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“Postoperative Radiotherapy for Lung Cancer: Is it worth the controversy?”

Charlotte Billiet MD [a b], Stéphanie Peeters MD, PhD [a], Herbert Decaluwé MD [c], Johan Vansteenkiste MD, PhD [d], Jeroen Mebis MD, PhD [b e], Dirk De Ruysscher MD, PhD [a f]

[a] KU Leuven - University of Leuven, Department of Radiation Oncology, B-3000 Leuven, Belgium
[b] Faculty of Medicine and Life Sciences, Hasselt University, Martelarenlaan 42, 3500 Hasselt, Belgium
[c] KU Leuven - University of Leuven , Department of Thoracic Surgery and Leuven Lung Cancer Group, B-3000 Leuven, Belgium
[d] KU Leuven - University of Leuven, Respiratory Oncology Unit (Department of Pneumology) and Leuven Lung Cancer Group, B-3000 Leuven, Belgium
[e] Department of Medical Oncology, Jessa Hospital, 3500 Hasselt, Belgium
[f] Department of Radiation Oncology (MAASTRO), Maastricht University Medical Centre, GROW, Maastricht, The Netherlands

Corresponding author:
Charlotte Billiet, MD
Address: Jessa hospital, department radiation oncology. Stadsomvaart 11, 3500 Hasselt
Email: charlotte.billiet@jessazh.be; charlotte.billiet@uzleuven.be
Tel: +32 11 30 99 60

Abstract

Introduction:

The role of postoperative radiation therapy (PORT) in patients with completely resected non-small cell lung cancer (NSCLC) with pathologically involved mediastinal lymph nodes (N2) remains unclear. Despite a reduction of local recurrence (LR), its effect on overall survival (OS) remains unproven. Therefore we conducted a review of the current literature.

Methods:

To investigate the benefit and safety of modern PORT, we identified published phase III trials for PORT. We investigated modern PORT in low-risk (ypN0/1 and R0) and high-risk (ypN2 and/or R1/2) patients with stage III-N2 NSCLC treated with induction chemotherapy and resection.

Results:

Seventeen phase III trials using PORT were selected. Of all PORT N2 studies, 4 were eligible for evaluation of LR, all in high-risk patients only. In these high-risk patients receiving PORT, the mean LR rate at 5 years was 20.9% (95% CI 16-24). Two trials were suitable to assess LR rates after chemotherapy and surgery without PORT. In these low-risk patients, the mean 5-year LR was 33.1 % (95 % CI 27-39).
No significant difference in non-cancer deaths between PORT vs. non-PORT patients was observed in N2 NSCLC.

Conclusion:

PORT is worth the controversy because data illustrate that PORT may increase the OS. However, prospective randomized trials are needed to verify this.

Key-words

post-operative radiotherapy, non-small-cell lung cancer, review

Introduction

Lung cancer is one of the main causes of cancer deaths [1]. Non-small-cell lung cancer (NSCLC) accounts for about 80% of all cases, and one-third of these patients are diagnosed with stage III disease.
Multimodality therapy is the standard of care for patients with stage III NSCLC, but there are several therapeutic options. Most patients with stage III-N2 NSCLC receive concurrent or sequential chemoradiotherapy, depending on their vital status. Alternatively, a surgical multimodality treatment can be offered for patients with resectable stage III NSCLC [2,3]. Three phase III studies have addressed the role of surgery in stage III-N2 NSCLC [2,4,5]. In the ESPATUE trial, after cisplatin-based induction chemotherapy followed by concurrent chemoradiotherapy (45 Gy), resectable patients were randomized between surgery and a chemoradiotherapy boost (20 to 26 Gy)[4]. No differences in overall survival (OS) or progression-free survival (PFS) were observed. The Swiss Group for Clinical Cancer Research randomly assigned patients with proven IIIA-N2 to induction chemotherapy with three cycles of cisplatin/docetaxel followed by surgery, versus induction sequential chemoradiotherapy consisting of three cycles of cisplatin/docetaxel and 44 Gy of radiation, followed by surgery. No significant benefit in OS or event-free-survival was reported [2]. The third trial compared concurrent induction chemoradiation (cisplatin-etoposide, 45Gy) followed by surgery to definitive concurrent chemoradiation (61 Gy)[5]. Again, no differences in OS were observed, although the PFS was longer in the surgical arm.
However, the general outcome remains poor in all treatment groups, with a 5-year OS between 25-35% and high rates of local and distant failures [2,4,6].

