



Defining oligometastatic non-small cell lung cancer: concept versus biology, a literature review

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Contributions: (I) Conception and design: JF Mentink, MS Paats, AMC Dingemans; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Objective: In this review, the concept of (synchronous) oligometastatic disease in patients with non-oncogene-driven non-small cell lung cancer (NSCLC) will be placed in the context of tumor biology and metastatic growth patterns. We will also provide considerations for clinical practice and future perspectives, which will ultimately lead to better patient selection and oligometastatic disease outcome.

Background: The treatment landscape of metastasized NSCLC has moved from “one-size fits all” to a personalized approach. Prognosis has traditionally been poor but new treatment options, such as immunotherapy and targeted therapy, brighten future perspectives. Another emerging development is the recognition of patients with so-called “oligometastatic” state of disease. Oligometastatic disease has been recognized as a distinct clinical presentation in which the tumor is stated to be early in its evolution of metastatic potential. It is suggested that this stage of disease has an indolent course, comes with a better prognosis and therefore could be considered for radical multimodality treatment.

Methods: Narrative overview of the literature synthesizing the findings of literature retrieved from searches of computerized databases, hand searches, and authoritative texts.

Conclusions: Oligometastatic NSCLC is a broad spectrum disease, with a variable prognosis. Although the biology and behavior of “intermediate state” of metastatic disease are not fully understood, there is evidence that a subgroup of patients can benefit from local radical treatment when integrated into a multimodality regime. The consensus definition of oligometastatic NSCLC, including accurate staging, may help to uniform future trials. The preferable treatment strategy seems to sequential systemic treatment with subsequent local radical treatment in patients with a partial response or stable disease. Prognostic factors such as N-stage, number and site of distant metastases, tumor volume, performance status, age, and tumor type should be considered. The local radical treatment strategy has to be discussed in a multidisciplinary team meeting, taking into account patient characteristics and invasiveness of the procedure. However, many aspects remain to be explored and learned about the cancer biology and characteristics of intermediate state tumors.

Keywords: Lung cancer; oligometastatic; non-small cell lung cancer (NSCLC)

Submitted Apr 05, 2021. Accepted for publication Jun 10, 2021.

doi: 10.21037/tlcr-21-265

View this article at: <https://dx.doi.org/10.21037/tlcr-21-265>

Introduction

Worldwide, lung cancer is the leading cause of cancer-related death in men and the second leading cause of death in women (1). Incidence and mortality are tightly linked to smoking, but numerous other risk factors have been identified (2). The five-year survival rates of non-small cell lung cancer (NSCLC) range from 80% for early-stage to 5–10% for metastatic disease (3). At presentation, 40% of patients have metastatic disease.

Metastatic NSCLC has traditionally been considered an incurable disease, with a median overall survival (OS) of less than one year (3). However, with the identification of oncogene-driven NSCLC and the introduction of tyrosine kinase inhibitors (TKIs), five-year survival rates have increased to 50% for this subgroup of patients (4,5). Moreover, with the introduction of immune checkpoint inhibitors (ICIs), five-year survival now ranges from 15% in previously treated patients to 30% in first-line for patients with high PD-L1 expression (6). Next to these developments an emerging field of interest to improve outcome is identification of oligometastatic NSCLC, which has been recognized as a distinct clinical presentation in which the tumor is suggested to be early in its evolution of metastatic potential. In 1995, Hellman and Weichselbaum introduced the concept of oligometastatic disease as an “intermediate metastatic state” (7). This disease state is characterized by a more indolent course of disease, resulting in a better prognosis and therefore a potential for exploration of (radical) multimodality treatment. Cancer progression may thus not constitute an absolute divergence into non-metastatic disease which can be cured, and metastatic disease which cannot.

In this review, the concept of (synchronous) oligometastatic disease in NSCLC without driver aberrations will be evaluated in the context of tumor biology and metastatic growth patterns. We will also provide considerations for clinical practice and future perspectives, which may ultimately lead to better patient selection and outcomes in oligometastatic disease.

