Review Article on Oligometastatic NSCLC: Definition and Treatment Opportunities

Clinical prognostic factors in surgically treated oligometastatic non-small cell lung cancer: a systematic review

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Background: Since the concept of oligometastatic (OM) disease was introduced in the oncological scenario of non-small cell lung cancer (NSCLC), these patients progressively became a new category of stage IV NSCLC in whom the multimodality approach, including surgery, may improve prognosis. This systematic review aimed to investigate the clinical prognostic factors in OM-NSCLC surgically treated with radical intent.

Methods: This systematic review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Cochrane's Collaboration Tool was used to determine the risk of bias for the included studies' primary outcome. A search strategy using a combination of free-text words, relevant MeSH headings and appropriate restrictions (time limit: from January 1997 to March 2020, language: English) was designed. Potentially qualified papers were subjected to an in-depth full-text examination after preliminary title/abstract screening to identify studies for inclusion in the systematic review. Data extracted included: study characteristics, baseline patient characteristics, primary and secondary outcomes. The Cochrane's Collaboration Tool was used to determine the risk of bias for included studies' primary outcome. The risk of bias due to incomplete outcome data was evaluated at an outcome level. However, at the study stage, the possibility of bias due to sequence generation, allocation concealment, blinding, selective reporting, or funding was assessed. Two independent observers calculated the probability of bias, and differences were resolved through dialogue and consensus.

Results: Nine studies were selected. Overall survival (OS) was 51.8 months and varied from 21.1 to 60 months, but results were not statistically significant. Positive prognostic factors for survival were cessation of smoking, age <60, a histologic grade of G1/G2, pN0. The presence of extra-brain OM and multiple metastases negatively affected survival.

Discussion: For otherwise stable patients with a single organ site with synchronous (or metachronous) extrathoracic M1 disease and no intrathoracic lymph node involvement, aggressive treatment should be used in the absence of randomized evidence to help determine the effective management of OM-NSCLC.

Keywords: Oligometastatic (OM); lung cancer; surgery; prognosis; systematic review

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Introduction

In 2018, 470,000 new cases of non-small cell lung cancer (NSCLC) were diagnosed, and just about 50% of patients have already staged IV at the diagnosis for distant metastasis (DM) (1,2). Stage IV NSCLC usually has a poor prognosis with a median survival of about 8–11 months (3,4) and is considered inoperable and often treated only with a palliative therapeutic approach. Surgery is used only in very particular cases and is more of a diagnostic tool than a therapeutic option.

To date, however, this group of patients is extraordinarily heterogeneous, and according to the 8th TNM Edition, the difference in survival in stage IV NSCLC is significantly related to the site and number of metastases (5).

Patients with oligo or "few" metastases and their different survival, probably related to better biology and less aggressiveness of the tumour, was first described more than 20 years ago by Hellman and Weichselbaum (6). Nevertheless, the terms oligometastasis (OM) is still unclear and often misunderstood. Several clinical scenarios for OM-NSCLC patients and their possible treatments have been described based on different sites (one or multiple organs), the number of metastasis (≤5 *vs.* ≤3), and timing of appearance of the DM (synchronous *vs.* metachronous) (1-8).

Since the concept of "OM disease" was introduced in the oncological scenario of NSCLC, the possible reluctance of oncologists towards the surgical approach for these patients has been weakened, in particular in the last decade thanks to the recent advances in the new medical treatments such as immunotherapy or target therapies, which have led to a significant improvement in survival (5,8,9).

Even if many questions about OM-NSCLC have no definite answer yet, these patients progressively became a new category of stage IV NSCLC. The multimodality approach, including surgery, may improve the prognosis.

Indeed, this systematic review of the literature aims to investigate the clinical prognostic factors in OM-NSCLC surgically treated with radical intent. We present the following article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-1123).

