Review Article

Salvage lung surgery in long-term survivors after biological and immunotherapeutic treatments

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Abstract: Despite increasing efforts regarding screening and early detection, the majority of new lung cancers are still diagnosed at an advanced stage. For advanced cases of non-small cell lung cancer (NSCLC), treatment is often based on systemic chemoradiotherapy (CRT). However, in the last few decades, emerging modalities such as targeted therapy and immunotherapy have altered treatment paradigms, and have vastly improved overall and disease-free survival for a large group of patients. Furthermore, tumours that were initially deemed inoperable may now demonstrate a downstaging of their cancer to operable disease status. In these patients, salvage lung resections can be considered as a treatment to obtain complete resection. However, data on patient selection criteria, optimal surgical timing, postoperative complications, and outcomes of salvage surgery in patients receiving these systemic therapies are scarce. In this review, we aim to summarize the most recent literature regarding salvage lung surgery in patients that have received targeted therapy or immunotherapy.

Keywords: Salvage surgery; non-small cell lung cancer (NSCLC); targeted therapy; immunotherapy; outcomes

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Introduction

Lung cancer is worldwide the most common malignancy and remains one of the leading causes of mortality (1,2). Despite the fact that rates of lung cancer vary around the world, an overall increase in new cases of non-small cell lung cancer (NSCLC) are seen, mainly due to rising incidences in developing countries (3). Recent estimates have shown a global incidence rate of 1.8 million lung cancer diagnoses, comprising 13% of all new global cancer diagnoses (4). Furthermore, the 5-year survival rate of lung cancer is around 18%, a significantly lower long-term survival rate compared to any of the other leading cancers (5). This low survival rate is mainly due to the fact that the vast majority of lung cancer patients are diagnosed with advanced-stage disease (6). Treatment for NSCLC depends on the stage and extensiveness of the disease. For early stage NSCLC, lobectomy with hilar and mediastinal lymph node dissection is considered the first line of therapy (7,8). However, in more advanced cases of NSCLC, surgery is often not indicated and systemic chemoradiotherapy (CRT) is considered the mainstay of treatment (9). If possible, a trimodal approach with chemotherapy, radiation therapy, and surgery is used in many cases to obtain optimal disease-free and overall survival (DFS and OS, respectively) rates. Earlier studies using this combined approach have shown acceptable results with 5-year OS rates ranging from 16–38% (10,11). However, despite these curative-intent treatments, approximately 39% of all patients develop locoregional recurrence or have residual tumour within 2 years after initial treatment (12,13). In cases of local failure, treatment options are often limited and results

of subsequent treatments are disappointing generally. Moreover, there is no clear consensus on which therapeutic approach would be most suitable in cases of local or regional failure (14). In recent years, a large number of targeted and immunotherapeutic treatments have been added to the therapeutic arsenal for the treatment of (advanced) NSCLC. New knowledge regarding cancer biology and cancer immune evasion have already altered treatment paradigms and vastly improved the expected outcomes of many patients with advanced stages of NSCLC (6). Despite the increasing availability of new modalities, many patients that are treated with systemic therapies for advanced stages of NSCLC will develop recurrence in time, often manifesting as distant metastases with or without local relapse (15). However, in a small proportion of these patients, the recurrence is an isolated local relapse that is not suitable for curative-intent radiotherapy. In these patients, complete resection is the only curative-intent treatment modality available. This type of surgery is referred to as 'salvage surgery' (16,17). Despite the growing knowledge regarding long-term outcomes of biological and immunotherapeutic treatments, there is a lack of data concerning (salvage) surgery in this patient group. In this study, we aim to summarize the latest results on salvage surgery in patients that have received targeted therapy of immunotherapy.

Treatment after local failure

Local failure is defined as recurrence and/or residual tumour, and is the leading cause of death in patients undergoing initial curative-intent definitive CRT (18). Several treatment modalities have been proposed for patients with local failure. In some cases, high-dose reirradiation after definitive CRT may be considered. Reported 2-year overall and disease-free survival rates in this patient group are 32% and 37%, respectively. Locoregional failure is present in approximately 49% of all patients at 1-year post-treatment. In addition, treatments with high-dose reirradiation are often associated with excess toxicities to surrounding organs-at-risk, including the heart, lungs, spinal cord, and oesophagus (14,18,19). Previous studies investigating high-dose reirradiation after local failure have shown increased frequencies of pneumonitis, oesophagitis, and fatal bleeding risks. Furthermore, radiation therapy can significantly reduce total lung and diffusion capacity, with lung function impairment even being reported 6 months post-treatment (14,20).

