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REVIEW

The Oligometastatic State in NSCLC: Where Does Radiotherapy Fit?

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Abstract

Non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related mortality worldwide, with the majority of patients presenting with or developing metastatic disease. The concept of oligometastatic disease (OMD) an intermediate state between localised and widely disseminated disease has emerged as a therapeutically relevant entity. Growing evidence supports the integration of local ablative therapies (LAT), particularly stereotactic body radiotherapy (SBRT) or stereotactic ablative radiotherapy (SABR), into the management of oligometastatic NSCLC (OM-NSCLC) alongside systemic therapy. This review synthesises the clinical rationale, key randomised trial data, and the evolving role of radiotherapy in both driver-mutation-negative and driver-mutation-positive OM-NSCLC. We discuss the interplay of radiotherapy with immunotherapy and targeted therapies, specific metastatic sites, and emerging strategies including oligoprogressive disease management. Challenges of patient selection, optimal timing, dose-fractionation, and the provocative negative results of the NRG-LU002 trial are also addressed. Finally, ongoing and future trials that will shape the next decade of practice are outlined.

Keywords: Oligometastatic NSCLC- stereotactic body radiotherapy- SBRT- SABR- local consolidative therapy- EGFR

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1. Introduction

Lung cancer remains the leading cause of cancer-related death globally, accounting for approximately 1.8 million deaths per year. Non-small cell lung cancer comprises roughly 85% of all lung cancers, with adenocarcinoma being the most prevalent histologic subtype. Approximately 57% of patients present with distant metastases at the time of diagnosis, a stage at which prognosis has historically been dismal, with 5-year overall survival (OS) rates of approximately 5–8% in the pre-immunotherapy era [1].

The conceptual breakthrough that fundamentally altered treatment thinking for a subset of stage IV NSCLC patients was the proposal of the 'oligometastatic state' by Hellman and Weichselbaum in 1995 [2]. They postulated that some tumours, before acquiring the full metastatic phenotype, exist in an intermediate state of limited, potentially curable dissemination. This biological hypothesis implied that aggressive local ablative therapy to all sites of disease most often surgery or radiotherapy could either cure or substantially delay progression in such patients. Importantly, they predicted that the prevalence of this state would increase as systemic therapies improved in controlling microscopic metastatic disease.

Early proof-of-concept for this paradigm emerged from surgical metastasectomy data across multiple tumour types. Long-term follow-up of patients undergoing colorectal liver metastasectomy demonstrated 10-year disease control in over 16% of cases [3]. Data from the International Registry of Lung Metastases, encompassing over 5,000 cases, showed an actuarial 15-year survival rate of 22% following lung metastasectomy [4]. These landmark observations established that durable survival was achievable with aggressive local therapy in selected patients with metastatic disease.

With the advent of stereotactic body radiotherapy (SBRT) also termed stereotactic ablative radiotherapy (SABR) a non-invasive, highly precise local ablative modality became available. SBRT utilises advanced image guidance, precise patient immobilisation, respiratory motion management, and tightly conformal, high-dose-per-fraction radiation delivered in one to five treatments. Its high rates of local control with acceptable toxicity made it an attractive alternative to surgical resection for many patients [5]. The intersection of SBRT with the oligometastatic disease paradigm in NSCLC has since generated one of the most rapidly evolving areas in thoracic oncology.

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This narrative review summarises the available evidence for radiotherapy in OM-NSCLC, covering: (i) the definition and classification of oligometastatic disease; (ii) the biological rationale for local ablative therapy; (iii) key randomised trial evidence in driver-mutation-negative NSCLC; (iv) the role of SBRT in driver-mutation-positive NSCLC; (v) the interplay with immunotherapy; (vi) site-specific considerations; (vii) management of oligoprogressive disease; and (viii) ongoing trials and future directions.

2. Definition And Classification Of Oligometastatic Disease

The definition of oligometastatic NSCLC has evolved considerably. The American Joint Committee on Cancer (AJCC) 8th edition introduced the M1b designation for a single extrathoracic metastatic site, and M1c for multiple extrathoracic metastases [6]. However, most clinical and research definitions consider 1 to 5 metastatic lesions as constituting OMD, reflecting a pragmatic approach.