Material and methods

This systematic review is reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (10). A search strategy using a combination of free-text words, relevant MeSH headings and appropriate restrictions (time limit: from January 1997 to March 2020, language: English) was designed. A systematic literature search was performed in EMBASE (via Ovid) *[('non small cell lung cancer'/exp OR 'non small cell lung cancer' OR 'non small cell' OR 'nonsmall cell' OR nsclc) AND ('oligometastasis'/exp OR oligometastasis OR oligometasta* OR 'oligo-metastasis' OR 'oligo-metastases' OR 'oligo-metastatic' OR oligoprogress* OR 'oligo-progression' OR 'oligo-progressive' OR oligopersisten* OR 'oligo-persistent' OR 'oligopersistence' OR oligorecurren* OR 'oligo-recurrent' OR 'oligo-recurrence' OR 'isolated metastasis' OR 'isolated metastases' OR 'limited metastasis' OR 'limited metastases' OR 'single organ metastasis' OR 'single organ metastases' OR 'solitary metastasis' OR 'solitary metastases') AND ('prognosis'/exp OR prognosis OR prognoses OR 'prognostic factor'/exp OR 'prognostic factor' OR prognostic) OR (('prognosis'/exp OR prognosis OR prognoses OR 'prognostic factor'/exp OR 'prognostic factor' OR prognostic) AND ('oligometastatic non small cell lung cancer'/exp OR 'oligometastatic non small cell lung cancer'))) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)]*, MEDLINE (via PubMed) *[(prognosis OR prognoses OR prognostic) AND (non small cell lung cancer OR "non small cell" OR "nonsmall cell" OR nsclc) AND (oligometasta* OR "oligo-metastasis" OR "oligo-metastases" OR "oligo-metastatic" OR oligoprogress* OR "oligo-progression" OR "oligo-progressive" OR oligopersisten* OR "oligo-persistent" OR "oligopersistence" OR oligorecurren* OR "oligo-recurrent" OR "oligo-recurrence" OR "isolated metastasis" OR "isolated metastases" OR "limited metastasis" OR "limited metastases" OR "single organ metastasis" OR "single organ metastases" OR "solitary metastasis" OR "solitary metastases")]* and Cochrane CENTRAL *[(oligometasta* OR "oligo-metastasis" OR "oligo-metastases" OR "oligo-metastatic" OR oligoprogress* OR "oligo-progression" OR "oligo-progressive" OR oligopersisten* OR "oligo-persistent" OR "oligopersistence" OR oligorecurren* OR "oligo-recurrent" OR "oligo-recurrence" OR "isolated metastasis" OR "isolated metastases" OR "limited metastasis" OR "limited metastases" OR "single organ metastasis" OR "single organ metastases" OR "solitary metastasis" OR "solitary metastases") in Title Abstract Keyword AND ("nonsmall cell" OR "non small cell" OR NSCLC)]*. Eligible studies were observational, describing clinical prognostic factors in OM-NSCLC wholly surgically treated with radical intent. Letters, editorials, case studies, expert opinions, meta-analyses, and reviews were all exempt from consideration. Our search strategy yielded documents, which were then imported into reference management software. In the event of a tie, the most recent paper was chosen. Based on the eligibility requirements, two authors independently

evaluated each identified research. When data from different studies overlapped, the most insightful study was selected. With the assistance of a third investigator, disputes were addressed and settled by consensus. Potentially qualified papers were subjected to an in-depth full-text examination after preliminary title/abstract screening to identify studies for inclusion in the systematic review. Data extracted included: study characteristics, baseline patient characteristics, primary and secondary outcomes.

The Cochrane's Collaboration Tool was used to determine the risk of bias for included studies' primary outcome (11). The risk of bias due to incomplete outcome data was evaluated at an outcome level.

However, at the study stage, the possibility of bias due to sequence generation, allocation concealment, blinding, selective reporting, or funding was assessed. Two independent observers calculated the probability of bias, and differences were resolved through dialogue and consensus. Details of the systematic review protocol were entered into the International Prospective Registry of Systematic Reviews (PROSPERO) (12). We conducted a pooled analysis aimed at assessing the main discrepancies in the selected studies. A total of 517 patients who underwent surgery for OM lung cancer were included. The age ranged from 33 to 84 years, and the median was comparable. Demographics and baseline characteristics were adequately balanced in all studies. The main characteristics are presented in *Table 1*.

Statistical analysis

The Mantel-Haenszel formula was used to produce pooled impact estimates in the form of risk ratios (RR) and their 95% confidence intervals for dichotomous variables. The mean differences (MD) for continuous outcomes were pooled and weighted by generic inverse variance before being calculated using random-effects modelling. When a continuous outcome was reported as a median, range, or interquartile range in some studies, means and standard deviations were calculated using methods defined in the literature (22). The studies' methodological consistency in this analysis was evaluated using the Cochrane Collaboration risk of bias tool (11). Factors that were assessed included: random sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. Benefit evaluation was performed using Pareto optimal analysis (23,24). Data analysis was performed using Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) (25) and RStudio (26).

