Results of emergency salvage lung resection after chemo- and/or radiotherapy among patients with lung cancer

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Received in revised form 7 January 2022; accepted 31 January 2022

Abstract

OBJECTIVES: This study aimed to elucidate the outcomes of emergency salvage surgery following life-threatening events (serious haemorrhage and/or infections) among patients with lung cancer who had undergone chemo- and/or radiotherapy.

Materials and Methods: We analysed the data of patients from 2015 to 2020, retrospectively. The clinical characteristics, including preoperative treatment, perioperative outcomes and survival time, were analysed.

RESULTS: Of the 862 patients who underwent primary lung cancer surgeries, 10 (1.2%) underwent emergency surgeries. The preoperative clinical characteristics were: median age, 63.7 years [interquartile range (IQR) 55–70.5]; sex (male/female), 9/1; clinical staging before initial treatment (I/II/III/IV), 1/1/3/5; initial treatment (chemoradiotherapy/chemotherapy/proton beam therapy), 5/4/1; and indications for emergency surgery (lung abscess/lung abscess with haemoptysis/haemoptysis/empyema), 5/3/1/1. The selected procedures and results were as follows: lobectomy/bilobectomy/pneumonectomy, 8/1/1 (all open thoracotomies); median operation time, 191.0 min

Presented at the 29th European Conference on General Thoracic Surgery, 20–22 June 2021 (VIRTUAL).
surgery 

In selected conditions, we performed an emergency salvage lung resection for the purpose of saving lives has not been elucidated, to date. Therefore, this study aimed to evaluate not only the feasibility but also the postoperative survival outcomes of emergent palliative salvage surgery in lung cancer patients with life-threatening haemoptysis and/or infections following chemo- and/or radiotherapy.

**MATERIALS AND METHODS**

**Ethics statement**

It was conducted in accordance with the Declaration of Helsinki and the Research Review Board at Kansai Medical University, Osaka, approved this study on 22 September 2021 (approval number 2021132). The requirement to obtain informed consent was waived.

This study was conducted retrospectively, using the clinical database of a single institution. The clinical data that were gathered included age, sex, initial treatment, aetiology of emergent condition, operative procedure, amount of bleeding, operative time, preoperative clinical and postoperative pathological stages, histological findings, postoperative complications, survival time and postoperative additional therapy. The inclusion criteria for emergency salvage surgery were as follows: patients who underwent definitive chemoradiotherapy or chemotherapy alone for locally advanced lung cancer or radiotherapy for early-staged lung cancer, as an initial treatment due to inoperable poor general condition or the desire of the patient (excluding those who received induction chemoradiotherapy followed by surgery); patients who had life-threatening complications, which could not be treated medically (e.g. haemoptysis from residual tumour, uncontrollable infection following tumour necrosis, empyema); and those who needed an emergency lung resection. The preoperative indications and optimal timing were discussed in multidisciplinary conferences or short additional meetings. All the included patients were treated previously by the thoracic oncology department of internal medicine and/or radiology department at our institute. Preoperative severe life-threatening events and postoperative complications were obtained retrospectively from a chart view with the latter being defined according to the Clavien–Dindo classification [15]. Overall survival (OS) time was calculated as the time from the date of initial treatment or surgery to the date of death or last follow-up. Preoperative severe life-threatening events and postoperative complications were obtained retrospectively from a chart view with the latter being defined according to the Clavien–Dindo classification [15]. Overall survival (OS) time was calculated as the time from the date of initial treatment or surgery to the date of death or last follow-up.

