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Outcome after post-operative radiotherapy (PORT) in ypN2 or R1/R2 versus no PORT in ypN0 stage III-N2 non-small cell lung cancer after induction chemotherapy and resection

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Abstract

Introduction:

We investigated contemporary staged and treated stage III-N2 NSCLC patients, treated with induction chemotherapy and surgery with or without post-operative radiotherapy (PORT). We focused on survival and toxicity and investigated what additional PORT may offer in patients with ypN2 status or incomplete resection.

Methods:

We identified 161 patients with pathologically proven, resectable stage III-N2 NSCLC from our prospective database who were treated between 1998 and 2012. From these, 150 patients without progressive disease after chemotherapy underwent resection. Patients with ypN2 status or R1/2 resection received 3D-PORT (n=70) to a dose of 50-66 Gy in 2 Gy fractions.

Results:

The mean follow-up time was 49 months. The 5-year overall survival (OS) was 35.1% in intention-to-treat analysis; relapse-free survival (RFS) was 31.8%, the cumulative LR rate 50.9% and DM rate 63.4%. The 5-year OS, RFS, cumulative LR and DM rate was 32.0%, 32.9%, 47.0% and 63.9% in the PORT-group vs. 38.1%, 30.7%, 54.1% and 63.2% in the non-PORT-group. These results were not significantly different, even though patients in the PORT-group had worse prognostic features.

Cardiac toxicity was higher in the non-PORT-group (p=0.02) but pulmonary toxicity was similar (p=0.15). 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).

Conclusion:

A similar outcome (OS, LR and toxicity) was seen in both patient groups (PORT vs. non-PORT-group). Despite the limitations of this retrospective study, PORT can be both effective and safe for stage III-N2 NSCLC patients with an R1/R2 resection or yN2 after induction chemotherapy and surgery.

Introduction

The long-term survival of patients with locally advanced non-small cell lung cancer (NSCLC) is poor. Five-year overall survival (OS) rates in patients with stage III-N2 NSCLC treated with combined modality treatment are about 25-35 % in recently published trials (1-4). The current standard treatment for most patients with stage III-N2 NSCLC is concurrent chemoradiation. Surgical multimodality treatment is often used for potentially resectable stage IIIA NSCLC (2,5). Recently published phase III studies have addressed the role of surgery in stage III-N2 NSCLC (1,2,6). In the ESPATUE trial, after induction chemotherapy followed by concurrent chemoradiotherapy, resectable patients were randomised between surgery and a chemoradiotherapy boost (1). No differences in 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 chemotherapy sequentially followed by 44 Gy of radiation and surgery. No significant benefit in OS or event-free-survival was reported. The third trial compared concurrent induction chemoradiation (cisplatin-etoposide, 45Gy) followed by surgery to definitive concurrent chemoradiation (61 Gy) (6). Again, no differences in OS were observed, although the PFS was longer in the surgical arm.

Preoperative chemotherapy followed by resection in responding patients is a frequently used strategy for resectable stage III-N2 NSCLC. However, even in these selected patients, 30% fail locally as first site, and cumulatively, about 60 % have a local recurrence (LR) (2,7,8). Modern postoperative radiotherapy (PORT) may decrease LR and improve OS as suggested in a recent meta-analysis based on published randomized phase III trials (9,10). However, in this meta-analysis, patients were not staged with fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET)/CT scans, brain imaging or endobronchial ultrasound (EBUS). Moreover, chemotherapy was not used. In more recent series, LR rates of 30% as first site of failure were also found in chemotherapy treated patients (11-14), but again, these were not staged according to contemporary standards.

If PORT can increase local control, questions arise about the toxicity. Other studies have demonstrated acceptable adverse effects using modern PORT without an excess of non-cancer related deaths (15-17). However, no information is available about the non-radiation related

toxicity in this patient group, often suffering from other comorbidities, which possibly predispose them to cardiac and pulmonary toxicity.

The question thus remains what the OS, LR and toxicity are after induction chemotherapy and resection in patients with stage III-N2 NSCLC staged and treated with current standard methods, and what PORT may offer in patients without nodal downstaging after induction chemotherapy. This is addressed in the present series.

Materials and Methods

Patients

Patients in whom stage III-N2 NSCLC was diagnosed and treated between September 1998 and December 2012 with induction chemotherapy followed by surgery at the University Hospital of Leuven or the Oncologic Centre Limburg, both in Belgium, were selected from a prospective database. N2 status was pathologically confirmed in all cases. Retrospective evaluation of the treatment and follow-up data was performed.

The Charlson comorbidity index adjusted by age was calculated for all patients and categorized in 3 subgroups (low 0-3; intermediate 4-6; high 7-9) (18). Patients were evaluated as potentially resectable by a multidisciplinary team (surgeon, radiologist, pulmonologist and radiation oncologist).

Pretreatment staging

Pretreatment staging included a history and clinical examination, a biochemical test (blood count, renal and liver function, the tumor marker carcinoembryonic antigen (CEA)), pulmonary function tests, bronchoscopy and a contrast-enhanced multi-slice CT scan of the thorax and upper abdomen. In addition, brain imaging (contrast-enhanced CT or MRI scan) and a FDG-PET/(CT) were performed, as well as invasive staging of the mediastinum, consisting of endobronchial ultrasound transbronchial needle aspiration (EBUS-TBNA) or esophageal ultrasound fine needle aspiration (EUS-FNA) and/or mediastinoscopy. Staging occurred according to the TNM 7th edition for all patients (19).

Treatment

All patients received induction chemotherapy, consisting of a platinum-based doublet or triplet regimen with a median of three cycles (range 2-6 cycles).

All patients without disease progression after induction chemotherapy were referred for surgery. Tumor response was assessed using RECIST criteria (Response Evaluation Criteria In Solid Tumors) (version 1.1) (20) for CT imaging, PERCIST criteria (PET response criteria in solid tumors) (21) for FDG-PET and using pathological information in case of remediastinoscopy.

All patients were surgically treated in the Leuven University Hospitals or the Oncologic Centre Limburg, the induction chemotherapy could also be performed in collaborating

hospitals.
In this intention-to-treat database, surgical treatment included a lobectomy, bilobectomy, wedge resection or pneumonectomy, and a systematic multilevel mediastinal lymph node dissection accordance to the ESTS guidelines (22). At least three mediastinal nodal stations (but always subcarinal) were routinely excised. The nodes were separately labeled and examined histologically. The hilar and the intrapulmonary lymph nodes were dissected as well. A complete surgical resection (R0), in line with the criteria of the International Association for the Study of Lung Cancer (IASLC), required 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 (23).

Patients with incomplete resection (R1/2) and/or persistent N2 disease (ypN2) received post-operative radiotherapy. Patients underwent a planning CT of the entire thorax using 3-mm–thick slices, and radiation treatment was planned using a 3D-planning system (Eclipse, Varian). Treatment occurred using a linear accelerator with 6- to 10-MV energy photons. The clinical target volume (CTV) included the bronchial stump, the ipsilateral hilum, the subcarinal region (N7) and all pathologically involved lymph node regions. The planning target volume (PTV) was determined as the CTV plus a 1 cm margin.
The prescribed dose ranged between 50 and 66 Gy in daily fractions of 2 Gy, 5 days/week. The level of radiotherapy dose varied according to the quality of surgery (completeness of resection). The dose was specified according to ICRU 50 guidelines (24). Dose prescription was defined so that 95% of the prescribed dose covered 99% of the PTV.

Follow-Up

Follow-up occurred in or in cooperation with the Leuven University Hospitals or the Oncologic Centre Limburg. Usually, patients were assessed at 3-month intervals for the first 2 years, every 6 months for the next 3 years, and then annually. Standard follow-up evaluation included a history and physical examination, biochemical tests (blood count, renal and liver function, CEA) and a chest x-ray. A CT scan of the thorax and upper abdomen with IV contrast was performed each 6 months. Further imaging modalities and pulmonary function tests were performed according to the physician's choice based on the patient's symptoms.

Toxicity scoring

Scoring of clinical symptoms (dyspnea and cough) occurred following the Common Toxicity Criteria (CTCAE version 4.0). Forced expiratory volume in 1 second (FEV1) and diffusion capacity (DLCO) were used as parameters to evaluate the lung function. Clinical symptoms and lung function parameters were assessed at 3 different time points from baseline (i.e. before PORT): during the first 3 months after the start of PORT (i.e. acute side effects), >12 months after the start of PORT (i.e. late side effects) and at the date of last known follow-up. Patients with disease relapse were excluded from the analysis from the relapse diagnosis date, in order to avoid interference of dyspnea caused by tumor progression.

In addition, the specific cardiac or pulmonary events were scored individually for all patients. All events, both immediately postoperative (within 30 days after the date of surgery) and during longer follow-up were registered. Pulmonary infections of acute exacerbations of chronic obstructive pulmonary disease (COPD) were considered clinically relevant if hospitalization was required. Radiation pneumonitis was considered significant if oral or IV administration of steroids or hospitalization was required. Radiation pneumonitis was defined by clinical as well as radiographic findings correlating to the irradiated lung volumes.

The number of non-cancer related deaths was recorded and specified for the PORT and the non-PORT-group as an additional measure of possible toxicity.

Statistical analysis

Analyses were done by intention-to-treat and per-protocol because not all patients finished the planned treatment.

OS was determined from the date of first pathological diagnosis to the date of death from any cause, or to the date of last follow-up, which is the last contact date and the last known date of the patient's vital status and disease status. Relapse free survival (RFS) was calculated from the date of first pathological diagnosis to the date of first documentation of tumor reappearance. A relapse involving the bronchial stump, hilar, mediastinal or clavicular lymph nodes was defined as local (LR); all other relapses were considered as distant (DM). The first site local recurrence rate (LR first site) was defined from the date of first pathological diagnosis to the date of first documentation of tumor reappearance when local, while the cumulative local recurrence rate (LR cumulative) was defined as the date of first pathological diagnosis until the presence of LR at any time. Cumulative metastasis rate (DM cumulative)

was calculated from the time of first pathological diagnosis until the cumulative presence of recurrence at distant sites at any time.