We present the following article in accordance with the Narrative Review reporting checklist (available at <https://dx.doi.org/10.21037/tlcr-21-265>).

Methods

Narrative overview of the literature synthesizing the findings of literature retrieved from searches of PubMed.

Only publication in English language were selected.

Defining oligometastatic disease

Oligometastatic disease is considered a clinical stage with a limited number of metastases in a limited number of organs, possibly reflecting an “intermediate state of metastasis” (7). For these patients radical treatment of all tumor sites might be a meaningful intervention resulting in long term OS. Regarding NSCLC, there is increasing consensus and some recent evidence to support this concept (8-11). The landmark study of Gomez *et al.* showed a clear benefit for local radical therapy versus maintenance therapy or observation in patients with NSCLC with a low metastatic burden who did not progress after front line systemic therapy (9). The study was closed prematurely because of a significant median progression free survival (PFS) advantage of 11.9 months [90% confidence interval (CI), 5.7–20.9] versus 3.9 months (90% CI, 2.3–6.6), with a hazard ratio (HR) of 0.35 (90% CI, 0.18–0.66, P=0.0054). Also, a significant OS benefit in the treatment arm was seen with a median of 41.2 months (95% CI, 18.9–not reached) versus 17 months (95% CI, 10.1–39.8, P=0.017) in the control arm (11). As this study was closed prematurely these results are based on only 48 patients, of whom 8 had oncogene driven NSCLC. In order to be eligible, up to three non-progressing metastatic lesions after frontline systemic treatment were allowed. Brain imaging was mandatory, however fluorodeoxyglucose (FDG) positron emission tomography (PET) computed tomography imaging (CT) was not. With this trial in mind the definition of oligometastatic NSCLC will be discussed.

It has been estimated that approximately 50% of patients with metastatic NSCLC present with a maximum of three metastatic sites (12). The accuracy of cancer staging has been improved by the introduction of more sensitive imaging techniques, FDG-PET-CT and magnetic resonance imaging (MRI). Approximately 15% of patients initially classified as stage I–III NSCLC will be upstaged to stage IV after performing an FDG-PET CT (13,14). Pre-operative FDG-PET-CT staging significantly improved five-year OS (58% versus 33%) in surgically resected NSCLC compared to conventional CT-staging (14). This can be explained by the “Will Rogers phenomenon”, defined as an improved overall outcome despite unaltered individual prognoses due to stage migration (15). Stage migration is essential in the concept of oligometastatic

NSCLC: by more accurate and sensitive staging methods such as FDG-PET-CT, we will identify more patients with this transitional state between strictly localized and widespread systemic disease. This comes with an element of uncertainty because some of these patients might still have a rapidly progressing disease that cannot be distinguished from the real oligometastatic state.

One of the major controversies is the maximum number of metastases that can be considered “oligo” metastatic. Most studies of oligometastatic NSCLC to date allow up to five metastases, however in reality the majority of patients included in these studies had a maximum of up to three metastases (16,17).

In the 8th TNM implemented in 2018 patients with metastases were subdivided into three categories of prognostic relevance: patients with only lung involvement (M1a), versus a single extra-thoracic organ metastasis (M1b), versus multiple extra-thoracic metastasis in one or more organs (M1c) (18). This reclassification reflects the differences in median survival. For M1a this is 22.5 months, in M1b 17.7 months and in M1c 13.6 months (19). Although this identifies patients with a solitary extrapulmonary metastasis, this is not a definition of oligometastatic NSCLC. The European Organization of Research and Treatment of Cancer-Lung Cancer Group (EORTC-LCG) has published a consensus statement on the definition of oligometastatic NSCLC (20). This goal of this statement was the provision of a uniform definition and staging of synchronous oligometastatic disease in NSCLC. It highlights that the concept of oligometastatic treatment should only be used when “a radical treatment that may modify the disease course (leading to long-term disease control) is technically feasible for all tumor sites with acceptable toxicity”. Histology, genomic background and tumor volume are not taken into account in the definition. A maximum of 5 metastases in 3 organs is proposed, but diffuse serosal (meningeal, pleural, pericardial, and mesenteric) or bone marrow metastases are excluded from this definition. Also noteworthy is that a pulmonary metastasis should be seen as a metastatic site. Mediastinal lymph nodes are considered loco-regional disease and are essential in determining whether or not radical treatment of the primary tumor can be applied. In the consensus statement, the importance of staging is stressed and both FDG-PET-CT and imaging of the brain are mandatory for the staging of oligometastatic NSCLC. This is in line with advice from the EORTC-imaging group (21).

