



Local ablative therapies in oligometastatic NSCLC-upfront or outback? – a narrative review

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Abstract: Patients with oligometastatic (OM) non-small cell lung cancer (NSCLC) have favorable outcomes compared to patients presenting with diffuse metastatic disease. Recent randomized trials have demonstrated safety and efficacy signals for local ablative therapies with radiotherapy, surgery, or radiofrequency ablation for OM-NSCLC patients alongside systemic therapies. However, it remains unclear whether local ablative therapy (LAT) should be offered either upfront preceding systemic therapies or following initial systemic therapies as local consolidative therapy (LCT). Establishing optimal timing of RT and systemic therapy combinations is essential to maximize efficacy while maintaining safety. Most published randomized trial evidence surrounding the benefits of LAT and systemic therapies were generated from OM-NSCLC patients receiving cytotoxic chemotherapy agents. With increasing use of novel agents such as targeted therapies (i.e., tyrosine kinase inhibitors) and immune checkpoint inhibitors in management of metastatic NSCLC patients, LAT timing may need to be modulated based on the use of specific agents. This narrative review will discuss the current evidence on either upfront LAT or LCT for OM-NSCLC based on published trials and cohort studies. We briefly explored the possible biological mechanisms of the potential clinical advantages of either approach. This review also summarized the ongoing trials incorporating both upfront LAT and LCT, and considerations for future LAT strategies.

Keywords: Non-small cell lung cancer (NSCLC); oligometastatic (OM); local ablative therapy (LAT); stereotactic ablative radiotherapy (SABR)

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Introduction

The majority of patients with non-small cell lung cancer (NSCLC) present with metastatic disease at diagnosis, which is historically associated with a dismal survival rate

of 7% at 5 years (1). Conventionally, metastatic NSCLC is primarily managed with systemic treatment, with the intent to delay progression and prolong survival, without the possibility of disease eradication (2). Challenging this

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convention, the oligometastatic (OM) paradigm postulates that patients with limited metastases represent an intermediate between purely localized disease and diffuse metastatic state, and thus amenable to potentially life-prolonging local ablative therapy (LAT) to all clinically-detected disease sites (2,3). Recently, the European Society of Radiotherapy and Oncology (ESTRO)-American Society for Radiation Oncology (ASTRO) consensus document defined OM disease as 1–5 metastases that can all be safely treated with local therapy (4). Similarly, the International Association for the Study of Lung Cancer (IASLC) consensus statement proposed that synchronous OM disease is defined as 1–5 distant metastases in up to 3 organs (5). This review will focus on *de novo* OM disease states: (I) synchronous OM: oligometastatic disease developing within 6 months after diagnosis, and (II) metachronous OM: oligometastatic disease developed after 6 months after non-metastatic cancer diagnosis (6). LAT aims to eradicate active metastatic sites for OM-NSCLC, most commonly via surgical resection, radiofrequency ablation, stereotactic ablative radiotherapy (SABR) (7-12).

Recently, the SABR-COMET Phase II screening design (two-sided $\alpha=0.20$) randomized controlled trial (RCT) of 99 patients included patients from various primary cancers with metachronous OM disease (1–5 metastases). This study demonstrated significant improvements with the addition of SABR to all metastatic sites compared to standard of care alone in overall survival (OS) and progression-free survival (PFS) as primary and secondary outcomes, respectively (13,14). While an OS benefit in SABR arm was not definitive ($P=0.09$), in the updated post-hoc long term results with a median follow-up of 51 months, 5-year OS was 42.3% with SABR compared to 17.7% without SABR ($P=0.006$) (14).

