Pulmonary resection after concurrent chemotherapy and high dose (60 Gy) radiation for non-small cell lung cancer is safe and may provide increased survival

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Abstract

Background: We have used doses of 60 Gy or higher for neoadjuvant chemoradiotherapy for select patients with advanced non-small cell lung cancer (NSCLC), including patients with N2 disease and those with Pancoast lesions, to avoid gaps in radiotherapy in case surgery is ultimately not offered. Methods: A retrospective cohort study using a prospective database. Patients underwent initial staging with CT, PET/CT and lymph node biopsy (mediastinoscopy, endoscopic esophageal ultrasound and endobronchial ultrasound) and then received neoadjuvant high dose radiotherapy and chemotherapy, followed by thoracotomy with intent to cure. Results: Between January 1998 and June 2008 there were 216 patients who were eligible for this study. The median dose of radiation was 60 Gy (range 60—72 Gy). Lobectomy was performed in 152 patients (70%) about 7 weeks after radiotherapy finished (mean 51 days, range 34—89 days). The bronchus was buttressed with an intercostal muscle flap in 97% patients. Median hospital stay was 4.5 days (range 2—57). Major morbidity occurred in 17%. There were five (2.3%) deaths. There were no bronchial-pleural fistulas after lobectomy, but two occurred after right pneumonectomy. Predictors of morbidity were FEV1 <50% (p < 0.001), DLCO <60% (p < 0.001) and age >75 years (p = 0.008). The overall 5-year Kaplan—Meier survival was 34%. It was 42% for those who underwent R0 resection, 38% for those with initial N2 disease and 45% for the 71 complete responders. Conclusions: Pulmonary resection after high dose (>60 Gy) neoadjuvant chemoradiation is safe. Lobectomy can be safely performed and bronchopleural fistula prevented. Sixty Gy allows for maximal medical therapy in case resection is not offered. Since complete response rates may be higher than when 45 Gy is used and since surgery is safe, its use deserves further investigation.

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Keywords: Radiation; Pulmonary resection; Non-small cell lung cancer

1. Introduction

The use of preoperative chemoradiotherapy or chemotherapy alone in patients with non-small cell lung cancer (NSCLC) is controversial. Since three large international studies have shown a survival advantage for adjuvant chemotherapy for patients with completely resected stage IB tumors greater than 4 cm and those with stage II NSCLC from N1 disease, the use of preoperative chemoradiotherapy is even more unclear [1—3]. However, for biopsy proven single station, non-bulky N2 disease neoadjuvant chemoradiotherapy remains a common choice despite the American College of Chest Physicians (ACCP) guidelines [4]. Recently we presented our experience with stage IIIA non-small cell lung cancer from N2 disease [5]. The confusion and controversy about the optimal treatment of N2 disease centers around the fact that it represents a heterogeneous group of patients. This is because N2 non-small cell lung cancer can be unfavorable: multi-station, fixed, bulky, and extra-nodal or it can be favorable: single station, microscopic, PET negative, or surprise N2 disease. Since we have used a relatively consistent algorithm for the last several years for a specific type of favorable N2 disease [6], we have...
2.2. Staging

and obtained for participation in the database. Although many prefer the use of preoperative radiotherapy concurrent with chemotherapy in these patients over chemotherapy alone [7,8], most surgeons favor a lower dose of radiation (usually 45 Gy) because of data that suggests increased complications with higher doses [9]. However, we favor using 60–66 Gy routinely and more recently are routinely using even 72 Gy prior to resection. This is because we believe the larger dose of radiation provides a higher complete response rate and complete pathologic response has been associated with improved survival [10–12]. Moreover, and perhaps more importantly, if surgical resection is not performed after the completion of the neoadjuvant therapy (which is not uncommon) the higher dose of preoperative radiation maximizes medical therapy and avoids a 1–2 month gap which decreases the efficacy of the completion of radiotherapy. In this study, we present our results in a highly selected group of patients who received preoperative high dose (>60 Gy) chemoradiotherapy followed by pulmonary resection via thoracotomy with intent for cure with resection of all disease.