**INTRODUCTION**

Lung cancer is the leading cause of cancer-related deaths worldwide, including Japan [1]. Generally, patients with advanced lung cancer (clinical stage III and IV) undergo definitive chemoradiotherapy; however, a local recurrence rate of between 28.1% and 34.1% was detected [2]. Similarly, among early-stage lung cancer patients treated with high-dose radiotherapy due to inoperability, a local recurrence rate of 0–67.0% was reported, which is currently an issue [3]. Recently, general thoracic surgeons demonstrated a rescue surgery targeted for pretreated patients with local recurrence or cancer persistence. The so-called salvage surgery has been performed in those with lung cancer who received chemotherapy and/or radiotherapy and in whom the outcomes of short-term morbidity, mortality and long-term survival were feasible, compared with those who were still receiving chemotherapy [4–9]. According to the variety of salvage surgery series for lung cancer that has been reported thus far, the patient characteristics have been stratified using pretreatment procedures, i.e. definitive chemoradiotherapy, targeted therapy using epidermal growth factor receptor–tyrosine kinase inhibitor (EGFR–TKI), high-dose stereotactic body radiation therapy or carbon ion therapy (CIT) and proton beam therapy (PBT) [10–12]. In investigating the value of elective salvage surgery for complete cancer curability, we encountered some emergency lung cancer patients with a life-threatening event such as a lung abscess from a serious infection, empyema or haemoptysis after/during chemotherapy or chemoradiotherapy or radiotherapy, which were defined differently from the other types of oncological salvage surgeries [13, 14]. In selected conditions, we performed an emergent palliative surgery for patients with a fatal lung cancer who met the criteria; however, we may have missed the chance or optimal timing for emergent rescue surgery. Since such cases are rarely encountered, the significance and impact of emergent salvage lung resection for the purpose of saving lives has not been elucidated, to date. Therefore, this study aimed to evaluate not only the feasibility but also the postoperative survival outcomes of emergent palliative salvage surgery in lung cancer patients with life-threatening haemoptysis and/or infections following chemo- and/or radiotherapy.

**ABBREVIATIONS**

| Abbreviation | Definition |
|--------------|------------|
| CIT          | Carbon ion therapy |
| EGFR–TKI     | Epidermal growth factor receptor–tyrosine kinase inhibitor |
| ICI          | Immune checkpoint inhibitor |
| IQR          | Interquartile range |
| OS           | Overall survival |
| PBT          | Proton beam therapy |

**CONCLUSIONS:** Emergency salvage lung resection is a technically challenging procedure; however, the results were feasible and acceptable when the surgical indication, procedure and optimal timing were considered carefully by a multidisciplinary team. Although the aim was palliation, some patients who received additional chemotherapy afterwards and, thus, had additional survival time.

**Keywords:** Emergency operation • Salvage lung resection • Chemotherapy • Radiotherapy • Lung cancer

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third to two-thirds, respectively, in the resected specimen), Ef.2: moderate response (viable cancer cells remaining in less than one-third in the resected specimen) and Ef.3: complete response (no viable cancer cells in the resected specimen).

**Data availability**

The data underlying this article will be shared on reasonable request to the corresponding author.

**Statistical analysis**

The continuous data were presented as either the mean and range or median and interquartile range (IQR). The categorical data were expressed as a frequency count and percentage. The survival curves were calculated using the Kaplan–Meier method. The statistical analysis was performed with JMP software ver. 12 (SAS Institute Inc., Cary, NC, USA).

**RESULTS**

We analysed the data of the patients retrospectively, from September 2015 to October 2020. A total of 862 patients with primary lung cancer underwent surgery. Among them, we included 10 patients (1.2%) who met the criteria for an emergency salvage lung resection. The preoperative clinical characteristics, including the initial clinical staging and treatment of all 10 patients, are shown in Table 1. The preoperative median age was 63.7 years (IQR: 55.0–70.5), and 9 patients were male. Five patients were diagnosed as stage IV under TNM staging at initial treatment. Four patients received definitive chemoradiotherapy for their initial therapy, 5 received chemotherapy alone and 1 received PBT for early-stage lung cancer. An immune checkpoint inhibitor (ICI) was used for 2 patients prior to surgery. The indications for emergent surgery were as follows: uncontrolled lung abscess [5 out of 10 patients (5/10; 50%)], uncontrolled lung abscess with haemoptysis (3/10; 30%), massive haemoptysis requiring intubation to prevent suffocation (1/10; 10%) [13], and acute empyema (1/10; 10%). While there was no specific predominant organism that caused the lung abscess, *Candida, Actinomyces*, an aerobic gram-positive rod and *Enterococcus faecalis* were identified as causative organisms in 4 out of 8 patients with a lung abscess formation. The preoperative images of the computed tomography scan in patient number 5 (lung abscess with haemoptysis) and 9 (acute empyema) are shown in Fig.1. The most common histopathological type of lung cancer observed was squamous cell carcinoma (7/10; 70%). The perioperative surgical results are shown in Table 2. The mean and median operation times were 220.2 and 191.0 min (range: 108–424, IQR: 151–279),

