Critical Reviews in Oncology / Hematology 218 (2026) 105096

Contents lists available at ScienceDirect

Critical Reviews in Oncology / Hematology

journal homepage: www.elsevier.com/locate/critrevonc

To ablate or not to ablate? Outcomes of local ablative treatments (LAT) for oncogene addicted (OA) oligo-metastatic (OM) non-small cell lung cancer (NSCLC): A systematic review

Fabrizio Citarella [a], Cristina Fragale [b], Matteo Fiorenti [c], Maria Luisa Di Guglielmo [b], Noemi Mindicini [b], Alessio Cortellini [a,c,d], Alessandro Russo [e,f,1], Giuseppe Bronte [b,g,1,*]

[a] Department of Medicine and Surgery, Università Campus Bio-Medico di Roma, Via Alvaro del Portillo 200, Roma 00128, Italy
[b] Department of Translational Medicine, University of Ferrara, Ferrara, Italy
[c] Operative Research Unit of Medical Oncology, Fondazione Policlinico Universitario Campus Bio-Medico, Via Alvaro del Portillo 200, Roma 00128, Italy
[d] Department of Surgery and Cancer, Imperial College of London, Hammersmith Hospital Campus, Du Cane Road, London, UK
[e] Medical Oncology Department, Humanitas Istituto Clinico Catanese, Misterbianco, Catania, Italy
[f] Department of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy
[g] Department of Oncology, University Hospital of Ferrara, Ferrara, Italy

ARTICLE INFO

Keywords:
NSCLC
Oncogene addiction
Oligo-metastatic
Local ablative therapy
Precision oncology

ABSTRACT

Oncogene-addicted non-small cell lung cancer (NSCLC) encompasses distinct molecular phenotypes, each associated with specific clinical behavior and variable sensitivity to targeted therapies. Therapeutic advancements in the field enhanced clinical outcomes and overall prognostic improvement. Beyond the molecular profile, disease burden serves as a predictive marker for treatment response and overall prognostic outcomes. The current disease staging categorizes patients based on the number and sites of metastatic involvement. In this context, the addition of local ablative therapies (LAT) is candidate to enhance or prolong the effectiveness of standard systemic therapies. Our systematic review aims to summarize current evidence dealing with the outcomes of LAT in the context of oncogene addicted NSCLC. Over response results, we also reported side effects whenever available.

1. Introduction

Cumulative evidence suggests that oligometastatic (OM) Non-Small Cell Lung Cancer (NSCLC) spread is characterized by unique biological features.

The VIII Edition of IASLC Lung Cancer staging broadened the classification of extra-thoracic metastases, introducing the category M1B in case of single metastasis occurring outside the thoracic area. This change has the aim of identifying a distinct stage with an intermediate prognosis between the pulmonary and/or pleural only and the poly-metastatic disease (Eberhardt et al., 2015).

A proper staging via PET/CT scan and brain MRI beyond conventional CT scan identifies a less aggressive disease phenotype. This has favorable clinical outcomes even after locoregional treatment delivered with consolidative or therapeutic extent in case of oligo-progression (Xu et al., 2022).

The OM definition in terms of the number of lesions and organs involved is debated (Dingemans et al., 2019; Lievens et al., 2020). In absence of clinical trials relying on uniform enrollment criteria, experts' consensus tried to identify specific clinical characteristics. Over time, the definition has been mainly focused on the realistic possibility of delivering integrated treatment in clinical practice settings (Hendriks et al., 2019).

Some scientific evidences suggest peculiar genomic features characterizing OM disease, and therapeutic strategies including local treatments have been retrospectively and prospectively explored. In the era of precision medicine, not only molecular diagnostics advancements but also the multidisciplinary therapeutic integration paves the way to outcomes' improvement. Being oligometastatic disease a distinct disease phenotype, it is likely that it may also benefit from therapeutic tools

* Correspondence to: University Hospital of Ferrara, Via Aldo Moro, 8, Ferrara 44124, Italy.
E-mail address: giuseppe.bronte@unife.it (G. Bronte).
[1] These authors equally contributed as senior authors.

https://doi.org/10.1016/j.critrevonc.2025.105096
Received 9 November 2025; Received in revised form 7 December 2025; Accepted 17 December 2025
Available online 18 December 2025

beyond standard systemic therapy. The present work aims to investigate reported outcomes of patients affected by oncogene-addicted NSCLC which received both systemic and local treatment along the clinical course.

2. Methods

2.1. Review design

This work complied with the relevant requirements of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines and we completed the PRISMA checklist (Supplementary Table 1). The work is designed as a systematic review of those studies which investigate local treatments for oligometastatic oncogene-addicted NSCLC. We aimed to assess if patients affected by oligometastatic oncogene-addicted NSCLC benefit from the integration of local ablative therapy.

The population includes patients with a diagnosis of oligometastatic NSCLC and evidence of oncogene driver alterations. We did not apply an *a priori* definition of oligometastatic disease, since it varies among the studies. We considered all those studies including patients with these characteristics undergoing at least one local ablative therapy (LAT) alongside systemic therapy usually tailored on precision medicine. A direct comparison between oligometastatic and polymetastatic was not feasible, but we evaluated how treatments in oligometastatic patients can integrate the conventional therapies for oncogene-addicted NSCLC. We focused our attention on overall survival (OS), progression-free survival (PFS) or time to treatment failure (TTF), and toxicity rates. We also made an insight into the various types, timing, dosing, and modalities of LAT. No exclusion criteria were applied to LAT strategies, as this allowed for a comprehensive assessment of approach heterogeneity, which is expected to vary considerably across institutions.

2.2. Search strategy

The search for publications on this topic was performed online in PubMed, Scopus and Embase. We used the following search terms combination: ("Non Small Cell Lung Cancer" OR "NSCLC" OR "Lung Cancer") AND ("Oligometastatic" OR "Oligo-metastatic" OR "Limited metastatic" OR "low volume" OR "low burden") AND ("Oncogene addicted" OR "Driver" OR "driven" OR "EGFR" OR "ALK" OR "BRAF" OR "MET" OR "RET" OR "NTRK" OR "ROS-1" OR "mutated" OR "mutation"). We limited the search to studies in the English language and in all time until July, 7 2025. We supplemented these search results with manual searches for meeting proceedings and references from already known selected articles.

2.3. Study selection

First, we read the abstracts of all the records from those databases and selection of the other mentioned sources.

We conducted a first screening according to the following inclusion criteria: 1) original articles; 2) English language; 3) any line of systemic treatment; 4) patients administered with local ablative treatment during oncogene-driven treatment starting; 5) staging systems via PET/CT/RM; 6) investigating only humans.

The records that met the above criteria based on the abstract were deeply analyzed in the full text articles. These articles were excluded if: 1) lacked information considered for data extraction; 2) article were written in language other than English; 3) in case of mixed population, i.e. oncogene and non-oncogene addiction, the amount of oncogene-positive population was too scarcely represented to allow meaningful conclusions.

2.4. Data extraction

We extracted data from each eligible study and reported these into a spreadsheet. The data we extracted included: 1) first author's name; 2) journal's name; 3) year of publication; 4) study phase, e.g. I, II, III; 5) study design, e.g. retrospective or prospective; 6) OS; 7) PFS or TTF; 8) ORR; 9) any toxicity rates; 10) number of included patients; 11) kind, setting, and line of systemic treatment; 12) type of local ablative therapy (LAT); 13) time to LAT; 14) median follow-up time. Two reviewer pairs (FC and MF; GB and CF) independently conducted the sequential screening of articles, beginning with titles and abstracts and subsequently evaluating full texts. Potential disagreements were solved by a consensus between the authors.

2.5. Risk of bias assessment

We evaluated the methodological quality of included studies by using the tool of Cochrane Collaboration Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I v2). Two independent authors (GB and CF) assessed seven domains: domain 1: risk of bias due to confounding; domain 2: risk of bias due to selection of participants; domain 3: risk of bias in classification of interventions; domain 4: risk of bias due to deviations from intended interventions; domain 5: risk of bias due to missing data; domain 6: risk of bias arising from measurement of the outcome; domain 7: risk of bias in selection of the reported result. Each domain was judged as "low", "moderate", "serious", or "critical" (13). Discrepancies were resolved through consensus or consultation with a third reviewer (FC).

3. Results

3.1. Literature search and study selection

The search for articles was performed by using three different databases. The last search was made on July 7th, 2025. The search on Pubmed, Scopus and Embase retrieved 183, 246 records and 581 records, respectively. Further 2 records were identified through manual search. Among these records, 386 were duplicates. After their removal, 626 records were selected for screening based on title and abstract. This screening allowed to exclude 546 records: a) 13 not written in English (3 Chinese, 1 Dutch, 1 French, 3 German, 5 Japanese); b) 179 not being original research articles (3 commentaries, 3 consensus, 17 editorials, 25 articles of educational material, 1 guidelines publication, 5 pharmacoeconomy studies, 1 pooled analysis, 1 preprint, 22 articles as rationale and hypothesis, 1 retracted article, 79 review articles, 1 survey, 20 trial presentations); c) 84 not dealing with NSCLC; d) 114 not dealing with oncogene-addiction; e) 105 not dealing with oligo-metastases; f) 16 not dealing with local ablative therapy; g) 12 were recognized as further duplicates; h) 6 for which full texts were not accessible; i) 17 for exploring only oligo-progression.

We further examined the full texts of the remaining 80 articles according to the eligibility criteria. We excluded 47 of them for various reasons: a) 6 were recognized as further duplicates; b) 1 not written in English (Chinese); c) 3 not being original research articles (1 review, 2 trials presentations); d) 1 not dealing with oncogene-addiction; e) 6 not dealing with oligo-metastases; f) 2 not dealing with local ablative therapy; g) 4 for exploring only oligo-progression; h) 19 for lacking data/outcomes; i) 5 articles excluded as the results were available as full-text works already included in the final analysis. Thirty-three articles remained to be included for final review. We depicted the whole process of literature search and study selection in the PRISMA flow diagram (Fig. 1).

The substantial variability observed across multiple key clinical factors (number of patients treated, time to LAT, LAT selection criteria, and follow-up) precluded the feasibility of a meta-analytic approach.

