Impact of Induction Therapy on Airway Complications After Sleeve Lobectomy for Lung Cancer

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Background. Sleeve lobectomy is a valid alternative to pneumonectomy for the treatment of centrally located operable non-small cell lung cancer (NSCLC), but concern has been evoked regarding a potentially increased risk of bronchial anastomosis complications after induction therapy. This study examined the impact of induction therapy on airway healing after sleeve lobectomy for NSCLC.

Methods. Bronchial anastomosis complications were recorded with respect to the induction regimen applied (neoadjuvant chemotherapy vs chemoradiotherapy) in a consecutive series of patients with sleeve lobectomy for NSCLC.

Results. Ninety-nine patients underwent sleeve resection, 28 of them after induction therapy. Twelve patients received chemotherapy alone, and 16 patients had radiochemotherapy. There were no significant differences in postoperative 90-day mortality (3.6% vs 2.8%) and morbidity (54% vs 49%) for patients with and without induction therapy. Bronchial anastomosis complications occurred in 3 patients (10.8%) with neoadjuvant therapy and in 2 (2.8%) without ($p = 0.3$). In the induction therapy group, two bronchial stenoses occurred after radiochemotherapy and one bronchopleural fistula after chemoradiotherapy alone. In patients without induction therapy, one bronchial stenosis and one bronchopleural fistula were observed. All bronchial stenoses were successfully treated by dilatation, and both bronchopleural fistulas occurring after right lower lobectomy were successfully treated by reoperation and completion sleeve bilobectomy with preservation of the upper lobe.

Conclusions. Sleeve lobectomy for NSCLC can be safely performed after induction chemotherapy and radiochemotherapy with mortality and incidence of airway complications similar to that observed in nonpretreated patients. The treatment of airway complications does not differ for patients with and without induction therapy.

(Bronchial sleeve lobectomy is accepted as a valid alternative to pneumonectomy for patients with resectable, centrally located non-small cell lung cancer (NSCLC), provided a complete resection can be obtained [1–3]. Sleeve lobectomy has demonstrated at least equivalent outcomes in terms of local control, overall survival, and quality of life compared with pneumonectomy in several series [1, 4–7]. However, concerns arise regarding airway healing if sleeve lobectomy is performed after neoadjuvant therapy, which is increasingly used for stage III disease to reduce the risk of local and distant recurrence and to facilitate complete resection [8]. Some studies have shown a detrimental effect of induction therapy, especially radiochemotherapy, on bronchial blood supply and bronchial anastomosis healing [9, 10], whereas other more recent reports have not confirmed a higher risk of anastomotic complications after neoadjuvant therapy [11–15].

The purpose of this study was to evaluate the incidence of airway complications with respect to the induction regimen applied (neoadjuvant chemotherapy vs radiochemotherapy) in a consecutive series of patients undergoing sleeve lobectomy for NSCLC.

Patients and Methods

We report on a consecutive series of patients who underwent sleeve lobectomy for NSCLC in our institution between January 1999 and December 2010. Patients undergoing sleeve lobectomy for benign or malignant diseases other than NSCLC were excluded from this study, as were those with carinal resections. Patients were evaluated in an interdisciplinary setting and investigated, treated, and followed up in a prospective manner. For patients receiving induction therapy, the treatment protocols were approved by the local ethical committee, and informed consent was obtained from the patients.
Patients
All patients underwent contrast medium–enhanced computed tomography (CT) of the chest, whole body fusion positron emission tomography (PET)-CT, brain imaging, and bronchoscopy to assess the tumor resectability. Pathologic confirmation of suspect mediastinal lymph nodes on PET-CT was obtained by mediastinoscopy or endobronchial ultrasound-guided biopsy. Lung functions were evaluated according to the guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons [16]. Patients with forced expiratory volume in 1 second or carbon monoxide lung diffusion capacity below 80% of that predicted underwent exercise testing. Patients with a maximum oxygen consumption below 20 mL/kg/min had split function testing by ventilation/perfusion scan and were operated on if the postoperative predicted maximum oxygen consumption was equal to or greater than 10 mL/kg/min. Patients older than 50 years and those with a history of coronary artery disease underwent echocardiography, and those with signs of myocardial ischemia had stress myocardium scintigraphy; operation was considered in the presence of preserved left ventricular ejection fraction and the absence of reversible myocardial ischemia.