| Number | Age | Sex | Pretreatment clinical stage | Initial treatment prior to surgery | Completeness of chemotherapy | Etiology for emergency | Histology |
|--------|-----|-----|-----------------------------|-----------------------------------|-------------------------------|------------------------|----------|
| 1      | 77  | M   | cT2aN2M0-IIIA               | Platinum doublet chemotherapy and concurrent RT (60 Gy) | Complete | Lung abscess and haemoptysis | Sq       |
| 2      | 66  | M   | cT3N2M0-IIIB                | Platinum doublet chemotherapy and concurrent RT (60 Gy) | Incomplete | Lung abscess | Sq       |
| 3      | 61  | M   | cT4N2M1b(OS-St)-IVA         | Platinum doublet chemotherapy      | Incomplete | Lung abscess | LCNEC    |
| 4      | 48  | M   | cT2aN1M0-IIIB               | Left upper lobectomy → platinum doublet chemotherapy and concurrent RT (60 Gy) for recurrence | Complete | Lung abscess and haemoptysis | Sq       |
| 5      | 68  | M   | cT3N2M1b(AD-R)-IVA          | Platinum doublet chemotherapy including angiogenesis inhibitor and immune checkpoint inhibitor | Complete | Lung abscess | Pleo     |
| 6      | 57  | M   | cT4N2M1a(EF-F)-IVA          | Platinum doublet chemotherapy → single agent | Complete | Lung abscess and haemoptysis | Sq       |
| 7 (13) | 70  | M   | cT1cN0M0-IA3                | Proton beam therapy (60.4 Gy)     | Complete | Hemoptysis   | Ad       |
| 8      | 69  | F   | cT4N2M0-IIIB                | Platinum doublet chemotherapy and concurrent RT (60 Gy) | Complete | Lung abscess | Sq       |
| 9      | 72  | M   | cT4N0M1a(EF)-IVA            | Platinum doublet chemotherapy including immune checkpoint inhibitor | Incomplete | Acute empyema | Sq       |
| 10     | 49  | M   | cT2aN1M1b(OS-St)-IVA        | Platinum doublet chemotherapy      | Incomplete | Lung abscess | Sq       |

Ad: adenocarcinoma; ADR: adrenal metastasis; EFF: malignant effusion; F: female; LCNEC: large cell neuroendocrine carcinoma; M: male; OSS: bone metastasis; Pleo: pleomorphic carcinoma; RT: radiation therapy; Sq: squamous cell carcinoma.
respectively, and the mean and median bleeding volumes were 1119.8 and 1071.5 mL (range: 63–2059, IQR: 540–1691.5), respectively; blood transfusions were needed in 8 patients. The operative procedures were as follows: lobectomy (8/10; 80%), bi-lobectomy (1/10; 10%) and pneumonectomy (1/10; 10%); these were all performed using open thoracotomy. Additional procedures included pulmonary artery plasty (1/10; 10%) and bronchial plasty (1/10; 10%). Coverage of the bronchial stump was carried out in 7 patients using a pericardial fat pad (7/10; 70%). Severe postoperative complications as per the Clavien–Dindo classification grade III or higher (i.e. postoperative empyema, pneumonia, chest drainage for haemothorax) were observed in 3 patients (3/10; 30%); however, 30-day postoperative mortality was not observed. The postoperative outcomes are shown in Table 3. The mean and median follow-up periods from the salvage surgery were 14.5 and 9.4 months (range: 1.9–53.9, IQR: 4.3–20.4), respectively, and those from the initial treatment were 37.4 and 19.4 months (range: 5.4–115.3, IQR: 8.0–66.9), respectively. Five patients were diagnosed as pathological stage IV (5/10; 50%) and 1 had no residual tumour. The most common pathological efficacy was confirmed to be Ef.1 (8/10; 80%). Five patients (5/10; 50%) received postoperative treatment including additional chemotherapy for residual tumour and radiotherapy for bone metastasis. The 3-year OS rate from the salvage surgery was 30.0% (95% confidence interval 10.0–62.4%; central image and Fig. 2) and the 3- and 5-year OS rates from initial treatment were both 30.0% (95% confidence interval 10.0–62.4%). At the end of the observation period, 7 patients died of lung cancer from distant organ metastasis (for example to the brain and bone), 1 patient was alive without cancer, another was alive with adrenal metastasis and was treated with chemotherapy and another was alive with cancer and was using EGFR–TKI for pleural dissemination for approximately 2 years with almost complete remission.

