Review Article

Surgical approaches in patients with oligometastatic non-small cell lung cancer

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Abstract: In recent years, retrospective analyses have suggested that an oligometastatic state could exist, but the best evidence to date that a temporary oligometastatic disease exists for lung cancer mainly derives from the survival data on retrospective patients underwent surgical resection of a single M1 site and all intrathoracic disease. The critical determinates of long-term survival include definitive treatment of the primary non-small cell lung cancer (NSCLC), a single organ site of synchronous or metachronous disease, a long disease-free interval between treatment of the primary NSCLC and development of metastases, and the absence of intrathoracic lymph node (N0) disease. The ongoing development of innovative approaches to local therapy and treatment directed to the oligometastatic sites should be defined in future studies.

Keywords: Lung cancer; oligometastatic; thoracic surgery

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Introduction

In recent years, retrospective analyses have suggested that an oligometastatic could exist, but the best evidence to date that a temporary oligometastatic disease state exists for lung cancer mainly derives from the survival data on retrospective patients underwent surgical resection of a single M1 site and all intrathoracic disease. Retrospective series had demonstrated that prognosis is different between single metastatic patients and multiple lesions/organs patients. Nonetheless, the retrospective characteristics of these studies and the definition differences in oligometastatic disease or different choices on tailored local treatment created heterogeneity without consensus statements. Distant metastases were subdivided into two groups basing on the prognostic differences for a single metastatic lesion in a single organ (M1b) versus multiple metastatic lesions in a single organ/multiple lesions in multiple organs (M1c). Based on the analyses of these data, the VIII Edition of TNM classification provide the recommendations of maintaining the use of the current M1a category, including pleural/pericardial effusion, contralateral/bilateral tumour nodules, pleural/pericardial nodules, and multiple M1a descriptors. TNM VIII Edition reclassifies the current M1b category for patients with a single metastatic lesion in a single organ site and introduces the new M1c category for patients with multiple lesions in single organ/multiple organs. Therefore, the changes in the M descriptors of the VIII Edition keep the compatibility with the M descriptors of the VII edition, define better oligometastatic disease, and improve the possibility of an indication of a prognosis (1). The first treatment for metastatic non-small cell lung cancer (NSCLC) is palliative chemotherapy with a reduced median survival and a minimal chance of long-term survival.

Despite these unfortunate outcomes, encouraging reports of long-term survival in select oligometastatic NSCLC treated with curative intent have emerged (2). It appears realistic to consider that solitary resectable NSCLC metastatic patients should undergo surgical resection of all visible disease, and in adenocarcinoma with lower T and N0–1 stages. A more wide-ranging knowledge of tumour biology should lead to the discovery of clinically biomarkers enabling improved patient selection (3).

Definition of oligometastatic status

The Halstead theory has profoundly influenced the paradigm of cancer pathogenesis showing the spread of breast cancer. In 1894, Halsted defined that spread extended continuously from a primary tumour through lymphatics vessels to lymph nodes first and then distant. The recently systemic hypothesis stated that cancer is a congenital disease. Small tumours are an early appearance of systemic disease, and lymph node involvement is not a connecting extension of cancer, but a marker of distant or micrometastatic disease. Unifying hypothesis presented by Hellman synthesises the previous theories and argues that cancer is a biologic range extending from a localised illness to a systemic one, even at the time of diagnosis, but with many intermediate states. Therefore, Hellman and Weichselbaum first proposed the oligometastatic concept in 1995. The anatomy and physiology of individual tumours may limit metastases to a single or a limited number of organs. The likelihood of an oligometastatic state correlates with the biology of a tumour (e.g., the primary tumour size and the tumour grade). Moreover, metastasis to organs is a function of the seeding cell number as of the receptiveness of the host. In this theory, the number of metastases should reflect the biologic behaviour of a tumour, determining the opportunity for potentially curative interventions. Tumours in early progression should be amenable to localised therapy, patients with the oligometastatic disease may be cured with ablative (e.g., surgery, radiotherapy) therapy of their metastatic lesions, and advanced disease patients should be treated with systemic palliative therapy (4,5).

