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REVIEW

The Evolving Role of Local Radiotherapy in the Management of Oligometastatic Non-Small Cell Lung Cancer

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Abstract: Oligometastasis represents an intermediate stage between locally advanced disease and widespread metastasis, typically referring to stage IV disease with a limited number of metastatic lesions (generally no more than five) and controlled primary disease. Traditionally, advanced non-small cell lung cancer (NSCLC) has been considered incurable, relying primarily on systemic therapies. However, the "oligometastasis hypothesis" proposes that radical local radiotherapy targeting metastatic lesions in such patients may eliminate all tumor burden, potentially achieving long-term survival or even cure. This review aims to elucidate the pivotal role of localized radiotherapy in oligometastatic NSCLC by examining its clinical landscape and therapeutic challenges. Furthermore, This review uniquely integrates biological stratification, technological innovation, and systemic treatment synergy to provide a comprehensive framework for patient selection and clinical decision-making in oligometastatic NSCLC.

Keywords: oligometastasis, non-small cell lung cancer, local radiotherapy, SBRT

Introduction

Clinically, Oligometastasis is commonly defined as stage IV disease with a limited number of metastatic lesions (often ≤3–5) in a restricted number of organs, where all lesions are technically amenable to definitive local therapy. Oligometastatic NSCLC refers to a type of NSCLC where tumor cells are confined to the primary site while simultaneously having a few distant metastases, lying between locally advanced and widely metastatic stages. It is important to distinguish oligometastatic disease from oligoprogressive disease. Oligometastasis generally represents a biologically limited metastatic state with a small number of lesions, whereas oligoprogressive disease occurs during systemic therapy when a limited number of lesions develop resistance while other disease sites remain controlled. Consequently, local therapy in oligometastatic disease is often applied with consolidative or potentially curative intent, while in oligoprogressive disease it is mainly used to control resistant lesions and prolong the benefit of ongoing systemic treatment. In recent years, there has been more exploration into the treatment of oligometastatic NSCLC. Given that oligometastatic NSCLC is characterized by a limited number of metastases and a relatively slow progression, treatment of the local lesions may confer benefits. Hellman and Weichselbaum introduced the concept of "oligometastasis," suggesting that local therapy can extend patient survival time and improve quality of life.[1] Although systemic treatment remains an important treatment modality for NSCLC patients, for those with oligometastasis, systemic treatment cannot completely address local issues, making local radiotherapy an integral part of their comprehensive treatment. Multiple clinical studies have also confirmed that stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR) can significantly improve local control rates, with some patients even achieving long-term survival benefits. In addition to radiotherapy, other local modalities such as surgical metastasectomy and percutaneous ablation have demonstrated clinical benefits in selected patients. Multidisciplinary discussion is therefore critical when determining optimal local treatment strategies. However, the treatment of oligometastatic NSCLC still faces many challenges, including the lack of unified biomarkers or clinical screening standards to precisely identify patients suitable for local radiotherapy, the need for further optimization of radiotherapy strategies for oligometastases at different sites to balance efficacy and toxicity,

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and the need for further exploration of the synergistic mechanisms between local radiotherapy and systemic treatment in the era of immunotherapy.

In this review, we systematically summarize the biological characteristics of oligometastatic NSCLC, recent technological advances in radiotherapy, synergistic strategies with systemic therapies, key clinical trials, site-specific radiotherapy strategies, and emerging biomarkers. Through this structured approach, we aim to provide actionable clinical insights and identify future research priorities.

The Biological Characteristics of Oligometastasis

With the progress of tumor genetics and tumor microenvironment research at the molecular level, the true nature of oligometastasis has been gradually revealed. The "biological inertia" of oligometastatic tumor cells – that is, the limited metastatic ability and relatively slow progression speed of the tumor – is considered a key biological characteristic that distinguishes it from widespread metastasis.[2] The tumor microenvironment also plays an indispensable role in the "inertia" of oligometastasis. The immune cell infiltration pattern of oligometastasis is significantly different from that of widespread metastasis.[3] A study has shown that in oligometastatic breast cancer, the infiltration density of CD8+ T cells is higher, while the proportion of regulatory T cells and myeloid-derived suppressor cells is lower, which not only reflects the relative integrity of local immune surveillance function but also provides clues for understanding its biological inertia.[4] Moreover, its microvessel density and degree of mesenchymal fibrosis are lower, further supporting its relatively slow progression.[5] Monitoring the dynamic changes of circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) can also provide a new perspective for observing the biological characteristics of oligometastasis. The total number of CTCs in oligometastatic patients is significantly different from that in patients with widespread metastasis,[6] and their ctDNA mutation burden (TMB) and clonal heterogeneity are significantly lower than those in patients with widespread metastasis. Relevant studies have shown that in NSCLC, the median TMB in the oligometastasis group is significantly lower than that in the widespread metastasis group (4.6 mut/Mb vs. 14.3 mut/Mb, $P<0.001$).[7] The ctDNA of oligometastasis is mainly monoclonal (accounting for 85%), with a low proportion of subclones; whereas widespread metastasis is mostly polyclonal heterogeneity (accounting for 62%).[8] In CTCs and ctDNA, the genomic instability of oligometastasis is lower and retains the molecular characteristics of the primary tumor.

