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Original Article

Is Surgery after Chemoradiotherapy Feasible in Lung Cancer Patients with Superior Vena Cava Invasion?

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Purpose: The purpose of this study is to explore the possibility of surgery after chemoradiotherapy (CRT) for locally advanced-non-small-cell lung cancer (LA-NSCLC) with superior vena cava (SVC) resection in terms of prognosis and early and late postoperative course.
Methods: The medical records of NSCLC patients who underwent surgery after CRT at our institution between January 2001 and March 2016 were reviewed. We evaluated the feasibility of surgery with SVC resection after CRT.
Results: A total of 8 LA-NSCLC patients were enrolled in this study. The SVC management included a graft replacement in two patients, pericardial patch repair in two, and direct suture closure in four. A complete resection was achieved in seven of the eight patients (87.5%). Postoperative early and late complication rate (Clavien-Dindo classification ≥ grade III) was 25%. All the complications were manageable, and no treatment-related deaths occurred in this series. Although seven out of eight patients showed good patency of reconstructed SVC, one patient exhibited the SVC occlusion during long-term follow-up period. Regarding the prognosis, the 5-year overall survival (OS) rate was 60.0%, and the 2-year recurrence-free survival (RFS) rate was 75.0%.
Conclusion: Our results suggest that surgery with SVC resection after CRT is a feasible procedure in terms of clinical outcomes and postoperative course.

Keywords: chemoradiotherapy, non-small-cell lung cancer, superior vena cava

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Introduction

Lung cancer continues to be the leading cause of cancer mortality worldwide. Among patients with non-small-cell lung cancer (NSCLC), approximately half of them have locally advanced (LA) cancer at the time of their initial diagnosis.[1)] Invasion to mediastinal structures is a feature of LA-NSCLC, and among such invasive LA-NSCLC, reports describing surgical resection with the superior vena cava (SVC) reconstruction for LA-NSCLC have been gradually increasing in recent years. However, the prognostic outcomes of initial surgery for LA-NSCLC

invading the SVC remain unsatisfactory.[2–4] On the other hand, the outcomes of treatment without surgery, including definitive chemoradiotherapy (CRT), are also not favorable.[5,6] Thus, the optimal treatment for patients with LA-NSCLC invading the SVC in the thorax remains controversial, and new therapeutic strategies are mandatory.

Induction CRT is one of the therapeutic options for LA-NSCLC. Induction therapy is expected to eradicate micrometastatic disease at distant sites and to prevent cancer cell microresidues at local sites, facilitating complete resection.[7] Conversely, there is a concern that intensive treatment may increase the risk of subsequent surgery because it impairs bone marrow function and wound healing potential. Therefore, it is necessary to verify the effectiveness of induction CRT not only from the viewpoint of prognosis, but also from that of influence on organs, such as airway and vessels. We previously examined the feasibility of induction CRT for LA-NSCLC requiring the median sternotomy approach or bronchial reconstruction, and reported its usefulness.[8–10] In this study, we retrospectively investigated the clinical course of LA-NSCLC patients who have undergone surgery with SVC resection after receiving CRT, and discuss about its feasibility in terms of prognosis and postoperative course.

Patients and Methods

Patient selection and evaluation

The medical records of LA-NSCLC patients who underwent surgery after CRT were reviewed, and pertinent data were compiled. The patient inclusion criteria were an age of 75 years or younger, an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1 and adequate functional reserves of major organs, as described previously.[11] The study protocol was approved by the Institutional Review Board/Ethical Committee of Okayama University (#1608-505). The International Association for the Study of Lung Cancer TNM staging system for NSCLC, 7th edition, was used to determine the disease staging and nodal location.[12] Disease stage was assessed 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 and bronchoscopy. A staging cervical mediastinoscopy was undertaken to evaluate bilateral node stations 2 and 4 and subcarinal station 7, as necessary.[8] After the accomplishment of tri-modality treatment, the patients were followed according to our follow-up procedure.[8]

Induction therapy, surgery, and adjuvant treatment

In principle, patients who were diagnosed as having clinical stage III and satisfied the inclusion criteria received induction CRT followed by surgery.[8] Platinum-based chemotherapy with concurrent radiation at a dose of 40 Gy (1999–2000) or 46 Gy (2000–2016) was used for the induction CRT. For poorly responding patients, an additional radiation dose of up to 14 or 20 Gy was administered to the boost volume. The details of the chemotherapy dose, schedule modification, and radiotherapy protocol including the irradiated field for the thorax were described in our previous study.[13] For patients with clinical stage IV disease, systemic chemotherapy was selected as the initial treatment.

