Long-Term Outcome After Resection of Non-Small Cell Lung Cancer Invading the Thoracic Inlet

Stéphane Collaud, MD, MS, Tiago Machuca, MD, PhD, Olaf Mercier, MD, PhD, Thomas K. Waddell, MD, PhD, Kazuhiro Yasufuku, MD, PhD, Andrew F. Pierre, MD, MS, Gail E. Darling, MD, Marcelo Cypel, MD, MS, Yoga R. Rampersaud, MD, Stephen J. Lewis, MD, MS, Frances A. Shepherd, MD, Natasha B. Leighl, MD, MS, John B. C. Cho, MD, PhD, Andrea Bezjak, MD, MS, Shaf Keshavjee, MD, MS, and Marc de Perrot, MD, MS

Divisions of Thoracic Surgery and Orthopedic Surgery, University Health Network, University of Toronto, Toronto, Ontario, Canada; and Departments of Medical Oncology and Hematology and Radiation Oncology, University Health Network, Princess Margaret Cancer Centre and the University of Toronto, Toronto, Ontario, Canada

Background. The aim of this study was to update our previous experience and describe long-term results after resection of non–small-cell lung cancer (NSCLC) invading the thoracic inlet.

Methods. Patients from a single center undergoing resection of NSCLC invading the thoracic inlet were reviewed with data retrieved retrospectively from their charts.

Results. Sixty-five consecutive patients with a median age of 61 (32–76) years underwent resection of NSCLC invading the thoracic inlet from 1991 to 2011. Tumor location was divided into 5 anatomic zones from anterior to posterior. Fifty-two (80%) patients had induction therapy, mostly with 2 cycles of cisplatin-etoposide and 45 Gy concurrent irradiation. All patients underwent at least first rib resection. Lobectomy was performed in 60 patients (92%). Twenty-four patients (37%) had vertebral resection. Arterial resections were performed in 7 patients (11%). Postoperative morbidity and mortality were 46% and 6%, respectively. Pathologic response to induction was complete (pCR) (n = 19) or nearly complete (pNR) (n = 12) in 31 patients (48%). Adjuvant treatment was administered in 14 (25%) patients. After a median follow-up of 20 (0–193) months, 34 patients are alive without recurrence. The overall 5-year survival reached 69%. Univariate analysis identified site of tumor within the thoracic inlet (p = 0.050), response to induction (p = 0.004), and presence of adjuvant treatment (p = 0.028) as survival predictors.

Conclusions. Survival after resection of NSCLC invading the thoracic inlet in highly selected patients reached 69% at 5 years. Tumor location within the thoracic inlet, pathologic response to induction therapy, and adjuvant treatments were significant survival predictors.


The thoracic inlet is the superior aperture of the thorax. It is delineated by the first thoracic vertebra (T1) posteriorly, the first rib laterally, and the manubrium anteriorly. Thoracic inlet tumors are defined by involvement of thoracic inlet anatomic structures on preoperative imaging and by the requirement of a first rib resection during the surgical procedure [1].

Tumors of the thoracic inlet are rare and account for less than 5% of all non–small-cell lung cancer (NSCLC) [2]. In an earlier study, we reported our experience with induction chemoradiation consisting of 2 cycles of cisplatin-etoposide and 45 Gy concurrent irradiation, followed by en bloc tumor resection in the setting of tumors located along the pulmonary sulcus and invading the spine [3]. In the present study, we focused on tumors of the thoracic inlet, with their potentially challenging T1 vertebral resection, and update our previous report with longer follow-up as well as potential predictive factors for survival [1].

Patients and Methods

This was a retrospective single-center study including patients with NSCLC invading the thoracic inlet who underwent multimodality treatment including surgical resection. Data were retrieved from patients’ electronic charts. The study was approved by the Institutional Research Ethics Board at University Health Network.