Statistical analyses were performed using SAS 9.4. The Kaplan–Meier method was used to calculate survival and recurrence rates, and the log-rank test was used to analyze differences between the groups. Univariate cox regression analysis was used to evaluate potential prognostic factors for OS, RFS, LR and DM. Covariates that were significant at p less than 0.05 were included in the multivariable Cox regression. For toxicity analysis, the linear mixed model was considered for repeated data analysis. To measure the evolution, the different time points were used in a mixed model as a class variable and each time point was compared with baseline. The unstructured residual correlation was considered in fitting mixed model.

Results

Patient and treatment characteristics

161 patients with pathological confirmed pN2 stage III NSCLC and documented follow-up were assessable for response evaluation after induction chemotherapy (Figure 1). In 11 patients no radical surgery was performed because of progression after induction chemotherapy: In seven patients, only an exploratory thoracotomy was performed and in one patient only a wedge resection, because a radical resection was not considered possible perioperatively. Another three patients were not referred for surgery, because of radiological disease progression after chemotherapy. 150 patients with response or stable disease after induction treatment were treated with surgery aiming for a complete resection. The mean and median follow-up time in the intention-to-treat group (n=161) was 49 months and 34 months respectively. In comparison, 650 patients were treated with a non-surgical multimodality treatment for stage III-N2 NSCLC in this time period.

Patient, tumor and treatment characteristics are listed in Table 1A and 1B. The median age at time of diagnosis was 61 years. Nearly all patients were staged with FDG-PET (98.1%) and brain CT or MRI (88.4%). There was single nodal involvement in 78.9% (127/161) of patients, while only 21.1% (34/161) had multiple positive nodal stations. This can be explained because patients were upfront evaluated as potentially resectable by the multidisciplinary board.

All patients received induction chemotherapy for at least 3 cycles, except 4 patients in which chemotherapy was discontinued after 2 cycles because of intolerance. Different chemotherapy regimens were used. In 105 cases patients received cisplatin or carboplatin plus gemcitabine; in 30 cases VIP (vinblastine-ifosfamide-cisplatin) and in 12 cases GIP (gemcitabine-ifosfamide-cisplatin) was used. Another 2 patients were treated with cisplatin-vindesine-ifosfamide; 5 patients received cisplatin-vinorelbine and in 7 patients cisplatin-pemetrexed was used.

After induction chemotherapy, patients were reassessed with a CT scan (100%), FDG-PET/(CT) (88.8%) and/or remediastinoscopy (37.7%) in case of doubt on persistent N2 disease.

The median time interval between the time of diagnosis and surgery was 114 days (range 76-

193 days).
In 116 patients, a (bi)lobectomy was performed, while 34 patients underwent a pneumonectomy. A complete resection was achieved in 76.7 % (115/150). Microscopic (R1) and macroscopic (R2) incomplete resection were observed in 19.3% (29/150) and 4.0% (6/150), respectively. Nodal downstaging to ypN0/1 was obtained in 46.0% (69/150) of patients. Persistent ypN2 was seen in 54.0% (81/150) of patients, two of which had unforeseen ypN3 status. In these latter patients, the N3 status was undetected preoperatively, therefore they were included in this analysis. Considering these two patients, one patient did not receive PORT because of postoperative complications, the other patient underwent PORT. They both developed distant metastases shortly after surgery, without evidence for LR at the time of death.
Of all persistent ypN2 patients (81/150), 23.5% (19/81) had multi-station N2 involvement and 76.5% (62/81) single station N2 involvement.

PORT vs. non-PORT

In 86 patients there was an indication for PORT (intention-to-treat analysis): in 53 patients because of persistent N2 disease (ypN2) only, in 6 patients because of incomplete surgery (R1 or R2 resection) only and 27 patients had both ypN2 and R1/2 resection. PORT was effectively performed in 70 patients (per-protocol analysis): 7 did not receive PORT because of postoperative complications, 5 because of comorbidity, 2 because of minimal residual ypN2 involvement and 2 patients refused PORT.

Patient characteristics were well balanced between the two groups in intention-to-treat analysis and per-protocol analysis (Table 1A). Regarding the Charlson comorbidity index, there was an equal distribution of comorbidities in both subgroups.
More positive resection margins and higher gross residual disease were seen in the PORT-group vs. the non-PORT-group per-protocol (34.3% vs. 6.3% R1 resections and 90.0% vs. 21.2% ypN2 disease), and in intention-to-treat analysis (32.5% vs. 0.0% R1 resections and 91.9% vs. 0.0% ypN2 disease) respectively, as expected by design (Table 1B). Additionally, more advanced T-stages (57.1% vs. 31.3% and 53.4% vs. 29.7% T3 stage) and less downstaging after chemotherapy (2.9% vs. 13.7% and 3.5% vs. 15.6% complete response) were also seen in the PORT per-protocol and PORT intention-to-treat group respectively.

The median time interval between surgery and start of PORT was 47 days, ranging from 18 to 89 days. The median overall-treatment-time of PORT was 41 days (range 28-50 days). Patients with R0 resection received a median dose of 56 Gy (range 50-60 Gy), whereas patients with R1 status received a total median dose of 60 Gy (range 50-66 Gy). In one patient the radiation dose was changed into a palliative treatment (39 Gy in fractions of 3 Gy) because of detection of cerebral metastases during radiation treatment. The mean CTV and PTV were 103.9 cm^3 and 214.7 cm^3 respectively, with a mean PTV coverage ranging between 93.8% and 105.3%. Dose-Volume histogram (DVH) parameters of the most important organs at risk (lung, heart and esophagus) were an average mean lung dose of 8.4 Gy, a mean proportion of the lung receiving 5 Gy of 37.1%, and a mean proportion of the lung receiving 20 Gy of 13.1%. The mean dose to the heart was 9.6 Gy with a mean maximum dose of 47.7 Gy. The mean esophageal dose was 23.9 Gy, with a mean maximum dose of 56.2 Gy.

Overall survival and relapse rates

OS was 35.1% at 5 years for all patients (n=161) and 36.1% in the resected patients (n=150) (Table 2A). RFS, LR first site, LR cumulative and DM cumulative at 5 years was 31.8%, 44.3%, 50.9% and 63.4% for all patients; and 34.1%, 41.0%, 47.9% and 62.8% in the resected group respectively.

There were no significant differences for OS, RFS, cumulative LR and DM in the PORT vs. non-PORT subgroup in intention-to-treat and per-protocol analysis. In the PORT-group OS, RFS, cumulative LR and DM were 32.0%, 32.9%, 47.0% and 63.9% vs. 38.1%, 30.7%, 54.1% and 63.2% in the non-PORT-group respectively (Table 2A).

A subgroup analysis in the PORT-group, according to the indication for PORT, is depicted in Table 2B. We observed a 5-year OS of 39.5%, 33.3% and 6.4% ($p<0.01$) in the ypN2, R1/2, and (ypN2 + R1/2) group, respectively. The results for RFS, cumulative LR and DM for the (ypN2+ R1/2) group were also clearly inferior compared to the R1/2 group and the ypN2 group. In this (ypN2+ R1/2) group, significantly more tumor burden (largest T + N diameter) ($p=0.02$) and no response after chemotherapy was seen. OS according to the resection status was depicted in Supplementary Digital Content 1.

The following covariates were associated with a significant improvement of OS, RFS and less LR and DM in univariate analysis for all patients (Table 3): complete resection ($p<0.01$), response to induction chemotherapy (CT-based) ($p<0.01$), single nodal involvement ($p<0.01$)

and younger age (p=0.02). The multivariate analysis revealed similar statistically significant prognostic factors OS, RFS, LR and DM (Supplementary Digital Content 2). There was no difference in OS according to the comorbidity of all patients.

In the 88 patients in whom cumulative DMs developed, most failures were thoracic (25 patients (28.4%) with ipsilateral, 30 patients (34.1%) with contralateral lung metastases and 20 (22.7%) malignant pleural lesions) and cerebral (37 patients, 42.0%). Other sites of distant failure were bone metastases in 32 patients (36.4%), liver metastases in 16 patients (18.2%), extra-thoracic nodal failures (axillary, cervical or abdominal) in 18 patients (20.5%), adrenal metastases in 5 patients (5.6%), (sub)cutaneous in 3 (3.4%) and other (renal, soft tissue) in 4 (4.5%) patients

Toxicity:

The most frequent postoperative complications were pneumonia (16%), atrial fibrillation (13%) and persistent air-leak (9%) in all resected patients (n=150). Other non-frequent complications are depicted in Table 4. There was no significant difference (p=0.67) between the PORT-group (55%) and the non-PORT-group (45%) in intention-to-treat analysis. Cardiac and pulmonary events that occurred from 30 days postoperatively until the last follow-up were separately documented during follow-up and also compared in the 2 groups. The most frequent cardiac events were atrial fibrillation (8%), acute coronary events (7%) and heart failure (5%). There were significantly more cardiac events in the non-PORT-group compared to the PORT-group, both in the intention-to-treat analysis ($p<0.01$) as in the per-protocol analysis (p=0.04) (Table 4).

The most common pulmonary events in all patients were pneumonia (7%), exacerbations of COPD (4%) and radiation pneumonitis (3%). The number of pulmonary events was similar in both subgroups in the intention-to-treat (p=0.28) and the per-protocol analysis (p=0.15). Radiation pneumonitis, requiring hospitalization and/or use of corticosteroids, was documented in 6 patients (8%) in the PORT-group.

