Combined Resection of Great Vessels or the Heart for Non-Small Lung Cancer

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Objectives: The surgical indications for non-small cell lung cancer (NSCLC) infiltrating a great vessel or the heart are controversial. We assessed clinical features and surgical outcomes of patients with non-small cell lung cancer who underwent combined resection of a lung and great vessel.

Methods: Fourteen patients underwent great vessel resection under a lobectomy (n = 9), sleeve lobectomy (n = 2), or pneumonectomy (n = 3) between 2000 and 2011, in whom the aorta was resected in 6, superior vena cava in 5, right atrium in 1, and left atrium in 2. The histological types were adenocarcinoma (n = 8) and squamous cell carcinoma (n = 6).

Results: Complete resection was performed in 12 patients. Of all patients, 7 had pN0 disease, 2 had pN1, and 4 had pN2. The postoperative morbidity rate was 28.6% and mortality rate was 7.1%. The 5-year survival rate was 26.8% for all patients, 46.9% for those with an adenocarcinoma, 0% for those with a squamous cell carcinoma, 53.6% for those with pN0, and 0% for those with pN1-2.

Conclusion: Resection of the great vessels and heart involved by NSCLC can be performed with acceptable morbidity and mortality, and results in prolonged survival in patients, with an adenocarcinoma or N0 status.

Keywords: non-small cell lung cancer, great vessels, heart, extended resection

Introduction

Lung cancer causes the highest number of cancer-related deaths. However one-third of patients with non-small cell lung cancer (NSCLC) can be assessed as operable candidates. Despite the major morbidity caused by thoracic tumors involving either the heart or great vessels, most patients are not offered surgical resection because of technical considerations, concerns regarding postoperative morbidity and mortality, or the negligible impact on survival.1) Although many authors have reported favorable results of surgical operations for T4 NSCLC infiltrating a great vessel, surgical indication for combined resection of a great vessel remains controversial.2) In the present study, we assessed clinical features and outcomes of NSCLC patients who underwent a radical resection for primary lung cancer and an infiltrated great vessel.

Materials and Methods

Between 2000 and 2011, 14 patients with NSCLC underwent lung surgical resection combined with resection of a great vessel or the heart at the Department of General Thoracic Surgery, Osaka University Graduate School of Medicine. Great vessels were defined as the aorta, superior vena cava, inferior vena cava, main pulmonary
artery, intrapericardial portions of the pulmonary artery, and intrapericardial portions of the superior and inferior pulmonary veins, based on the tumor-node-metastasis (TNM) classification of the International Association for the Study of Lung Cancer, 7th edition. Eight were classified as stage IIIA and 6 as stage IIIB. Preoperative evaluations showed that 10 patients had cancer with great vessel invasion by direct tumor extension (aorta invasion in 4, superior vena cava in 3, aorta and intrapericardial pulmonary artery in 1, right atrium in 1, left atrium in 1) and 2 by metastatic lymph nodes (superior vena cava in 1, left atrium in 1), while 2 had no invasion of a great vessel (Table 1).

Nine patients diagnosed as either cT4 or cN2 received preoperative induction therapy, of whom 5 underwent chemoradiotherapy and 4 chemotherapy. The regimen of chemotherapy was cisplatin-based doublet in 5 patients, carboplatin-based doublet in 3, and both sequentially in 1. Radiotherapy was started on the first day of chemotherapy and a total radiation dose of 40 Gy was planned using conventional fractionation, with dose escalation allowed up to 60 Gy. All 9 of these patients were restaged after completion of induction therapy, with down-staging obtained in 4 (Table 2), and the period from preoperative therapy to surgery in the present patients ranged from 4 to 8 weeks.

Nine patients underwent a lobectomy, 3 a pneumonectomy, 1 a sleeve lobectomy, and 1 a sleeve bi-lobectomy (Table 2). Combined resection of the lung with a single additional organ was performed in 13 patients and 2 additional organs in 1. The aorta was resected in 6 patients (including aortic tunica adventitia in 1), superior vena cava in 5, left atrium in 2, intrapericardial portion of the left pulmonary artery in 1, and right atrium in 1. Seven patients who underwent resection of the aorta, or right or left atrium needed a cardio-pulmonary bypass. In the case with a resected aortic tunica adventitia, that was done after insertion of an aortic endostent.