Following induction CRT, the responses of the patients were re-evaluated using imaging analyses. The radiological response was assessed using the ECOG criteria with certain modifications and was classified as either a complete response (CR), a partial response (PR), stable disease (SD), or progressive disease (PD).[14] Patients without PD were scheduled to receive surgery within 6 weeks of completing the induction CRT.

The surgical procedure was determined based on the disease extent. In particular, the extent of the combined resection was determined based on intraoperative findings, rather than preoperative images. As for the SVC resection, when tumor invasion to the SVC was less than 25% of the vessel circumference, a tangential resection with a direct repair using a Satinsky side clamp was preferred, and when tumor invasion was 25% or more and 50% or less, a patch repair was preferred. Tumors invading more than 50% of the SVC required the circumferential resection of the SVC and total replacement with a ringed polytetrafluoroethylene (PTFE) graft. The external shunt was prepared for patch repair and graft replacement after the heparinization. The bronchial stump was basically wrapped with the omental pedicled flap, pericardial fat pad, or muscle with prophylactic intent. While a posterolateral thoracotomy was used as the basic approach, a median sternotomy with or without a thoracotomy or a trap door approach was applied for patients with supraclavicular lymph node or contralateral mediastinal lymph node metastasis, for patients with a Pancoast-type tumor, or when the great vessels needed to be secured for a safe resection.[8,10] The details of our regular lymphadenectomy have been described previously.[8] The Clavien-Dindo classification was used to assess early and late postoperative complications.[15] Postoperative adjuvant treatment was left to the physician's discretion.

Statistical analysis

The overall survival (OS) and recurrence-free survival (RFS) rates were calculated from the date of the initiation of treatment until the date of death or the last follow-up for OS and until confirmed disease recurrence based on cross-sectional imaging studies or death for RFS. The survival curves were calculated using the Kaplan–Meier method, and differences between the groups were compared using a log-rank test. All the data were analyzed using JMP 9.0.0 for Windows (SAS Institute, Inc., Cary, NC, USA). Probability values less than 0.05 indicated statistically significant differences.

Results

Patient characteristics

Between January 2001 and March 2016, a total of 151 NSCLC patients underwent surgery after CRT at Okayama University Hospital. Among them, a total of eight NSCLC patients who underwent a radical surgery with SVC resection were included in this study. Some cases had already been reported in our previous study.[9,10] and the patient characteristics are shown in **Table 1**. The median patient age was 57 years (range: 39–72 years). The histological subtype was squamous cell carcinoma in four patients, adenocarcinoma in three, and adenosquamous carcinoma in one. Case #4 had a Pancoast-type tumor. Two patients with c-stage IV (Case #1 and Case #3) were included in this study. These patients had the possibility of having metastasis to the 5th lumbar vertebra (Case #1) and to the 6th rib (Case #3) based on the results of bone scintigraphy. As for Case #2, although only mediastinal lymph node swelling was observed, and the primary lesion was not detectable in the lung field during a pre-treatment imaging examination, a metastasis of NSCLC was diagnosed based on the pathological findings.

Chemoradiotherapy

Except for patients with stage IV, induction CRT was performed in six patients using docetaxel and cisplatin with concurrent thoracic radiation. Of the six patients, four patients completed the planned induction CRT. The radiation dose was 46 Gy in five patients, 40 Gy in one patients. The radiological response was PR in three patients and SD in three patients. For Case #1, concomitant therapy with docetaxel, cisplatin, and irinotecan was used for first-line chemotherapy. After the treatment, while the primary lesion and metastatic lymph nodes exhibited shrinkage, the intensity of the uptake in the initially suspected metastatic

Table 1 Characteristics of patients who underwent SVC resection after chemoradiotherapy

Case	Sex	Age	Histology	cStage	RT dose (Gy)	Resected lung	SVC management	Additional resection	Postoperative complication
1	M	39	Sq	IV	36	RUML	Direct suture closure		None
2	M	72	AdSq	IIIA[a]	46	None	Graft replacement		Graft occlusion (grade II)
3	M	39	Ad	IV	60	RUL	Direct suture closure	Phrenic nerve, S6	Empyema (grade IIIb), SVC occlusion (grade I)
4	M	54	Sq	IIIB	40	RUL	Direct suture closure	Rib, Clavicle, Sleeve, Brachial plexus	none
5	M	48	Sq	IIIA	46	RUL	Patch repair		AMI (grade IVa), Bronchial fistula (grade IIIb)
6	M	60	Ad	IIIB	46	RUL	Graft replacement	Phrenic nerve	None
7	F	64	Ad	IIIA	46	RUL	Direct suture closure		None
8	F	66	Sq	IIIA	46	RUL	Patch repair	Sleeve	None

Sq: squamous cell carcinoma; LC: large cell carcinoma; AdSq: adenosquamous carcinoma; Ad: adenocarcinoma; LUL: left upper lobe; RUML: right upper-middle lobe; RUL: right upper lobe; RMLL: right middle-lower lobe; LULL: left upper-lower lobe; SVC: superior vena cava; AMI: acute myocardial infarction; RT: radiation therapy

[a]The patients with TXN2M0 was classified as c-stage IIIA.