Oligometastasis has evolved from a one-dimensional experience based solely on clinical experience and some imaging techniques to a multi-dimensional comprehensive evaluation process that combines modern imaging and molecular diagnostic techniques. In the past, the concept of oligometastasis was more based on judgments made with limited imaging techniques and clinical experience, defining oligometastasis solely as a small number of metastatic foci, usually defined as 1–5, and specific anatomical structures. However, with the application of high-precision PET-CT, MRI, and other technologies, the definition of oligometastasis has been expanded to include not only the number and distribution of lesions but also multiple indicators such as biological behavior.

These biological characteristics suggest that oligometastatic NSCLC may represent a distinct disease state with limited metastatic potential rather than simply an early stage of widespread dissemination. Integrating molecular features such as ctDNA dynamics, TMB levels, and immune microenvironment profiles into clinical evaluation may improve patient stratification and help identify individuals most likely to benefit from definitive local radiotherapy.

Technological Progress in Local Radiotherapy

Clinical Application of SBRT/SABR

Stereotactic body radiation therapy (SBRT) and stereotactic ablative radiotherapy (SABR) have emerged as one of the main methods for treating locally advanced and metastatic NSCLC, with numerous clinical trials and retrospective studies demonstrating their efficacy in local control rates and survival benefits.[9] SBRT/SABR uses high-dose, hypofractionated radiation, ensuring that the tumor lesion is targeted while minimizing the dose to adjacent normal tissues, thereby improving efficacy while reducing the occurrence of adverse reactions.

For oligometastatic NSCLC, the optimization of SBRT/SABR technical parameters is an indispensable part. The choice of dose fractionation scheme directly affects efficacy and safety. For example, studies have found that the use of

a BED>100 Gy regimen for lung metastases can significantly improve local control rates, while also paying attention to dose-limiting toxicities (DLTs), especially in lung SBRT, where BED>100 Gy may increase the risk of radiation pneumonitis;[10] the accuracy of target delineation is also an indispensable part. With the progress of four-dimensional CT and respiratory gating imaging guidance technology, the accuracy of target delineation has been significantly improved, effectively reducing the range of irradiation outside the target area.[11]

The long-term follow-up results of the SABR-COMET trial provide a solid basis for the application of SBRT/SABR in oligometastatic NSCLC.[12] The trial mainly enrolled patients with oligometastasis whose disease was stable after first-line treatment. The data showed that the median progression-free survival (mPFS) and overall survival (OS) of patients receiving SABR treatment were significantly better than those receiving only systemic treatment. Notably, this benefit was observed in patients with different metastatic sites such as lung, liver, and bone, fully demonstrating the broad applicability of SBRT/SABR. However, the trial also found that some patients experienced late toxic reactions, indicating that there is still room for optimization in dose selection and protection of normal tissues. In addition, the STOMP trial evaluated the potential curative effect of SBRT combined with systemic treatment for oligometastatic NSCLC in detail, suggesting that the combination of SBRT and systemic treatment can achieve long-term control of the disease in some patients, with some achieving disease-free survival.[13]

Proton Therapy and Other Emerging Technologies

In recent years, proton therapy, as an emerging radiotherapy technology, has shown unique advantages in the treatment of oligometastatic NSCLC. Compared to traditional photon therapy, proton therapy utilizes the physical properties of the Bragg peak to focus high-dose radiation on the tumor target area, while the dose received by the distant healthy tissue is lower, which is particularly important for lesions adjacent to critical organs such as the heart and spinal cord.[14] Multiple studies have shown that proton therapy has great potential for local control and reducing toxicities such as radiation pneumonitis. For example, a small sample, single-center clinical study in Japan showed that proton therapy could achieve a local control rate of 80% in patients with oligometastatic NSCLC, with 13% of patients in the proton therapy group experiencing grade 2 toxicity (such as radiation pneumonitis), and another 13% experiencing grade 3 toxicity, with no grade 4 or 5 toxicity.[15] However, the high cost of treatment and the availability of equipment limit its clinical application. Moreover, the standardization of dose distribution optimization and target delineation planning still requires time. Recent research has found that proton therapy may have a synergistic effect with immunotherapy, with preliminary results showing that proton therapy can enhance the effect of immunotherapy by regulating the tumor microenvironment,[16] but more clinical research is needed to further confirm this.