Perspectives on the different oligometastatic states

Four different states of oligometastatic disease in NSCLC can be distinguished (22). First is “synchronous oligometastatic disease”, in which at initial work up one or more metastases are found. Secondly, “metachronous oligometastatic disease” is considered a limited relapse after treatment with curative intention. Third is “oligopersistent disease” or “oligoresidual disease”, reflecting oligometastatic disease after initial treatment. Fourthly the term “oligoprogression” is used if over time only a few metastatic sites progress. For the purpose of this review we will mainly focus on this type of oligometastatic disease.

In synchronous oligometastatic disease more than one-third of the patients who were able to complete treatment with radical intent on both primary and metastatic sites, have a two-year survival similar to the stage III NSCLC patient population who are treated with definitive chemoradiotherapy (23). Although this would appear to represent promising long term survival, there is an unfavorable subgroup of patients that progress during treatment. Moreover, most patients tend to progress within a short period, which suggests the presence of micrometastases at the time of treatment (24). Therefore, an acceptable multimodality strategy could be to initiate systemic treatment and re-stage the patient before initiating local radical treatment for the primary tumor and metastasis, as exemplified by the study design of Gomez *et al.* (8-10). Another option is to start with radical treatment of metastases followed by systemic treatment. However, results following this approach are poor and possibly explained by the lack of adequate patient selection (24).

Prognostic factors in oligometastatic NSCLC

As stated before, it seems that not all patients with oligometastatic NSCLC have long term benefit from local radical treatment. There have been multiple, mainly retrospective, studies focusing on prognostic factors in oligometastatic NSCLC. A systematic review, published in 2013, retrieved 23 studies (on total 1,064 patients) in which a multivariable analysis for prognostic factors for survival of patients with metastatic NSCLC and up to five metastases showed that N-stage was a highly significant prognostic factor (25). More recently, Frost *et al.* conducted a retrospective study to identify prognostic factors for survival in oligometastatic NSCLC (26). They found

that a limited primary tumor size (T1a), adenocarcinoma histology, low nodal status (N0, N1 versus N2), a low number of metastases (especially solitary metastases), and good performance status (ECOG 0 or 1) were associated with a better outcome. This was confirmed in a prospective study by Parikh *et al.*, which showed that poor performance status (ECOG ≥ 2), advanced nodal status (N2 or N3), squamous histology and metastases to multiple organs were associated with a higher HR of death (27). In NSCLC in general, favorable outcomes have been described in patients with skip lymph nodes metastases. The five-year OS of patients with pN2 but negative N1 was found to be 41% compared to only 14% in patients with pN2 in addition to N1 involvement (28). In a large cohort of patients with stage M1a NSCLC from the Surveillance Epidemiology and End Results (SEER) program, nodal status had an impact on survival, as patients with N0-1 status in particular had a better outcome (29). Unfortunately, only one out of six patients with metastatic NSCLC present with N0 status (30). In 25.3% of patients with resected lung cancer micrometastases are detected in lymph nodes by additional analysis (e.g., multiple-level sectioning, additional immunohistochemical and molecular biological techniques) (31). This is currently not implemented in daily clinical practice as it has no therapeutical consequences. However, such additional techniques could lead to better prognostic stratification in patients with oligometastatic NSCLC. In patients with an isolated adrenal gland metastasis who underwent adrenalectomy, 5-year OS in N0 disease was 53% compared to 0% when mediastinal lymph node metastases are present (32).

