile Floraspe Renzetti – Lanciano	37	28	29	57
Ospedale SS. Nicola e Filippo – Avezzano	36	33	53	51
Casa di cura Pierangeli - Pescara	27	1	18	36
Ospedale San Massimo – Penne	21	30	30	35
Ospedale San Pio da Pietrelcina – Vasto	32	12	37	32
Ospedale Gaetano Bernabeo – Ortona	17	31	39	20
Ospedale SS. Trinita' – Popoli	14	11	16	20
Ospedale SS. Annunziata – Sulmona	13	9	12	18
Ospedale San Salvatore – Atri	17	2	10	17
Villa Pini d' Abruzzo – Chieti	14	0	2	16
Casa di cura Santa Maria – Avezzano	11	0	7	12

Presidio ospedaliero Val Vibrata – Sant' Omero	8	16	7	11
Casa di cura Dott. Spatocco – Chieti	8	1	5	11
Ospedale San Camillo de Lellis - Atessa	4	0	1	6
Casa di cura Villa Serena – Citta' Sant' Angelo	2	0	2	4
Ospedale Maria Santissima dello Splendore – Giulianova	4	8	1	3
Ospedale Giuseppe Consalvi – Casoli	3	0	0	3
Ospedale civile di Castel di Sangro	2	0	1	3
Casa di cura L' Immacolata – Celano	2	0	1	3
Casa di cura Villa Letizia – Preturo	2	1	3	3
Presidio ospedaliero Serafino Rinaldi – Pescina	2	0	0	3
Casa di cura Sanatrix – L' Aquila	2	0	0	2
Ospedale Umberto I – Tagliacozzo	1	0	0	1
Ospedale SS. Immacolata – Guardiagrele	1	5	0	1
Casa di cura Dott. Nicola di Lorenzo – Avezzano	0	1	0	0
Total	**627**	**497**	**554**	**808**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/abruzzo/2008/mdc13.shtml

Fig. 7.71: Abruzzo



Average distance to oncology center: 10,74 km

Population: 1.339.317

Area: 10.763 km²

Importance weight: 1.339.317/60.494.632 = 0,02214

Lazio

Table 7.30: Oncology centers in region Lazio

Hospital	Hospitali-zation	Day Care	Surgeries	Medicare Weight
Policlinico universitario Agostino Gemelli – Roma	2.331	223	679	2.644
Istituto nazionale tumori Regina Elena I.R.C.C.S. – Ifo – Roma	350	130	238	458
Azienda policlinico Umberto I - Roma	351	297	215	441
Ospedale San Carlo – Idi – Roma	206	32	140	232
Universita' Campus Biomedico – Roma	176	2	53	214
San Giovanni Calibita – Fatebenefratelli – Roma	142	69	95	198
San Camillo Forlanini – Roma	145	44	90	191
Azienda ospedaliera Sant' Andrea – Roma	111	10	84	156
Azienda ospedaliera San Giovanni – Addolorata – Roma	107	2	83	149
Azienda complesso ospedaliero "San Filippo Neri" – Roma	83	20	89	135
Ospedale Santa Maria Goretti – Latina	89	25	63	116
Ospedale Sant' Eugenio – Roma	90	74	126	102
Ospedale San Pietro Fatebenefratelli – Roma	78	2	72	94
Casa di cura Marco Polo – Clinica Oncologica monospecialistica – Roma	95	36	0	92
Azienda ospedaliera-universitaria Policlinico Tor Vergata – Roma	73	13	34	88

Ospedale Santo Spirito – Roma	46	20	45	75
Ospedale "Cristo Re" – Roma	55	4	42	70
Casa di cura Fabia Mater della Sacli SPA – Roma	49	7	55	65
Polo ospedaliero Centrale "Belcolle" – Viterbo	45	11	28	56
Ospedale Giovanni Battista Grassi – Roma	54	2	50	52
Policlinico Casilino – Roma	32	29	56	52
Ospedale Sandro Pertini – Roma	39	8	26	51
Casa di cura Quisisana – Roma	42	0	21	49
Ospedale Regina Apostolorum – Albano Laziale	27	1	14	42
Ospedale Madre Giuseppina Vannini – Roma	33	10	35	42
Idi – Istituto Dermatologico dell' Immacolata – Roma	40	13	9	41
Ospedale San Giovanni di Dio – Fondi	35	3	22	40
Ospedale SS. Trinita' – Sora	31	13	27	39
Casa di cura Citta' di Roma	30	17	44	39
Aurelia Hospital – Roma	27	0	24	34
San Camillo de Lellis – Rieti	29	12	28	32
Casa di cura Nuova Itor – Roma	19	3	17	31
Ospedale San Giovanni Evangelista – Tivoli	24	10	17	30
Casa di cura Villa Pia – Roma	18	6	22	29
Casa di cura Paideia – Roma	26	34	8	27
Casa di cura privata Sant' Anna S.R.L. – Cassino	16	6	18	26
Casa di cura Madonna delle Grazie –	18	0	16	26

Velletri				
Ospedale San Giuseppe – Marino	18	2	20	26
Casa di cura Annunziatella – Roma	24	0	23	25
Ospedale Santa Scolatica – Cassino	27	0	16	24
Casa di cura privata Nuova Villa Claudia – Roma	21	8	29	23
Ospedale Fabrizio Spaziani – Frosinone	24	9	15	22
Presidio ospedaliero "Ercole de Santis" – Genzano di Roma	18	0	16	22
Ospedale Paolo Colombo – Velletri	16	1	14	22
Policlinico Luigi di Liegro – Roma	14	12	23	21
Ospedale San Paolo – Civitavecchia	16	9	7	21
Casa di cura Villa Margherita – Roma	21	0	19	21
Ospedale pediatrico Bambino Gesu' – Roma	15	11	4	20
Ospedale Parodi Delfino – Colleferro	13	9	9	19
Casa di cura Villa Gioia – Sora	18	0	17	19
SS. Gonfalone – Monterotondo	15	2	16	19
Ospedale A. Angelucci – Subiaco	15	3	12	19
Ospedale di Tarquinia	13	7	9	18
Casa di cura Villa Flaminia – Roma	18	0	4	17
Casa di cura Mater Dei – Roma	16	1	12	16
Ospedale San Benedetto – Alatri	13	0	12	15
Casa di cura Pio XI – Roma	11	0	7	14
Clinica Casa del Sole – Formia	12	1	11	13
Ospedale Anzio – Nettuno	12	9	10	13
Ars Medica – Roma	13	4	5	13
Casa di cura "Villa Santa Maria di Leuca" – Roma	7	0	7	13

Casa di cura Sant'Anna – Policlinico Citta' di Pomezia	8	0	6	12
Ospedale Civita Castellana	9	3	8	12
Rome American Hospital – Roma	8	2	3	11
Casa di cura Santa Famiglia – Roma	9	3	12	11
Ospedale Dono Svizzero – Formia	9	1	0	10
Istituto Neurotraumatologico Italiano SRL – Divisione Grottaferrata	10	0	0	10
Casa di cura Villa Mafalda – Roma	11	4	8	10
Casa di cura Salvator Mundi – Roma	7	0	6	9
Ospedale civile Padre Pio – Bracciano	8	0	4	9
Casa di cura Guarnieri SRL – Roma	10	16	25	9
Casa di cura Villa Valeria – Roma	5	0	5	9
Villa Tiberia S.R.L. – Roma	4	1	4	9
Casa di cura Madonna della Fiducia – Roma	8	0	1	9
Ospedale San Giacomo – Roma	6	9	3	8
Casa di cura Nuova Santa Teresa – Viterbo	9	0	0	8
Ospedale Coniugi Bernardini – Palestrina	5	0	5	8
Ospedale di Acquapendente	5	3	7	7
Casa di cura NS. Signore delle Mercede – Roma	3	2	3	7
C.T.O. Centro traumatologico ortopedico "Andrea Alesini" – Roma	3	0	2	6
Casa di cura Villa del Rosario – Roma	7	0	4	6
Ospedale Alfredo Fiorini – Terracina	8	3	2	5
Clinica Siligato SRL - Civitavecchia	4	0	4	5
Ospedale civile – Anagni	3	2	3	4

Clinica addominale All' Eur – Roma	2	0	1	4
Presidio ospedaliero Villa Betania – Roma	2	3	2	4
Casa di cura San Marco – Latina	4	1	5	4
Casa di cura San Luca – Roma	4	0	4	4
Casa di cura Villa Aurora – Roma	4	0	2	3
Ospedale Regina Elena – Priverno	4	2	6	3
Presidio ospedaliero "Pasquale del Prete" - Pontecorvo	3	0	1	3
Casa di cura Assunzione di Maria SS. – Roma	2	0	2	3
Ospedale Don Luigi di Liegro – Gaeta	3	4	4	3
Casa di cura Villa Azzurra – Terracina	3	0	0	2
Casa di cura Villa Stuart – Roma	4	0	0	2
Casa di cura "Santo Volti" – Roma	1	0	1	2
Presidio ospedaliero "Della Croce" – Atina	2	0	0	2
Casa di cura Citta' di Aprilia	2	0	2	2
Ospedale "Marzio Marini" – Magliano Sabina	1	0	1	2
Casa di cura Salus – Viterbo	1	0	0	1
Casa di cura "Villa Domelia" – Roma	1	0	0	1
Casa di cura "Nostra Signora del Sacro Cuore" – Roma	1	0	0	1
Casa di cura San Feliciano – Roma	1	0	0	1
Momentana Hospital – Fontenuova	1	0	0	1
Casa di cura "San Raffaele" – Velletri	1	0	0	1
Casa di cura Villa Serena – Cassino	1	0	0	1
Casa di cura Villa Verde – Roma	1	0	0	1
Ospedale San Sebastiano Martire – Frascati	2	8	0	1
Concordia Hospital – Roma	1	0	1	1

European Hospital – Roma	1	0	1	1
Casa di cura Santa Teresa – Isola del Liri	1	0	1	1
Ospedale Israelitico – Roma	1	4	0	1
Ospedale San Carlo – Sezze	1	1	0	1
Ospedale "Santa Croce" – Arpino	1	0	0	1
Casa di cura San Giuseppe – Roma	0	5	5	0
Polo ospedaliero centrale – Ospedale di Ronciglione	0	4	3	0
Centro per la salute della donna S. Anna - Roma	0	6	3	0
Ospedale nuovo Regina Margherita – Roma	0	2	1	0
Polo ospedaliero centrale – Ospedale di Montefiascone	0	1	0	0
Presidio ospedaliero San Giuseppe – Albano Laziale	0	6	0	0
Ospedale SS. Salvatore – Palombara Sabina	0	5	0	0
Inrca – Istituto di Riposo e Cura a Carattere Scientifico – Roma	0	9	0	0
Total	**5.773**	**1.38**	**3.163**	**6.972**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/lazio/2008/mdc13.shtml

