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Oligometastatic Disease in Lung Cancer for Surgeons: An Update

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Abstract
Purpose of review Stage IV non-small cell lung cancer (NSCLC) is a heterogenic disease with constant challenges for physicians. In the case of oligometastatic disease, surgery has a crucial role. In selected cases of a possible indolent progression of the malignancy, a surgical approach is recommended to control the disease. The management of this subset of patients should be performed in a multidisciplinary team in order to define the best strategy for each patient.
Recent findings The implementation of optimizing surgical management has demonstrated better outcomes in terms of long-term survival with no detrimental impact in morbidity and mortality. The progressive identification and use of molecular targeted therapies and immunotherapy has led to considerable improvements in responses among patients with advanced, unresectable NSCLC. As a result, the new concept of oligoprogressive disease is another demanding task to manage for oncologists and surgeons.
Summary Further studies are needed in order to best select patients, and to identify the best strategy to adopt also with the association among surgery, radiotherapy and oncological drugs.

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Introduction

Lung cancer remains the principal cause of cancer-related death worldwide [1].

The awareness and management of lung cancer is continually progressing. In patients with NSCLC with distant metastases, considerable improvements in treatment outcomes have been achieved. Stage IV NSCLC is a challenging disease since it includes a heterogenic group of patients in terms of histology and type, location and number of metastases. The complexity of this disease management has been highlighted by the authors to revised o the TNM stage classifications for lung cancer [2••]. In fact, the 8th TNM classification now classifies oligometastatic disease as a distinct different category, the M1b (extrathoracic distant oligometastasis), differentiating it from M1c (multiple distant lesions).

Even if there is not a defined standard definition of oligometastatic disease (generally from 1 to 5 lesions and restricted organ involvement), the new concept of this group of patients has allowed physicians to try to identify patients who would benefit from surgery. In selected cases, the literature shows that surgery is a feasible approach to implement long-term survival [3, 4].

Therefore, it is acknowledged that in case of oligometastasis in the brain, lungs or adrenals, surgery can provide curative results [5].

Oligometastatic Disease: Patient Selection

As mentioned above, selection is extremely important. Patients may be amenable for local therapy with curative intent if both the primary and all known metastatic lesions can be radically treated [6]. Therefore, the selection criteria for determining patients best suited for this management should include the location and number of metastases, the stage on intrathoracic tumour (T and N), histology and molecular characteristics. Regarding nodal involvement, according to the recent study of Johnson et al. [7], it is suggested that patients with N2 disease for local therapy with curative intent are excluded, which is in line with international guidelines [8••].

Focusing more on lung metastases, frequently the manifestation of localized disease, pulmonary metastasectomy provides better long-term survival and has a potentially curative intent in selected cases with a fair amount of risk factors [3, 9]. In recent years, surgical approaches have been developed guaranteeing safer surgical operations with less morbidity and improving survival [10–12].

In a recent meta-analysis, aggressive thoracic therapy (surgery or radiotherapy with at least 40 Gy delivery) was investigated in oligometastatic NSCLC in order to verify a possible impact on survival. The retrospective data showed that the treatment provided a 52% overall reduction in terms of risk of death. The survival rates in patients receiving this therapeutic approach had more than doubled [13].

Also the study of California Cancer Registry patients described an improvement in median overall survival (mOS) in stage IV NSCLC undergoing surgery in a multimodality treatment approach. In that study, mOS ranged from 9.4 to 28 months (depending on incorporation of chemotherapy and radiotherapy with surgery) versus 2–10 months in patients not receiving surgery [14]. A recent review analysed the feasible employment of surgery as an approach for therapeutic "consolidation" in selected patients with stage IV NSCLC receiving combined modality treatment. This strategy appears intriguing, and further studies should be undertaken [15].

According to the positive results, as previously mentioned, international guidelines recommend lung resections for selective stage IV NSCLC [5, 8]. However, the accurate selection of patients may demonstrate that the better outcomes are associated either to the indolent tumour characteristics or to the treatment interventions. In either case, the expected benefit has been proven.

Oligoprogressive Disease

The role of surgery is becoming more and more relevant to the management of NSCLC with the availability of new targeted therapies and immunotherapeutics. In patients with molecular mutations in EGFR, ALK, ROS1 and MET genes, molecular-targeted agents provide better outcomes in terms of progression for disease-free and overall survival associated with strong responses in objective response rates (ORRs) (with respect to the wild-type population) [16•]. As a result, especially in this subset of patients, local therapy for oligometastases may strongly increase progression-free and overall survival outcomes. The new, distinctive identity named "oligoprogressive" state should be highlighted. It represents disease progression at a restricted number of sites while maintaining responsive or stable disease at other sites of the tumour. This is a special condition frequently described in oncogene-driven NSCLC treated with such tyrosine kinase inhibitors.

