Classifying Oligometastatic Non-Small Cell Lung Cancer

Subjects: Surgery | Oncology

Contributor: Alisa Blumenthaler

Oligometastatic non-small cell lung cancer (NSCLC) represents a subset of patients with limited metastatic spread and the potential for achieving long-term survival, or even cure, with LCT to all sites of disease. Patient selection for aggressive local treatment of oligometastatic NSCLC would be facilitated by a common definition of what constitutes oligometastasis. The definition of oligometastasis by LCT treatment feasibility is vague and elusive, particularly in the context of ever-improving local treatment modalities.

oligometastasis lung cancer local consolidative therapy

1. Introduction

The concept of oligometastatic cancer was first postulated by Hellman and Weichselbaum in 1995, as they described an intermediate state of neoplastic malignant potential with limited metastatic spread and potential, existing on a continuum ranging from localized to widely disseminated disease states [1]. It was hypothesized that patients with oligometastatic disease could achieve long-term survival benefits if all sites of disease could be treated aggressively prior to progression of the metastatic malignant potential of the primary tumor or metastatic sites. Evidence for an oligometastatic state in non-small cell lung cancer (NSCLC) has since been provided, first by multiple retrospective studies, small phase II trials, and systematic reviews and more recently with randomized phase II trials demonstrating improved progression-free survival (PFS) and overall survival (OS) in patients who received locally aggressive treatment to all sites of disease [2][3][4][5][6][7]. However, the inclusion criteria for patients with oligometastatic NSCLC have varied widely amongst studies, which renders a comparison of the results challenging. It is imperative that a common definition of oligometastatic NSCLC be established for inclusion in future clinical trials in order to optimize the use of resources as well as patients' outcomes. In this entry, we hope to summarize the current definitions of synchronous oligometastatic NSCLC as presented by multiple national cancer guidelines and consensus working groups, as well as to discriminate oligometastatic disease from the distinct entity of oligoprogressive NSCLC.

2. Oligometastatic Disease

Close to 50% of patients with NSCLC have metastatic disease at the time of diagnosis, with an estimated 5-year survival rate of 6% (8, 9). However, a proportion of patients presenting with metastatic disease will have a limited metastatic burden, rather than widely disseminated disease. Oligometastasis can be broadly defined as a state of

limited metastatic tumor burden, with only one or a few sites of metastasis, and the potential to benefit from curative intent treatment (1). Hellman and Weichselbaum theorized that the oligometastatic state is an intermediate state along a tumor's natural historical progression from a localized primary to widely disseminated metastasis, which represents a condition in which the tumor's full metastatic potential has not yet been realized (**Figure 1**). Early in the malignant trajectory, the metastatic cells from the primary tumor have a restricted capacity for growth in distant sites (10). As the primary tumor grows and gains genetic mutations, cellular clones develop additional growth characteristics, the requirements for metastatic growth are less, and additional sites are established (10). It was proposed that if eradication of the primary tumor and the oligometastatic sites could be achieved early in the metastatic continuum, progression to the widely disseminated state could be prevented, and cure potentially possible (1, 11-13).

Since Hellman and Weichselbaum's description, further evidence for the presence of an oligometastatic state in NSCLC has been substantiated by a breadth of oncologic research. Initial support for improved outcomes after local treatment of oligometastases in NSCLC was identified in patients with solitary brain or adrenal metastases (14-18). Additional proof of improved survival outcomes has emerged from retrospective analyses, meta-analyses, and single-arm prospective trials of local consolidative therapy (LCT) in patients with lesions in other (non-brain/non-adrenal) organs, and even those with more than a single metastasis (5, 19-26). More recently, multiple randomized phase II trials have provided additional, high-quality data in support of LCT as an attractive treatment strategy for oligometastatic NSCLC (2, 3, 27). As lung cancer screening has improved and become more standardized, and imaging modalities have become more sensitive, oligometastatic states have been more readily and confidently identified with the most common sites of oligometastasis being the brain, lung, and adrenal gland, followed by metastases of the bony skeleton (5, 28-30). Given the preponderance of evidence demonstrating significantly longer survival in patients after treatment of oligometastases compared to widely disseminated disease, the 8th Edition of the TNM staging classification included adjustments to the M stage subclassifications in order to account for these distinct metastatic entities (31).

Recently, the European Organisation for Research and Treatment of Cancer (EORTC) and the European Society for Radiotherapy and Oncology (ESTRO) OligoCare Project undertook the task of defining biologically distinct oligometastatic disease states, for all primary tumor types. The individual oligometastatic disease entities were classified based on the timing of oligometastasis diagnosis in relation to the diagnosis of the primary tumor and ongoing systemic therapy, a history of treated oligometastatic or polymetastatic disease, and the nature of the disease response to previous or ongoing treatment (32). Broadly speaking, the umbrella term "oligometastasis" represents a state with "few" metastases. For the purposes of this review, our focus is on the disease entity which falls into the categories that the EORTC-ESTRO consensus refers to as "genuine oligometastasis" (no history of polymetastasis) and "de novo oligometastasis" (no history of previously treated oligometastatic disease) (32).