In addition to proton therapy, other emerging radiotherapy technologies such as Flash radiotherapy and MRI-guided radiotherapy also show promise for oligometastatic NSCLC. Flash radiotherapy uses a high-dose rate radiotherapy mode, completing the irradiation in the shortest time possible while reducing the toxic side effects to normal tissues. Animal experiments and early clinical trials have shown that it has advantages in tumor control and toxicity control, but lacks human data support. How to strictly control the dose rate and complex treatment planning is still an obstacle on the road to clinical transformation of Flash therapy.[17] MRI-guided radiotherapy, with its real-time imaging and treatment plan real-time follow-up adjustment functions, improves the accuracy of radiotherapy and significantly improves the target area radiotherapy for lung and other sites with large respiratory movement[18] (Table 1).

Technological advancements such as SBRT optimization, proton therapy, and MR-guided adaptive radiotherapy expand the therapeutic window of local treatment in oligometastatic NSCLC. The choice of modality should be individualized based on lesion location, proximity to critical organs, and anticipated toxicity, with the ultimate goal of maximizing local control while preserving systemic treatment continuity and quality of life.

Synergistic Effects of Radiotherapy and Systemic Treatment

Synergistic Effects of Radiotherapy and Immunotherapy

The combination of radiotherapy and systemic treatment is a key research area for oligometastatic NSCLC. Previous studies have reported that radiotherapy can improve treatment efficacy by improving the tumor microenvironment and

Table 1 Evolution of Radiotherapy Techniques for NSCLC

Technical/ Category	Explanation	Major Advantages
Three-Dimensional Conformal Radiotherapy (3DCRT)	Uses 3D imaging for more accurate targeting of the tumor.	Increases targeting; decreases profit margins; decreases toxicity.
Intensity-Modulated Radiotherapy (IMRT)	An advanced form of RT that modulates the beam intensity and contour. VMAT is a subtype that uses continuous arcs to deliver RT.	More precise inverse planning based on tumor and organ anatomy; potentially higher tumor doses.
Stereotactic Body Radiotherapy (SBRT)	Delivers high-dose radiation in fewer treatments; requires precise target delineation.	Effective for small local tumors; fewer treatment sessions; utilizes the radiobiological effects of ablative doses.
Image-Guided Radiotherapy (IGRT)	Applies to different radiation therapy techniques. Uses imaging for alignment during treatment to improve precision by considering tumor and organ movement.	Increases precision; reduces side effects.
Adaptive Radiotherapy	Adjusts treatment plans based on changes in tumor/organ anatomy during treatment. Can be done on-line or off-line during treatment.	Tailored treatment.
Proton Therapy	Uses protons instead of X-rays to achieve a dose distribution with no exit dose. Although a higher entrance dose is required, when using multiple beam angles, the treatment plan is often similar to photon plans. Intensity-Modulated Proton Therapy (IMPT) is comparable to Intensity-Modulated Radiation Therapy (IMRT) in terms of effect compared to traditional passive scattering proton techniques.	Overall benefits are similar to IMRT. But with lower harm to surrounding tissue; lower dose to the heart.
FLASH Radiotherapy	Delivers ultra-high doses in an extremely short time, theoretically minimizing side effects while maintaining efficacy	Reduces side effects; currently applied to electron beams or proton beams; still in the experimental phase
MRI-linac	Combines MRI imaging with a linear accelerator (linac) to achieve real-time soft tissue visualization during radiotherapy.	Advanced IGRT technology combined with real-time soft tissue anatomy identification; particularly suitable for central/supercentral tumors.

immune regulation. Radiotherapy can not only directly kill cancer cells but also promote the maturation and activation of antigen-presenting cells by releasing tumor-associated antigens and damage-associated molecular patterns (DAMPs), further enhancing T cell infiltration and activity, which is the "in situ vaccination" phenomenon.[19] This provides a theoretical basis for the synergistic effect of immunotherapy. Secondly, radiotherapy has been proven in preclinical models to upregulate the expression of programmed death ligand 1 (PD-L1) on the surface of tumor cells, thereby promoting the proliferation of tumor-infiltrating lymphocytes (TILs), providing a theoretical basis for improving the efficacy of PD-1/PD-L1 inhibitors[20] (Figure 1). The Phase II randomized controlled trial named PEMBRO-RT showed that the objective response rate (ORR) was 36% in patients with previously treated or untreated advanced NSCLC who received SBRT followed by pembrolizumab treatment, compared to 18% in the pembrolizumab monotherapy group (P=0.07). Notably, the patients enrolled in this study were mainly from a population with a high tumor burden and widespread metastasis, not specifically the oligometastatic NSCLC patient population.[21]

