Sacrificing the pulmonary arterial branch to the spared lobe is a risk factor of bronchopleural fistula in sleeve lobectomy after chemoradiotherapy

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Abstract

OBJECTIVES: A sleeve lobectomy is a widely accepted procedure for enabling the pulmonary parenchyma to be spared. Induction chemoradiotherapy (CRT) followed by surgery is one treatment option for locally advanced non-small cell lung cancer (NSCLC), but CRT is considered to have a negative effect on subsequent surgery, especially for anastomotic healing. In this study, we describe our experience performing sleeve lobectomies and the associated anastomotic complications after induction CRT.

METHODS: The medical records of NSCLC patients who underwent surgery after receiving CRT were reviewed. The relationships between anastomotic complications and clinicopathological factors were examined.

RESULTS: Between December 1998 and October 2011, a total of 104 patients received CRT followed by surgery. Among them, 14 NSCLC patients underwent a bronchial sleeve resection: nine patients underwent a right upper lobe resection, two patients underwent a left lingular division and lower lobe resection and one patient each underwent a right lower lobe, a right upper and middle lobe and a right middle and lower lobe resection. A bronchopleural fistula at the anastomosis occurred in two patients. A pulmonary arterial (PA) branch to the spared lobe had been sacrificed in both of these patients because of tumour involvement. In contrast, the PA branches to the spared lobes were preserved in 11 of the 12 patients who did not exhibit anastomotic complications ($P = 0.033$).

CONCLUSIONS: Our experience strongly suggests that the sacrifice of the PA branch to the spared lobe is a possible risk factor for anastomotic complications for a sleeve lobectomy after induction CRT.

Keywords: Sleeve lobectomy • Lung cancer • Bronchopleural fistula • Induction chemoradiotherapy

INTRODUCTION

Sleeve lobectomy was introduced in 1947 for the resection of lung tumours in a manner enabling the pulmonary parenchyma to be spared [1]. Recent studies have indicated that a sleeve lobectomy is comparable or superior to a pneumonectomy in terms of survival and quality of life among patients with lung cancers [2–5]. Based on this evidence, many surgeons have intentionally avoided a pneumonectomy by using a sleeve lobectomy whenever technically and oncologically appropriate.

Induction therapy followed by surgery is one treatment option for locally advanced (LA) non-small cell lung cancer (NSCLC). Chemoradiotherapy (CRT) is used as an induction therapy, and its feasibility and clinical benefits have been strongly suggested for some types of LA-NSCLC, although the negative effect of chemotherapy or radiotherapy on tissue healing is a concern [6–10]. Regarding this issue, Rendina et al. [11] have reported that a sleeve lobectomy could be safely performed in patients who had received induction chemotherapy. A recent report has also shown that a sleeve lobectomy after CRT can be performed with acceptable morbidity and mortality [12]. We have applied induction CRT for LA-NSCLC since 1998 [13]. Among our patients, 14 subsequently underwent a sleeve lobectomy, and two of them developed a bronchopleural fistula (BPF) at the anastomosis. In this study, we discuss our patients who have undergone a sleeve lobectomy after receiving induction CRT from the viewpoint of risk factors for anastomotic complications.

MATERIALS AND METHODS

Patients

We have used the induction CRT for LA-NSCLC in Okayama University Hospital since 1998 [13, 14]. Medical records of NSCLC patients who underwent CRT followed by surgery were

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reviewed. The International Association of the Study of Lung Cancer TNM staging system for NSCLC, 7th edition, was used for disease staging [15]. Disease stage was evaluated using chest radiography, enhanced chest and abdominal computed tomography (CT) scans, enhanced brain magnetic resonance imaging (MRI), and radionuclide bone scan, or (18-fluoro-2-deoxyglucose positron emission tomography—CT scan), and bronchoscopy. A staging cervical mediastinoscopy was performed for some patients to evaluate bilateral node stations 2 and 4 and subcarinal station 7.

**Induction therapy and surgery**

Induction CRT was performed as previously described [13]. Briefly, docetaxel (40 mg/m²) was administered intravenously followed by cisplatin (40 mg/m²) before radiotherapy on Days 1 and 8. Chemotherapy was repeated with a 3- or 4-week interval. Radiotherapy was started on the first day of chemotherapy using a linear accelerator (6-10 mV). A total radiation dose of 46 Gy was planned using a conventional fractionation (2 Gy/day). The original volume included the site of the primary tumour with a margin of 2 cm around the mass and the ipsilateral hilum, and the whole width of the mediastinum with a margin of 1 cm around the radiographically visible region of involvement extending inferiorly to 2 cm below the carina or 2 cm below the radiographically demonstrated tumour mass. Following induction CRT, patients were evaluated for response. Patients without progressive disease (PD) or good general condition underwent surgery. This study was approved by the Institutional Review Board/Ethical Committee of Okayama University.

