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PERSPECTIVE

Local consolidative therapy in oligometastatic non-small-cell lung cancer after effective systemic treatment: who will benefit?

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Non-small cell lung cancer (NSCLC), as the leading cause of cancer-related deaths, poses a serious health issue worldwide[1], according to the Global Cancer Statistics 2022. Approximately 30% of NSCLC patients are diagnosed at an advanced or metastatic stage with a 5-year overall survival (OS) rate ranging from 7%–18%[2]. Unlike localized NSCLC, which can be treated with curative intent, patients with metastatic NSCLC typically undergo systemic treatment to delay progression and prolong survival.

The concept of oligometastasis, first described in 1995, refers to an intermediate stage between localized disease and widespread metastasis[3]. Oligometastasis is traditionally defined as a limited number of radiographically identifiable metastases. The International Association for the Study of Lung Cancer (IASLC) consensus statement has proposed the definition of oligometastatic NSCLC as a maximum of 5 distant metastases in up to 3 organs[4]. For patients with a limited metastatic burden, local treatment, such as surgery or radiotherapy, might provide the possibility for a cure. Local therapy can be offered upfront before systemic therapy or following induced systemic therapy as local consolidative therapy (LCT) for residual disease in patients with oligometastatic NSCLC. Residual disease at the time of maximal response to systemic therapy indicates that prior systemic therapy did not completely eradicate the tumor, which often harbors drug-resistant clones. LCT for oligometastatic NSCLC after induced systemic therapy has been reported to improve survival in patients with advanced NSCLC and oligo-residual disease following effective systemic treatment in several clinical trials. However, the recent NRG-LU002 trial demonstrated no survival benefit from LCT, highlighting the need to identify which patients truly benefit from this approach.

Current evidence regarding the application of LCT in oligometastatic NSCLC is introduced herein from several randomized clinical trials. Additionally, unresolved issues in clinical practice focusing on the beneficial patient population are discussed. Furthermore, a novel treatment paradigm is proposed based on biomarkers in oligometastatic NSCLC.

Current randomized evidence regarding the application of LCT in oligometastatic NSCLC

Several randomized prospective studies have suggested that LCT for residual lesions in oligometastatic NSCLC after effective systemic chemotherapy prolongs progression-free survival (PFS) and OS and may even be curative for some patients with acceptable toxicity. Forty-nine patients with limited metastases who did not develop disease progression after first-line drug therapy were randomly assigned to either maintenance systemic therapy or LCT (radiotherapy or surgery) for all active residual disease in a multicenter phase II study, as reported by Gomez et al. (NCT01725165). The LCT arm demonstrated significant benefits in PFS and OS (median

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PFS, 14.2 months *vs*. 4.4 months; $P = 0.022$ and median OS, 41.2 months *vs*. 17.0 months; $P = 0.017$). The incidence of grade ≥ 3 toxicity was 20% in the LCT arm compared to 8% in the non-LCT arm[5,6]. Another randomized phase II trial by Iyengar et al. (NCT02045446) included 29 patients with oligometastatic NSCLC using radiotherapy as the sole LCT method. LCT administered after induction chemotherapy prolonged the median PFS (9.7 months *vs*. 3.5 months; $P = 0.01$). The incidence of grade ≥ 3 toxicity was 29% in the LCT arm compared to 20% in the non-LCT arm[7]. The majority of participants in these two trials received induction chemotherapy. Both trials were recommended for premature cessation by the Ethics Committee based on the efficacy results of the interim analysis.