Table 2 Details of surgery

Variables	Value
Operation time (min) (Median, range)	483 (240–990)
Blood loss (mL) (Median, range)	1565 (270–3000)
Approach	
Lateral thoracotomy	2
Median sternotomy	5
Trap door	1
Lymph node dissection	
N2 level	7
N3 level	1
Invasion to cardiovascular system	
Main tumor	6
Metastatic lymph node	2
Coverage of bronchus	
Omentum	3
Pericardial fat	2
Muscle or thymus	2
None	1
Residual tumor	
R0/R1	7/1

lesion (5th lumbar vertebra) did not seem to be affected, suggesting that the uptake reflected osteoarthritis. Therefore, we aimed at a cure and applied low-dose cisplatin with concurrent thoracic radiation (36 Gy) followed by surgery. For Case #3, concomitant therapy with docetaxel and cisplatin was used for first-line chemotherapy. Following that therapy, sequential thoracic radiotherapy (60 Gy) and chemotherapy using vinorelbine were performed. As a result of the fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography/CT, the initially suspected metastatic lesion in the 6th rib was not pointed out. After a thorough informed consent, we performed a curative surgery.

The median time from the end of induction CRT until surgery was 39 days. The pathological response to CRT was classified into three categories: pathological CR, pathological major response, and pathological minor response.[14] Two patients exhibited a pathological CR, five patients exhibited a pathological major response, and one patient exhibited a pathological minor response.

Surgery

The characteristics of the surgical factors are shown in **Tables 1** and **2**. The surgical procedures included a lobectomy in four patients, a sleeve lobectomy in two patients, and a left pneumonectomy in one patient. In Case #2, only a mediastinal lymph node dissection was performed. A lateral thoracotomy was used for two patients, a median sternotomy was used for five patients, and a trap door approach was used for one patient. Combined resection of the SVC was required because of main tumor invasion in six patients, and metastatic lymph node invasion in two.

The details of SVC management are as follows: PTFE graft replacement, n = 2; pericardial patch repair, n = 2; direct suture closure, n = 4. In Case #4, reconstruction of both the SVC and the subclavian artery was required. Whereas the bronchial stump was usually covered with an omental pedicled flap or pericardial fat pad, no coverage after SVC repair was performed. The complete resection rate was 87.5% (7/8); one patient, Case #3, had an incomplete tumor resection with a microscopically positive surgical margin of the visceral pleura detached from the SVC.

Postoperative complications and adjuvant therapy

Major postoperative complications defined as equal or more than grade III with Clavien-Dindo classification developed in two patients (Case #3 and Case #5). The details of the postoperative complications are described in **Table 1**. One patient (Case #3) exhibited the SVC occlusion during long-term follow-up period. In Case #3, the main tumor located in the right upper lobe was extensively adhered to the SVC. To avoid the total replacement of the SVC, the tumor was dissected from the SVC as much as possible. A partial resection of the SVC was performed, and the defect was directly sutured. The early postoperative course was generally uneventful, and the patient was discharged from hospital on postoperative day 32. Concomitant therapy with carboplatin and paclitaxel was used for adjuvant therapy. While over 10 years have passed without a recurrence, empyema developed 9 years after the surgery. Although fenestration was performed, the empyema did not improve, and a completion pneumonectomy was eventually required. Furthermore, stenosis of the SVC gradually progressed during the treatment course, and the SVC ultimately became completely occluded. Follow-up CT images obtained during the first and ninth year after surgery are shown in **Figs. 1a, 1b**, and **1c**. In Case #5, the SVC had been infiltrated by a metastatic lymph node and was partially resected using an external shunt between the SVC and right atrium. The defect was repaired with a patch closure. After intensive care unit (ICU) admission, acute myocardial infarction caused by a coronary spasm occurred, and the patient suddenly went into cardiopulmonary arrest. The patient was rescued by cardiopulmonary resuscitation, but a bronchial stump fistula had developed.