Secondly, we compared 2 clinical parameters (dyspnea and cough) and lung function parameters (FEV1 and DLCO) during follow-up between the PORT vs. non-PORT-group (per-protocol and in intention-to-treat analysis) (Figure 2 and Supplementary Digital Content 3). There was no significant difference for cough (p=0.37), dyspnea (p=0.32), FEV1 (p=0.30) or DLCO (p=0.61) between the PORT vs. non-PORT subgroup per-protocol. In intention-to-

treat analysis, there was no significant difference between the PORT and non-PORT-group for cough (p=0.07), FEV1 (p=0.17) or DLCO (p=0.85); only the dyspnea score was significant worse in the PORT-group (p=0.02).

We evaluated the evolution of these parameters over time after treatment (acute, late and last known follow-up), compared to baseline (before PORT) (Figure 2). FEV1 in the PORT-group changed in absolute values from a mean baseline value of 68.2% to 60.8%, 67.2% and 65.2% for the acute, late and last follow-up respectively (Supplementary Digital Content 4). In the non-PORT-group we found an evolution of 64.8% to 70.7%, 72.7% and 65.4%. As a 10% of variability in lung function parameters is considered normal, these changes are not significant. Also for DLCO, the changes in time in the PORT and non-PORT-group were not significantly different: in the PORT-group there was a change from 52.3% baseline to 49.1%, 54.5% and 59.0% for the acute, late and last follow-up respectively. In the non-PORT-group, this was from 52.1% to 57.9%, 61.5% and 58.4% respectively. Evolution of dyspnea scoring per grade is depicted in Supplementary Digital Content 5.

Causes of death

In total 115/161 deaths (71.4%) were recorded, of these, 92 were cancer related. From the 23 non-cancer related deaths, 8 (34.8%) were in the PORT-group and 15 (65.2%) in the non-PORT-group (p=0.29) per-protocol; in intention-to-treat analysis there were 13 (56.6%) in the PORT vs. 10 (43.5%) in the non-PORT-group. The cause of non-cancer related deaths in the PORT-group were: 3 patients died of pulmonary insufficiency, 2 patients had a cardiac arrest, there was 1 toxic death following chemotherapy for relapse, 1 acute abdomen (GI perforation) and 1 postoperative death after surgery for a second primary in the lung.

In the non-PORT-group we documented 5 postoperative deaths caused by postoperative complications. Another 4 died of a pulmonary infection, 2 of a cardiac arrest, 1 of an aortic rupture, 2 of secondary cancer (colon, lung) and 1of a sudden death without known etiology

Discussion

There are several therapeutic options for stage III NSCLC. The current standard treatment for most patients with stage III-N2 NSCLC is concurrent chemoradiotherapy; a reasonable alternative can be induction chemotherapy followed by surgery for resectable tumors (2,5). However, the general outcome remains poor in all treatment groups, with high rates of local and distant failures (2,7,8). We assessed the survival, relapse and toxicity rates in contemporary staged and treated stage III-N2 NSCLC patients after induction chemotherapy and resection. We found similar survival and toxicity in patients treated with or without additional PORT (in case of ypN2 status or R1/2 resection).

In the present study the 5 year- OS for all patients was 35.1% by intention-to-treat analysis. These results are in line with a recently published, prospective phase III randomized trial, also using an intention-to-treat analysis in contemporary staged and treated patients with a surgical multimodality treatment for stage III NSCLC (2).

In the present series, the LR rate as first site was 44.3%, with a cumulative 5-year LR rate of 50.9% for the whole group. The LR rates in this study are in line with those reported in literature. Betticher et al. reported a 29% first site and a 60% cumulative LR rate after induction cisplatin-docetaxel and resection (7). Several other trials also demonstrated 5-year LR rates of about 30% as first site of failure after neo-adjuvant chemotherapy and surgery (11,25) in stage III NSCLC. These findings support the need for additional local therapy in selected subgroups. Moreover, in our study an incomplete resection still occurred in 23.8%, and persistent N2 involvement was seen in 53.6% of patients.

We found no significant difference in 5-year OS, DFS or LR between the PORT subgroup and the non-PORT subgroup. The negative selection in the PORT subgroup can probably explain this. Patients treated with PORT had positive resection margins and/or higher gross residual disease (ypN2) as negative prognostic features. Also higher T-stages and less downstaging after chemotherapy were seen in the PORT-group. Thus, despite this negative selection, no inferior results were seen in the patients having received PORT. Because some patients with comorbidities have not received additional PORT, despite having ypN2 or R1/2 disease, we performed a separate intention-to-treat analysis. These non-significant results were confirmed, supporting indirectly the efficacy of PORT.

An interesting and intriguing finding in our study is the similar cardiac and pulmonary toxicity in the non-PORT and the PORT-group. Only a slight increase in dyspnea scoring was seen in the PORT-group in intention-to-treat analysis. However this effect disappeared during follow-up, at the time of last follow-up. In contrast, there were more cardiac events in the non-PORT-group. These results were confirmed in the intention-to-treat analysis. The number of pulmonary events and postoperative complications were similar in both subgroups. Other studies already reported the safety of modern PORT (15,16). New in this study is the information about the non-PORT toxicity in a matched patient group. These results can probably be explained according to upfront cardiac and pulmonary comorbidity.

Adding PORT to surgery in case of complete resection (negative resection margins) remains controversial. The PORT meta-analysis showed a detrimental effect of PORT on OS in resected NSCLC patients (26), while several recent, although retrospective, studies were able to demonstrate a benefit (27,28). However, an excess of toxicity (mostly cardiac and pulmonary) and non-cancer related deaths observed in the PORT meta-analysis, caused by obsolete radiation techniques, could probably explain these results. Using the distinction between cobalt vs. linear accelerators as surrogate for the radiation treatment quality, we previously suggested, however non-significant, the possible benefit of PORT using modern treatment techniques in a meta-analysis based on phase III randomized trials (9).

An alternative trimodality surgical treatment for stage III-N2 NSCLC patients is preoperative chemo-radiation therapy. A recently published phase 3 randomised trial compared induction chemo-radiation with induction chemotherapy, followed by surgery in stage IIIA NSCLC patients (2). PORT was only performed in case of incomplete resection in the chemotherapy group. A German trial randomized between induction chemo-radiation followed by surgery in one arm, and induction chemotherapy followed by surgery and additional PORT with doses up to 69 Gy in the other arm (29). In both studies, there were no significant differences in OS of DFS. Although excellent 5-year OS results were described in the SAKK trial with induction chemo-radiotherapy, they were not superior compared to our OS results with PORT. Both studies used contemporary staging and treatment methods, and an intention-to-treat analysis.

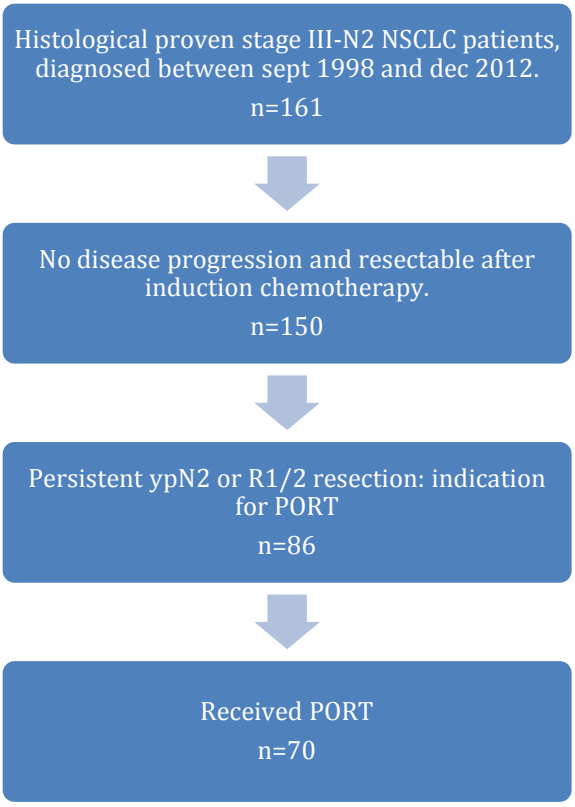
In a subgroup analysis, we clearly demonstrated lower OS and higher LR rates in the subgroup having an incomplete resection. Complete resection was also a significant

prognostic factor for OS, as already demonstrated in other studies (13,14,30). The patient group with ypN2 and R1/2 had an even worse outcome. These results emphasize the importance of achieving an R0 resection and thus of proper patient selection for surgical multimodality treatment.

Limitations of our study are the small patient number and the retrospective analysis, performed however, on a prospective database. About 10% of patients (16/150) in the non-PORT-group had N2 involvement but did not receive PORT because of postoperative complications or morbidity. We therefore performed a separate intention-to-treat analysis. The main strengths of this study are the optimal staging and radiation treatment techniques. Radiation treatment was given with linear accelerators and most of the patients had accurate staging using FDG-PET/ (CT), brain imaging (contrast-enhanced CT- or MRI scan) and EBUS/EUS. Secondly, although this was a retrospective study, we used an intention-to-treat analysis which leads to more accurate results, as patients that were progressive after induction chemotherapy were also included.

According to our results, our suggested policy is to add PORT in case of ypN2and/or incomplete resection in patients with stage III-N2 NSCLC. However, high-level evidence to guide the optimal management of postoperative N2 NSCLC patients is still lacking and randomized trials are needed. The randomized phase III trial Lung Adjuvant Radiotherapy Trial (Lung ART), comparing 3D conformal PORT to no PORT in completely resected pN2 NSCLC is ongoing and results are awaited (31).
The present study also supports the safety of PORT, however further investigation of possible predictive factors for radiation toxicity is warranted. A correlation of clinical and lung function parameters with the dosimetric parameters is under investigation and will be the topic of another study.

