

Salvage Surgery

Subjects: Oncology

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The representative surgical intervention for unresectable stage III/IV NSCLC is salvage surgery, which refers to surgical treatment for local residual/recurrent lesions after definitive non-surgical treatment. Surgical intervention is also used for an oligometastatic stage IV NSCLC.

Keywords: non-small cell lung cancer ; immunotherapy ; unresectable ; salvage surgery ; oligometastasis ; targeted therapy

1. Introduction

Treatment of patients with lung cancer depends on the histology, tumor stage, molecular characteristics, and assessment of a patient's overall medical condition. Currently, various guidelines for lung cancer treatment, including those from the American Society of Clinical Oncology, European Society of Medical Oncology, National Comprehensive Cancer Network (NCCN), and The Japan Lung Cancer Society, have been used ^{[1][2]}. Patients with stage I-II non-small cell lung cancer (NSCLC) are generally treated with curative-intent surgery if they are operable. Patients with stage III NSCLC are generally treated with a multimodality approach, including surgery, chemotherapy, and radiation therapy (RT). Those with stage IV or recurrent NSCLC are treated with systemic drug therapies, including chemotherapy, tyrosine kinase inhibitors (TKIs), and immune checkpoint inhibitors (ICIs). Molecular-targeted therapies such as TKI are selected if the epidermal growth factor receptor (*EGFR*) gene is mutated, while an ICI and/or cytotoxic chemotherapy is selected if this gene is not mutated.

In general, surgical treatment is selected for tumors that can be completely resected, whereas RT or drug therapy is offered for patients whose tumors cannot be completely resected or who cannot tolerate surgery. In practice, the term “resectable” not only applies to technically resectable, which is “resectable” in a narrow sense, but also refers to cases when resection can be expected to have a favorable prognosis to some extent, which is “resectable” in a broad sense. Although “unresectable” is defined as “unable to be removed using surgery” in the National Cancer Institute dictionary, there is no general consensus regarding the definition of “unresectable” in lung cancer.

Unresectable lung cancer is considered to be represented by stage III and IV disease. Unresectable factors in stage III lung cancer are direct invasion to unresectable organs (T4) or mediastinal/extrathoracic lymph node metastasis (N2/N3). An unresectable feature of stage IV lung cancer is distant metastasis (M1). Regarding mediastinal lymph node metastasis, the 2013 American College of Chest Physicians (ACCP) guidelines defined N2 nodes that have extranodal progression and an invasive nature as infiltrative nodes, while other nodes were defined as discrete nodes. Discrete nodes were considered to likely benefit from surgical therapy ^[3]. In general, bulky/multi-station/infiltrative nodes are regarded as unresectable, while T4 tumors are tumors sized >7 cm or those invading the mediastinum/heart/diaphragm/carina/trachea/great vessels/recurrent nerve/esophagus/spine, or separate tumor nodule(s) in a different ipsilateral lobe. In patients with unresectable stage III lung cancer, the current standard treatment is concurrent chemoradiotherapy (CRT) ^{[4][5]}, which provides a median overall survival (OS) of 22–25 months and a 5-year OS of 20% ^[6].

2. Salvage Surgery for Stage III NSCLC

2.1. Salvage Surgery after Definitive CRT

The incidence of local recurrence after definitive CRT in patients with stage III NSCLC was 24–35% ^[7], and the survival rates after CRT were as low as 5–25% ^[8]. In 2019, Grass et al. showed a high relapse rate after CRT (64%) ^[9]. Salvage surgery for residual/recurrent tumors is almost the only treatment that can provide a cure. Compared with upfront surgery, salvage surgery after definitive CRT has greater surgical difficulty and a greater possibility of perioperative complications because a high dose of RT strongly affects the target tissue, resulting in more tissue changes ^{[10][11]}.

To date, there have been limited reports of salvage surgery after definitive CRT for primary lung cancer. Dickhoff et al. reported a systematic review of the literature concerning salvage surgery after definitive CRT for locally advanced NSCLC in 2018 [12]. They reviewed eight papers including 158 patients. For patients undergoing resection ($n = 152$), a total of 44 pneumonectomies, 11 bilobectomies, 89 lobectomies, 6 segmentectomies, and 3 wedge resections were performed. Complete resection was achieved in 85–100%, with vital tumors in 61–100%. Where reported, the 90-day mortality rate was 0–11.4%. The reported survival metrics varied but included a median survival time (MST) 9–46 months and a 5-year OS rate of 20–75%. Recently, Romero et al. reported about 27 patients who underwent surgical resection after CRT. Complications were observed in 5 (18.5%) patients. The 3- and 5-year OS rates were 57.8% and 53.3%, respectively [13]. Furthermore, Kobayashi et al. reported 23 cases that underwent salvage surgery after CRT in a single center, with no perioperative death, a 5-year recurrence-free survival rate of 17.3%, and a 5-year OS rate of 41.9% [14]. Based on this evidence regarding salvage surgery after CRT, perioperative mortality appears to be acceptable, and long-term survival is possible in selected patients.

2.2. Salvage Surgery after Definitive Radiotherapy

Radiation monotherapy is indicated for patients with stage III NSCLC who are unsuitable for CRT. Stereotactic body radiotherapy (SBRT) is a good indication, especially for local lesions such as stage I NSCLC. Salvage surgery after definitive radiotherapy is more localized than definitive CRT. Since there is minimal effect on normal tissues, especially in SBRT and heavy-ion radiotherapy, the incidence of complications is expected to be low. In 2018, Dickhoff et al. performed a systematic review of salvage surgery after local recurrence of NSCLC after SBRT (7 case series with a total of 47 patients) [15]. The 5-year local recurrence rate after SBRT was approximately 10% and surgery was performed as salvage surgery in selected patients. The morbidity rate was 29–50%, and the 90-day mortality rate was 0–11%. MST ranged between 13.6 and 82.7 months. In addition, 12 patients who underwent salvage surgery after heavy-ion radiotherapy were reported by Mizobuchi et al. in 2015 [16]. There were no serious complications in any of the cases, and the 3-year survival rate after surgery was 82%. Although there is only limited evidence regarding salvage surgery after radiotherapy for locally relapsed NSCLC, this treatment can be considered feasible and can provide acceptable morbidity and mortality rates for selected patients.

2.3. Salvage Surgery after Combination Therapy with CRT and Immunotherapy

In the phase III PACIFIC study, eligible patients received durvalumab after CRT, and this combination therapy significantly prolonged progression-free survival (PFS) compared with that in the placebo group (16.8 months versus 5.6 months) [17].

Regarding the addition of surgery to this combination therapy, the significance of surgical intervention after CRT followed by ICI remains unclear. Recently, a clinical trial (JCOG1807C) was initiated to clarify the safety and efficacy of multimodality treatment of pre- and postoperative durvalumab therapy after preoperative CRT for resectable superior sulcus tumor (SST) and durvalumab maintenance therapy after CRT for unresectable SST. In this study, eligible patients were assigned to two groups: concurrent CRT (cisplatin+S-1+radiotherapy 66 Gy) + two courses of durvalumab followed by surgery and adjuvant durvalumab for resectable SST and CRT followed by maintenance durvalumab for unresectable SST. The primary end-point is 3-year OS. We await the results of this trial.

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