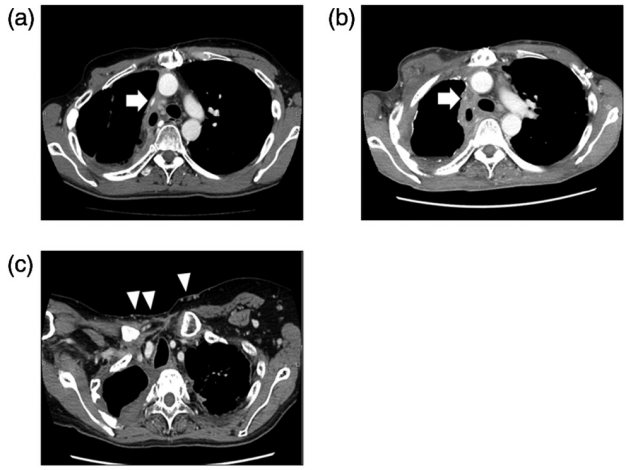

Fig. 1 Images of CT scan of patients in Case #4. (**a**) CT scan obtained 1 year after surgery shows mild stenosis of the SVC (arrow). (**b**) CT scan obtained 9 years after surgery shows severe stenosis of the SVC (arrow). (**c**) CT scan obtained 9 years after surgery shows extensive subcutaneous collateral circulation from the subclavian vein into the femoral vein (arrow head). CT: computed tomography; SVC: superior vena cava

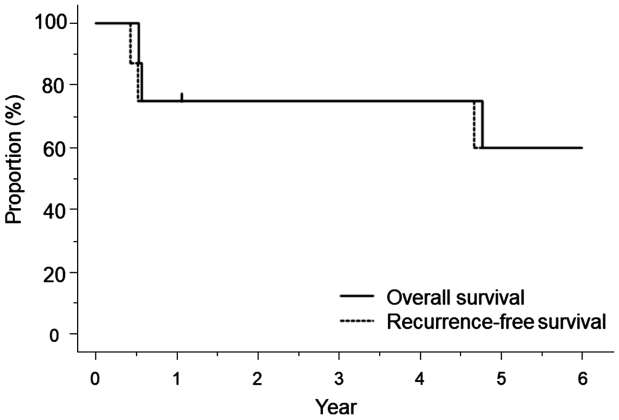

Fig. 2 Survival curves of patients who underwent surgery with SVC resection after CRT. CRT: chemoradiotherapy; SVC: superior vena cava

On postoperative day 2, an omentopexy was performed. The patient was finally discharged from hospital 49 days after the initial operation. Despite some serious complications, no treatment-related deaths occurred in this series. Of the eight patients, two patients received postoperative adjuvant chemotherapy.

Survival and pattern of relapse

At the time of data analysis in December 2016, a total of three patients had died because of NSCLC and one patient had died from another cause. The disease recurrence patterns were classified as loco-regional sites (e.g., surgical margin, intrapulmonary, regional lymph node, and pleural cavity) and distant sites. Disease relapse occurred in three patients, consisting of only a distant relapse in one patient, only a loco-regional relapse in one patient, and both distant and locoregional relapses in one patient at the time of the initial diagnosis of the relapse.

For the entire population, the 3-year and 5-year OS rates were 75.0% and 60.0%, respectively, and the 2-year RFS rates were 75.0% (**Fig. 2**). In this study, seven patients with N2 disease were included, and the 5-year OS and the 2-year RFS rates were 57.1% and 71.4%, respectively. Among the pathologically confirmed N2 patients, one patient (Case #5) was alive and the other (Case #2) had died from cancer-related reasons as of the end of the study. Case #2 had survived for 6 years since the initial surgery without a recurrence. However, a recurrence at the hilar lymph node occurred during the seventh year after surgery, and the patient died during the tenth year after surgery. Case #5 survived for more than 7 years after the initial surgery without experiencing a recurrence.

Discussion

In this study, we showed that radical surgery with SVC resection after CRT is a feasible procedure for patients with LA-NSCLC in terms of their early and late postoperative course and prognosis. Although the number of patients was too small to make a define conclusion, the clinical outcomes were relatively acceptable, and all the complications in this series were manageable. However, the prolonged operation time (median: 483 minutes) and heavy blood loss (median: 1565 mL) may have led to some severe postoperative complications, suggesting that this therapeutic strategy is still challenging and should be performed in experienced facilities.