Induction Therapy
Patients with potentially resectable T1–3N2M0 disease underwent either standard neoadjuvant chemotherapy consisting of three cycles of cisplatin/docetaxel combination or an experimental multimodal strategy of three cycles of cisplatin/docetaxel induction chemotherapy and sequential radiotherapy of 44 Gy. This treatment was delivered in the context of a Swiss prospective randomized phase III trial (Swiss Association for Clinical Cancer Research 16/00 trial, NCT00030771), having recently completed accrual. Patients with T4N0–2M0 disease received three cycles of cisplatin/docetaxel induction chemotherapy with sequential accelerated radiotherapy of 44 Gy after inclusion in a prospective phase II Swiss multicenter study (Swiss Association for Clinical Cancer Research 16/01 trial) dedicated to resectable stage IIIB disease according to the Sixth TNM classification [17]. In both trials, the chemotherapy regimen consisted of three cycles of docetaxel 85 mg/m² and cisplatin 100 mg/m². In case of renal insufficiency after the initial cisplatin administration, substitution for carboplatin was to be given in subsequent cycles. All patients with neoadjuvant radiotherapy underwent sequential 3-dimensional conformal radiation therapy to the primary tumor and regional lymph nodes, based on the extent of disease after induction chemotherapy. Treatment was started 3 weeks after the last chemotherapy administration. Accelerated radiation therapy, using a concomitant boost schedule, delivered a total dose of 44 Gy at 2 Gy per fraction in 3 weeks. The planning target volume receiving 30 Gy included all known areas of disease, the ipsilateral hilum, and the mediastinum. The boost volume receiving the total 44 Gy included the primary tumor and abnormal lymph nodes with a 1.5- to 2-cm margin. According to the trial protocols, the clinical response after induction therapy was assessed by CT scan or PET-CT, and surgical procedures were performed within 3 weeks after the completion of neoadjuvant therapy in patients without tumor progression.

Intervention
Double-lumen intubation was routinely used, and continuous epidural anaesthesia was offered to all patients in the absence of contraindications. Postoperatively, all patients underwent routine avoidance of fluid overload and prevention of atelectasis by early mobilization and chest physiotherapy. All patients received routine thromboprophylaxis with low-molecular-weight heparin. Patients with an increased risk profile underwent postoperative surveillance in the intensive care unit; all other patients were referred to the intermediate care unit. All patients underwent intraoperative control bronchoscopy and routine bronchoscopy on postoperative day 1.

Resection consisted of complete en bloc removal of the lobe together with involved adjacent structures, if required, through a posterolateral thoracotomy. Frozen section examination of both bronchial resection margins was routinely performed. End-to-end bronchial anastomosis was performed with interrupted 4-0 polydioxanone sutures (Ethicon, Inc, Somerville, NJ). For upper sleeve (bi) lobectomy, an intrapericardial hilar release maneuver was routinely performed with circumferential incision of the pericardium around the inferior pulmonary vein and intrapericardial division of the septum between the heart and the inferior vena cava. Bronchial anastomoses were routinely covered by a pedicled intercostal muscle flap. Complete mediastinal lymph node dissection was performed in all patients, after induction therapy and after division of the ayzygos vein on the right side and of the Botalli ligament on the left side. In case of pulmonary artery involvement, either a double sleeve resection was performed with an end-to-end anastomosis of the pulmonary artery or a partial resection of the pulmonary artery with arterial reconstruction by use of a pericardial patch.

Adjuvant Treatments
Adjuvant cisplatin-based chemotherapy (mainly cisplatin-vinorelbine) was offered to all patients with pathologic stage I T2N0M0 with a tumor whose largest diameter was more than 4 cm and with stage II disease. Patients with postoperatively diagnosed stage IIIA N2 disease or with incomplete resections underwent cisplatin-based adjuvant chemotherapy (mainly cisplatin-vinorelbine) and, respectively, sequential or concomitant adjuvant mediastinal radiotherapy up to 64 Gy.

Patient Records
The data were analyzed from the individual patients’ records and completed through their referring physicians. The patients’ records were analyzed with respect to the patient’s demographics, type of operation, histology and tumor stage, type of neoadjuvant treatment, postoperative mortality and morbidity, duration of
hospitalization, adjuvant treatments, and long-term outcome (survival and local recurrence). Special consideration was given to the registration of airway complications occurring in the postoperative period and during follow-up.