In 2020, the European Society for Radiotherapy and Oncology (ESTRO) and the American Society for Radiation Oncology (ASTRO) jointly published a consensus document on the characterisation and classification of OMD [7]. This document made several critical points: (i) OMD is largely independent of primary tumour type, metastatic location, or disease-free interval; (ii) both synchronous (present at initial diagnosis) and metachronous (arising after a disease-free interval) OMD are recognised; (iii) the oligometastatic state cannot currently be reliably identified by a single imaging or biomarker criterion; and (iv) clinical judgement alongside imaging remains the standard approach for patient selection.

A critical refinement came from the ASTRO/ESTRO joint clinical practice guideline on local therapy for oligometastatic NSCLC, published in 2023 [8]. This guideline emphasised a multidisciplinary team approach, advocated for pathological confirmation of at least one metastatic lesion (as recommended by the EORTC), and distinguished between distinct clinical scenarios that include: (i) synchronous OMD at initial diagnosis; (ii) metachronous OMD or oligorecurrence after a disease-free interval; (iii) oligopersistence residual disease remaining after systemic therapy; and (iv) oligoprogression limited progression at a subset of sites while others remain controlled under systemic therapy.

Comprehensive staging with positron emission tomography-computed tomography (PET-CT) and brain magnetic resonance imaging (MRI) is considered essential prior to characterising disease as oligometastatic and committing to local ablative therapy with curative intent. The European Organisation for Research and Treatment of Cancer (EORTC) imaging group has proposed minimal criteria for diagnostic imaging in this context.

3. Biological Rationale for Local Ablative Therapy in OM-NSCLC

The biological underpinning of the oligometastatic hypothesis rests on the theory that the limited number of metastatic deposits reflects a biologically distinct disease state one characterised by an incomplete acquisition of a fully metastatic phenotype. Weichselbaum and Hellman further proposed that if resistant clones driving progression from oligometastatic to polymetastatic disease are eradicated by local therapy, long-term disease control or cure may be achievable [2].

Patterns of failure analyses in the pre-immunotherapy era provided strong indirect support for local ablative therapy. In patients with stage IV NSCLC receiving platinum-doublet chemotherapy, approximately 70–80% achieved disease control (partial response or stable disease) [8]. However, after first-line chemotherapy, roughly 64% of patients progressed at the initial site of disease or locoregionally, 27% progressed both locally and distantly, and only 9% had exclusively new distant progression [9]. This pattern implies that local disease is a major driver of treatment failure, and that eliminating residual local disease may prevent subsequent systemic spread.

Radiobiologically, SBRT delivers doses per fraction well above conventional 2 Gy, typically 7.5–15 Gy per fraction over 1–5 fractions. At these ablative doses, the linear-quadratic model begins to break down, and tumour cell death occurs not only through direct DNA damage but also through vascular damage, immune modulation, and activation of cell death pathways not seen at conventional doses. The steep dose gradients of SBRT allow delivery of these ablative doses while sparing adjacent critical structures.

4. Radiotherapy In Driver-Mutation-Negative OM-NSCLC

4.1 Early Phase II Evidence

Prior to the era of randomised trials, multiple single-arm phase II studies established the feasibility and promising activity of SBRT in OM-NSCLC. De Ruysscher et al. conducted a phase 2 study of metastasis-directed radiotherapy (or chemoradiotherapy) to all sites of synchronous OMD with ≤5 lesions, inclusive of the primary. Median OS was 13.5 months, with three patients remaining alive at 5 years on long-term follow-up [10]. Another phase 2 study by Petty et al., initiating in 2010, enrolled patients with ≤5 metastatic lesions following platinum-based chemotherapy and treated all sites with consolidative radiation. Long-term data from this study showed a median OS of approximately 23 months, with acceptable late toxicity [11].

