Primary lung cancer surgery after curative chemoradiotherapy for esophageal cancer patients

Kazuhiro Shien\textsuperscript{a,b,*}, Motohiro Yamashita\textsuperscript{a}, Mikio Okazaki\textsuperscript{a}, Hiroshi Suehisa\textsuperscript{a}, Shigeki Sawada\textsuperscript{a}, Shinichiro Miyoshi\textsuperscript{b}

\textsuperscript{a}Department of Thoracic Surgery, National Hospital Organization Shikoku Cancer Center, 160 Minami-Umemoto, Matsuyama 791-0280, Japan
\textsuperscript{b}Department of Cancer and Thoracic Surgery, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan

Received 9 December 2010; received in revised form 25 February 2011; accepted 1 March 2011

Abstract

The safety and perioperative problems of primary lung cancer surgery after curative chemoradiotherapy (CRT) for thoracic esophageal cancer (EC) are controversial. We retrospectively evaluated six patients who had received curative CRT for EC from 2003 to 2009, in whom the lung nodule was identified as a primary lung cancer and who subsequently underwent pulmonary resection. The treatment for EC consisted of chemotherapy with cisplatin and 5-fluorouracil with concurrent curative thoracic radiotherapy (60 Gy). The median age at the surgery was 75 years (range 69–80 years). The median time from radiation to pulmonary resection was 26 months (range 7–70 months). All patients had a predicted postoperative forced expiratory volume in 1 s (FEV\textsubscript{1})% of >40% before lung surgery. The surgical difficulty involves mediastinal lymph node dissection following tissue fibrotic changes after thoracic radiation. Postoperative complications occurred in two patients, and included arrhythmia and empyema. The patient who developed empyema had a massive pericardial effusion after CRT and underwent pericardial fenestration at the time of pulmonary resection. There was no operative mortality. Lung cancer surgery after curative CRT for EC is feasible in carefully evaluated and selected patients.

Keywords: Lung cancer; Esophageal cancer; Chemoradiotherapy

1. Introduction

Chemoradiotherapy (CRT) for the treatment of patients with esophageal cancer (EC) has revealed promising results and has been the widely accepted treatment for those patients who have received non-surgical treatment for EC [1]. As a consequence, the incidence of a second primary malignancy has increased in these patients. It is well known that squamous cell carcinoma of the esophagus can be associated with carcinomas of other organs [2]. Féketé et al. reported that 3.2% of patients with esophageal squamous cell carcinoma had primary lung carcinoma [2]. In our institution, we have performed surgery for a second primary lung cancer in patients whose primary malignancy has been controlled, even after curative CRT for EC. The safety of pulmonary resection for primary lung cancer after induction CRT has not been established, and similarly, the safety of pulmonary resection after curative CRT for thoracic EC is controversial. We report here the results of lung cancer surgery in patients after curative CRT for EC.

2. Materials and methods

2.1. Data collection

We retrospectively reviewed the patients who underwent primary lung cancer surgery at the National Hospital Organization Shikoku Cancer Center from 2003 to 2009. Six patients who underwent pulmonary resection after curative CRT for EC were identified. Collection of patients’ medical records was approved by the institutional Review Board.

2.2. Treatment for esophageal cancer

The characteristics of the six patients are shown in Table 1. The histological findings of the EC all revealed squamous cell carcinoma. In our institution, surgery has usually been performed for resectable (T1–3, N0–1, M0) thoracic EC, and induction chemotherapy or curative CRT for locally advanced (T3–4, N0–1, M0–1a) disease. Because cases 1, 2, 4 and 6 had T3–4 tumor or multiple regional lymph node metastasis, curative CRT was chosen. In cases 3 and 5, the patient rejected esophagectomy, and curative CRT was performed.

