Review Article

State of the art and new perspectives in surgical treatment of lung cancer: a narrative review

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Background and Objective: Lung cancer is the leading cause of cancer-related deaths worldwide, and its incidence has increased over the past two decades. The standard care for stage I, stage II, and selected cases of stage IIIA non-small cell lung cancer (NSCLC) is surgical resection; in some cases, patients may be offered adjuvant systemic therapy after surgical resection. Patients with lung cancer presenting with distant metastases belong to stage IV: in this setting, some carefully selected patients may benefit from surgery within a multimodality approach.

Methods: We performed a comprehensive, non-systematic review of the latest literature to define the present role of surgery in lung cancer treatment.

Key Content and Findings: The literature review disclosed a pivotal role of surgery in early stage lung cancer and a complimentary role in locally advanced lung cancer; in very selected cases, surgery might be considered in oligometastatic disease.

Conclusions: Surgical treatment of lung cancer still plays a pivotal role in early stages of the disease while, in locally advanced stages, it may contribute to improve overall survival in combination with medical treatments and radiotherapy. More recently, an effective role of surgery has been advocated in carefully selected oligometastatic patients with encouraging initial results.

Keywords: Lung cancer; early stage; locally advanced; metastatic stage; surgery

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Introduction

Objectives

To focus on the present role of surgical treatment of early stage, locally advanced and oligometastatic lung cancer patients.

Rationale/background

Lung cancer is one of the most frequently diagnosed cancers and is the leading cause of cancer-related death worldwide (1). It accounts for more than 1.8 million newly diagnosed cancer cases—representing 13% of the total

Table 1 The search strategy summary

Items	Specification
Date of search	25 May 2022
Databases and other sources searched	PubMed/Medline, Scopus and guidelines of relevant thoracic/oncologic societies
Search terms used	(((lung cancer))) AND ((surgery) OR (surgical) OR (procedure) OR (resection)) AND ((early) OR (advanced) OR (oligometastatic) OR (metastatic))
Timeframe	1995–2022
Inclusion and exclusion criteria	Inclusion criteria: Original Articles, Review Articles
	Exclusion criteria: non-English language; Case Reports; Letters to the Editor
Selection process	FP and SR independently conducted the search; all the authors contributed to final version of the paper

diagnosed cancer cases—and 1.6 million cancer-related deaths (19.4% of the total) in the world every year (2). Although the incidence of lung cancer is decreasing in developed countries, it is rising in less developed parts of the world (South America, Africa, China and Eastern Europe) probably due to less rigorous smoking regulations (2). Smoking cessation, in fact, is crucial for preventing lung cancer, and public health actions aimed at quitting smoking have effectively helped to reduce the incidence of lung cancer (3-5). In addition, after receiving a lung cancer diagnosis, smoking cessation is significantly related to better overall survival, decreased post-operative complications, enhanced response to systemic therapies, better response to radiation therapy and—above all—significantly improved quality of life (6). Clinical outcomes in lung cancer are strictly related to the cancer stage at the time of diagnosis, ranging from good results in early stages to extremely poor outcomes in advanced disease (7).

The standard care for stage I, stage II, and selected cases of stage IIIA non-small cell lung cancer (NSCLC) is surgical resection; in some cases, patients may be offered adjuvant systemic therapy after surgical resection (8,9). Stage III NSCLC is a heterogeneous disease and therapeutic options vary depending on tumor burden, symptoms as well as several patient factors. Surgical approach to stage III NSCLC is still widely debated (8).

Patients with lung cancer presenting with distant metastases belong to stage IV; in this setting, the goals are to improve quality of life and to prolong overall survival; the best options for cure in this stage are chemotherapy, targeted therapy and immunotherapy (8). We present the following article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1491/rc).

Methods

Research selection

English literature review from 1995 to 2022 from PubMed and Scopus was performed (*Table 1*).

Discussion

Early stage

Surgical resection is the gold standard of treatment for early-stage lung cancer and lobectomy with lymphadenectomy represents the standard surgical approach since 1960 (9). In 1995, a first randomized controlled trial compared sublobar resection with standard lobectomy in stage IA lung cancer patients in terms of overall survival with detrimental results. Patients submitted to sublobar resection, in fact, disclosed a higher death rate and a three-fold risk for local relapses (10); since then, sub-anatomical resections for early-stage lung cancer have therefore only been taken into consideration for very selected patients with poor cardiopulmonary function or other significant comorbidities contraindicating lobectomy.