2. Materials and methods

2.1. Patients

This is a retrospective cohort study using an electronic prospective database. From January 1998 to June 2008, one general thoracic surgeon preformed 9907 operations but only 6798 operations were elective pulmonary resection (including video-assisted thoracotomy as well as via thoracotomy). Patients who underwent rigid bronchoscopy and laser resection of mediastinal masses or esophageal masses, etc. or those that were not NSCLC were eliminated. Only those patients with biopsy proven NSCLC who underwent preoperative high dose radiotherapy (defined as 60 Gy or higher) were eligible for this study. Additional inclusion criteria mandated that patients have received neoadjuvant carboplatinum-based chemotherapy with concurrent radiotherapy, underwent re-staging and thoracotomy with intent to completely resect for cure. Patients were excluded if they were less than 19 years old, had a time interval of greater than 12 weeks between completion of radiochemotherapy and resection, were deemed to be unfit to tolerate surgical procedure, had biopsy proven M1 disease or did not undergo thoracotomy. The University of Alabama at Birmingham’s institutional review board approved the electronic prospective database used for this study. Individual consent was waived for inclusion in this specific study but it was required and obtained for participation in the database.

2.2. Staging

All patients were staged as previously described [6]. In brief, this was done using computed tomography (CT) with 5 mm collimated slices of the chest and upper abdomen. In addition, from January 1998 to August 2002 patients underwent a dedicated positron emission tomography using fluorodeoxyglucose F-18 (FDG-PET). FDG-PET was performed on a dedicated ECAT EXACT scanner (CTI, Knoxville, TN) until August 2002. After this date patients were staged using an integrated PET-CT scanner on a GE Discovery LS PET-CT Scanner (Milwaukee, WI, USA). PET scans were performed as previously described [13].

All suspicious N2, N3 or M1 areas on CT scan and/or on FDG-PET scan (with a maximum standardized uptake value, maxSUV >2.5) were biopsied prior to pulmonary resection. Mediastinoscopy was used to biopsy suspicious lymph nodes in the paratracheal area (stations 2R, 4R, 2L, and 4L) and proximal subcarinal (7) stations and endoscopic tranesophageal ultrasound with fine needle aspiration (EUS-FNA) was used to biopsy suspicious posterior aorta-pulmonary window nodes (5), subcarinal (7), periesophageal (8) and inferior pulmonary ligament nodes (9). Endobronchial ultrasound (EBUS) was also employed for preoperative staging starting November 2007.

Patients with suspected M1 disease in the liver, adrenal, or contra-lateral lung underwent biopsy to prove or disprove M1 cancer. If the bone or brain was suspected to harbor metastases, MRI was considered the standard reference. Neoadjuvant chemotherapy was given using carboplatinum-based chemotherapy. After the completion of neoadjuvant therapy, patients were meticulously re-staged. If they had a EUS-FNA that proved N2 disease initially it was repeated and the same node in the same nodal station was re-biopsied. In general, if the patient had recalcitrant N2 disease then resection was not offered. If mediastinoscopy initially proved N2 disease then it was not repeated. If restaging in these patients suggested no other metastatic sites then thoracotomy was performed and the initially involved node was sent for intra-operative frozen section pathologic analysis. In general, resection was performed if the node was benign. In selected patients, if there was only microscopic residual N2 nodal disease and the primary could be resected with a lobectomy, lobectomy was performed but if pneumonectomy was required resection was not performed. Pulmonary resection was performed mainly via a rib-sparing muscle sparing technique [14–17] by one general thoracic surgeon. A complete thoracic lymphadenectomy was also performed as previously described [5]. Pathologic review was performed via standard techniques and immunohistochemical staining was employed when appropriate. Pathologic complete response was defined as <1% tumor cells seen on any of the resected specimen or lymph nodes. The pathologic stage was assessed using the international staging system [18].

2.3. Radiation

In this series conformal 3D radiotherapy was used for all patients treated at our institution (UAB). The chest radiotherapy was delivered with 6 MV and when appropriate with a combination of 6 MV and 15 MV photons. The primary tumor in the lung and regional N2 and N1 lymph nodes at risk were covered with a 1.5–2.0 cm blocked margin. N3 areas such as supraclavicular areas were not treated for these carefully staged patients with N2 disease. Areas of assumed microscopic risk received a dose of 45 Gy. Gross tumor as determined by staging was given 60–72 Gy at 2 Gy per fraction 5 days a week. Lung correction factors were used. Dose volume histograms for the planned target volumes and normal tissues were generated. The V20 for lung (volume of lung which receives 20 Gy) was held at 36 Gy.
2.4. Definitions and follow-up

National Cancer Institute (NCI) guidelines for classification of adverse events were used to define complications. We categorized complications as major or minor as previously described [19]. Briefly, major complication was defined as any morbidity that caused transfer to the intensive care unit (ICU), required re-operation of any kind and also included complications such as air leaks that required discharge home with chest tube, etc. Minor complications included transient atrial arrhythmias, urinary retention, small air leaks and/or a pneumothorax that resolved by postoperative day (POD) 3 or did not require intervention as well as mild confusion. Operative mortality was defined as any death prior to discharge or within 30 days of surgery for any reason. A low FEV1% was defined as a value <50% and a low DLCO% was defined as a value less than 60%.