Statistical analyses were performed using JMP for Windows (version 9; SAS Institute Inc., Cary, North Carolina, USA). Survival curves were calculated by the Kaplan-Meier method and tests for significance were based on log rank test results. Preoperative and postoperative characteristics were examined as prognostic factors by univariate analyses. Characteristics examined as variables were procedure (lobectomy including sleeve lobectomy and bi-lobectomy vs. pneumonectomy), resected organ, use of cardio-pulmonary bypass, induction therapy, downstaging following induction therapy, pattern of infiltration, preoperative lymph node status (c/ycN), histological type, and pathologic lymph node status.

### Results

The surgical approach was hemi-clamshell approach used in 8 patients and posterolateral thoracotomy in 6. The reconstruction methods were graft replacement in 5 patients, a Hemashiel vascular graft for Aortic reconstruction in 5, a ringed Gore-Tex graft for superior vena cava (SVC) reconstruction in 3, direct closure of the SVC in 2 and of the atrium in 2, bovine pericardium repair in of the atrium 1, and aortic endostent placement in 1 (Table 2). Nodal dissection (ND) 2a-1 was performed in 4 patients, and ND2a-2 in 10. Twelve patients underwent complete resection, while there was one case of incomplete resection due to a locally residual tumor in the resection margin of the aorta and one that showed extra-capsular invasion from lymph node metastasis. Major postoperative complications occurred in four patients, including one who needed re-exploration for postoperative hemorrhage, 1 with a prolonged air leakage, one with recurrent nerve paralysis, and 1 with a bronchus-right pulmonary artery fistula that caused death. The morbidity and mortality rates were 28.6% and 7.1%, respectively. Finally, 10 patients were histopathologically evaluated as pT4 status with infiltration of a great vessel. In two patients with pT1a or pT2b status, a metastatic lymph node was involved in the superior vena cava.

| Table 1 Patient characteristics |
|--------------------------------|
| Age | 62.3 (48–74) |
| Sex | Male 13, Female 1 |
| Location | Right 6, Left 8 |
| Histology | Adenocarcinoma 8, Squamous cell carcinoma 6 |
| cstage | III A 8, III B 6 |
| Neoadjuvant therapy | Chemotherapy + Radiation therapy 5, Chemotherapy 4 |
| Surgical procedure | Lobectomy (including sleeve lobectomy) 11, Pneumonectomy 3 |
| Combined resection | Aorta 6, Superior vena cava 5, Left atrium 2, Right atrium 1 |
Table 2  Clinical feature and surgical outcome of patients

| Case | Histology/ pTNM status | Surgical Procedure/ Approach | Resected organ/ Reconstructive procedure | Invasion | cTNM status/ ycTNM status | ECC | Resection | Complication (≥ Grade III) | Recurrence | Outcome | Survival (years) |
|------|------------------------|-------------------------------|------------------------------------------|----------|---------------------------|-----|------------|----------------------------|------------|---------|------------------|
| 1    | Sq/ T4N0M0             | Lobectomy/ hemiclamshell     | right atrium/ bovine pericardium repair  | direct   | cT4N2M0/ ycT4N2M0         | Y   | R0        | Hematoma                   | Y          | Dead    | 2.3              |
| 2    | Sq/ T2aN2M0            | Lobectomy/ posterolateral    | left atrium/ direct closure              | LN       | cT4N3M0/ ycT2aN2M0        | N   | R0        | none                       | Y          | Dead    | 1.1              |
| 3    | Sq/ T4N2M0             | Lobectomy/ posterolateral    | superior vena cava/ graft replacement    | direct   | cT2aN2M0/ ycT2aN2M0       | N   | R0        | Bronchu-PA fistula         | -          | Dead    | 0.1              |
| 4    | Sq/ T1aN2M0            | Lobectomy/ posterolateral    | superior vena cava/ graft replacement    | LN       | cT4bN2M0/-                | Y   | R0        | none                       | N          | Dead    | 2.2              |
| 5    | Sq/ T4N0M0             | Pneumonectomy/ hemiclamshell| Aorta/ graft replacement                  | direct   | cT4N1M0/ ycT4N2M0         | Y   | R0        | none                       | Y          | Dead    | 1.8              |
| 6    | Sq/ T4N1M0             | Pneumonectomy/ hemiclamshell| Aorta/ graft replacement                  | direct   | cT4N1M0/-                 | Y   | R0        | none                       | Y          | Dead    | 0.6              |
| 7    | Ad/ T4N2M0             | Lobectomy/ posterolateral    | superior vena cava/ direct closure       | direct   | cT4N2M0/ ycT4N2M0         | N   | R1        | none                       | Y          | Dead    | 3.3              |
| 8    | Ad/ T4N0M0             | Lobectomy/ hemiclamshell     | Aorta/ graft replacement                  | direct   | cT3N1M0/-                 | Y   | R0        | none                       | N          | Alive   | 9.8              |
| 9    | Ad/ T4N0M0             | Lobectomy/ hemiclamshell     | Aorta/ graft replacement                  | direct   | cT4N2M0/ ycT4N0M0         | Y   | R0        | recurrent nerve paralysis  | N          | Dead    | 4.7              |
| 10   | Ad/ T4N0M0             | Lobectomy/ hemiclamshell     | Aorta/ graft replacement                  | direct   | cT4N2M0/ ycT4N0M0         | Y   | R0        | none                       | N          | Alive   | 9.3              |
| 11   | Ad/ T4N1M0             | Lobectomy/ posterolateral    | Aortic tunica adventitia/aortic endovascular repairing | direct | cT4N1M0/ ycT4N1M0         | N   | R1        | none                       | Y          | Dead    | 2.4              |
| 12   | Ad/ T3N0M0             | Sleeve bilobectomy/ hemiclamshell | superior vena cava/ graft replacement  | none     | cT4N3M0/ ycT4N0M0         | N   | R0        | none                       | N          | Alive   | 6.5              |
| 13   | Ad/ T2bN2M0            | Sleeve lobectomy/ posterolateral | superior vena cava/ direct closure      | none     | cT4N0M0/-                 | N   | R0        | none                       | Y          | Dead    | 1.2              |
| 14   | Ad/ T4N0M0             | Pneumonectomy/ hemiclamshell| Aorta/ graft replacement                  | direct   | cT4N0M0/-                 | Y   | R0        | none                       | N          | Alive   | 3.8              |