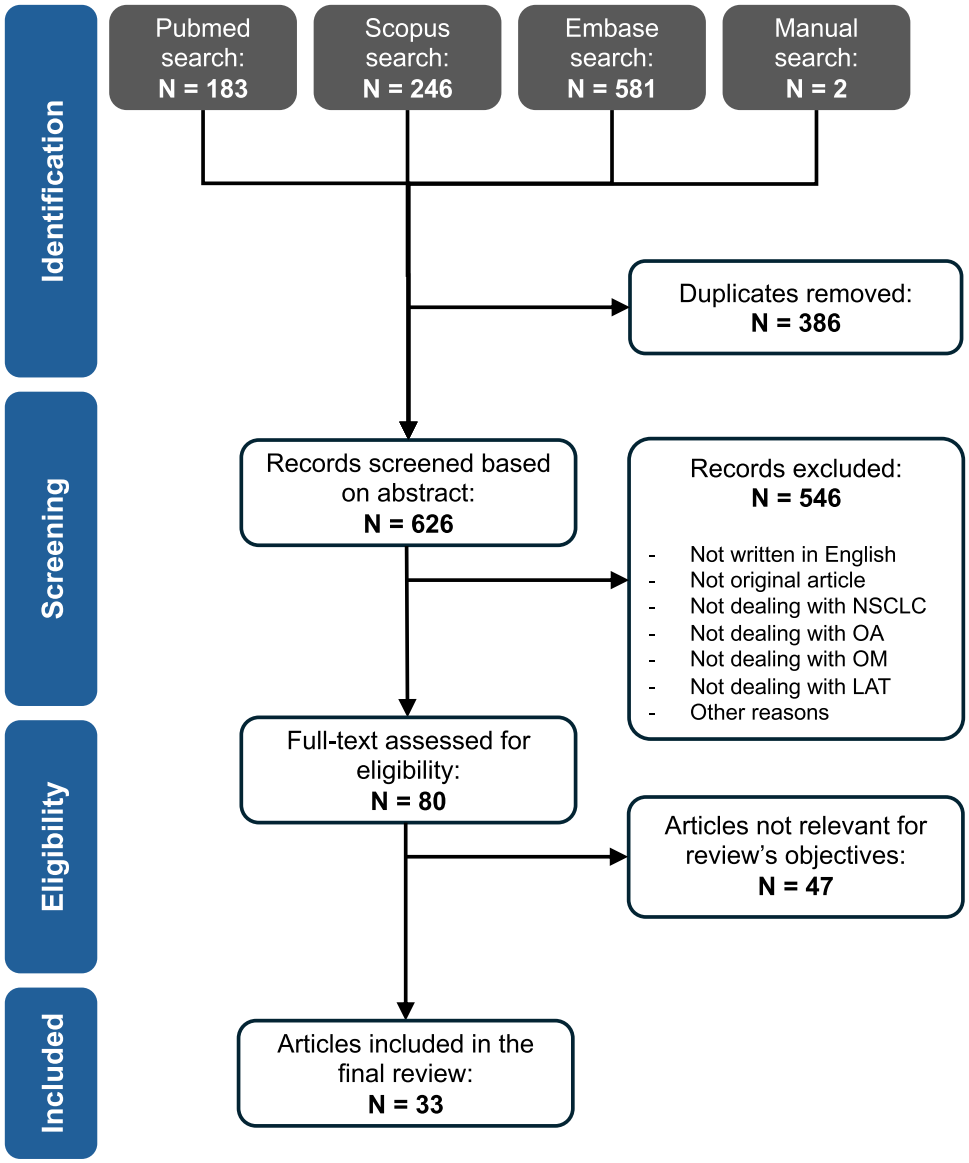

Fig. 1. PRISMA flow diagram. The diagram shows the process of article identification and study selection by using the search strategy and the eligibility criteria, respectively. NSCLC, non-small cell lung cancer. OA, oncogene addiction. OM, oligo-metastases. LAT, local ablative therapy.

3.2. Study characteristics

The articles selected for the final review were 33. These include 28 retrospective (Table 1) and 5 prospective studies (Table 2).

The articles of retrospective studies were published between October 2016 and May 2025. We also included in this group of articles case reports (4 articles) and case series (1 article with 3 cases). Overall, the retrospective works described a total number of 2867 (range 1–436) NSCLC patients, including non-OA and OA disease. As expected, among the oncogene-addicted patients those EGFR mutated were the majority. The definition of oligo-metastatic disease was not homogeneous in all the articles, mainly considering up to 5 synchronous metastases. Twenty studies reported the OS as outcome, and 14 also the PFS. In 6 articles, the authors also described the toxicity of local and/or systemic therapy. Systemic therapy was highly heterogeneous in these studies because it investigated both non-oncogene-addicted and oncogene-addicted, so that chemotherapy or targeted therapy were used. This might be due to the time of publication data: some papers, mainly the less recent ones, evaluated the outcomes of oncogene-addicted patients before the extensive administration of target treatments in clinical practice. As LAT, radiation therapy was reported in 20 articles, 14 papers reported some kinds of surgery in the primary tumor or metastases, alone or as an alternative to radiotherapy or combined with radiotherapy. We could not find the median follow-up in all the studies, but in the 21 articles which reported this detail, it ranged from 9 months to 8 years.

Among the 5 prospective studies, 4 were phase II trials and 1 phase III trial, and were published between December 2016 and April 2025. Oligo-metastases were predominantly defined by the presence of up to 5 synchronous metastases. The total number of patients in this group of studies was 304 (range 25–133), with a predominance of EGFR-mutated NSCLC patients. Four studies used only targeted therapy, and in the other one some patients received platinum-based chemotherapy, because of non-oncogene-addiction. All these prospective studies assessed toxicity, PFS and OS. Three studies locally treated patients with only radiation therapy, and the other two included surgery in addition in primary tumors or metastases. The median follow-up ranged from 12 to 32 months.

The timing of publication of these selected articles is summarized in a bar plot (Fig. 2).

Additional and complete information on retrospective and

Table 1
Retrospective studies. Studies listed in chronological publication order. Enrollment criteria and clinical outcomes are summarized.

Authors	N patients	Outcomes			
		OS	PFS	TTF	Other outcomes
Deng et al. (Oct 2016) Deng et al., (2016)	38 EGFR-mutant potentially SBRT eligible	mOS 47.1 vs 33.7 months for eligible and non-eligible, respectively (p = 0.029)	-	-	-
Sakai et al. (Nov 2016) Sakai et al., (2016)	6 EGFR-mutant receiving TKI+LAT	mOS in EGFR-mutant 58.5 vs 15.9 months EGFR-WT (p = 0.66)	-	-	-
Zhang et al. (Nov 2017) Zhang et al., (2017)	127 among which NA N EGFR-mutant	Among patients receiving LAT, EGFR mutation correlated with longer OS (58.3 vs 25.7 months, HR=0.40, p = 0.017)	-	-	-
Xu et al. (Sep 2018) Xu et al., (2018)	145 EGFR-mutant: 51 all-LAT, 55 part-LAT 49 no-LAT (all +TKI)	LAT to T (40.5 vs 31.5 months, p < 0.001), brain (38.2 vs 29.2 months, p = 0.002) and adrenal mets (37.1 vs 29.2 months, p = 0.032) correlated with mOS. mOS for all-LAT, part-LAT, and non-LAT 40.9, 34.1 months, and 30.8 months, respectively (p < 0.001) Statistic difference between all-LAT vs part-LAT/non-LAT; no difference between part-LAT vs non-LAT.	mPFS for all-LAT, part-LAT, and non-LAT 20.6, 15.6, and 13.9 months, respectively (p < 0.001). LAT to T (p < 0.001) and one met (p < 0.001) correlated with mPFS.	-	-
Hu et al. (Oct 2018) Hu et al., (2018)	253 EGFR-mutant: 149 LCT+TKI, 104 TKI-only	mOS 33 vs 20 months for LCT+TKI vs TKI-only, respectively (HR=0.56, p < 0.01)	mPFS 14 vs 9 months for LCT+TKI vs TKI-only (HR=0.57, p < 0.01)	-	-
Hu et al. (Jan 2019) Hu et al., (2019a)	231 EGFR-mutant: 143 LCT+TKI, 88 TKI-only	mOS 34 and 21 months for LCT+TKI vs TKI-only (HR=0.593, p = 0.001)	mPFS 15 and 10 months for LCT+TKI vs TKI (HR=0.61, p < 0.001)	-	-
Elamin et al. (Jan 2019) Elamin et al., (2019)	129 EGFR-mutant: 8 OM TKI+LCT, 4 > 3 mets TKI+LCT, the others TKI-only	No difference in mOS between LCT+TKI and TKI-only (p = 0.06)	mPFS for LCT+TKI and TKI-only: 36 vs 14 months (HR=0.29, p = 0.0024)	-	-
Borghetti et al. (Feb 2019) Borghetti et al., (2019)	42 EGFR-mutant and 10 ALK positive in OM/OP setting, receiving RT+TT	-	-	OP or no progression more frequent in OM/OP vs polymetastatic patients (p = 0.002)	-
Jiang et al. (May 2019) Jiang et al., (2019)	43 EGFR-mutant: 23 TKI+LCT, 20 TKI-only	mOS LT+TKI and TKI-only: 36.8 vs 21.3 months, HR= 0.47, p = 0.034). Addition of LCT associated with longer OS (p = 0.018).	mPFS LCT+TKI and TKI-only: 12.9 vs 7.9 months, HR= 0.55, p = 0.041. Lower mets N associated with better PFS (p = 0.036). LCT associated with longer PFS (p = 0.009).	-	-
Hu et al. (Sep 2019) Hu et al., (2019b)	127 EGFR-mutant: 67 TKI + LCT, 65 TKI-only	mOS for TKI+LCT and TKI-only and 36.3 vs 21 months, respectively (HR=0.537, p = 0.01). HR of OS for TKI+LCT vs TKI= 0.646 (p = 0.04). Better mOS in patients with metachronous bone mets (HR=0.265, p = 0.00).	mPFS for TKI+LCT and TKI-only and 14 vs 8.1 months, respectively (HR=0.613, p = 0.01). HR PFS for TKI+LCT vs TKI-only= 0.675 (p = 0.04).	-	-
An et al. (Sep 2019) An et al., (2019)	98 EGFR mutant: 49 TKI + LCR, 49 TKI-only	mOS longer for TKI+LCR vs TKI-only: 38 vs 29 months, p = 0.043. Brain mets OM: mOS 31 for TKI+LCR compared to 24 months (p = 0.019) for TKI-only. Extra-cranial OM: mOS 43 for TKI+LCR compared to 34 months (p = 0.0338) for TKI-only.	mPFS longer for TKI+LCR vs TKI-only: 17 vs 10 months, respectively, p = 0.002. Brain mets OM: mPFS 17 for TKI+LCR compared to 10 months (p = 0.035) for TKI-only. Extra-cranial OM: mPFS 18 for TKI+LCR compared to 10 (p = 0.034) months for TKI-only.	-	-
Tsai et al. (Nov 2019) Tsai et al., (2019)	C1: EGFR-mutant, receiving LAT+TT	-	No progression at follow-up	-	-

(*continued on next page*)

Table 1 (*continued*)