**DISCUSSION**

In this study, we demonstrated that the short- and long-term results of emergency salvage lung resection in as many as 10 patients were feasible and acceptable. Although the aim of the procedure was palliation, mainly to rescue patients from life-threatening complications such as a lung abscess and/or haemoptysis during or after chemotherapy and/or chemoradiotherapy, the patients were able to recover from these fatal events, and some of them even lived for over a year with additional postoperative chemotherapy. Although the procedure demanded technical skills and adequate decision-making for optimal patient selection with appropriate operative timing, the postoperative results were considered reasonable and permissible, which had a different meaning compared with other types of elective salvage surgery where a patient did meet the optimal operative criteria.

Prior studies regarding the classification of salvage lung cancer surgery have stratified it into 4 categories based on the type of preoperative treatment and condition of the patient [10–12]: category 1, a procedure for lung cancer recurrence or persistence after definitive chemoradiation therapy [4–8, 18, 19, 20]; category 2, surgery for lung cancer recurrence or persistence after high-dose stereotactic body radiation therapy, CIT and PBT for a patient who refused surgery or had inoperable early-stage lung cancer due to multiple comorbidities [4, 8, 9]; category 3, an operation for relapse after targeted therapies with EGFR–TKI or anaplastic lymphoma kinase inhibitor [21, 22]; and category 4, a rescue procedure against an emergent condition caused by serious adverse events of haemoptysis, lung abscess or empyema after chemotherapy and/or radiotherapy different from such as categories 1, 2 and 3 above [11, 12, 23].

To describe and compare those surgical results precisely, the morbidity/mortality/OS from surgery stratified into 3 categories was 14.8–40%/0–11.1%/31–75% for the 5-year OS (category 1) [6, 19, 24–27], 0–25%/0–4.8%/57.7–82% for 3-year OS (category 2) [4, 8, 9, 28] and 5.6–11.1%/0%/75% for 3-year OS or 17 months of the median OS (category 3) [21, 22], respectively. Although category 4 case series were limited, the results of 3 cases were reported with a morbidity/mortality/mean OS rates of 100%/0%/13 ± 5 months, respectively [12].

In this study that included a total of 10 patients, the morbidity/mortality/survival rates were 30%/0%/30% for 3-year OS, which were comparable to prior reports. Unlike the other categories, which were generally performed as elective surgeries with the aim of completely resecting the residual tumour, the main purpose of category 4 was to rescue a symptomatic lung cancer.
Table 2: Perioperative results of 10 patients who underwent emergency salvage lung cancer surgery

