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Patterns of loco-regional relapses in contemporarily staged stage III-N2 non-small cell lung cancer patients treated with induction chemotherapy and resection: Implications for postoperative radiotherapy target volumes

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Running Head: Loco-regional relapse patterns for stage III-N2 NSCLC

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ABSTRACT

Background:

To evaluate loco-regional patterns of relapse after induction chemotherapy and surgery for stage III-N2 non–small-cell lung cancer (NSCLC), staged with current standard methods, and their impact on radiation target volumes for postoperative radiotherapy (PORT).

Material/Methods:

150 patients with stage III-N2 NSCLC were included from a prospective database at the University Hospitals of Leuven or the Oncologic Centre Limburg between 1998 and 2012. Patients were staged with FDG-PET-CT and brain imaging and treated with induction chemotherapy and surgery. PORT was performed for incomplete resection (R1/R2) and/or persistent nodal disease (ypN2). For the non-PORT group, we created a virtual planning target volume (PTV). In general, the clinical target volume encompassed the bronchial stump, the ipsilateral hilum, the subcarinal region (station 7) and the initially involved mediastinal lymph nodes.

Results:

After a mean follow-up time of 49 months, the 5-year overall survival was 35.1% in all patients; disease-free survival was 31.8%.
PORT was delivered in 70 patients. Loco-regional recurrence (LR) was seen in 26 patients in the PORT (37%), and 32 in the non-PORT group (40%). Fifty-eight nodal relapse sites were seen in the PORT group (2.2 sites/patient), vs. 113 in the non-PORT group (3.5 sites/patient) ($p<0.01$).
In the PORT-group, the most common sites of LR were ipsilateral hilum (21%), lymph node station 7 (15%), ipsilateral 4 (9%), 5 (9%) and 6 (9%). For the non-PORT group these were station 7 (19%), ipsilateral 4 (16%) and ipsilateral hilum (14%).
The dominant pattern of failure was inside (in or both in-and outside) the PTV. Regarding the out-of-PTV relapses, 47% and 69% of LRs occurred in the contralateral mediastinum for the PORT vs. non-PORT group, respectively. Out-of-PTV relapses occurred mostly in initially left-sided tumors.

Conclusion:

Despite the limitations of this retrospective study, our data support the role of PORT in decreasing local relapses. Because of the large number of out-of-PTV relapses in the contralateral mediastinum, inclusion of elective contralateral lymph node stations in the PTV could be considered in left-sided tumors. However, prospective randomized trials are needed to verify this.

Introduction:

Non-small cell lung cancer (NSCLC) continues to be one of the leading causes of cancer mortality (1). One-third of NSCLC patients are diagnosed with locally advanced, stage III, disease, with 5-year survival rates ranging from 25% to 35% in recently published trials (2,3,4,5). The treatment of stage III NSCLC consists of combined modality therapy, but the optimal regimen remains unclear in this heterogeneous patient population (6). Besides a combination of chemotherapy and radiation therapy, surgical resection, mostly after induction chemotherapy, is a reasonable alternative for selected patients (3,6). However, even after complete resection and chemotherapy, the loco-regional recurrence (LR) rate remains high, with 30% as first site of failure and up to 60% cumulative LR rates (3,7). Despite a reduction of LR after postoperative radiotherapy (PORT) for completely resected stage III NSCLC, its effect on overall survival (OS) remains unproven. Several large retrospective studies have suggested a benefit of PORT (9,10). However, a large meta-analysis did not reveal an improved OS (11). It has been hypothesized that obsolete radiation techniques with excessive toxicity could explain these results. In a more recently published meta-analysis, we hypothesized with modern PORT techniques a decrease in LR of 20% leading to a 13% increase in OS for stage III-N2 NSCLC patients (12,13).

If PORT is to be successful, optimal target volumes need to be defined. Current target volumes definitions rely on patients that were treated in an era without contemporary staging such as fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET)-CT scans, and endobronchial ultrasound (EBUS) or esophageal ultrasound (EUS). Moreover, older studies in the PORT meta-analysis used relatively large radiation fields with coverage of the bronchial stump, ipsilateral hilum, and entire mediastinum, causing an increased cardiopulmonary toxicity. 3D-planned PORT using a limited clinical target volume (CTV) may reduce treatment toxicity and increase local control. With 2D techniques, geographical misses may have occurred, even with large radiation fields (14). Surgical techniques have evolved as well, with improved mediastinal clearing as a result (15). Lastly, modern adjuvant chemotherapy also reduces LR rates (16).