Diagnosis of the oligometastatic status

An oligometastatic status consists of patients with metastases limited in number and organ site(s) who may have a more indolent biology and progression at existing sites without widespread metastases (6). The improved survival published is an echo of improved staging due to the higher sensitivity of Positron Emission Tomography (PET) for metastatic disease and the more appropriate selection of oligometastatic status. Evaluating oligometastatic NSCLC, it is also crucial the use of brain MRI (more sensitive evaluating solitary intracranial lesions). Computed tomography (CT) alone is insensitive to potentially smaller intercurrent intracranial lesions and may lead to an underestimation of a patient's actual metastatic disease burden. In this molecular era, it is also crucial to remember that NSCLC is not a single disease entity, but a compilation of molecularly distinct subtypes with differing biologies, natural histories and responses to therapy. Little is known of the natural history of an oligometastatic wild-type NSCLC versus an oligometastatic mutated or rearranged. The biology differences necessitate different approaches to treatment. Regarding the management, aggressive treatment of both local and oligometastatic sites should be reserved only for a period of observation of 6–12 months, allowing the natural history of the oligometastatic disease and the better selection of more favourable underlying biology who will obtain the benefit from aggressive surgical resection (4). There is a paucity of randomised study about the management of synchronous or metachronous oligometastatic NSCLC. Although some highly selected patients achieve long-term survival, most develop progression within first-year. Long-term survival predictors include the definitive treatment of a primary tumour, a long disease-free interval between treatment and development of metastases, and lack of intrathoracic nodal metastasis (2). Nevertheless, the decision on all oligometastatic patients should be discussed at the multidisciplinary meeting.

Principles of surgical treatment

When considering surgery in the treatment of oligometastatic NSCLC, a careful investigation into the presence of intrathoracic nodal metastases is mandatory. Despite negative mediastinal lymph nodes on staging CT-PET, invasive mediastinal staging with endobronchial ultrasound or mediastinoscopy is highly recommended in this high-risk population. Patients who demonstrate pathologic N2 disease should be excluded from surgery. A primary tumour should be amenable to complete R0 resection; anything less would argue against a therapeutic approach to oligometastatic disease. Oligometastatic disease sites should be responsive to dynamic full local control either by surgery or by an

ablative modality, such as stereotactic body radiotherapy (SBRT). There is no consensus on how and when to institute systemic chemotherapy about local control of either the oligometastatic site or the primary. Different approaches could be found in literature:

(I) Local control of the oligometastatic site followed by neoadjuvant chemotherapy first and lung surgery;
(II) Local control of the oligometastatic site followed by lung surgery;
(III) Induction chemotherapy followed by lung surgery and then local control of the oligometastatic site;
(IV) Lung surgery and treatment of the oligometastatic site simultaneously (6-9).

In patients with an apparent oligometastatic disease at initial diagnosis, one of the dilemmas is the timing of surgery vis-à-vis of chemotherapy. Theoretical reasons for surgery first are the obtainment of tissue for analysis/genomics. At surgery, treatment-naïve patients have an improved performance status, and the chemotherapy effects are potentially better. Also, a minimally invasive approach (if feasible) should be achieved to allow a faster recovery and, therefore, early beginning of the systemic therapy. On the other hands, the arguments in favour of chemotherapy first are the early starting of the systemic treatment, the better compliance/delivery of chemotherapy, and the discovering of individuals with possible new occult M1 disease (10). Authors in literature concluded that there is no advantage to any sequence of therapy. Nevertheless, predictors of favourable outcome included the single site of the disease diagnosed by CT-PET, the absence of weight loss higher than 10%, complete resection, and pathologic N0 disease (6). Probably, the N2 disease is the most important independent prognostic factor; therefore, oligometastatic patients should be aggressively treated after 6–12 months of wait and see. As they should have a favourable biology, these patients are the best candidates (11). Although extended survival can be achieved in a subgroup of patients, a high proportion of patients with oligometastatic NSCLC fail locally and systemically soon after treatment, with a median time to recurrence of 12 months (6). Metastases to different organs should not necessarily be considered equivalent. The differences between sites include the feasibility of extensive surgical resection, the penetration of chemotherapy to the site to eradicate residual micrometastatic disease, and the likelihood that the clones of cells giving rise to metastases in different organs are fundamentally different. The limited information available suggests that there may be a small group of patients with primary lung cancer with a single extrathoracic site of metastatic disease who would benefit from therapy other than systemic chemotherapy alone. The best treatment (e.g., surgical resection of both sites without chemotherapy, surgical resection with chemotherapy and/or radiation therapy) cannot be defined from the available literature. Separate algorithms for the synchronous and metachronous disease could be considered (12). Significant statistical differences in survival after treatment were offered by lung metastasis contrary to extrapulmonary metastasis, low-grade primary tumour opposite to G3 and overall, pN0/pN1 versus pN2/pN3 lymph nodes (11). Definitive ablation of metastatic sites, which may be either at presentation, if necessary, or after induction chemotherapy and with or without radiation therapy, as deemed appropriate. At the end, the surgical resection of residual disease at the primary site (12). Although done in few patients, the surgical approach could be advantageous for oligometastatic patients. In a narrative review of the literature on surgical intervention in the multimodality management of stage IV NSCLC, surgical resection can result in an excellent 5-year survival heavily influenced by the presence of mediastinal nodal disease (13). Therefore, mediastinal lymph nodes status should be evaluated before therapeutic surgical procedures. Additionally, diagnostic or palliative surgical procedures can play a significant role in the tailored treatment of stage IV as a strategy for consolidation (13).