In addition to nodal involvement, other factors seem relevant to outcome, including the site of extra-thoracic metastases and tumor volume. In particular, data from a small retrospective series indicate that lesions in the brain or adrenal glands are associated with prolonged survival compared with bone or liver metastases (33). A systematic review on solitary metastases did not show differences in survival between less common metastatic sites such as bone, liver, spleen, and kidney (34). Also, satisfactory outcomes have been reported for pancreatic metastases, albeit in small cohorts (35).

Several studies have shown that tumor volumes can also hold prognostic value. Thus, gross primary tumor volume was associated with OS (36), while another study showed that larger tumor volumes were predictive of high rates of local failure (37). In this light, T stage upon initiation of treatment needs to be taken into account for treatment planning.

Cancer biology

To achieve a better understanding of the oligometastatic state, we need to consider the biology of cancer in general. This might help to select patients with an actual intermediate state of disease. The original well-known six hallmarks of cancer provide a widely accepted insight into carcinogenesis (38). The first hallmark is the capacity of the cancer cell to initiate and sustain proliferative signaling: in normal tissue the cellular growth and division cycle is carefully controlled, but cancer cells can deregulate growth signals and thereby sustain chronic proliferation. Evading the influence of growth suppressors is an important second hallmark. A dozen tumor suppressors negatively regulate cell growth, including the RB and TP53 proteins, which act as critical gatekeepers and govern the cellular switch to either continue proliferation or activate senescence and apoptosis. Third, cancer cells can resist forms of cell death which are typically induced by anticancer therapy or physiological stress. Fourth, the acquisition of replicative immortality is necessary to generate a macroscopic tumor; this characteristic contrasts with normal cell lineages that can only undergo a limited number of successive growth cycles. Fifth is the capacity to induce angiogenesis, which is essential to match tumoral oxygen and nutrient demand and evacuate metabolic waste. The sixth hallmark is the physical dissemination of cancer cells from the primary tumor and the ensuing spread to distant organs. This involves processes of loss of cellular adhesion, epithelial-to-mesenchymal transition (EMT), and degradation of extracellular matrix by matrix metalloproteases (MMPs), as initiated by alteration of E-cadherin/ β -catenin signaling and activation of transcription by the transcription factors Twist, Snail, Slug, and ZEB (39,40). These processes are also crucial for distant colonization, including adaptation to the new microenvironment (including a reverse process of mesenchymal-to-epithelial transition), following which micrometastases can grow and form a distant macroscopic tumor. This is a trial and error process and explains why years after radical treatment of the primary tumor, distant metastasis can still occur. In an update of the paradigm, reprogramming of cellular metabolism and avoidance of immune destruction were added to the known hallmarks (41). It is noteworthy that underlying these hallmarks are (I) the enabling characteristics of genome instability, which give cancer cells the ability to mutate, and (II) the inflammatory

state driven by our own immune system that, unfortunately, can also sustain a tumor-promoting inflammatory environment.

That being said, the oncogenic transformation and pathways of spread are only partially understood, and metastatic spread in general remains a challenging problem in NSCLC. A series of interactions ranging from alteration and escape of the tumor microenvironment, entry and survival in the circulation, seeding and invasion into a distant site, and finally adaptation to, or development of, the appropriate microenvironment are necessary before distant organ colonization can occur (42). Only a small proportion of tumor cells that escape the primary tumor ultimately colonize a distant organ site (43).

More than a century ago the “seed and soil” theory was introduced by Paget (44), which suggested that tumor cells (seeds) selectively (and not randomly) colonize compatible distant organs (soil). Various animal studies have tested and confirmed this concept (45-47). It has become clear that metastases do not solely depend on trapping and lodging tumor cells from the bloodstream to colonize distant organs. Each organ is variable in its accessibility, stromal characteristics, amounts of vascular and nutrient supply (43). Numerous growth factors, chemokines, guidance molecules, signaling pathways and genes have been discovered to be involved (48). Shortfalls in this metastatic cascade could result in a phenotype with limited metastatic potential (49), a particular example of which is metastatic tumor dormancy. According to this concept, disseminated tumor cells arrive at a secondary site but stop proliferating and remain quiescent for an extended latency (50). Maintaining a state of tumor dormancy has the potential to transform cancer into a chronic disease, although it is preferable to attempt elimination of all cancer cells because of the risk of proliferation under the influence of new stimuli (51).

