**Review
Article**

Current Topics on Salvage Thoracic Surgery in Patients with Primary Lung Cancer

Hidetaka Uramoto

Salvage primary tumor resection is sometimes considered for isolated local failures after definitive chemoradiation, urgent matters, such as hemoptysis (palliative intent), and in cases judged to be contraindicated for chemotherapy or definite radiation due to severe comorbidities, despite an initial clinical diagnosis of stage III or IV disease. However, salvage surgery is generally considered to be technically more difficult, with a potentially higher morbidity. This review discusses the current topics on salvage thoracic surgery such as the definition of salvage surgery and its outcome, and future perspectives.

Keywords: salvage, thoracic, operation, lung cancer

Introduction

Lung cancer remains a leading cause of death worldwide.¹⁾ However, advanced non-small lung cancer (NSCLC), which is the most prevalent type of lung cancer, is not generally indicated for surgery as a radical cure, and systemic chemotherapy is the mainstay of treatment.²⁾ For instance, medical treatment is not well-defined in stage III, contrary to stage I/II patients. One of the reasons is diversity in therapeutic approaches for various subgroups.²⁾ Thus, chemoradiation (CRT) generally remains the gold standard for stage III disease. However, select patients may benefit from surgery. We previously reported that induction chemoradiotherapy followed by surgery for locally advanced NSCLC provided a favorable prognosis for select patients. A complete pathological response was found in approximately half of the cases.³⁾ Therefore, these phenomena suggest that surgery may be effective for

curative intent. Furthermore, stage IIIB and IV NSCLC are generally considered to be contraindicated for surgery, similar to breast cancer.⁴⁾ However, salvage operations are occasionally performed under certain conditions in patients with advanced colon cancer⁵⁾ and esophageal cancer,⁶⁾ in addition to malignant thymoma.⁷⁾ Nonetheless, there is a paucity of information regarding salvage surgery in patients with primary lung cancer, and the efficacy and safety of salvage thoracic operations have not yet been fully elucidated. This review discusses the clinical significance of surgery, current provisions for treatment and perspectives regarding salvage surgery for patients with lung cancer.

The definition of salvage thoracic surgery

In a narrow sense, salvage thoracic surgery is interpreted as surgical resection of persistent or recurrent primary lung tumors after previous local treatments. Bauman et al.⁸⁾ described that most common reasons for a salvage operation are obvious relapse by computed tomography (CT), persistently abnormal fluorodeoxyglucose-positron emission tomography (FDG-PET) findings after completion of radiotherapy, and a delayed decision to convert to a trimodal approach. However, in a wider sense,⁹⁾ salvage thoracic surgery can be defined as surgical resection of persistent or recurrent primary lung tumors after previous local treatments, in addition to urgent matters such as hemoptysis (**Table 1**).

Division of Thoracic Surgery, Saitama Cancer Center, Kita-adachi-gun, Saitama, Japan

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Corresponding author: Hidetaka Uramoto. Divisions of Thoracic Surgery, Saitama Cancer Center, 780 Komuro, Ina, Kita-adachi-gun, Saitama 362-0806, Japan
Email: hidetaka@cancer-c.pref.saitama.jp
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Table 1 The definition of salvage thoracic surgery

Narrow sense	Wider sense
<ul style="list-style-type: none"> • Obvious local relapse, defined by CT/ FDG-PET imaging • Delayed conversion to trimodality • Chronic bronchopleural fistula 	<ul style="list-style-type: none"> • Persistent or recurrent primary lung tumors after previous local treatment • A matter of urgency, such as hemoptysis (palliative intent)

CT: computed tomography; FDG-PET: fluorodeoxyglucose-positron emission tomography

Accumulation of scientific knowledge

This study searched PubMed, a service of the National Library of Medicine (<http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) to identify and extract information published since 2000 regarding salvage thoracic surgery in patients with primary lung cancer. The search focused on the keywords including salvage, thoracic, operation, and lung cancer. The search identified 53 English reports. Furthermore, I added the some reports which think they are qualified for citation. Eventually, eleven papers (cases series) including various treatment methods before salvage surgery were identified (**Table 2**).^{8–18)} These studies were all retrospective in nature and performed at a single institution. Furthermore, there were imbalances in the patients' characteristics that cannot be excluded due to the small number of patients. Nevertheless, the studies highlighted an important issue, that surgery should be performed safely, which will be discussed in greater detail in the following sections.