Figure 1: Patient inclusion algorithm



NSCLC: non-small cell lung cancer; PORT: post-operative radiotherapy

Table 1A: Clinical patients' characteristics

			INTENTION-TO-TREAT ANALYSIS			PER-PROTOCOL ANALYSIS		
Characteristic	All patients (n=161)	Resected group (n=150)	PORT (n=86)	Non-PORT (n=64)	p-value	PORT (n=70)	Non-PORT (n=80)	p-value
Age of diagnosis (years)								
Median	61	61	61	63	0.75	60	64	0.69
Range	34-80	34-80	34-80	38-79	-	34-80	38-79	-
Gender								
Male	115 (71.4%)	109 (72.7%)	67 (77.9%)	42 (65.6%)	0.38	54 (77.1%)	55 (68.8%)	1
Female	46 (28.6%)	41 (27.3%)	19 (22.1%)	22 (34.4%)	0.15	16 (22.9%)	25 (31.2%)	0.28
Comorbidity index [a]								
Low	41 (25.4%)	39 (26.0%)	23 (26.7%)	16 (25.0%)	0.84	20 (28.6%)	19 (23.7%)	0.56
Intermediate	95 (59.0%)	87 (58.0%)	47 (54.7%)	40 (62.5%)	0.53	38 (54.3 %)	49 (61.3%)	0.58
High	25 (15.5%)	24 (16.0%)	16 (18.6%)	8 (12.5%)	0.36	12 (17.1%)	12 (15.0%)	0.74
Performance status (WHO)								
0	105 (65.2%)	98 (65.3%)	56 (65.1%)	42 (65.6%)	0.97	46 (64.7%)	52 (65.0%)	0.61
1	53 (32.9%)	49 (32.7%)	29 (33.7%)	20 (31.3%)	0.79	23 (32.9%)	26 (32.5%)	0.67
2	3 (1.9%)	3 (2.0%)	1 (1.2%)	2 (3.1%)	0.40	1 (1.4%)	2 (2.5%)	0.56
Inclusion hospital								
University hospitals Leuven	134 (83.2%)	125 (83.3%)	76 (88.4%)	49 (76.6%)	0.43	63 (90.0%)	62 (77.5%)	0.40
Oncologic Centre Limburg	27 (16.8%)	25 (16.7%)	10 (11.6%)	15 (23.4%)	0.08	7 (10.0%)	18 (22.5%)	0.06
Smoking status [a]								
Never smoked	6 (3.7%)	6 (4.0%)	4 (4.7%)	2 (3.1%)	0.64	3 (4.3%)	3 (3.8%)	1
Ex-smoker	66 (41.0%)	62 (41.3%)	39 (45.3%)	23 (35.9%)	0.38	32 (45.7%)	30 (37.5%)	0.80
Active smoker	85 (52.8%)	79 (52.7%)	42 (48.8%)	37 (57.8%)	0.45	34 (48.6%)	45 (56.2%)	0.22
Unknown	4 (2.5%)	3 (2.0%)	1 (1.2%)	2 (3.1%)	0.40	1 (1.4%)	2 (2.5%)	1
Dyspnea [c]								
0	97 (64.2%)	90 (60.0%)	49 (57.0%)	41 (64.1%)	0.58	39 (55.7%)	51 (63.8%)	0.52
1	40 (24.8%)	37 (24.7%)	21 (24.4%)	16 (25.0%	0.94	17 (24.3%)	20 (25.0%)	0.93
2	24 (14.9%)	23 (15.3%)	16 (18.6%)	7 (10.9%)	0.24	14 (20.0%)	9 (11.2%)	0.17

Cough [c]								
0	63 (39.1%)	59 (39.3%)	34 (39.5%)	25 (39.1%)	0.88	29 (41.4%)	30 (37.5%)	0.70
1	65 (40.4%)	59 (39.3%)	34 (39.5%)	25 (39.1%)	0.96	27 (38.6%)	32 (40.0%)	0.89
2	33 (20.5%)	32 (21.3%)	18 (21.0%)	14 (21.9%)	0.90	14 (20.0%)	18 (22.5%)	0.74
Hemoptysis [c]								
0	125 (77.6%)	118 (78.7%)	69 (80.2%)	49 (76.6%)	0.80	56 (80.0%)	62 (77.5%)	0.86
1	36 (22.4%)	32 (21.3%)	17 (19.8%)	15 (23.4%)	0.63	14 (20.0%)	18 (22.5%)	0.74
FEV1								
Range	38% -134%	38% - 134%	52%-129%	61%-127%	-	38% - 122%	51% - 134%	-
Median	85%	85%	86%	85%	-	85%	84%	-
DLCO								
Range	38% - 140%	38% - 140%	38%-140%	46% - 115%	-	38% - 140%	46% - 115%	-
Median	74%	75%	77%	74%	-	78%	74%	-

All characteristics are at time of diagnosis.

[a] Charlson comorbidity index age adjusted: low (O-3), intermediate (4-6), high (7-9)[b] Ex-smoker: smoking cessation > 1 month

[c] Scoring of symptoms according Common Terminology Criteria for Adverse Events Scoring of symptoms (CTCAE)

PORT: post-operative radiotherapy; p: p-value; WHO: World Health Organization; DLCO: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume 1

Table 1B: Tumor and treatment characteristics

			INTENTION-TO-TREAT ANALYSIS			PER-PROTOCOL ANALYSIS		
Characteristic	All patients (n=161)	Resected group (n=150)	PORT (n=86)	Non-PORT (n=64)	p-value	PORT (n=70)	Non-PORT (n=80)	p-value
Tumor side								
Left	51 (31.7%)	48 (32.0%)	32 (37.2%)	16 (25.0%)	0.19	26 (37.1%)	22 (27.5%)	0.56
Right	110 (68.3%)	102 (68.0%)	54 (62.8%)	48 (75.0%)	0.37	44 (62.9%)	58 (72.5%)	0.20
Tumor location								
Upper-middle	109 (67.7%)	100 66.6%)	56 (65.1%)	44 (68.7%)	0.79	48 (68.6%)	52 (65.0%)	0.77
Lower	52 (32.3%)	50 (33.3%)	30 (34.9%)	20 (31.3%)	0.70	22 (31.4%)	28 (35.0%)	0.40
Histological subtype								
Squamous cell carcinoma	73 (45.3%)	71 (47.3%)	43 (50.0%)	28 (43.7%)	0.58	33 (47.1%)	38 (47.5%)	0.64
Adenocarcinoma	74 (46.0%)	67 (44.7%)	39 (45.3%)	28 (43.7%)	0.89	33 (47.1%)	34 (42.5%)	0.90
Large cell carcinoma	12 (7.5%)	10 (6.7%)	3(3.5%)	7 (10.9%)	0.08	3 (4.3%)	7 (8.8%)	0.21
Other	2 (.2%)	2 (1.3%)	1 (1.2%)	1 (1.6%)	0.83	1 (1.4%)	1 (1.2%)	1
Mediastinal lymph node involvement								
Single station N2	127 (78.9%)	121 (80.7%)	66 (76.7%)	55 (85.9%)	0.53	52 (74.3%)	68 (85.0%)	0.14
Multiple station N2	34 (21.1%)	29 (19.3%)	20 (23.3%)	9 (14.1%)	0.21	18 (25.7%)	12 (15.0%)	0.21
Radiological T-stage								
cT1	28 (17.4%)	27 (18.0%)	12 (14.0%)	15 (23.4%)	0.18	7 (10.0%)	20 (25.0%)	**0.01**
cT2	52 (32.3%)	49 (32.7%)	22 (25.6%)	27 (42.2%)	0.08	17 (24.3%)	32 (40.0%)	**0.03**
cT3	71 (44.1%)	65 (43.3%)	46 (53.4%)	19 (29.7%)	**0.03**	40 (57.1%)	25 (31.3%)	**0.05**
cT4	10 (6.2%)	9 (6.0%)	6 (7.0%)	3 (4.7%)	0.60	6 (8.6%)	3 (3.7%)	0.32
N2 status assessment								
Mediastinoscopy	123 (76.4%)	114 (76.0%)	64 (74.4%)	50 (78.1%)	0.80	50 (71.4%)	64 (80.0%)	0.55
EBUS and/or EUS	36 (22.4%)	34 (22.7%)	21(24.4%)	13 (20.3%)	0.60	19 (27.1%)	15 (18.7%)	0.28
Explorative thoracotomy	1 (0.6%)	1 (0.6%)	0 (0%)	1 (1.2%)	0.25	0 (0%)	1 (1.3%)	0.35
Transbronchial biopsy	1 (0.6%)	1 (0.6%)	1 (1.6%)	0 (0%)	0.39	1 (1.4%)	0 (0%)	0.29
Type of	103 (64.0%)	97 (64.7%)	55 (64.0%)	42 (65.6%)	0.90	48 (70.0%)	49 (61.2%)	0.58