A randomized phase II trial (NCT03595644) assessed the efficacy and safety of radiotherapy as LCT after induced first-line EGFR-tyrosine kinase inhibitors (TKIs), as reported by Peng et al. Sixty-one patients with oligometastatic NSCLC harboring *EGFR*-sensitive mutations who had received first-generation EGFR-TKIs were included and randomly assigned to receive radiotherapy for primary and/or metastatic sites. The results showed that patients receiving radiotherapy had a significantly prolonged median PFS (17.6 months *vs*. 9.0 months; $P = 0.016$) and OS (33.6 months *vs*. 23.2 months; $P = 0.026$). No grade ≥ 3 toxicity was observed in either group[8]. Recent data from the unicentric phase II NORTHSTAR trial (NCT03410043), which added LCT (radiotherapy or surgery) for patients with *EGFR*-mutant advanced NSCLC who did not progress within 6–12 weeks of osimertinib (a third-generation EGFR-TKI), reported that osimertinib plus LCT was well tolerated without a significant increase in grade ≥ 3 adverse events compared to osimertinib alone (29% *vs*. 16%; $P = 0.09$), with 2.3% of patients experiencing grade 3 pneumonitis[9]. Survival data is anticipated.

In contrast, findings for immunotherapy appeared different. The phase II/III NRG-LU002 trial (NCT03137771) reported negative results, including 215 patients with oligometastatic NSCLC receiving first-line chemotherapy or immunotherapy with or without subsequent LCT (radiotherapy and/or surgery), with 90.7% of patients receiving immunotherapy. The 1- and 2-year PFS and OS rates were not statistically different between the LCT and non-LCT arms (PFS: HR = 0.93; $P = 0.664$; OS: HR = 1.05, $P = 0.821$). Patients receiving LCT with maintenance systemic therapy experienced a higher incidence of grade ≥ 3 pneumonitis (10% *vs*. 1%). Results from the NRG-LU002 trial do not support the routine use of LCT in oligometastatic NSCLC after immunotherapy[10]. Reasons for the negative outcome of the NRG-LU002 trial remain unclear because further details have not yet been disclosed. The NRG-LU002 trial mainly included patients without disease progression after 4 cycles of immunotherapy, of whom the proportion with stable disease (SD) was 57.8%. It appears that this population did not truly identify patients who benefit from aggressive LCT. Specifically, it remains unclear if patients with the best overall SD response will benefit less from local treatment compared to patients with a partial response to immunotherapy.

A summary of the randomized clinical trials evaluating the application of LCT in patients with oligometastatic NSCLC is shown in **Table 1**.

Unsolved issues in clinical practice

The results from different randomized clinical trials appear controversial, leading to unresolved issues in clinical practice (i.e., how are patients selected who might benefit from LCT after effective systemic treatment?).

In these trials, the same imaging criteria are often used to select NSCLC patients with oligometastasis along with a uniform time frame for systemic treatment. However, it is crucial to recognize the heterogeneity of tumors, which presents a challenge: the enrollment population may not be sufficiently precise if based solely on the same clinical characteristics. One key to treatment selection in patients with oligometastatic NSCLC is identifying patients likely to benefit from aggressive LCT. Precision biomarkers are needed to aid in selecting these beneficiary populations.

Optimal exposure duration of prior systemic therapy

In theory, patients typically exhibit the lowest tumor burden at the time of maximum response to systemic therapy when LCT targeting residual sites is most likely to yield substantial efficacy with minimal side effects. However, defining the time of maximum response poses a challenge. There is a lack of research on the optimal duration of induced systemic therapy before local treatment. However, most studies have mandated that induced systemic therapy last at least 3 months. Some phase III clinical trials reported that > 80% of responders experienced the first response to EGFR-TKIs or chemotherapy within 12 weeks,

Table 1 Randomized clinical trials evaluating the application of LCT in oligometastatic NSCLC