One of the most important issues for the treatment of LA-NSCLC is to identify patients who are likely to benefit from surgery. Many retrospective studies of NSCLC invading thoracic great vessels have been published; however, the clinical outcomes remain unsatisfactory. Regarding the survival rate, AI-Ayoubi et al.[16] reported a review article about resected NSCLC that had invaded the mediastinum. In that paper, they mentioned the following survival rates according to invaded great vessels: 1) SVC; 5-year OS rate range between 11% and 31%. 2) Aorta; 5-year OS rate range 31% and 48%. 3) Left

atrium; 5-year OS rate range between 14% and 44%. 4) Main pulmonary artery; 5-year OS rate range between 41% and 46%. Thus, the prognosis of LA-NSCLC invading SVC is particularly poor, and our results suggest that the therapeutic strategy including preoperative CRT might help improve the treatment outcome. Some studies also have shown that the existence of N2 lymph node metastasis and an incomplete resection resulted in a poor patient outcome.[2,17–20] In our series, some patients with N2 lymph node metastasis achieved long-term survival. In particular, in Case #3, although the patient was diagnosed as having N2 lymph node metastasis and surgery after CRT resulted in an incomplete resection, the patient has survived for 12 years without a recurrence. Thus, the clinical outcomes of patients with N2 disease and an incomplete resection are not necessarily dismal in our cohort. Considering the rarity of cases, however, treatment standardization is difficult. Therefore, patients who are likely to benefit from surgery should be carefully selected so as not to overlook patients for whom a cure is potentially possible. Our good clinical outcomes may reflect an excellent patient selection, and we consider preoperative treatment, especially CRT, to be one of the most effective methods for patient selection.

Regarding postoperative course, five out of eight patients were able to follow-up for more than 4 years, and SVC occlusion occurred in one patient (Case #3). In this case, although the SVC already appears narrow at the first year after surgery, subcutaneous collateral circulation between the subclavian vein and the inferior vena cava occurred, suggesting that the stenosis of the SVC had gradually progressed. There are the following possible causes of the occlusion. The first cause is that the SVC management is not appropriate, and the other is the negative effect of CRT, especially radiotherapy. As in this case, if the invasion of the tumor to the SVC is widespread at the initial diagnosis, patch repair or graft replacement should be considered. As for the possibility of negative effect by CRT, radiation therapy itself is known to cause the stenosis or obstruction of arteries, including the carotid artery and coronary artery.[21–23] On the other hand, radiation-induced stenosis in veins is relatively rare, and only a few cases have been previously reported.[24–28] Among them, the cases with venous stenosis in vessels other than the peripheral vein are summarized in **Table 3**. In all the cases, no evidence of local tumor recurrence was seen. Regarding the treatment methods, stenting was eventually required in most of the cases. On the other hand, in case with the development of sufficient collateral circulation, such as in our case, invasive treatment may be

Table 3 Previously reported cases of vein stenosis

Author, year	Age	RT dose (Gy)	Period before onset	Vein	Thrombosis	Symptom	Collaterals	Treatment
Van Putten JW, et al. 2000	47	60	5 year	SVC	–	+	+	Anticoagulation, stenting
	36	70	7 year	BCV	–	+	+	Anticoagulation
Zhou W, et al. 2004	75	ND	16 month	EIV, CFV	+	+	–	Anticoagulation, thrombectomy, Stenting
Tsuruga Y, et al. 2013	54	50.4	9 month	PV	–	+	–	Stenting
	44	50.4	5 month	PV	–	+	+	Stenting
	68	50.4	5 month	PV	–	+	–	Stenting
Elias HK, et al. 2015	55	50.4	6 month	CFV	+	+	+	Anticoagulation, thrombectomy Stenting
Our case	39	60	9 year	SVC	–	+	+	None

SVC: superior vena cava; BCV: brachiocephalic vein; EIV: external iliac vein; CFV: common femoral vein; PV: portal vein; RT: radiation therapy

unnecessary. Van Putten et al. also reported a case with extensive collateral circulation that was treated using only prophylactic anticoagulation therapy, which resulted in an improvement of the patient's symptoms. A standard treatment has not yet been decided, and appropriate treatment should be selected on an individual basis.

As limitations of this study, the small number of patients limits the utility of the statistical analysis, and the overall patient numbers are too small to make definite conclusions. In terms of prognosis, the follow-up period was not long enough to determine the final survival rate. These factors could be sources of potential bias in our results.

Conclusion

In conclusion, our results suggest that surgery with SVC resection after CRT is a feasible procedure and that CRT might be the most effective strategy for patient selection. We believe that aggressive treatment for locally extended disease is a possible therapeutic option.

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Katsuyuki Kiura had honorarium from Astra Zeneca, Ono Pharmaceutical, Boehringer-Ingelheim, Astellas, BMS, Taiho Pharmaceutical, Chugai Pharmaceutical, Novartis, Eli Lilly Japan and MSD.

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No other authors have conflict of interest to declare.

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