There is lack of data on the patterns of relapse in contemporarily staged and treated patients, which may affect not only the incidence but also the site of recurrence. Therefore, we investigated the patterns of LR relapse after induction chemotherapy followed by surgical resection in stage III-N2 NSCLC patients, staged and treated with current standard methods.

Materials & Methods:

From a prospective database (lung cancer multidisciplinary team), we identified patients with pathological proven stage III-N2 NSCLC who underwent surgical resection after cisplatin-based induction chemotherapy between January 1998 and December 2012 at the University Hospitals of Leuven or the Oncologic Centre Limburg. Postoperative radiation therapy (PORT) was delivered in case of persistent nodal involvement (ypN2) and/or incomplete resection (R1/2). All patients were more than 18 years old and had a World Health Organization (WHO) performance status between 0 and 2. The radiology, nuclear medicine, surgery and pathology reports for each patient were reviewed.
Pretreatment staging included a history and clinical examination, a biochemical test (blood count, renal and liver function and the tumor marker carcinoembryonic antigen (CEA)), pulmonary function tests, bronchoscopy and a contrast-enhanced CT scan of the thorax and upper abdomen. In addition, brain imaging (contrast-enhanced CT or MRI scan) and a ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)-CT were performed, as well as an invasive staging of the mediastinum, consisting of EBUS-TBNA (endobronchial ultrasound transbronchial needle aspiration) or EUS-FNA (esophageal ultrasound fine needle aspiration) and/or mediastinoscopy. Staging occurred according to the TNM 7th edition for all patients (17).
The initially involved lymph nodes (LN) were documented with CT scan, FDG-PET and/or pathology report. A positive lymph node was defined as enlarged ≥1 cm in the short axis on CT scan, hypermetabolic uptake above mediastinal background on FDG-PET, or harboring malignancy after invasive mediastinal staging. In this study, we considered only the LN positive on FDG-PET or pathology at time of diagnosis as involved, as CT only has limited sensitivity and specificity for identifying mediastinal LN involvement (18).

In this intention-to-treat database, surgical treatment included a (bi)lobectomy or pneumonectomy, and a systematic multilevel mediastinal lymph node dissection accordance to the ESTS guidelines (19). At least three mediastinal nodal stations (but always subcarinal) were routinely excised. The nodes were separately labeled and examined histologically. Beside the mediastinal nodes, 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 (20).

Follow up occurred in or in cooperation with the University Hospitals Leuven 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 physical examination, biochemical tests (blood count, renal and liver function and CEA) and a chest x-ray. A CT scan of the thorax and upper abdomen with IV contrast was done each 6 months. Further imaging modalities and pulmonary function tests were performed according to the physician's choice based on the patient's symptoms.

Nodal failure was defined as a new or enlarged LN, measuring ≥1 cm in short axis on a follow-up CT scan. For patients who also underwent an FDG-PET/(CT) scan at the time of tumor recurrence, LN

being FDG-avid, regardless of size, were registered and considered as being pathological. When available, pathological data were used to supplement the imaging findings.

Local recurrence (LR) was identified as a relapse involving the bronchial stump, hilar, mediastinal or sub/supraclavicular lymph nodes; all other relapses were considered as distant metastases (DM). Tumor recurrence at the bronchial stump after lobectomy or pneumonectomy was scored as "bronchial stump recurrence". The lymph node map was used as a reference to define the involved lymph node stations on cross-sectional imaging (21). The LR as first site rate (LR first site) was calculated from the date of first pathological diagnosis to the date of first documentation of LR and the cumulative LR from the date of first pathological diagnosis until the presence of LR at any time.

In patients receiving PORT, radiotherapy was planned using a 3D-planning system (Eclipse, Varian). For each individual patient we registered which LNs were included in the planning target volume (PTV). In general, the clinical target volume (CTV) encompassed the bronchial stump, the ipsilateral hilum, the subcarinal region (station 7) and the initially involved mediastinal LNs. The contralateral hilum and the supraclavicular fossae were not routinely included. The PTV was determined as the CTV plus 1-cm margin. Dose prescription was defined such that 95% of the prescribed dose covered 99% of the PTV. Radiotherapy was delivered with linear accelerators, using 6 to 10 MV photons at 2 Gy per fraction, 5 days per week, with a total dose ranging from 50 Gy to 66 Gy. Patients with R0 resection received a median dose of 56 Gy (range 50-60 Gy), whereas patients with R1 or R2 status received a total median dose of 60 Gy (range 50-66 Gy).

