

Surgical approach in oligometastatic non-small cell lung cancer

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Abstract: The vast majority of lung cancer (80%) are non-small cell lung cancer (NSCLC) presenting in huge proportion of patients in a metastatic stage at the time of diagnosis with an overall survival (OS) of only 6 months. Standard treatment at this stage involves systemic platinum based chemotherapy improving the OS for only few months. For the vast majority of patients disease progression occurs and cure cannot be achieved. An exception to this general rule is represented by patients with a limited number of metastases (approximately 7% of patients with metastatic NSCLC): in 1995 Hellman and Weichselbaum introduced the term “oligometastatic” for a selected group of patients with metastatic disease. Several retrospective studies have been published and documented an improved outcome in patients managed surgically. The purpose of this narrative review is to gather all relevant information and present the various clinicopathological and generic aspects of diagnosis, management strategies and prognostic factors in patients with oligometastatic NSCLC. The key for long term survival includes radical treatment of the primary NSCLC, single organ site with either synchronous or metachronous presentation, a disease free interval to be as long as possible and the absence of intrathoracic lymph node spread (N0). A more accurate staging with combination of FDG-PET and CT scan can have an impact on the survival rates due to an increased accuracy in mediastinal staging and in the diagnosis of distant metastasis. No randomized data but only retrospective series are available to date to address this topic: in the future, additional prospective studies will be necessary to provide robust evidence to support the surgical resection as treatment of oligometastatic NSCLC.

Keywords: Lung cancer surgery; lung metastases; thoracic surgery

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Introduction

Lung cancer remains one of the most lethal neoplasm with a high incidence worldwide (1). The vast majority (80%) are non-small cell lung cancer (NSCLC) presenting in huge proportion of patients in a metastatic stage at the time of diagnosis with an overall survival (OS) of only 6 months (2). Standard treatment at this stage involves systemic platinum based chemotherapy (3) unfortunately improving the OS for only few months (2). Metastasis of

cancer should be microscopically present in the systemic circulation, justifying the need for systemic chemotherapy. Despite chemotherapy can improve survival, for the vast majority of patients disease progression occurs and cure cannot be achieved. An exception to this general rule is represented by patients with a limited number of metastases (approximately 7% of patients with metastatic NSCLC), where since the 1930s (4) efforts were made to eradicate the lesions with ablative therapy (with surgery or radiotherapy). In 1995 Hellman and Weichselbaum introduced the term

“oligometastatic” for a selected group of patients with metastatic disease (5). Several retrospective studies have been published and documented an improved outcome in patients managed surgically (6-9).

The purpose of this narrative review is to gather all relevant information and present the various clinicopathological and generic aspects of diagnosis, management strategies and prognostic factors in patients with oligometastatic NSCLC.

Definition of oligometastatic disease

Hellman and Weichselbaum (5) in 1995 originally introduced the term oligometastases describing a state of limited systemic metastatic disease whereby local therapies could be curative (10). This term suggests a restricted capacity of the tumor to aggressively spread considering the limited number of metastases that can be found: in these cases the slow progression of the malignancy raises the opportunity to an aggressive local approach to control the disease (5). According to the 7th Edition of TNM staging for NSCLC, curative surgery and local control of metastatic disease is reserved for M1b status where the M1a includes separate tumor nodules in a contralateral lobe, tumor with associated pleural nodule, malignant pleural or pericardial effusion) and the M1b describe the presence of extrathoracic metastases (11). The new 8th edition will consider M1b as a single metastatic lesion in one organ and M1c as multiple metastatic spread in a single organ or different organs. Prognosis is significantly better in patients with single metastatic lesion compared to patient with multiple metastatic spread (12,13). There is no clear consensus in the literature about the number of metastases as a cut-off point between the oligometastatic status and the metastatic status. We are considering the inclusion criteria of Hasselle *et al.* (14) defining the oligometastatic stage on patients with ≤ 5 extrapulmonary metastases. Oligometastatic stage can occur in a different number of clinical situation (5): patients with limited number of metastases at the time of diagnosis; patients with multiple metastasis with limited residual lesion post systemic treatment or patients where one lesion only progresses after systemic treatment (defined as oligoprogression) or patients where the limited disease reoccurs after systemic treatment (defined as oligo-recurrence).