Although the combination of radiotherapy and immunotherapy has brought new hope to patients with oligometastatic NSCLC, we must be aware of the dual role of radiotherapy in immune regulation. While it enhances immune response through the "in situ vaccination" effect and upregulation of PD-L1 expression, it also induces strong immune suppression through mechanisms such as induction of systemic lymphopenia (RIL), recruitment, and activation of immune suppressive cells (MDSCs and Tregs).[23,24] Therefore, the focus of future research should shift from simply verifying the "synergistic" concept to how to "play to one's strengths and avoid one's weaknesses."

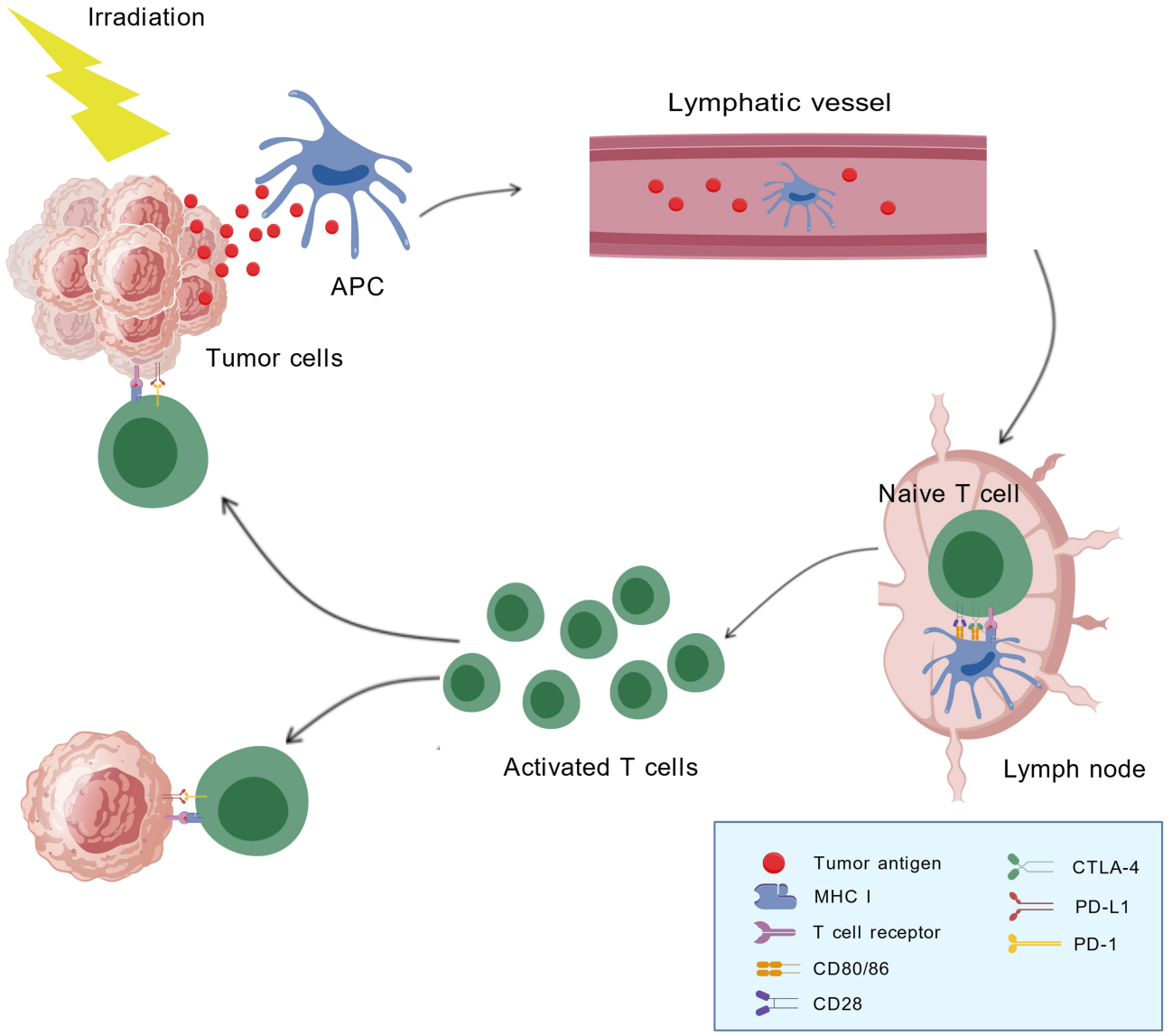

Figure 1 Schematic Diagram of Synergistic Mechanism Between Local Radiotherapy and Immunotherapy.[22] Radiotherapy (RT) can induce immunogenic cell death and promote the post-irradiation release of tumor antigens by tumor cells. These neoantigens are presented by antigen-presenting cells (APCs), such as dendritic cells (DCs) and macrophages. After capturing tumor antigens, APCs migrate to lymph nodes and prime T cells by presenting antigens via the MHC pathway together with co-stimulatory signals (eg., CD80 and CD28). T cells—particularly CD8+ T cells—become activated in response to these signals and undergo clonal expansion. The activated effector T cells then egress from the lymph nodes and infiltrate tumors, including the primary lesion and non-irradiated metastatic sites, where they exert cytotoxic activity against tumor cells.

Synergistic Effects of Radiotherapy and Targeted Therapy

The synergistic effects of radiotherapy and targeted therapy have also received extensive attention. Taking EGFR-TKI as an example, its combination with radiotherapy has shown survival benefit advantages in EGFR-mutated oligometastatic NSCLC. Radiotherapy may inhibit the DNA repair ability of tumor cells, enhancing the killing effect of targeted drugs.[25] However, it is necessary to carefully evaluate the toxicity of combined treatment, especially the risks of radiation pneumonitis and liver toxicity. A Phase III SINDAS trial showed that the median progression-free survival (mPFS) of the group receiving radiotherapy combined with EGFR TKI (gefitinib, erlotinib, or afatinib) was 20.2 months, significantly longer than that of the monotherapy targeted group (12.5 months); the incidence of grade 3–4 radiation pneumonitis was 6% in the combined group, but no significant increase in liver toxicity was reported.[26] Other studies have reported relevant toxicities, suggesting that osimertinib monotherapy may lead to elevated liver enzymes or interstitial lung disease.[27]

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Furthermore, Existing studies have shown that local radiotherapy can not only have synergistic effects with systemic treatment but can also inhibit immune effects through a series of complex signaling pathways. The interaction between radiotherapy and systemic therapy is bidirectional and complex. Successful integration requires careful consideration of treatment sequencing, radiation dose, and systemic regimen selection to enhance synergistic antitumor effects while minimizing overlapping toxicities. Future strategies should move toward biomarker-guided combination approaches rather than empiric combination therapy.