chemotherapy								
Cisplatin-Gemcitabin	2 (1.2%)	2 (1.3%)	1 (1.2%)	1 (1.6%)	0.83	1 (1.4%)	1 (1.3%)	0.93
Carboplatin-Gemcitabin	5 (3.1%)	5 (3.3%)	18 (20.9%)	9 (14.1%)		0 (0%)	5 (6.2%)	**0.04**
Cisplatin-Vinorelbine	7 (4.3%)	6 (4.0%)	7 (8.1%)	4 (6.3%)	0.33	2 (2.8%)	4 (5.0%)	0.51
Cisplatin – Pemetrexed	2 (1.2%)	2 (1.3%)	3 (3.5%)	3 (4.7%)	0.67	1 (1.4%)	1 (1.3%)	0.93
Cisplatin – Ifosfamide	30 (18.6%)	27 (18.0%)	1 (1.2%)	4 (6.3%)		11(15.7%)	16 (20.0%)	0.54
- Vindesine	12 (7.5%)	11 (7.3%)	1 (1.2%)	1 (1.6%)	0.09	7 (10.0%)	4 (5.0%)	0.26
VIP					0.83			
GIP								
CT-based response induction chemotherapy (RECIST 1.1)								
Stable	57 (35.4%)	49 (32.7%	34 (39.5%)	15 (23.4%)	0.08	31 (44.3%)	18 (22.5%)	**0.05**
Partial	88 (54.7%)	88 (58.7%)	49 (57.0)	39 (60.9%)	0.75	37 (55.7%)	51 (63.7%)	0.14
Complete	13 (8.0%)	13 (8.7%)	3 (3.5%)	10 (15.6%)	**0.01**	2 (2.9%)	11 (13.7%)	**<0.01**
Progressive	3 (1.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	-	-	-	-
PET-based response induction chemotherapy (PERCIST)								
Stable	6 (20.0%)	3 (11.1%)	2 (8.7%)	1 (8.3%)	0.74	2 (2.8%)	1 (1.3%)	0.56
Partial	21 (70.0%)	21 (77.8%)	12 (52.2%)	9 (75.0%)	0.98	10 (14.1%)	11 (13.8%)	0.83
Complete	3 (10.0%)	3 (11.1%)	9 (39.1%)	2 (16.7%)	0.10	1 (1.4%)	2 (2.5%)	0.56
Pathological response induction chemotherapy (remediastinoscopy)								
Stable	22 (36.7%)	20 (34.5%)	16 (47.1%)	21 (95.5%)	0.08	19 (26.8%)	1 (1.3%)	**<0.01**
Partial/Complete	38 (63.3%)	38 (65.5%)	18 (52.9%)	1 (4.5%)	**<0.01**	14 (19.7%)	23 (28.8%)	0.14
Surgery type								
Lobectomy/bilobectomy	-	116 (77.3%)	61 (70.9%)	55 (85.9%)	0.30	51 (72.9%)	65 (81.3%)	0.19
Pneumonectomy	-	34 (22.7%)	25 (29.1%)	9 (14.1%)	0.06	19 (27.1%)	15 (18.7%)	0.49
Completeness	-	115 (76.7%)	52 (60.5%)	64 (100%)	**<0.01**	41 (58.6%)	74 (92.5%)	**<0.01**

of resection **R0** **R1** **R2**	- -	29 (19.3%) 6 (4.0%)	28 (32.5%) 6 (7.0%)	0 (0.0%) 0 (0.0%)	**<0.01** **0.03**	24 (34.3%) 5 (7.1%)	5 (6.3%) 1 (1.2%)	**<0.01** 0.06
Downstaging of mediastinal lymph nodes								
Downstaging **Persistent ypN2/3**	- -	69 (46.0%) 81 (54.0%)	7 (8.1%) 79 (91.9%)	64 (100%) 0 (0.0%)	**<0.01** **<0.01**	7 (10.0%) 63 (90.0%)	63 (78.8%) 17 (21.2%)	**<0.01** **<0.01**

a complete resection: negative resection margin (R0), no involvement of the highest mediastinal lymph node removed and no extracapsular nodal extension of the tumor.

PORT: post-operative radiotherapy; p: p-value; EBUS: endobronchial ultrasound; EUS: endoscopic ultrasound; RECIST response evaluation criteria in solid tumors; PERCIST: PET response criteria in solid tumors

Table 2: 5-year results for OS, RFS, LR and DM

2A: For all patients

			INTENTION-TO-TREAT			PER-PROTOCOL		
	All patients (n=161)	Resected patients (n=150)	PORT (n=86)	Non-PORT (n=64)	p-value	PORT (n=70)	Non-PORT (n=80)	p-value
OS	35.1%	36.1%	27.8%	47.9%	0.06	32.0%	41.5%	0.44
RFS	31.8%	34.1%	32.1%	36.8%	0.37	32.9%	34.6%	0.47
LR first site	44.3%	41.0%	41.9%	39.8%	0.70	37.4%	44.8%	0.60
LR cumulative	50.9%	47.9%	50.1%	54.4%	0.52	47.0%	49.5%	0.95
DM cumulative	63.4%	62.8%	66.7%	58.1%	0.19	63.9%	61.1%	0.47

OS: overall survival; RFS: relapse free survival; LR: local recurrence rate; DM: distant metastasis rate; PORT: post-operative radiotherapy

2B : For PORT subgroup-analysis: ypN2, R1/2 or (ypN2 + R1/2)

	ypN2 (N=51)	R1/2 (N=6)	ypN2 and R1/2 (N=24)	p-value
OS	39.5%	33.3%	6.4%	**<0.01**
RFS	40.3%	33.3%	11.9%	**0.02**
LR first site	38.8%	58.3%	57.5%	0.72
LR cumulative	39.8%	50.0%	81.8%	0.10
DM cumulative	58.1%	55.6%	85.8%	**0.04**

OS: overall survival; RFS: relapse free survival; LR: local recurrence rate; DM: distant metastasis rate; PORT: post-operative radiotherapy

Table 3: Univariate analysis in all patients (n=161))

Covariate	Death	Relapse (LR or DM)	LR first site	LR cumulative	DM
	P-value	P-value	P-value	P-value	P-value
Sex (M/F)	0.31	0.64	0.31	0.16	0.47
Nicotine use (never/active/ex[a])	0.24	0.09	0.09	0.24	**0.05**
WHO PS (0-2)	**0.03**	0.056	0.11	0.09	**0.04**
T stage (1-4)	0.90	0.96	0.76	0.62	0.63
Single/Multiple node involvement	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Histology(squamous, adeno, large cell, other)	0.27	0.31	0.23	0.15	0.36
Completeness of resection (R0-1-2-3)	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Pathology downstaging (N/Y)	0.72	0.65	0.63	0.52	0.66
FDG -PET downstaging (N/Y)	0.82	0.28	0.16	0.48	0.47
CT downstaging (N/Y)	**<0.01**	**<0.01**	**<0.01**	**<0.01**	**<0.01**
Nodal downstaging (N/Y)	0.25	0.76	0.58	0.82	0.22
Age at diagnosis (continuous)	**0.02**	**0.02**	**0.02**	**0.02**	**0.02**
Comorbidity index	0.12	0.56	0.27	0.19	0.38

a Ex-smoker: smoking cessation > 1 month

WHO: World Health Organization; OS: overall survival; RFS: relapse free survival; LR: local recurrence rate; DM: distant metastasis rate

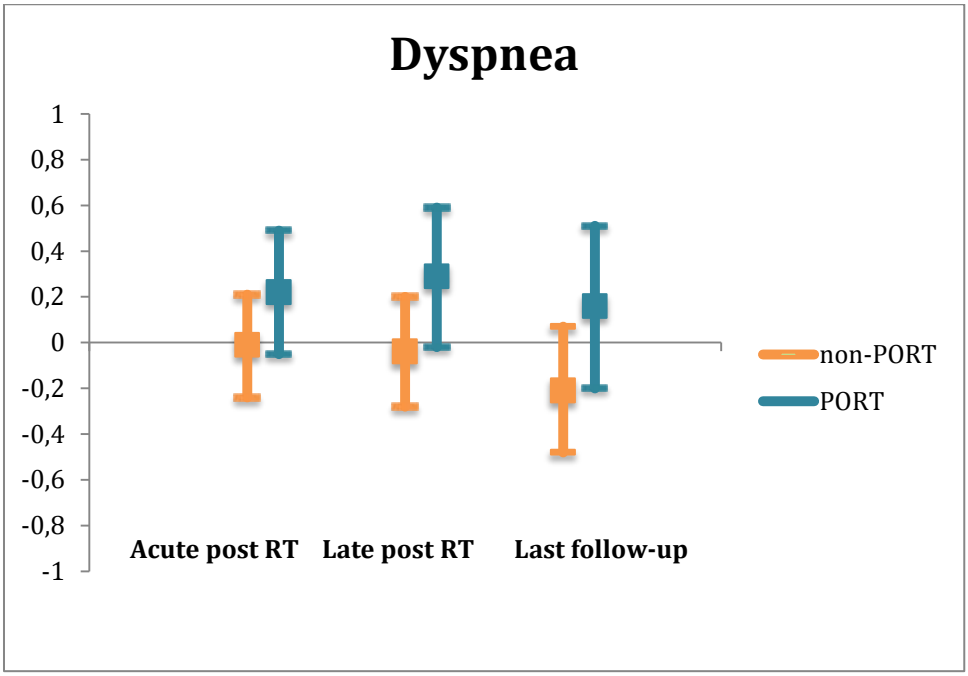
Significant p-values (p<0.05) are in bold.

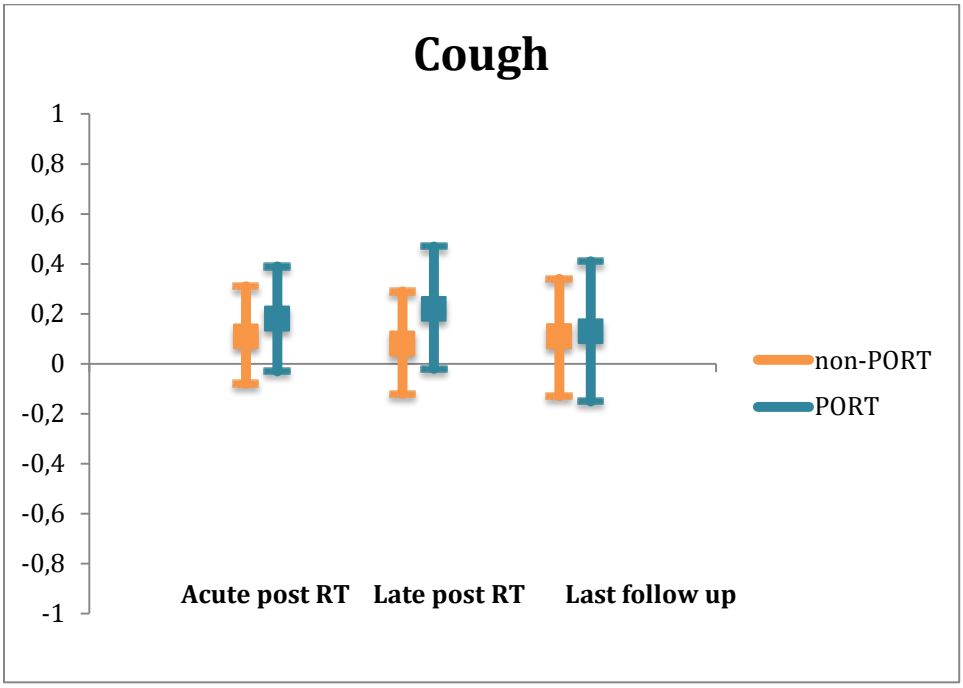
Table 4: Toxicity in all resected patients