Preoperative tumor staging comprised computed tomography (CT) of the chest and abdomen, CT or magnetic resonance imaging (MRI) of the brain, bone scan, and integrated positron emission tomography with CT (PET/CT) after 2005. MRI of the spine/thoracic inlet was indicated in patients with suspicion of spinal invasion. Tumors were classified into zone 1 to 5 as described
elsewhere, according to the chest computed tomographic scan [4]. In case of tumor invasion into multiple zones, the zone with the most predominant involvement was chosen. Briefly, zone 1 (or the anterolateral zone) is located between the sternum and the anterior scalene muscle including the subclavian vein. Zone 2 (or anterocentral zone) is the area containing the subclavian artery, medial to zone 1. Zone 3 (or posterosuperior zone) is located between the subclavian artery and the T1 vertebra. Zone 4 (or posteroinferior zone) is situated below the posterior portion of the first rib toward the spine. Zone 5 (or inferolateral zone) is located below the lateral portion of the first rib toward the distal subclavian artery (Fig 1).

The mediastinum was systematically assessed by cervical mediastinoscopy or endobronchial ultrasonographically guided fine-needle aspiration. Patients with mediastinal node involvement generally were not considered candidates for surgical intervention.

Induction treatment consisted mainly of 2 cycles of cisplatin-etoposide with concurrent 45 Gy irradiation to the primary tumor alone (25 daily fractions over 5 weeks). Restaging was performed with CT of the chest and abdomen and CT or MRI of the brain. MRI of the spine/thoracic inlet was performed if spinal involvement was suspected before induction. Patients without distant disease or local progression underwent surgical resection and compose the cohort of this study.

An anterior, posterior, or combined approach was selected by the surgeon according to tumor location and morphologic features, as described elsewhere [1]. All patients underwent resection of the first rib, per definition.

Tumors were classified and staged according to the seventh edition of the TNM classification of malignant tumors [5]. The relative amount of tumor necrosis after induction treatment was used to define response and was categorized as complete (100%), nearly complete (≥95%), and partial (<95%) on final pathologic

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**Fig 1.** Computed tomographic images depicting tumor involvement of the 5 different zones of the thoracic inlet: (A) zone 1, (B) zone 2, (C) zone 3, (D) zone 4, and (E) zone 5. Tumors are indicated by asterisk.

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### Abbreviations and Acronyms
- CT = computed tomography
- LOS = length of stay
- MRI = magnetic resonance imaging
- NSCLC = non-small cell lung cancer
- pCR = pathologic complete response
- PET/CT = integrated positron emission tomography with computed tomography
- pNR = pathologic nearly complete response
- pPR = pathologic partial response
- R0 = microscopic complete resection
examination, respectively. Up to 2 postoperative consolidation chemotherapy cycles were administered, depending on the patients’ postoperative condition.

Statistical analysis was performed using IBM SPSS Statistics, version 19.0 for Windows software (SPSS Inc, Chicago, IL). Univariate logistic regression was used to assess the impact of relevant variables on the incidence of postoperative complications and in-hospital/30-day mortality. Overall survival was estimated from the date of operation until last follow-up using the Kaplan-Meier survival analysis method. The Cox regression for continuous variables and the log-rank test or Breslow test, when necessary, for discrete variables were used to identify survival predictors. A p value less than or equal to 0.05 was considered significant.

Results

Sixty-five patients, including 36 men (55%) with a median age of 61 (range 32–76) years, underwent resection of NSCLC of the thoracic inlet from December 1991 to June 2011. Chest CT allowed the classification of tumors into zone 1 (n = 5 [8%]), zone 2 (n = 7 [11%]), zone 3 (n = 12 [18%]), zone 4 (n = 22 [34%]), and zone 5 (n = 7 [11%]). Computed tomographic scans were not available at the time of classification in 12 cases (18%). Tumor histologic subtype was adenocarcinoma in 23 (35%) patients, squamous cell carcinoma in 18 (28%) patients, large-cell carcinoma in 6 (9%) patients, and undetermined or other NSCLC histologic subtype in 18 (28%) patients. Clinical stages were IIB in 38 patients, and undetermined or other NSCLC histologic subtype in 18 (28%) patients. Clinical stages were IIB in 1 patient. Data were not available in 8 patients (12%).