Survival data was obtained every 6 months. A chest CT with intravenous contrast was performed every 6 months in a majority of patients. In addition, if patients became symptomatic appropriate testing (i.e., bone scan, brain scan) was performed as well. Information was obtained using clinic letters, hospital computer information systems, treatment updates, social security death index, telephone calls and letters from oncology clinics and other physicians. Follow-up data acquisition concluded on June 30, 2008.

2.5. Statistics

A univariate analysis was performed to assess for differences amongst patient characteristics and risk factors for morbidity and mortality. Age (>75, ≤75 years), gender (male vs female), FEV1% (>50%, ≤50%), DLCO% (>60%, ≤60%), procedure type, history of smoking, and reason for radiation had a p value <0.10 on univariate analysis and were entered into a forward, step-wise regression analysis. A chi-squared analysis was used for discrete variables, with p <0.05 according to two-tailed Fisher’s exact test used to select factors with potential significance. Generalized linear model (GLM) analysis of variance (ANOVA) was used to evaluate discrete non-dichotomous variables. For continuous variables, Student’s t-test or the Mann–Whitney U-test was used to compare means for non-normally distributed variables. Survival was determined using Kaplan–Meier (for univariate analysis) and Cox proportional hazards statistics (multivariable model). Age, gender, FEV1% (>50%, ≤50%), DLCO% (>60%, ≤60%), procedure type, response to neoadjuvant therapy, history of smoking, and reason for radiation were entered into a forward, step-wise regression analysis. Patients who were alive at the end of our study were censored. All comparisons were two-sided with a p value of less than 0.05 used to indicate statistical significance. All statistical analysis was performed using SAS version 9.1 (SAS Institute, Cary, NC).

3. Results

Between January 1998 and June 2008 there were 216 patients who met the eligibility criteria for this study. Patient characteristics are shown in Table 1. All patients received both neoadjuvant radiation and chemotherapy. The most common indication for the neoadjuvant chemoradiotherapy was biopsy proven N2 disease. As shown in Table 1, 26 patients had clinically suspected N2 disease only and radiation and chemotherapy started at outside hospitals prior to our seeing them. The median dose of radiotherapy in the 216 patients was 60 Gy (range 60–72 Gy). Repeat staging with repeat CT scan and repeat integrated PET/CT scan was performed no sooner than 4 weeks after the completion of radiotherapy (mean 37 days, range 30–65 days). Thoracotomy was performed on average at 51 days (34–89 days) after the completion of the radiotherapy. The surgical outcomes are summarized in Table 2. The most common type of pulmonary resection was lobectomy in 152 (70%) patients. The bronchus was most commonly stapled. It was then buttressed with an intercostal muscle flap in 97% of patients. Table 3 depicts the pathologic response to the neoadjuvant chemoradiotherapy. The 26 patients who had assumed N2 disease that were not biopsy proven prior to starting their neoadjuvant therapy were eliminated from this table. Table 4 shows the morbidity and mortality for this group of patients. Complete pathologic response occurred in 71 (33%) patients. There were no bronchopleural fistulas (BPF) after lobectomies, but there were two after right pneumonectomies. The most common causes of major morbidity were pneumonia (6) and re-intubation for respiratory distress (8). The most common causes of minor morbidity were transient atrial-fibrillation (16) and air leak (9). On univariate analysis, FEV1% (<0.001), DLCO% (p < 0.001), older age (p = 0.014) and smoking history (p = 0.031) were associated with morbidity or operative mortality. Surgical procedure, gender, and reason for receiving neoadjuvant chemoradiotherapy did not significantly impact risk of morbidity. Only FEV1% (p < 0.001), DLCO% (p < 0.001) and older age (p = 0.006) remained significant predictors for morbidity or operative mortality on multivariable analysis.