Authors	N patients	Outcomes			
		OS	PFS	TTF	Other outcomes
Zhang et al. (Nov 2019) Zhang et al., (2019)	436 patients: 77 and 82 for training and testing sets, respectively, receiving LAT+ST	EGFR mutation correlated with better mOS (HR=0.667, p = 0.043)	-	-	-
Ni et al. (Jan 2020) Ni et al., (2020)	86 EGFR-mutant: 34 MWA+TKI, 52 TKI-only	mOS for MWA+TKI and TKI-only: 34.8 vs 22.7 months, HR= 0.45, p = 0.04. MWA correlated with better OS (HR=0.57, p = 0.02)	mPFS for MWA+TKI and TKI-only: 16.7 vs 12.9 months, HR= 0.44, p = 0.02. MWA correlated with better PFS (HR=0.46, p < 0.01).	-	-
Citarella et al. (Jun 2021) Citarella et al., (2021)	C1: 1 RET-mutant, receiving LAT+TT	-	No progression at follow-up	-	-
Hu et al. (Jan 2022) Hu et al., (2022)	122 EGFR-mutant: 72 TKI-alone, 50 TKI plus LCT for all sites	Median OS for TKI+LCRT 38 vs 29 months for TKI-only (p < 0.001)	Median PFS for TKI+LCRT 17 vs 12 months for TKI-only (p < 0.001)	-	-
Liu et al. (Mar 2022) Liu et al., (2022)	C1: ALK-positive, receiving LAT+TT	-	No progression at follow-up	-	-
Wu et al. (Apr 2022) Wu et al., (2022)	C1: EGFR-mutant, receiving LAT+TT	-	No progression at follow-up	-	-
Yang et al. (Nov 2022) Yang et al., (2022)	53 patients, among which: 25, 4 and 9 EGFR, ALK and ROS1-mutant, respectively	-	23 patients treated with TKI plus all metastatic sites RT: 1-yr PFS 86.7 % (vs 37.5 %, p = 0.029 for those not treated with all site RT). EGFR and ALK mutations correlated with better PFS (HR=0.24 and 0.04, respectively).	-	-
Yoo et al. (Jan 2023 Yoo et al., (2023)	117 patients among which 53 EGFR/ALK/ROS1 mutant, receiving LAT+TT/ST	1-year, 3-year, 5-year survival rates: 98 %, 64 %, and 42.7 %, respectively (vs 70.3 %, 43.5 %, and 32.8 % in non-OA patients, p = 0.031)			
De et al. (Jan 2023) De et al., (2023)	194 among which 24 EGFR-mutant	EGFR mutation associated with longer OS (HR=0.53; p = 0.044) in the whole cohort and among patients receiving comprehensive LCT (HR=0.45, p = 0.032). Median OS in EGFR-mutant patients with comprehensive LAT: 98 months. Lower risk of death for EGFR-mutant patients (HR=0.53, p = 0.044).	-	-	-
Antonoff et al. (Mar 2023) Antonoff et al., (2023)	21 EGFR or ALK-mutant, receiving LAT+TT	-	-	-	Surgeons' report on difficult operations: 76.2 % Adhesions: 28.6 %; Severe impact on nodal dissection: 52.4 %; Severe hilar fibrosis: 81 %.
Açikgöz et al. (Aug 2023) Açikgöz et al., (2023)	134, among which: 15, 7, 3 and 1 EGFR, ALK, ROS1 and BRAF-mutant, respectively, receiving LAT+TT/ST	Driver mutation correlated with survival after progression (p = 0.005). Worse mOS in patients with driver mutation (23.1 vs 39.1 months)	Driver mutation correlated with better mPFS (31.5 vs 14.4 months, p = 0.034). mPFS NR for patients treated with target therapy.	-	-
Semenkovich et al. (Oct 2023) Semenkovich et al., (2023)	53 EGFR, 9 ALK, 2 ROS1, 8 MET, 1 RET, 9 BRAF, 16 KRAS and 3 ERBB2 alterations receiving RT+ST	At multivariate analysis, driver mutations not associated with OS	At multivariate analysis, driver mutations not associated with PFS	-	-
Wang et al. (Jun 2024) Wang et al., (2024)	C1: EGFR-mutant, receiving LAT+TT	-	No progression at follow-up	-	-
Werner et al. (Jun 2024) Werner et al., (2024)	46 patients with brain mets, receiving LAT+ST	mOS 23 and 56 months in patients with and without a private alteration in brain mets. Cumulative incidence of death at	-	-	An oncogenic alteration present in 31 primary tumors (67.4 %) and 40 brain

(*continued on next page*)

Table 1 (*continued*)

Authors	N patients	Outcomes			
		OS	PFS	TTF	Other outcomes
		50 months: 47.6 % and 61 % in patients with and without a KRAS mutation in the primary tumor (p = 0.43). Presence of private alterations in brain mets predicted shorter OS (p = 0.019).			mets (86.9 %). T: 10 KRAS G12C, 2 EGFR mutant, 1 ALK fusion. Private alterations in 16 brain mets: 2 KRAS G12C, 2 EGFR, 1 RET, 1 ALK fusion and 1 MET ampl.
Abudureheman et al. (Nov 2024) Abudureheman et al., (2024)	40 among which a NA N with driver mutation. 20 treated with ST, 20 with iodine-125 seed implantation+ST.	Driver mutations correlated with better OS	-	-	-
Jin et al. (May 2025) Jin et al., (2025)	67 patients among which 24 EGFR-mutant and 2 ALK-positive: 21, 2 and 1 treated with EGFR-TKI, EGFR-TKI + CT and ALK-TKI, respectively	mOS NR and 30.7 months (p = 0.095) for CLT+EGFR-TKI vs EGFR-TKI-only, respectively	mPFS 46.8 vs 15.7 months (p = 0.023) for CLT+EGFR-TKI vs EGFR-TKI-only, respectively	-	-

prospective studies is available in Supplementary Tables (Supplementary Table 2 and Supplementary Table 3). Toxicity rates, enrollment period, time to LAT, type of LAT, follow-up duration, and treatments combined with LAT are reported in detail.

3.2.1. *Risk of bias*

The methodological quality of included studies was represented through a traffic light plot and a summary plot (Figs. 3 and 4). Only 4 studies met at least 5 low-risk criteria. Major limitations involved domain 1 and 3.

3.3. *Retrospective studies*

In the first retrospective study, published in 2016, the authors questioned whether oligo-metastatic NSCLC patients with a common EGFR mutation, who were eligible to stereotactic body radiation therapy (SBRT), benefited from this type of LAT before TKI progression. They collected data of 166 patients, but just 38 of them were SBRT-eligible. They observed a pronounced advantage in survival for these patients, with progression mainly in isolated original sites. So, they concluded that upfront SBRT can achieve a possible advantage (Deng et al., 2016).

A subsequent study evaluated node-negative NSCLC patients with oligo-metastatic disease, not only those with EGFR mutations. The authors explored the outcomes of 18 patients with these characteristics. A trend toward favorable OS was pointed out among EGFR-positive patients, despite the data should be taken with caution due to the limited number of 6 EGFR-positive cases. They observed a failure in brain metastases, which were located outside the sites treated with surgery or radiosurgery. This finding made them suppose that LAT with surgery or radiosurgery for brain metastases together with primary tumor could be beneficial (Sakai et al., 2016). In a similar population of 127 patients, i.e. oligo-metastatic node-negative NSCLC patients, mainly EGFR positive, other authors found that LAT after systemic treatment improved OS, compared to those who did not receive local therapy (Zhang et al., 2017).

A study included 436 patients regardless of EGFR status, who were treated or not for oligo-metastatic disease with radiotherapy or surgery or both as LAT. This study was designed with a singular stratification in 4 groups: 1) never smokers with N0 disease; 2) never smokers with N + disease; 3) smokers with T0–2 disease; 4) smokers with T3–4 disease. OS was improved in groups 1–3, but not in group 4. The authors concluded that smokers with T3–4 oligometastatic NSCLC could not benefit from LAT (Zhang et al., 2019). A real-life experience on 134 patients with oligo-metastatic NSCLC evaluated local treatment with SBRT, surgery or both. The authors described a prolonged OS and PFS, but also survival after progression in oligo-metastatic patients. They deduced a relevant role of local treatment in combination with systemic therapy for a radical intention in oligo-metastatic disease (Açikgöz et al., 2023).

Some authors focused on EGFR-mutant patients only. In their retrospective study, they included oligometastatic EGFR-mutant NSCLC and considered as oligo-metastatic disease those with no more than 5 metastases within 2 months from diagnosis. They included 145 patients who received first-line EGFR-TKIs, in some patients together with consolidative LAT, such as surgery, radiotherapy or both. They stratified patients according to LAT: all-LAT group applied to all sites of disease, part-LAT group applied to either primary tumor or oligo-metastases, non-LAT group if LAT was not applied. The best improvement in OS and PFS was achieved in the all-LAT group, so that this could be considered not only a feasible approach but also a more beneficial strategy (Xu et al., 2018). In a similar study, 253 EGFR-mutant patients with oligo-metastatic lung adenocarcinoma received EGFR-TKIs or this treatment associated with LAT. This study confirmed the good feasibility of LAT in combination with EGFR-TKIs and its role in improving PFS and OS (Hu et al., 2019a).

In another retrospective study on EGFR-mutant metastatic NSCLC patients, 129 of them received only EGFR-TKI and 12 both EGFR-TKI and LAT. Two thirds of these 12 were oligo-metastatic because no more than 3 metastatic lesions were present at the time of diagnosis. The use of LAT, as hypofractionated radiotherapy or SBRT or surgery, yielded a greatly longer PFS (36 vs 14 months). So, this study empowered the usefulness of LAT, despite the retrospective nature and the small number of patients treated with LAT (Elamin et al., 2019). Similar results were obtained in 20 EGFR-mutant oligo-metastatic NSCLC with liver metastases. The combination of EGFR-TKI with LAT achieved a significantly better PFS, and OS too, than EGFR-TKIs alone (Jiang et al., 2019). Other authors performed a study to compare EGFR-mutant oligo-metastatic NSCLC with bone metastases. Also in this case, 62 patients receiving the combination of EGFR-TKI with LAT, versus 65 receiving EGFR-TKI alone, obtained significantly longer PFS and OS (Hu et al., 2019b). More recently, in a study on 23 EGFR-mutant NSCLC patients with solitary skeletal oligo-metastasis, LAT combined with EGFR-TKI achieved an advantage in terms of PFS but not OS in comparison to those treated with EGFR-TKI alone (Jin et al., 2025). For almost one hundred EGFR-mutant oligo-metastatic NSCLC patients from another center, first-line EGFR-TKI combined with radiotherapy as LAT improved PFS and OS in comparison with EGFR-TKI alone, but these results were significant and remarkable for patients with brain

Table 2
Prospective studies. Studies listed in chronological publication order. Enrollment criteria and clinical outcomes are summarized.