The surgical procedure was determined based on the disease extension before induction therapy. While a posterolateral thoracotomy was used as the basic approach, a median sternotomy or a trap-door approach was applied for patients with supraclavicular lymph node or contralateral mediastinal lymph node metastasis, with the pancoast type tumour, or when great vessels, such as the main pulmonary artery (PA), needed to be secured for a safe resection. A complete ipsilateral superior mediastinal and subcarinal lymph node dissection was routinely undertaken. For patients with primary lower lobe lesions, stations 8 and 9 lymph nodes were also resected. Bronchial anastomosis was performed with a running 4-0 PDS II (Ethicon, Somerville, NJ, USA) for the bottom portion on the anastomosis for the individual approach. Interrupted 4-0 PDS II were placed on the other portion. The bronchial anastomosis was basically wrapped with the omental pedicled flap or pericardial fat pad with prophylactic intent. Bronchoscopy was routinely performed to assess the suture line before discharge.

**Estimation**

Radiological response was assessed using the Eastern Cooperative Oncology Group criteria, with some modifications as previously reported and classified as complete response (CR), partial response (PR), stable disease (SD) and PD [13, 16]. Anastomotic complications were defined as bronchopleural or bronchovascular fistula, bleeding, bronchial stenosis and malacia. As part of the routine follow-up care, a chest and abdominal CT and an enhanced brain MRI examination were repeated every 6 months. The overall survival (OS) and the disease-free survival (DFS) were calculated from the date of initiating induction CRT until the date of death or the last follow-up for OS and until confirmed death of any cause or recurrence at local or distant site for DFS. Local recurrence was defined as that which occurred in the ipsilateral chest or mediastinum and distant recurrence was defined as that which occurred elsewhere. The survival curve was calculated by the Kaplan–Meier method. Fisher’s exact test was used to compare differences between the two groups. The statistical test was two-sided and probability values <0.05 was defined as being statistically significant.

**RESULTS**

**Patient characteristics**

Between September 1998 and October 2011, a total of 104 NSCLC patients underwent CRT followed by surgery at Okayama University Hospital. Induction CRT using docetaxel and cisplatin was performed for 100 patients. Among them, 14 patients underwent a sleeve lobectomy. The patient characteristics are shown in Table 1. The median patient age was 60 years (range 46–70 years). There were 12 men and two women. The histological subtype was squamous cell carcinoma in 10 patients and adenocarcinoma in four patients. Eight patients had clinical stage (c-stage) IIIA, five patients had c-stage IIIB and one patient had c-stage IIA. Mediastinal lymph node metastasis was pathologically confirmed in four patients using a mediastinoscopy or endobronchial ultrasound-guided transbronchial biopsy before induction CRT.

**Trimodality therapy**

Of the 14 patients, 10 patients completed the planned induction CRT. The toxicities were similar to those described previously [13]. The radiation dose was 46 Gy in 12 patients and 40 Gy in two patients. The radiological response was CR in one patient (7.1%), PR in six patients (38.5%), SD in seven patients (50.0%) and PD in 0.

The median time from the end of induction CRT until surgery was 35 days. All the patients underwent a complete resection, with a negative bronchial margin confirmed by frozen section. A posterolateral thoracotomy was used for seven patients, a median sternotomy was used for six patients and a trap door approach was used for one patient. As the main procedure, a sleeve lobectomy was performed for the right upper lobe in nine patients, for the left upper and middle lobe in two and for the right lower lobe, the right upper and middle lobe and the right middle and lower lobe in one patient each. A sleeve lobectomy was required because of a central tumour location in 12 patients and because of metastatic lymph node invasion in 2. Additionally resected structures are shown in Table 1. A tangentially partial or sleeve resection of the PA was performed in one patient each. A complete pathological response was obtained in five patients.

**Anastomotic and other major complications**

Two patients, Case #4 and Case #9, developed BPF as a result of anastomotic dehiscence. In Case #4, a right upper sleeve
Table 1: Characteristics of patients who underwent sleeve resection after induction chemoradiotherapy

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age</th>
<th>Histology</th>
<th>TNM</th>
<th>Stage</th>
<th>RT dose (Gy)</th>
<th>Resected lung</th>
<th>Additional resection</th>
<th>Coverage</th>
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SQ: squamous cell carcinoma; AD: adenocarcinoma; RUL: right upper lobe; RUML: right upper and middle bilobectomy; RMLL: right middle and lower lobe; GO: greater omentum; PTP: pericardial fat pad; BPF: bronchopleural fistula.