We evaluated the patterns of relapse, according to the PTV, to define 3 subgroups whether the LR was inside, outside or in- and outside the PTV. For patients with LR, but not having received PORT, an individual virtual PTV was created, following the LungART contouring guidelines (addendum C) in regard to the initially involved LNs.

Statistical analysis was performed using SAS 9.4. Comparisons of categorical variables between the groups were computed using the Chi-square test. A value of $P < 0.05$ was considered statistically significant. We performed both a per-protocol analysis, according to the actual treatment each patient received, as an intention-to-treat analysis as added value because not all patients received the treatment according the indication.

Results*:*

Between September 1998 and December 2012, a total of 161 patients were identified. In 11 patients no radical surgery was performed because of progression after induction chemotherapy. Table 1 depicts the patient characteristics of the resected patients (n=150). In 86/150 patients there was an indication for additional PORT (ypN2 status and/or incomplete resection). PORT was effectively performed in 70 patients.

In the intention-to-treat analysis, the 5-year overall survival (OS) was 35.1% for all 161 patients. Disease-free survival (DFS) was 31.8% after 5 years. The first site and cumulative LR rate at 5-years was 44.3% and 50.9% respectively; the 5-year cumulative distant metastasis (DM) rate was 63.4%. The mean follow-up time was 49 months; the mean time for the first follow-up CT scan after treatment was 6 months.

Lymph node involvement at the time of diagnosis

First we documented the initially involved LN stations for all resected patients (n=150) on FDG-PET and/or with pathological confirmation. LN stations 4R (24%), 4L (10%), 7 (21%), 10R (15%) and 10L (8%) were most frequently involved at time of diagnosis (addendum A).
Pathologically proven LNs were in 89% of cases also detected on imaging (CT scan and/ or FDG-PET); 36% of all LNs were positive on all three modalities, while 37% were visualized on CT scan and FDG-PET scan without further invasive sampling. In addendum B we present in detail which LN stations were detected by which diagnostic modality (CT, FDG-PET or pathology).

Lymph node involvement at the time of loco-regional relapse

Fifty-eight patients (38.6%) had a LR (first site or cumulative) during the course of their disease. Median time to LR was 20 months. Most LR occurred as first site and concomitant with distant relapse (58.6%). LR was confirmed by pathology in 34%, FDG-PET/CT in 41%, and by CT in all patients. The dominantly affected LN stations for all patients were 7 (18%), 10R (16%) and 4R (16%)(Figure 1A). These LN stations were initially involved in 57% for station 7, 50% for 10R and 56% for 4R.
For right-sided lung tumors (n=42) the most frequent LN stations of relapse were 10R in 19%; 7 in 16% and 4R in 15% (Figure 1B-D). LN station 10R was also initially involved in 57% of cases, station 7 in 53% and 4R in 72%.
For left sided tumors (n=16) the relapse pattern was more bilateral, especially in lower left sided tumors: 22% in station 7; 10% in 10R and 10L each, and 18% and 10% in 4R and 4L respectively (Figure 1E-G) for all left sided tumors. In most cases, the left mediastinal LN stations were also initially involved: station 4L (80%), 10L (80%) and 7 (73%).

Lymph node involvement PORT vs. non-PORT

Because not all patients received the planned treatment, analyses were done by intention-to-treat and per-protocol. PORT was performed in 70/150 patients (per-protocol analysis), however 86 patients had an ypN2 status and/or incomplete resection (intention-to-treat analysis). Seven patients 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 in these different subgroups are shown in Table 1. As expected, a major imbalance between the two groups (in intention-to-treat analysis and per-protocol analysis) was

seen regarding more positive resections margins and higher gross residual disease 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 (32.5% vs. 0.0% R1 resections and 91.9% vs. 0.0% ypN2 disease) respectively. Besides this, also 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 seen in the PORT per-protocol and PORT intention-to-treat group respectively (Table 1). The other characteristics were well balanced between the two groups in intention-to-treat analysis and per-protocol analysis.