| Number | Procedure | Coverage of bronchial stump | Radicality | Interval from initial pretreatment (months) | Interval from last pretreatment (months) | Operation time (min) | Bleeding amount (mL) | BT | Postoperative stay (days) | Complications | Grade | 30-Day mortality |
|--------|-----------|-----------------------------|------------|--------------------------------------------|------------------------------------------|---------------------|---------------------|----|--------------------------|--------------|--------|-------------------|
| 1      | Open right upper lobectomy | Pedicled pericardial fat pad | R1         | 16.50                                      | 15.07                                    | 294                 | 986                 | Yes | 44                      | Empyema       | II     | No                |
| 2      | Open right lower lobectomy | Intercostal muscle and pedicled pericardial fat pad | R0         | 0.57                                       | 0.43                                     | 274                 | 1569                | Yes | 50                      | Prolonged air leak | II     | No                |
| 3      | Open right lower lobectomy | None                          | R1         | 1.37                                       | 0.30                                     | 154                 | 694                 | Yes | 15                      | None          | No     | No                |
| 4      | Open left pneumonectomy | Pedicled thymus              | R0         | 5.70                                       | 2.90                                     | 424                 | 554                 | Yes | 125                     | Empyema       | IIb    | No                |
| 5      | Open left upper lobectomy | None                          | R2         | 12.47                                      | 0.87                                     | 203                 | 2094                | Yes | 58                      | Postoperative haematoma | IIIa   | No                |
| 6      | Open right upper/middle lobectomy and bronchoplasty | Pedicled pericardial fat pad | R2         | 12.37                                      | 0.43                                     | 261                 | 1157                | No  | 24                      | None          | No     | No                |
| 7 (13) | Open left upper lobectomy and pulmonary artery plasty | Pedicled pericardial fat pad | R2         | 79.73                                      | 0.23                                     | 179                 | 498                 | Yes | 31                      | Subacute interstitial pneumonia | II     | No                |
| 8      | Open left upper lobectomy | None                          | R0         | 96.17                                      | 93.17                                    | 163                 | 2059                | Yes | 12                      | None          | No     | No                |
| 9      | Open right lower lobectomy and lavage | Pedicled pericardial fat pad | R1         | 0.40                                       | 0.37                                     | 108                 | 1524                | Yes | 86                      | Postoperative pneumonia | IV     | No                |
| 10     | Open right upper lobectomy | Pedicled pericardial fat pad | R2         | 3.57                                       | 0.77                                     | 142                 | 63                  | No  | 25                      | None          | No     | No                |

BT: blood transfusion.
Table 3: Postoperative results of 10 patients who underwent emergency salvage lung cancer surgery

| Age | Sex | Postoperative stage | Pathological stage (8th) | Pathological tumour size (cm) | Pathological efficacy | Postoperative therapy | Final outcomes | Survival from surgery (months) | Survival from initial treatment (months) |
|-----|-----|---------------------|--------------------------|------------------------------|----------------------|----------------------|-----------------|-------------------------------|---------------------------------------|
| 1   | 77  | M                   | ypT2bN0M0                | IIA                          | 4.7                  | efla                 | Immune check point inhibitor | Cancer death      | 11.6                          | 28.1                                  |
| 2   | 66  | M                   | ypT2aN1M0                | II B                         | 7                   | eflb                 | No                           | Alive with another lung cancer | 53.9                      | 54.5                                  |
| 3   | 61  | M                   | ypT4N2M1a (OSS)          | IVA                          | 10                  | efla                 | Platinum doublet            | Cancer death      | 7.3                           | 8.6                                   |
| 4   | 48  | M                   | No residual tumour       | No residual tumour           | 0                   | efl3                 | No                           | Cancer death      | 6.9                           | 12.6                                  |
| 5   | 68  | M                   | ypT4N2M1b (ADR)          | IVA                          | 10.5                | eflb                 | No                           | Cancer death      | 1.9                           | 14.4                                  |
| 6   | 57  | M                   | ypT4N1M0                 | IIA                          | 10.7                | eflb                 | Platinum doublet radiation | Cancer death      | 12.1                          | 24.4                                  |
| 7 (13)| 70 | M                   | ypT2bN0M1a (PLE)         | IVA                          | 4.5                  | eflb                 | EGFR-TKI                    | Alive with cancer | 24.3                          | 104.1                                 |
| 8   | 69  | F                   | ypT1N0M0                 | IA3                          | 2.2                  | No                   | Alive without cancer         | 19.1              | 115.3                         |                                       |
| 9   | 72  | M                   | ypT4N1M1a (EFF)          | IVA                          | 10                  | efla                 | No                           | Cancer death      | 5.0                           | 5.4                                   |
| 10  | 49  | M                   | ypT1N0M1b (OSS)          | IVA                          | 0.2                  | efl2                 | Palliative radiation        | Cancer death      | 2.4                           | 6.0                                   |