NCT (name)	Phase	Oligometastasis characteristics	Number of lesions	Prior systemic therapy	Tumor response before LCT	Timing of LCT	Sample size (LCT *vs.* non-LCT)	LCT	Primary endpoint
NCT01725165	II	≤ 3 disease sites (not including primary tumor)	0–1 (65.3%) 2–3 (34.7%)	Chemo (83.7%), EGFR-TKI (12.2%) ALK-TKI (4.1%)	SD (63.3%) PR/CR (36.7%)	≥ 4 cycles (Chemo); ≥ 3 months (TKIs)	49 (25 *vs.* 24)	RT ± surgery	PFS: 14.2 *vs.* 4.4 months
NCT02045446	II	Up to 6 sites of extracranial disease (including primary, ≤ 3 sites in the liver or lung)	1 (17.2%) 2 (48.3%) 3 (31.0%) 4 (3.5%)	Chemo (100%)	Not reported	4–6 cycles	29 (14 *vs.* 15)	RT	PFS: 9.7 *vs.* 3.5 months
NCT03410043/ NORTHSTAR	II	LCT to at least one site of disease	Not reported	Osimertinib (100%)	Not reported	6–12 weeks	122 (59 *vs.* 63)	RT ± surgery (if ≤ 3 lesions, LCT to all lesions; if > 3 lesions, LCT to number of lesions at investigator discretion)	PFS: Not reported
NCT03595644	II	≤ 5 metastatic foci	1 (52.4%) 2 (27.9%) 3 (19.7%)	First-generation EGFR-TKIs (100%)	Not reported	3 months	61 (30 *vs.* 31)	RT (sites of RT was decided by the investigator)	PFS: 17.3 *vs.* 9.0 months
NCT03137771/ NRG-LU002	II/III	0–3 extracranial metastases	1 (58.6%) 2 (26.5%) 3 (14.0%) 4 (0.5%) 5 (0.5%)	IO (90.7%) Chemo (9.3%)	SD (57.8%) PR (32.7%) NE (6.0%) CR (3.5%)	4 cycles	215 (134 *vs.* 81)	RT ± surgery	2-year PFS: 40.1% *vs.* 35.9%, 2-year OS: 54.1% *vs.* 58.1%

LCT, local consolidative therapy; NSCLC, non-small cell lung cancer; Chemo, chemotherapy; EGFR, epidermal growth factor receptor; ALK, anaplastic lymphoma kinase; TKI, tyrosine kinase inhibitor; SD, stable disease; PR, partial response; CR, complete response; RT, radiotherapy; PFS, progression-free survival; IO, immunotherapy; NE, not evaluable; OS, overall survival.

which may partly explain the cut-off duration. It was also noted that the most significant tumor shrinkage usually occurs within 40 days after the initiation of EGFR-TKI treatment and further shrinkage becomes difficult after 90 days[11]. Greater than 80% of first responses to immunotherapy occur within 12 weeks after 4 cycles of administration[12]. However, exploratory analysis data indicate that in 75% of responders receiving chemoimmunotherapy tumors continue to regress to maximum tumor remission after achieving initial remission with a median time from the first response to maximum tumor response reported to be 109 days (ranging from 26–438 days)[13]. Persistent tumor regression represents one of the differences in response characteristics between immunotherapy and other anti-tumor therapies, such as conventional chemotherapy and targeted therapy. Unlike conventional chemotherapy and targeted therapy, which directly target tumor cells, immunotherapy induces indirect antitumor effects by restoring systemic antitumor immunity. The immune cells activated by immunotherapy provide a more comprehensive and lasting attack on tumor cells. Consequently, an exposure duration of 4 cycles before LCT may not be sufficient to achieve optimal efficacy during the immunotherapy period, which might also be a protentional reason for negative outcomes in the NRG-LU002 trial.

Elusive inclusion of oligometastatic disease by imaging

The inclusion criteria for oligometastasis varied among different trials, although all utilized the number of metastases for patient enrollment. The trial by Gomez et al. included patients with < 3 metastases (excluding the primary tumor) after frontline systemic therapy. Each lesion was counted separately but regional lymph node metastases were counted collectively as one lesion. Central nervous system lesions were counted towards the total number of metastases even if local treatment had been administered before randomization. The majority of patients in this trial had 0–1 metastases (65.3%), followed by 2–3 metastases (34.7%)[5]. The trial by Iyengar et al. allowed patients with up to 6 sites of extracranial disease (including the primary tumor, with ≤ 3 sites in the liver or lung) prior to the initiation of LCT. Up to 2 contiguous vertebral metastases were considered a single site of disease. The median number of disease sites prior to induction chemotherapy was 2–3, with a range of 2–6[7]. The trial by Peng et al. admitted patients with ≤ 5 discrete distant metastases with most exhibiting 1 metastatic organ (51.5%)[8]. The NRG-LU002 trial enrolled patients with ≤ 3 extracranial metastases after induction systemic therapy, with the majority of patients presenting with 1 lesion (59%), followed by 2 lesions (26%), 3 lesions (14%), and 4–5 lesions (1%)[10].