*Case #8 was a pancoast-type tumour, which needed combined resection of the clavicular artery and vein, the tracheal wall and the first-second ribs.

Disease relapse and survival

At the time of data analysis in February 2012, disease relapse was observed in three patients as distant metastasis and no patient as locoregional recurrence. The 2- and 5-year OS rates were both 75.0% (Fig. 2). The 1- and 2-year DFS rates were 66.7 and 65.6%, respectively.

DISCUSSION

In our series of patients undergoing a sleeve lobectomy after induction CRT for NSCLC, two patients developed BPFs as an anastomotic complication. The CT and pathological findings for both patients revealed severe inflammation and ischaemia, suggesting changes in the spared lungs. Of note, some of these changes may represent secondary effects of the BPF. Based on the investigation and clinical outcomes of our patients, the sacrifice of a PA to the spared lung may be a possible risk factor for anastomotic complications.

Radiation-induced lung injury is a well-known event, potentially resulting in severe complications in the treatment of malignancies. In addition, chemotherapeutic agents are considered to be sensitizers. In the acute phase after irradiation (0–2 months), injury to the microvasculature causes capillary congestion and thrombosis that can develop into ischaemia [17, 18]. The sacrifice of a PA in irradiated lung may worsen the negative effect of radiation, and the presence of severely injured pulmonary tissue near the suture line is likely to impair the healing potential of the anastomosis. Needless to say, the effect of radiation and lymph node dissection on the proximal bronchus is one of the predisposing factors for bronchial complications.

Which procedure would be most appropriate for this situation when performing a sleeve resection? Coverage with an omental pedicled flap did not prevent the BPF in Case #4. In addition, the remnant segment belonging to the sacrificed PA does not theoretically have a proper function in the lung. Considering the points mentioned above, one possible option may be a combined resection of the segment corresponding to the sacrificed
PA. For our patients, an S6 and an S2 segmentectomy for Case #4 or Case #9, respectively, combined with a sleeve lobectomy may have been the optimal procedure of choice. Other options may be the aggressive reconstruction of PA to preserve blood flow when technically feasible or a pneumonectomy. The favourable long-term outcome of PA reconstruction in sleeve lobectomy has been reported [4]. Of note, our experience is limited and it is unknown whether the sacrifice of small PA branches such as A1+2 a, b or c to left S1 + 2 when the left superior division is spared causes BPF or not. In our two cases of sleeve resection of the left lingular division and lower lobe, all PA branches to the spared superior division were preserved and no anastomotic complication occurred.

Except in two patients described above, there were no life-threatening complications. There was no perioperative death in our series and the prognosis is acceptable. These outcomes are compatible with previous reports [5, 12], confirming that sleeve lobectomy after CRT is generally safe and one of the treatment options for LA-NSCLCs.

In conclusion, our experience strongly suggests that the sacrifice of the PA branch to the spared lobe can be a possible risk factor of anastomotic complications in sleeve lobectomy after induction CRT.

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Conflict of interest: none declared.

REFERENCES

Sleeve resection of the bronchus and pulmonary artery (PA) is nowadays considered a reliable procedure for radical resection of lung cancer when anatomically feasible [1]. Patients receiving induction therapy for stage IIIA and IIIB non-small-cell lung cancer often fall into this category; however, they usually pose additional problems when compared with the standard population. In fact, after neoadjuvant therapy, it might be difficult to distinguish desmoplastic reaction and fibrosis related to induction from a residual tumour, and a sharp dissection around the bronchus is often required; this can make dissection around the hilar structure more difficult. For this reason, when sleeve resection is required, the anastomosis is often performed in a devascularized and fibrotic field; tumour contamination might also be possible. Frozen sections are mandatory to avoid the latter situation. Protection of the bronchial anastomosis with vital tissue is also required to favour revascularization and prevent the onset of broncho-pleural fistula in case of partial or complete dehiscence [2]. The association of PA reconstruction does not increase risks at the anastomotic site [3].

Toyooka et al. [4] reported in the present study a series of 14 patients undergoing bronchial sleeve resection after induction chemo-radiotherapy; in 2 patients PA reconstruction (1 tangential and 1 sleeve) was associated (14.3%); this is a relatively high incidence when compared with other studies published in the literature. In both patients, they had to sacrifice a PA branch of the residual lobe; this was the only significant risk factor for the onset of this complication. This condition has never been reported and analysed before. This is a relatively high incidence when compared with other studies published in the literature. In both patients, they had to sacrifice a PA branch of the residual lobe; this was the only significant risk factor for the onset of this complication.

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**Safety of bronchovascular reconstructions after induction therapy**

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