ADR: adrenal metastasis; EFF: malignant effusion; EGFR–TKI: epidermal growth factor receptor–tyrosine kinase inhibitor; F: female; M: male; OSS: bone metastasis; PLE: pleural dissemination.
With regard to the preoperative clinical characteristics of our emergent salvage series, the clinical stage IV at initial treatment, a histology of squamous cell carcinoma with a large tumour size and short interval from the last date of chemotherapy and/or radiation therapy accounted for the majority compared with those who had elective salvage surgery of categories 1, 2 and 3. Comparing the perioperative characteristics, an open thoracotomy, significant intraoperative bleeding, postoperative pathological status of Ef.1 and 2, non-down-staged case and R2 resection were the clinical features of our 10 emergency cases. With regard to the perioperative clinical course among these cases, we were able to tolerate a pulmonary complication, such as aspergilloma or non-tuberculous mycobacteriosis, for the purpose of controlling these life-threatening infections [29]. New effective chemotherapeutic agents for lung cancer have been developed recently and 4 of the 10 patients (4/10; 40%) in this case series were receiving chemotherapeutic agents (ICIs) prior to or after the salvage surgery [30]. Since a greater number of good responses are being reported in patients with advanced lung cancer, candidates for salvage surgery are expected to increase in future.

With regard to the prognostic indices among the recipients of salvage lung cancer surgery after chemoradiotherapy, a simple lobectomy (versus complex resection), macroscopic and microscopic complete resection (versus R1 and R2 resection; microscopic and macroscopic tumour remnants), pathological non-necrotic lymph node metastasis (versus positive lymph node metastasis) and down-staged condition (versus unchanged or upstaged condition) were the significantly favourable prognostic factors for long-term survival (category 1) [4, 6, 20]. In this study, 2 of 3 patients whose conditions were down-staged with R0 resection after the use of definitive chemoradiotherapy and chemotherapy, survived for over a year with cancer and cancer-free status, respectively. This suggested that patients who underwent emergency salvage surgery had some common prognostic factors regardless of the different pretreatment agents and conditions. A patient who underwent PBT for stage I lung cancer and emergency salvage lung resection for massive haemoptysis also survived for almost 2 years with pleural dissemination, receiving EGFR-TKI with almost complete remission [13]. This patient demonstrated that the use of additional chemotherapy after emergency salvage surgery contributed to longer survival. Accordingly, newly developed anti-cancer drugs such as ICIs and postoperative chemotherapy may enable longer survival after salvage surgery if the pretreatment clinical staging is less than IV.

**Limitations**

This study had some limitations. We had a selection bias for performing emergent salvage surgery, because the previous treatment of the patients and the aetiology of the emergent conditions differed considerably, and the indications for the operation were decided by the surgeons and multidisciplinary team at that time in a single institution. Another limitation was that the results of our emergency salvage surgery were not compared with those who had not had emergency surgery. Moreover, chemotherapeutic agents, including the newly developed ICI, were administered recently in some of the patients, which had substantial effects on lung cancer survival. However, we were able to analyse selected patients who received emergency life-saving surgery for uncontrollable infections or massive bleeding; this allowed for a robust analysis of possibility for emergency salvage lung resection for patients with pretreated lung cancer. In the future, we will conduct a multicentre trial to elucidate the
CONCLUSIONS

Emergency salvage lung resection is technically challenging and involves difficulty in decision-making for the optimal procedure and timing for surgery; however, the results of this study were feasible and acceptable. It is also advisable that patient selection, optimal timing and procedures against a life-threatening event are discussed carefully and considered by a multidisciplinary team. Although the aim was palliation, our results suggested that emergent salvage lung resection played an important role in controlling serious haemorrhage and/or infections, and consequently, afforded some patients additional long-term survival. A similar study with a larger sample size should be performed in future, the results of which may demonstrate the significance of the procedure.

ACKNOWLEDGEMENT

We are grateful to Editage for English proofreading.

Funding

This study received no funding from any institutions.

Conflict of interest: none declared.

Author contributions

Haruaki Hino: Conceptualization; Data curation; Investigation; Writing—original draft. Takahiro Utsumi: Data curation. Natsumi Maru: Data curation. Hiroshi Matsui: Data curation. Yohei Taniguchi: Data curation. Tomohiro Murakawa: Conceptualization; Supervision.

Reviewer information

Interactive CardioVascular and Thoracic Surgery thanks Albert Rodriguez-Fuster, Larry R Kaiser, Mohamed Rahouma and the other, anonymous reviewer(s) for their contribution to the peer review process of this article.

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