More recently, thanks to computed tomography (CT) screening of lung cancer and advances in diagnostic modalities, such as thin-section CT, the detection rate of early stage tumors as well as ground glass opacities has significantly increased. As a result, the practical indication of sublobar resections has been more frequently considered

as a valuable alternative to standard lobectomy for treating early-stage lung cancer even in fit patients (11).

In a recent multicenter, open-label, phase III, randomized, controlled, non-inferiority trial form the West Japan Oncology Group and Japan Clinical Oncology Group, segmentectomy was compared to lobectomy in small-sized peripheral NSCLC. At a median follow-up of 7.3 years, the 5-year overall survival was 94.3% for segmentectomy and 91.1% for lobectomy, thus showing improved overall survival across all predefined subgroups in the segmentectomy group. Moreover, the 5-year relapse-free survival was 88% for segmentectomy and 87.9% for lobectomy (P=0.9889) and the proportions of patients with local relapse were 10.5% for segmentectomy and 5.4% for lobectomy (P=0.0018), in both cases without any significant difference (12). This study was the first trial showing the advantages of segmentectomy compared to lobectomy—in terms of overall survival—in patients with small-peripheral NSCLC. The results suggested that segmentectomy should be the standard surgical treatment for this cohort of patients, irrespective of cardiopulmonary functions and comorbidities (12). Nevertheless, the present gold-standard treatment for NSCLC remains standard lobectomy with lymphadenectomy.

Jang *et al*. recently analyzed the trend—during the last two decades—of stereotactic body radiation therapy (SBRT) as an alternative to surgery for treating early-stage NSCLC (13). They showed that, although lobectomy remains the most frequent and preferred therapeutic approach, there was a significant increase in the rate of SBRT from 2004 to 2016, with a corresponding decrease in patients receiving no treatment (13). Moreover, they observed that the size of neoplastic lesions decreased across all therapeutic approaches, thus reflecting early detection and consequently less extensive diseases to be treated; in fact, patients who did not receive any local treatments (SBRT or surgery) tended to have the largest neoplastic lesions (13).

As reported before, surgery still represents the standard of care for early-stage NSCLC patients in good clinical conditions; anyway, for those who are in poor conditions or unwilling to receive surgery, SBRT represents the best alternative therapeutic option (14). However, radiotherapy may generate toxicity which depends on several factors, such as the whole amount of healthy tissue irradiated and natural variation of radiosensitivity of the healthy tissues (15). Side effects of radiation therapy can be acute or late: in the first case, they occur within the first 90 days after treatment and usually resolve totally although in some cases they may significantly affect quality of life and occasionally may even cause death (16). Moreover, when radiotherapy-related acute side effects are not properly resolved, they may culminate in a clinical scenario defined as "consequential late damage" (17). On the other hand, late adverse events are more frequently impossible to reverse, being progressive and thus impacting more significantly than acute adverse events on the patient's quality of life (17).

Locally advanced stage

About 10–20% of new diagnoses of NSCLC are patients with stage IIIA disease, presenting with mediastinal ipsilateral lymph node involvement. In very selected cases, these patients may benefit from surgery but, in the light of the significant heterogeneity of this cohort of patients, a multimodality approach must always be considered. In fact, mediastinal lymph node involvement may range from very limited N2 disease (single station N2 disease) to a multi station or bulky mediastinal involvement (18). This explains the wide variety of therapeutic options in locally advanced disease, the multimodality approach being the best option in this setting. Preoperative chemotherapy—defined as induction treatment—followed by pulmonary resection has shown to favorably impact on progression-free survival and overall survival in potentially resectable N2 patients (19). In fact, radically resected N2 patients after induction treatment disclosed a five-year overall survival of 35% that was significantly higher than that of patients receiving exploratory thoracotomy or incomplete resection, whose five-year overall survival was 8% (19-21) thus emphasizing the therapeutic role of surgery to treat the residual neoplastic disease in selected patients.