A possible biological explanation for the origin of oligometastases is that there may be primary tumor cells with a limited capacity regarding one or more of the required biological hallmarks for metastasis (7). However, to which extent the metastatic potential and possible dormancy are already deterministically enshrined in phylogenetic subgroups defined by different combinations and sequences of genetic alterations, remains to be resolved for NSCLC (52). Nevertheless, this could offer the possibility of subtyping tumors according to their likely future metastatic patterns, and thus suitability for oligometastatic treatment approaches.

Clinical considerations

Although we are still searching for a better understanding of the oligometastatic concept, it is currently being applied in daily clinical practice using local radical therapies aimed at long-term disease control or possibly even cure. The most pivotal question is which patients truly present with an intermediate metastatic state of disease and thus benefit from oligometastatic-based treatment. Therefore, it is advisable to first evaluate tumor response to systemic treatment before initiating local consolidative treatment, conform the concept of the Gomez trial (9).

The type of radical treatment is also important to consider. Nowadays (minimally invasive) surgery, stereotactic radiotherapy and cryo-ablation are examples of treatment options with acceptable safety profiles. Weighing all options, in particular the site of disease, performance status of the patient and recovery time (which might delay initiation of treatment) play a pivotal role. There is some evidence suggesting that surgery, or even minor trauma such as a biopsy, can influence disease course in a way that leads to unfavorable outcomes (53). It has been suggested that this is related to pathophysiological processes that enhance postoperative tumor spread, which lead to recurrent disease. These mechanisms can cause a paradoxical growth of metastases after surgical intervention. However, others have reported that in NSCLC with a solitary extrathoracic synchronous metastasis, surgical metastasectomy was not prognostically better or worse than radiotherapy with or without chemotherapy (54). Stereotactic radiotherapy is feasible in selected patients and well-tolerated (55). Another potential advantage of radiotherapy is the induction of the so-called “abscopal effect” (56). The abscopal effect is a rare phenomenon in which the regression of tumor lesions outside the treated volume is seen. There is evidence of enhanced anti-tumor immunity via CD8+ T-cells and cellular stress signals after high-dose, hypofractionated radiation. It is believed to be a relatively uncommon phenomenon in lung cancer due to its inherent low immunogenicity. The proposed mechanism is that radiotherapy stimulates the immune system by releasing anti-tumor proliferative agents and cytokines (57). It is thought that the tumor and the immune system of the host are in a constant fight in which, on the one hand of the spectrum, (I) tumor is eliminated, through (II) an equilibrium of subclinical tumor (“tumor dormancy”), to (III) resistance and evolution of a clinically detectable tumor

mass on the other end of the spectrum. Therefore, apart from local benefit, an emerging advantage of stereotactic ablative body radiation may be fortification of the immune system. Additional immunotherapy treatment might have a further synergistic effect (58). SBRT releases neo-antigens and stimulates maturation and proliferation of naive T-cells, while immunotherapy activates and amplifies those naive T-cells, enhancing tumoricidal effects (59).

Future perspectives

More sensitive prognostic staging and the identification of additional biomarkers (e.g., tumor-genetic profiles, circulating cell-free DNA (cfDNA) or circulating tumor cells) in combination with classical (Bayesian) modeling or artificial intelligence will allow future upfront selection of the patient population that will benefit from this approach. This is especially important because the direct initiation of local radical treatment will result in overtreatment in a subgroup of patients.

Emerging opportunities can be found in the optimization of staging afforded by improvement and availability of radiology techniques. This will enable a more thorough selection of patients with a low metastatic burden in whom multimodality treatment can be applied to all metastatic sites.

Circulating tumor DNA (ctDNA) analysis has revolutionized care in patients on targeted treatment (60,61). In the Gomez trial decrease in ctDNA was observed in the patients treated with local consolidative treatment (62).