Second-line chemotherapy has also been described as a treatment modality after local failure and for patients with progressive disease. However, recent studies have shown only minimal survival benefits in this patient population, with median long-term survival and progressive-free survival rates of 9 and 6 months, respectively (21,22). Furthermore, previous studies have shown very low response rates of only 10% to platinum-based chemotherapy for recurrent NSCLC after definitive CRT (23).

In recent years, salvage lung surgery has increased in popularity as studies have shown improved OS and DFS rates in selected patient groups (24-27). The term salvage surgery generally refers to surgical resections of persistent or recurrent primary lung tumours after previous local and/or systemic therapies have failed (28). Currently, there are no guidelines regarding specific indications for salvage surgery. In the majority of cases, this type of surgery is performed in patients with progressive disease after definitive chemo- and/or radiotherapy (29). However, other indications may be possible based on the specific evaluation of each patient (16). The clinical significance of salvage lung surgery remains controversial and comparing results of studies is often complicated due to differences in the definition of salvage lung surgery among investigators and in the patient selection of these studies (28).

Previous studies have shown that salvage lung surgery is technically feasible and has acceptable mortality and morbidity rates (23-25). Even in patients undergoing extended anatomical resections greater than a lobectomy, such as a pneumonectomy, long-term outcomes seem to be acceptable (14). Five-year overall survival rates range widely between 20–75% in earlier studies, mostly due to varying indications and results based on small patient populations (14,25,26,30,31). In a recent retrospective study by Sonobe *et al.*, 29 patients undergoing salvage resection after chemotherapy or CRT were included for further analysis. Five-year overall and recurrence-free survival were 51% and 49%, respectively. Despite promising results from this study and other similar studies, there is still a lack of prospective data and results based on larger sample sizes (32).

Neoadjuvant biological and immunotherapy in resectable patients

The introduction of targeted therapies and immunotherapy has caused a paradigm shift in the treatment of NSCLC in the last few decades (6,33). Therapies that target specific mutations of the epidermal growth factor receptor (EGFR) and on the abnormal fusion of the anaplastic lymphoma

kinase (ALK), and treatments that exploit the mechanisms which tumours use to evade immune recognition—such as the use of monoclonal antibodies targeting the immune regulatory proteins cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death-ligand 1 (PD-L1)—have now become viable therapeutic modalities for advanced NSCLC (33-37). With these new therapies, survival outcomes of a substantial proportion of patients with advanced NSCLC have improved immensely. Results of recent clinical trials have shown favourable treatment responses in specific subsets of patients with metastatic NSCLC (38). Despite the success of these systemic therapies, cancer surgery remains the most effective treatment strategy for resectable disease (7). However, data on the safety and feasibility of lung surgery after immunotherapy and targeted therapies is scarce.

Earlier studies have suggested that patients treated with immunotherapy have increased risks of complications such as pneumonitis, adrenal insufficiency, and thyroiditis (39,40). Although the majority of these complications are not severe, the effects on the perioperative care of patients and the technical aspects of lung resections are not clear. In a retrospective study by Bott *et al.*, 19 patients with metastatic or unresectable tumours underwent 22 lung resections (lobectomy, bilobectomy, or pneumonectomy) after therapy with anti-PD-1 agents (nivolumab and pembrolizumab), anti-CTLA-4 agents (ipilimumab), or anti-PD-L1 agents (durvalumab and atezolizumab). The most common tumours were NSCLC (n=9) and melanoma (n=7). In 95% of all cases, an R0 resection could be achieved. Two-year OS and DFS were 77% and 42%, respectively. Postoperative complications were mostly minor; however, the authors noted that operations may be more challenging due to post-treatment adhesions (34).