CRT for EC consisted of two cycles of cisplatin (40 mg/m\textsuperscript{2}) on days 1 and 8, and continuous infusion of 5-fluorouracil (400 mg/m\textsuperscript{2}/day) on days 1–5 and 8–12, repeated every
five weeks with concurrent radiotherapy of 60 Gy in 30 fractions over eight weeks. An additional two cycles of cisplatin (80 mg/m²) on day 1 and continuous infusion of 5-fluorouracil (800 mg/m²/day) on days 1–5 every four weeks were administered. Radiation therapy (40 Gy) was delivered with megavoltage equipment using anterior–posterior opposed fields, including the primary tumor, metastatic lymph nodes and regional nodes. A booster of 20 Gy was administered using bilateral or multiple fields to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy. The evaluations described below were performed every three months for the first year and every six months thereafter.

All of the six patients received CRT, and one patient (case 1) received additional intraluminal radiation with a remote-controlled afterloading system (RALS) for residual disease. All patients achieved a complete response after CRT. One patient (case 2) received salvage esophagectomy for recurrent locoregional disease. Late toxicity after CRT occurred in three patients: radiation pneumonitis (case 4), radiation pericarditis (case 4), and esophageal stricture (case 6).

2.3. Treatment for lung cancer

For all patients, the diagnosis of primary lung cancer was defined on the basis of the clinicopathological findings. We excluded metastases from the EC by sampling lung tissue preoperatively, comparing these two sets of pathological findings by referring to immunohistochemical staining. Each patient underwent spirometry, electrocardiography and arterial blood gas analysis to evaluate the operative risk. The predicted postoperative (ppo) forced expiratory volume in 1 s (FEV₁) was calculated using the formula

\[
\text{ppoFEV₁} = \left( \frac{\text{preoperative FEV₁}}{19} \right) \times \left( \frac{1}{S} \right)
\]

where \( S \) represents the number of bronchopulmonary segments to be removed, and 19 is the total number of bronchopulmonary segments in both lungs [3].

3. Results

The two malignancies were detected synchronously in one patient and metachronously in five, with a mean tumor-free interval of 25 months (range 3–71 months). In the patients with metachronous disease, second malignancies were all detected on the follow-up chest computed tomography scans after the patients had undergone CRT for EC. The median age of the patients at time of the lung cancer surgery was 75 years (range 69–80 years). The surgical results are shown in Table 2. The mean preoperative FEV₁ and (FEV₁%) were 1.73 l (range 1.31–2.24 l) and 69% (range 52%–78%), respectively. All patients had a ppoFEV₁% of > 40%. Although one patient (case 4) showed poor pulmonary function after CRT (ppoFEV₁% of 36%), the patient’s pulmonary function improved after preoperative treatment with tiotropium, a long-acting inhaled anticholinergic drug, and pulmonary rehabilitation for three months (ppoFEV₁% of 45%). The preoperative clinical stages of lung cancer were all IA. The median time from the end of radiation to pulmonary resection was 26 months (range 7–70 months).

Table 2. Perioperative results

<table>
<thead>
<tr>
<th>Case</th>
<th>Location of lung cancer</th>
<th>Preoperative pulmonary function</th>
<th>Pulmonary resection/lymph node dissection</th>
<th>Operation time (min)</th>
<th>Blood loss (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>FVC (l) FEV₁ (l) ppoFEV₁%</td>
<td>VATS segmentectomy/mediastinal nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.</td>
<td>Left upper</td>
<td>2.55 1.45 68%</td>
<td>VATS segmentectomy/mediastinal nodes</td>
<td>130</td>
<td>145</td>
</tr>
<tr>
<td>2.</td>
<td>Left upper</td>
<td>2.75 2.01 68%</td>
<td>VATS segmentectomy/mediastinal nodes</td>
<td>151</td>
<td>20</td>
</tr>
<tr>
<td>3.</td>
<td>Left lower</td>
<td>3.04 2.24 70%</td>
<td>VATS segmentectomy/mediastinal nodes</td>
<td>105</td>
<td>50</td>
</tr>
<tr>
<td>4.</td>
<td>Right upper</td>
<td>2.72 1.42 45%</td>
<td>Open lobectomy/mediastinal nodes</td>
<td>257</td>
<td>500</td>
</tr>
<tr>
<td>5.</td>
<td>Right upper</td>
<td>3.17 2.09 68%</td>
<td>VATS lobectomy/mediastinal nodes</td>
<td>130</td>
<td>150</td>
</tr>
<tr>
<td>6.</td>
<td>Right lower</td>
<td>1.67 1.31 78%</td>
<td>VATS segmentectomy/none</td>
<td>150</td>
<td>140</td>
</tr>
</tbody>
</table>