Results

A total of 637 papers were found using the given search terms. Twelve papers were excluded due to duplication, leaving 625 articles. 8 disagreements were discussed and solved with the help of a third reviewer. The preliminary title/abstract screening restricted our search to 16 potentially eligible papers. According to our inclusion criteria, 7 articles were excluded at full-text reviewing, and 9 studies (13-21) were selected for the systematic review (*Figure 1*). A summary of the risk of bias for each included study is shown in *Figure 2*.

Median overall survival (OS) was 51.8 months and varied from 21.1 months (20) to 60 months (16), but results were not statistically significant. The disease-free survival (DFS) was reported only by two studies recently published (14,18). The first reported a 21% 5-year DFS and the second 23%.

At the analysis, the positive prognostic factors for survival were smoking cessation, age <60, a histologic grade of G1/G2, pN0. The presence of extra-brain OM and multiple metastases negatively affected survival. For the formal presentation of our systematic review and the show of variations in score values provided by different target prediction tools in the recurrent method, we used the Pareto analysis. All the Pareto fronts produced provided by different target prediction tools were convex, as predicted from their representation as approximations of the correct Pareto fronts (*Figure 3*). The group had a favourable multi-criteria analysis. . Nonetheless, the definition of an optimum solution for the OMTS-NSCLC cannot be described without additional constraints based on these assumptions.

Discussion

Since the introduction of target therapies and the significant increase in OM-NSCLC patients' survival, it becomes mandatory to find a common direction on stage IV patients' therapeutic approach for the OM cohort. However, the clinical heterogeneity and the multiple therapeutic strategies for these patients make it difficult to find a common thread. Besides, most of the literature studies are retrospective and based on insufficient patients, making it challenging to define guidelines for this type of patient (27).

In this systematic review, we tried to investigate the clinical prognostic factors in OM-NSCLC radically treated

Table 1 Main characteristics of the selected studies

First author (ref)	Year	Study location	No. of patients	Sex (M/F ratio)	Median age	Range	Median follow-up (months)	Histology	Site of DM	Prognostic factors	OS 5-year	DFS
Ambrogi (13)	2001	Italy	9	0.13	58.7	45–69	59.3	4 SCC; 3 large cells; 2 ADK	5 adrenals; 2 skin; 1 nodal; 1 kidney	Lymph node status	55.6%	NR
Casiraghi (14)	2020	Italy	57	2.03	59.0	34–79	30	46 ADK; 5 SCC; 2 ADK-SCC; 4 others	35 brain; 12 bone; 6 adrenals; 2 skin; 1 eye; 1 lung	Lymph node involvement, size of the primary tumour, neoadjuvant chemotherapy and time between metastasis diagnosis and primary tumour removal	30%	21%
Cheufou (15)	2014	Germany	37	1.47	55.6	38–72	17.3	20 ADK; 10 SCC; 7 large cells	Brain	None	24% (2 years)	NR
Daniels (16)	2005	Australia	15	1.14	53.5	33–81	24	10 ADK; 2 large cells; 3 SCC	Brain	None	60%	NR
Loi (17)	2019	France	32	1.32	60.0	38–83	42	37 ADK; 9 SCC; 3 neuroendocrine; 2 large cells	41 brain; 9 adrenals 1 both	Cessation of smoking and lymph vascular and perineural spreading in the tissues	34.4%	NR
Opitz (18)	2020	Switzerland	124	1.70	60.0	51–70	60	87 ADK; 18 SCC; 8 Large-cell; 3 Neuroendocrine; 8 Other	76 brain; 13 adrenals; 12 bone; 8 lungs; 12 others	Age <60 years, pathological mediastinal nodal status and bone location	36%	23%
Tönnies (19)	2014	Germany	99	1.83	62.0	36–84	36	68 ADK; 22 SCC; 6 large cells; 3 others	57 lungs; 21 brain; 10 adrenals; 4 bone; 2 hepatics; 2 diaphragms; 2 mediastinal; 1 pleural	High lymph node descriptor and extrapulmonary metastasis	38%	NR
Wang (20)	2018	China	82	1.05	56.4	NR	48	47 SCC; 29 ADK; 6 large cells	74 brain; 51 bone; 20 liver; 16 adrenals; 11 others	Site of metastasis	21.1%	NR
Zhang (21)	2019	China	62	1.59	54.7	NR	20.9	68 ADK; 11 SCC; 9 others	35 pleural; 25 no-brain; 18 brain; 10 multiples	Age, clinical T stage, site of metastases and adjuvant treatment	42.2% (3 years)	NR

ADK, adenocarcinoma; DSF, disease free survival; NR, not reported; OS, overall survival; SCC, squamous cell carcinoma.