In the recent CheckMate-159 trial, neoadjuvant PD-1 inhibitor nivolumab was administered to patients with surgically resectable, early-stage NSCLC (stage I, II, or IIIa) 4 weeks preoperatively. The primary endpoints of this trial were safety and feasibility. A total of 21 patients were included for treatment with neoadjuvant nivolumab followed by surgical resection of the tumour. In 20 patients, an R0 resection was achieved, and a major pathological response (MPR) occurred in 9/20 resected tumours (45%). Furthermore, results showed a recurrence rate of 73% within 18 months and an overall survival rate of 95%. Treatment-related adverse events of any grade occurred in 5 patients, with one patient having a grade 3-4 adverse event (pneumonia). No treatment-related surgical delays were found in this study. The authors concluded that neoadjuvant nivolumab is a safe and feasible treatment with minimal side effects and favourable pathological response (41). In a similar trial, Bott *et al.* investigated the results of pulmonary resection after neoadjuvant nivolumab in patients with untreated stage I-IIIa NSCLC. A total of 20 patients underwent resection (15 lobectomies, 2 pneumonectomies, 1 bilobectomy, 1 sleeve lobectomy, and 1 wedge resection) via thoracoscopic surgery or thoracotomy. The authors found that nivolumab did not cause delays to surgical resection. There were no operative mortalities and rates of perioperative morbidities were minimal. In 9/20 patients (45%), MPR was identified. However, 7/13 (54%) procedures that were performed using thoracoscopic approaches had to be converted to thoracotomy, often due to hilar inflammation and fibrosis (42).

In the NEOSTAR phase II trial, nivolumab and nivolumab+ipilimumab were compared in 44 resectable NSCLC patients. The results showed a pathological complete response in 6 patients (15%) and overall MPR rate of 24%. Further subgroup analysis of 34 resected patients showed an MPR rate of 29%. Postoperative complication rates were similar in both treatment arms; however, the nivolumab+ipilimumab arm showed higher rates of non-viable tumour. In the phase II, multi-centre NADIM trial, the efficacy of combining nivolumab with conventional chemotherapy was investigated. A total of 41 patients underwent surgical resection, with no delay due to neoadjuvant treatment. R0 resections were achieved in all patients. MPR was seen in 34/41 patients (83%) and a total of 24 patients (71%) had a complete pathological response. The authors concluded that neoadjuvant chemotherapy combined with immunotherapy yields excellent pathological response rates (43). In addition to these trials, there are currently a number of ongoing randomized phase III trials regarding neoadjuvant immunotherapy in early-stage and (locally) advanced NSCLC. These are listed in *Table 1*.

Regarding targeted therapy, several studies have shown that EGFR-tyrosine kinase inhibitors (TKIs) and ALK inhibitors can significantly improve progression-free survival in specific subsets of patients with advanced stages of NSCLC (48-50). However, data from large prospective studies regarding the safety and efficacy of targeted therapies in a neoadjuvant setting are still lacking. A number of trials have been published in recent years regarding neoadjuvant targeted therapy. The EMERGING trial was a randomised phase II clinical trial that compared the safety and efficacy of erlotinib, an EGFR-TKI, with platinum-based doublet

Table 1 Overview of ongoing randomized phase III trials regarding neoadjuvant immunotherapy

NCT identifier (name)	Status	Intervention	Estimated enrolment (N)	Primary endpoint
NCT02998528 (CheckMate 816) (44)	Active, not recruiting	Arm A: 3 cycles nivolumab+ipilimumab → Surgery → CT±RT	350	EFS, pCR
		Arm B: 3 cycles platinum doublet → surgery → CT±RT		
		Arm C: 3 cycles nivolumab+platinum doublet → surgery → CT±RT		
NCT03456063 (IMpower030) (45)	Active, recruiting	Arm A: 4 cycles atezolizumab+ platinum doublet → surgery → atezolizumab	374	EFS, MPR
		Arm B: 4 cycles placebo+platinum doublet → surgery → placebo		
NCT03425643 (KEYNOTE-671) (46)	Active, recruiting	Arm A: 4 cycles pembrolizumab+ platinum doublet → surgery → pembrolizumab	786	EFS, OS
		Arm B: 4 cycles placebo+platinum doublet → surgery → placebo		
NCT04025879 (47)	Active, recruiting	Arm A: nivolumab+ platinum doublet → surgery → nivolumab	452	EFS
		Arm B: placebo+platinum doublet → surgery → placebo		

CT, chemotherapy; EFS, event-free survival; MPR, major pathological response; NCT, national clinical trial; OS, overall survival; pCR, pathologic complete response; RT, radiotherapy.