Authors	Study phase	N patients	Outcomes	
			OS	PFS
Gomez et al. (Dec 2016) Gomez et al., (2016)	II	25 patients treated with immediate LCT after (TKI-based) IT vs 24 patients receiving maintenance therapy/observation after IT. LCT group: 3 EGFR-mutant, 2 ALK-positive. Non-LCT group: 3 EGFR-mutant.	-	EGFR/ALK status correlated with better median PFS (HR=0.19)
Arrieta et al. (Apr 2019) Arrieta et al., (2019)	II	37 patients among which 15 EGFR-mutant, 1 ALK-positive, receiving LAT+TT/ST	No difference in mOS depending on OA	mPFS 17.9 vs 23.5 months for OA and non-OA patients, respectively (HR= 1.49, p = 0.347; no difference depending on OA)
Blake-Cerda et al. (Feb 2021) Blake-Cerda et al., (2021)	II	47 patients, among which 19 EGFR mutant, 2 ALK-positive, receiving pulmonary SABR+TT/ST	No difference in mOS between OA and non-OA patients.	mPFS of 34.3 months for OA patients (not different from non-OA)
Wang et al. (Jun 2023) Wang et al., (2023)	III	133 EGFR-mutant: 68 RT+TKI, 65 TKI-only	Median OS 25.5 for TKI+RT vs 17.6 months for TKI-only (p < 0.001, HR=0.44)	Median PFS 20.2 for RT+TKI versus 12.5 months for TKI-only (p < 0.001, HR=0.22). 6-month PFS: 99.1 % for RT+TKI vs 95.2 % for TKI-only (p > 0.05). At last FUP, T and M control 91.2 % for RT+TKI vs 55.4 % for TKI-only (p < 0.001).
Peng et al. (Apr 2025) Peng et al., (2023)	II	62 EGFR-mutant patients, among which 31 SBRT+TKI and 31 TKI-only	mOS 35.2 and 23.2 months for SBRT+TKI and TKI-only (HR=0.53, p = 0.033). OS for T-only SBRT: 49.1 months. OS for M-only SBRT: 24.8 months. OS for T and M SBRT: 28.8 months.	mPFS 17.3 and 9 months for SBRT+TKI and TKI-only, respectively (HR=0.52, p = 0.016). PFS for T-only SBRT: 27.3 months. PFS for M-only SBRT: 10.6. PFS for T and M SBRT: 17.6 months.

Tables 1 and 2 - **Abbreviations:** CLT: comprehensive local therapy; CT: chemotherapy; HR: hazard ratio; FUP: follow-up; IT: induction therapy; LAT: local ablative therapy; LCR: local consolidative radiotherapy; LCT; local consolidative therapy; LT: local treatment; M/mets: metastases; mOS: median Overall Survival; mPFS: median Progression Free Survival; MWA: microwave ablation; N: number; NA: not available; NR: not reached; OA: oncogene addicted/addiction; OM: oligo-metastatic; OP: oligo-progressive; RT: radiation therapy; SABR: Stereotactic Ablative Body Radiotherapy; SBRT: Stereotactic Body Radiation Therapy; ST: systemic therapy; T: primary tumor; TKI: tyrosine kinase inhibitor; TT: target therapy; TTF: time to treatment failure; WT: wild type.
*Systemic therapy is meant non-target treatment or cases in which target treatment is not deductible.

oligo-metastases (An et al., 2019).

A study focused on elderly patients with EGFR-mutant oligo-metastatic NSCLC. The authors included 122 elderly patients who received or not radiotherapy as LAT in combination with EGFR-TKI. In agreement with similar studies, LAT improved PFS and OS. Moreover, local therapy was safe in these patients because only grade 1–2 toxicity was observed, without treatment-related deaths (Hu et al., 2022).

A new form of LAT, the image-guided percutaneous microwave ablation (MWA), was also investigated. This is a minimally invasive technique studied for the treatment of both primary and metastatic lung malignancies. The authors retrospectively studied 86 EGFR-mutant stage IIIB or IV NSCLC patients with extracranial oligo-metastases. Thirty-four patients without progression after first-line EGFR-TKI received consolidation therapy with MWA and achieved significant improvement in PFS and OS in comparison with those receiving EGFR-TKI only (Ni et al., 2020). So, this form of local therapy could be considered for patients with oligo-metastasis. Another potential new form of LAT is the iodine-125 seed implantation in patients with oligo-metastatic NSCLC. Some researchers retrospectively reviewed 40 patients receiving or not this local treatment in combination with systemic therapy. They found longer median PFS and OS in patients who received this form of LAT (Abudureheman et al., 2024).

There are further retrospective studies which include patients with other oncogenic drivers. A study collected data of 46 paired samples of primary lung tumor and brain metastases in oligo-metastatic NSCLC patients. Brain metastases have a good concordance of genetic alterations with the primary tumor. Private genetic alterations in the brain metastasis were found in one third of cases, and if present these are associated with shorter OS (Werner et al., 2024).

SBRT was related to better OS in a study including both EGFR-mutant and ALK-translocated NSCLC patients treated with respective conventional TKIs. Interestingly, SBRT was significantly associated with a longer duration of TKI treatment than palliative RT (Borghetti et al., 2019). Another study included more than half of oncogene addicted (EGFR-, ALK- and ROS1-positive) oligo-metastatic (no more than 3 metastases) NSCLC patients. An early radiotherapy as LAT to all sites of disease improved PFS, mainly for EGFR- and ALK-positive while receiving TKI (Yang et al., 2022). Similarly, a study including almost half of the EGFR-, ALK- or ROS1-positive oligo-metastatic NSCLC patients evaluated OS after the resection of primary tumor associated with surgery or radiotherapy for metastases. The authors observed a survival benefit in patients younger than 65 years and in those oncogene-addicted (Yoo et al., 2023).

The study by De et al. also evaluated the impact of other gene mutations (i.e. TP53, KRAS, STK11) in addition to EGFR mutations. However, only oligo-metastatic (namely 3 synchronous metastatic sites) NSCLC patients harboring EGFR mutations achieved a survival benefit when treated with LAT (surgery or radiotherapy to all disease sites) in addition to systemic therapy (De et al., 2023).

In 2023, Semenkovich et al. published a paper about the role of liquid biopsy to identify patients who could benefit from RT as LAT in patients with oligo-metastatic NSCLC. They included 1487 patients with oligo-metastatic NSCLC, but in around three hundred of them circulating tumor DNA (ctDNA) was measured before RT. They measured maximum variant allele frequency (VAF) and mutational burden of ctDNA. Both parameters inversely correlated with PFS and OS, so that greater was the amount of ctDNA shorter were the survival outcomes (Semenkovich et al., 2023). A validation of these findings in a larger population of prospective studies could provide a valuable tool to optimize the use of LAT in oligo-metastatic disease.

Finally, the study by Antonoff et al. is merely descriptive, because the authors characterized the intraoperative nuances of lung resection as a component of LAT in oligometastatic NSCLC patients. They included patients harboring EGFR mutations or ALK fusions, who were treated with Osimertinib and Brigatinib, respectively, before LAT. Two-thirds of operations were overall severely difficult, but no operative mortalities or

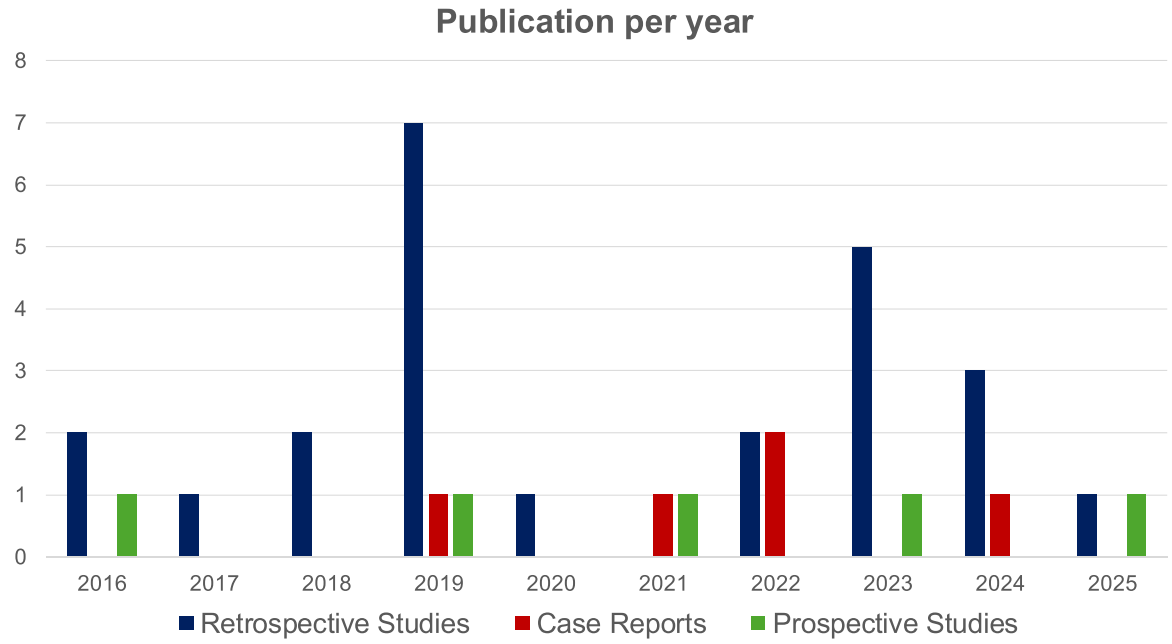

Fig. 2. Bar plot of publication year clustered according to the type of study. X-axis: year; Y-axis: number of articles.

post-operative ICU admissions were described in the 21 patients included. Therefore, we can conclude that the surgical approach to EGFR- or ALK-positive oligo-metastatic NSCLC patients is quite feasible (Antonoff et al., 2023).

3.4. Case reports / Case series

Four single case reports and 1 case series are available from literature about the topic of this systematic review. These articles are useful to understand the applicability of the approaches investigated in the retrospective studies above described.

First, Tsai et al. reported a case of EGFR-mutant lung adenocarcinoma stage cT2aN0M1b, where M1b refers to a single bone metastasis at L3. Therefore, we can consider this patient as oligo-metastatic. After starting treatment with Afatinib, she achieved regression of the primary tumor. So, she underwent surgery of the primary tumor, which showed pathological complete response of the lung nodule, and curative intent radiotherapy to the bone metastasis. Finally, the authors report a long follow-up of 32 months due to this successful approach of combined surgery and radiotherapy as LAT. However, it is not clear whether the patient continued the TKI after the LAT (Tsai et al., 2019).

The case by Wu et al. regards a patient who underwent craniotomy for a symptomatic intracranial tumor, leading to the diagnosis of metastasis from EGFR-mutant lung cancer. Subsequently, lung mass with regional lymph node involvement were found. The patient started treatment with Osimertinib leading to tumor response. She underwent surgery to the primary tumor and regional lymph nodes, with evidence of post-surgical residual invasive adenocarcinoma, and continued Osimertinib. However, in this case report the follow-up is too short, i.e. 6 months, to express the opinion whether this approach was successful, namely surgery to metastasis, then starting systemic treatment and finally surgery to primary tumor and regional involvement (Wu et al., 2022).

