ORIGINAL ARTICLE

Patterns of Locoregional Relapses in Patients with Contemporarily Staged Stage III-N2 NSCLC Treated with Induction Chemotherapy and Resection: Implications for Postoperative Radiotherapy Target Volumes

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ABSTRACT

Objectives: Our aim was to evaluate locoregional relapse (LR) patterns after induction chemotherapy and surgery for stage III-N2 NSCLC staged with current standard methods and their impact on radiation target volumes for postoperative radiotherapy (PORT).

Methods: A total of 150 patients with stage III-N2 NSCLC from a prospective database of patients who underwent surgical resection at the University Hospitals of Leuven or the Oncologic Centre Limburg between 1998 and 2012 were included. Patients were staged with fluorodeoxyglucose F 18 positron emission tomography/computed tomography 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 to 70 patients. LR was seen in 26 patients in the PORT group

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(37%) and 32 in the non-PORT group (40%). Fifty-eight nodal relapse sites were seen in the PORT group (2.2 sites per patient) versus 113 in the non-PORT group (3.5 sites per patient) ($p < 0.01$). In the PORT group, the most frequent sites of LR were the ipsilateral hilum (21%), lymph node station 7 (15%), ipsilateral station 4 (9%), ipsilateral station 5 (9%) and ipsilateral station 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 (inside or both inside and outside) the PTV. Regarding the out-of-PTV relapses, 47% and 69% of LRs occurred in the contralateral mediastinum for the PORT and non-PORT groups, respectively. Out-of-PTV relapses occurred mostly in initially left-sided tumors.

Conclusions: 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.

Keywords: Postoperative radiotherapy; NSCLC; Local recurrence; N2; Stage III; Target volume

Introduction

NSCLC continues to be one of the leading causes of cancer mortality.[1] In one-third of patients with NSCLC, the disease is diagnosed when it is locally advanced stage III disease, with 5-year survival rates ranging from 25% to 35% in recently published trials.[2–5] 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] Even after complete resection and chemotherapy, however, the locoregional relapse (LR) rate remains high, with 30% as first site of failure and cumulative LR rates up to 60%.[3,7] Despite a reduction of LR after postoperative radiotherapy (PORT) for completely resected stage III NSCLC, its effect on overall survival (OS) remains unproved.[8] 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 that modern PORT techniques provide a decrease in LR of 20%, leading to a 13% increase in OS for patients with stage III-N2 NSCLC.[12,13]

If PORT is to be successful, optimal target volumes need to be defined. Current definitions of target volumes rely on patients who were treated in an era without contemporary staging methods such as ^{18}f-fluorodeoxyglucose (FDG) positron emission tomography (FDG-PET/CT) scans and endobronchial ultrasound (EBUS) or esophageal ultrasound. 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. Three-dimensional planned PORT using a limited clinical target volume (CTV) may reduce treatment toxicity and increase local control. With two-dimensional 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 a 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 after induction chemotherapy followed by surgical resection in patients with stage III-N2 NSCLC that was staged and treated with current standard methods.

Materials and Methods

From a prospective database (lung cancer multidisciplinary team), we identified patients with pathologically 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. PORT was delivered in case of persistent nodal involvement (ypN2) and/or incomplete resection (R1/2). All patients were older than 18 years and had a WHO performance status between 0 and 2. The radiology, nuclear medicine, surgery, and pathology reports for each patient were reviewed.

Pretreatment staging included a medical history and clinical examination, a biochemical test (blood count, renal and liver function tests, and a test for the tumor marker carcinoembryonic antigen), pulmonary function tests, bronchoscopy, and a contrast-enhanced CT scan of the thorax and upper abdomen. In addition, brain imaging (contrast-enhanced CT or magnetic resonance imaging scan) and FDG-PET/CT were performed, as well as an invasive staging of the mediastinum consisting of EBUS–transbronchial needle aspiration or esophageal ultrasound–fine-needle aspiration and/or mediastinoscopy. Staging occurred according to the 7th edition of