Fig. 7.72: Lazio

Average distance to oncology center: 15,76 km

Population: 5.710.490

Area: 17.236 km²

Importance weight: 5.710.490/60.494.632 = 0,0944

Campania

Table 7.31: Oncology centers in region Campania

Hospital	Hospitali-zation	Day Care	Surgeries	Medicare Weight
Casa di cura Malzoni "Villa dei Platani" – Avellino	242	222	267	426
Azienda ospedaliera rilievo nazionale San Giuseppe Moscati – Avellino	235	46	114	299
Istituto nazionale per lo studio e la cura dei tumori "Fondazione Pascale" – Napoli	204	90	184	294
Azienda ospedaliera-universitaria Federico II – Napoli	209	210	170	267
Sacro Cuore di Gesu' – Fatebenefratelli – Benevento	222	23	48	248
Ospedale Evangelico Betania – Napoli	102	19	55	125
Azienda ospedaliera di rilievo nazionale Antonio Cardarelli – Napoli	90	42	49	117
Buon Consiglio – Fatebenfratelli – Napoli	69	12	69	98
Alba Clinica San Paolo – Aversa	42	8	50	91
Azienda ospedaliera Sant' Anna e San Sebastiano – Caserta	84	22	88	87
Santa Maria delle Grazie – Pozzuoli	71	21	11	77
Presidio ospedaliero Santa Maria del Popolo degli Incurabili – Napoli	47	0	41	73
Azienda ospedaliera-universitaria San Giovanni di Dio e Ruggi d' Aragona – Salerno	51	1	36	72

Casa di cura Tortorella S.P.A. – Salerno	60	7	12	60
Ospedali riuniti Pagani-Nocera ASL SA – Nocera Inferiore	38	60	22	53
Clinica Mediterranea SPA – Napoli	36	5	36	48
Presidio ospedaliero San Giovanni Bosco – Napoli	28	1	23	43
San Giuseppe Moscati – Aversa	25	5	19	36
Clinica Sanatrix SPA – Napoli	23	3	23	33
Azienda ospedaliera Gaetano Rummo – Benevento	22	14	15	32
Casa di cura Tasso – Napoli	22	11	33	32
Ospedale San Leonardo – Castellamare di Stabia	20	2	17	28
Azienda ospedaliera Seconda Universita' degli Studi – Napoli	19	40	8	25
Casa di cura Pineta Grande – Castel Volturno	17	1	15	25
Ospedale San Paolo – Napoli	16	1	10	23
Presidio ospedaliero dell' Immacolata – Sapri	18	5	9	22
Casa di cura N.S. di Lourdes – Massa di Somma	20	23	6	22
P.O. San Giuliano di Giugliano	19	21	17	21
Azienda ospedaliera Domenico Cotugno – Napoli	20	9	1	21
Clinica Villalba – Napoli	20	1	4	20
Presidio ospedaliero Villa Malta – Sarno	14	1	9	19
Casa di cura Villa Stabia – Castellamare	13	0	12	19

di Stabia				
Casa di cura San Francesco – Telese Terme	14	3	14	18
Presidio ospedaliero Luigi Curto – Polla	13	7	8	18
Ospedale Santa Maria di Loreto Mare – Napoli	13	0	7	17
Clinica Villa del Sole - Caserta	13	0	9	16
Casa di cura Villa Fiorita – Capua	16	8	9	16
Casa di cura La Madonnina – San Gennaro – Vesuviano	13	0	13	16
Ospedale SS. Annunziata – Napoli	11	8	17	16
Presidio ospedaliero San Luca – Vallo della Lucania	13	15	22	15
Casa di cura Maria Rosaria SPA – Pompei	12	1	12	15
Hyppocratica SPA – Casa di cura Villa del Sole – Salerno	12	0	12	14
Ospedale internazionale casa di cura – Napoli	12	1	13	14
Ospedale San Gennaro – Napoli	15	63	8	14
Casa di cura Villa delle Querce - Napoli	13	5	13	14
Ospedale San Rocco – Sessa Aurunca	9	3	7	14
Casa di cura Villa Cinzia - Napoli	14	0	14	14
Casa di cura privata Malzoni S.P.A. – Agropoli	12	11	9	13
Presidio ospedaliero Mauro Scarlato – Scafati	10	3	9	13
Casa di cura Santa Rita – Atripalda	8	2	9	13
Casa di cura Villa dei Fiori – Mugnano di	13	0	4	13

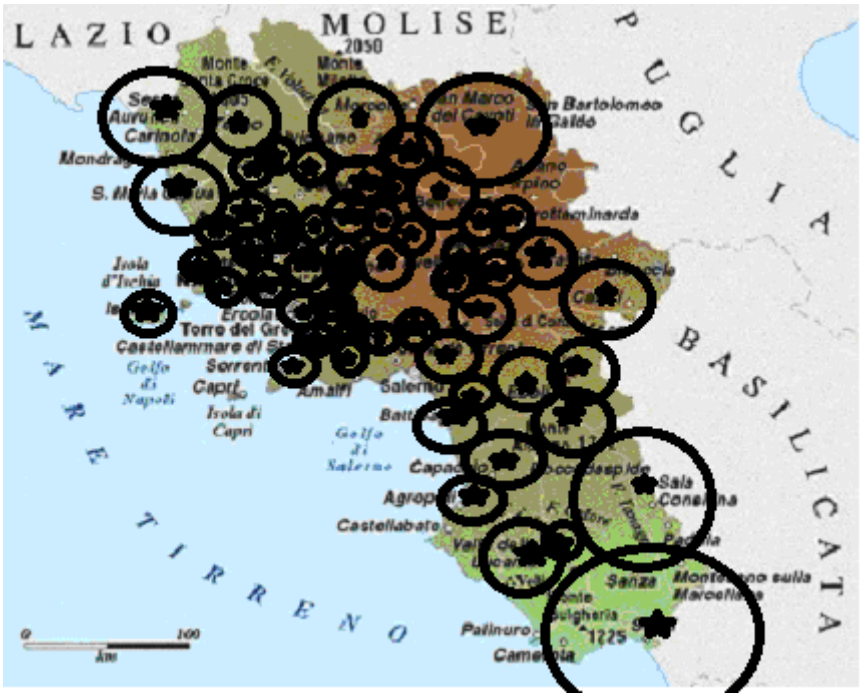
Napoli				
Ospedale Amico Gaetano Fucito – Mercato San Severino	9	4	11	12
Clinica Santa Patrizia – Napoli	11	1	8	12
Ospedale A. Landolfi – Solofra	9	2	9	12
Casa di cura A. Grimaldi – San Giorgio a Cremano	10	0	9	11
Casa di cura San Michele – Maddaloni	9	3	11	11
Clinica Salus – Battipaglia	9	4	7	11
Presidio ospedaliero S. Maria della Pieta' - Casoria	10	19	0	11
Casa di cura Trusso – Ottaviano	9	16	5	10
Presidio ospedaliero di Piedimonte Matese	10	22	4	10
Casa di cura Villa dei Fiori – Acerra	6	0	6	10
Ospedale civile Torre Annunziata – Boscotrecase	7	0	6	10
Ospedale dei Pellegrini – Napoli	4	2	4	9
Casa di cura Maria Venosa – Battipaglia	10	0	9	8
Ospedale San Giovanni di Dio – Frattaminore	7	7	8	8
Ospedale De Luca e Rossano – Vico Equense	6	3	7	8
Ospedale Maresca – Torre del Greco	8	0	5	8
Azienda ospedaliera pediatrica Santobono – Pausilipon – Napoli	6	10	4	8
Santa Maria della Pieta' – Nola	6	0	1	7
Ospedale di Ariano Irpino	6	9	5	7
Presidio ospedaliero di Maddaloni	6	2	5	6

Ospedale Cardinale Ascalesi - Napoli	4	3	3	6
Presidio ospedaliero di Marcianise	5	4	9	6
Ospedale Santa Maria della Speranza – Battipaglia	6	2	4	6
Casa di cura Villa delle Margherite – Torre del Greco	3	1	4	6
Ospedale Andrea Tortora – Pagani	3	1	3	5
Ospedale Cav. Apicella – Pollena Trocchia	4	4	3	5
Casa di cura Meluccio SRL – Medicina Future Group – Pomigliano d' Arco	3	0	3	5
Ospedale Maria SS. Addolorata – Eboli	6	2	5	5
Casa di cura Santa Lucia – San Giuseppe Vesuviano	5	0	5	5
Ospedale Santa Maria Incoronata dell' Olmo – Cava de Tirreni	5	0	2	5
Azienda ospedaliera V. Monaldi – Napoli	2	3	3	5
Casa di cura Villa Maione – Villaricca	5	1	6	4
Casa di cura Santo Stefano – Napoli	5	0	5	4
Ospedale G. Criscuoli – Sant' Angelo dei Lombardi	2	3	3	3
Ospedale Anna Rizzoli – Ischia	2	0	1	3
Casa di cura Santa Maria della Salute – Santa Maria Capua Vetere	2	1	3	3
Casa di cura Villa Maria – Baiano	1	0	1	2
Casa di cura Villa Maria – Mirabella Eclano	1	0	1	2
Casa di cura Cobellis – Vallo della Lucania	2	0	0	2
Presidio ospedaliero San Giuseppe e	2	0	2	2

Melorio – Santa Maria Capua Vetere				
Ospedale San Francesco d' Assisi – Oliveto Citra	2	2	2	1
Presidio ospedaliero di Rocca d' Aspide	2	0	1	1
Ospedale F. Palasciano - Capua	1	1	0	1
CTO – Centro Traumatologico Ortopedico - Napoli	1	0	0	1
Villa dei Pini – Piedimonte Matese	1	1	2	1
Ospedale Maria delle Grazie – Cerreto Sannita	1	0	0	1
Casa di cura Villa Russo – Napoli	1	0	0	1
Casa di cura Santa Maria la Bruna – Torre del Greco	0	3	3	0
Presidio sanitario intermedio Santa Maria di Loreto Crispi – Napoli	0	1	1	0
Ospedale G. Guglielmo – Bisaccia	0	1	0	0
Ospedale G. Da Procida - Salerno	0	11	0	0
Ave Grazia Plena – San Felice a Cancello	0	12	0	0
Ospedale nuovo di Gragnano	0	10	0	0
Total	**2.589**	**1.22**	**1.881**	**3.418**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/campania/2008/mdc13.shtml