LR was confirmed by CT in all patients and by pathology in 23% and FDG-PET/CT in 42% for the PORT group, versus 44% and 38% for the non-PORT group (per-protocol analysis). The cumulative LR rates in the 2 different subgroups are shown in Table 2. LR was seen in 26 (37.1%) patients in the PORT group and 32 (40%) in the non-PORT group (per-protocol). In the patients with a LR (n=58), 58 nodal relapse sites were seen in the PORT group (2.2 sites/patient), and 113 in the non-PORT group (3.5 sites/patient) ($p<0.01$). For intention-to-treat analysis, 34 (39.5%) patients had a LR in the PORT indication group and 24 (37.5%) in the non-PORT indication group. There was a similar number of 3.0 nodal relapse sites per patient in both groups (101 and 72 relapse sites respectively).

Only in ipsilateral LN stations 2 and 4 a significant difference in LR was seen between the non-PORT group (7% and 16% respectively) and the PORT group per-protocol (2% and 9% respectively)(Table 2). In LN station 7 the rate of LR in the non-PORT (19%) group outweighed the PORT group (15%), but this difference was not significant ($p=0.08$). For the intention-to-treat analysis, there were no significant differences between the 2 subgroups.
The distribution of the nodal relapses was similar in both subgroups (Table 2). In the PORT-group, the most common site of failure was the ipsilateral hilum (21%), followed by stations 7 (15%), ipsilateral 4 (9%), 5 (9%) and 6 (9%). The most common site of failure in the non-PORT group was station 7 (19%), followed by ipsilateral station 4 (16%) and the ipsilateral hilum (14%). These results were similar in the intention-to-treat analysis.
Figure 2 shows the distribution of LR comparing left vs. right sided tumors. Both in the PORT and the non-PORT group left sided tumors have a high number contralateral (right-sided) mediastinal relapses compared to right sided tumors: 16% and 20% in LN station 4R, and 11% and 8% is LN station 2R in the PORT and non-PORT group respectively.

Relapse pattern PORT vs. non-PORT according to PTV

Finally, we evaluated the patterns of relapse, according to the PTV, for the per-protocol analysis. Relapses inside of the virtual PTV were seen in 16 (50%) patients in the non-PORT group and in the real PTV in the PORT group in 9 (35%) patients ($p= 0.45$; Figure 3). In 15 (47%) and 10 (38%) patients, a local relapse both in- and outside the PTV was detected in the non-PORT vs. PORT group respectively ($p= 0.56$). Another 1 (3%) and 7 (27%) patients had a LR outside the PTV in the non-PORT vs. PORT group respectively ($p= 0.02$; Figure 3). The dominant pattern of failure was inside (in or both in-and outside) the PTV. Numerically, there were less LR inside the PTV in the PORT group (97%) compared to the non-PORT group (73%). Although these differences were not statistically significant ($p= 0.30$), this is another indirect evidence in favor of PORT.
To evaluate the impact on radiation target volumes for PORT, we investigated the pattern of relapse in patients with a LR outside the PTV. Forty-seven percent and 69% of the out-of-PTV relapses occurred in the contralateral mediastinum (lymph node station 2, 4, 5 or 6) in the PORT and non-PORT group, respectively. Further analysis showed that these contralateral mediastinal relapses resulted mainly from left sided tumors (66% in the PORT-group and 86% in the non-PORT group).

Other out of PTV relapse sites (sub/supraclavicular fossa, contralateral hilum, central LN stations 3 and 8) were less frequently involved in both patient groups and more equally distributed in left- vs. right sided tumors.

Discussion:

There is lack of data on the patterns of relapse in contemporarily staged and treated patients, which may affect not only the incidence but also the site of recurrence. Older studies investigating patterns of relapse used outdated staging (without FDG-PET-CT or EBUS) and treatment (surgery, chemotherapy and radiotherapy) techniques. Moreover there is currently no clear consensus on the extent of the PORT CTV in this modern setting. The aim of this study was to evaluate loco-regional patterns of relapse after induction chemotherapy and surgery for stage III-N2 NSCLC patients, staged with current standard methods, and their impact on radiation target volumes for postoperative radiotherapy (PORT). We compared the patterns of LR in 2 subgroups, whether they received additional PORT (in case of ypN2 and/or R1/R2) or not, in 2 different analyses: by intention-to-treat and per-protocol. We demonstrated a decrease of relapse sites in the PORT group and a large number of out of PTV relapses in the contralateral mediastinum in left-sided tumors.