3.1. Survival

The overall 5-year Kaplan–Meier survival was 42% for those who underwent R0 resection, 38% for those with initial

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### Table 1

<table>
<thead>
<tr>
<th>Patient characteristics.</th>
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<tbody>
<tr>
<td>Number of patients</td>
</tr>
<tr>
<td>Age (age range) years</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>History of smoking (&gt;100 cigarettes in lifetime)</td>
</tr>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
</tbody>
</table>

* Of this group, 26 (16%) were clinically suggested but not biopsy proven (all initially treated preoperatively at outside institutions) and 135 (84%) were biopsy proven.
The role of preoperative chemoradiotherapy is controversial. Despite the current American College of Chest Physicians guidelines certain subsets of patients with N2 disease still often receive preoperative radiation and/or chemotherapy at many cancer centers. In addition, it is the standard of care for patients with Pancoast tumors. For these reasons the general thoracic surgeon is more frequently asked to consider thoracotomy and pulmonary resection after chemoradiotherapy. In this retrospective study that evaluates safety, we have shown that surgical resection with dissection of the pulmonary artery branches and closure of the bronchus as required for lobectomy is safe in a highly irradiated field. When a pedicled muscle flap is employed to buttress the closed lobar bronchus, bronchopleural fistula is exceedingly rare even after doses of 60 Gy or higher of preoperative radiation.

Since the operation can be performed safely, the advantages of using a higher dose of preoperative therapy must now be shown. The potential benefits of this higher dose of 60 Gy over the conventional 45 Gy is two-fold. The first and perhaps most important fact is that if patients are denied pulmonary resection after neoadjuvant therapy either because of oncologic reasons (recalcitrant N2 disease or marginal response to therapy) or for physiologic reasons (poor pulmonary function or weak from their therapy), then the patients would have already undergone maximal medical therapy. Too often patients are given a non-curative dose of preoperative radiotherapy, then they wait 1 month or longer to get restaged with repeat PET/CT and CT and then are restaged with biopsies such as repeat EUS-FNA or repeat EBUS and then are denied surgical resection. When these patients are sent back to complete their radiotherapy, a 4—12 week hiatus has often occurred and this seriously reduces the efficacy of the remaining radiotherapy. Second, the higher dose of radiotherapy may increase the pathologic response of the tumor and even though this only improves local control (as is true of surgical resection) a higher complete response rate has been linked to improved overall survival [12].

Although the vast majority of thoracic centers use a low dose of preoperative radiotherapy because of the findings of the Faust study in 1993 [9] that showed higher rates of complications with higher doses, the reason for choosing a lower dose is because of the misrepresented facts that surgery is not safe in a highly irradiated field. Three previous large prospective studies documented the safety of induction doses of 45 Gy [20—22]. In this study we have shown that patients can undergo lobectomy and avoid bronchopleural fistula using even higher doses of preoperative therapy. The intercostal muscle used to buttress the bronchus as required for lobectomy is safe in a highly irradiated field. When a pedicled muscle flap is employed to buttress the closed lobar bronchus, bronchopleural fistula is exceedingly rare even after doses of 60 Gy or higher of preoperative radiation.

### Table 2
Pathologic and surgical outcomes.

<table>
<thead>
<tr>
<th>Histology</th>
<th>N</th>
<th>86 (40%)</th>
<th>99 (46%)</th>
<th>31 (14%)</th>
<th>181 (84%)</th>
<th>35 (16%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other NSCLC or NOS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resected</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not resected</td>
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</tbody>
</table>

### Table 3
Pathologic response to radiation (excludes patients sent to us from outside hospitals after radiation and chemotherapy who did not have biopsy proven N2 disease prior to the initiation of therapy).

<table>
<thead>
<tr>
<th>Initial stage</th>
<th>N</th>
<th>5</th>
<th>135</th>
<th>8</th>
<th>28</th>
<th>9</th>
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<tbody>
<tr>
<td>T0 N0 M0</td>
<td></td>
<td>3</td>
<td>42</td>
<td>2</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>T1/2 N0 M0</td>
<td></td>
<td>2</td>
<td>50</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>T3/4 N0 M0</td>
<td></td>
<td>0</td>
<td>16</td>
<td>0</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Tx N1 Mx</td>
<td></td>
<td>0</td>
<td>13</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Recalcitrant or new N2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

* Twenty-six patients with unproven N2 excluded.
they are to safely undergo trimodality therapy. They have to have an outstanding performance status and the mental toughness and desire to complete their therapy including surgery.

Pneumonectomy remains a controversial operation after high dose radiation, especially right pneumonectomy. It too can also be safely preformed after high dose neoadjuvant chemoradiotherapy. However, the right bronchial stump is at greater risk than any other part of the bronchial tree after resection. We now recommend using the omental or the serratus as a prophylactic buttress for the highly irradiated right main stem bronchus after right pneumonectomy and no longer believe that an intercostal muscle flap provides sufficient protection. The weakness of this study surrounds the survival data. Obviously, any retrospective study is biased by the patients that are selected. This retrospective study is no different. First, it represents a very highly selected group of patients with N2 disease. In general, these patients had favorable N2 disease (single station, non-fixed and non-bulky N2) and then operated only on those that were responders as evidenced by the repeat PET results or the repeat biopsies of mediastinal lymph nodes that suggested the N2 disease had been downstaged. Another weakness involves the heterogeneous group of patients, some of whom had N2 disease and some of whom had Pancoast tumors. However, the main message of this study is about safety.