LAT has also been shown to improve outcomes in OM settings in specific primary malignancies, including prostate, colorectal, and NSCLC (7,15,16). LAT may improve OM-NSCLC outcome through several mechanisms. Classically, the Norton-Simon hypothesis suggests that LAT complement systemic therapies by (I) reducing overall disease burden through direct cytoreduction and (II) inducing a more systemic treatment-sensitive proliferative phase of surviving clonogens in the target lesion (17-20). More recent evidence indicates that cancer growth and metastases are evolutionary processes spurred by high degree of genetic instability, resulting in intratumoral and intertumoral genetic heterogeneities (21-23). Reducing cancer genetic diversity by treating each OM site with LAT

is postulated to curb this evolutionary process, delaying progression due to emergence of treatment-resistant clonogens and further seeding from the metastatic sites (2,21,23). Lastly, with widespread adoption of immune checkpoint inhibitors such as PD-1/PD-L1 and CTLA-4 inhibitors, there has been increasing interest in LAT (e.g., with SABR) to bolster antitumor immune-mediated effect by promoting cancer antigen presentation and lymphocytic tumor infiltration (24-26).

Current clinical and biological evidence support the addition of LAT to standard palliative management for OM-NSCLC patients. Nonetheless, it is not yet clearly established whether LAT should be given upfront or following systemic therapies such as cytotoxic chemotherapies, targeted therapies, and immunotherapies in this population. This narrative review summarizes and discusses current evidence and ongoing trials investigating upfront LAT prior to systemic therapies, as well as consolidation LAT for OM-NSCLC patients.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-994>).

Methods

For this review, literature search using Medline database through PubMed was performed to identify clinical trials and cohort studies relevant to upfront or consolidative LAT in OM-NSCLC patients from inception until July 8, 2020, limiting the search to English-language articles. A combination of search terms to capture articles reporting on LAT (“ablative” or “ablation” or “consolidation” or “surgery” or “stereotactic” or “SABR” or “SBRT”) among metastatic NSCLC patients (“oligo-” or “metasta-” or “advanced”) and (“NSCLC”). We also queried ongoing clinical trials involving both upfront and consolidative LAT in ClinicalTrials.gov using the search term “NSCLC stage iv” and “oligo”, and “oligometastatic NSCLC”.

Upfront local ablative therapies

Despite major advances in the last decade, objective radiologic response [i.e., complete (CR) or partial response (PR)] to modern systemic therapies in metastatic (mNSCLC) patients remain relatively low. In the KEYNOTE-024 trial investigating treatment-naïve mNSCLC patients, objective response rates were 44.8% with pembrolizumab, and 27.8% with platinum-based chemotherapy (27). In

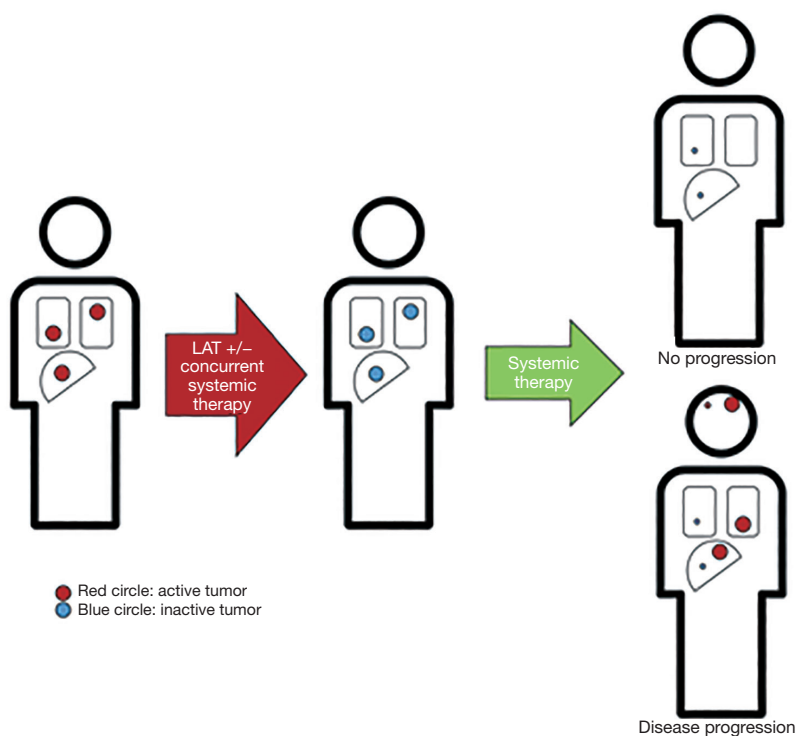


Figure 1 Illustration of upfront LAT approach for a metachronous OM-NSCLC disease with 3 disease sites (1 each in left lung, right lung, and liver) using SABR as LAT modality. All known disease sites presumed inactive after LAT. Systemic therapy commonly started soon after LAT completion, prior to objective tumor response (i.e., shrinkage). Reduction in tumor circle size represents partial response, while disappearance represents complete response. LAT, local ablative therapies; OM, oligometastatic; NSCLC, non-small cell lung cancer; SABR, stereotactic ablative radiotherapy.