The beneficial effect of adjuvant or induction chemotherapy has been proven in many phase III studies. An update of the 1995 MRC meta-analysis [7] in 2010 [8] including a total of 8447 patients in 34 trials, showed an absolute difference in the 5-year OS rate of 4% at 5 years (64% versus 60%; HR=0.86) in favor of chemotherapy. The beneficial effect of adjuvant chemotherapy was also observed in the Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis, which pooled individual patient data from 5 trials, with an absolute OS increase of 5.4% at 5 years in patients with completely resected NSCLC (HR=0.89) [9,10].

In contrast with the consensus about (neo)-adjuvant chemotherapy, the role of postoperative radiotherapy (PORT) remains controversial. PORT could be a logical choice because, even after downstaging with chemotherapy followed by surgery, local recurrence rates (LR) remain high. The first site of recurrence is local in about 30 % of the patients and the cumulative rate of LR is 50-60 % [2,6,11-13]. PORT may decrease LR and improve OS, when using modern (linac-based) treatment techniques. In a recent meta-analysis, based on published randomized phase III trials, PORT significantly decreased LR when administered with linear accelerators (RR 0.31, 95 % CI 0.12–0.79, p=0.01). Based on these results, we hypothesized that PORT could decrease LR by 20% (from 30% to 10%) when delivered with modern techniques (figure 1). This could theoretically lead to a 13% absolute increase in OS for stage III-N2 NSCLC patients [14,15]. PORT thus consistently reduces LR rates by 20% (absolute gain), but its effect on overall survival remains unproven.
To administer PORT or not remains controversial. In this review we will evaluate the data of PORT on LR and OS in order to answer the question if the discussion of PORT is

worth the controversy, i.e. should the subject be closed or is continued research worthwhile?

Materials and Methods

A. *PORT in phase III trials*

A comprehensive review of the literature was performed on MEDLINE to identify publications relating to the use of postoperative radiotherapy in NSCLC. Following key-words were used: 'non-small cell lung cancer', 'postoperative radiotherapy', 'radiation therapy', 'adjuvant treatment', 'toxicity', 'local recurrence and 'overall survival'. Both prospective and retrospective trials were eligible. Only studies published in English were included with inclusion period between 1960 and March 2016. Studies were excluded when they did not include radiotherapy or non-small cell lung cancer (NSCLC) patients, when they studied other radiation qualities than photons (e.g. protons) or when no surgery was performed. Titles and abstracts were screened by the main author; papers that were selected were verified by the co-authors.
We used I^ 2 statistics, which estimate the proportion of variability of the results related to heterogeneity rather than to sampling error. An I^ 2 of 25% or less corresponds to a low heterogeneity [16].

B. *LR after resection and induction chemotherapy +/- PORT*

We performed another MEDLINE search to identify published data investigating current LR rates in stage III-N2 NSCLC patients in particular, treated with a surgical resection and (neo)-adjuvant chemotherapy without PORT.

Secondly, we selected studies from the above collected PORT data to obtain information about LR rates in stage III-N2 NSCLC patients treated with a surgical resection and (neo)-adjuvant chemotherapy. Trials were eligible for inclusion if the study population was at least 40 patients with at least 2 years of follow-up and if patients received cisplatin-based chemotherapy. Only recent studies from the year 2000 onwards were selected as a surrogate for modern staging and treatment techniques.