Clinical Evidence and Key Trials

With the continuous development of medicine, the application of local radiotherapy in oligometastatic NSCLC patients has made significant progress. Phase II clinical trials such as SABR-COMET have shown that local radiotherapy plays an important clinical role in patients with oligometastatic NSCLC. The latest long-term follow-up data from the SABR-COMET trial showed that local radiotherapy can significantly prolong the PFS and OS of patients, with a mPFS of 12 months in the SABR group, which was superior to the systemic treatment group alone (6 months); and the mOS of the SABR group was significantly longer than that of the control group (41 months vs. 28 months), with statistically significant differences in survival data between the two groups.[12] These results also provide strong evidence for the important position of local radiotherapy in oligometastatic NSCLC. The STOMP study also showed clinical benefits of local radiotherapy in patients with oligometastatic NSCLC.[13] This study compared SABR combined with systemic treatment and systemic treatment alone and found that the trial group had significantly improved local control rates and control rates of distant metastases. Notably, the study also found that SABR had a significant advantage in improving the quality of life of patients, especially in relieving pain and maintaining physical fitness.[28] However, due to the heterogeneity of trial design (such as differences in patient populations and radiotherapy techniques), the evaluation of the results needs to be more cautious, and further standardization is necessary.

However, it is noteworthy that the NRG-LU002 trial, a Phase II/III clinical study, provided unexpected negative results. This randomized phase II/III trial did not demonstrate a significant improvement in overall survival or progression-free survival with the addition of local consolidative therapy and reported a higher incidence of grade ≥3 adverse events in the local therapy arm. Several factors may account for these findings. Compared with earlier positive phase II trials, NRG-LU002 included patients with stable disease after systemic therapy, potentially introducing greater biological heterogeneity. In addition, a substantial proportion of patients received contemporary immunotherapy-based regimens, reflecting the evolving standard of care. As systemic therapies become more effective, the incremental benefit of local treatment may be attenuated.[29] These results underscore that the role of local radiotherapy is context-dependent and highlight the need for refined patient selection and careful interpretation of trial design differences (Table 2).