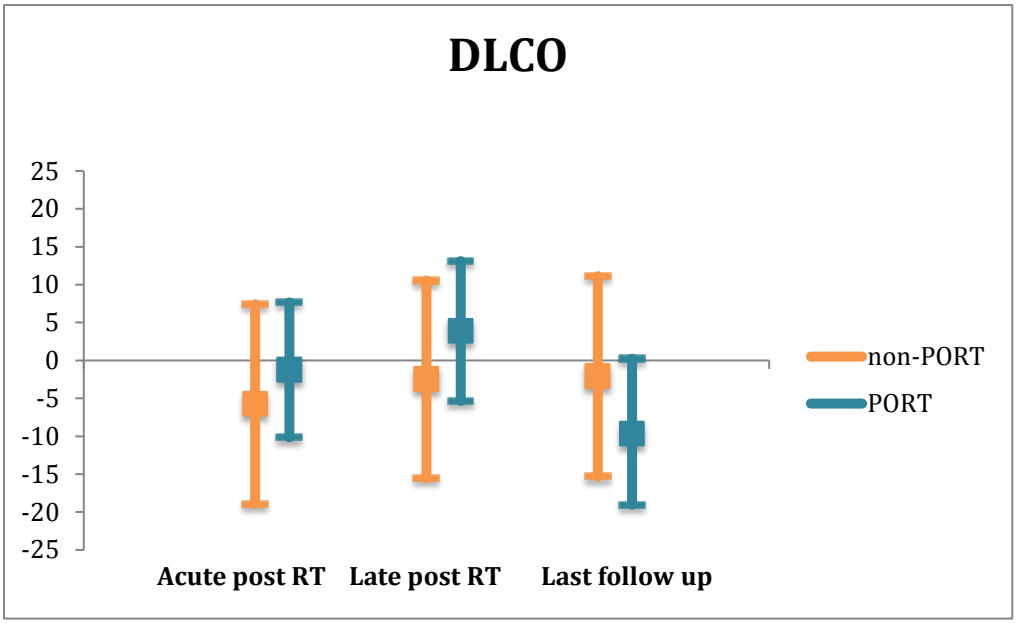
		INTENTION-TO-TREAT			PER-PROTOCOL		
	All resected patients (n=150)	PORT (n=86)	Non-PORT (n=64)	p-value	PORT (n=70)	Non-PORT (n=80)	p-value
POSTOPERATIVE EVENTS							
Atrial fibrillation	20 (13%)	13 (15%)	7 (11%)	0.49	9 (13%)	11 (14%)	0.95
Pneumonia	24 (16%)	14 (15%)	10 (16%)	0.92	7 (10%)	17 (21%)	0.10
Persistent air leak	13 (9%)	6 (6%)	7 (11%)	0.42	3 (4%)	10 (12%)	0.10
Acute coronary event	2 (1%)	0 (0%)	2 (3%)	0.10	0 (0%)	2 (3%)	0.19
Bleeding	2 (1%)	0 (0%)	2 (3%)	0.10	0 (0%)	2 (3%)	0.19
Drug induced pneumonitis	1 (1%)	1 (1%)	0 (0%)	0.39	0 (0%)	1 (1%)	0.36
Chylothorax	1 (1%)	0 (0%)	1 (2%)	0.32	0 (0%)	1 (1%)	0.36
ARDS	1 (1%)	1 (1%)	0 (0%)	0.39	0 (0%)	1 (1%)	0.36
TOTAL	64 (43%)	35 (41%)	29 (45%)	0.67	19 (27%)	45 (56%)	**0,01**
CARDIAC EVENTS							
Acute coronary event	9 (7%)	3 (3%)	6 (14%)	0.27	3 (4%)	6 (8%)	0.09
Atrial fibrillation	12 (8%)	4 (5%)	8 (13%)	0.09	4 (6%)	8 (10%)	0.39
Heart failure	7 (5%)	1 (1%)	6 (9%)	**0.02**	1 (1%)	6 (8%)	0.09
Valvular heart disease	4 (3%)	1 (1%)	3 (5%)	0.19	1 (1%)	3 (4%)	0.56
Aortic rupture	1 (1%)	1 (1%)	0 (0%)	0.39	0 (0%)	1 (1%)	0.36
Pericarditits	2 (1%)	1 (1%)	1 (2%)	0.83	1 (1%)	1(1%)	0.90
Cardiac arrest	2 (1%)	1 (1%)	1 (2%)	0.83	1 (1%)	1(1%)	0.90
TOTAL	37 (25%)	12 (14%)	25 (39%)	**<0.01**	11 (16%)	26 (33%)	**0,04**
PULMONARY EVENTS							
Pneumonia	11 (7%)	7 (8%)	4 (6%)	0.67	6 (8%)	5 (6%)	0.56
Radiation pneumonitis	6 (4%)	6 (7%)	0 (0%)	**0.04**	6 (8%)	0 (0%)	**<0.01**
COPD exacerbation	5 (3%)	3 (3%)	2 (3%)	0.90	2 (3%)	3 (4%)	0.80
ARDS	1 (1%)	1 (1%)	0 (0%)	0.39	1 (1%)	0 (0%)	0.28
Chylothorax	1 (1%)	0 (0%)	1 (2%)	0.25	0 (0%)	1 (1%)	0.36
Chronic hiccup	1 (1%)	0 (0%)	1 (2%)	0.25	0 (0%)	0 (0%)	0.36
TOTAL	25 (17%)	17 (19%)	8 (13%)	0.28	15 (21%)	10 (12%)	0.15

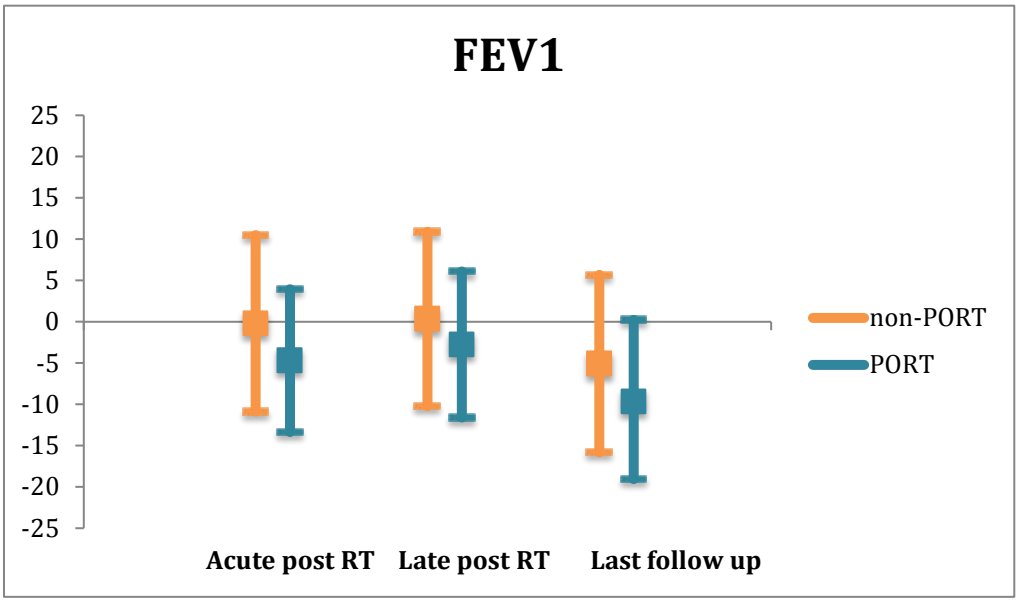
PORT: post-operative radiotherapy; ARDS: acute respiratory distress syndrome; COPD: chronic obstructive pulmonary disease

Figure 2: Changes compared to baseline of clinical parameters (dyspnea and cough) and lung function parameters (FEV1 and DLCO) in follow-up in PORT vs. non-PORT-group (per-protocol)









FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity; PORT: post-operative radiotherapy; acute post RT: <= 3 months after start RT

late post RT: >= 12 months after start RT

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Supplemental Digital Content 1. Word document