the KEYNOTE-189 trial with treatment-naïve non-squamous mNSCLC without *EGFR* mutations or *ALK* rearrangements, objective response rate with the addition of pembrolizumab to chemotherapy was 47.6% (28). Similarly, in KEYNOTE-407 the objective response rate was 57.9% when adding pembrolizumab to chemotherapy and 38.4% without, for squamous m-NSCLC (29).

Upfront LAT studies primarily in patients without driver mutations

Upfront LAT may prevent further mono and polyphyletic metastatic seeding from initial OM sites that may progress despite systemic therapies. Illustration of upfront LAT strategy for a hypothetical case of an OM disease can be seen in *Figure 1*. To date, published data on upfront LAT for OM-NSCLC are limited to retrospective studies and small single arm prospective trials (25,30). Griffioen *et al.* retrospectively reported on 61 patients with synchronous OM-NSCLC

(1–3 metastatic lesions) receiving LAT after locoregional radical treatment, and noted 1 and 2-year OS of 54% and 38%, and PFS of 32% and 8%, respectively (10). In a similar cohort study by Kwint *et al.* of 91 synchronous OM-NSCLC (1–4 metastases) patients with good performance status treated with LAT after locoregional radical treatments, 1 and 2-year OS were 85% and 58%, and, corresponding PFS were 55% and 27%, respectively (9). Better patient performance status in this study may account for the superior OS outcomes observed (48.4% WHO performance status of 0 compared to 16.4% ECOG performance status 0 in the former study), perhaps highlighting the importance of patient selection in this population (9,10).

In terms of prospective data, Liu *et al.* described 63 metachronous (≤ 3 lesions) OM-NSCLC patients who had blood samples collected 3 days prior to upfront LAT with SABR. Interestingly, OS and PFS were worse among patients with higher pre-SABR regulatory T cells (30). Only 25% of patients received post-SABR

systemic therapies, and 1 and 2-year OS were 63.4% and 44.0%, with corresponding PFS rates 55.2% and 30.9%, respectively (30). In a Phase II single-arm trial by Bauml *et al.*, 45 patients with OM-NSCLC (14 synchronous, 34 metachronous) received LAT to all active sites, followed by up to 16 cycles of pembrolizumab, regardless of PD-L1 status (25). PFS after LAT compared to a historical median of 6.6 months was the primary outcome (10,25). Designed to detect a median PFS after LAT increase from historical rate of 6.6 months to 10.0 months, the results showed median PFS after LAT of 19.1 months, indicating a significant improvement ($P=0.005$) (25). OS was 90.9% at 1 year, and 77.5% at 2 year, without any noted toxicity concern. While not a randomized controlled study, this study showed the promise of upfront LAT followed by PD-L1 inhibitors such as pembrolizumab.

To our knowledge, the only published RCT on upfront LAT focused exclusively on OM-NSCLC is a Phase III study of 105 patients with 1–4 asymptomatic synchronous “cerebral oligometastases”, which did not demonstrate an OS benefit of upfront stereotactic radiosurgery (SRS) to the brain lesions prior to first-line palliative chemotherapies versus chemotherapies alone (14.6 *vs.* 15.3 months; $P=0.418$) (31). Interpreting the results of this trial in the context of OM disease is challenging, as 73% of the patients had extracranial metastatic disease, indicating that some of these patients actually had widespread disease (31). Moreover, these patients did not have radical treatment for either the primary disease or extracranial metastases (31). Therefore, the applicability of these data is uncertain.