In the Intergroup 0139 study, patients treated by lobectomy disclosed a considerable benefit in terms of survival thanks to the addition of surgery to induction chemotherapy and radiation (22); on the other hand, patients undergoing pneumonectomy did not show a similar advantage in terms of survival because of marked perioperative mortality (22). At this stage appropriate patient selection for surgical approach therefore plays a pivotal role and should be carefully balanced by a multidisciplinary approach (23). An update from the PACIFIC trial disclosed a reduced risk of death by 29% thanks to consolidation therapy with one year of durvalumab; moreover, patients receiving consolidation immunotherapy had a four-year overall survival of 49.6% compared to 36.3% observed in

patients not receiving immunotherapy (24).

Additional promising data has come from studies focusing on preoperative immunotherapy with durvalumab combined with chemotherapy (induction chemo-immunotherapy) followed by surgical resection in patients with multiple stations or single station lymph node involvement (25) as well as from chemo-radio-immunotherapy (26). Surgical specimens disclosed major pathological response in 62% of treated patients and complete pathological response up to 10% of patients, findings that have been favorably correlated with overall survival and represent the new frontier of multimodality treatments in stage III NSLCC patients (25).

From the surgical point of view, we have to take into consideration that induction treatments increase surgical difficulty and risks because of increased vascular frailty and development of tissues adhesions, thus contributing to higher postoperative morbidity and mortality rate (27,28). Video-assisted thoracoscopic surgery (VATS) resections after induction treatments have thus represented a relative contraindication due to the additional technical difficulties related to the thoracoscopic approach (29-32). Nevertheless, thanks to thoracoscopic techniques and instrument developments, an improved learning curve and a significantly greater experience acquired in recent years, VATS indications have been extended to more challenging procedures (31,32), and some studies suggested that thoracoscopic resection after induction treatments can be safely performed (33-35) although clinical evidence of its safety is still widely debated (35,36).

Oligometastatic stage

Almost half of all lung cancer patients already have stage IV disease at the diagnosis for distant metastases (37-39). They are therefore usually judged not eligible to surgery and approached by medical therapy and palliative procedures if needed. Surgical approach is limited to diagnostic or palliative purposes, curative intent being almost anecdotal. Anyway, stage IV NSCLC patients includes a very heterogeneous population, with significantly different overall survival, depending on the number and sites of metastases.

In 1995, Hellman and Weichselbaum first proposed the "oligometastatic" setting, in which the few metastases observed reflect a specific biology of the primary tumor and a less aggressive attitude compared to standard metastatic disease (40). Some major points should be clearly addressed when dealing with oligo metastatic disease, in particular the number of metastases, their appearance in relation to the primary tumor (metachronous versus synchronous) and the involvement of single or multiple target organs (41,42).

The local treatment of oligometastatic patients has recently become more frequent and clinically relevant, in particular during the last few years thanks to significant improvements in target therapies and immunotherapy, thus overcoming the oncologic approach to contraindicate surgery in this setting (37).

Interestingly, dostarlimab—which is an anti-programmed cell death protein-1 antibody—disclosed encouraging antitumor activity in advanced and relapsing NSCLC that progressed after platinum-based chemotherapy, showing an acceptable safety profile.

Considering the lack of randomized controlled trials focusing on oligometastatic patient treatment, an aggressive approach is recommended for otherwise healthy patients disclosing only one extrathoracic metastatic site, without mediastinal lymph node involvement. In this setting, local control by resection of both primary and metastatic site, or by SBRT is indicated. Patients with a single brain lesion and patients with synchronous metastatic disease rather than metachronous disease disclosed the best overall survival when treated as reported above (43-45).

Casiraghi *et al.*—in their retrospective analysis of surgically treated synchronous oligometastatic NSCLC—showed an encouraging 30% 5-year overall survival, similar to the previous experience of Ashworth *et al.* (37,46). Although the majority of treated patients (75%) presented an early recurrence with a median time to recurrence of 9 months, it is worth reporting that 25% of patients did not present any relapse with a median overall survival of 39 months, ranging from 5 to 178 months (37).

Summary

Surgical treatment of lung cancer still plays a pivotal role in early stages while, in locally advanced stages, it may contribute to improve overall survival in combination with medical treatments and radiotherapy. More recently, an effective role of surgery has been advocated in carefully selected oligometastatic patients with encouraging initial results.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1491/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1491/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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