The absence of biomarkers renders imaging the most relevant diagnostic method for defining oligometastatic disease. Despite some consensus on an image-based definition of oligometastatic disease, clinical outcomes after LCT for this condition vary widely[14]. There is still a lack of biological or pathologic evidence suggesting that a clinical condition exists which separates oligometastatic NSCLC with a defined number of detectable metastases from those with widespread metastases. Furthermore, it remains unclear whether patients with synchronous oligometastasis exhibit different biological characteristics compared to patients with metachronous oligometastasis or whether induced oligometastasis differs from repeated oligometastasis. From the perspective of precision medicine, incorporating biomarkers that reflect the underlying biological characteristics of the tumor and immune contexture could enhance these definitions.

Potential factors on selecting benefit population

Clinical characteristics of the potentially beneficial population

Clinical characteristics should be considered when identifying the potential beneficial population for LCT, including age, performance status, co-morbidities, exposure duration of prior systemic therapy, classification of oligometastasis (*de novo*, repeated, or induced), number of metastases, and site of lesions. Although all prospective clinical trials established a definitive exposure duration of prior systemic therapy before LCT, most trials set this duration at 3 months. However, a longer duration of systemic therapy has been associated with a better PFS. One study divided patients receiving LCT into longer and shorter duration groups based on pre-LCT systemic treatment duration using the median PFS in corresponding phase III trials as a reference and found that a longer pre-LCT systemic treatment duration correlated with longer PFS (not reached *vs.* 23.9 months, $P = 0.036$)[15]. Regarding radiologic characteristics, the prognostic factors associated with survival varied across different studies[16]. Currently, the definition of oligometastasis is constrained by existing staging technologies. Rapid advances in diagnostic technologies, such as 18-fluorodeoxyglucose-PET (18FDG PET/CT), have made it possible to identify minimally active disease, allowing for

finer classifications of oligometastasis and potentially aiding in the decision-making regarding the timing of LCT.

Circulating tumor DNA (ctDNA) could help define molecular oligometastatic NSCLC

All imaging methods for detecting metastases have a finite resolution. Even when imaging methods detect only a limited number of metastases, undetected micro-metastases are likely to be present. Identification of molecular biomarkers for oligometastatic NSCLC remains an area of ongoing research. With advances in liquid biopsy technologies, ctDNA in peripheral blood can be utilized to assess tumor burden and has demonstrated the ability to detect changes in molecular disease prior to imaging in NSCLC regardless of clinical stage. A multi-institutional cohort study involving 1,487 patients with oligometastatic NSCLC undergoing liquid biopsy analysis of ctDNA showed that patients with undetectable ctDNA before radiotherapy (RT) had a significantly improved PFS ($P = 0.004$) and OS ($P = 0.030$)[17]. A prospective study (NCT05648370) assessed the clinical feasibility of ctDNA-based liquid biopsy in patients with oligometastatic NSCLC confirmed by 18FDG PET/CT receiving LCT, which revealed that patients with negative plasma ctDNA before LCT experienced better PFS compared to those with positive ctDNA before LCT (HR = 3.42, $P = 0.001$)[15]. These findings suggested that patients with undetectable pre-LCT ctDNA may represent truly induced oligometastatic disease and that patients meeting radiologic oligometastatic criteria with negative plasma ctDNA before LCT could be classified as having molecular oligometastatic NSCLC. However, in another phase II prospective trial, ctDNA metrics before LCT were not associated with OS or PFS ($P > 0.05$)[18]. These discrepancies might reflect the role of highly sensitive detection assays.

