

The radical approach to the oligometastatic not small cell lung cancer patient: which? how? when? where?

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In 1894, Halsted defined that a primary tumour spread first through lymphatics vessels to lymph nodes and then to distant organs. Hellman argued that cancer, even at the time of diagnosis, is a biologic variety from a local to systemic illness with several transitional states. Subsequently, in 1995, Hellman and Weichselbaum first suggested the oligometastatic theory, where the number of metastases should imitate the biologic behaviour of a tumour, determining the chance for potential therapeutic interventions (1). In the eighth edition of the TNM classification, intrathoracic metastatic disease recollects the M1a classification. Extrathoracic metastatic disease is nowadays classified in the case of a single metastasis as M1b (2). Even so, regarding lung cancer oligometastatic non-small cell lung cancer (OMTS) patients, the eighth edition of the TNM classification is not clear and does not allow the uniformity of the studies and the results. Therefore, OMTS is clinically assessed as lung cancer in an advanced stage, but it is dissimilar from advanced lung cancer in general. Nevertheless, controversies remain regarding the treatment approaches (3).

In a prospective open-label phase II clinical trial published in the *Lung Cancer* Journal, Arrieta *et al.* favoured the use of radical consolidative treatments in patients with OMTS. Since a complete metabolic response predicts longterm survival outcomes, positron emission tomography (PET) scan was used as a tool to evaluate the response in these patients (4). Furthermore, as reported by Authors, some limitations affect this interesting study. A selection bias requiring substantial, multicentre studies (in other words, more robust sample sizes) should be noted. Initial systemic therapy was selected at the discretion of the treating physician. Lastly, the limited availability of the last generation target therapy should also be noted (4).

Approximately one-quarter of all patients with metastatic disease discussed in a multidisciplinary meeting is in an oligometastatic state (5). Until recently, the cornerstone of OMTS management was characterised by systemic therapy. However, consensus statements and guidelines progressively sustain the integration of locally ablative therapies (like surgery or stereotactic body radiation therapy) (6). Several factors have hampered broad adoption of surgery in OMTS since all the supporting data for surgery are retrospective, the experience is limited to patients with a single metastatic site, and the survival advantage could be attributed to selection bias (7).

Whatever the site of the metastatic disease, OMTS is still an exedra of open discussion. Most of the published Literature established that the best treatment and doubtless the gold standard for selected patients were combined surgical therapy, while the identification of prognostic factors influencing survival remains unclear (8). An essential distinction in OMTS is the synchronous (metastatic lesions recognised at diagnosis or following an initial disease-free period) and metachronous disease

(respectively termed). The amount of patients with synchronous disease augmented, due to the widespread utilisation of advanced imaging technologies and, then, the increased identification of previously occult metastases. The metachronous disease could be the isolated progression of one or a small number of metastases after initial therapy. In around 60% of relapsed NSCLC, metastases return in sites previously known affected by cancer (9). After synchronous or metachronous resections of lung cancer and oligometastatic lesion, proper control of local disease at each site and long-term survival are readily achievable. Positive predictive factors for the long-term outcome of the OMTS patients were the single metastasis (identified by PET), the nonappearance of weight loss <10%, the possible surgical resection, and the pathologic N0 status (8). The management of OMTS is undergoing a paradigm shift, and patients with dismal prognosis, heretofore measured in months, could nowadays be measured in years (10). Therefore, the selection of patients who could benefit from radical treatment is of paramount importance (11). Active smoking showed a detrimental effect on local control and overall survival in OMTS patients undergoing radical treatments. The other variables favourably associated with overall survival were the absence of perineural and lymphovascular neoplastic emboli in the pulmonary tumour specimens (6). Synchronous OMTS receiving multimodality treatments (radical treatment of the primary tumour and locally ablative treatment of metastases) show promising outcomes. Clinical presentation of metastatic disease, location, and size of the lesion, and availability of specialised surgery or stereotactic body radiation therapy facilities may also influence the choice of treatment and sequence (6). Other critical determinants of long-term survival could lastly include female gender, lower nodal stage, adenocarcinoma histology, thoracic stage (12). To stratify OMTS patients for individualised care, nomograms could be used. The scoring system could also select or stratify OMTS patients in trials. Also, in clinical practice, the nomograms could guide the multidisciplinary tumour board in choosing the most appropriate therapeutic project (13).

OMTS patients could undergo different therapeutic orders: metastasis treatment, neoadjuvant therapy, and lung surgery; metastasis treatment and lung surgery; neoadjuvant therapy, lung surgery, and metastasis treatment; and lung surgery and metastasis treatment. Above all, brain metastases were treated before the lung resection at the level of the brain; adrenal gland metastases underwent initial lung resection (according to the principle of conserving the adrenocortical function for lung surgery). Preoperative treatment, with the dual purpose of local control of the disease (neoadjuvant intent) and systemical control, was also described with significant local control with consequent clinical downstaging (8). Significant gaps between patient selection, optimal systemic therapy, and the tumour microenvironment still exist. Despite these limitations, however, there still is a population where long-term treatments are possible. OMTS patients could reliably be treated and ultimately cured with aggressive therapies (14). For OMTS unable to undergo surgery or receive systemic therapies, stereotactic body radiation therapy provides a reasonable alternative with improved survival (15).

With the advances in cancer immunotherapy, excellent durable responses are observed in OMTS treated with immunotherapy. The addition of local radiotherapy, particularly stereotactic body radiotherapy, could improve the effects of immunotherapy and, then, more abscopal effects are detected. Understanding the molecular mechanisms and interactions of specific immunotherapy and stereotactic body radiation therapy, particularly the mechanisms underlying abscopal therapeutic effects upon the interaction of these treatment modalities, could be very supportive in providing probable control (cancer as a chronic disease) or even cure in OMTS patients (16).

The multispecialty effort plays an ultimate role in the management of lung cancer and is accurately reproduced in TNM classification since it is the intersection of frontline thoughts in pathology, biomolecular medicine, radiology, surgery, medical and radiation oncology (17). Only retrospective series and no randomised data are available to address the treatment of OMTS. In the future, supplementary prospective studies will be compulsory to deliver robust evidence supporting as treatment of OMTS patients the surgical resection (18). Lastly, due to the therapeutic complexity, OMTS patients should be only treated in high volume referral oncological centres.

In conclusion, all these pieces of evidence demonstrate how the OMTS topic is at the beginning and needs a thorough discussion. The *to be or not to be question*, nowadays, is not whether we could treat the OMTS patients with systemic and loco-regional treatments; the real question is what are the current selection criteria for these patients. Without an answer to this question, we remain in pure speculation.

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Footnote

Conflicts of Interest: 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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