Fig. 7.73: Campania



Average distance to oncology center: 14,75 km

Population: 5.825.569

Area: 13.590 km²

Importance weight: 5.825.569/60.494.632 = 0,09630

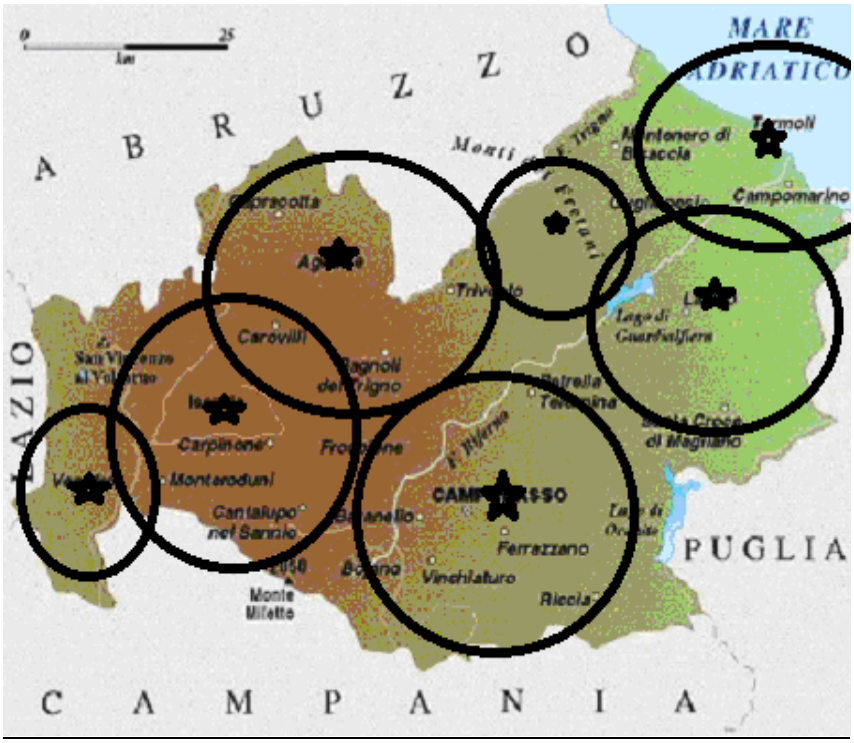
Molise

Table 7.32: Oncology centers in region Molise

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Centro di ricerca Universita' Cattolica del Sacro Cuore – Campobasso	1.095	110	275	1.255
Presidio ospedaliero Antonio Cardarelli – Campobasso	137	21	17	142
Ospedale San Timoteo – Termoli	15	0	10	20
Ospedale F. Veneziale – Isernia	12	2	10	19
Ospedale Giuseppe Vietri – Larino	9	2	1	12
San Francesco Caracciolo – Agnone	11	1	6	11
Ospedale SS. Rosario – Venafro	3	0	2	6
Total	**1.282**	**136**	**321**	**1.465**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/molise/2008/mdc13.shtml

Fig. 7.74: Molise



Average distance to oncology center: 13,78 km

Population: 320.042

Area: 4.438 km²

Importance weight: 320.042/60.494.632 = 0,00529

Puglia

Table 7.33: Oncology centers in region Puglia

Hospital	Hospitali-zation	Day Care	Surgeries	Medicare Weight
I.R.C.C.S. Casa Sollievo della Sofferenza - San Giovanni Rotondo	1.004	5	109	1.127
Azienda ospedaliera-universitaria Policlinico di Bari	1.071	7	168	840
Ospedale Vito Fazzi – Lecce	221	55	107	254
Ospedale SS. Annunziata e San Giuseppe Moscati – Taranto	138	60	98	188
Ospedale Cardinale G. Panico – Tricase	78	6	43	109
Istituto Tumori "Giovanni Paolo II" I.R.C.C.S. Ospedale oncologico – Bari	76	39	48	106
Ospedali riuniti di Foggia	70	20	63	90
Presidio ospedaliero di Summa-Antonio Perrino – Brindisi	66	53	46	72
Presidio ospedaliero "Di Venere" – Bari	50	13	41	70
Ente Ecclesiastico Ospedale Miulli – Acquaviva delle Fonti	51	8	28	69
Casa di cura La Madonnina – Bari	51	0	48	66
Presidio ospedaliero di Copertino e Nardo'	44	22	29	66
Presidio ospedaliero Teresa Masselli – San Severo	48	0	33	63
Ospedale civile "Sacro Cuore" – Gallipoli	46	13	13	55
Ospedale San Paolo – Bari	49	9	48	51
Presidio ospedaliero di Putignano – Noci e	30	1	20	48

Gioia del Colle				
Casa di cura Villa Verde – Taranto	37	0	0	39
Presidio ospedaliero Occidentale – Castellaneta	28	67	12	28
Presidio ospedaliero di Bisceglie e Trani	16	4	10	21
Presidio ospedaliero di Francavilla Fontana e Ceglie Messapica	24	22	25	21
Casa di cura Santa Maria – Bari	15	0	15	20
Casa di cura Bernardini – Taranto	17	0	14	17
Presidio ospedaliero di Casarano e Gagliano	19	13	13	17
Presidio ospedaliero di Manfredonia e Monte Sant' Angelo	18	3	14	15
Presidio ospedaliero di Conversano e Monopoli	15	1	13	15
Ospedale Lorenzo Bonomo – Andria	13	1	7	14
Ospedale civile Caduti in Guerra – Presidio ospedaliero Canosa di Puglia ASL BAT	13	3	5	14
Ospedale di Barletta	9	11	3	14
Ospedale di Corato e Ruvo di Puglia	10	2	10	12
Ospedale di Martina Franca	11	12	9	12
Clinica San Francesco – Galatina	13	0	11	11
Presidio ospedaliero di Scorrano – Maglie e Poggiardo	9	2	5	11
Ospedale Marianna Giannuzzi – Manduria	10	15	7	10
Ospedale Santa Caterina Novella – Galatina	10	27	8	10
Casa di cura Salus SRL – Brindisi	9	6	14	9
Casa di cura Petrucciani – Lecce	6	0	6	7
Presidio ospedaliero unico ASL Bari 3 –	6	2	0	6

Altamura				
Presidio ospedaliero di Ostuni – Fasano – Cisternino	7	15	7	5
Presidio ospedaliero Giuseppe Tatarella – Cerignola	4	0	2	5
Casa di cura Prof. Brodetti – Foggia	2	0	2	4
Casa di cura d' Amore – Taranto	4	0	4	4
Casa di cura San Michele – Manfredonia	3	0	0	4
Casa di cura Villa Serena – Foggia	3	0	3	3
Casa di cura Santa Rita – Bari	1	0	1	2
Ospedali di Terlizzi e Bitonto	2	0	0	2
Ospedale Francesco Lastaria – Lucera	2	11	1	1
Don Tonino Bello – Presidio ospedaliero di Molfetta	1	2	0	1
I.R.C.C.S. Ospedale Saverio de Bellis – Castellana Grotte	1	0	0	1
Casa di cura San Camillo – Taranto	1	0	1	1
Casa di cura Villa Giustina – Molfetta	1	0	1	1
Total	**3.433**	**530**	**1.165**	**3.629**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/puglia/2008/mdc13.shtml

Fig. 7.75: Puglia

Average distance to oncology center: 16,61 km

Population: 4.087.369

Area: 19.358 km²

Importance weight: 4.087.369/60.494.632 = 0,06757

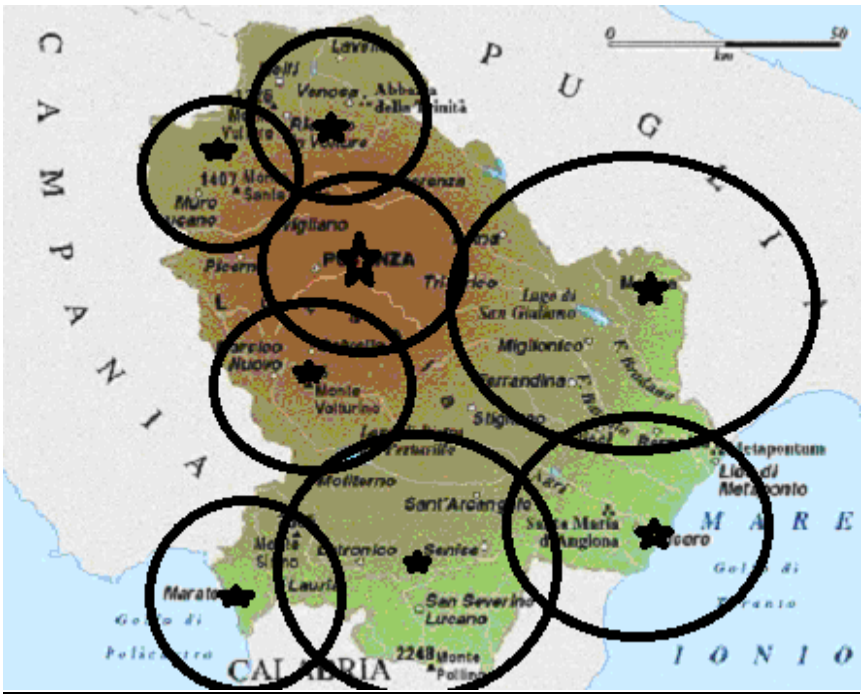
Basilicata

Table 7.34: Oncology centers in region Basilicata

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Azienda ospedaliera Regionale "Ospedale San Carlo" – Potenza	157	53	58	184
Ospedale Madonne delle Grazie – Matera	43	20	50	68
I.R.C.C.S. centro di Riferimento oncologico Della Basilicata – Rionero in Vulture	45	24	23	59
Presidio ospedaliero Unificato – Venosa – Melfi – Pescopagano	10	10	6	12
Ospedale civile Villa d' Agri – Marsicovetere	8	4	1	8
Presidio ospedaliero di Policoro – Policoro	9	6	4	7
Ospedali unificati del Lagonegrese – Lagonegro – Lauria – Maratea	4	7	1	5
Clinica Luccioni spa – Potenza	2	0	2	3
Ospedale San Giovanni Battista – Chiaromonte	2	1	0	3
Total	**280**	**125**	**145**	**349**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/basilicata/2008/mdc13.shtml