ECC: extracorporeal circulation; Sq: squamous cell carcinoma; Ad: adenocarcinoma; Y: yes; N: no
Combined Resection of Great Vessels for Lung Cancer

The follow-up period after surgery for all patients ranged from 1.5 to 113 months (mean, 43 months). Seven patients had recurrent disease, with distant metastasis occurring in 4 and local recurrence in 3. Two patients died of non-lung cancer-related causes (esophagus cancer in 1, aorto-bronchial fistula 2 years after surgery in 1). The 5-year survival rate for all patients was 26.8%. Univariate analysis findings are shown in Table 3. There was a significant difference in prognosis between patients with c/ycN0 status and those with c/ycN1-2 status (37.5% vs. 20%) (Fig. 1A), patients with an adenocarcinoma and those with a squamous cell carcinoma (46.9% vs. 0%) (Fig. 1B), and patients with pN0 status and those with pN1-2 status (53.6% vs. 0%) (Fig. 1C). As for the resected organ, there was a significant difference in prognosis between patients who underwent aorta resection and those who underwent left or right atrium resection (44.4% vs. 0%) (Fig. 1D). In contrast, there was no significant difference in prognosis related to surgical procedure (27.3% in lobectomy), extracorporeal circulation (38.1% in cases with extracorporeal circulation vs. 14.3% in cases without extracorporeal circulation), down-staging by induction therapy (50.0% in cases with down-staging vs. 0% in cases without down-staging), or type of invasion (26.7% in cases with direct invasion vs. 0% in cases with lymph node invasion).

**Discussion**

Lung cancer infiltrating a great vessel has a poor prognosis, thus surgical resection is controversial for affected patients. Tsuchiya, et al. reported a hospital mortality rate of 13% and 5-year survival rate of 13% among 101

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**Table 3 Univariate analyses for the 5-year survival rate**

| Outcome | n | 5 year-survival (%) | MST (months) | P value |
|---------|---|---------------------|--------------|---------|
| **Surgical procedure** | | | | 0.68 |
| Lobectomy | 11 | 27.3 | 29 |
| Pneumonectomy | 3 | | 22 |
| **Resected organ** | | | | |
| Aorta | 6 | 44.4 | 57 |
| Superior vena cava | 5 | 20.0 | 26 |
| Others (left or right atrium) | 3 | 0 | 13 |
| **Extracorporeal circulation** | | | | 0.23 |
| Yes | 7 | 38.1 | 57 |
| No | 7 | 14.3 | 26 |
| **Neoadjuvant therapy** | | | | 0.9 |
| Yes | 9 | 22.2 | 29 |
| No | 5 | 40 | 26 |
| **Downstage by induction therapy** | | | | 0.062 |
| Yes | 4 | 50.0 | NR |
| No | 5 | 0 | 27 |
| **Type of invasion** | | | | 0.13 |
| Direct invasion | 10 | 26.7 | 34 |
| Lymph node invasion | 2 | 0 | 20 |
| **c/ycN status** | | | | 0.055 |
| c/ycN0 | 4 | 37.5 | 57 |
| c/ycN1-2 | 10 | 20 | 27 |
| **Histology** | | | | 0.0009 |
| Ad | 8 | 46.9 | 57 |
| Sq | 6 | 0 | 18 |
| **pN status** | | | | 0.0048 |
| pN0 | 7 | 53.6 | NR |
| pN1-2 | 7 | 0 | 14 |