First, we compared the distribution of pathologic LN involvement at the time of diagnosis for all patients with the pattern of LR. Loco-regional relapses were mostly seen in the LNs that were also involved at the time of diagnosis (station 7 (18%), 4R (16%) and 10R (16%)). Differentiating between left and right-sided tumors showed a mainly unilateral LN relapse pattern in right-sided tumors, while in left-sided tumors LR occurred more bilaterally. The lower LR rate in left-sided tumors is proportional with their lower frequency (62%), as there is a predominance for right lung cancer (68%). These findings are consistent with literature and with the anatomic lymphatic drainage of the lung (22-27).

Comparing the PORT group with the non-PORT group, the LR rate was in the same range. We hypothesize that PORT compensates for the clearly negative prognostic features (positive resection margins and/or higher gross residual disease) that normally would make these patients at risk for higher LR. These results are confirmed in the per-protocol analysis, were PORT effectively was delivered: there were significantly more sites of LN relapse in the non-PORT group compared to the PORT group (3.5 vs. 2.2 sites/patient), demonstrating indirectly the efficacy of PORT in eradicating microscopic tumor cells after neo-adjuvant chemotherapy and surgery. Besides this, the sites of LN relapse per patient are equal (3.0 sites/patient) in both groups in intention-to-treat analysis. This analysis was performed as added value, but actually strengthens the results compared to the patients that effectively received the radiation treatment.
This was also seen when we assessed the LR in regard to the (virtual) PTV, as there were less relapses inside the PTV in the PORT patient group compared with the non-PORT group with our simulated PTV (= virtual PTV). As we estimate a 25% LR decrease by adding PORT (from 97% to 76% in field PTV relapses and 3.5 to 2.2 relapse sites), LR rates from 40% to 30% could be expected in the non-PORT group by addition of PORT.

To our knowledge, this is the first study that evaluates the distribution of involved LN stations comparing PORT vs. non-PORT patient groups with LR.
The LN stations that are generally included in the PTV (ipsilateral mediastinal LN 2 and 4 and LN station 7) were sites of less recurrence in the patient group that effectively received PORT. On the other hand there was an equal distribution of the (non-irradiated) contralateral mediastinal LN in the PORT and non-PORT group (intention-to-treat and per-protocol analysis). The ipsilateral hilum however remains an important site of relapse, also in the PORT group, although we have to acknowledge that these results may be overestimated due to stump recurrences (only 3%), as these are radiographically difficult to differentiate with hilar LN relapses. A wide range of bronchial stump LR (7-44%) was described in other studies (25-26,28-29).
Compared to the literature, we noted a large number of relapses outside the PTV in the PORT group