Morbidity and Mortality

The extent of surgical resection was lobar or greater in 130 patients (101 lobectomies and 29 pneumonectomies) and sub-lobar in 6 (four segmentectomies and two wedge resections). The postoperative stay was not long in any of the previous reports. Furthermore, the postoperative stay and total hospital stay in our salvage surgery cases were not much longer than those previously reported in the other cases, despite a higher incidence of advanced stage disease in our previously reported salvage cases.⁹⁾ Additionally, although the patients are generally in relatively good conditions, because salvage surgery often requires a long operation, such as extended vascular or pulmonary resection, it might result in high postoperative morbidity rates.⁷⁾ However, the mortality was surprisingly low. This phenomenon might include a cautious patient selection and publication bias. Thus, salvage pulmonary resection can be successfully performed, and a salvage operation might be considered to be reasonable and proper treatment for carefully selected patients.⁹⁾

Event-free survival

We require dividing thought with respect to survival. Because they have a difference of treatment results between salvage surgery after stereotactic body radiation therapy (SBRT) for patients with early stage lung cancer and that after definitive chemoradiation for those with advanced stage cancer. Phillip et al. reported that aggressive thoracic therapy (defined as surgical resection of the primary disease or radiotherapy at a dose greater than 45 Gy) in 38 NSCLC patients with 1–4 synchronous brain metastases was associated with a significantly prolonged overall survival (OS) concerning the former.¹⁴⁾ Furthermore, five patients who underwent salvage lung resection for early-stage NSCLC after stereotactic body radiation therapy (SBRT) were successfully treated, and all patients were alive after a median follow-up of 27 months,¹¹⁾ which was consistent with the results of another report.¹³⁾

On the other hands, Bauman et al. described that the median progression-free survival (PFS) and OS of their patients were 12 and 30 months concerning the latter, respectively.⁸⁾ Yang et al. also showed that the median PFS and OS were 10.3 and 32.5 months, respectively.¹⁸⁾ These results indicate that salvage lung resection after definitive chemoradiation is feasible, with an encouraging survival. The median recurrence-free survival (RFS) after surgery was reported to be just 6 months after response to gefitinib administration.¹⁰⁾ The mean event-free survival (EFS) was reported to be 5.9 months according to our previous data,⁹⁾ which was consistent with other reports.¹⁵⁾ However, these results are difficult to compare due to differences in the patient selection; thus the clinical significance of salvage surgery remains controversial. However, performing a salvage operation might be feasible with appropriate patient selection because the median survival by other modalities, such as subsequent radiation or chemotherapy, is less than 1 year for recurrent lung cancer.^{19,20)} Therefore, salvage surgery should not necessarily be dismissed in patients previously deemed to be medically inoperable.¹³⁾ A careful patient

selection combined with surgical expertise can allow for successful salvage surgery with minimal morbidity.¹³⁾

Perspective

There are several limitations associated with this review. First, all data were retrospectively collected and the study was performed at a single institution. Furthermore, due to the small sample size, the results should be interpreted with caution. To overcome these limitations, prospective studies in a larger cohort of patients and at different institutions are necessary to clarify the efficacy of salvage surgery. A detailed examination of a prospective trial can produce new information about the patient selection and the relationships between the survival and timing of surgery, as well as the therapeutic effects in pathological specimens. Salvage thoracic surgery might represent an alternative treatment option for select patients due to the development of new pharmaceuticals to repress the systemic tumor burden.

Disclosure Statement

There were no conflicts of interest or financial interests for the author.

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Table 2 The outcome of patients who underwent salvage surgery

Authors (year)	No. pts. (percentage for all cases)	Surgical procedure ^a	Postoperative stay (median: days)	Morbidity (%)	Mortality (%)	EFS ^b (median: months)
Bauman et al. (2008)	24	L: 14, P: 10	n.d	58	4	12
Hishida et al. (2008)	9	L: 7, P: 2	9	11.1	0	6
Chen et al. (2010)	5 (3.5)	L: 5	n.d	0	0	Disease free after 27 months
Neri et al. (2010)	7 (8.6) (5 cases: metastatic cancer)	L: 6, Seg: 1	n.d	14.3	0	2-39
Allibhai et al. (2012)	4 (1.9)	L: 4	n.d	0	0	Disease free after 30 months
Phillip et al. (2013)	19	n.d	n.d	n.d	n.d	n.d
Kuzmik et al. (2013)	14 (5.7)	W: 1, Seg: 2, L: 9 P: 2	10	43	0	33 (after CRT)
Uramoto et al. (2014)	8 (2.3)	W: 1, Seg: 2, L: 4, P: 1	16	n.d	0	5.9
Suzuki (2015)	32 (2.4)	L: 19, P: 11, unknown: 2	n.d	37.5	0	n.d
Mizobuchi et al. (2015)	12 (2.0)	L: 8, P: 3, Exploratory thoracotomy: 1	n.d	0	0	20
Yang et al. (2015)	31	L: 31	n.d	48	0	10.3

^aW: wedge resection; Seg: segmentectomy; L: lobectomy; P: Pneumonectomy; ^bEFS: event free survival; n.d: not described; CRT: chemoradiation

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