Novel treatment paradigm in oligometastatic NSCLC based on biomarkers

ctDNA-guided maintenance treatment or observation after LCT

It has been reported that a decreased ctDNA burden post-LCT at an early follow-up time compared to pre-LCT levels reflect the reduction in tumor burden achieved by LCT. Additionally, the first detection of increasing ctDNA occurred at a median of 5.0–6.7 months before radiographic progression in NSCLC[19]. These findings support the application of ctDNA monitoring for the dynamic assessment of disease changes in advanced NSCLC after LCT, further guiding subsequent treatment. An exploratory proof-of-concept study based on a prospective trial proposed a new treatment paradigm of ctDNA-guided maintenance treatment or observation for oligometastatic NSCLC after LCT. This study included patients with oligometastatic NSCLC harboring driver mutations after TKI therapy and LCT. Treatment discontinuation was performed in those with radiologically undetectable disease, undetectable ctDNA, and normal serum carcinoembryonic antigen (CEA) levels following LCT. Surveillance, including radiologic examination and ctDNA and CEA analyses, was conducted every 2–3 months. Participants received retreatment with prior TKIs for progressive disease or ctDNA or CEA positivity, whichever occurred first. Treatment was discontinued again during surveillance once a complete response was achieved and molecular indicators were negative. The median PFS was 18.4 months and the median treatment break duration was 9.1 months with a median duration of preceding TKI therapy of 12.0 months in the cohort of 60 patients enrolled. The TKI retreatment response rate was 96% and no grade ≥ 3 adverse events were observed[20]. These results suggest that this adaptive de-escalation maintenance TKI strategy based on ctDNA status is feasible for oligometastatic NSCLC after LCT. A novel treatment paradigm based on biomarkers in oligometastatic NSCLC is shown in **Figure 1**.

Although the above results are encouraging, the limitations of ctDNA-guided treatment paradigm must be noted. Currently, ctDNA detection *via* liquid biopsy technology still has false negatives and the risk of ctDNA-guided "drug holidays" cannot be overlooked, especially for patients with brain metastases. In addition, because of tumor heterogeneity ctDNA analysis may not fully reflect all mutations in the tumor and the value of detecting non-driver genes mutations in ctDNA analysis remains controversial, which may lead to limited effectiveness in individual patients. The applicability of this treatment paradigm to oligometastatic patients with non-*EGFR* mutations requires further exploration. These limitations still need to be gradually overcome in future studies to further improve their clinical application value.

Future directions

The definition, assessment, and overall management of treatment strategies in oligometastatic NSCLC remain controversial and challenging. We conclude that three aspects should