Cerebral metastases

Apparently, single brain metastasis sustains a possible role for following pulmonary resection. In these patients should be obtained a complete staging with a CT/PET scan and the contrast-enhanced MRI brain imaging. On the other hand, a negative mediastinoscopy before lung resection should be obtained. In patients with isolated brain M1, the problem is the timing: brain or chest first? If brain metastases are usually symptomatic, they should be addressed first. Even if asymptomatic, the brain should first be treated since the development of symptoms (10).

Adrenal metastases

The N0 status is the best predictor of better results. In literature, we also have one dataset suggesting the metastatic adrenal site as a prognostic factor where the contralateral involvement negatively affected the survival (10).

Contralateral lung

In the new VIII classification, the stage IV diseases also include in the M1a descriptor the contralateral lung nodule. The lesions are frequently synchronous at diagnosis. Since the prognosis and the treatments are different, the differential diagnosis between a synchronous primary from an advanced lung cancer is crucial (14). The diagnostic challenge is if the patient has a metastatic disease or a multifocality of a still localised cancer. The Martini-Melamed criteria, even if described in 1975, remain useful (15). Nevertheless, in a fit patient with a full preoperative staging including also a negative video-mediastinoscopy, a segmentectomy should be encouraged. The diagnosis of a regional nodal involvement (pN1/N2) in a side should reconsider the contralateral approach. All oligometastatic patients should always be discussed in a multidisciplinary meeting. In some patients, it could be offered a segmentectomy on one side and a contralateral stereotactic ablation. Nevertheless, surgical options offer additional information that SBRT cannot provide (10). Selected bilateral NSCLC may benefit from these approaches achieving an acceptable morbidity/mortality, and an excellent long-term survival (14). A meta-analysis indicated that aggressive thoracic therapy might improve overall survival in patients with synchronous oligometastatic NSCLC. The relative overall survival benefits of aggressive thoracic therapy were also seen in patients with brain metastases and patients of all thoracic stages. These findings have significant implications for clinical trial design and intervention. However, randomised controlled trials are still warranted to support the results further, to optimise treatment regimen of aggressive thoracic therapy, and to identify clinical or molecular predictors for the tailored selection of patients (16).

Metachronous disease

The steps for the synchronous condition should be the histologic confirmation of a primary NSCLC within the previous 5 years. A radiographic staging should suggest a single site of extrathoracic metastatic spread and should be followed by definitive ablation of the metastatic site by surgery, with or without radiation therapy, as deemed appropriate, with either neoadjuvant or adjuvant chemotherapy (12).

Conclusions

The oligometastatic disease is an anew category of patients where multimodality therapy may improve prognosis. Many intriguing enquiries about the oligometastatic disease have no definite answer now (17). Without randomised data to better define the appropriate management of oligometastatic NSCLC, an aggressive therapy for fit patients with a single organ site of synchronous (or metachronous) extrathoracic M1 disease and without intrathoracic lymph nodes involvement should be used. Local control of both the primary and oligometastatic site can be achieved by either complete surgical resection or by SBRT modality. A therapeutic strategy for patients who harbour multiple synchronous or metachronous sites of oligometastatic NSCLC should be carefully considered on a case-by-case basis. Systemic chemotherapy is often used somewhere in this strategy, but the timing and efficacy remain unclear. Targeted chemotherapy (in addition to a dynamic local control) should be strongly encouraged in the treatment strategy of patients with oligometastatic NSCLC who harbour sensitising driver mutations. Long-term survival determinants include the aggressive treatment of the lung NSCLC, a single organ metastasis (synchronous or metachronous), a long disease-free interval between the surgical approach of the lung and development of metastases, and the pN0 status. Future possibilities should include the ongoing development of innovative approaches to local therapy where SBRT could minimise the morbidity associated with surgical approaches. The biologic differences might also distinguish, in the next future, the oligometastatic from widely metastatic NSCLC and the differences between an indolent and an aggressive course of the disease.

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Footnote

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