Based on current limited data, upfront LAT followed by chemotherapy and/or immunotherapy appears to be safe and efficacious for non-mutated OM-NSCLC. Further level I evidence will be needed to establish upfront LAT approach among OM-NSCLC. Specifically, future RCTs directly comparing upfront and consolidation LAT with modern systemic therapies will be needed to establish optimal strategies for these patients.

Upfront LAT studies primarily in patients with driver mutations

The development of tyrosine kinase inhibitors (TKI) targeting mutant receptors in metastatic NSCLC patients that harbor oncogenic drivers such as *EGFR* mutations or *ALK* rearrangements has resulted in better outcomes and prolonged survival in these patients (32–35). Therefore, results of upfront LAT studies followed by chemotherapy

and/or immunotherapy among patients without driver mutations may not be generalizable to this population. Dedicated studies are needed to establish benefit of upfront LAT among OM-NSCLC patients with driver mutations. Two retrospective studies suggested that patients with *EGFR/ALK* alterations treated with TKI predominantly progress locally in the initial tumor sites, supporting LAT role in this setting (36,37).

The SINDAS study (NCT02893332) is a Phase III RCT investigating upfront concurrent first generation TKI (e.g., gefitinib or erlotinib) with versus without SABR for synchronous *EGFR* mutated OM-NSCLC, followed by maintenance TKI. While the fully published manuscript is pending, the RCT data have recently been presented in abstract form indicated that SABR plus TKI was associated with an improvement in OS (median 25.5 *vs.* 17.4 months; $P<0.01$) and PFS (median 20.2 *vs.* 12.5 months; $P<0.01$) compared to TKI alone (38). SABR was not associated with an increase in the rate of adverse events (38).

Based on the SINDAS trial results, upfront SABR is a promising strategy in synchronous *EGFR* mutation positive patients planned for first line TKI (38). On the other hand, the TKIs utilized in this study gefitinib and erlotinib are considered less effective than newer generation TKIs such as osimertinib (32). Compared to earlier generation TKIs, osimertinib is associated with improved survival as well as increased CNS activity (32). Whether an upfront LAT strategy utilizing more potent TKIs confers the same advantage is currently unknown.

Local consolidative therapies

By definition, local consolidative therapies (LCT) in patients with *de novo* OM-NSCLC with LAT are performed in those who are first treated with systemic therapy and remain OM. A major benefit of this strategy is that it allows for response assessment before considering LAT. Patients with tumors refractory to systemic therapy or harboring aggressive subclinical micrometastases who were destined for progression despite systemic therapy are no longer eligible for LCT. The LCT strategy for a hypothetical case of an OM disease is illustrated in *Figure 2*.

LCT studies primarily in patients without driver mutations

Outcomes of LCT for OM-NSCLC have been described in multiple single arm Phase II trials (39–41). De Ruyscher