and outside of the virtual PTV in the non-PORT group in our study.
One important explanation is the lack of standardization in a definition of LR. In our analysis all loco-regional recurrences (hilum, mediastinal and sub/supraclavicular fossa) were defined as LR, while in other studies the definition of LR is often more strict, encompassing only those sites that typically would be included within the PORT field (26,30,31). Two other recent retrospective trials in resected stage IIIA-N2 NSCLC reported on the relapse pattern with regard to the CTV (26,32). In these studies, FDG-PET was not performed in all patients. The findings of Feng et al in patients without PORT were also described according to a virtual created PTV, which included 89% of all LR, although only the bronchial stump, ipsilateral mediastinum and hilum were defined as LR (26). A second study of 151 patients having received PORT, found 58% of relapses inside the CTV, with a LR definition similar as in our study (32).
Another reason for the large number of out-of-PTV relapses can be the large inter-observer variability in CTV delineation (33). Therefore in our analysis, we described for each patient individually which regions encompassed the PTV. The ongoing Lung ART study (34) is a currently open phase III trial that compares PORT with no PORT in patients with completely resected stage III-N2 disease. We aimed to re-evaluate the delineation guidelines used in this trial that started in 2007. FDG-PET-CT was recommended, but not mandatory, as staging examination. Therefore we constructed a virtual PTV according to these delineation guidelines (addendum C). In the PORT group, we tested this virtual PTV, that was only for 2 patients different compared to the real conducted PTV: the LR would have been completely covered by the virtual PTV instead of partially in and out as in the real PTV.
We demonstrated that the relapses situated outside the PTV were predominantly in the contralateral mediastinum, especially in case of left-sided tumors. These regions are not included in the PORT CTV according to the Lung ART contouring guidelines. Although the contralateral latero-tracheal nodes will be included in the PTV by expanding the CTV. In the study of Feng et al, where the contralateral lymph nodes in left-sided tumors were included in the CTV, only 11% of LR outside the PTV was reported (26). A recent phase III trial randomly assigned patients with proven IIIA-N2 to induction chemotherapy with three cycles of cisplatin/docetaxel followed by surgery versus induction chemotherapy sequentially followed by 44 Gy of radiation and surgery. The contralateral mediastinal LN at risk of subclinical disease were included in the CTV, but no detailed information about the treatment volume was available (3). Five-year event-free survival rates of 23% (value from graph) were described in the chemoradiation group. Complete left sided LN exploration has also been described as more difficult than its right-sided counterpart (19,29). In this study, the percentage of 4L explored was 33.3%.
Therefore, for left-sided tumors, we believe that an inclusion of the contralateral mediastinal lymph nodes in the CTV could be considered. We realize however that these findings are based on limited patient data and hope that future prospective and/or larger trials will confirm these results.
In general, the dominant pattern of failure for all patients is inside (in or both in-and outside the PTV). From all patients with a LR inside PTV, the majority (84% in the PORT group, vs. 84%) in the non-PORT group) also had distant metastases at the time of diagnosis of a LR. We assume that PORT is not able to control the disease in these patients with disseminated disease.

An important strength in this analysis is that all patients were staged with current staging methods, received an FDG-PET/(CT) scan, and invasive staging if needed according to the ESTS guidelines. This can have an impact on the radiation volume as this is constructed from the initially affected lymph node stations. The quality of surgery also affects the locoregional outcome. Systematic lymph node dissection was performed according to the ESTS guidelines (19) and completeness of resection was defined towards the criteria of Rami-Porta (20). The newly revised 8th edition of the tumor, node,

and metastasis (TNM) classification of lung cancer will also improve the precision of staging and the classification in prognostic subgroups.
The main limitation of this study is its retrospective nature: There is no standardization in follow-up intervals and radiological evaluation at the time of relapse. However the diagnostic requirements for staging at diagnosis are more stringent than those at time of relapse. Therefore pathological confirmation and an FDG-PET were not available for all patients at time of diagnosis. However there was no significant difference in 5-year overall survival between the patients with or without pathologically proven LR (p=0.10). Another limitation is the limited patient number that makes it difficult to draw conclusions towards delineation target volumes. Finally there is a discrepancy in prognostic factors between the PORT and the non-PORT group, making it difficult to compare the outcomes. It is not possible to correct for this as this is caused by the PORT indication (ypN2 and R1/2 resection).

In conclusion, there is indirect evidence that PORT can eradicate microscopic tumor cells after neo-adjuvant chemotherapy and surgery, thereby decreasing the sites of relapse. Further results on OS and LR rates in different subgroups are beyond the scope of this article, but will be reported in a separate analysis.
Furthermore, left-sided tumors have high risk for relapsing in the contralateral mediastinum; therefore we believe that inclusion of the contralateral upper mediastinal lymph nodes in the CTV in left-sided tumors could be considered. We will perform a planning study to conduct the feasibility of these changes in regard to the toxicity. As this study is only based on limited patient data, prospective randomized trials are awaited. Results from the ongoing Lung ART trial will hopefully bring important information and eventually confirm this.

Figure 1: Overview of loco-regional relapses per lymph node station in all patients (A) and right (B) vs. left sided tumors (C)

LR: loco-regional relapse

Figure 2. Overview of loco-regional relapses per lymph node station in right vs. left sided tumors in the PORT vs. non-PORT group

PORT: postoperative radiation therapy

Figure 3: Relapses according to the (virtual) PTV and distribution of LR outside the (virtual) PTV in PORT group (A) vs non-PORT group (B) per-protocol

PORT: postoperative radiation therapy; PTV: planning target volume; LR: loco-regional recurrence

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