In addition to radiotherapy, other local therapeutic modalities have also been explored in carefully selected patients with oligometastatic NSCLC.[13] Surgical resection of both the primary tumor and metastatic lesions has been evaluated mainly in retrospective studies and small prospective series involving patients with limited metastatic burden, controlled systemic disease, and good performance status.[33] These reports suggest that long-term survival may be achievable in a subset of patients, particularly when complete resection (R0) is feasible and multidisciplinary evaluation is applied. Image-guided percutaneous ablative techniques, including radiofrequency ablation, microwave ablation, and cryoablation, have similarly been utilized for limited pulmonary or extracranial metastases. These approaches are particularly relevant for patients who are medically inoperable or unsuitable for high-dose radiotherapy. Available evidence indicates that local control rates can be favorable with acceptable toxicity profiles, although most data are derived from non-randomized studies.[34] Overall, surgery and ablation should be considered complementary components within a multidisciplinary strategy for oligometastatic NSCLC, with careful patient selection and integration with systemic therapy remaining critical to optimize outcomes.

Local radiotherapy shows potential benefits in oligometastatic NSCLC. Trials such as SABR-COMET and STOMP reported improved survival and quality of life with SABR plus systemic therapy, while NRG-LU002 did not confirm these benefits, emphasizing the importance of patient selection and evolving systemic treatments. Surgery and image-guided ablation may also offer effective local control in selected patients, supporting a multidisciplinary treatment approach.

Table 2 Key Clinical Trials of Local Radiotherapy for Oligometastatic NSCLC

Clinical trial	Installment	Experimental Design	The End	Significance
Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non-Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study[13]	II	Patients (n = 49) who received first-line treatment for oligometastatic non-small-cell lung cancer; Comparison of local treatment (LCT, n = 25) with maintenance/ observation (MT/O, n = 24)	mPFS: (LCT 14.2 months vs. MT/O 4.4 months) mOS: (LCT 41.2 months vs. MT/O 17.0 months)	LCT significantly improved progression-free survival (PFS) and overall survival (OS), indicating that aggressive local treatment can delay disease progression and improve prognosis.
SABR-COMET: Stereotactic ablative radiotherapy versus standard of care palliative treatment in patients with oligometastatic cancers (SABR-COMET): A randomized, Phase 2, open-label trial[12]	II	Subgroup of non-small-cell lung cancer patients (n = 18); Comparison of stereotactic ablative body radiotherapy (SABR, n = 12) with standard palliative treatment (n = 6)	mPFS: (SABR 12 months vs. Control group 4 months) OS: (SABR 41 months vs. Control group 17 months)	SABR significantly improved overall survival (OS) and progression-free survival (PFS) in patients with oligometastatic non-small-cell lung cancer compared to standard palliative treatment.
ATOM: A phase II study to assess efficacy of preemptive local ablative therapy to residual oligometastases of NSCLC after EGFR TKI[30]	II	Non-small-cell lung cancer (NSCLC) patients with residual oligometastases after EGFR TKI treatment; Assessment of prophylactic local ablative therapy (LAT) using SABR (n = 16)	mOS: 43.3 months	In NSCLC patients with residual limited metastases after EGFR TKI treatment, prophylactic local ablative therapy using SABR effectively prolonged progression-free survival and was well tolerated.
Consolidative stereotactic ablative radiotherapy to intrapulmonary lesions is associated with prolonged progression-free survival and overall survival in oligometastatic NSCLC patients: A prospective phase 2 study[31]	II	Patients with oligometastatic NSCLC with intrapulmonary lesions; Use of SABR (n = 34)	mPFS: 34.3 months, median PFS in patients achieving complete metabolic response (CMR): 53.9 months, DCR: 93.6%; 79.5% of patients experienced grades 1–2 pneumonia	SABR was associated with prolonged progression-free survival (PFS) and overall survival (OS) in patients with oligometastatic NSCLC and had good safety.
SINDAS: Randomized trial of first-line tyrosine kinase inhibitor with or without radiotherapy for synchronous oligometastatic EGFR-mutated non-small cell lung cancer[26]	III	Patients (n = 133) with first-line oligometastatic EGFR-mutated non-small cell lung cancer; Comparison of TKI + RT (n = 68) with TKI alone (n = 65).	mPFS: 20.2 months (TKI + RT) vs. 12.5 months (TKI), mOS: 25.5 months (TKI + RT) vs. 17.4 months (TKI).	Adding radiotherapy to first-line TKI treatment significantly improved progression-free survival (PFS) and overall survival (OS) with an acceptable toxicity level.
CURB: Standard-of-care systemic therapy with or without stereotactic body radiotherapy in patients with oligoprogressive breast cancer or non-small-cell lung cancer (Consolidative Use of Radiotherapy to Block [CURB] oligoprogression): An openlabel, randomised, controlled, phase 2 study[32]	II	Patients with oligoprogressive NSCLC (n = 59) or breast cancer; NSCLC subgroup compared SBRT (n = 31) with standard therapy (n = 28) NSCLC subgroup: mPFS: 10.0 months (SBRT) vs. 2.2 months (standard therapy).	NSCLC subgroup: mPFS: 10.0 months (SBRT) vs. 2.2 months (standard therapy).	SBRT significantly improved progression-free survival (PFS) in patients with oligoprogressive NSCLC, highlighting its special role in the management of NSCLC.