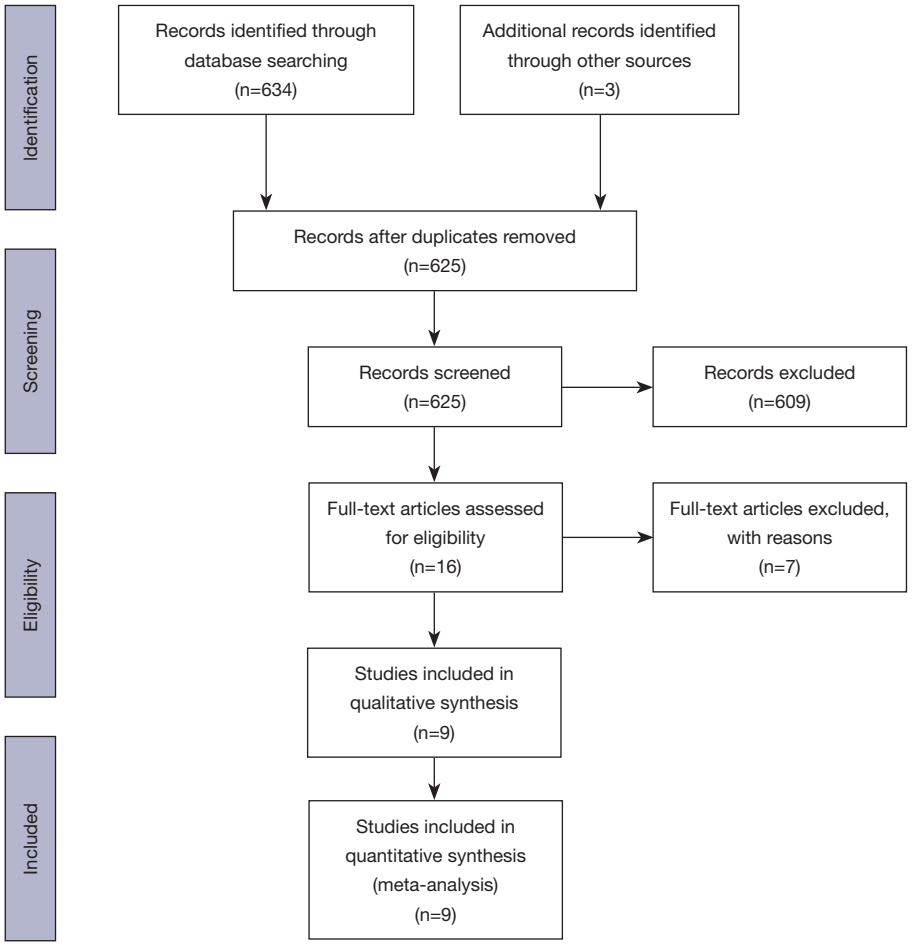

Figure 1 PRISMA flow chart.

to find a common denominator in such a heterogeneous group of patients for a better selection.

To date, the control of the primary disease and its distant metastases are the most important prognostic factors of OM-NSCLC. Many factors could influence the OS, even if only local treatments are associated with a significant improvement (28) in a multidisciplinary setting. Suppose we considered that a possible disease progression is usually more likely to occur at the DM sites at diagnosis rather than in new sites. In that case, patients with OM-NSCLC could benefit in terms of survival from the local treatment of the metastasis, such as surgery or radiotherapy (29-31).