Timing: synchronous vs. metachronous lesions

In 1975 Martini and Melamed (15) initially proposed

a diagnostic criterion to discriminate synchronous and metasynchronous multiple lung cancers from intrapulmonary metastases in 50 patients.

According to a concept introduced by Slaughter *et al.* in 1953 (16) smoker related carcinogenic insults affects bronchial tree cells resulting in invasive tumors of the lung that can appear simultaneously or sequentially. In addition, genetic changes have been also observed in the entire bronchial tree in long term NSCLC survivors. Therefore it is presumed that the development of a metachronous lung cancer may be related to the persistent exposure to carcinogenic stimuli on several areas of the lung with different risk for neoplastic development.

Several retrospective studies support a better prognosis in patients with metachronous presentation compared to patients with synchronous oligometastatic lesions: Ashworth *et al.* (17), after systematic review of the literature with data obtained from 757 patients with NSCLC concluded that OS was influenced by the timing of oligometastatic presentation ($P < 0.001$) and by the adenocarcinoma histology ($P < 0.036$). Five-year OS was 47.8% for cases with metachronous presentation while OS for patient with synchronous metastases with N0 and patients with synchronous metastases and N1/N2 disease was 36.2% and 13.8% respectively.

In patients with metachronous metastasis the subgroup with oligometastatic disease represent the subset with a more favourable prognosis (18-20). We have also to take into consideration that several variables like male sex, non-adenocarcinoma histology, smoking history and short DFI (disease free interval) play a crucial role influencing negatively the long term survival after curative intent treatment as described by Shimada and colleagues (20).

Organ specific consideration

Brain, adrenal glands, lung and bone have been proved to be the most frequent sites of NSCLC metastasis. Plones *et al.* (21) reported a survival rate of 23.4 months for patients with soft tissue metastasis, 16 months for patients with brain metastasis, 9.5 months in patient with adrenal gland involvement and 4.3 months in patients with bony dissemination ($P < 0.005$). Different case reports and small case series have been published describing metastases at the gastrointestinal tract (22), pancreas (23), breast (24), muscle (25), omentum (26), spleen (27), kidney (28), liver (29) and skin (30). Although the limit of these case studies, Salah *et al.* (30) published a study after collecting

data from extracranial and extra-adrenal cases showing a 63% survival rate at 5 years in patients with non-visceral metastasis and 39% in patients with visceral lesions.

Brain

Brain represents the most common site of extrathoracic distant metastasis in NSCLC with intracranial lesion found in 25% to 35% of patients with newly diagnosed NSCLC. Several retrospective studies have been published reporting long term survival in patients with solitary brain metastases managed with aggressive treatment of both the brain and the locoregional disease in the lung (6,31-33): in these series 5 years survival range from 1% to 35% (average 21%) in patients with complete resection. Mayo clinic study published in 2001 (32) showed that 5 years survival was far superior in patients with N0 disease compared with patients with N1/N2 disease (median survival 44 *vs.* 10 months). No patient with lymph node involvement survived more than 3 years after resection.

In order to select the appropriate candidates for curative treatment a precise staging has to be performed with PET CT scan, brain MRI and invasive mediastinal staging. Patients with intrathoracic nodal metastasis they have often a relapse after aggressive therapy as described by Wronski *et al.* (9) with an OS shorter than 3 years. Regarding the timing for the correct surgical management of the brain lesion patients symptomatic for brain metastasis should undergo surgical resection or stereotactic radiosurgery with or without brain irradiation before the surgical management of the primary lesion. Surgical resection followed by brain irradiation has been proved to be a better treatment due to improved local control of the tumor bed (34). The American College of Chest Physician in the latest review of lung cancer treatment (35) recommended that in case of synchronous presentation of brain metastasis with resectable N0-1 lung primary, resection or radiosurgical ablation is indicated; in patients with a previous resected NSCLC who present with metachronous single brain metastasis resection or radiosurgical ablation is recommended.