Fig. 7.76: Basilicata



Average distance to oncology center: 14,51 km

Population: 588.246

Area: 9.992 km²

Importance weight: 588.246/60.494.632 = 0,009724

Calabria

Table 7.35: Oncology centers in region Calabria

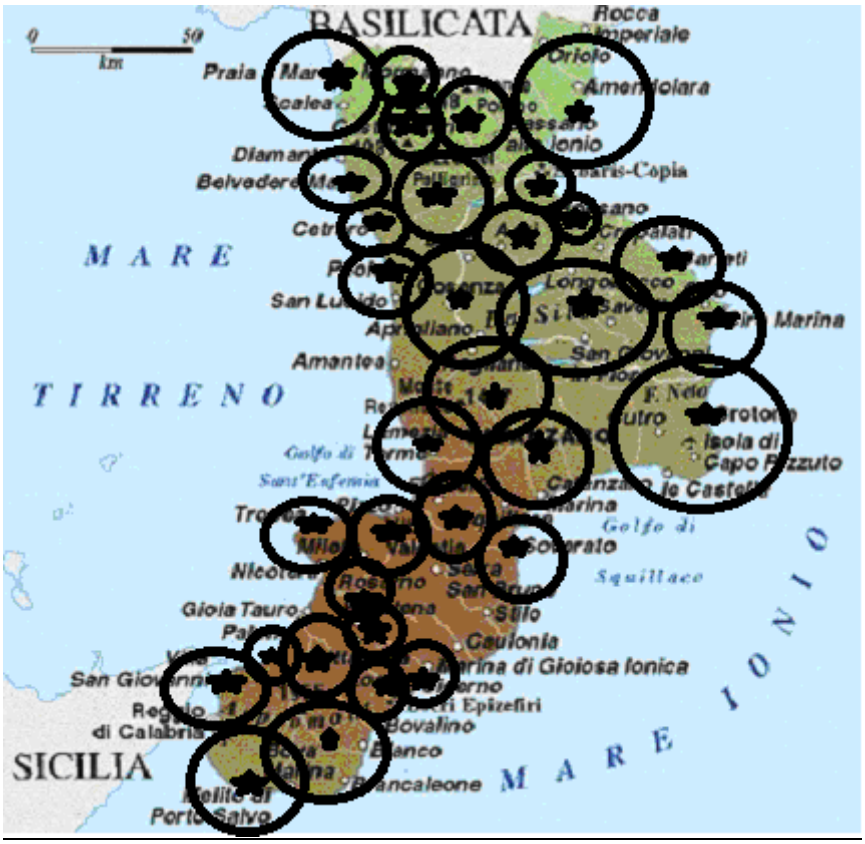
Hospital	Hospitali-zation	Day Care	Surgeries	Medicare Weight
Fondazione Tommaso Campanella – Catanzaro	184	34	111	224
Azienda ospedaliera di Cosenza	118	25	62	131
Presidio ospedaliero de Lellis – Catanzaro	90	29	73	126
Azienda ospedaliera Bianchi Melacrino Morelli – Reggio Calabria	72	38	36	93
Presidio ospedaliero di Siderno	81	27	0	77
Casa di cura Villa Aurora – Reggio Calabria	32	0	26	51
Casa di cura Cascini – Belvedere Marittimo	15	0	11	20
Ospedale Giovanni Paolo II – Lamezia Terme	19	3	12	20
Ospedale civile Ferrari – Castrovillari	17	22	27	19
Casa di cura Sacro Cuore – Cosenza	19	0	17	18
Ospedale Giovanni Iannelli – Cetraro	14	8	16	17
Policlinico Madonna della Consolazione – Reggio Calabria	10	4	10	14
Ospedale Tiberio Evoli – Melito Porto Salvo	8	2	6	13
Ospedale Nicola Giannettasio – Rossano	10	19	5	13
Casa di cura Villa dei Gerani – Vibo	8	0	7	12

Valentia				
Presidio ospedaliero di Locri	7	2	2	9
Ospedale Guido Compagna – Corigliano Calabro	9	2	6	8
Presidio ospedaliero Beato Angelo – Acri	7	8	4	8
Istituto Ninetta Rosano S.R.L. – Belvedere Marittimo	6	0	3	8
Casa di cura privata Villa Michelino – Lamezia Terme	6	0	6	7
Ospedale Guido Chidichino – Trebisacce	7	0	3	7
Ospedale San Giovanni di Dio – Crotone	5	5	5	7
Villa Elisa SPA - Cinquefrondi	6	0	6	6
Inrca – Istituto di Ricovero e Cura a Carattere Scientifico – Cosenza	5	0	0	6
Casa di cura Caminiti – Villa San Giovanni	3	0	3	5
Ospedale Vittorio Cosentino - Cariati	4	1	3	5
Casa di cura privata S. Rita – Ciro' Marina	4	0	2	5
Ospedale Luigi Pasteur – San Marco Argentano	4	2	0	5
Ospedale San Francesco di Paola – Paola	3	39	2	5
Presidio ospedaliero di Praia a Mare	2	1	2	5
Azienda ospedaliera Mater Domini – Catanzaro	2	0	1	3
Ospedale Jazzolino – Vibo Valentia	4	1	1	3
Ospedale Ignazio Toraldo – Tropea	2	10	0	3
Ospedale Santa Maria degli Ungheresi –	2	3	0	3

Polistena				
Villa Giose Hospital – Crotone	2	0	2	2
Casa di cura La Madonnina – Cosenza	2	0	2	2
Villa Ortensia – Cosenza	2	0	1	1
Ospedale di Soverato	1	2	1	1
Ospedale di Lungro	1	0	0	1
Ospedale civile Minervini - Mormanno	1	0	0	1
Casa di cura Villa del Sole SRL – Cosenza	1	0	0	1
Ospedale San Biagio – Chiaravalle Centrale	1	1	0	1
Ospedale Maria Pia di Savoia – Oppido Mamertina	1	0	0	1
Ospedale civile di San Giovanni in Fiore	1	1	0	1
Ospedale civile pentimalli – Palmi	1	0	0	1
Presidio ospedaliero di Soveria Mannelli	0	2	0	0
Ospedale di Soriano Calabro	0	1	0	0
Total	**799**	**292**	**474**	**968**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/calabria/2008/mdc13.shtml

Fig. 7.77: Calabria



Average distance to oncology center: 15,00 km

Population: 2.010.911

Area: 15.079 km²

Importance weight: 2.010.911/60.494.632 = 0,03324

Sicilia

Table 7.36: Oncology centers in region Sicilia

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Azienda ospedaliera per L'emergenza Cannizzaro – Catania	613	255	219	596
A.R.N.A.S. Garibaldi – Presidio Ospedaliero Nesima – Catania	234	125	111	307
Ospedale San Vincenzo – Taormina	228	150	154	292
A.R.N.A.S. civico di Cristina Benefratelli Palermo	160	100	208	237
Azienda ospedaliera Vincenzo Cervello – Palermo	162	100	73	200
Ospedale Buccheri la Ferla – Fatebenefratelli – Palermo	157	46	63	177
Casa di cura la Maddalena – Palermo	116	41	49	157
Azienda ospedaliera universitaria Policlinico Gaetano Martino – Messina	80	35	29	128
Casa di cura Villa dei Gerani – Erice	91	22	7	97
Casa di cura Villa Salus - Messina	82	24	2	83
Azienda ospedaliera civile – Maria Paterno' Arezzo – Ragusa	72	51	27	82
Azienda ospedaliera universitaria Policlinico di Catania	62	13	26	78
Azienda ospedaliera universitaria Policlinico Paolo Giaccone - Palermo	58	52	49	69
Humanitas centro Catanese di	57	1	21	69

Oncologia – Catania				
Ospedale Santo Bambino – Catania	56	14	50	63
Azienda ospedaliera Umberto I – Siracusa	45	14	41	62
Presidio ospedaliero Giovanni Paolo II - Sciacca	37	23	38	48
Presidio ospedaliero Vittorio Emanuele e Ferrarotto – Catania	36	51	36	47
Fondazione Istituto San Raffaele – G. Giglio – Cefalu'	36	18	38	46
Centro clinico e diagnostico G.B. Morgagni – Catania	40	3	6	45
Presidio ospedaliero Sant' Elia – Caltanissetta	38	14	14	39
Casa di cura Candela – Palermo	24	6	30	36
Azienda ospedaliera Papardo – Messina	20	0	17	34
Presidio ospedaliero Umberto I – Enna	23	16	27	31
Ospedale San Giovanni di Dio – Agrigento	21	6	17	29
Casa di cura Villa Serena – Palermo	15	6	18	25
Azienda ospedaliera Gravina – Caltagirone	17	10	22	19
Ospedale G.F. Ingrassia – Palermo	13	3	14	17
Casa di cura Orestano – Palermo	13	4	12	16
Ospedale Santa Marta e Santa Venera – Acireale	9	4	11	16
Ospedale civile R. Guzzardi – Vittoria	16	12	15	16
Ospedale civile di Lentini	9	9	12	16

Casa di cura Carmona – Messina	16	1	0	16
Presidio ospedaliero M. Raimondi – San Cataldo	11	7	4	15
Presidio ospedaliero di Trapani	13	29	17	15
Ospedale Salvatore Cimino – Termini Imerese	13	5	12	14
Ospedale Barone Lombardo – Canicatti'	10	4	5	14
Ospedale Abele Ajello – Mazara Del Vallo	8	1	8	14
Casa di cura Sant' Anna – Erice	15	12	20	13
Casa di cura Cappellani – Messina	9	6	15	13
Casa di cura Noto-Pasqualino – Palermo	11	1	6	12
Ospedale Maggiore – Modica	12	5	14	12
Casa di cura Musumeci – Catania	13	4	1	12
Istituto oncologico del mediterraneo Spa – Viagrande	12	5	3	12
Casa di cura Gibiino – Catania	9	2	11	11
Ospedale Maria SS. Addolorata – Biancavilla	11	6	10	11
Ospedale Carlo Basilotta – Nicosia	13	2	9	11
Ospedale G. Trigona – Noto	9	7	13	10
Casa di cura Triolo Zancla – Palermo	9	1	0	10
Azienda ospedaliera Vittorio Emanuele – Gela	7	6	7	10
Casa di cura Santa Barbara – Gela	6	0	3	10
Ospedale Muscatello – Augusta	7	4	7	9
Nuovo ospedale Cutroni Zodda – Barcellona Pozzo di Gotto	6	5	3	9

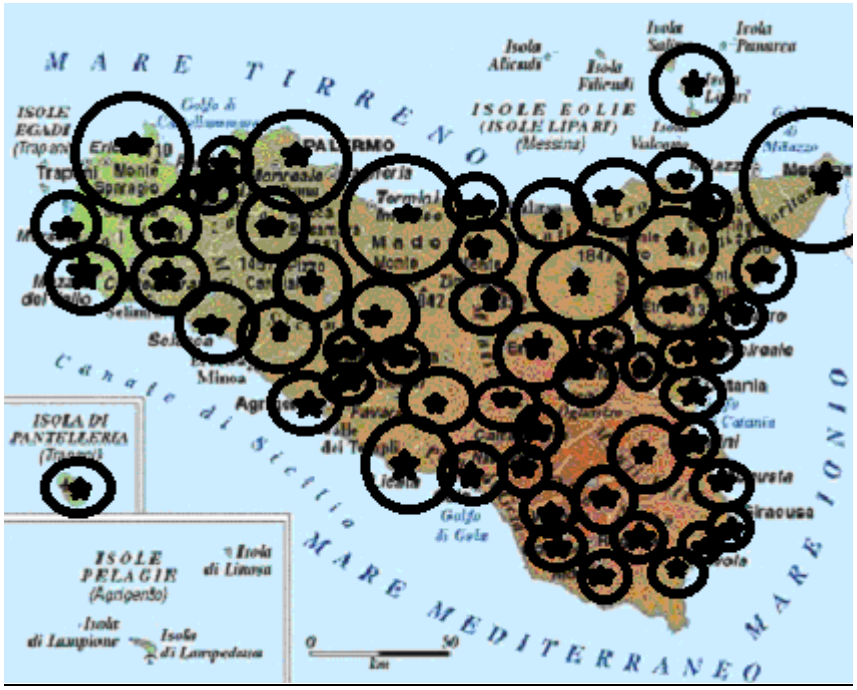
Ospedale dei Bianchi – Corleone	8	1	6	9
Ospedale Barone Romeo – Patti	8	4	3	8
Casa di cura San Camillo – Messina	6	0	3	8
Ospedale Madonna Santissima dell' Alto – Petralia Sottana	7	3	7	8
Ospedale Vittorio Emanuele II – Castelvetrano	7	15	10	8
Casa di cura Argento – Catania	7	1	8	8
Clinica del mediterraneo – Ragusa	4	0	4	8
Ospedale civico – Partinico	6	2	5	8
Ospedale Ferro Branciforte Capra – Leonforte	9	2	7	7
Casa di cura Falcidia – Catania	6	4	10	7
Casa di cura Lucina – Catania	6	5	9	7
Nuova casa di cura Demma – Palermo	4	4	8	7
Presidio ospedaliero Paolo Borsellino – Marsala	6	4	3	6
Ospedale San Giovanni di Dio e San Isidoro – Giarre	7	5	10	6
Ospedale San Vito e Santo Spirito – Alcamo	5	7	10	6
Casa di cura Santa Rita – Messina	6	2	0	6
Casa di cura Villa Mauritius – Siracusa	6	0	0	6
Casa di cura Santa Lucia – Siracusa	3	0	3	5
Ospedale Vittorio Emanuele III – Salemi	5	0	3	5
Ospedale Michele Chiello – Piazza Armerina	4	1	3	5