Another EGFR-mutant oligo-metastatic NSCLC case is described by Wang et al. This patient was diagnosed with stage IV lung EGFR-mutant adenocarcinoma for the presence of bilateral lung lesions and a single rib metastasis. She started gefitinib with partial response and negative bone scan. Then, treatment was shifted to Osimertinib for evidence of T790M mutation. After 12 months she experienced progression, so Anlotinib was added to Osimertinib. Because of the enlargement of probable primary tumor and no evidence of distant metastases, the patient underwent surgery to the primary tumor. The pathology revealed residual adenocarcinoma and the presence of a new EGFR mutation, i.e. L718Q, together with the initial mutation L858R. The patient started Afatinib and stayed progression-free at 12 months follow-up (Wang et al., 2024).

Liu et al. described a patient who underwent surgery to the chest for lung nodule with locoregional lymph node involvement and concurrent choroidal metastasis, with the diagnosis of ALK-positive lung adenocarcinoma, stage T2aN1M1. The patient refused eye enucleation. She started Crizotinib, with subsequent regression, and continued this systemic treatment for 27 months staying progression-free. In this case, surgery to the primary tumor was the optimal LAT, given that the patient refused surgery to the single metastasis. However, also this option appears to be successful at the time of the publication of this case (Liu et al., 2022).

In a series of 3 cases, the authors describe oligo-metastatic NSCLC patients harboring RET fusions. Patients with these genomic alterations have not been included in the studies described above. In this paper, case 1 fits well with the eligibility criteria of this systematic review. This patient started platinum-based systemic therapy. Upon the finding of tumor response, he received SBRT to the primary tumor, regional lymph nodes, and then to single rib metastasis. So, he achieved a long-lasting complete metabolic response at PET-CT scan (Citarella et al., 2021).

3.5. Prospective studies

Despite these interesting observations from retrospective studies and case reports, data from 5 prospective studies attempted to clarify the advantages provided by LAT in addition to systemic therapy.

The first prospective study focusing on this topic was published in 2016. This was a phase II randomized trial. The authors randomized 49 patients treated with chemotherapy if non-oncogene-addicted, or targeted therapy if oncogene-addicted (EGFR- or ALK-positive), to receive LAT (i.e. radiotherapy or resection of all lesions), or maintenance (i.e. systemic therapy or observation only). These patients were included if they were oligo-metastatic, namely no more than 3 metastases after first-line systemic therapy. The patients who received LAT experienced significantly improved PFS (hazard ratio 0.35 with $p = 0.0054$) (Gomez et al., 2016).

A subsequent study was phase II too, but single arm. All the 37

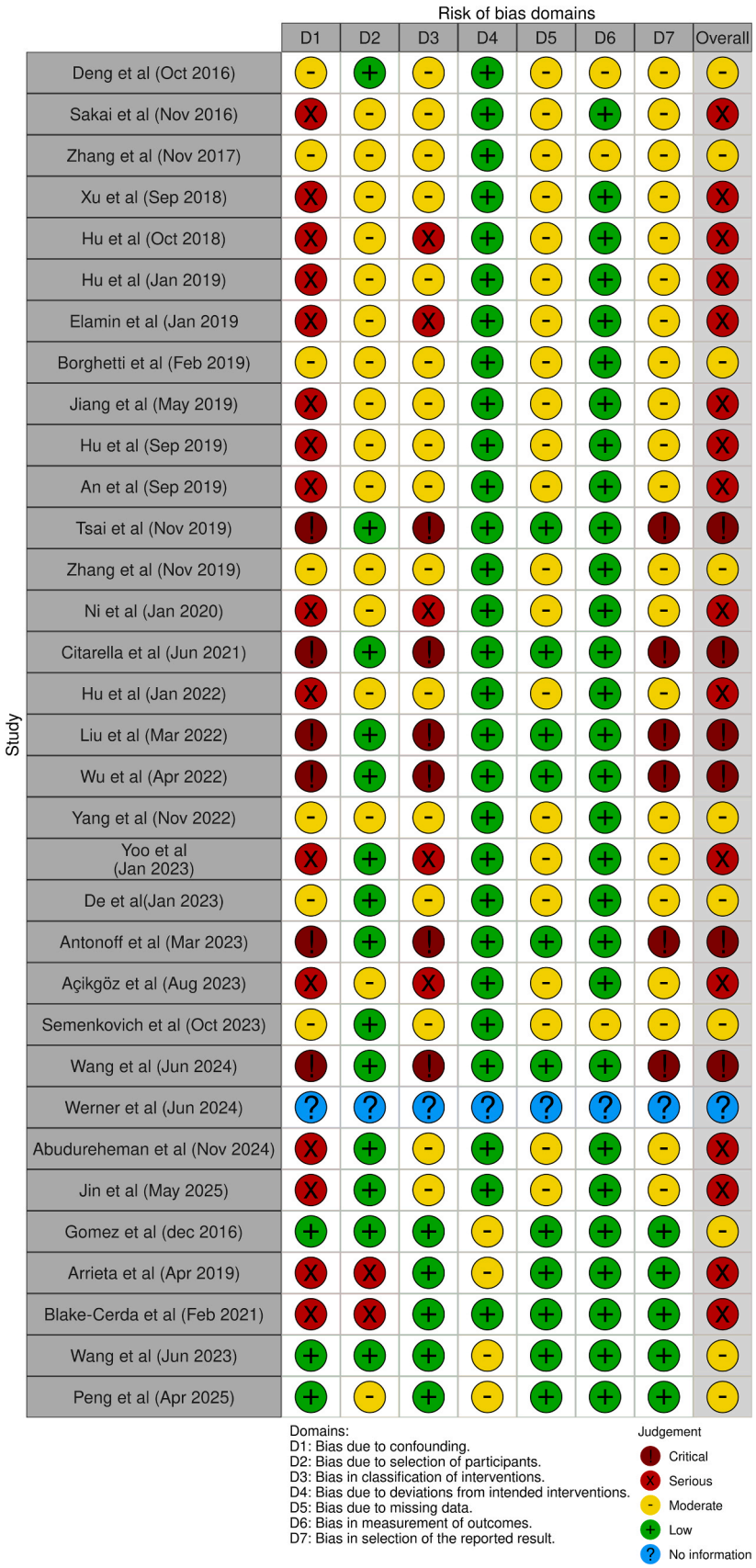

Fig. 3. Traffic light plot of the quality assessment of the included studies according to the Cochrane Collaboration's ROBINS-I v2 tool.

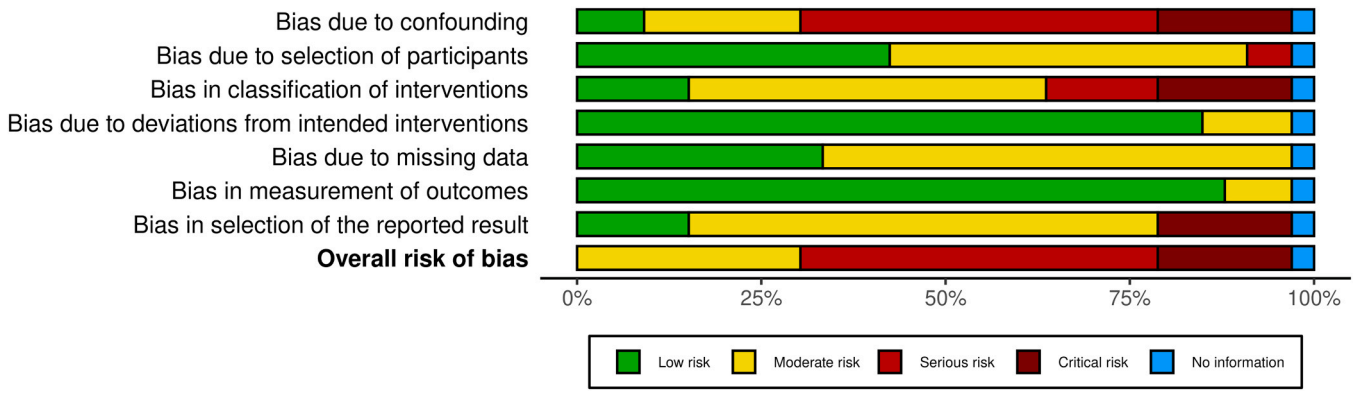

Fig. 4. Summary plot of the quality assessment of the included studies according to the Cochrane Collaboration's ROBINS-I v2 tool.

enrolled patients were oligo-metastatic NSCLC patients with no more than 5 synchronous metastases at any site including the brain. After initial systemic therapy, i.e. chemotherapy or TKI, the patients who experienced partial response or stable disease underwent LAT to primary tumor and/or metastases with surgery, radiotherapy, chemo-radiotherapy, SBRT or radiofrequency ablation. Half of patients had complete response, and achieved improved PFS and OS in comparison to those without complete response (Arrieta et al., 2019).

Another single-arm phase II study with a similar design to the previous one was focused on SBRT as LAT. The authors enrolled 47 patients and accordingly observed two-thirds of them experiencing complete response. These ones achieved longer PFS and OS in comparison to the patients without complete response (Blake-Cerda et al., 2021).

These findings led some researchers to design a phase III trial (SINDAS trial). They included 133 patients with EGFR-mutant adenocarcinoma, oligometastatic for synchronous no more than 5 metastases (2 lesions in any one organ) excluding those with brain metastases. These patients were randomized to receive upfront RT as LAT vs no RT together with EGFR-TKI. Also in this study, similarly to the previous randomized trial, the patients receiving LAT experienced improvement of PFS, but also of OS. However, this paper is related to prespecified interim analysis at 68 % accrual (Wang et al., 2023). In the meantime, a phase II randomized trial including 62 EGFR-mutant oligometastatic (i.e. no more than 5 metastases) NSCLC patients was published. The design of this trial was similar to the phase III trial, with SBRT plus EGFR-TKI compared to EGFR-TKI only. A benefit in terms of PFS and OS for the addition of SBRT was obtained also in this study (Peng et al., 2023). Thus, all the findings described are oriented to confirm LAT as a valuable approach when oligo-metastatic disease is present in NSCLC patients regardless of mutation status. However, more complete and extensive data are needed.

4. Discussion

Oligometastatic (OM) disease is an umbrella term used to identify a small subgroup of NSCLC patients, but there is no maximum number of metastases (Guckenberger et al., 2020). Among the studies selected in this systematic review, there was a high heterogeneity of OM definition in inclusion criteria. This variability concerned more than one factor: number of metastases (e.g. up to 3), synchronous and/or metachronous, number of organs involved (e.g. up to 2), limitation to one organ (e.g. liver or bone). Overall, the most common criterion was up to five synchronous metastases.