It has been difficult to specifically define oligometastatic disease, and different authors have employed widely variable definitions, both in regard to the number of metastatic lesions and number of organs involved. Variability has also existed regarding the inclusion of patients with metastases in specific sites, such as intracranial lesions or mediastinal nodal disease (33). The current TNM staging paradigm characterizes M1a disease as the presence of

pleural metastasis or contralateral pulmonary metastases in the absence of extrathoracic metastasis. M1b disease is classified as a single extrathoracic metastasis while M1c subclassification includes multiple extrathoracic metastases, in one or more organs (31). Current literature, however, does not directly align with this classification of oligometastasis, as a systematic review found that the maximum number of metastases for inclusion in studies of oligometastasis has ranged from 1 to 8 sites, and up to 3 organs (33). There is also variability in the definition of oligometastatic disease for the purpose of inclusion in previously published randomized phase 2 trials of LCT for oligometastatic NSCLC (**Table 1**). Many trials have not specified a maximum number of organs with metastasis allowable for study inclusion and have not included details about the inclusion of intrathoracic nodal disease as an independent metastatic site.

Even national treatment guidelines for NSCLC have failed to provide specific definitions for oligometastasis (**Table 1**). The National Comprehensive Cancer Network (NCCN) treatment guidelines do not specifically define what is referred to as “limited” metastatic disease for which LCT for oligometastasis can be considered, though it is noted in the guidelines that prior clinical trials have included limitations of 3-5 metastases (34). The 2018 European Society for Medical Oncology (ESMO) guidelines recommend LCT for patients with less than 3 metastatic lesions, without specifying a limit of number of organs that can be included in the oligometastatic state (35). This variability in the understanding of what constitutes an oligometastatic state has posed significant challenges in comparing outcomes across different trials, as well as determining treatment paradigms for specific patient groups. Thus, attempts have been made to establish a single definition for oligometastatic NSCLC to better guide inclusion criteria for future clinical trials.

The European Organization of Research and Treatment of Cancer Lung Cancer Group (EORTC-LCG) recently undertook a systematic review, international survey, and multidisciplinary conference, with the goal of developing a consensus definition for oligometastatic NSCLC. A number of issues were taken under consideration in reaching agreement (36). The overarching consensus was that oligometastatic disease can be considered to be present when there is the potential for modifying the disease course with the treatment of all disease sites by a technically feasible local treatment with an acceptable toxicity or risk profile (36). The definition of treatment feasibility can be elusive in the era of consistently evolving and improving modalities for local therapy, such as minimally invasive surgical techniques, enhanced recovery surgical pathways, and more precise radiation therapy modalities (i.e. stereotactic body radiotherapy [SBRT], gated radiotherapy), which make LCT increasingly safe and well-tolerated. This is an important point as multiple studies have demonstrated the substantial benefit of comprehensive treatment to all sites of disease. Patients who receive subcomprehensive LCT, with treatment of one or more, but less than all, sites of disease, have been shown to experience worse survival outcomes than those who receive LCT to the primary tumor as well as all sites of metastasis (4, 7). As we gain experience with offering LCT to wider patient populations and utilizing evolving treatment strategies, the potential for comprehensive LCT will also increase and will be a valid treatment option for a growing number of patients.

Further, however, it is important to provide a more specific definition for the nature of the metastatic disease itself for patient inclusion in clinical trials as well as risk stratification for those trials that include patients with oligometastatic, polymetastatic, and oligoprogressive disease. In considering the number of metastatic lesions that

constitutes oligometastatic NSCLC, the EORTC-LCG was able to reach only a limited definition due to the sparsity of prospective data regarding the maximum number of lesions that can be beneficially treated with LCT (36). The definition recommended by the EORTC-LCG based on disease burden includes a maximum of five metastatic lesions, in up to three organs. Importantly, the presence of diffuse serosal metastases of the meninges, pericardium, pleura, or mesentery, as well as bone marrow involvement, were exclusionary for the EORTC-LCG definition of oligometastatic disease, as it was a general consensus amongst the working group that these sites are rarely, if ever, amenable to complete consolidation (36).