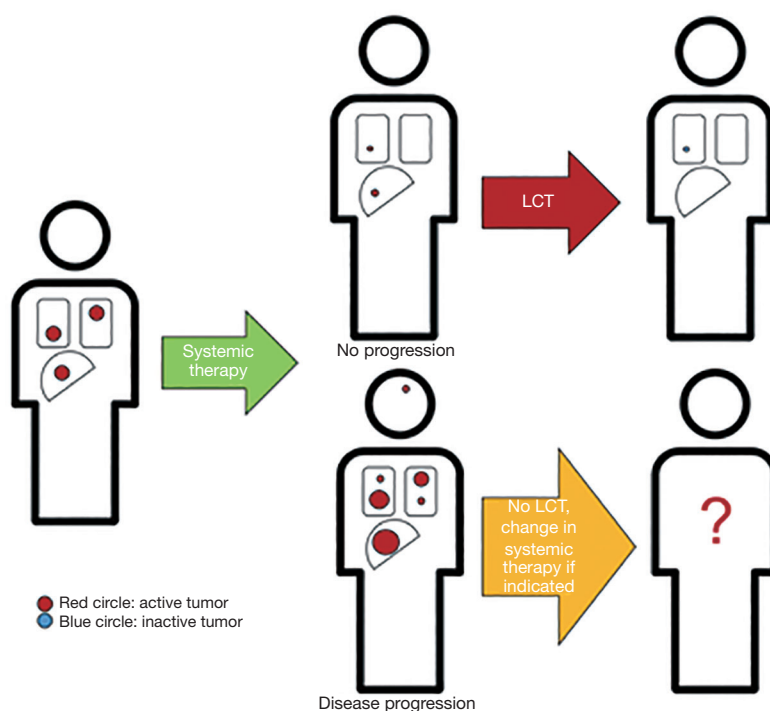


Figure 2 Illustration of LCT approach for a metachronous OM-NSCLC disease with 3 disease sites (1 each in left lung, right lung, and liver) using SABR as LAT modality. Only patients without distant disease progression with systemic therapy proceed with LCT. Reduction in tumor circle size represents partial response, while disappearance represents complete response. LCT, local consolidative therapies; OM, oligometastatic; NSCLC, non-small cell lung cancer; SABR, stereotactic ablative radiotherapy; LAT, local ablative therapies.

et al. published long term results from an early single arm Phase II trial of an LCT approach between 2006 to 2010, in which 39 synchronous OM-NSCLC patients treated with radical local treatments (surgery or radiotherapy) with median follow-up of 28 months; 95% of the cohort had systemic therapies as their primary treatments (41). Reflecting the era, stereotactic radiotherapy was only utilized for intracranial metastases, while extracranial sites were treated with surgery or radical dose of conventional radiotherapy (e.g., 54 Gy in 30 fractions) (41). In this cohort, 1, 2, and 5-year OS were 56.4%, 23.3%, and 7.7%, respectively, while corresponding PFS were 51.3%, 13.6%, and 7.7%, respectively. Although no extracranial SABR was used, only 7.7% had local failures, all within the primary tumor radically treated conventional radiotherapy field (41).

Two randomized Phase II RCTs have demonstrated LCT benefit to systemic therapies (7,42,43). Iyengar *et al.*'s Phase II RCT with 29 OM-NSCLC patients without EGFR/ALK mutations investigated the addition of consolidative LAT with SABR alongside maintenance chemotherapy following 4–6 cycles of induction chemotherapy (42). The

trial was planned to accrue 36 patients, but stopped early as an interim analysis showed a significant PFS benefit favoring the LAT arm (9.7 *vs.* 3.5 months; $P=0.01$) (42). In a multi-institutional Phase II RCT, Gomez *et al.* randomized 49 OM-NSCLC patients with ≤ 3 oligometastases without progression after induction systemic therapy to LCT *vs.* maintenance therapy or observation (7). The primary outcome was PFS, with a two-sided P value <0.10 considered significant. Eight patients (16%) received TKI as induction therapy for known EGFR/ALK mutations (7). The study stopped early due to a significant benefit of consolidative LAT (surgery, RT or SABR) in PFS (median 14.2 *vs.* 4.4 months; $P=0.022$) and OS (median 41.2 *vs.* 17.0 months; $P=0.034$) with no observed grade ≥ 3 toxicities (7). Immunological and serological analyses from this trial indicated that LCT was associated with less circulating tumor DNA (ctDNA), a lower number of detected mutations, and fewer tumor clonal expansions (43).

LCT studies primarily in patients with driver mutations

To our knowledge, published data on LCT after TKIs for

OM-NSCLC patients with driver mutations are currently limited to retrospective cohorts and a small single-arm Phase II trial (44-47). In one of the larger retrospective series, Hu *et al.* reported OS (median 34 *vs.* 21 months; $P=0.001$) and PFS (median 15 *vs.* 10 months; $P<0.001$) benefit of LCT among 231 EGFR mutant OM-NSCLC patients (143 with LCT, 88 without) with ≤ 5 metastases receiving EGFR-TKI (48). Xu *et al.*'s study in 145 EGFR mutant OM-NSCLC patients with ≤ 5 metastases receiving EGFR-TKI also demonstrated OS and PFS benefits of LCT to all disease sites compared to either partial LCT (only to primary or OM sites) or TKI alone (45).