FEV₁, forced expiratory volume in 1 s; FVC, forced vital capacity; ppo, predicted postoperative; VATS, video-assisted thorascopic surgery.
Table 3. Postoperative results

<table>
<thead>
<tr>
<th>Case</th>
<th>Histology</th>
<th>Pathological stage</th>
<th>Postoperative hospital stay (days)</th>
<th>Postoperative complications</th>
<th>Prognosis (month)/dead (D) or alive (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Sq</td>
<td>IA</td>
<td>7</td>
<td>Arrhythmia</td>
<td>28/D</td>
</tr>
<tr>
<td>2</td>
<td>Sq</td>
<td>IA</td>
<td>8</td>
<td>None</td>
<td>13/A</td>
</tr>
<tr>
<td>3</td>
<td>Ad</td>
<td>IA</td>
<td>13</td>
<td>None</td>
<td>73/A</td>
</tr>
<tr>
<td>4</td>
<td>Ad</td>
<td>IA</td>
<td>12</td>
<td>Emphyema</td>
<td>13/A</td>
</tr>
<tr>
<td>5</td>
<td>Sq</td>
<td>IA</td>
<td>7</td>
<td>None</td>
<td>60/A</td>
</tr>
<tr>
<td>6</td>
<td>Sq</td>
<td>IA</td>
<td>7</td>
<td>None</td>
<td>22/D</td>
</tr>
</tbody>
</table>

Ad, adenocarcinoma; Sq, squamous cell carcinoma.

Video-assisted thoracoscopic surgery (VATS) was attempted in all patients. The VATS procedure has been preferred in our institution because of its minimal invasiveness. Our VATS procedure has meant a surgical approach of video-assisted minithoracotomy without rib sparing. Segmentectomy was performed on four patients and lobectomy was performed on two. Application of our segmentectomy means that an anatomical segmentectomy includes individual dissection and stapling of the involved pulmonary vein, artery and segmental bronchus, as well as appropriate management of the hilar lymph nodes. In our institution, lobectomy has been the standard treatment for early-stage non-small cell lung cancer, and segmentectomy has been typically performed for high-risk patients whose tumor has existed in a peripheral region. Although segmentectomy was attempted in all six cases because the patients had histories of EC and were thought to be high-risk patients after thoracic radiation, the lung tumor in cases 4 and 5 existed in a non-peripheral region, so lobectomy was performed on these patients.

Because of tissue fibrosis after thoracic radiation, mediastinal lymph node dissection could not be performed in one patient (case 6), and VATS was converted to open thoracotomy in another patient (case 4). To avoid a bronchopleural fistula, bronchial stump coverage with pericardial fat tissue was undertaken in one patient (case 4). The median operation time and blood loss were 140 minutes (range 105–257 minutes) and 142 ml (range 20–500 ml), respectively. Histopathological diagnoses of primary lung cancer were obtained in all patients, consisting of squamous cell carcinoma in four patients and adenocarcinoma in two. Postoperatively, all were stage IA.

Postoperative complications occurred in two patients, and included arrhythmia (case 1) and emphyema (case 4) (Table 3). There was no operative mortality. The patient who had pericardial effusion after CRT for EC (Fig. 1) underwent pericardial fenestration at the time of pulmonary resection (Fig. 2) and left our hospital 12 days after the operation. However, 30 days after surgery, a febrile pleural effusion appeared and developed into empyema.

At a median follow-up period of 25 months after lung cancer surgery, four patients were alive and two had died of EC recurrence.

4. Discussion

The proportion of patients receiving curative CRT for EC has been increasing. Late toxicities after CRT for EC include radiation pericarditis, heart failure, pleural effusion and radiation pneumonitis [4]. The influence of CRT, especially for thoracic radiation, on pulmonary function and mediastinal structure is unclear, and no reports about the safety of lung cancer surgery after CRT for EC have been published.