According to our results, OM patients who were radically treated had a more robust OS and a significant prognostic difference depending on the metastatic site (i.e., a favourable factor in brain lesions) and the timing of presentation (synchronous *vs.* metachronous) (1,28). Besides, OM patients at diagnosis had a better OS than patients with oligo-recurrence and/or oligoprogression during or after medical treatments (29). Then, positive prognostic factors for survival included single organ metastasis, the pN0 status, smoking cessation, age <60, and histologic grade of G1/G2. Indeed, a multidisciplinary strategy, including surgery, for patients with multiple sites of OM-NSCLC, should always be carefully considered on a case-by-case basis. When it comes to merging data from multiple studies, choosing between meta-analysis and pooled analysis is essential. The first approach is unquestionably less expensive and faster, but it suffers from performance limitations due to a lack of raw data. The basic criteria for performing a pooled study should be used when the exposure or outcome variables are difficult to measure and record, when there are several unpublished studies in the field, and when the monitoring of potential confounders is likely to be improved. The principle of Pareto efficiency (or

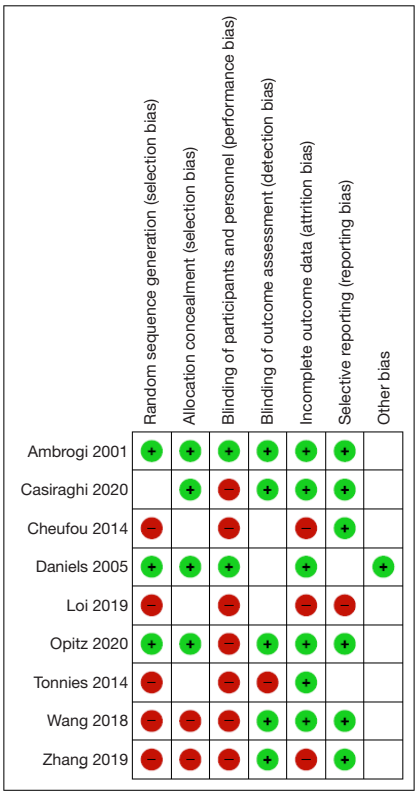

Figure 2 Risk of bias summary: Review the authors' evaluations of each risk of bias item for each study included.

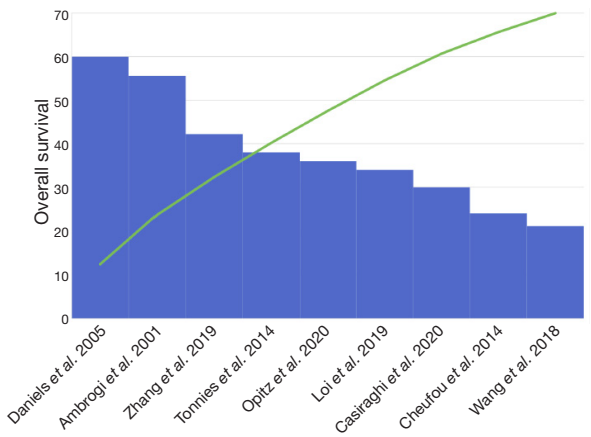

Figure 3 Pareto analysis of the pooled group.

Pareto optimality) is a tool for assessing the efficiency of a series of decisions taken by the participants in game theory and economics. Pareto diagrams may be used in medical process design to recognize mistakes, defects, and accidents, as well as in the implementation of a framework to minimize the risk of medical treatment and the review of performance data in health organizations.

Despite the absence of randomized prospective clinical trials evaluating the therapy sequence (metastases care before/after surgical operation and before/after medical treatment), brain metastases are generally treated before lung resection. On the other hand, adrenal gland metastases are treated after resection to maintain adrenocortical activity for lung surgery. Unfortunately, both the timing and the type of induction treatments, even if already demonstrated to be related to local control and clinical downstaging (32), could not be meta-analysed due to the population's heterogeneity included in the studies.

Another important key point is the biological feature of the tumour since, in the future, it might be able to distinguish the OM cohort from generally stage IV disease, as well as the differences between an indolent and an aggressive tumour. However, it also is the target of future therapy (in addition to local control) for patients who harbour sensitising driver mutations.

Our study presents some limitations: the studies reviewed were incredibly diverse, and some potentially essential studies were likely ignored. Given our best efforts, we could not find all acceptable facts due to our extensive searches lacking the so-called grey literature (dissertations, conference abstract, book chapters, and policy documents). The effect of grey literature, on the other hand, should not be considered. Second, the technique used is quite different. Because of the various disease states and operations involved, the mortality analyses focused on these studies (which involve all events) cannot be used to draw any conclusions.

In the absence of randomized data to help describe the effective treatment of OM-NSCLC, aggressive therapy should be used in otherwise stable patients with synchronous (or metachronous) extrathoracic M1 disease and no intrathoracic lymph node involvement.

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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.

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tlcr-20-1123). The series "Oligometastatic NSCLC: definition and treatment opportunities" was commissioned by the editorial office without any funding or sponsorship. 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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