From the collected data above, we calculated the mean of the first relapse rates. Upper and lower limits of the 95% confidence intervals were calculated. We divided the studies in two different patient groups: high-risk patients having no mediastinal downstaging after chemotherapy (ypN2) and/or an incomplete resection after surgery (R1/2), and low-risk patients with mediastinal downstaging (ypN0/1) and a complete resection (R0). We performed a separate analysis in these two subgroups as the effect of adding PORT can be different.

Results

A. *PORT in phase III trials*

PORT according to nodal stage: pN0-1

A randomized trial conducted in 1980 in 175 patients without lymph node involvement showed a 5-year OS after a complete resection of 24% in the RT arm versus 43% in the control arm. PORT was clearly detrimental, especially after pneumonectomy [17]. This old trial was conducted with Cobalt-60 techniques. A decade later, the same team highlighted the potential benefit of modern facilities (linear accelerator and computed tomography-based treatment planning), although the results were not superior compared to the control group [18].
A more recent Italian randomized trial, using CT-planned treatment and linear accelerators, performed a similar trial in 104 patients with completely resected pathological stage I disease [19]. There was a slightly significant difference of the OS after 5-year (67% in the PORT group (50.4 Gy) vs. 58% in the control group; p= 0.048), however a significantly lower risk for LR was seen in the PORT group. The same conclusions were drawn in some other recent trials, using modern radiotherapy techniques. An analysis of a SEER database (Surveillance Epidemiology and End Results) in 7465 stage II and III NSCLC patients, treated between 1988 and 1995, showed a detrimental effect on survival for N0 and N1 patients with PORT [20].
In current guidelines, such as the ones from European Society of Medical Oncology (ESMO) or the US National Comprehensive Cancer Network (NCCN), it is acknowledged that PORT has a negative effect on survival in completely resected (R0) stage pT1–2 and pN0–1 patients and PORT is therefore not recommended [21,22].

PORT according to nodal stage: pN2

In 1998, the PORT meta-analysis concluded that PORT was detrimental in terms of OS to patients with early-stage completely resected NSCLC, but that the role in case of N2 involvement was unclear [23]. Another older study from the Mayo Clinic included 224 pN2 patients resected between 1987 and 1993 [24]. The regression analysis confirmed that PORT was an independent prognostic factor for LR (17% vs. 60%; $p<0.05$) and OS (43% vs. 22%; $p<0.05$). Growing evidence from other more recent trials, however mostly small and retrospective, shows a favorable effect of PORT in patients with pN2 disease [25-38]. A larger cohort study of the SEER database investigated 7465 patients with resected NSCLC between 1998 and 2002 [20]. They suggested that PORT in pN2 patients was associated with an increase in cancer-specific survival (30% vs. 25%) and 5-year OS (22% vs. 16%). In addition, the prospective randomized ANITA trial (Adjuvant Navelbine International Trialist Association) demonstrated in a post-hoc subgroup analysis that PORT (45-60 Gy) led to improved OS in patients with resected pN2 NSCLC, both in the chemotherapy arm (median survival of 23.8 months without PORT and 47.4 months with PORT) and in the observation arm (median survival of 12.7 months without PORT and 22.7 months with PORT) [39].
We classified these N2 PORT studies according to the use of current staging and treatment techniques in Table 1. In case the pretreatment staging protocol was unknown, the inclusion period was used as estimation.

Unfortunately, there is certain heterogeneity between the different studies. Not all patients received additional neo- or adjuvant chemotherapy, a complete resection was not always required and the time period of inclusion varied substantially. A possible publication bias has to be mentioned as well. We calculated an I^ 2 of 39% for OS evaluating the studies using PET, brain imaging and pathological N2 confirmation for staging and treatment planning (Appendix A).