In contrast, pulmonary resection after induction CRT for primary lung cancer has been reported to be associated with a high morbidity and mortality [5]. However, recent data have demonstrated both its feasibility and its effectiveness in the treatment of patients with locally advanced lung cancer [6, 7]. Postoperative complications related to...
mortality after induction CRT include severe pneumonia, adult respiratory distress syndrome, cardiovascular event and pulmonary embolism, and those related to morbidity include arrhythmia, pneumonia, atelectasis and broncho-pulmonary fistula [8]. These postoperative complications after induction CRT would not be consistent in CRT for EC because of three dissimilarities: the administered dose of radiation, the interval between radiation and surgery, and the radiation field.

Although the curative dose of radiation for EC has reached 60 Gy, the induction dose of radiation for lung cancer has conventionally been limited to 40–50 Gy because of early reports of unacceptable morbidity and mortality when lung resection was performed after 60 Gy of radiation [5]. Recently, the conventional limitation on the induction radiation dose has been challenged, and several studies have reported the feasibility of this method with induction doses exceeding 59 Gy [9]. The lower complication rate in these studies may be attributable to the improvements in radiation techniques and perioperative management.

The second dissimilarity between induction CRT and esophageal CRT is that the majority of lung cancer surgeries are performed at a later time than the optimal period of 4–8 weeks after radiation administration in esophageal CRT. In our series, the median time from the end of radiation to pulmonary resection was 26 months (range 7–70 months). In one patient (case 4), the time from radiation to surgery was 22 months, and a conversion from VATS to open thoracotomy was required owing to dense fibrotic tissue around the major vessels following thoracic radiation (Fig. 3). In another patient (case 6), the time from radiation to surgery was 26 months, and mediastinal lymph node dissection could not be performed owing to mediastinal tissue fibrosis. In general, the fibrotic response to radiation is more progressed after a delayed interval [10]. In a rat model, the early postradiation phase (6–12 weeks) is characterized by parenchymal and vascular inflammation, and the late phase (34–38 weeks) is characterized by fibroblast hypercellularity and collagen deposition [11]. As a result of similar changes that occurred in our patients, tissue around the major vessels and mediastinal lymph nodes was hard and hemorrhagic, and we experienced difficulties in dissecting them.

The third dissimilarity is the field of radiation. In esophageal CRT, the target of radiation exists on the mediastinum, and the mediastinal organs are primarily influenced. Ishikura et al. reported that the incidence of grade 3 or higher pericarditis after esophageal CRT was 10%, and the incidence of grade 2 or higher pleural effusion was 19% [4]. They reported that the main cause of benign pleural effusion after thoracic radiation is thought to be lymphatic obstruction resulting from mediastinal fibrosis, and it may be related to heart disease, such as heart failure and pericardial effusion [4]. In our series, one patient had a pericardial effusion due to radiation pericarditis and required pericardial fenestration at the time of pulmonary resection. After surgery, a massive pleural effusion appeared and developed into empyema. Therefore, meticulous postoperative care, such as sufficient chest tube drainage, will be required to avoid postoperative complications, especially in patients who have a late toxicity related to esophageal CRT, such as radiation pericarditis.

Both meticulous postoperative care and preoperative management are essential. A postoperative FEV1% of <60% is a predictor of complications and respiratory morbidity, and the lower limit of postoperative FEV1% is 40% [12–14]. In our series, all patients had a ppoFEV1% of <40%. In a patient with a poor preoperative pulmonary function test result (case 4), pulmonary rehabilitation and tiotropium were applied in the perioperative period, and the ppoFEV1% improved from 36% to 45%. Tiotropium is the preferred maintenance therapy for patients with chronic pulmonary obstructive disease, and its efficacy in the perioperative period has been demonstrated in recent studies [15]. Because of the small number of patients, our study did not lead to a definitive conclusion. However, our experience suggests that lung cancer surgery after curative CRT for EC is feasible in carefully evaluated patients. The surgical problem lies in the difficulty of mediastinal lymph node dissection due to tissue fibrotic changes after thoracic radiation, and meticulous perioperative care will be needed to avoid postoperative complications, especially in those patients who have a late toxicity related to esophageal CRT, such as radiation pericarditis.

References