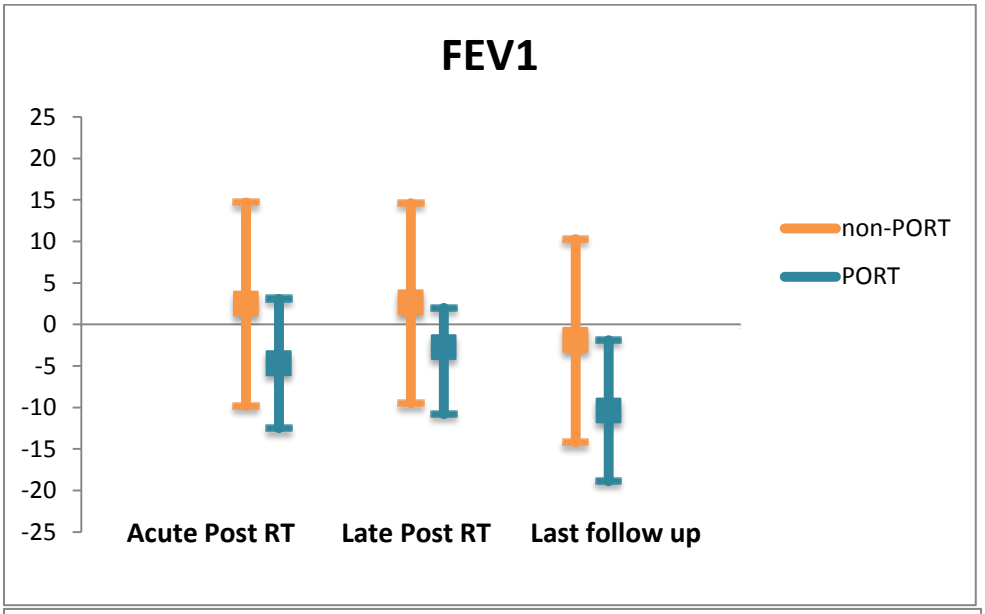
SUPPLEMENTARY FILES

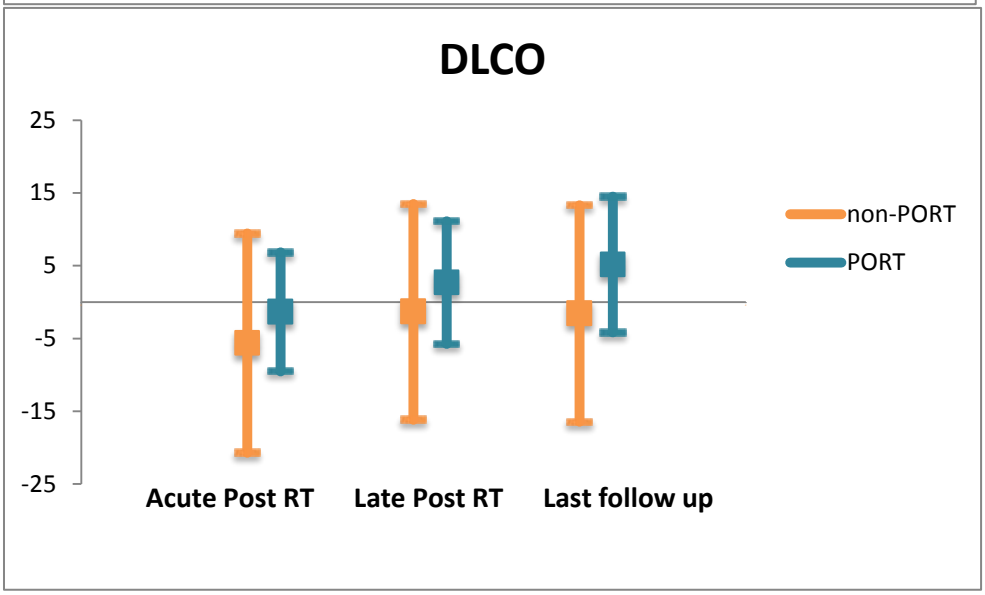
Appendix A: Multivariate analysis in all resected patients

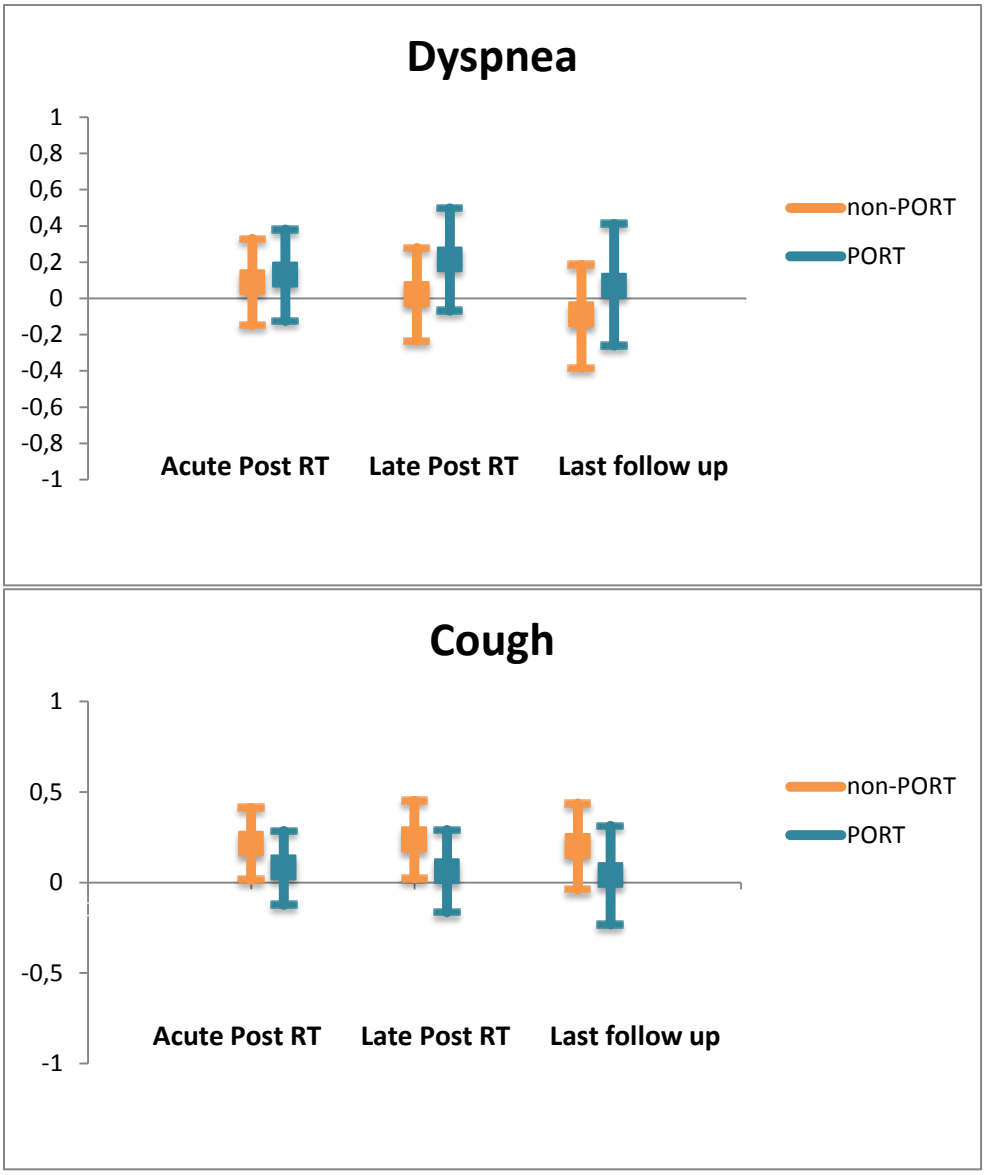
Covariate	Death			Relapse (LR or DM)			LR first site			LR cumulative			DM		
	p-value	HR	SE	p-value	HR	SE	p-value	HR	SE	p-value	HR	SE	p-value	HR	SE
Single nodal involvement	**<0.01**	0.42	0.23	**<0.01**	0.31	0.24	**<0.01**	0.40	0.34	**<0.01**	0.44	0.31	**<0.01**	0.37	0.25
Completeness of resection **R0** **R1**	**<0.01** 0.05	0.20 0.39	0.44 0.48	**<0.01** **<0.01**	0.18 0.28	0.44 0.48	**<0.01** **<0.01**	0.14 0.15	0.55 0.66	**<0.01** **0.02**	0.14 0.26	0.55 0.60	**<0.01** **0.04**	0.19 0.34	0.48 0.52
CT downstaging **Complete** **Partial**	**0.02** **<0.01**	0.29 0.56	0.53 0.22	0.18 **<0.01**	0.57 0.48	0.42 0.23	- -	- -	- -	**0.06** 0.03	0.24 0.54	0.74 0.29	0.11 **<0.01**	0.49 0.44	0.45 0.24
Age at diagnosis (continuous)	**<0.01**	1.04	0.01	-	-	-	**<0.01**	1.05	0.02	**<0.01**	1.05	0.02	-	-	-

Cox Proportional Hazard regression model illustrating associations between variables and death, relapse, local recurrence and distant metastasis. Significant p-values (p<0.05) are in bold.
HR: hazard ratio; SE: standard error; OS: overall survival; RFS: relapse free survival; LR: local recurrence rate; DM: distant metastasis rate

Appendix B: Changes compared to baseline of clinical parameters (dyspnea and cough) and lung function parameters (FEV1 and DLCO) in follow up in PORT vs. non-PORT (intention-to-treat analysis)