Istituto ortopedico Villa Salus Innocenzo Galatioto S.R.L. – Augusta	3	0	3	5
Azienda ospedaliera ospedali riuniti Papardo Piemonte – Messina	3	5	2	5
Casa di cura Gretter – Catania	2	5	7	4
Casa di cura Ignazio Attardi – S. Stefano Quisquina	3	2	5	4
Casa di cura S. Anna – Agrigento	3	0	2	4
Ospedale San Giacomo d' Altopasso – Licata	4	3	3	4
Ospedale Grazia di Maria – Avola	2	3	1	4
Ospedale Regina Margherita – Comiso	3	10	8	4
Ospedale Basso Ragusa – Militello in Val di Catania	3	0	1	3
Casa di cura Torina – Palermo	3	0	1	3
Presidio ospedaliero SS. Salvatore – Mistretta	3	4	2	3
Presidio ospedaliero Sant' Agata di Militello	4	6	7	3
Ospedale SS. Salvatore – Paterno'	3	2	4	3
Nuova clinica Villa Rizzo SRL – Siracusa	2	0	2	3
Ospedale Castiglione Prestianni –Bronte	1	3	4	2
Casa di cura Regina Pacis – San Cataldo	1	1	2	2
Istituto ortopedico Franco Scalabrino - Ganzirri – Messina	1	0	1	2
Casa di cura Mater Dei di G. Nesi & C. S.P.A. – Catania	2	0	1	2
Ospedale di Lipari	1	3	1	2

Azienda ospedaliera Villa Sofia C.T.O - Palermo	2	4	0	2
Ospedale Fratelli Parlapiano – Ribera	2	2	3	1
Ospedale Suor Cecilia Basarocco – Niscemi	1	0	0	1
Presidio ospedaliero di Milazzo	1	0	0	1
Casa di cura Cristo Re – Messina	1	0	0	1
Casa di cura Macchiarella - Palermo	1	0	0	1
Centro Catanese di medicina e Chirurgia – Catania	1	0	1	1
Clinica Basile – Tigano – Catania	1	0	1	1
Casa di cura Valsalva Aurora – Catania	1	2	2	1
Presidio ospedaliero Bernardo Nagar - Pantelleria	1	0	0	1
Ospedale Maria Immacolata Longo – Mussomeli	1	1	0	1
Ospedale Busacca – Scicli	1	1	0	1
Casa di cura di Stefano Velona – Catania	1	0	0	1
Casa di cura Latteri – Palermo	1	0	0	1
Centro Andros – Palermo	0	2	2	0
Ospedale Santo Stefano – Mazzarino	0	1	1	0
Centro di chirurgia Genesi – Palermo	0	1	1	0
Istituto clinico polispecialistico Cot – Messina	0	1	0	0
Total	**3.043**	**1.46**	**1.804**	**3.650**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/sicilia/2008/mdc13.shtml

Fig. 7.78: Sicilia



Average distance to oncology center: 11,69 km

Population: 5.046.654

Area: 25.711 km²

Importance weight: 5.046.654/60.494.632 = 0,08342

Sardegna

Table 7.37: Oncology centers in region Sardegna

Hospital	Hospitali-zation	Day care	Surgeries	Medicare Weight
Ospedale Armando Businco – Cagliari	244	151	146	325
Azienda ospedaliera Universitaria di Cagliari	141	71	107	203
Azienda ospedaliera Universitaria – Sassari	105	50	69	133
Ospedale San Francesco – Nuoro	51	28	35	73
Ospedali Giovanni Paolo II – Olbia	37	9	29	48
Presidio ospedaliero San Martino – Oristano	39	19	22	44
Policlinico Sassarese S.P.A – Sassari	26	7	28	35
Presidio ospedaliero Sirai – Carbonia	30	13	5	34
Azienda ospedaliera G. Brotzu – Cagliari	36	26	38	34
Ospedale civile SS. Annunziata – Sassari	29	0	1	31
Ospedale Nostra Signora di Bonaria – San Gavino Monreale	26	16	12	24
Ospedale Paolo Dettori – Tempio Pausania	18	2	13	23
Presidio ospedaliero Santa	18	31	11	23

Barbara – Iglesias				
Ospedale civile presidio Ospedaliero Alghero	17	4	15	16
Presidio ospedaliero Nostra Signora della Mercede – Lanusei	9	4	11	16
Ospedale SS. Trinita' – Cagliari	10	4	7	11
Ospedale Antonio Segni – Ozieri	8	0	6	9
Policlinico citta' di Quartu - Quarto Sant' Elena	8	2	8	8
Ospedale marino – Cagliari	4	0	1	6
Nuova casa di cura – Decimomannu	3	0	2	6
Casa di cura privata Polispecialistica Sant' Elena – Quartu Sant' Elena	3	7	10	6
Casa di cura Villa Elena – Cagliari	6	1	7	5
Presidio ospedaliero Antonio Gaetano Mastino – Bosa	5	3	4	5
Casa di cura Lay – Cagliari	4	0	0	4
Casa di cura Sant' Anna Ost. Ginec. – Cagliari	4	2	4	3
Clinica Tommasini – Jerzu	2	0	0	3
Ospedale G.P. Delogu – Ghilarza	1	1	1	1
Ospedale civile di Thiesi	1	0	0	1
Casa di cura Sant' Antonio Spa – Cagliari	1	0	0	1
Casa di cura Madonna del Rimedio - Oristano	1	0	0	1

Ospedale San Giuseppe Calasanzio – Isili	1	0	0	1
Ospedale di Muravera	1	0	0	1
Ospedale regionale per le Microcitemie – Cagliari	1	1	0	1
Ospedale Cesare Zonchello – Nuoro	0	114	0	0
Total	**890**	**566**	**592**	**1.137**

Source: Il Corriere della Sera, available on http://www.corriere.it/sportello-cancro/db/mdc/sardegna/2008/mdc13.shtml

Fig. 7.79: Sardegna

Average distance to oncology center: 19,75 km

Population: 1.672.804

Area: 24.090 km²

Importance weight: 1.672.804/60.494.632 = 0,02765

Average distance to an oncology center in Italy

(39,91 km * 0,00211) + (12,61 km * 0,07357) + (24,16 km * 0,02671) + (7,5 km * 0,16309) + (11,06 km * 0,07302) + (16,25 km * 0,0171) + (7,94 km * 0,08147) + (13,93 km * 0,02041) + (13,27 km * 0,06173) + (13,80 km * 0,01496) + (12,32 km * 0,02580) + (10,74 km * 0,02214) + (15,76 km * 0,0944) + (14,75 km * 0,09630) + (13,78 km * 0,00529) + (16,61 km * 0,06757) + (14,51 km * 0,009724) + (15,00 km * 0,03324) + (11,69 km * 0,08342) + (19,75 km * 0,02765)

↓

0,0842 km + 0,928 km + 0,6453 km + 1,223 km + 0,808 km + 0,278 km + 0,647 km + 0,284 km + 0,819 km + 0,206 km + 1,488 km + 1,420 km + 0,073 km + 1,122 km + 0,141 km + 0,499 km + 0,975 km + 0,546 km + 0,318 km + 0,238 km

↓

Average distance to an oncology center in Italy = 12,74 km

Chapter 8: Future of nanomedicine: Obstacles and remedies

This chapter is based on the article "Future of nanomedicine: Obstacles and remedies" found in *Rita Bosetti, Lode Vereeck. Future of nanomedicine: Obstacles and remedies. Nanomedicine 2011; (6)4:747–55*

8.1. Introduction

Nanomedicine started almost half a century ago when the first lipid vesicles were described.[53] However, in the past fifteen years, nanoparticulate-based technology has really taken off.[1] Scaling down the size of materials to their molecular level radically changes and improves their physico-chemical properties.[1,9] Hence, their use in medicine offers good prospects for significant advances in the treatment and prevention of diseases.[7,9,22] Although nanomedicine is very promising, its economic, social, and health impacts need to be managed in an integrated and safe way. Its further development requires a thorough technical and medical understanding of nanomedicines and the social and economic obstacles that hamper their commercialization. To that end, it is important to distinguish between ineffective, redundant, and time-consuming obstacles on the one hand and effective, quality- and safety-enhancing filters on the other. Ineffective obstacles have to be removed

and replaced by effective filters. For instance, proper risk assessment based on collected data is a necessary step before commercialization.

The chapter is structured as follows. First, it describes the problems that threaten the future of nanotherapeutics. Then, it discusses some strategies to overcome these issues, i.e. how to transform obstacles into filters. Finally, it provides conclusions aimed at improving the future success rate of nanomedicines.

8.2. Obstacles to success

The success of a new technology depends largely on the existence of a viable market that creates investment opportunities. Although, at this moment, business analysts find it difficult to estimate the volume and growth rates of the nanomedicine market, it is undeniably a billion dollar market expected to grow rapidly.[205,26]

In spite of economic opportunities, nanotherapeutics face some serious obstacles. For instance, successful commercialization is foremost dependent on their reputation with the citizens.[206] Unfortunately, governments, industry, and the general public are poorly informed and prepared for the new health practices.[7,206] Moreover, there is no coordinated strategy among researchers that addresses the

[26] For an overview of approved nanotherapeutics and nanoparticle-based therapies that promise a lot of benefit and might be ripe for commercialization in the not so distant future can be found in: Nanoparticles in medicine: Therapeutic applications and developments. Clinical Pharmacology and Therapeutics (2008); 83(5):761–769 and in particular: table 1: Clinically approved nanoparticle-based therapeutic on page 762; table 2: Nanoparticle-based therapeutics in clinical trials on page 764; and table 3: Nanoparticle-based therapeutics in preclinical development on page 766

potential hazards for health and the environment.[6,7,15,157,206] This might endanger the future of this new and promising technology.