The therapeutic management of these patients is evolving, driven by effective LAT combined with advances in systemic treatment (Jasper et al., 2022). In the studies selected for this systematic review, LAT was practiced through various techniques, such as surgery, radiation therapy (i.e. SBRT, WBRT, hypofractionated RT, radiosurgery), MWA, radiofrequency ablation for liver metastases. However, the approach of LAT for each patient is applied as per physician's choice. Nowadays, LAT is increasingly used in clinical practice for OM NSCLCs harboring oncogenic drivers in addition to targeted therapies. However, there is a lack of substantial high-level evidence to widely adopt this strategy, as most of the studies conducted so far are retrospective, with few prospective studies. This therapeutic strategy has been included in international guidelines for selected patients; however, enrollment in clinical trials is recommended (Hendriks et al., 2023).

While the delivery of local treatment is widely explored in the non-OA NSCLC (Sun et al., 2025), the multiplicity of predictive mutations, the variability of therapeutic strategies, and frequently their durations hinder the generation of scientific evidence in the setting of oncogene addiction.

Nevertheless, there is scientific evidence to support the view that oligometastatic disease represents a distinct disease phenotype, amenable to integrated and personalized treatment approaches (Torresan et al., 2025).

Despite the challenges in conducting randomized trials or studies with large populations, current guidelines recommend a case-by-case assessment within a multidisciplinary setting in order to optimally apply modern local ablative techniques (Iyengar et al., 2023).

The aim of this study was to conduct a systematic review on OM oncogene-addicted NSCLC patients who had received both systemic and local treatments during their disease. Collectively, the results of retrospective studies show that LAT during targeted therapy in OM NSCLC harboring actionable genomic alterations is associated with a longer PFS and, in some cases, also with survival gain. These results are confirmed by 5 small prospective studies, including mostly patients harboring *EGFR* mutations. These studies reported significant longer median PFS and OS in patients treated with LAT plus systemic therapy, with the highest benefit seen in those with complete response (Arrieta et al., 2019; Blake-Cerda et al., 2021). Several ongoing studies are focusing on the addition of LAT to targeted therapy in oncogene-addicted NSCLCs, including the phase 2 studies with the ALK inhibitor Brigatinib, OPTALK (NCT06620835) and BRIGHTSTAR (NCT03707938), the NORTHSTAR (NCT03410043) with Osimertinib, and additional studies with other TKIs (NCT05167851, TARGET-01/NCT05277844). Harmonization of OM definition will be critical in ongoing studies.

Recently, tumor volume has emerged as a potential more efficient measure of benefit for OM rather than lesion counts (OA07.01 - Yasir Elamin; OA07.02 - Matthew McMillan (2025 World Conference on Lung Cancer, 2025)), suggesting this could represent a novel biomarker for PFS benefit or rather a stratification factor for patients' enrollment. Baseline tumor volume has been also correlated with ctDNA positivity, a strong prognostic factor, which has been recently investigated in the context of OM NSCLC (Cortinovis et al., 2021). Single studies showed site-specific prognostic value but also genomic signature according to metastatic involvement.

Even the cumulative sum of synchronous oligometastatic disease

tends to correlate with the time to novel metastases in patients treated with local therapy directed to all the lesions (Moore et al., 2022). The clinical outcomes and the genomic features suggest that the mechanisms underlying the limited systemic involvement may confer differential disease evolution. Due to clonal-specific tumor growth patterns, it is plausible that biology and evolution of oncogene addicted OM NSCLC differ from the wild-type disease (Incorporation of EGFR, 2019). The scenario is, however, enriched by the increasing spectrum of therapeutic strategies available, whose synergic effect with local therapies has been in some cases demonstrated also *in vitro* (Golden et al., 2020). In 51 oligometastatic patients with both primary tumor and resected brain metastases, a molecular alteration occurred in 33 cases, among which concordance between primary and metastatic sites was observed in 31 of them (21 KRAS and 4 EGFR mutations, predominantly) (Werner et al., 2023). High Tumor Mutational Burden (TMB) has been demonstrated to correlate with oligometastatic ($\leq$ 4 lesions) brain involvement (Kam et al., 2024).

The use of liquid biopsy is promising in this context. It might favor escalating or de-escalating therapeutic strategies based on the ctDNA clearance during treatment or minimal residual disease detection during follow-up. Comparing liquid biopsies from 51 patients with brain metastases in OM setting ($\leq$ 5 extra-cranial lesions in absence of single organ invasion) matched with 79 non-OM patients, a significant enrichment ($p < 0.01$) with mutations in ATM, JAK2, MAP2K2 and NTRK1 genes was observed. ARID1A and CCNE1 mutations recurred in spread disease. A specific signature predictive of OM showed remarkable predictive value towards the OM status and the risk of OM progression (Choi et al., 2024).

Liquid biopsy has already demonstrated potential for monitoring and predicting response to local treatment. Circulating tumor DNA and immunologic markers correlate with disease course over time. Future studies will clarify its role in monitoring OA and OM NSCLC patients (Zafra et al., 2024).

The matched genomic tissue and liquid profiling of 77 patients affected by oligometastatic NSCLC ($\leq$3 lesions in a single organ) compared with 21 poly-metastatic patients showed differential mutational prevalence. TP53 (64 %), EGFR (56 %), CDKN2A (22 %), RB1 (13 %) and SMARCA4 (12 %) were most frequently altered in the OM population. In comparison with the poly-metastatic population, lower frequency of some mutations was described: ERBB2 ($p = 0.011$), ALK ($p = 0.035$), MLL4 ($p = 0.04$), PIK3CB ($p = 0.044$) and TOP2A ($p = 0.044$) (Liao et al., 2023a).

Intra-tumoral heterogeneity (ITH) in terms of somatic single nucleotide variants and small insertions and deletions correlated with TMB and tumor neoantigen burden ($p < 0.01$) in 17 patients diagnosed with OM NSCLC receiving first line therapy. The authors observed a trend towards inverse proportion between ITH and PFS. Significant reduction in PFS ($p = 0.03$) occurred in patients with high homologous recombination deficiency (HRD) status of primary cancer (Fu et al., 2023).

Malignant pleural effusion did not correlate with the outcomes of 51 oncogene-mutated and wild type patients affected by adenocarcinoma with a maximum of 5 metastatic sites. It was not predictive of OS ($p = 0.167$), independently from the number of metastatic sites and the mutational status (Amini et al., 2020).

In a retrospective series of 20 patients undergoing curative treatment for primary cancer ($T < 4$ as inclusion criterion) and surgical therapy for adrenal metastasis, the 5-year Overall Survival (OS) and median survival were 34.5 % and 50 months, respectively. For 14 patients with genomic data availability, mutational status concordance was present in 12 cases, whereas only 2 additional and 1 missing mutations completed the scenario. Eleven primary cancers and 13 metastases showed TP53 mutations. One case carried EGFR amplification, absent in the respective pulmonary tissue. EGFR mutations occurred in the same paired primary and metastatic tissues, while KRAS mutations in 2 and 4 primary and metastatic sites, respectively (Mazzella et al., 2019).

Genomic data from paired blood and tissue specimens from 32 patients with one only bone metastatic lesion revealed most frequent mutations regarding EGFR (58 %), TP53 (55 %), KRAS (16 %), CDKN2A (13 %), MET (13 %), ARID2 (10 %), ATM (10 %), CTNNB1 (10 %), MYC (10 %) and SMARCA4 (10 %). In comparison with unselected NSCLC patients, EGFR, MYC and FAT2 were more frequently altered, differently from KRAS. Sixty-one percent of EGFR-positive patients had concurrent TP53 alteration. There was a significant occurrence of co-mutations regarding ATM/ERBB2, CDKN2B/MYC, CDKN2A/ CDKN2B and CDKN2A/MYC (Liao et al., 2023b).

In a series of 32 Asiatic patients affected by NSCLC with only one hepatic metastasis as extra-thoracic lesion, the most frequent mutated genes detected in the blood and respective tissues were TP53 (72 %), EGFR (50 %), RB1 (19 %) and SMARCA4 (12 %). Compared to unselected cohort of patients, the authors pointed out a significant enrichment in TP53 and MLL3 alterations. Significant co-occurrence of TP53 and EGFR mutations (81.25 %) was observed in EGFR-positive patients; 5 patients (15.63 %) showed TP53 and RB1 mutations, compared to 4.81 % in unselected series ($p = 0.026$). Other statistically relevant concomitant alterations were KEL/GRIN2A, KEL/KEAP1, KEL/LRP1B, MLL3/PIK3CG, PTCH2/PIK3CG and PTCH/MLL3 ($p < 0.01$). PI3K-AKT and JAK-STAT mutations were present in 29 and 23 patients, respectively (Liao et al., 2025).

In light of this evidence, it is plausible that, in the near future, specific molecular profiles combined with liquid biopsy findings will further refine the definition of oligometastatic disease.

One of the most important issues in clinical practice for LAT during targeted therapy is the safety profile of SBRT. A previous meta-analysis showed that SBRT is relatively safe with estimated acute G3–5 side effects at 5 years of 1.2 % and estimated late G3–5 side effects at 5 years of 1.7 % (Lehrer et al., 2021). However, this meta-analysis collected data from studies in different solid tumors and with different systemic therapies, including targeted therapies, immunotherapy or chemotherapy. Conversely, our systematic review focused on OM NSCLC with actionable genomic alterations treated with targeted therapies and reassures on the favorable safety profile of this strategy. Seven retrospective studies and all five prospective studies reported the safety profile. All these papers described manageable known toxicities of radiation therapy. However, the optimal timepoint for LAT remains unclear, as well as targeted therapy discontinuation or not during SBRT is still matter of debate.

Precision oncology has increasingly enabled the refinement of therapeutic strategies. The molecular profile and disease extent serve as predictive criteria for selecting optimal therapies and for integrating systemic treatment with the most appropriate local ablative approach (Fig. 5). A case-by-case multidisciplinary assessment is required to optimize and determine the most appropriate therapeutic sequence.

4.1. Limitations

The present study has some limitations. First, the studies included in this analysis are mostly focusing on *EGFR* mutant NSCLCs and only few included patients harboring other oncogenic drivers. In addition, the definition of OM disease was heterogenous among the different studies, albeit up to five synchronous metastases was the most common in both retrospective and prospective studies included in this systematic review. Different types of LAT were used in these studies, mainly as per physician's choice, although SBRT was the most adopted loco-regional strategy. Moreover, the new combination strategies of systemic therapy in EGFR-mutant NSCLC (i.e. Amivantamab + Lazertinib (Yang et al., 2025) and Osimertinib + platinum-based chemotherapy (Jänne et al., 2025)) could question the findings of the studies discussed in this review. The benefit in terms of efficacy outcomes, and toxicity rates, could change when these new treatments will be combined with LAT in NSCLC patients with OM disease.