All patients underwent chest wall resection including at least the first rib (median 3, range 1–5 ribs). Tumors were mostly right-sided (n = 37 [57%]). Lung resections performed included wedge resection (n = 3 [5%]), lobectomy (n = 60 [92%]), or pneumonectomy (n = 2 [3%]). Twenty-four (37%) patients had an additional vertebral resection of up to 5 levels (median, 3 levels). Considering the most extended vertebral resection, total vertebrectomy with anterior-posterior spinal stabilization was required in 6 patients (25%), hemivertebrectomy with posterior spinal stabilization in 15 (62%) patients, and partial vertebrectomy without stabilization in 3 (13%) patients. Thirty-four patients had up to 6 nerve roots resected. Arterial resections were performed in 7 patients (11%) and included the subclavian artery in 5 (72%) patients, the subclavian and vertebral artery in 1 (14%) patient, and the subclavian as well as the carotid arteries in 1 (14%) patient. Microscopic complete resection (R0) was achieved in 55 patients (85%).

The median postoperative length of stay (LOS) was 11 (4–73) days, whereas 18 (28%) patients were admitted to the intensive care unit for 1 to 140 days. Thirty (46%) patients experienced at least 1 complication. Four (6%) patients died in-hospital or within 30 days of operation. Three patients died of respiratory failure and 1 died of septic shock after an intestinal anastomotic leak after bowel resection for ischemia.

Univariate logistic regression was used to test the variables—sex, age, side of operation, type of lung resection, number of vertebrae/nerve roots/ribs resected, presence of arterial resection, neoadjuvant therapy, zone of the tumor within the thoracic inlet, postoperative LOS, and intensive care unit LOS—as predictors of postoperative complications or mortality, but none was significant.

Pathologic response to induction treatment was complete (pCR), nearly complete (pNR), partial (pPR), and unknown in 19 (30%), 12 (19%), 26 (41%), and 6 (10%) patients, respectively. Pathologic stages were 0 in 19 (29%) patients, IB in 1 (2%) patient, IIB in 28 (43%) patients, IIIA in 15 (23%) patients, and IIIB in 2 (3%) patients. Adjuvant therapy was administered in 14 (25%) patients and consisted of chemotherapy in 13 patients and chemoradiation in 1 patient. Data were not available in 8 patients (12%).

After a median follow-up of 20 (0–193) months, 34 (52%) patients are alive without recurrence, with 19 patients followed for more than 5 years. Four patients had local recurrence within the thorax and 10 patients had distant metastases mainly to the brain and bone. Seventeen patients died: 11 from their lung cancer, 2 from unrelated causes, and 4 from postoperative complications. The 5-year overall survival for the entire cohort is 69% (standard error = 0.066) (Fig 2).

Table 1 summarizes the results of the Cox regression analysis and log-rank/Breslow tests. These identified the zone of thoracic inlet (p = 0.050), response to induction treatment (p = 0.004), and administration of adjuvant
The need for arterial resection showed a trend toward worse survival \( (p = 0.063) \). Distribution of survival predictors were studied both in patient populations with tumors located in zones 1 and 3 and in patient populations with tumors in zones 2, 4, and 5 (Table 2). This showed that patients with tumors in zones 1 and 3 required significantly more arterial resections and received less adjuvant therapy than did those with tumors in zones 2, 4, and 5. Survival curves for the different predictors are shown in Figs 3–6.

Comment

Multimodality treatment for tumors located along the pulmonary sulcus has evolved over the years. Historically, the first successful operation for a tumor of the pulmonary sulcus was described by Chardack and MacCallum in 1956 [6], who described a disease-free survivor 5 years after en bloc tumor resection followed by adjuvant irradiation. In 1961, Shaw and Paulson [7] reported results in 18 patients who underwent en bloc tumor resection after induction radiotherapy with 30 to 35 Gy. The debate as to whether induction or adjuvant treatments are most beneficial is ongoing because no prospective randomized studies are available. In the largest retrospective pooled data analysis of 135 patients with tumors located along the pulmonary sulcus and invading the spine, induction or adjuvant treatments provided similar survival [8]. In our center, we have been applying the treatment strategy described in the Southwest Oncology Group Trial 9416 (Intergroup Trial 0160), consisting of 2 cycles of cisplatin-etoposide concurrently with 45 Gy irradiation, followed by operation and 2 cycles of boost chemotherapy [9, 10].