**Statistical Analysis**

For statistical comparison, the \( \chi^2 \) and Fisher exact tests were applied where appropriate. Survival was assessed by use of Kaplan-Meier and log-rank analyses. A two-tailed hypothesis was used, and significance accepted at \( p < 0.05 \).

**Results**

From January 1999 to December 2010, 99 patients underwent sleeve lobectomy for NSCLC: 75 men and 24 women, with a mean age of 62 years (range, 29–83 years). Twenty-eight of the patients underwent induction therapy, 12 with chemotherapy alone, and 16 with radiochemotherapy. The patients' demographic characteristics are shown in Table 1. There were no significant differences between patients with and without induction therapy with respect to age, sex, and pulmonary functions. Tumor characteristics are shown in Table 2. Patients receiving neoadjuvant therapy more frequently had adenocarcinoma (\( p = 0.03 \)) than those without. The clinical tumor stages in patients without induction therapy were stage I and II in 86% and stage III in 14% of the patients, 4% of them with T3N1 tumors. The reasons to refrain from induction therapy in preoperatively diagnosed stage III disease (\( n = 7 \)) were T4 tumors with poststenotic lung abscess (\( n = 4 \)) or those with two lesions in two different lobes in patients unfit for pneumonectomy (\( n = 3 \)). The pathologic tumor stage in patients without induction therapy was stage I or II disease in 65%. Twenty-five patients (35%) had stage III disease, 5 (7%) with pT3N1 tumors, 8 (11%) with postoperatively diagnosed N2 disease, and 12 (17%) with T4 tumors either preoperatively diagnosed (\( n = 7 \)) or found during operation (\( n = 4 \)) or at definitive pathologic examination (\( n = 1 \)). The group with induction therapy had clinical stages IIIA and IIIB in 75% and 25% of patients, respectively, and pathologic stages I, II, IIIA, and IIIB in 25%, 29%, 28%, and 7%, respectively. Tumor sterilization (ypT0N0) was found in 3 patients (11%). Eleven patients (62%) with preoperatively diagnosed N2 disease had a pathologic downstaging, 6 patients with ypN1 and 7 with ypN0 disease. Downstaging of preoperatively diagnosed T4 tumors was found in 10 patients (71%). Patients with induction therapy had a more advanced clinical tumor stage than did those without (\( p < 0.0001 \)).

Table 3 shows the type of operation and the completeness of resection in both groups. There was no significant difference in localization (upper vs lower lobectomy) and extent of resection (lobectomy vs bilobectomy). Twenty-six patients (26%) underwent additional procedures such as resection and reconstruction of the pulmonary artery (17), vena cava superior (1), or chest wall (8) without significant difference between the groups. Pulmonary artery reconstruction was performed by end-to-end anastomosis after double sleeve resection in 6 patients and by pericardium patch angioplasty after noncircumferential resection in 9 patients, without difference between the two groups. Complete resection was obtained in 75% and 86% of patients with and without induction therapy, respectively (\( p = 0.4 \)). The reason for microscopically incomplete resection in 10 patients without induction therapy was a discrepancy between frozen section and definitive pathologic examination at the bronchial resection margin (\( n = 5 \)) and unexpected microscopic residual disease at the vena cava.

### Table 1. Demographic and Tumor Characteristics of 99 Patients Undergoing Sleeve Lobectomy for NSCLC With and Without Induction Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Induction n = 21</th>
<th>Induction n = 28</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age mean (years)</td>
<td>62.2 ± 10.4</td>
<td>60.2 ± 9.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Age &lt;70 years</td>
<td>52 (73%)</td>
<td>23 (82%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>56 (79%)</td>
<td>19 (68%)</td>
<td>0.3</td>
</tr>
<tr>
<td>FEV1 (% predicted)</td>
<td>77.4 ± 20.3</td>
<td>78.9 ± 21.6</td>
<td>0.7</td>
</tr>
<tr>
<td>DLCO (% predicted)</td>
<td>67.4 ± 19.7</td>
<td>62.7 ± 17.6</td>
<td>0.3</td>
</tr>
</tbody>
</table>

DLCO = Diffusion lung capacity for carbon monoxide; FEV1 = forced expiratory volume in 1 second; NSCLC = non-small cell lung cancer.