Pulmonary metastases are included in the maximum lesion count as defined by the EORTC-LCG. While nodules within the same lobe (T3) or lung (T4) are not considered metastases under the TNM definition, their presence may influence the feasibility of achieving comprehensive LCT. Further, the extent of intrathoracic tumor burden is an independent prognostic factor in patients being treated with LCT for oligometastatic NSCLC (4, 5, 37). Similarly, the presence of intrathoracic nodal metastases is associated with a worse prognosis and decreased benefit from LCT in the case of oligometastasis (3-5, 30). The landmark randomized controlled trial by Gomez et al, which demonstrated improved PFS in patients randomized to LCT compared to those who received maintenance therapy or observation, included positive intrathoracic nodes in the total metastasis count for the purpose of inclusion in the trial, with intrathoracic nodes counting as a single site of disease (regardless of the total number of nodes involved) (2). This same inclusion criterion has since been applied to current ongoing trials evaluating the role of LCT in oligo- and polymetastatic disease (38-42). In contrast, mediastinal nodal disease has not been considered an independent metastatic site in the EORTC-LCG definition. While the EORTC consensus statement considers mediastinal nodes to be regional rather than metastatic disease, it does emphasize, however, that the extent of nodal disease can play a role in determining the feasibility of comprehensive LCT, and thus is still important to consider (36).

3. Required Staging Workup

A generally agreed upon requirement for oligometastatic disease is the confirmation that a patient's cancer burden is indeed limited, rather than representative of an occult disseminated metastatic state [1][8]. Patients who experience disease recurrence after LCT more often experience systemic recurrence and appearance or progression of disease at sites different than those treated with LCT [4][9][10][11][12]. This fact underscores the importance of ruling out the presence of widespread polymetastatic disease to the extent of the capabilities and sensitivity of the current evaluation strategies. With continuously improving imaging modalities and the associated gains in sensitivity and specificity for identifying metastatic lesions, delineating an oligometastatic state may be confirmed with increasing confidence [13][14].

General agreement has been reached regarding the necessary staging workup that is required to identify an oligometastatic disease state. The EORTC-LCG consensus statement includes mandatory 18F-FDG PET/CT and imaging of the brain, of which MRI is the preferred modality [8]. The NCCN guidelines provide similar recommendations [15]. Mediastinal staging should be clinically inferred by PET/CT, with pathologic confirmation by endobronchial/endoscopic ultrasonography (EBUS/EUS) or mediastinoscopy, if the confirmation would influence

treatment decision making. Pathologic confirmation of metastatic lesions, particularly in cases of suspected solitary metastasis, is recommended unless a multidisciplinary tumor board determines that the risk of biopsy outweighs any possible benefit or influence on clinical decision making [8]. For patients with a solitary metastasis in the liver or ipsilateral pleura, additional workup is recommended including liver MRI or thoracoscopy with biopsy, respectively.

Table 1. Comparison of Recent Definitions for Oligometastatic Non-Small Cell Lung Cancer in Clinical Trials, National Treatment Guidelines, and Consensus Definitions. Modern definitions for oligometastatic non-small cell lung cancer have varied widely.

Author	Year	Study Type	Maximum Number of Metastases	Maximum Number of Organ Sites	Maximum Lesions in Each Organ	Intrathoracic N+ as Metastasis	Pulmonary Lesion as Metastasis	Includes Intracranial Lesions	No Disease Progression after First Line Therapy	Notes
Ashworth [5]	2014	Meta-analysis	5	NS	NS	NS	Yes	Yes	NS	
Gomez [2,3]	2016, 2019	RCT phase II	3	NS	NS	Yes	NS	Yes	Yes	
Iyengar [27]	2018	RCT phase II	5	NS	3 in lung or liver	NS	Yes	Exclude uncontrolled intracranial	Yes	
Palma [12,13]	2019, 2020	RCT phase II	5	NS	3	NS	NS	Exclude if only site of disease	Yes	Not lung cancer-specific
Dingemans [36] (EORTC-LCG)	2019	Consensus working group	5	3	NS	No	Yes	Yes	NS	

TNM stage M1a [31]	2017	Staging Guidelines	1	1	1	No	Contralateral	Yes	NA
NCCN [34]	2021	Treatment Guidelines	3-5	NS	NS	No	Treat as second primary	Yes	NS
ESMO [35]	2018	Treatment Guidelines	3	NS	NS	NS	Treat as second primary	Yes	NS

Abbreviations. NS, not specified; RCT, randomized controlled trial; EORTC-LCG, The European Organization of Research and Treatment of Cancer - Lung Cancer Group; NCCN, National Comprehensive Cancer Network; ESMO, European Society for Medical Oncology.