ATOM was a Phase II single-arm trial investigating LCT in EGFR mutation positive OM-NSCLC with ≤ 4 PET-avid lesions after 3 months of TKI (47). The study was planned to recruit 34 patients but stopped at 18 due to slow accrual. All received LCT with SABR, one-year PFS was 68.8% with median OS of 43.3 months. When compared to 48 screen-failure patients, LCT reduced progression risk ($HR = 0.41$; $P=0.0097$) (47). Based on these limited data, LCT in OM-NSCLC patients with driver mutations seems to be promising. Xu *et al.*'s study may have underlined the importance of complete LCT to all active sites when proceeding with this strategy (45). High-quality RCTs to verify these preliminary findings will be severely needed to establish LCT as standard option, especially with emerging level I evidence of upfront LAT benefit from a Phase III RCT (SINDAS) (38). Similarly, NORTHSTAR is an active Phase II RCT (NCT03410043) randomizing EGFR mutant Stage IIIB-IV NSCLC patients to LCT or no LCT alongside osimertinib after 6-12 weeks of induction osimertinib. While open to Stage IIIB and more extensive Stage IV patients, a PFS subgroup analysis for OM-NSCLC patients is planned.

Special consideration with immunotherapy

Immunotherapy, using PD-1 or PD-L1 inhibitors, is now established in the standard management of both locally advanced and metastatic NSCLC (27,28,49), on the basis of improvement in OS in RCTs (27,50-52). There has been growing laboratory and clinical evidence of radiotherapy enhancing anticancer immune activation by tumor neoantigen release and presentation (24,53-56). In fact, there may be a synergistic effect of SABR and immunotherapy combinations, through induction of anticancer T lymphocytes-mediated activities (54,57,58).

Considering the objective response rate of below 50% in mNSCLC patients with immunotherapy, the use of RT prior to immunotherapy is of interest to potentially enhance systemic effects. In secondary analysis of KEYNOTE-001 trial showed that among mNSCLC patients treated with pembrolizumab, prior RT use was associated with improved OS and PFS (26). A Phase II RCT by Theelen *et al.* with 76 mNSCLC patients who progressed with chemotherapy investigated the addition of SABR to a single metastatic site alongside pembrolizumab, and noted a doubling of objective response rate at 12 weeks from 18% to 36% ($P=0.07$) and trend towards an OS benefit (median 15.9 *vs.* 7.6 months; $P=0.16$) in SABR group (58). While in second line setting for mNSCLC patients, the results highlighted the potential synergistic effect of LAT and immunotherapies which could be harnessed for OM-NSCLC patients.

Other nuances when combining immunotherapy and SABR are noteworthy. Upfront SABR may result in challenges in response assessment using traditional measures like RECIST after immunotherapy, owing to fibrotic effects within tumor targets, most notably within the lung (59). In addition, patients treated with immunotherapy may experience delayed tumor response due to pseudoprogression, which refers to tumor flare due to immune cell tumor infiltration prior to tumor shrinkage (60). Or worse, another phenomenon known as hyperprogression may occur, wherein accelerated tumor progression is observed in small proportion of NSCLC patients after immunotherapy (60-63). Considering these, perhaps ensuring local control upfront with LAT will be important for OM-NSCLC receiving immunotherapies. The merit of upfront SABR followed by immunotherapy for OM-NSCLC patients was demonstrated in the previously discussed Bauml *et al.*'s Phase II single arm study, which yielded high 1-year OS of 90.9% and significantly higher PFS compared to historical control (25).

Nonetheless, the optimal sequencing of LAT has yet to be clearly elucidated and may depend on the mechanism of action of specific immunomodulatory agents (64). For instance, In a subcutaneous colorectal adenocarcinoma mouse model, LAT with SABR after CTLA-4 inhibition resulted in superior tumor regression compared to prior (65). On the other hand, upfront LAT 1 day prior to anti-OX40 antibody resulted in optimal anticancer immunity in the same mouse model (65). Establishment of optimal sequencing of RT and commonly used immunotherapies in m-NSCLC will be essential in informing future practice.