### Table 2. Tumor Characteristics of 99 Patients Undergoing Sleeve Lobectomy for NSCLC With and Without Induction Therapy

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No Induction n = 21</th>
<th>Induction n = 28</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td>54 (76%)</td>
<td>17 (61%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>12 (17%)</td>
<td>11 (39%)</td>
<td></td>
</tr>
<tr>
<td>Clinical tumor stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>32 (45%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>29 (41%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>7 (10%)</td>
<td>21 (75%)</td>
<td></td>
</tr>
<tr>
<td>T3 N1</td>
<td>3 (4%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>T1-3N2</td>
<td>2 (3%)</td>
<td>14 (50%)</td>
<td></td>
</tr>
<tr>
<td>T4N0-1</td>
<td>2 (3%)</td>
<td>7 (25%)</td>
<td></td>
</tr>
<tr>
<td>IIIBa</td>
<td>3 (4%)</td>
<td>7 (25%)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Pathologic tumor stageb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>3 (11%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>18 (25%)</td>
<td>7 (25%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>28 (39%)</td>
<td>8 (29%)</td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>18 (26%)</td>
<td>8 (29%)</td>
<td></td>
</tr>
<tr>
<td>pT3 N1</td>
<td>5 (7%)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>pT1-3N2</td>
<td>8 (11%)</td>
<td>6 (21%)</td>
<td></td>
</tr>
<tr>
<td>pT4N0-1</td>
<td>5 (7%)</td>
<td>2 (7%)</td>
<td></td>
</tr>
<tr>
<td>IIIBb</td>
<td>7 (10%)</td>
<td>2 (7%)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

a T4N2 tumors.  b ypTNM classification after induction therapy.  
NSCLC = non-small cell lung cancer.
superior, pulmonary artery, or pulmonary parenchyma resection margins (n = 5). In patients with induction therapy, 7 had microscopically incomplete resections because of a discrepancy between frozen section and definitive pathologic examination (n = 2) and a lack of further surgical options (n = 5). Postoperative chemotherapy and radiotherapy were delivered to 32 and 21 patients, respectively.

There were no significant differences in postoperative mortality (3.6% vs 2.8%) and morbidity (54% vs 49%) for patients with and without induction therapy (Table 4). In both groups, the most frequent complications were pulmonary (pneumonia, adult respiratory disease syndrome) and cardiac (atrial fibrillation, myocardial infarction), followed by pulmonary embolism. The mean length of hospital stay was similar in both groups.

Bronchial anastomosis complications occurred in 5 patients of the entire series (5%): in 3 of the 28 patients (10.8%) with neoadjuvant therapy and in only 2 of the 71 patients of the entire series (5%): in 3 of the 28 patients with induction therapy, 7 had microscopically incomplete resections (n = 3), which might have been related to the small sample size with a power of less than 50% (Table 4). In patients with induction therapy, 1 patient required temporary stenting with a coated stent. The two bronchopleural fistulas occurred 7 and 10 days after right lower sleeve lobectomy and were successfully treated by reoperation, middle lobe resection, and reimplantation of the upper lobe bronchus into the main stem bronchus, followed by anterior transposition of the intrathoracic serratus to avoid right completion pneumonectomy.

The mean follow-up times for patients with and without induction therapy were 25 months (range, 1–104 months) and 41 months (range, 1–108), respectively. The 5-year survival, local recurrence, and distant recurrence for patients with and without induction therapy were 28% and 45% (p = 0.06), 29% and 7% (p = 0.007), and 40% and 31% (p = 0.6), respectively. However, careful interpretation of this analysis is indicated because of the small sample size, unequal follow-up times, and an unequal distribution of early and advanced tumor stages within the two groups.

**Comment**

Many centers favor sleeve lobectomy over pneumonectomy for centrally located NSCLC, provided a complete resection can be obtained with a sleeve procedure, given that for adjusted tumor stages, sleeve lobectomy has shown similar survival and recurrence rates but is associated with lower postoperative mortality and morbidity and a better quality of life compared with pneumonectomy [1, 4–7]. After sleeve lobectomy, reported postoperative mortality and morbidity rates range between 2% and 5%, and 15% and 47%, respectively [10, 11, 13, 18, 19], even if sleeve lobectomy is combined with additional surgical procedures such as pulmonary artery, superior vena cava, or chest wall resection and reconstruction [7, 14, 20].