4.2 Key Randomised Phase II Trials

The pivotal shift from hypothesis to clinical evidence came with three seminal phase II randomised controlled trials (RCTs), summarised in Table 1:

Gomez et al, a multicentre RCT was the first prospective randomised study conducted exclusively in OM-NSCLC. Patients with ≤3 metastatic sites who did not progress after initial systemic therapy (either ≥4 cycles of platinum doublet chemotherapy or ≥3 months of erlotinib or crizotinib) were randomised to local consolidative therapy (LCT radiation or surgery) versus

Table 1. Key Randomised Trials of Radiotherapy in Oligometastatic NSCLC (Including Mixed Populations)

Study	Design	N	Population	Treatment Arms	PFS (months)	OS (months)	Key Findings
Gomez et al. 2016/2019 (Lancet Oncol / JCO)	Phase II RCT	49	≤3 mets; no progression after IST	LCT vs MT/O	14.2 vs 4.4 (p=0.022)	41.2 vs 17.0 (p=0.017)	First RCT showing OS benefit with LCT in OM-NSCLC
Iyengar et al. 2018 (JAMA Oncol)	Phase II RCT	29	≤5 mets; stable/PR after chemo	SBRT + maintenance vs maintenance alone	9.7 vs 3.5 (p=0.01)	NR	Stopped early; significant PFS benefit
SABR-COMET (Palma et al. 2019/2020, Lancet / JCO)	Phase II RCT (1:2)	99 (18 NSCLC)	1–5 mets, controlled primary	SOC vs SOC + SABR	6 month improvement	50 vs 28 (p=0.006)	5-year OS 42.3% SABR arm; 3 treatment-related deaths
NRG-LU002 (Robinson et al. 2024, ASCO)	Phase II/III RCT (1:2)	215	≤3 extracranial mets; SD/PR after 4 cycles; 90.7% IO	MST vs LCT + MST	HR 0.93; p=0.664	HR 1.05; p=0.821	Negative trial; LCT not beneficial in IO era

maintenance therapy or observation. The trial was stopped early at 49 patients due to a dramatic PFS improvement. Updated long-term results showed median PFS of 14.2 months with LCT versus 4.4 months without (p=0.022), and a significant OS advantage: 41.2 versus 17.0 months (p=0.017), with a hazard ratio of 0.37 (95% CI 0.17–0.78) [12, 13]. These results provided the first randomised OS evidence supporting LCT in OM-NSCLC.

Iyengar et al, a single-institution phase II RCT at UT Southwestern randomised 29 patients with stage IV NSCLC with ≤5 metastatic sites and disease control after 4–6 cycles of platinum-based chemotherapy to SBRT plus maintenance chemotherapy versus maintenance chemotherapy alone. The trial was terminated early on unplanned interim analysis. SBRT significantly prolonged median PFS from 3.5 to 9.7 months (p=0.01), and importantly demonstrated a shift in the pattern of failure from known sites to new sites, suggesting SBRT was not merely delaying local progression but genuinely preventing further dissemination [14].

The SABR-COMET study, conducted across 10 hospitals in Canada, the Netherlands, Scotland, and Australia, was the first RCT across all solid tumour histologies to demonstrate an OS benefit with SBRT in OMD. Ninety-nine patients (18 with NSCLC) with 1–5 metastatic lesions and a controlled primary tumour were randomised 1:2 to palliative standard of care (SOC) alone versus SOC plus SABR. The primary endpoint was OS, using an alpha of 0.20 (phase II screening design). Median OS in the SABR arm was 50 months versus 28 months (hazard ratio 0.48; 95% CI 0.30–0.75; p=0.006 in long-term follow-up), with 5-year OS of 42.3% in the SBRT group [15, 16]. These results were maintained on post-hoc sensitivity analysis excluding the prostate cancer subgroup. However, the SABR arm experienced three (4.5%) treatment-related deaths, underscoring the importance of careful patient selection and expertise in SBRT delivery.

4.3 The NRG-LU002 Trial and The Immunotherapy Question

The NRG-LU002 trial was the largest phase II/III RCT designed to evaluate LCT in oligometastatic NSCLC in the contemporary immunotherapy era. This multicentre US study enrolled 215 patients with ≤3 extracranial metastatic sites who had stable disease or partial response after 4 cycles of first-line systemic therapy. Crucially, 90.7% of patients received immunotherapy-based regimens. Patients were randomised 1:2 to maintenance systemic therapy versus LCT (radiation and/or surgery) plus maintenance systemic therapy.

Reported at ASCO 2024, the trial yielded negative results: 1-year and 2-year PFS rates were not significantly different between arms (HR 0.93; p=0.664), and OS showed no benefit from LCT (HR 1.05; p=0.821). Patients receiving LCT experienced a significantly higher rate of grade ≥3 pneumonitis (10% versus 1%) [17].