Table 1 Selected active clinical trials with both upfront and consolidative local ablative therapies for OM-NSCLC

ClinicalTrials.gov Trial ID	Study design	Patient OM characteristics	Intervention	Primary end point	Study status
NCT03827577 (OMEGA)	Phase III randomized 1:1 parallel assignment	Metachronous and synchronous, 1–3 metastases. Can be enrolled prior or after primary systemic therapy if no progression (Target: 195)	Systemic therapy (platinum doublet chemotherapy or EGFR-TKI or immunotherapy directed by molecular status) ± upfront LAT or LCT consisting of primary resection (if primary in place) and OM LAT with surgery, SABR, or RFA.	OS up to 60 months	Recruiting
NCT02076477 (OITROLC)	Phase III randomized 1:1 parallel assignment	Synchronous, 1–5 metastases (Target: 450)	Upfront LAT with concurrent chemoradiation to all disease sites followed by 2 cycles of platinum-doublet chemotherapy vs. initial 2 cycles of platinum-doublet chemotherapy followed by LCT with chemoradiation	Response rate 3 months after treatment	Recruiting

OM, oligometastatic; NSCLC, non-small cell lung cancer; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; LAT, local ablative therapies; LCT, local consolidative therapies; OS, overall survival.

Ongoing clinical trials with both upfront LAT and LCT for OM-NSCLC

Two ongoing clinical trials are investigating upfront LAT and post-systemic therapy LCT for NSCLC (*Table 1*). OMEGA (NCT03827577) is a Phase III RCT recruiting synchronous and metachronous OM-NSCLC patients (target 195) with potentially resectable or locally controlled primary disease. Patients may be enrolled either prior to systemic therapy (upfront) or after 3 months of systemic therapy (consolidative) without progression according to institutional decision and randomized to: standard therapy alone (platinum doublet chemotherapy or TKI or immunotherapy depending on molecular status, and brain LAT for brain lesions) or standard therapy and primary site surgical resection and LAT to metastases with surgery, RFA, or SABR.

The Optimal Intervention Time of Radiotherapy for Oligometastatic Stage IV Non-small Cell Lung Cancer (OITROLC; NCT02076477) is a large (target accrual of 420) multicenter Phase III RCT in China that is comparing upfront LAT to LCT in synchronous OM-NSCLC patients with up to 5 metastases. Patients in the upfront LAT arm receive concurrent chemoradiotherapy followed by 2 cycles of chemotherapy, while patients in the LCT arm receive 2 cycles of chemotherapy followed by concurrent chemoradiotherapy. The primary outcome is response rate at 3 months, with PFS, quality of life, and grade

≥3 toxicities as secondary outcomes. Interestingly, OS is not an outcome of interest of OITROLC. Nonetheless, this is an interesting trial which will inform future practice for aggressive LAT approach in synchronous OM-NSCLC.

Future considerations

While there has been a growing evidence supporting LAT integration in the management of OM-NSCLC using either upfront or consolidative approach, the optimal timing of LAT relative to systemic therapies has not been adequately addressed. To date, there has been no published RCT comparing upfront LAT to LCT for synchronous or metachronous OM-NSCLC. A large RCT such as OITROLC trial will provide us with data surrounding clinical outcomes and adverse events associated with either strategy. Future studies investigating the potential of upfront LAT to defer cytotoxic chemotherapy in frail or borderline performance status OM-NSCLC patients will be interesting to inform management in this subset of patients.

Our OM-NSCLC paradigm is constrained on current staging technologies, mainly biopsies and medical imaging. Advances in diagnostic technologies, such as detection of malignant cells in systemic circulation or more sensitive imaging of will allow finer classifications of OM-NSCLC patients and may change LAT role and timing in their managements (66). In terms of currently available modalities, a recent pan-European consensus has advocated

for at minimum 18F-FDG PET/CT use for staging synchronous OM-NSCLC (5). Upfront LAT or LCT is increasingly being utilized in the management of OM patients, with both approaches appearing to be acceptable. Both strategies warrant further investigation to establish the optimal management strategies for these patients.

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Footnote

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