The hypothesis to explain this behaviour is related to the clonal heterogeneity and better extrinsic selection pressure linked to the administration of targeted therapies. This type of therapy heralds in the power of individualized medicine.

Therefore, in this particular situation, local ablative therapy is not only confined to symptom palliation but also the clinical benefit of such treatments in patients who develop resistance. As a result, it is possible to avoid switching systemic treatments too early preserving the patient with more options and different strategies over time [17, 18].

Surgery for Symptoms Palliation

As reported, thanks to the development of new drugs and novel therapeutics, immunotherapies and biologics, the overall survival of patients suffering from advanced NSCLC has gradually increased [19]. On the other hand, several complications—related to longer survival—like pleural effusions, pericardial effusions and tracheobronchial stenoses have become more frequent.

Surgery may also play a pivotal role in the treatment of this cohort of complications, improving quality of life and preventing major life-threatening conditions.

Operative rigid bronchoscopy with tracheobronchial laser and stenting allows for airway lumen restoration, preventing fatal airway bleeding and obstruction [20]; video-assisted thoracic surgery is ideal for pleural effusions treated by talc pleurodesis, as well as for pleural biopsies; pericardial—peritoneal window is indicated for the definitive treatment of constrictive pericardial effusion, preventing a life-threatening tamponade.

Table 1 Lung cancer staging, tumour, node, metastasis staging 8th edition

T	Primary tumour	
	Tx	Cannot be assessed; tumour in sputum/bronchial washings not in imaging/bronchoscopy
	T0	No evidence
	Tis	Carcinoma in situ
	T1	$\leq$ 3 cm surrounded by lung/visceral pleura, not involving main bronchus
	T1a (mi)	Minimally invasive adenocarcinoma
	T1a	$\leq$ 1 cm
	T1b	$>$ 1 to $\leq$ 2 cm
	T1c	$>$ 2 to $\leq$ 3 cm
	T2	$>$ 3 to $\leq$ 5 cm or Involves main bronchus without carina involvement or visceral pleural invasion or atelectasis/post-obstructive pneumonitis extending to hilum
	T2a	$>$ 3 to $\leq$ 4 cm
	T2b	$>$ 4 to $\leq$ 5 cm
	T3	$>$ 5 to $\leq$ 7 cm or separate tumour in same lobe or direct invasion of chest wall (includes parietal pleura and superior sulcus)/parietal pericardium/phrenic nerve
	T4	$>$ 7 cm or separate tumour in different lobe of ipsilateral lung or invasion of heart/great vessels/diaphragam/mediastinum/trachea//oesophagus/recurrent laryngeal nerve/vertebral body
N	Regional lymph node	
	Nx	Cannot be assessed
	N0	No involvement
	N1	Ipsilateral peribronchial and/or hilar nodes and intrapulmonary nodes
	N2	Ipsilateral mediastinal and/or subcarinal nodes
	N3	Contralateral mediastinal or hilar; ipsilateral/contralateral scalene/supraclavicular
M	Distant metastasis	
	M0	No distant metastasis
	M1	Distant metastasis is present
	M1a	Tumour(s) in contralateral lung; pleural/pericardial nodule/malignant effusion
	M1b	Single extrathroacic metastasis
	M1c	Multiple extrathoracic metastases, in one/more organs

Adapted from Reference [24]

Surgery as Diagnostic Tool

Finally, the advantage of using the surgical approach is also to have more information about histological and biomolecular characteristics of the tumour. Obtaining tumour tissue is pivotal to analysing the potential markers for novel therapeutics and the mechanism of resistance. The better and deeper understanding of these mechanisms in addition to the research of new potential biomarkers can help to administer more effective disease-management therapies to patients. Moreover, obtaining more tumour tissues gives the opportunity to enter in clinical trials, thereby implementing the possibility to be cured or have the most cutting-edge therapies utilized.

The research of a much more detailed diagnosis with mutational status assessment, as well as the need for new histological confirmations following several treatments, led to the development of a new branch of surgery, specifically devoted to diagnostic acquisitions, done primarily by minimally invasive approaches.