However, neoadjuvant chemotherapy, especially radiochemotherapy, has been the subject of controversy if applied in the context of sleeve lobectomy because induction-related injury of the bronchial microvascularization may predispose to airway complications [9]. Milman and colleagues [13] published a series of 64 patients undergoing sleeve lobectomy, 21 of them after cisplatin-based induction radiochemotherapy. No
significant difference was observed between patients with and without induction therapy with respect to postoperative mortality and morbidity. A similar study endorsed these findings [18], but Rea and colleagues [10] observed a significantly increased mortality rate in patients undergoing sleeve lobectomy after neoadjuvant radiotherapy, mainly related to bronchial anastomosis complications.

In our series of 99 consecutive patients, 28 underwent sleeve lobectomy after induction therapy, 12 after chemotherapy, and 16 after radiochemotherapy. There were no significant differences in postoperative 90-day mortality (3.6% vs 2.8%) and morbidity (54% vs 49%) for patients with and without induction therapy. These results are similar to those observed in other reports.

Special consideration was given to bronchial anastomosis healing in our series. Common airway complications after sleeve lobectomy include bronchopleural or bronchovascular fistula and bronchial stenosis. Bronchovascular fistulas may occur occasionally, but bronchopleural fistulas are more common, with a reported incidence of 1% to 5% after sleeve lobectomy [10, 18, 19, 21, 22]. The reported incidence of stenosis at the site of bronchial anastomosis ranges between 1% and 4% [10, 18, 19, 23]. These complications may result from inappropriate surgical procedures such as tension at the level of the anastomosis or bronchial devascularization during dissection, or from nutritional deficiencies or advanced tumor stage [3]. Induction therapy may additionally compromise bronchial healing as a result of radiochemotherapy-induced microvascular injury and desmoplastic tissue reactions. In the series of Milman and colleagues [13], airway complications after sleeve lobectomy occurred only in patients with induction therapy, with an incidence of 4.7%.

In our series, bronchial anastomosis complications occurred in 3 patients (10.8%) with neoadjuvant therapy and in 2 (2.8%) without. In patients without induction therapy, one bronchial stenosis and one bronchopleural fistula were observed. In the induction therapy group, two bronchial stenoses occurred after radiochemotherapy and one bronchopleural fistula after chemotheraphy alone. All bronchial stenoses were successfully treated by dilation, as proposed by Rea and colleagues [10], and both bronchopleural fistulas were successfully treated by sleeve bilobectomy with preservation of the upper lobe. Our results indicate that airway complications after sleeve resection after induction therapy can be equally successfully treated as in nonpretreated patients: stenosis by dilatation and bronchopleural fistulas by sleeve bilobectomy while avoiding a completion pneumonectomy. This also holds true for induction radiochemotherapy. However, a higher airway complication rate may be expected by adding radiotherapy to induction protocols, especially at higher doses above 44 Gy. Unfortunately, the size of the induction group in our series did not allow us to perform a statistical analysis for airway complications separately for patients with chemotherapy alone and those receiving radiochemotherapy.

No patient experienced a bronchovascular fistula in our series despite the fact that in 17 patients additional pulmonary artery resections and reconstructions were performed, in 6 of them after induction therapy. This may be attributed to the routine coverage of bronchial anastomosis by a muscular flap. Storelli and colleagues [23] have recently reported on 25 patients undergoing sleeve lobectomy after induction therapy without bronchial complications despite the fact that no anastomosis wrapping had been performed. However, most authors recommend routine coverage of bronchial anastomosis of sleeve resections after induction therapy.

The 5-year survival after sleeve lobectomy for NSCLC generally ranges between 39% and 53% according to the published literature [1–5, 18]. In our series, the 5-year survival stands at 28% and 45% for patients with or without neoadjuvant treatment, respectively. This difference is explained by the imbalance in tumor stage with more advanced disease observed in the induction group. Local recurrence reported in different studies is equally comparable among sleeve lobectomy and pneumonectomy and varies from 4% to 22% to 8 to 35%, respectively [5, 7]. In our series, the local recurrence rate was higher for patients with induction treatment (28%) than in patients without (7%). These differences will similarly be the consequence of the higher tumor stage observed in the induction group, with 25% of these patients presenting with T4 tumors.

In conclusion, sleeve lobectomy for NSCLC can be safely performed after induction chemotherapy and radiochemotherapy, with similar mortality and airway complications as observed in nonpretreated patients. The treatment of airway complications does not differ for patients with and without induction therapy.

References