8.2.1. Lack of financial resources and profitability

In spite of high research and development (R&D) costs, the development of nanotherapeutics is primarily driven by start-ups and small and medium sized enterprises (SMEs).[206,207] For the majority of them, however, it proves an unfeasible challenge to commercialize nanomedicines because they lack sufficient financial resources to fully exploit and market their inventions. Evidence shows that SMEs are seldom successful in commercializing nanotherapeutics.[207] Collaboration with larger pharmaceutical firms is, therefore, crucial.[31,207] However, for large pharmaceutical companies, the profitability of their blockbuster traditional drugs is put at risk by investing in new alternative nanotherapeutics. Consequently, for large companies there is almost no commercial incentive to switch. The situation is similar to fossil fuel engine and electrical car. In spite of the ecological need, there is little commercial argument to change technology. Likewise, nanotherapeutics could lead to better efficacy and less treatment-related adverse events, but the commercial need to switch remains low. Moreover, profitability is threatened by diseconomies of scale which results in high acquisition costs for patients.[207]

8.2.2. Lack of confidence

Public knowledge of nanotechnology remains limited. Researchers at the North Carolina State University (NC, USA) found that, in 2004, 80%-85% of American citizens were hardly or not aware of this new technology.[206,208] This finding was consistent with previous studies carried out in Europe and Canada.[206] In 2010, awareness of nanotechnology has grown to approximately 34% among American citizens, and is higher among men (46%) than women (23%).[209] In spite of its huge potential health benefits, citizens are relatively ignorant of nanotechnology. Even amongst informed citizens, perceptions vary widely, leading to a plethora of visions and raising questions about toxicity, environmental damage, and harmful long term effects.[206] Lack of information and inadequate communication give rise to doubts, distrust, and even fear. While this may lead to the dismissal of a specific nanomedical project, it also endangers the future of nanotechnology as a whole since successful commercialization is built upon consumer confidence as shown by the following examples.[206]

MagForce Nanotechnologies, located in Berlin (Germany), is an important player in the field of nanotechnology cancer therapies. It has developed a new treatment with minimal side-effects that aims to cure tumors with the aid of magnetic particles. To promote this therapy, which is in the final stages of clinical trials and could, therefore, be expected on the market in the near future, the company started a campaign in journals and on television. Although MagForce heavily invested in communication and this therapy is well known in the nanotechnology community, it is not in the medical community. Their communication efforts were thus not sufficient to gain a widespread acceptance. Consequently, the desired

impact was not achieved. This example shows that although this promising therapy is ripe for commercialization, it is not accepted by the general public.[210] Moreover, the acceptance of a new safe nanoproduct may falter due to problems with other nanoproducts as the second example shows. In late March 2006, Germany experienced the first nanotechnology incident resulting in health problems among citizens from a bath and tile treatment called Magic Nano. The product caused significant health problems, with approximately hundred citizens affected with respiratory problems and six hospitalized with pulmonary edemas. Although experts were not able to determine whether nanomaterials were the cause of the health problems (manufacturers were not able to supply the full formulations because information was missing from their suppliers), this incident had serious implications for the public perception of nanomedicine in Germany.[206]

8.2.3. Potential hazards

Public acceptance may falter due to the possible toxicities caused by nanotherapeutics. The biologic activity and biokinetics of nanomaterials depend on their size, shape, chemistry, and surface properties. These variables are likely to modify responses and cell interactions and could induce toxicity.[7,158] For instance, bacteria, foreign particles and dead or dying cells are destroyed in the blood stream by the phagocytes. This cellular process, known as phagocytosis, is part of the human immune system. Nanoparticles thus have to try and mislead the immune system in order to survive and prolong their circulation time.[157] This is typically done by surface modification with polyethylene glycol (PEG).[9,157] While this protracts the therapeutic effect, it also increases the risk of bioaccumulation in

organs and tissues which is damaging to human health.[7] Particles with a size of 20-50nm may enter healthy cells and the central nervous system; particles smaller than 70nm can enter the pulmonary interstitium because the macrophages present on the alveolar surfaces of the lungs have difficulties recognizing them.[7,157,211] Inhaled nanoparticles can reach bone marrow, heart, and spleen via the respiratory tract and next through the blood stream and lymph nodes.[7,157,158] Furthermore, nanoparticles as large as 1µm can penetrate the skin.[7,157,158] Finally, some particles invade cells through the gastrointestinal tract while others accumulate in the liver.[7,157] Shape and surface properties (chemistry, area, porosity, and charge) also lead to translocation across epithelia from portal of entry to other organs and tissues.[158] Another source of concern is a supra-optimal bioactivity. Beneficial effects, such as carrier capacity for therapeutics and penetration of cellular barriers for drug delivery, may also entail a risk for inflammatory and pro-oxidant activity.[7,157,158]

If nanoscale particles are not properly contained, they can create serious health and environmental damage. The harm to human health is more likely to manifest itself in the long term and is not limited to the patients under treatment, but affecting the entire population.[7,9,157,158,212] Since nanosized particles are easily aerosolized, the remedy may become worse than the disease. The effect of nanosizing on living organisms and the environment remains, however, unclear.[213] Scientists' knowledge about the stability of nanoparticles is still limited.[7,157,158] Nanoscale particles can cause subtle changes in plant and animal tissues with unclear cascade effects. This lack of knowledge is a major issue for nanomarketeers trying to gain the trust and confidence of citizens.[158]

8.2.4. Inadequate regulation

The behavior and functionality of materials with nanoscale dimensions differ significantly from their parent form.[157,158] Nanoparticles are composed of various materials, have unique surface characteristics, and an enhanced reactivity. While these properties offer great potential benefits, they might also create hazards.[7] However promising nanomedicines might be, their beneficial effects should be placed against the possible hazards.[6,7] Necessary regulation of the latter is hampered by the lack of nanotoxicology studies.[157,158] Since drugs, medical devices, and biological agents are regulated differently at this moment, it is not quite clear how nanotherapeutics should and will be evaluated.[120] For the moment, the tripartite nature of nanoparticle-based therapeutics challenges the three regulatory bodies since no specific and integrated requirements exist to test the health and safety impacts of nanomedicines.[6,157] Current regulation is, therefore, inappropriately based on the ones drawn up for bulk materials. For that reason, advisory agencies and regulatory authorities take a case-by-case approach.[120,206] Not only does the multifunctional nature of nanomedicines require a regulatory approval for each of its three components, also the combined therapy has to be approved. The whole process thus takes a significant amount of time. A more integrated regulatory approach would certainly shorten the approval time.[6] As long as the regulatory process is not attuned to the specific needs of nanomedicine, investors will remain reluctant to invest in nanomedicine projects.[207]

8.2.5. Ineffective patenting

Successful development of nanotherapeutics hinges on the protection of intellectual property rights by means of patents.[214] A patent is an exclusive right to make, use, and sell an invention for a given period of time. It is a crucial incentive for commercialization. Therefore, pharmaceutical firms and laboratories are spending an increasing part of their budgets to acquire and defend patents.[31,214,215] This is particularly true for start-ups.[215] Moreover, patents provide credibility for the companies' stakeholders.[214,215] Alternately, unpatented technology will find it hard to attract investments.[214,215]

Once patents expire, competitors have free access to the technology. Generally, in the first year after expiration generic products are priced 30-40% cheaper than the brand product and to 80% cheaper two years after expiration.[76] Generic manufacturers can market their medicines at much lower prices because they do not incur huge costs of R&D or marketing.[216] Due to long development durations of nanomedicine, most patents risk to expire shortly after commercialization.[212] The long R&D procedures are thus insufficiently taken into consideration in the current patent framework. Consequently, the number of years to recover development costs and earning a reasonable profit (that is needed to encourage further innovation in this particular area) is simply too short.

In principle, a well-designed patent system should be capable of delivering effective patents that signal both safety and medical efficacy into the market. This way, it functions as a trust-enhancing filter. However, if the patenting system is dysfunctional, for instance, by creating unnecessarily long procedures, it may

hinder the spread of nanomedicines. Moreover, companies may be facing overlapping patents owned by others.[215] Current patent legislation thus presents a serious bottleneck for future innovation.[31,214]

8.2.6. Generic and insurance market failure

Theoretically, there should be no difference between brand and generic medicines but their price.[217] In practice, however, some generics are composed of materials of poor quality. This is particularly true for those produced in developing countries.[218] In those countries, there is also a significant risk of counterfeiting, and regulatory authorities are sometimes misled by falsified test results or compliance certificates.[219] Cheap products of poor quality can obviously cause a myriad of side-effects and even a premature death.[218] Furthermore, the marketing of a generic requires only proof of its bioequivalence in healthy subjects, thus assuming comparable clinical efficacy and tolerance in the patient population. This is, however, not an established fact.[217] Generic manufacturers file an Abbreviated New Drug Application (ANDA). Generic drug applications are abbreviated because they are generally not required to include preclinical (animal) and clinical (human) data to establish safety and effectiveness. Instead, generic manufacturers must scientifically demonstrate that their product is bioequivalent. One way this is demonstrated is to measure the time it takes for the generic drug to reach the bloodstream in 24-36 healthy volunteers. This results in the rate of absorption (bioavailability) of the generic drug, which can be compared to that of the brand product. The generic drug must deliver the same amount of active ingredients into the patients' bloodstream in the time period as the brand product. Generic drugs

that are poorly tested could cause significant damages for human health. The arguments above apply to generic medicines in general. However, these problems are many times larger for generic nanotherapeutics such as, for instance, AmBiL (a generic formulation of AmbiSome®, a treatment for anti-fungal infections) or Doxisome™ (a generic formulation of Doxil®/Caelyx®, a cancer agent). These products are not on the market yet because it is not clear how generic versions of nanotherapeutics should be tested and regulated. The problem is that it is almost impossible to define a generic version of nanotherapeutics. Gaspar states: "When we look at potential generic formulations of a nanotherapeutic, the differences on the surface properties related to the manufacturing process are theoretically so wide that we currently can not conceive of having a generic formulation going through as a generic product". He also points out that it is impossible to translate equivalence between innovative nanomedicines and its generic version based solely on physical and chemical data.[220] Since nanotherapeutics have an increased bioavailability, faster onset of action, dose uniformity, and smaller yet more stable dosage forms, they do not fit into abbreviated generic approval pathways.[221] It is thus unclear which tests should be used to show equivalence.