PORT according to resection status

About 1% to 17% of surgical resections for NSCLC result in positive surgical margins or gross residual disease [40]. Incomplete resection is associated with increased local failures and negatively impacts on survival [41,42]. PORT is often recommended to improve LR and OS in patients with incompletely resected NSCLC. The ESMO and NCCN guidelines support the use of PORT or chemoradiation therapy in selected patients, depending on the extent of residual disease, nodal status, and disease stage [21,22]. However, there is little supporting evidence and the reported clinical results are limited. The literature only comprises of small retrospective studies collected over many years [40-44].

PORT and safety

In most trials, radiation toxicity was reported as mild. Toxicity was most commonly encountered in the form of mild esophagitis, cough, and pneumonitis requiring steroid therapy.
Table 2 gives an overview of all PORT trials evaluating the risk of non-cancer related deaths (intercurrent deaths), as surrogate for treatment toxicity. We demonstrated no significant difference in non-cancer related deaths between PORT vs. non-PORT patients in the four trials comparing both groups (p=0.80). There was a mean of 7.3% of non-cancer related deaths in all PORT patients.

A. *LR after resection and induction chemotherapy +/- PORT*

Eligible trials, using modern treatment strategies, were evaluated to calculate the LR rates with and without additional PORT in low- and high-risk stage III-N2 NSCLC patients.
We first reviewed recent studies evaluating stage III-N2 NSCLC patients treated with surgery and (neo)-adjuvant chemotherapy without PORT. Two trials including patients with N2 involvement, for a total of 217 patients, were identified for LR analysis (Table 3) [13,14]. The mean LR rate at 5 years was 33.1 % (72/217) (95 % CI 0.27-0.39). These trials were conducted in low-risk patients (R0 and ypN0/1). No trials in high-risk patients without receiving PORT could be retrieved.

Secondly we investigated stage III-N2 NSCLC patients treated with PORT after surgery and (neo)-adjuvant chemotherapy. Four trials from the PORT N2 studies in Table 1 were eligible for evaluation of LR using PORT in high-risk stage III-N2 NSCLC patients [14,26,32,33]: PORT was performed in case of persistent N2 status [14,32,33], incomplete resection [14] or not specified and depending on the decision of the multidisciplinary board [26]. A total of 288 patients with a mean LR rate of 20.9%

(60/288) (95% CI 0.16-0.24) was seen (Table 3). No trials in low-risk patients treated with PORT were found.

Discussion

The treatment of locally advanced NSCLC is based on a combined modality approach. In patients treated with surgery, the administration of (neo)-adjuvant platinum-based chemotherapy is considered the standard of care. The role of postoperative radiation therapy (PORT) however remains controversial. PORT can increase local control and potentially improve survival, but also has the potential to cause serious toxicity.
We reviewed the existing literature and found that PORT could be delivered safe with possible increase in OS. A 20% mean first site LR was seen in high-risk patients treated with PORT after induction chemotherapy and resection.

The PORT meta-analysis clearly illustrated the potential toxic effects of adjuvant radiotherapy and concluded that PORT was detrimental in terms of OS with an absolute 7% lower survival rate at 2 years, 48% versus 55% (p=0.001) in patients with completely resected NSCLC [23]. Only a possible benefit of additional PORT in pN2 NSCLC patients was demonstrated in subgroup analysis with a statistical significant better local control (74% vs. 59 %) in the N2 subgroup. Updates of this meta-analysis published in 2005 and 2010, with former data correction and inclusion of new trials, came to the same conclusions (45,46). Following the meta-analysis, the use of PORT declined worldwide. However, this meta-analysis was criticized in several points, e.g. the use of obsolete radiation techniques (2D, not CT planned) with suboptimal, outdated radiotherapy volumes (large fields), dose regimens (large fractions), that are not part of currently accepted practice. Moreover, there was lack of detailed information about surgery, inclusion of patients with poor performance status, and a long period of recruitment. Some trials had been initiated as early as 1965, and three had not been published in the peer-reviewed literature. These older studies were performed in an era where staging evaluation did not comprise FDG-PET/CT scan and brain imaging, so that several patients included in these trials, especially those with N2 disease, might have been metastatic at the time they were included. Thus, the potential effect of PORT on local control may also have been diluted by the occurrence of distant metastases. Finally chemotherapy was not used.
In view of the recent technical developments in treatment planning and increase in the knowledge of radiobiological concepts of doses and fractionation, a renewed interest in PORT has occurred. Modern three-dimensional radiation treatment planning facilitates more conformal radiation delivery with an improved therapeutic ratio. Recent retrospective and non-randomized studies, as well as subgroup analyses of recent randomized trials evaluating adjuvant chemotherapy, provide evidence of the possible benefit and safety of PORT in patients with persistent nodal disease (Table 1). Besides a reduction of LR, the effect of PORT on OS remains unproven.