(*Continued*)

Table 2 (Continued).

Clinical trial	Installment	Experimental Design	The End	Significance
NRG-LU002: Randomized phase II/III trial of maintenance systemic therapy versus local consolidative therapy (LCT) plus maintenance systemic therapy for limited metastatic non-small cell lung cancer (NSCLC)[29]	II/III	Patients (n = 215) with limited metastatic non-small cell lung cancer (NSCLC) after systemic therapy with ≤ 3 extracranial metastases; Comparison of LCT plus maintenance systemic therapy (n = 134) with maintenance systemic therapy alone (n = 81).	LCT group: No significant difference in PFS (HR 0.93) or OS (HR 1.05), higher toxicity.	Adding LCT to maintenance systemic therapy did not significantly improve PFS or OS and was associated with higher toxicity.

Radiotherapy Strategies for Different Metastatic Sites

Radiotherapy Options for Brain Metastases

In clinical practice, the treatment of brain metastases in patients with oligometastatic NSCLC primarily involves stereotactic radiosurgery (SRS) and whole-brain radiotherapy (WBRT), with both approaches showing significant differences in efficacy and toxicity. With the continuous advancement of imaging and radiotherapy technologies, individualized treatment strategies are gradually becoming the clinical trend. SRS is characterized by high precision and low toxicity, making it the preferred treatment option for oligometastatic brain metastases. Multiple clinical studies have found that SRS achieves high local control rates and survival rates, with minimal damage to normal brain tissue.[35] According to reported trials, the risk of cognitive function decline associated with SRS treatment is much lower than that of WBRT. The clinical application of SRS should be strictly limited, generally used only for patients with a few metastases (such as 1 to 3) and small tumor volumes.[36] WBRT was once the standard treatment for brain metastases, but its long-term impact on cognitive function has led to its restricted use in oligometastatic patients. For patients with multiple brain metastases or those with leptomeningeal metastases, WBRT remains irreplaceable.[37] In recent years, the application of hippocampal protection techniques has somewhat mitigated the neurotoxicity associated with WBRT, but further optimization of its application in oligometastatic NSCLC is still needed. The combination of radiotherapy for brain metastases with systemic treatment is an area worthy of anticipation.

Radiotherapy Strategies for Bone Metastases and Other Sites

Due to the anatomical and biological heterogeneity of patients with oligometastatic NSCLC, clinical treatment strategies for bone, liver, adrenal glands, and other sites are heterogeneous. In clinical practice, bone metastases are the most common and have a high probability of associated pain and pathological fractures. Radiotherapy plays a key role in improving patient symptoms and controlling local lesions. Traditionally, external beam radiation therapy (EBRT) has been the standard therapy for bone metastases in NSCLC. Currently, SBRT, due to its high precision and dosimetric accuracy, has become a hot research topic. Some clinical studies have reported trials involving SBRT for spinal oligometastatic NSCLC patients, confirming its ability to effectively improve local control rates and reduce the risk of injury to nearby organs, while also showing a higher pain relief rate than conventional radiotherapy.[38] The radiotherapy strategy for adrenal and liver oligometastatic NSCLC is determined based on the size, location, and general condition of the metastases. Adrenal oligometastases generally receive SBRT treatment, which can precisely locate the lesion and reduce the damage to adjacent organs such as the kidneys and liver. Relevant research on SBRT treatment for adrenal oligometastatic patients has shown a local control rate of up to 77% with extremely low toxicity.[39,40] The treatment of liver oligometastases is more challenging, which may be related to the size and location of the lesions. The treatment needs to consider both efficacy and safety. The liver is highly radiosensitive, and strict dose control is required to avoid radiation-induced liver injury. MRI-guided radiotherapy technology, with its superior performance in resolving soft

tissues, can real-time track and adjust the dose of radiation, making it a technique with a clear advantage for liver oligometastases.[41]

Radiotherapy strategies for oligometastatic NSCLC must be tailored according to metastatic site, anatomical constraints, and organ tolerance. In the future, with the development of artificial intelligence and imaging genomics, local radiotherapy for oligometastases will move towards more precise individualized directions. Functional imaging technology based on MRI is expected to achieve precise delineation of target areas and prediction of treatment response. The potential of novel technologies such as flash radiotherapy to shorten treatment time and reduce toxicity is also worth further exploration.