References

1. Hellman, S.; Weichselbaum, R.R. Oligometastases. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 1995, 13, 8–10.
2. Gomez, D.R.; Blumenschein, G.R., Jr.; Lee, J.J.; Hernandez, M.; Ye, R.; Camidge, D.R.; Doebele, R.C.; Skoulidis, F.; Gaspar, L.E.; Gibbons, D.L.; et al. Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study. Lancet. Oncol. 2016, 17, 1672–1682.
3. Gomez, D.R.; Tang, C.; Zhang, J.; Blumenschein, G.R., Jr.; Hernandez, M.; Lee, J.J.; Ye, R.; Palma, D.A.; Louie, A.V.; Camidge, D.R.; et al. Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2019, 37, 1558–1565.
4. Mitchell, K.G.; Farooqi, A.; Ludmir, E.B.; Corsini, E.M.; Zhang, J.; Sepesi, B.; Vaporciyan, A.A.; Swisher, S.G.; Heymach, J.V.; Zhang, J.; et al. Improved Overall Survival With Comprehensive Local Consolidative Therapy in Synchronous Oligometastatic Non-Small-Cell Lung Cancer. Clin. Lung Cancer 2020, 21, 37–46.e7.

5. Ashworth, A.B.; Senan, S.; Palma, D.A.; Riquet, M.; Ahn, Y.C.; Ricardi, U.; Congedo, M.T.; Gomez, D.R.; Wright, G.M.; Melloni, G.; et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. Clin. Lung Cancer 2014, 15, 346–355.
6. Fleckenstein, J.; Petroff, A.; Schäfers, H.J.; Wehler, T.; Schöpe, J.; Rübe, C. Long-term outcomes in radically treated synchronous vs. metachronous oligometastatic non-small-cell lung cancer. BMC Cancer 2016, 16, 348.
7. Sheu, T.; Heymach, J.V.; Swisher, S.G.; Rao, G.; Weinberg, J.S.; Mehran, R.; McAleer, M.F.; Liao, Z.; Aloia, T.A.; Gomez, D.R. Propensity score-matched analysis of comprehensive local therapy for oligometastatic non-small cell lung cancer that did not progress after front-line chemotherapy. Int. J. Radiat. Oncol. Biol. Phys. 2014, 90, 850–857.
8. Dingemans, A.C.; Hendriks, L.E.L.; Berghmans, T.; Levy, A.; Hasan, B.; Faivre-Finn, C.; Giaj-Levra, M.; Giaj-Levra, N.; Girard, N.; Greillier, L.; et al. Definition of Synchronous Oligometastatic Non-Small Cell Lung Cancer-A Consensus Report. J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer 2019, 14, 2109–2119.
9. Palma, D.A.; Olson, R.; Harrow, S.; Gaede, S.; Louie, A.V.; Haasbeek, C.; Mulroy, L.; Lock, M.; Rodrigues, G.B.; Yaremko, B.P.; et al. Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomised, phase 2, open-label trial. Lancet 2019, 393, 2051–2058.
10. De Ruysscher, D.; Wanders, R.; Hendriks, L.E.; van Baardwijk, A.; Reymen, B.; Houben, R.; Bootsma, G.; Pitz, C.; van Eijsden, L.; Dingemans, A.C. Progression-Free Survival and Overall Survival Beyond 5 Years of NSCLC Patients With Synchronous Oligometastases Treated in a Prospective Phase II Trial (NCT 01282450). J. Thorac. Oncol. Off. Publ. Int. Assoc. Study Lung Cancer 2018, 13, 1958–1961.
11. Iyengar, P.; Wardak, Z.; Gerber, D.E.; Tumati, V.; Ahn, C.; Hughes, R.S.; Dowell, J.E.; Cheedella, N.; Nedzi, L.; Westover, K.D.; et al. Consolidative Radiotherapy for Limited Metastatic Non-Small-Cell Lung Cancer: A Phase 2 Randomized Clinical Trial. JAMA Oncol. 2018, 4, e173501.
12. Mitchell, K.G.; Farooqi, A.; Ludmir, E.B.; Corsini, E.M.; Sepesi, B.; Gomez, D.R.; Antonoff, M.B. Pulmonary resection is associated with long-term survival and should remain a therapeutic option in oligometastatic lung cancer. J. Thorac. Cardiovasc. Surg. 2021, 161, 1497–1504.e2.
13. Chee, K.G.; Nguyen, D.V.; Brown, M.; Gandara, D.R.; Wun, T.; Lara, P.N., Jr. Positron emission tomography and improved survival in patients with lung cancer: The Will Rogers phenomenon revisited. Arch. Intern. Med. 2008, 168, 1541–1549.
14. Rieber, J.; Abbassi-Senger, N.; Adebahr, S.; Andratschke, N.; Blanck, O.; Duma, M.; Eble, M.J.; Ernst, I.; Flentje, M.; Gerum, S.; et al. Influence of Institutional Experience and Technological

Advances on Outcome of Stereotactic Body Radiation Therapy for Oligometastatic Lung Disease. Int. J. Radiat. Oncol. Biol. Phys. 2017, 98, 511–520.

15. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology; Non-Small Cell Lung Cancer Version 2. 2021. Available online: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (accessed on 22 December 2020).