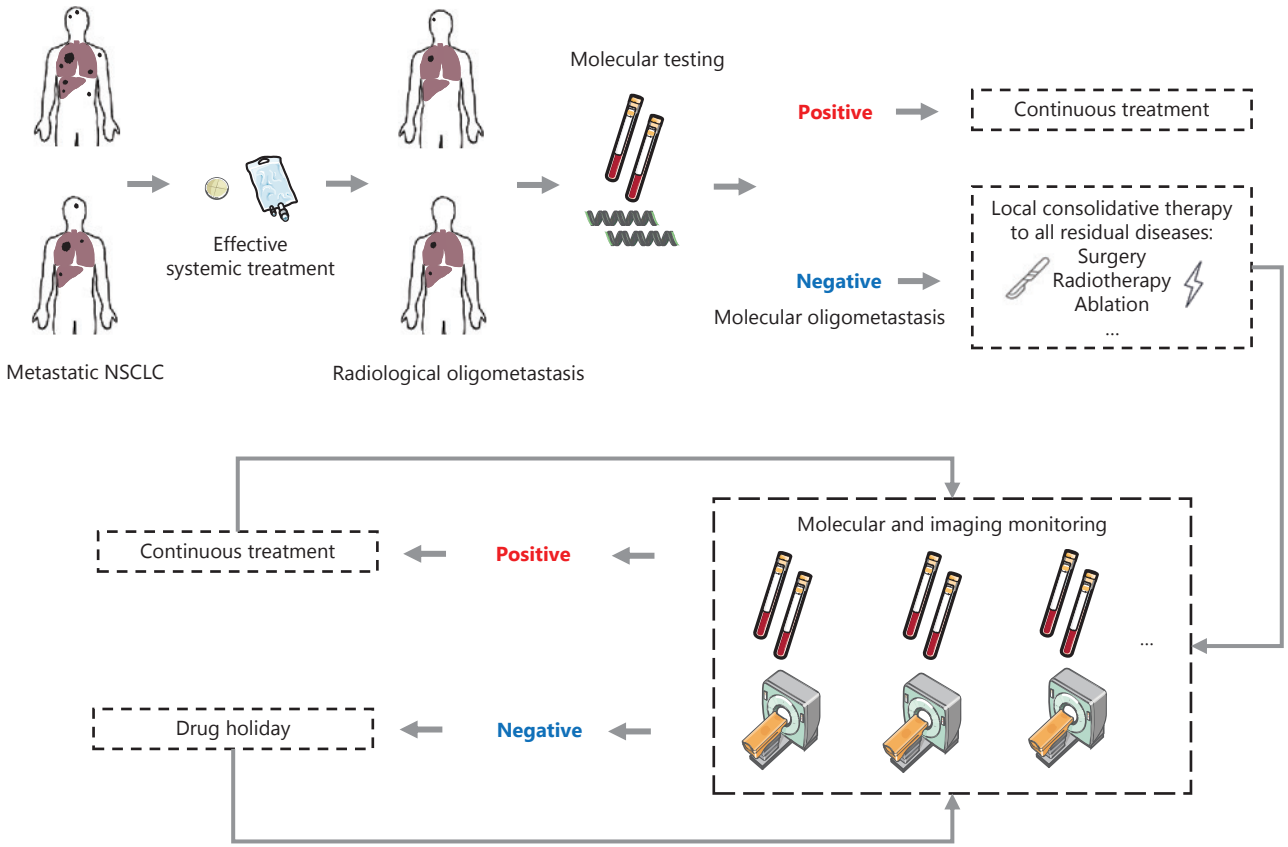


Figure 1 Novel treatment paradigm in oligometastatic NSCLC based on biomarkers. Patients with metastatic non-small cell lung cancer (NSCLC) who met the criteria of radiologic oligometastasis after an optimal duration of induced systemic therapy receive peripheral blood molecular testing, such as circulating tumor DNA (ctDNA) and carcinoembryonic antigen (CEA). Those with negative plasma molecular testing could be defined as molecular oligometastasis and receive local consolidative therapy (LCT) for all residual diseases. After LCT, regular molecular and imaging monitoring was recommended. Treatment discontinuation could be performed in those with undetectable radiologic and peripheral blood molecular disease following LCT.

be considered when evaluating the benefits of LCT for oligometastatic NSCLC: 1) systemic treatment strategies and durations before LCT; 2) radiologic criteria for oligometastatic disease; and 3) pre-treatment ctDNA status before LCT. Future research is warranted to further clarify the criteria for defining oligometastatic disease and to determine optimal treatment strategies to improve patient survival and quality of life. Additionally, the rational use of biomarkers for personalized treatment and the collaboration of multidisciplinary teams will become central to future research efforts.

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Conflict of interest statement

Professor Qing Zhou reports honoraria from AstraZeneca, Boehringer Ingelheim, BMS, Eli Lilly, MSD, Pfizer, Roche, and Sanofi outside the submitted work. The other authors have no competing interests to declare.

Author contributions

Conceived and designed the analysis: Jiayi Deng, Qing Zhou.
Collected the data: Jiayi Deng, Mingyi Yang.
Wrote the paper: Jiayi Deng, Mingyi Yang.

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