In the present study, an excellent overall 5-year survival of 69% was achieved. These results confirmed our initial experience of 59% survival at 5 years [1]. These results are superior to the results published from the Southwest Oncology Group Trial 9416, in which 5-year survival was 44% [10]. However, the difference in survival probably results from patient cohort heterogeneity, because all patients underwent surgical intervention in our series compared with 80% (88 of 110) in the Southwest Oncology Group Trial 9416. With prolonged follow-up, it is possible to confirm the presence of long-term survivors. Fadel and colleagues [11] were the first to report a total of 5 (9%) patients who were alive and free of disease 10 years after operation [11]. In our study, 19 (29%) and 7 (11%) patients survived more than 5 and 10 years after en bloc tumor resection, respectively. These findings definitively emphasize major advances in the treatment of thoracic inlet tumors, which historically were deemed unresectable and fatal.

Induction chemoradiation provides better pathologic response than does induction chemotherapy or radiation

### Table 1. Identification of Survival Predictors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number of Patients</th>
<th>( p ) Value</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)*</td>
<td>65</td>
<td>0.600</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Clinical stage (IIB versus IIIA versus IIIB)</td>
<td>38 versus 26 versus 1</td>
<td>0.821</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Zone of thoracic inlet (1 and 3 versus 2, 4, and 5)</td>
<td>17 versus 36b</td>
<td>0.050</td>
<td>1.035</td>
<td>0.239–4.482</td>
</tr>
<tr>
<td>Induction treatment (no versus yes)</td>
<td>2 versus 59c</td>
<td>0.520</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Number of ribs resected*</td>
<td>65</td>
<td>0.335</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Number of nerve roots resected*</td>
<td>65</td>
<td>0.772</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Number of vertebral resected*</td>
<td>65</td>
<td>0.759</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Arterial resection (no versus yes)</td>
<td>58 versus 7</td>
<td>0.063</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Pathologic stage (0 versus I versus II versus III)</td>
<td>19 versus 1 versus 28 versus 17</td>
<td>0.576</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Response rate to induction (pCR/pNR versus pPR)</td>
<td>31 versus 26d</td>
<td>0.004</td>
<td>4.046</td>
<td>1.012–16.170</td>
</tr>
<tr>
<td>Residual disease (R0 versus R1/R2)</td>
<td>55 versus 10</td>
<td>0.256</td>
<td>.</td>
<td>.</td>
</tr>
<tr>
<td>Adjuvant treatment (no versus yes)</td>
<td>43 versus 14e</td>
<td>0.028</td>
<td>0.184</td>
<td>0.022–1.541</td>
</tr>
</tbody>
</table>

* From Cox regression analysis. b NA in 12 patients. c NA in 4 patients. d no induction in 2 patients and NA in 6 patients. e NA in 8 patients. CI = confidence interval; HR = hazard ratio; NA = not available; pCR/pNR = pathologic complete response/pathologic nearly complete response; pPR = pathologic partial response.