Insurance companies and other third party payers favor and encourage the production of generics by refunding only the cheapest products.[76] They seldom cover the costs of medicines for experimental therapies, however safe and effective. The costs related to 'unproven' technology are not included in current health insurance policies. Although this is a problem related to medicines in general, nanomedicines suffer even more by these policies. Nanotherapeutics often are effective in treating diseases other than the ones listed on the drug's label. If the non-listing implies that they are not covered by insurance policies, there is a

significant risk of loosing cures for life-threatening diseases. Nevertheless, the fast growth of the medicine market is driven by cheap generics, and less by innovative products. While the overall pharmaceutical market is expected to rise by 7-9%, the generics market is estimated to grow by 10-15%. In the end, generics may lead to market erosion. Stated otherwise, a booming market may lead to more revenues and high gains, but small incremental medical benefits for patients.

8.3. Lifting the barriers

8.3.1. Availability of clinical data and cost-effectiveness analyses

Commercialization starts with a business plan that convinces private investors or third party payers. Since only cost-effective drugs will make their way to the market, cost-effectiveness analysis (CEA) is helpful in demonstrating that the cost per additional health effect is worth paying for. CEA compares the costs and effects of two or more treatments. It allows health administrators to efficiently allocate limited resources and maximize health effects at the lowest cost. Objectified CEA may also facilitate strategic collaborations between SMEs and skeptical large companies.

The failure rate for new drug molecules is very high. While in the early stages of the development process this is mainly due to an inadequate therapeutic index, in late-stage clinical development, economic reasons take the lead. Because the cost of failure rises with duration, unsuccessful drugs have to be abandoned as soon as possible.[167] An important venue to avoid waste of scarce resources and maximize

therapeutic value for patients is economic evaluation (cost-effectiveness analysis), which should be pursued in the early phases of the drug development cycle. If the new nanotherapeutic does not save a sufficient number of quality-adjusted life years (QALYs) to break even, it should not be developed further. Firstly, nanotechnologists should provide an estimate of how many QALYs the new nanotherapeutic could save during its entire lifecycle. Secondly, health economists should provide a rough estimate of the cost for developing and commercializing the new nanotherapeutic. Organizations like the National Institute for Health and Clinical Excellence (NICE) or the National Cancer Institute (NCI) consider a new medicine or technology as cost-effective if its cost is lower than a threshold value of US$35.000-US$50.000 per QALY. If the new drug costs more than the threshold value, it is considered not cost-effective and its further development and commercialization should be abandoned.

The scarcity of clinical data is, however, a major impediment for any serious CEA of nanomedicine. Rendering the necessary data available is an absolute precondition for the success of CEA and, in turn, nanomedicine. To that end, a platform needs to be developed where health economists can work closely together with technologists, clinical researchers from industry and academia, clinicians, health care providers, and patient associations.

8.3.2. Public communication

Consumer confidence is another precondition for successful commercialization of nanomedicine. Therefore, the general public should be properly informed about the benefits and potential hazards of new nanotherapeutics.[205] Since most individuals are risk-averse, all possible risks should be thoroughly assessed in advance.[222,223] An important way of informing the citizens is via active public debate in citizens' panels, consensus conferences, and educational events. This is a first step in dealing with the concerns of people and fostering a broader dialogue that goes beyond risks versus benefits.[206] Sufficient financial resources have to be devoted to other forms of communication as well. For instance, medical doctors are supplemented by websites as a primary source of information. Therefore, public authorities should provide accessible information of excellent quality on the internet.

8.3.3. Nanotoxicology studies

Engineered nanoparticles can enter the body through inhalation, ingestion, skin uptake, and injection.[7,157,158] While their objective is to increase the chance of recovery and minimize adverse events, their impact on health and the environment remains largely unknown.[7,158] It is subject of great concern among the general public.[158] To overcome public distrust, more nanotoxicological risks assessments need to be carried out.[7,158] Information about potential harm is not only necessary for an objective debate, but also to improve the use of nanotherapeutics. In developing a strategy for risk assessment, a balance needs to be found between

identifying potential hazards and developing new nanomedicines. To select the right materials in the right situation, the toxicology and potential hazards associated with a specific material have to be known. Furthermore, this information has to be communicated with personnel, and regulators.[224] Firstly, sufficient resources should be allocated to risk assessment, and correct procedures for risk management have to be established. Secondly, international and multidisciplinary expert workshops, including materials scientists, chemists, toxicologists, physicians, and regulators, should be set up to establish a nanoparticle classification scheme and testing guidelines. This is currently being done under the auspices of the Organisation for Economic Co-operation and Development (OECD). Thirdly, the stability of surface properties has to be determined both in vivo and in ecologic settings, leading to the selection of appropriate doses and concentrations.[158,225,226] Finally, there is currently a lack of Good Laboratory Practice (GLP) quality toxicology studies, which are needed for regulatory evaluation.

In general, scientists should stop further development if the nanomedicine is too risky. This is the case if the expected damages (D^e) are equal or larger than the expected benefits (B^e). The further development and commercialization of a new nanotherapeutic should thus be abandoned if the expected benefits are smaller than expected damages ($B^e < D^e$), i.e. the benefits multiplied by the probability that the new drug is beneficial are smaller than the damages multiplied by the chances of damages ($P_b\ B < P_d\ D$). In other words, the development should be halted if the chance that the new drug results in positive QALYs is smaller than the chance of negative QALYs.

8.3.4. Smart regulation of new nanomedicines

Regulation that is SMART (Specific, Measurable, Attainable, Relevant and Time-bound), delivers results in the least burdensome way for all parties. Therefore, governments should be creative in developing new models of technology governance. Effective governance of nanomedicine urgently requires a better coordination and harmonization of existing regulatory procedures.[214] Firstly, new tests to asses the health, environmental, and social impact of nanotherapeutics should be developed.[7,157] Furthermore, additional research about potential workplace hazards is required.[206]

Secondly, nanoscale therapeutics also raises some legal issues. Currently, the rule of strict product liability applies regardless of the complexity and unpredictability of the therapy. A legal change away from ex post strict liability towards entry requirements and ex ante negligence may be necessary to avoid fatal delays in the clinical setting.[227] However, negligence requires clear standards of quality and safety, by which to judge care and precaution of the producer. Since such clear standards and tests are not developed yet, the optimal, well-understood solution in the case of unilateral accidents (i.e. with no impact of the victim's behavior to avoid the accident) remains strict liability.[228] Due to the lack of comprehensive data about adverse effects held by one provider, regulation is also needed to fill the data gap and put an ex ante filter on adverse events.[229]

Stricter tests address both issues of safety and lack of data in a way to win the confidence of the general public. The government should take the lead in this regulatory reform.[156,158] Once the regulatory issues are solved, the process of commercializing nanotherapeutics will become a lot easier.[216]

8.3.5. Patent dispute prevention and resolution

Successful commercialization of nanotherapeutics depends also upon the effective protection of intellectual property rights. Different strategies and solutions exist at different stages during the patenting process to avoid and overcome patent disputes (table 8.1).[230] The best way to avoid patent disputes is to prevent them from happening by drawing broad and well-described patents. To avoid disputes, every step in research has to be recorded. In turn, this requires clear policies. Dates become decisive when competitors claim the same invention. Companies should also avoid early publication or any public disclosure before a patent application has been filed. Furthermore, foreign patent protection should be part of a long-term competitive plan. As soon as an invention is realized, maximum patent protection is obtained by filing a provisional patent application, which should contain a description of the invention (but no claims). Understanding what else is in the field is imperative. Therefore, a thorough prior art search should be conducted before filing a patent application. Moreover, it is important to research other patents and products that are similar enough to create disputes. Nanotechnology in general and nanomedicine in particular is a difficult topic. This is partly due to the proliferation of 'nano'-terms as well as the confusion in the definition. To avoid confusion, synonyms and repeating phrases have to be avoided. Therefore,

companies have to clearly define what the patent covers by using standard language. Finally, strong employment confidentiality agreements should be established.[230]

Pending patent applications are published after eighteen months. Disputes can be avoided by monitoring relevant patent applications and issued patents. A competitor's patent can be attacked by using inference practices. When overlap is suspected, a request with the United States Patent and Trademark Office (PTO) can be filed. The latter determines which company was the first to conceive the invention. In this case, it is crucial to have documents that contain the date of conception of the invention. The testimony of a witness could be decisive.[230]

Furthermore, strategies to resolve patent disputes are available. Re-examination occurs when the validity of an issued patent is questioned. This practice often takes place when a company did not file an application, but distrusts the validity of a competitor's issued patent.[230] In case of overlap, an efficient and often mutually beneficial method for resolving disputes is to consider cross-licensing agreements. An important advantage of this practice is that each party gains access to the technology that could be necessary for further development and commercialization of individual technologies. Moreover, cross-licensing can create a synergy between parties that could lead to a low-risk exchange of intellectual property in exploiting individual as well as jointly developed technologies. It will also be easier to exclude third competitors.[230] Litigation is a final, yet expensive way to resolve a patent dispute. This could be as plaintiff to enforce own patents or as a defendant. Pharmaceutical companies can, however, buy intellectual property infringement insurance covering the costs of a patent infringement trial.[230]

Table 8.1: Solutions for patent disputes

Strategies		Tactics
Pre-dispute strategies	Strategic patenting	• strive for clarity while seeking the broadest patents possible • signal the scope of a company's claims to competitors • document each research step • do not release information in publications or during negotiations • seek foreign patents next to national patent protectio • file a provisional patent application at least one year prior to the definitive application • conduct a thorough prior art search • use a well-established language in the field of endeavor
	Interference practices	• monitor relevant patent applications and issued patents for potential disputes • record the date of invention • routinely and methodically date and sign materials in front of witnesses carrying more weight than the inventor
Post-dispute strategies	Invalid patent	• re-examine patents
	Overlapping patents	• cross-licensing patents
	Conflict of interests	• patent arbitration • patent litigation • intellectual property infringement insurance

Source: based on Harris et al. (2004)[230]

8.3.6. Regulation of generics and the insurance market

Effective, safe, and affordable medicines should be accessible to all patients.[218] Generic products may reduce the acquisition cost; their overall cost is usually significantly higher due to lower standards of effectiveness and safety. To mitigate this problem, regulatory authorities should carry out more bioequivalence studies.[217] However, it is much more difficult to define a regulatory pathway for generic nanotherapeutics. Desai clearly states: "Generic nanomedicines pose potential regulatory problems. The generics ultimately will have to show that they are equivalent to the nanotechnology product, so what tests would they use to show this?"[220] In the future, nanomaterials have to be fully characterized in such a way that they do not only get regulatory approval today, but also provide a basis for comparison of generic versions that are created later.[220]

Moreover, the adherence to safe manufacturing standards should be closely monitored. Quality is essential in each stage of the production process. Providing drugs of high quality at the lowest price requires quality control in each stage of the production process (raw materials, in-production process, and finished product), an audit of the manufacturer's process validation and quality assurance, and registration of the drug in both manufacturing and importing country.[218] These procedures should be established for generics in general and for nanomedicines in particular. Finally, the further development and successful commercialization of nanotherapeutics also requires that insurance companies come up with new policies that refund experimental treatments.