In conclusion, pulmonary resection after high dose (≥60 Gy) neoadjuvant chemoradiotherapy is safe. Lobectomy can be safely performed and bronchopleural fistula prevented by the liberal use of a pedicled muscle flaps such as an intercostal muscle. Sixty Gy or higher of preoperative radiotherapy allows for maximal medical therapy up front, in case resection is not offered and this regimen avoids large time gaps in the completion of the radiotherapy. This maximizes oncologic medical treatment. Finally, since complete response rates may be higher when 60 Gy is used instead of when the more traditional preoperative dose of 45 Gy is used and since surgery is safe, its use deserves further investigation perhaps in a multi-institutional study.

References


Appendix A. Conference discussion

Dr C. Choong (Cambridge, United Kingdom): I have a few questions. Firstly, you have a very impressive median hospital stay for your patients of 4.2 days. What are some of the strategies that you have utilized to get such good results? Obviously air leakage is one of the major problems that prohibits patients from an early discharge. I would appreciate your comments

Dr Cerfolio: Well, right now the way I take the omentum is, I actually do a midline incision, put a feeding jejunostomy in, have one hand in the chest, one hand in the belly, find a good spot in the diaphragm, bring it through. Dr Rendina has a little technique where he opens the diaphragm and can pull the omentum up directly. I've tried that a few times. I probably don't have the skill of Dr Rendina because it hasn't worked as well for me. But those are the two ways to do it. I usually use an intercostal muscle flap for the irradiated bronchus after a lobe, if it is a pneumonectomy then I use a pedicled pericardial patch, not the fat pad but pericardium itself.

Dr M. Saute (Petach-Tikva, Israel): My question is, how do you restage the mediastinum? We do just PET-CT, and if the PET-CT is negative, go on to surgery. My question is if you do mediastinoscopy in these patients.

Dr Cerfolio: Mediastinoscopy in my hands is not safe. After a mediastinoscopy and high dose radiation, I think for me to do a re-mediastinoscopy is inaccurate and unsafe. So we don’t do that too often at all. But we do repeat EBUS, and we do repeat EUS-FNA all the time, and everybody gets a repeat PET, and we usually re-biopsy the same N2 lymph node in the same manner it was initially biopsied after the repeat PET (except for repeat mediastinoscopy).

Dr J. Kim (Seoul, South Korea): Let me ask just one quick question. We usually use preoperative chemoradiation, but the radiation dose is usually 45 Gy. In our experience, the compliance rate of the patients of the induction therapy, is less than 70% . What is the compliance rate in your patients? How many patients can be included in the surgery and all the procedures from the beginning?

Dr Cerfolio: Well, there is a select group. We just presented some of this concept at the STS this year and it is now published in The Annals of Thoracic Surgery. Most patients finish their planned neoadjuvant therapy but this may be because in the USA we used Carbop/Taxol which is easier to give. However, only about 20% of patients ever come back to the surgical area with biopsy proven N2 disease, even in the favorable group of N2 disease. So your point is well taken. If you look at all comers with N2, the vast majority do not come back to the surgical arena because they have dis-favoruable N2 disease, such as fixed, multi-stationed, or gross N2 disease.

Dr D. Grunenwald (Paris, France): We published years ago such an approach in stage IIIb disease with a lot of N3 patients, and we found that the patients who were not controlled by the preoperative chemoradiotherapy had a very good survival, for example, 36% at 5 years. Those patients obviously were dead without the surgery. Did you take a look at your noncontrolled patients, I mean the N2 persistent patients.

Dr Cerfolio: The ones who did not go to surgery?

Dr Grunenwald: Yes.

Dr Choong: The last question is, what is the role of postoperative adjuvant chemo or radiotherapy for your group of patients?

Dr Cerfolio: For patients who are complete responders, we don’t do anything but observe them with surveillance. For patients who have had residual disease, significant residual disease, we take their tumors out, we do analysis, whether you believe in Oncotech or Precision Therapy, we do that, and then that helps guide second-line chemotherapy. But I think it’s a lot to give a patient chemo, radiation, surgery, followed by more chemo.