Video-assisted thoracic surgery still plays a crucial role in this field, in particular for pleural and lung biopsy, as well as lymph node sampling or biopsy; mediastinoscopy has almost been replaced by less-invasive endobronchial ultrasound transbronchial needle aspiration (TBNA) for mediastinal staging before surgery [21], although it may be still indicated in some cases; supraclavicular biopsies according to Daniel's description is useful for neoplasm characterization as well as for N3 disease staging.

Other Procedures

Thermal ablation techniques have been used as therapeutic method for both non-resectable primary and secondary lung cancers (Table 1 and Fig. 1).

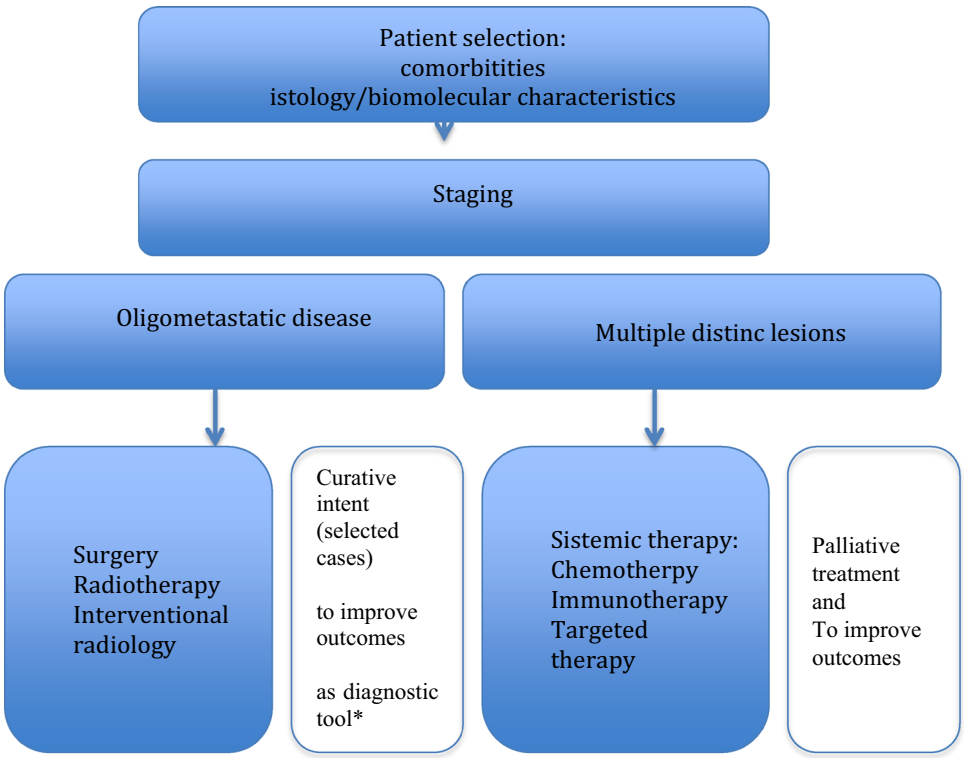

Fig. 1 Work-up and management scheme

*only surgery

Percutaneous ablation procedures, like microwave ablation (MWA), radiofrequency ablation (RFA) and laser-induced thermotherapy (LITT) are safe and efficacious choices for subjects who are not candidates for surgery [22•].

MWA uses higher frequencies than RFA (915 MHz and 2.45 GHz vs. 460–500 kHz for RFA) and adopts direct heating. This leads to the utilization of higher temperatures and to improve the efficacy with more homogenous areas of thermal coagulation rapidly and with lesser heat sink effect [23].

Conclusions

In selected subjects, metastases resection is a safe and feasible approach with no detrimental impact on mortality and morbidity, associated with increased survival and beneficial outcomes. Data show the important role of surgery in the setting of oligometastatic NSCLC with the challenge of increasing number of patients being referred to surgery for resection. Pushing for multidisciplinary team approach is mandatory in order to provide optimal treatment for each patient with the potential association of other techniques as radiofrequency ablation, radiotherapy and chemotherapy/immunotherapy/biologic drugs.

The availability of new molecular-targeted drugs and immunotherapy is rapidly changing the treatment scenario for NSCLC. Consequently, the role of surgery for selected stage IV NSCLC is intended to increase the survival benefit for curative intent. The possibility to obtain more tumour tissues to analyse provides a deeper understanding of NSCLC while also providing more therapeutic options to choose from in order to treat our patients.

Further studies are needed in order to best select patients, and to identify the best strategy to adopt also with the association among surgery, radiotherapy and oncological drugs.

Compliance with Ethical Guidelines

Conflict of interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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