8.4. Conclusions

Over the next 10 to 20 years, nanotechnology may revolutionize science, technology, and society. However, if medical nanotechnology wants to realize its full potential, major impediments blocking serious steps forward have to be removed. The future of nanomedicine is undermined by the lack of financial profitability, consumer distrust, ineffective regulation of new and generic medicines, weak patent protection, and insurance market failure. Successful commercialization thus requires a whole set of measures and actions summarized in table 8.2.

The profitability of the nano-industry can be enhanced by smarter regulation creating a level playing field for all competitors. It also requires the establishment of a multidisciplinary platform providing clinical data in an early stage to substantiate cost-effectiveness analyses and business plans. Successful commercialization of nanomedicines also depends on consumer confidence which, in turn, requires education, nanotoxicological risk assessments, and an adequate regulatory framework which includes new tests and testing guidelines used as ex ante entry requirements that complement strict liability. Success is also conditional upon the effective protection of intellectual property rights. Patent disputes can be avoided and solved by strategic patenting, interference practices and cross-licensing. Imperfect competition by generic products can be solved by integrating bioequivalence studies in the regulatory process. Finally, innovative insurance policies should also cover experimental therapies to promote medical progress.

Table 8.2: Obstacles and remedies for the commercialization of nanomedicines

Obstacle 1: lack of profitability and financial resources
• Setting up a multidisciplinary platform providing clinical data in the earliest stage as possible to underpin cost-effectiveness studies and business plans • Designing smarter regulation to overcome regulatory uncertainty and subsequently investors' reluctance (see obstacle 4) • Reinforcing the interfaces between large pharmaceutical companies and SME's
Obstacle 2: lack of public confidence
• Carrying out more nanotoxicology studies • Developing new tests assessing the health, environmental, and social impa of nanomedicines • Informing the public by means of panels, conferences, education and, in particular, internet
Obstacle 3: potential hazards
• Carrying out more nanotoxicology studies and subsequently risk assessments • Setting up an international, multidisciplinary expert workshop to establish a nanoparticle classification scheme and new testing guidelines and to select appropriate doses and concentrations
Obstacle 4: inadequate regulation
• Setting up a regulatory framework attuned to the needs of nanomedicines, meaning: • Developing new, ideosyncratic tests assessing the health, environmental, and social impact of nanomedicines • Installing entry requirements cum strict liability

Obstacle 5: ineffective patenting
• Avoiding disputes by means of strategic (i.e. broad, well-described) patents, research records, prior art, provisional filing • Monitoring patent applications and issued patents by applying interference practices • Re-examining patents • Customizing cross-licensing in case of overlapping patents
Obstacle 6: generics and insurance market failure
• Close monitoring of manufacturing standards • Carrying out more bioequivalence studies of generic products in the patient population • Drawing up insurance policies on the basis of cost-effectiveness analysis, instead of acquisition cost • Providing innovative insurance policies covering experimental therapies

Chapter 9: Conclusions and future perspectives

9.1 Conclusions

In developed countries, cancer belongs to the top three causes of death.[13] In spite of the existence of several effective cancer prevention and screening interventions, the number of new cancer cases will increase from an estimated 10 million cases in 2000 to an estimated of 15 million in 2020. Since the 1950s great strides have been made in cancer treatment. This is particularly true for early detected, localized malignancies. Nevertheless, still more than half of cancer patients do not respond to therapy or progress to the metastatic stage. The low effectiveness of current chemotherapeutic treatments is not due to the efficacy of the drug itself, but to the ineffective delivery of those agents to the cancerous regions. After the intravenous administration, drugs encounter some biological barriers that have a negative impact on the particles' ability to reach the target cells at desired concentrations. Striking is the declaration that only 1-10 out of 100.000 drug molecules are able to reach their parenchymal targets. Consequently, many healthy cells will be irreversibly damaged causing patient suffering and this at the expense of therapeutic action. This, in turn, causes a decreased therapeutic index. A technology that could give rise to important opportunities to overcome some challenges related to current chemotherapy regimens is cancer nanotechnology. The promise of nanotechnology is to find the right combination of therapeutics and targeting moieties to attack diseased cells without or with minimal side-effects. To achieve this objective, significant

investments have to be made to develop the right nanotherapeutic for each disease. Scaling down the size of materials to their molecular level radically changes and improves their physico-chemical properties. Hence, their use in medicine offers good prospects for significant advances in the treatment and prevention of diseases.

Although nanomedicine is very promising, its economic, social, and health impacts need to be managed in an integrated and safe way. The future of nanomedicines is undermined by the lack of financial profitability, consumer distrust, ineffective regulation of new and generic products, weak patent protection, and insurance market failure. Its economic breakthrough is dependent on a series of countervailing measures and actions. Success requires more investments induced by cost-effectiveness analyses and business plans based on clinical data, public education based on nanotoxicology studies, smart regulatory reform in the areas of testing, market entry and liability, effective and strategic patenting, patent dispute prevention and resolution, and innovative insurance policies.

This dissertation addressed the problem of lack of profitability. More specifically, cost-effectiveness studies comparing conventional and nanotechnology-based cancer therapies were investigated. Current studies show significant methodological heterogeneity and some important deficiencies. These are: (1) only direct medical costs are considered; (2) indirect costs are completely neglected; and (3) quality of life is almost never considered. Since cancer treatments not only affect the length but even more so the quality of life and since indirect costs are substantial, the results of cost-effectiveness analyses are

unreliable, if not misleading. It follows that there is an urgent need for economic research on cancer therapies including both QALYs and indirect costs.

A cost-effectiveness taxonomy comprising all relevant direct and indirect costs as well as quality of life was developed. Costs of treatment, management of adverse events, and recurrent disease are included. Relevant direct costs are drug (study drug and pre-treatment), administration (in- and outpatient visits), expected administration (e.g. drug administration at home), monitoring (diagnosis and follow-up) costs, and expected costs of after care (psychological assistance, rehabilitation, palliation, additional therapies). Lost production of patients and relatives, transportation costs, expected costs related to caregivers, visiting costs (for hospitalization only), the interests forgone on funeral expenses due to a premature death, and administration costs of health insurances can not be directly attributed to a specific treatment. These are the tangible indirect costs of cancer. Moreover, intangible indirect costs, which are the emotional costs of pain, suffering and reduced quality of life, are conceptualized into quality-of-life estimates.

The cost-effectiveness taxonomy was used in the case study comparing gemcitabine (conventional therapy) and PEGylated liposomal doxorubicin (a first generation nanotherapeutic). Furthermore, results were compared with the more common method of cost calculation, i.e. from a hospital perspective. Liposomal therapy remains the most cost-effective treatment regimen under all scenarios. However, adjusting the effectiveness outcomes with quality of life estimates gives a more accurate estimate because it incorporates the non-financial costs. Including all costs results in better estimates. Despite its high

acquisition cost, more accurate results favor liposomal therapy. Considering only direct hospital costs penalizes more expensive but also more effective and less toxic nanotechnology-based therapies. Consequently, it is important to calculate the cost-effectiveness of cancer therapies from a social perspective, including all relevant direct and indirect costs and adjusting effectiveness outcomes with quality of life estimates. Only then, cost-effectiveness studies can lead to effective choices in health care.

However, the failure rate for new drug molecules is very high. While in the early stages of the development process this is mainly due to an inadequate therapeutic index, in late-stage clinical development, economic reasons take the lead. Because the cost of failure rises with duration, unsuccessful drugs have to be abandoned as soon as possible. An important venue to avoid waste of scarce resources and maximize therapeutic value for patients is economic evaluation (cost-effectiveness analysis), which should be pursued in the early phases of the drug development cycle. If the new nanotherapeutic does not save a sufficient number of quality-adjusted life years to break even, it should not be developed further. Firstly, nanotechnologists should provide an estimate of how many QALYs the new nanotherapeutic could save during its entire lifecycle. Secondly, health economists should provide a rough estimate of the sales revenues required to recover costs and earn a reasonable profit. Organizations like the National Institute for Health and Clinical Excellence (NICE) or the National Cancer Institute (NCI) consider a new medicine or technology as cost-effective if its cost is lower than a threshold value of US$35.000-US$50.000 per QALY. If the new drug costs more than the threshold value, it is considered not cost-

effective and its further development and commercialization should be abandoned.

Unfortunately, the scarcity of clinical data is a major impediment for any serious CEA of nanomedicines. Rendering the necessary data available is an absolute precondition for the success of CEA and, in turn, nanomedicines. To that end, a platform needs to be created where health economists can work closely together with technologists, clinical researchers from industry and academia, clinicians, health care providers, and patient associations.

9.2 Future perspectives

In the past fifteen years, nanotechnology has taken off. A very futuristic form of a nanotechnology-based medicine is the nanorobot. The use of nanoscale robots could radically revolutionize today's health care. While current health strategies are mainly reactive, future interventions could be proactive. In turn, pain and illness could be prevented. First generation nanorobots are expected to monitor chemistry and deliver drug molecules directly into diseased cells. Next generation nanorobots, on the contrary, will probably be aided by advanced artificial intelligence. Therefore, these devices could be able to search for diseased cells and tissues and failing body parts. Moreover, they could possibly help re-grow healthy tissues. Nanorobots are expected to work as nanoscale surgeons, able to reach diseased cells and make the necessary repairs by reformatting new atoms and molecules.

At the Nanotech Conference in 2007, scientists from the University of Miami and the University of Berkeley revealed that nanotechnology paves the way for nerve cell regeneration. They state that the central nervous system could be regenerated after spinal cord injury. This is possible because magnetic nanoparticles and exotic nanofibers can influence the neurons in the central nervous system. Therefore, nanotechnology could also be used to cure Alzheimer's and Parkinson's disease as well as other brain diseases.

Advanced nanotherapeutics require a thorough economic assessment. Since the use of such futuristic nanodevices could revolutionize medicine, their economic impact could be huge. In spite of the difficulties in retrieving the indirect costs of disease, these costs should always be assessed since they will become more significant with the introduction of new, more advanced nanotherapeutics. This is particularly true for economic output losses related to disease and mortality. Moreover, future nanodevices could prevent disease recurrence. Future economic analyses should, therefore, include the costs related to disease recurrence.

In the future, licensing and co-development of drugs and medical devices will be more the norm than the exception. This is due to the high and increasing development cost of medicines, which seems to continue its upward trend in the future. Pharmaceutical companies use licensing with the objective to access a broad portfolio of new medicines and technologies. Licensing agreements provide strategic options through which the parties can develop successful technologies while creating low risk synergies. However, effective partnerships and collaborations can only exist where the parties understand and respect each

others' objectives. Partnering companies should approach negotiations only when they understand the partners' desired level of risk, responsibility and rewards. Only then, it is possible to quickly establish consensus with regards to deal terms and structure. Success will only be possible within the commitment of all involved parties.