chemotherapy. The primary endpoint of this trial was the objective response rate (ORR) of the preoperative induction therapy. Although there was no significant difference in ORR, the ORR value of the erlotinib arm was objectively better than the chemotherapy arm (54.1% *vs.* 34.3%, respectively. The rate of R0 resections for the erlotinib and chemotherapy arm were 73% and 63%, respectively. The progression-free survival was significantly better in the erlotinib group compared to the chemotherapy group (21.5 *vs.* 11.4 months, P<0.0001). No significant difference was found regarding OS rates. Median overall survival of the erlotinib and chemotherapy groups were 45.8 and 39.2 months, respectively. Furthermore, a lower incidence rate of grade 3-4 adverse events was noted in the erlotinib group compared to the chemotherapy group (51). In the single-arm, single-centre, phase II ESTERN study, the safety and efficacy of erlotinib as neoadjuvant treatment for patients with IIIa-N2 NSCLC was evaluated. The primary endpoint of this study was the radical resection rate after 8 weeks of treatment. A total of 16 patients underwent lung resection and in 15/16 patients (93.8%), a complete resection was achieved (52).

Regarding outcomes of ALK inhibitors as neoadjuvant, only limited data is available. In a retrospective analysis of 11 ALK-positive patients with pathologically confirmed N2 NSCLC, neoadjuvant treatment with crizotinib resulted in a partial response in 10 patients (91%). Furthermore, R0 resections were achieved in 10 patients and a complete pathological response was seen in 2 patients. Grade 4 hepatic damage was noted in 1 patient. Recurrent disease occurred in 6 patients, however, 5 patients showed a long duration of response to first-line crizotinib. The authors concluded that neoadjuvant crizotinib may be feasible and well tolerated in locally advanced NSCLC before complete resection. Furthermore, neoadjuvant crizotinib did not seem to influence response rates for the reuse of first-line crizotinib (53). Currently, there are a number of ongoing phase II trials regarding neoadjuvant targeted therapies investigating the efficacy of osimertinib (NCT03433469) and crizotinib (NCT03088930) in early-stage and locally advanced NSCLC (54,55).

Discussion

Treatment for NSCLC has entered the era of precision medicine with new emerging therapies being introduced at an increasingly rapid pace. Although these new modalities seem promising, incorporating them in the current treatment approaches is still controversial (56). Trials regarding neoadjuvant targeted therapy and immunotherapy have shown that favourable outcomes can be achieved in early-stage and advanced stages of NSCLC (41-43,48-53). Furthermore, surgical outcomes after biological and immunotherapeutic treatments seem to be encouraging. However, the majority of data published regarding the combination of immunotherapy or targeted therapy and

surgery have incorporated surgery immediately after systemic therapy. There is still very limited data regarding salvage surgery in long-term survivors after immunotherapy or targeted therapy.

In a case series of 5 patients, Chaft *et al.* presented their results of patients treated with lung resections after T-cell checkpoint inhibitor therapy for advanced stage NSCLC. They showed that lung cancer surgery is feasible and safe in long-term survivors after immunotherapy, even in patients who develop pneumonitis or other immune-related toxicities during their treatment. The authors noted that dense fibrosis may develop in some patients as a result of excellent response to the systemic therapy, often making mediastinal and hilar dissection more technically challenging for thoracic surgeons (57). In another recent case series, Hamaji *et al.* described 2 patients that underwent salvage surgery after nivolumab administration. The salvage surgery was performed 9 and 12 months post-nivolumab in these 2 patients. Both patients underwent video-assisted thoracoscopic resection of the lesions and had no postoperative complications. The authors concluded that delayed salvage surgery after nivolumab was feasible and was associated with little fibrosis in the hilar region intraoperatively (58).

Regarding salvage surgery after targeted therapy, Hishida *et al.* posted a case series of 9 patients that underwent surgical resection after treatment with gefitinib for advanced NSCLC. R0 resection was accomplished in all patients and no major postoperative complications were seen. However, 7/9 patients showed a more advanced pathological stage than their preoperative clinical stage. OS and DFS were 32 and 6 months, respectively. The authors commented that although salvage surgery was feasible and safe, postoperative survival outcomes were not satisfactory. They concluded that surgery after gefitinib should be limited to patients without initial evidence of disseminated and distant metastases (59). More recent data from limited case series have shown similar results for gefitinib and other EGFR-TKIs (60).

All these results seem to suggest that salvage surgery after immunotherapy and targeted therapy is feasible with favourable outcomes regarding local control in selected patient groups. However, the optimal timing and validity of salvage surgery for residual lesions after biologicals and immunotherapy remains unclear. More data is needed to define the optimal criteria for proceeding with lung resections in patients receiving these systemic therapies. Future clinical trials will hopefully provide answers to these questions and clarify which subset of patients will benefit from a multimodal approach combining these emerging therapies and (salvage) surgery.

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Footnote

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