If PORT can increase local control, another important concern is toxicity. In this review, no difference in intercurrent deaths between PORT and non-PORT patients was seen. Several retrospective databases examined the hypothesis that more modern radiation techniques do not lead to increased intercurrent deaths. Machtay et al. compared the risk of death from intercurrent disease (DID) in 202 patients with stage II or III NSCLC treated with PORT (median dose 55 Gy) to that of age and sex matched controls who did not have lung cancer [47]. A 13.5% 4 years actuarial rate of DID was documented, not significantly different from an expected rate of 10%. The Eastern Cooperative Oncology Group (ECOG) prospectively assessed the cardiac and pulmonary morbidity and quality

of life after PORT (50.4 Gy) using 3D-CRT technique in pN2 patients with radical tumor resection compared to those with pN1 disease after surgery not receiving PORT. They also concluded that modern PORT for NSCLC does not significantly increase the rate of DID [48]. In a prospective study comparing 171 N2 patients treated with 3D-planned PORT against 120 N1 patients treated with no PORT, non-cancer related deaths, cardiopulmonary morbidity and quality of life surveys again showed no significant differences [49]. An analysis of the Surveillance, Epidemiology, and End Results (SEER) database to investigate the timing of cardiac-related mortality in 6148 patients treated with or without PORT, with a median follow-up of 10 years, found that PORT was associated with significantly increased deaths from heart disease in patients diagnosed with NSCLC between 1983 and 1988 (HR 1.49; p= 0.009), but not in those diagnosed between 1989 and 1993 (HR 1.08; p= 0.64) [50]. Another SEER analysis and a secondary analysis of data from the Adjuvant Navelbine International Trialist Association (ANITA) trial suggest in an unplanned N2 subgroup analysis that PORT may be safely delivered in a modern (Linac-based) cohort of patients with a potential OS benefit for stage IIIA (N2) disease [20,39,50].

Besides the modern radiation techniques, the total dose, fractionation and the treated volume are also of major concern when considering toxicity. Firstly, the total dose delivered to the majority of patients included in the meta-analysis [17,51-53] was as high as 60 Gy, whereas 54 Gy would be sufficient in a prophylactic setting and less harmful [25,46]. Corso et al. demonstrated a superior survival in completed resected NSCLC patients who received 45 to 54 Gy compared to patients without PORT (5-year OS 38 vs. 27.8%, $p < 0.001$), although patients who received more than 54 Gy had an equivalent survival to patients treated without PORT (5-year OS 27.6 vs. 27.8%, $p = 0.784$) [36].

Secondly, it is well demonstrated that fractionation schedules with more than 2.5/3 Gy per fraction lead to a higher rate of cardiac and pulmonary injury [54,55]. Dautzenberg et al. [51] were able to determine that the use of fraction sizes >2 Gy resulted in a high-risk for late toxicity. There was a correlation between fractionation and morbidity. The risks for non-cancer-related death were 7% in the control group, 16%– 18% among patients who had PORT with daily fractions ≤ 2 Gy, and 26% among those who had higher doses per fraction.