Adrenal gland

Adrenal Glands represent a common site of metastasis in patient with NSCLC being less frequent than brain metastasis with an incidence ranging from 1.6% to 4% in resectable NSCLC (36).

Despite PET CT may represent a valuable tool to distinguish metastatic disease, histopathologic confirmation should be always achieved before lung cancer surgery as the prevalence of adrenal incidentalomas is 4% to 5% in radiological series where more than 80% are benign (37). Recent anatomical studies demonstrated the presence of a direct retroperitoneal lymphatic channels between the chest and the adrenal gland suggesting that some adrenal gland metastasis may represent locoregional lymphatic spread rather than hematogenous metastasis: this can also explain why the incidence of adrenal involvement is more frequent in patient with clinical N1-3 disease (38).

Currently there are no randomized data on the treatment of synchronous or metachronous oligometastatic disease involving the adrenal gland in NSCLC. In a systematic review by Tanvetyanon *et al.* (39) patient with synchronous lesion had a shorter median survival than those with a metachronous lesion despite the 5-year survival estimates are equivalent (25% for both categories). In terms of timing for surgery for synchronous adrenal metastasis in patient with resectable N0-N1 primary NSCLC, the treatment strategy is to operate on the lung first followed by the adrenal lesion (40). In patients who have undergone curative resection for isolated adrenal metastasis, adjuvant chemotherapy is recommended.

Bone

Different studies suggested that bone metastasis cannot be considered an oligometastatic stage in any situation: Tonnies *et al.* in 2014 (41) reported a very low median survival in patients with bone metastasis (5 *vs.* 40 months), Xu *et al.* (42) reported a median survival time of 13 months in patients managed with surgery and radiotherapy versus 11.6 months in patients managed with radiotherapy alone. Other studies (20,43) reported even worse outcomes after surgical resection summarizing that bone metastasis are never associated with favourable long-term prognosis regardless the surgical approach even if we consider the location of the bone metastasis (like on a rib on the ipsilateral side of the tumor easily accessible via thoracotomy).

Lung

When dealing with a separate lesion in the same lung or in the contralateral lung the diagnostic dilemma is

to determine whether we are dealing with a metastatic disease or with a multifocal localized process. The Martini and Melamed Criteria (15) still represent a valuable tool despite some concerns have been raised to its current usefulness (44). Metastasis seems to be more frequent in the ipsilateral lung (21). In case of synchronous single contralateral lesion in a patient with good cardiopulmonary reserve who has undergone full assessment including a negative EBUS/mediastinoscopy, the treatment of choice is to accept the multifocality pattern and manage accordingly with surgical sparing anatomical resection (21). The presence of N1-2 disease on one side may lead to a full reconsideration of the planned contralateral intervention.

Summary and conclusions

Two developments are changing the role of surgery in the management of oligometastatic NSCLC. Surgery has achieved an increased role in this population: evidence support aggressive management of both primary and oligometastatic site on patients who present with a single organ site of synchronous or metachronous disease with no evidence of lymphatic spread. On the other hand stereotactic radiation will eventually lead to a decreasing role for surgery in patients in whom surgery was considered. The key for long term survival includes radical treatment of the primary NSCLC, single organ site with either synchronous or metachronous presentation, a disease free interval to be as long as possible and the absence of intrathoracic lymph node spread (N0).

A more accurate staging with combination of FDG-PET and CT scan can have an impact on the survival rates due to an increased accuracy in mediastinal staging and in the diagnosis of distant metastasis (45,46).

No randomized data but only retrospective series are available to date to address this topic: in the future, additional prospective studies will be necessary to provide robust evidence to support the surgical resection as treatment of oligometastatic NSCLC.

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Footnote

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