As we showed in Fig. 2, several papers investigating the combination strategies were published over time without clear incremental rate,

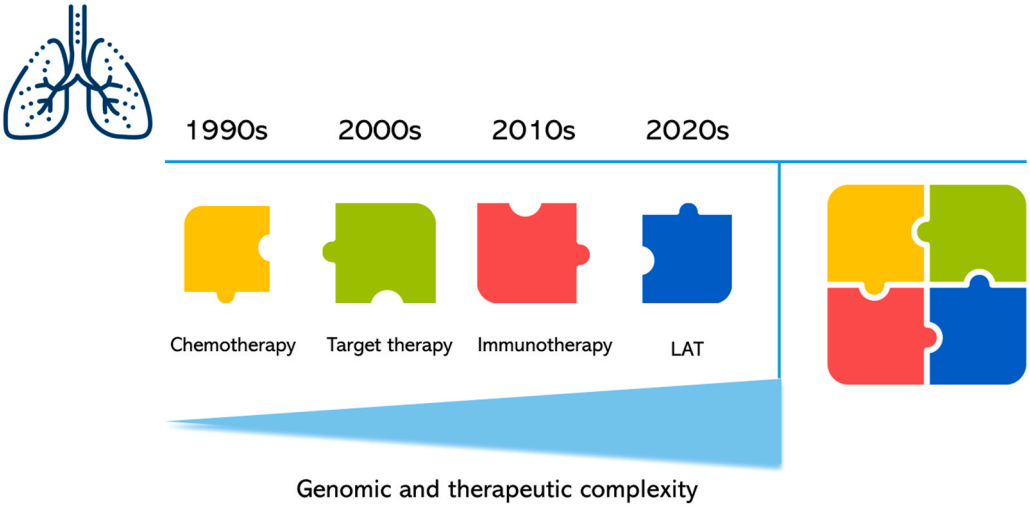

Fig. 5. Timeline of studying oligometastatic disease in non-small cell lung cancer.

despite the interest raised in the scientific community. Our paper aims to answer the question regarding LAT effectiveness and safety in a complex scenario in which generating evidence is hindered by the heterogeneous factors mentioned.

4.2. Future perspectives

In conclusion, our systematic review supports further exploration of LAT in OM oncogene-addicted NSCLC, as this strategy is associated with prolonged PFS and, in some cases, also OS as compared with systemic targeted therapy alone. Future prospective studies should define the optimal inclusion criteria for patients' enrollment (number of metastatic sites <5 vs. tumor volume), the potential role of circulating biomarkers (i.e. ctDNA clearance), the ideal timing for LAT and the most effective and less toxic combinatorial strategy with loco-regional treatments and targeted agents.

Funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Fabrizio Citarella: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review and editing.

Cristina Fragale: Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – review and editing.

Matteo Fiorenti: Data curation, Formal analysis, Investigation, Methodology, Writing – review and editing.

Maria Luisa Di Guglielmo: Data curation, Formal analysis, Investigation, Writing – review and editing.

Noemi Mindicini: Data curation, Formal analysis, Investigation, Writing – review and editing.

Alessio Cortellini: Formal analysis, Supervision, Writing – review and editing.

Alessandro Russo: Data curation, Supervision, Visualization, Writing – original draft, Writing – review and editing.

Giuseppe Bronte: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review and editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

FC received editorial activity support from Lilly, BMS, Novartis, boards' honoraria from Novartis and Astrazeneca, travel support from Sanofi.

AR received advisory board or consultancy from AstraZeneca, MSD, Novartis, Pfizer, BMS, Takeda, Amgen, Regeneron, Daiichi Sankyo, Merck, Johnson & Johnson, Abbvie, Roche, and Boehringer Ingelheim.

GB received honoraria from Pfizer, Novartis, and travel support from Astrazeneca, Roche, Novartis.

Acknowledgements

None

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2025.105096.

References

Eberhardt, W.E.E., et al., 2015. The IASLC Lung cancer staging project: proposals for the revision of the M descriptors in the forthcoming eighth edition of the TNM classification of lung cancer (Nov.). J. Thorac. Oncol. 10 (11), 1515–1522. https://doi.org/10.1097/JTO.0000000000000673.

Xu, D., et al., 2022. Clinical value of PET/CT in identifying patients with oligometastatic/oligoprogressive disease among first-line tyrosine kinase inhibitor-treated advanced EGFR-mutant non-small cell lung cancer: implications from survival comparisons (Aug.). Br. J. Radio. 95 (1136), 20220035. https://doi.org/10.1259/bjr.20220035.

Dingemans, A.-M.C., et al., 2019. Definition of synchronous oligometastatic non-small cell lung cancer-a consensus report (Dec.). J. Thorac. Oncol. 14 (12), 2109–2119. https://doi.org/10.1016/j.jtho.2019.07.025.

Lievens, Y., et al., 2020. Defining oligometastatic disease from a radiation oncology perspective: an ESTRO-ASTRO consensus document (Jul.). Radio. Oncol. 148, 157–166. https://doi.org/10.1016/j.radonc.2020.04.003.

Hendriks, L.E.L., et al., 2019. Defining oligometastatic non-small cell lung cancer: a simulated multidisciplinary expert opinion (Dec.). Eur. J. Cancer 123, 28–35. https://doi.org/10.1016/j.ejca.2019.09.013.

Deng, L., et al., 2016. Failure pattern of oligometastatic EGFR-mutant non-small cell lung cancer treated with tyrosine kinase inhibitors: implication of upfront stereotactic body radiation therapy (Oct.). Int. J. Radiat. Oncol. Biol. Phys. 96 (2), S131–S132. https://doi.org/10.1016/j.ijrobp.2016.06.321.

Sakai, K., et al., 2016. Clinical outcome of node-negative oligometastatic non–small cell lung cancer. Thorac. Cancer 7 (6), 670–675. https://doi.org/10.1111/1759-7714.12386.

Zhang, J.-T., et al., 2017. Propensity score-matching analysis of local consolidative therapy for patients with oligometastatic non-small cell lung cancer without