MST: median survival time; NR: not reached; Ad: Adenocarcinoma; Sq: Squamous cell carcinoma
lung cancer patients who underwent extended resection of the left atrium, a great vessel, or both. Recently, Spaggiari, et al. found that the mortality rate and 5-year survival rate for patients with superior vena cava invasion were 12% and 21%, respectively, while Ohta, et al. reported rates of 12.5% and 48.2%, respectively, in patients with infiltration of the aorta. Our findings are consistent with those reports.

Few studies have examined differences based on histological type in cases with combined resection of a great vessel. Hsu, et al. noted that even though the rate for complete resection for squamous cell carcinoma was significantly higher in comparison with adenocarcinoma, the survival times were the same between those patients. In our experience, favorable prognosis is more easily obtained in patients with an adenocarcinoma than in those with a squamous cell carcinoma. It is probably because patients with squamous cell carcinoma had pN2 status or invasion of the pericardium such as extension to the right atrium, left atrium, or intrapericardial portion of the pulmonary artery. We had difficulties securing adequate excisional margins because of anatomical reasons in cases with a centrally located squamous cell carcinoma.

Some have reported that pathologic nodal status did not contribute to prognosis. On the other hand, Suzuki, et al. found a significant difference in survival between patients with superior vena cava invasion by metastatic lymph nodes as compared to direct tumor extension, whereas others have noted that patients with pN0 status had a good prognosis. In the present study, some c/cyN0

Fig. 1 (A) Overall survival rates for 14 patients with lung cancer with combined resection of a great vessel. The 5-year survival rate was 26.8%. (B) Cumulative survival curves based on cell type (solid line, adenocarcinoma [n = 8]; broken line, squamous cell carcinoma [n = 6]). Ad: Adenocarcinoma; Sq: Squamous cell carcinoma. (C) Cumulative survival curves based on pathologic node status (solid line, pN0 status [n = 9]; broken line, pN1-2 status [n = 5]). (D) Cumulative survival curves based on resected organ (solid line: aorta; broken line: superior vena cava; dotted line: left or right atrium). Ao: aorta; SVC: superior vena cava; LA: left atrium; RA: right atrium.
or pN0 status patients were long-term survivors after combined resection of a great vessel, while outcome was poor in patients with c/cyN1-2 or pN1-2 status or those with lymph node invasion to a great vessel. Although there was no significant difference between patients who did and did not obtain down-staging by induction therapy, patients down-staged from cN2-3 to ycN0 had no recurrence, thus long-time survival is possible in patients who achieve ycN0 status by induction therapy. Therefore, it is necessary to estimate nodal status before resection for good prognosis of patients with NSCLC requiring resection of great vessels.

There was a significant difference in prognosis between patients who underwent aortic resection and those who underwent a left or right atrium resection. Tumor invasion through the myocardium was seen in patients with a tumor invading the right or left atrium, whereas tumor invasion of the wall of aorta but not into the lumen was seen in patients with a tumor invading the aorta. Indeed, patients with a tumor invading the atrium suffered from early distant recurrence and died of cancer-related death. Although extracorporeal circulation did not affect prognosis, there is a possibility that circulating cancer cells from a tumor with transmural invasion will pass through the whole body via extracorporeal circulation. We usually tried to reduce this risk by avoiding pump suction and re-transfusion from cell-saving devices.

In one of the present cases, we attempted to perform a combined resection of the aortic tunica adventitia after aortic endovascular repairing in order to avoid extracorporeal circulation. However, tumor cells remained in the resection margin, which caused local recurrence. Some reports have shown the value of using an endostent to allow extended resection of the infiltrated aortic wall without the need for thoracic aorta cross-clamping and graft replacement. An aortic endovascular repairing may be a useful method in poor risk cases requiring resection of an infiltrated aortic wall when an adequate margin can be secured. We think that the resection of whole layer of the aortic wall is preferable in such cases.

In conclusion, resection of a great vessel or the heart because of NSCLC involvement can be performed with acceptable morbidity and mortality in patients with an adenocarcinoma or N0 status, and leads to prolonged survival in those with N0 status.

Disclosure Statement

The authors have no conflict of interest to declare.

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