### Table 2. Distribution of Relevant Predictors Between Tumors Located in Zones 1 and 3 and Zones 2, 4, and 5

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Zones 1 and 3</th>
<th>Zones 2, 4, and 5</th>
<th>( p ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>R0 resection</td>
<td>13 of 18</td>
<td>30 of 35</td>
<td>0.279</td>
</tr>
<tr>
<td>Presence of arterial resection</td>
<td>7 of 18</td>
<td>0 of 35</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Presence of adjuvant treatment</td>
<td>1 of 16</td>
<td>11 of 32</td>
<td>0.04</td>
</tr>
<tr>
<td>Partial response to induction</td>
<td>10 of 16</td>
<td>14 of 34</td>
<td>0.227</td>
</tr>
</tbody>
</table>

* Fisher’s exact test (bilateral).
alone. The rate of complete pathologic response (ypT0N0 or pCR) after 2 cycles of cisplatin/etoposide and concurrent 45 Gy of irradiation was 30% in our early and present reports, confirming the results of the Southwest Oncology Group Trial 9416 [1, 10]. Of note, pathologic response to induction chemoradiation was found to be a strong predictor of survival in our study. Patients with pCR or pNR had a 5-year survival of 89% compared with 46% for patients with only pPR. These findings confirmed the results of the long-term results of Southwest Oncology Group Trial 9416, which found that 5-year survival was approximately 70% and 40% for patients with pCR and incomplete response to induction, respectively [10].
With careful patient selection and preoperative planning, complete R0 resection was achieved in 85% of patients. In the present study, no significant difference in survival was shown between patients with complete (R0) and incomplete (R1/2) resection. This is extremely surprising because many other reports including patients with tumors located along the pulmonary sulcus and invading the spine demonstrated the benefit of complete resection on patient survival and the reduced benefit of incomplete resection. However, the number of patients with incomplete resection in this cohort was small and, therefore, insufficiently powered to find and confirm a difference.

Adjuvant therapy was administered in a quarter of the included patients. This is far less than in the original report of the Southwest Oncology Group Trial 9416, in which 49 patients had 2 cycles of adjuvant chemotherapy of the 60 patients (82%) registered for this treatment. Interestingly, we found that patients who had adjuvant chemotherapy had a significantly better survival than did patients who had not received adjuvant chemotherapy. This, however, probably results from selection bias because healthier patients were more likely to receive adjuvant treatment.

The need for arterial resection (subclavian/vertebral/carotid) was associated with a trend toward worse survival in our study. In a recent report by Fadel and colleagues on 54 patients undergoing en bloc resection for NSCLC invading the thoracic inlet and the spine, involvement of the subclavian artery also was found to be an independent factor affecting survival in a multivariate analysis. This observation may relate to the fact that tumors extending to the subclavian vessels may be more prone to develop distant metastases than tumors located more posteriorly in the thoracic inlet. With current knowledge, however, this statement is purely speculative and would need further studies to be confirmed.

Thoracic inlet tumors are challenging for the surgeon because of the potential invasion of neighboring vessels, spine, or brachial plexus. To achieve complete tumor resection, careful patient selection and cautious surgical planning for the most appropriate surgical approach is mandatory. Generally, the thoracic inlet is divided into anterior, middle, and posterior compartments based on the insertion of the different scalene muscles. The anterior and middle compartments are accessed with an anterior approach, whereas a posterior approach is favored for tumors of the posterior compartment. Recently, division of the thoracic inlet into 5 zones attempted to improve guidance in the selection of the optimal surgical approach, potentially increasing the likelihood of complete tumor resection and minimizing invasiveness of the approach. In this study, tumors were allocated retrospectively to these 5 different zones according to preoperative computed tomographic findings. Interestingly, patients with tumors located in zones 1 or 3 had significantly worse survival compared with patients with tumors situated in zones 2, 4, or 5. The study of survival predictor distribution between these 2 populations showed that tumors in zone 1 or zone 3 were more likely to require arterial resection and received adjuvant therapy less commonly than tumors in zones 2, 4, and 5.

In conclusion, induction cisplatin/etoposide with concurrent 45 Gy irradiation followed by en bloc tumor resection offers excellent 5-year survival. Tumor allocation into the 5 zones based on preoperative computed tomographic findings may help select the optimal surgical approach for resection and may carry predictive value for survival as well. Additional prognostic factors for survival were the pathologic response to induction and the presence of adjuvant chemotherapy.

Dr Collaud was supported for this work by the American Association for Thoracic Surgery's Evarts A. Graham Memorial Traveling Fellowship.

References