progression after front-line systemic therapy (Nov.). Ann. Oncol. 28, x136–x137. https://doi.org/10.1093/annonc/mdx671.033.
Xu, Q., et al., 2018. Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs (Sep.). J. Thorac. Oncol. 13 (9), 1383–1392. https://doi.org/10.1016/j.jtho.2018.05.019.
Hu, F., et al., 2018. OA07.06 efficacy of local consolidative therapy for oligometastatic lung adenocarcinoma patients harboring EGFR mutations (Oct.). J. Thorac. Oncol. 13 (10), S337. https://doi.org/10.1016/j.jtho.2018.08.273.
Hu, F., et al., 2019a. Efficacy of local consolidative therapy for oligometastatic lung adenocarcinoma patients harboring epidermal growth factor receptor mutations (Jan.). Clin. Lung Cancer 20 (1), e81–e90. https://doi.org/10.1016/j.cllc.2018.09.010.
Elamin, Y.Y., et al., 2019. Local consolidation therapy (LCT) after first line tyrosine kinase inhibitor (TKI) for patients with EGFR mutant metastatic non-small-cell lung cancer (NSCLC) (Jan.). Clin. Lung Cancer 20 (1), 43–47. https://doi.org/10.1016/j.cllc.2018.09.015.
Borghetti, P., et al., 2019. Concomitant radiotherapy and TKI in metastatic EGFR- or ALK-mutated non-small cell lung cancer: a multicentric analysis on behalf of AIRO lung cancer study group (Jul.). Radio. Med 124 (7), 662–670. https://doi.org/10.1007/s11547-019-00999-w.
Jiang, T., et al., 2019. EGFR-TKIs plus local therapy demonstrated survival benefit than EGFR-TKIs alone in EGFR-mutant NSCLC patients with oligometastatic or oligoprogressive liver metastases. Int. J. Cancer 144 (10), 2605–2612. https://doi.org/10.1002/ijc.31962.
Hu, F., et al., 2019b. Additional local consolidative therapy has survival benefit over EGFR tyrosine kinase inhibitors alone in bone oligometastatic lung adenocarcinoma patients (Sep.). Lung Cancer 135, 138–144. https://doi.org/10.1016/j.lungcan.2019.07.024.
An, N., Wang, H., Jing, W., Zhu, H., Yu, J., 2019. Local Consolidative radiation prolongs disease control of patients with oligometastatic NSCLC harboring EGFR activating mutation treated with first-line EGFR-TKIs (Sep.). Int. J. Radiat. Oncol. Biol. Phys. 105 (1), E494–E495. https://doi.org/10.1016/j.ijrobp.2019.06.1402.
Tsai, P.-C., Yeh, Y.-C., Huang, C.-S., Chiu, C.-H., 2019. Pathological complete response after afatinib treatment of stage IV oligometastatic adenocarcinoma of the lung: the role of pulmonary surgery (Nov.). Surg. Case Rep. 5 (1), 178. https://doi.org/10.1186/s40792-019-0741-3.
Zhang, J.-T., Liu, S.-Y., Yan, H.-H., Wu, Y.-L., Nie, Q., Zhong, W.-Z., 2019. Recursive partitioning analysis of patients with oligometastatic non-small cell lung cancer: a retrospective study (Nov.). BMC Cancer 19 (1), 1051. https://doi.org/10.1186/s12885-019-6216-x.
Ni, Y., et al., 2020. Microwave ablation as local consolidative therapy for patients with extracranial oligometastatic EGFR-mutant non-small cell lung cancer without progression after first-line EGFR-TKIs treatment (Jan.). J. Cancer Res Clin. Oncol. 146 (1), 197–203. https://doi.org/10.1007/s00432-019-03043-6.
Citarella, F., et al., 2021. Effectiveness of pemetrexed-based chemotherapy and radiation therapy in RET-rearranged lung adenocarcinoma: a mono-institutional case series (May). Precis. Cancer Med. 0 (0). https://doi.org/10.21037/pcm-21-1.
Hu, X., et al., 2022. First-line tyrosine kinase inhibitors combined with local consolidative radiation therapy for elderly patients with oligometastatic non-small cell lung cancer harboring EGFR activating mutations (Jan.). Front. Oncol. 12. https://doi.org/10.3389/fonc.2022.766066.
Liu, S., et al., 2022. Effective systemic treatment of choroidal metastases NSCLC with surgery after crizotinib: a case report (Mar.). Front. Oncol. 12. https://doi.org/10.3389/fonc.2022.789941.
Wu, H., et al., 2022. Osimertinib as induction therapy for oligometastatic non-small cell lung cancer with EGFR mutation: a case report (Apr.). Transl. Lung Cancer Res. 11 (4), 686–696. https://doi.org/10.21037/tlcr-22-251.
Yang, G., Kim, K.H., Lee, C.G., Yoon, H.I., 2022. The radiotherapeutic factors associated with reduced risk of progression in patients with oligometastatic non-small cell lung cancer treated with local ablative radiotherapy (Nov.). Int. J. Radiat. Oncol. Biol. Phys. 114 (3), e408. https://doi.org/10.1016/j.ijrobp.2022.07.1585.
Yoo, S., et al., 2023. Long-term surgical outcomes in oligometastatic non-small cell lung cancer: a single-center study (Jan.). J. Chest Surg. 56 (1), 25–32. https://doi.org/10.5090/jcs.22.101.
De, B., et al., 2023. Benchmarking outcomes for molecularly characterized synchronous oligometastatic non–small-cell lung cancer reveals EGFR mutations to be associated with longer overall survival (Jan.). JCO Precis Oncol. (7), e2200540. https://doi.org/10.1200/PO.22.00540.
Antonoff, M., et al., 2023. PP01.18 surgical resection after targeted therapy in stage IV NSCLC: nuances and considerations (Mar.). J. Thorac. Oncol. 18 (3), e18. https://doi.org/10.1016/j.jtho.2022.09.044.
Açikgöz, Ö., et al., 2023. Survival outcomes of patients with oligometastatic non-small cell lung cancer who were treated with radical therapy: a multicenter analysis (Aug.). Turk. J. Med. Sci. 53 (4), 949–961. https://doi.org/10.55730/1300-0144.5659.
Semenkovich, N.P., et al., 2023. Pre-radiotherapy ctDNA liquid biopsy for risk stratification of oligometastatic non-small cell lung cancer (Oct.). npj Precis. Oncol. 7 (1), 100. https://doi.org/10.1038/s41698-023-00440-6.
Wang, H., et al., 2024. Sequential epidermal growth factor receptor tyrosine kinase inhibitor-induced radical surgery in oligometastatic non–small cell lung cancer: a case report (Jun.). Oncologist 29 (6), 543–545. https://doi.org/10.1093/oncolo/oyad339.
Werner, R.S., et al., 2024. Genetic profiles of oligometastatic non-small-cell lung cancer and corresponding brain metastases (Jun.). Eur. J. Cardiothorac. Surg. 65 (6), ezae217. https://doi.org/10.1093/ejcts/ezae217.
Abudureheman, Z., Zhu, T., Liu, D., 2024. MSOR3 Presentation Time: 5:10 PM: prognosis analysis in oligometastatic non-small cell lung cancer with systemic therapy and iodine-125 seed implantation: a retrospective study (Nov.). Brachytherapy 23 (6), S36–S37. https://doi.org/10.1016/j.brachy.2024.08.037.
Jin, J.-N., Song, Z.-B., Wang, W.-X., Li, Y., Wu, S.-Y., 2025. The impact of comprehensive local therapy on treatment outcomes of non-small cell lung cancer with solitary skeletal oligometastasis (Jun.). J. Bone Oncol. 52, 100688. https://doi.org/10.1016/j.jbo.2025.100688.
Gomez, D.R., et al., 2016. 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 (Dec.). Lancet Oncol. 17 (12), 1672–1682. https://doi.org/10.1016/S1470-2045(16)30532-0.
Arrieta, O., et al., 2019. Radical consolidative treatment provides a clinical benefit and long-term survival in patients with synchronous oligometastatic non-small cell lung cancer: a phase II study (Apr.). Lung Cancer 130, 67–75. https://doi.org/10.1016/j.lungcan.2019.02.006.
Blake-Cerda, M., et al., 2021. Consolidative stereotactic ablative radiotherapy (SABR) to intrapulmonary lesions is associated with prolonged progression-free survival and overall survival in oligometastatic NSCLC patients: a prospective phase 2 study (Feb.). Lung Cancer 152, 119–126. https://doi.org/10.1016/j.lungcan.2020.12.029.
Wang, X.-S., et al., Jun. 2023. Randomized Trial of first-line tyrosine kinase inhibitor with or without radiotherapy for synchronous oligometastatic EGFR-mutated non-small cell lung cancer. J. Natl. Cancer Inst. 115 (6), 742–748. https://doi.org/10.1093/jnci/djac015.
Peng, P., et al., 2023. EGFR-TKIs plus stereotactic body radiation therapy (SBRT) for stage IV Non-small cell lung cancer (NSCLC): a prospective, multicenter, randomized, controlled phase II study (Jul.). Radio. Oncol. 184, 109681. https://doi.org/10.1016/j.radonc.2023.109681.
Guckenberger, M., et al., 2020. Characterisation and classification of oligometastatic disease: a European society for radiotherapy and oncology and European organisation for research and treatment of cancer consensus recommendation (Jan.). Lancet Oncol. 21 (1), e18–e28. https://doi.org/10.1016/S1470-2045(19)30718-1.
Jasper, K., Stiles, B., McDonald, F., Palma, D.A., 2022. Practical management of oligometastatic non–small-cell lung cancer (Feb.). J. Clin. Oncol. 40 (6), 635–641. https://doi.org/10.1200/JCO.21.01719.
Hendriks, L.E., et al., 2023. Oncogene-addicted metastatic non-small-cell lung cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up (Apr.). Ann. Oncol. 34 (4), 339–357. https://doi.org/10.1016/j.annonc.2022.12.009.
Sun, Z., Wen, J., Cui, W., Yu, M., Li, Y., Meng, X., 2025. Additions and subtractions of radiotherapy in patients with oligometastatic non-small cell lung cancer under the era of immunotherapy (Oct.). Crit. Rev. Oncol. /Hematol. 214, 104853. https://doi.org/10.1016/j.critrevonc.2025.104853.
Torresan, S., Costa, J., Zanchetta, C., De Marchi, L., Rizzato, S., Cortiula, F., 2025. Oligometastatic NSCLC: current perspectives and future challenges (Jan.). Curr. Oncol. 32 (2), 75. https://doi.org/10.3390/curroncol32020075.
Iyengar, P., et al., 2023. Treatment of oligometastatic non-small cell lung cancer: An ASTRO/ESTRO clinical practice guideline. Pract. Radiat. Oncol. 13 (5), 393–412. https://doi.org/10.1016/j.prro.2023.04.004.
2025 World Conference on Lung Cancer, September 6-9, 2025, Barcellona, ABSTRACT BOOK. wclc.iaslc.org.
Cortinovis, D., et al., 2021. Diagnostic and prognostic biomarkers in oligometastatic non-small cell lung cancer: a literature review (Jul.). Transl. Lung Cancer Res. 10 (7). https://doi.org/10.21037/tlcr-20-1067.
Moore, N.S., Laird, J., Verma, N., Park, H.S.M., 2022. Oligometastatic tumor size as a predictor of distant failure in synchronous oligometastatic NSCLC (Nov.). Int. J. Radiat. Oncol. *Biol. *Phys. 114 (3), e406. https://doi.org/10.1016/j.ijrobp.2022.07.1580.
Incorporation of EGFR, 2019. mutation status into M descriptor of new TNM classification influences survival curves in non-small cell lung cancer patients (Nov.). Radiol. Oncol. 53 (4), 453–458. https://doi.org/10.2478/raon-2019-0053.
Golden, E.B., Pilones, K.A., Kraynak, J., Formenti, S.C., 2020. Timing of osimertinib impacts RT-induced tumor immunogenicity (Nov.). Int. J. Radiat. Oncol. Biol. Phys. 108 (3), e126–e127. https://doi.org/10.1016/j.ijrobp.2020.07.1268.
Werner, R.S., et al., 2023. OA18.05 tumor immune microenvironment profiling in oligometastatic non-small cell lung cancer with brain metastases (Nov.). J. Thorac. Oncol. 18 (11), S86–S87. https://doi.org/10.1016/j.jtho.2023.09.094.
Kam, T.Y., et al., 2024. 169P Genomic landscape of NSCLC brain metastases and its potential association with TP53 and tumor mutation burden: a territory-wide program in Hong Kong (Mar.). ESMO Open 9. https://doi.org/10.1016/j.esmoop.2024.102744.
Choi, A.R., et al., 2024. Genomic signature for oligometastatic disease in non-small cell lung cancer patients with brain metastases (Sep.). Front. Endocrinol. 15. https://doi.org/10.3389/fendo.2024.1364021.
Zafra, J., et al., 2024. Novel blood biomarkers for response prediction and monitoring of stereotactic ablative radiotherapy and immunotherapy in metastatic oligoprogressive lung cancer (Apr.). Int. J. Mol. Sci. 25 (8), 4533. https://doi.org/10.3390/ijms25084533.
Liao, R., et al., 2023a. Genomic characteristics and the potential clinical implications in oligometastatic non–small cell lung cancer (Jan.). Cancer Res. Treat. 55 (3), 814–831. https://doi.org/10.4143/crt.2022.1315.
Fu, R., et al., 2023. P2.03-05 clinical impact of genomic characterization in induced oligometastatic non-small cell lung cancer (Nov.). J. Thorac. Oncol. 18 (11), S303–S304. https://doi.org/10.1016/j.jtho.2023.09.522.

Amini, A., et al., 2020. Prognostic impact of malignant pleural effusion in patients with oligometastatic lung adenocarcinoma (Oct.). Int. J. Radiat. Oncol. Biol. Phys. 108 (2), E50. https://doi.org/10.1016/j.ijrobp.2020.02.586.

Mazzella, A., et al., 2019. Clinical characteristics, molecular phenotyping, and management of isolated adrenal metastases from lung cancer (Nov.). Clin. Lung Cancer 20 (6), 405–411. https://doi.org/10.1016/j.cllc.2019.06.003.

Liao, R., et al., 2023b. Genomic features and its potential implication in bone oligometastatic NSCLC (Feb.). BMC Pulm. Med. 23 (1), 59. https://doi.org/10.1186/s12890-023-02354-2.

Liao, R., et al., 2025. Characterization of the genomic landscape in liver oligometastatic NSCLC (Jan.). BMC Cancer 25 (1), 93. https://doi.org/10.1186/s12885-025-13478-5.

Lehrer, E.J., et al., 2021. Safety and survival rates associated with ablative stereotactic radiotherapy for patients with oligometastatic cancer: a systematic review and meta-analysis (Jan.). JAMA Oncol. 7 (1), 92–106. https://doi.org/10.1001/jamaoncol.2020.6146.

Yang, J.C.-H., et al., 2025. Overall survival with amivantamab–lazertinib in EGFR-mutated advanced NSCLC (Oct.). N. Engl. J. Med. 393 (17), 1681–1693. https://doi.org/10.1056/NEJMoa2503001.

Jänne, P.A., et al., 2025. Survival with osimertinib plus chemotherapy in EGFR-mutated advanced NSCLC (Oct.). N. Engl. J. Med.. https://doi.org/10.1056/NEJMoa2510308.