Selection and Validation of Biomarkers

In recent years, biomarkers have shown significant application potential in predicting the efficacy of local radiotherapy in patients with oligometastatic NSCLC. These markers not only help in identifying patient populations that may benefit from local treatment but also provide a scientific basis for the development of individualized treatment plans. Current research mainly focuses on immunologically related markers, indicators related to tumor genomic instability, and circulating tumor markers. Immunologically related markers include PD-L1 expression levels and tumor mutation burden (TMB). Studies have shown that NSCLC oligometastatic patients with high PD-L1 expression levels are more likely to benefit from SBRT/SABR, which may be related to the responsiveness of radiotherapy-induced immune activation.[42] Additionally, TMB is an indicator that reflects the tumor's new antigen load and has been found to better reflect the level of radiotherapy-induced immune activation.[43] However, the detection of these markers involves different study populations, established indicators, and thresholds, and how to standardize the detection methods is an urgent issue. Tumor genomic instability-related markers mainly include microsatellite instability (MSI) and homologous recombination repair defect (HRD), which are currently hot research markers.[44] They reflect the tumor's inherent sensitivity to DNA damage, and the reason why radiotherapy can achieve radical and local effectiveness is the result of DNA damage, so its efficacy may be correlated with MSI and HRD levels. Some preliminary studies suggest that NSCLC with MSI-H and/or HRD positivity may have a better radiotherapy response rate,[45] but whether this result supports treatment still requires validation through large-scale clinical studies. Circulating tumor markers (such as CTCs and ctDNA) have shown unique potential in efficacy prediction due to their non-invasiveness and dynamic monitoring advantages. Monitoring the dynamic changes of CTCs and ctDNA before and after radiotherapy can directly monitor the tumor's response to radiotherapy and guide the adjustment of subsequent treatment strategies.

Although emerging biomarkers such as circulating tumor DNA and immune-related indicators show potential in refining risk stratification, their clinical utility remains investigational. Therefore, Patient selection for local radiotherapy in oligometastatic NSCLC should be based on a comprehensive evaluation rather than reliance on biomarkers alone. In clinical practice, several factors require integration. First, patient-related characteristics such as performance status, comorbidity burden, and overall treatment tolerance remain fundamental prerequisites for considering ablative local therapy. Second, disease-related parameters—including the number and anatomical distribution of metastatic lesions, synchronous versus metachronous presentation, and organ-specific involvement—may reflect biological aggressiveness and influence expected benefit. Third, response to initial systemic therapy provides important prognostic information. Patients achieving partial response or durable disease control may represent a more favorable biological subset compared with those with rapidly progressive disease.

In short, Biomarker research is still evolving, integrating molecular markers with clinical parameters may refine patient selection for local radiotherapy. Dynamic monitoring tools such as ctDNA hold promise for response-adapted strategies, but prospective validation is necessary before routine implementation.

Conclusion and Outlook

Current evidence suggests that local radiotherapy has a meaningful role in the management of selected patients with oligometastatic NSCLC, particularly when incorporated into a multidisciplinary treatment framework. Phase II data, including long-term follow-up from trials such as SABR-COMET, indicate that local ablative therapy may prolong

progression-free and overall survival in carefully chosen patients. In clinical practice, SBRT/SABR is generally preferred due to its precision, established safety profile, and feasibility for delivering ablative doses to limited metastatic lesions.

Despite these advances, several practical issues remain unresolved. Clear and standardized criteria for patient selection are still lacking, and the optimal timing, sequencing, and dose of radiotherapy in the context of modern systemic therapies—especially immunotherapy—require further prospective evaluation. In addition, the comparative roles of radiotherapy, surgery, and other ablative modalities have not been fully defined. Biomarkers such as ctDNA and immune-related indicators show potential but are not yet ready for routine clinical implementation.

Future research focusing on prospective validation, standardized trial design, and integration of clinical and molecular parameters will be important to clarify the role of local radiotherapy and to support its appropriate and evidence-based application in oligometastatic NSCLC.

Disclosure

The authors report no conflicts of interest in this work.

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