Finally, we assume that techniques could further decrease PORT-related toxicity. Image-guided radiotherapy (IGRT) offers several ways to deal with respiratory motion, such as the deep-inspiration breath-hold radiotherapy, the breathing-synchronized radiotherapy or the 4-dimensional CT scan, which allows to generate a personalized treatment volume. However, also non-radiation related factors are of importance. Locally advanced NSCLC patients often also are suffering from other comorbidities, which possibly predispose them to cardiac and pulmonary toxicity. In a retrospective analysis, we previously demonstrated a similar cardiac and pulmonary toxicity comparing PORT vs. non-PORT stage III-N2 NSCLC patients after induction chemotherapy and surgery [56]. There was no difference between the two groups regarding dyspnea (p=0.32), cough (p=0.37), FEV1 (p=0.30) and DLCO (p=0.61) overall. Cardiac events were even higher in the non-PORT-group (p=0.02) but pulmonary events were similar (p=0.15).

Aside from improved radiation techniques, the last decade also witnessed a major progress in terms of preoperative staging, quality of surgery and chemotherapy. Patients are much better selected for a surgical multimodality based on adequate staging with

PET/CT, brain imaging or endobronchial ultrasound (EBUS). PET/CT is highly sensitive and specific in detecting mediastinal nodal spread and extracranial metastases. As for surgery, the International Association for the Study of Lung Cancer (IASLC) staging committee proposed a definition of complete resection, requiring in brief: microscopically free resection margins; systematic nodal dissection or lobe-specific systematic nodal dissection; no extracapsular nodal extension; and the highest mediastinal node removed negative for tumor [57]. Systematic nodal examination should comprise at least three intrapulmonary and hilar nodes and at least 3 nodes mediastinal nodal stations according to the location of the primary tumor [58]. Patients referred to PORT can consequently be better selected. This is important as patients with stage III-N2 NSCLC are a heterogeneous group with different clinicopathologic features and different prognosis. While the most favorable outcome is seen in patients with minimal N2 disease, bulky and/or multilevel N2 disease carries a significantly worse prognosis. A retrospective study involving 702 patients who underwent surgery were classified according to the nodal involvement [59]: minimal (mN2: no preoperative detection of N2 disease) versus clinical (cN2: enlarged lymph node on CT scan) and single (L1) versus multiple (L2) lymph node involvement. The 5-year OS rates differed significantly within the subgroups: 34% for mN2 L1 patients; 11% for mN2 L2, 8% for cN2 L1 only 3% 5-year OS for cN2 L2 patients. In addition, it has been demonstrated that the LR rate is proportional according to the stage and grade of lymph node involvement. In a large SEER population-based study, the lymph node ratio (the number of pathologically positive LNs divided by the number of LNs examined) was also reported to be an important prognostic factor in resected node positive NSCLC [34]. Furthermore, there was a benefit of PORT only in pN2 patients with a lymph node ratio of 50% or more.

Mediastinal downstaging and completeness of resection are important prognostic factors [60]. PORT can be considered in all high-risk patients without nodal downstaging after induction chemotherapy (ypN2) or with incomplete resection after surgery (R1/2). Probably the benefit of PORT is larger in case of multiple N2 nodal involvement or extracapsular extension, however randomized evidence is missing. In contrast, LR rates remain high in all pathological proven N2 NSCLC patients, independent of their response on chemotherapy (+/- 30% without PORT in low-risk patients).

This study has several limitations that need to be pointed out. First, a lot of studies are based on retrospective data as no other data are available in literature. Second there is considerable heterogeneity between the different trials, as measured for the PORT trials using current staging and treatment techniques. Third, there may be some overlap between the different trials concerning patient selection.

The ongoing Lung ART study (NCT00410683) is a currently open phase III trial that compares PORT with no PORT in patients with completely resected stage III-N2 disease [61]. The results of this prospective randomized trial will hopefully confirm these findings and establish a new standard of care in resected N2 NSCLC patients.

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Figure 1. Local tumor failure as a function of the beam quality used (copyright [13]).

PORT: post-operative radiotherapy; RR: Relative Risk