In-depth tumor-genetic analysis could also hold prognostic value. For example, in breast cancer several genes have been identified that seem to play a role in development of site-specific metastases (63). Another promising tool is micro-RNA, which are small non-coding RNA strands of which some can regulate tumor proliferation and apoptosis, and in pre-clinical studies some micro-RNAs appear to mediate a metastatic phenotype (64). This can help to identify more rapidly progressive tumors in which oligometastatic treatment has no additional value. Micro-RNAs can also be used as additional staging tool (65). Furthermore, investigations have found micro-RNAs that suppressed crucial steps in the formation of distant organ colonization, such as cellular adhesion and invasion (66). Ultimately, if micro-RNAs could be targeted, this could hold great potential for limiting the extent of metastasis.

It is also important to continue the study of cancer biology, including tumor stroma heterogeneity and the role of micro-environmental factors which modulate therapy

resistance (67). In this light, the role of local radical therapy combined with immunotherapy and targeted therapies should also be investigated.

Conclusions

Oligometastatic NSCLC is a broad spectrum disease, with a variable prognosis. Although the biology and behavior of “intermediate state” of metastatic disease are not fully understood, there is evidence that a subgroup of patients can benefit from local radical treatment when integrated into a multimodality regime. Furthermore, until recently, there was no clear definition of oligometastatic disease in NSCLC, but a consensus definition has now been developed. This definition relies on accurate staging with improved imaging techniques. Currently, there are no biomarkers or other techniques that can reliably identify patients with oligometastatic disease who are in a true oligo-metastatic state.

A promising strategy is to first monitor tumor behavior during initial systemic treatment, followed by reassessment after four cycles. The advantages of this approach are the reduction of tumor burden in a short period of time and the selection of patients who rapidly progress and are thus unlikely to benefit from local radical treatment. Subsequent local radical treatment in synchronous oligometastatic disease seems desirable if there is a partial response or stable disease under systemic treatment. Prognostic factors such as N-stage, number and site of distant metastases, tumor volume, performance status, age, and tumor type should be considered. The local radical treatment strategy has to be discussed in a multidisciplinary team meeting, taking into account patient characteristics and invasiveness of the procedure. A limitation of this review is that we did not perform a systematic review. However, this is not feasible as we did not have one research question.

While the time trend is already showing improved OS in oligometastatic NSCLC treated with radical intent, an effect that we might be able to enhance in the near future, many aspects remain to be explored and learned about the cancer biology and characteristics of intermediate state tumors. In this way, we can further define the concept of oligometastatic disease and develop and implement novel treatment strategies.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Maurizio Infante & Thierry Berghmans) for the series “Oligometastatic NSCLC: definition and treatment opportunities” published in *Translational Lung Cancer Research*. The article has undergone external peer review.

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at <https://dx.doi.org/10.21037/tlcr-21-265>

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <https://dx.doi.org/10.21037/tlcr-21-265>). The series “Oligometastatic NSCLC: definition and treatment opportunities” was commissioned by the editorial office without any funding or sponsorship. DWD reports consulting fees from Roche, MSD, Novartis, Pfizer, Astra Zeneca, BMS, outside the submitted work. RC reports speaker fee from Roche, Pfizer and BMS, personal fees from Advisory board of MSD, Roche and Spectrum, outside the submitted work. AMCD reports personal fees from Roche, eli Lilly, Boehringer Ingelheim, Astra Zeneca, Pfizer, BMS, Amgen, Novartis, Takeda, Pharmamar and MSD, grants from BMS and Amgen, non-financial support from Abbvie, outside the submitted work. The authors have no other 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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Cite this article as: Mentink JF, Paats MS, Dumoulin DW, Cornelissen R, Elbers JBW, Maat APWM, von der Thüsen JH, Dingemans AMC. Defining oligometastatic non-small cell lung cancer: concept versus biology, a literature review. *Transl Lung Cancer Res* 2021;10(7):3329-3338. doi: 10.21037/tlcr-21-265