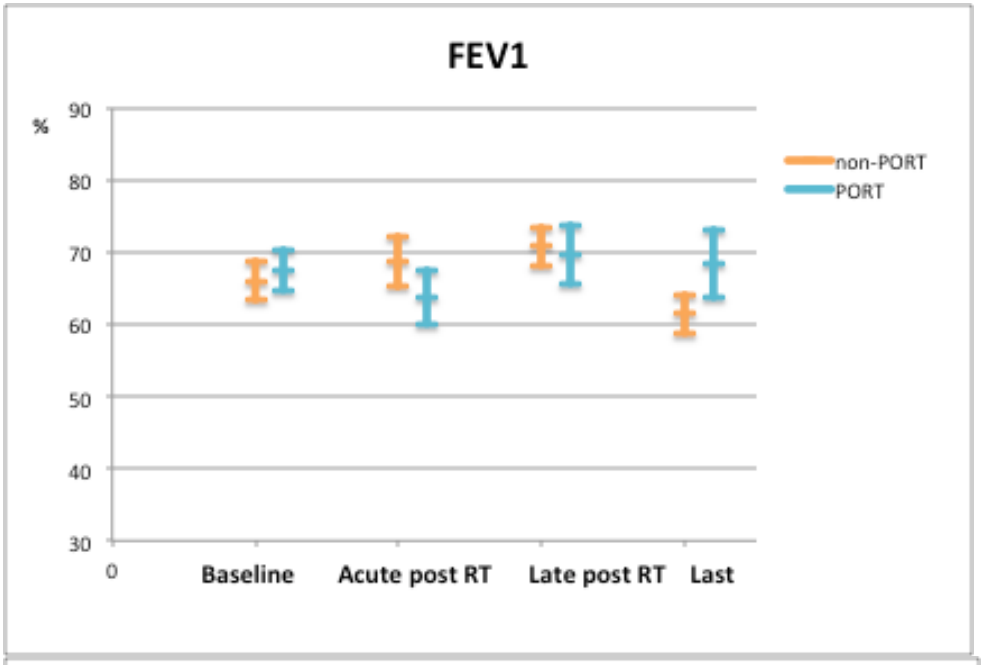


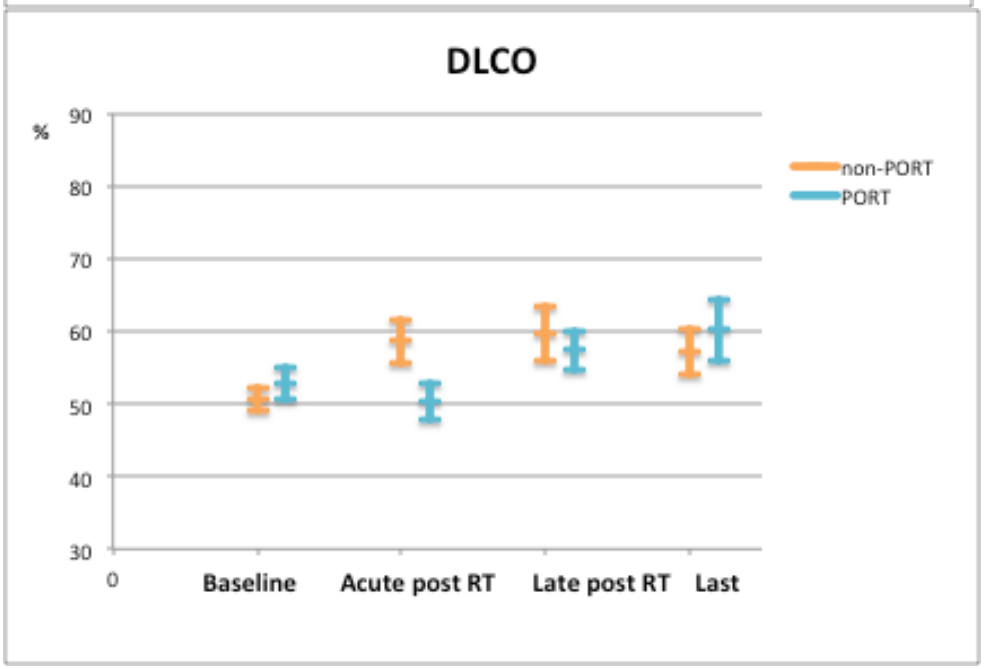


FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity; PORT: post-operative radiotherapy;
acute post RT: <= 3 months after start RT or matched time point in non-PORT-group
late post RT: >= 12 months after start RT or matched time point in non-PORT-group

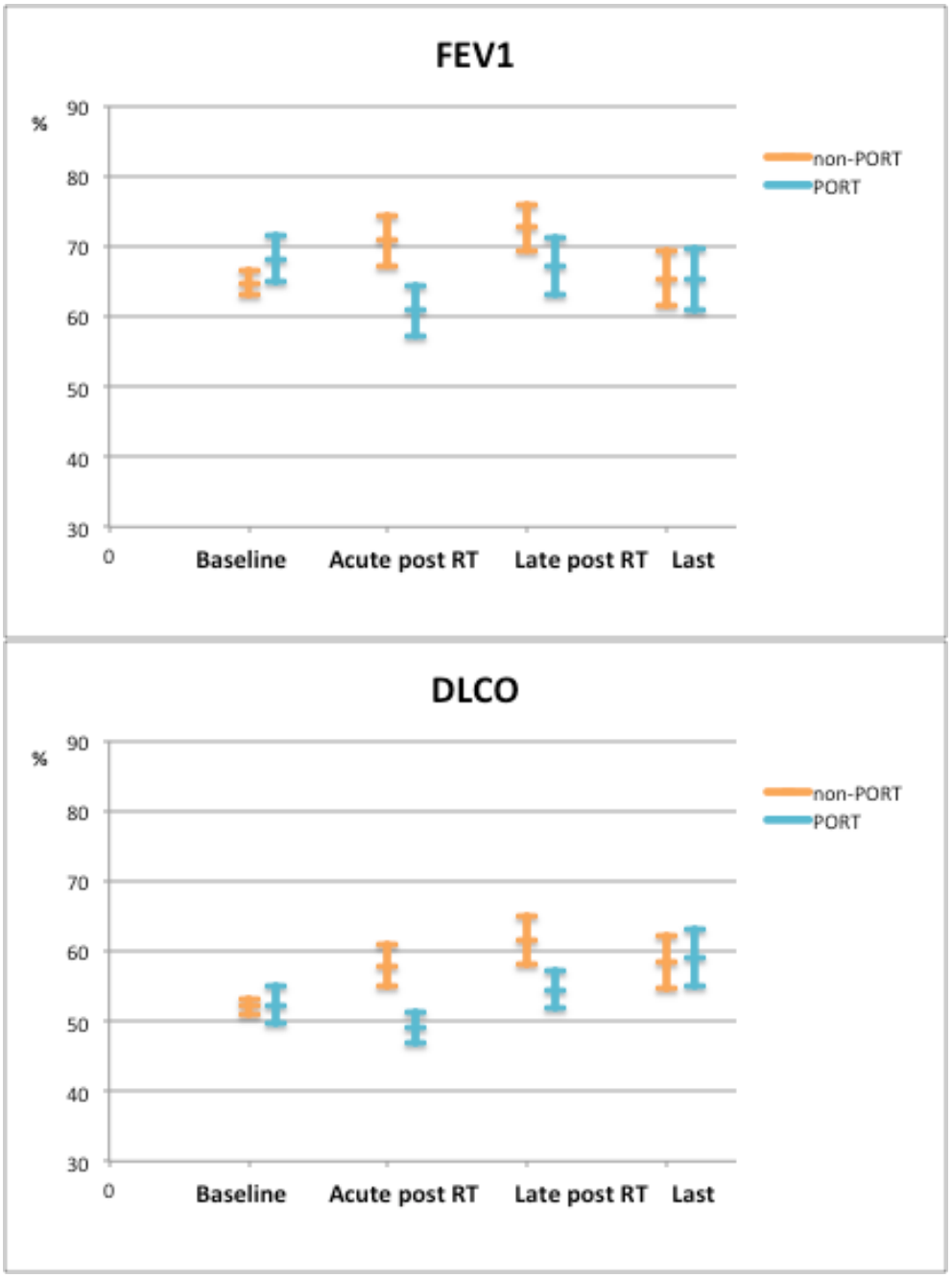
Appendix C: Absolute changes in lung function parameters (FEV1 and DLCO) compared to baseline in follow-up in PORT vs. non-PORT (intention-to-treat and per-protocol analysis)

A. Intention-to-treat analysis



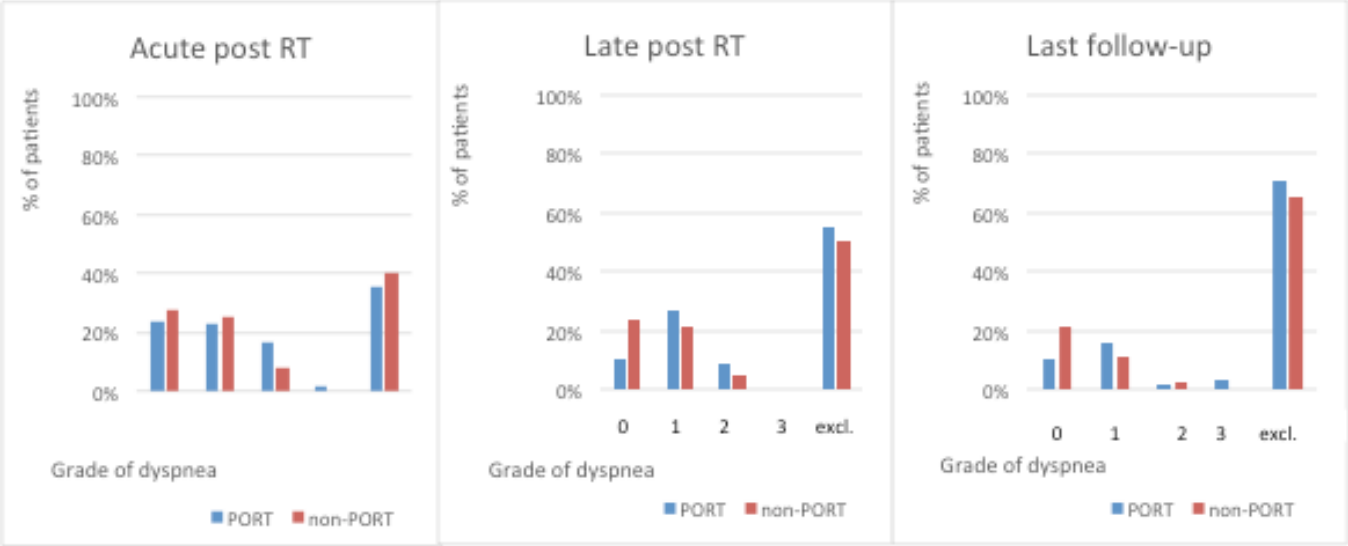


B. Per-protocol analysis



FEV1: forced expiratory volume in 1 second; DLCO: diffusing capacity; PORT: post-operative radiotherapy;
acute post RT: <= 3 months after start RT or matched time point in non-PORT-group
late post RT: >= 12 months after start RT or matched time point in non-PORT-group
last = last known follow-up

Appendix D: Dyspnea scoring during follow-up in PORT vs. non-PORT-group



Excl.: excluded because of disease relapse or unknown follow-up; RT: post-operative radiotherapy;

Appendix E: Overall survival according to resection status in all patients