Several explanations for this negative outcome have been proposed. First, the predominant use of immunotherapy (90.7%) in NRG-LU002 contrasts with the chemotherapy-dominant populations of earlier positive trials (Gomez et al., Iyengar et al.). Immunotherapy, particularly checkpoint inhibition, is a potent systemic therapy capable of providing durable disease control across sites potentially reducing the incremental benefit of additional local therapy. Second, the high proportion of patients with stable disease (57.8%) after immunotherapy in NRG-LU002 may have selected patients who were not responding deeply to systemic treatment, representing a suboptimal population for LCT. Third, the unique immunological dynamics of residual disease after immunotherapy are poorly understood. Local ablative therapy may disrupt ongoing immune responses at residual sites. These observations suggest that while LCT may benefit selected patients in the immunotherapy era, it should not be offered routinely to all OM-NSCLC patients, and individualised multidisciplinary decision-making is essential [18].

5. Radiotherapy in Driver-Mutation-Positive OM-NSCLC

The discovery of actionable oncogenic drivers particularly mutations in the epidermal growth factor receptor (EGFR) gene and rearrangements of anaplastic lymphoma kinase (ALK) and ROS1 transformed the treatment of advanced NSCLC. Tyrosine kinase inhibitors (TKIs) targeting these alterations produce response rates of 60–80%, substantially superior to chemotherapy. However, virtually all patients develop acquired

resistance to TKIs, typically within 10–14 months for first-generation EGFR TKIs and approximately 15–18 months for later generations.

5.1 EGFR-Mutant Oligometastatic NSCLC

EGFR mutations (exon 19 deletions and exon 21 L858R substitutions are most common) account for approximately 15% of NSCLC in Western populations and up to 40–50% in East Asian populations. The rationale for adding SBRT to TKI therapy in EGFR-mutant OM-NSCLC is twofold: (i) to ablate known sites of disease that would otherwise become eventual sources of systemic failure; and (ii) to eliminate resistant clones that might emerge and drive acquired TKI resistance.

The most definitive evidence comes from the SINDAS trial, a phase III RCT that enrolled 133 patients with EGFR-mutant oligometastatic NSCLC (≤5 metastatic sites) and randomised them to upfront SBRT plus TKI versus TKI alone. This was a landmark study: not only did it show a significant improvement in median PFS (20.2 versus 12.5 months; $p<0.001$) but also, uniquely for this setting, a significant OS benefit: 25.5 versus 17.4 months ($p<0.001$) with a hazard ratio of 0.41 (95% CI 0.27–0.62) [19]. This was the first phase III positive trial of SBRT plus TKI versus TKI alone in this population and represents the highest level of evidence for SBRT in driver-mutation-positive OM-NSCLC.

Supporting evidence comes from a prospective multicentre phase II RCT by Peng et al. (2023), which randomised EGFR-mutant OM-NSCLC patients to EGFR-TKI plus SBRT versus TKI alone. The addition of SBRT significantly prolonged median PFS from 9.0 to 17.6 months ($p=0.016$) and OS from 23.2 to 33.6 months ($p=0.026$), with no grade ≥3 toxicity observed in either arm a particularly reassuring safety profile [20].

A prospective pilot study at the 2023 ASCO annual meeting evaluated concurrent osimertinib (a third-generation EGFR TKI with superior CNS penetration) plus SBRT for oligo-residual disease sites at maximum TKI response. With a median follow-up of 18 months, no disease progression was observed, and the combination was well tolerated with no grade 3/4 acute or late radiation toxicity [21].

The NORTHSTAR trial, a unicentric phase II study, enrolled EGFR-mutant advanced NSCLC patients who had not progressed within 6–12 weeks of osimertinib and assessed osimertinib plus LCT. The combination was well tolerated with no 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. OS and PFS data are awaited [22].

For EGFR-mutant oligoprogressive disease a critically important and common clinical scenario the standard approach is to continue the TKI while applying local ablative therapy to the site(s) of radiological progression. A retrospective study from Memorial Sloan-Kettering Cancer Center of local therapy (radiation, surgery, or radiofrequency ablation) for oligoprogressive EGFR-mutant NSCLC on TKI demonstrated a median time to change in systemic therapy of 22 months, with median OS of 41 months substantially longer than would be expected with immediate TKI switching [23]. This approach of 'TKI continuation plus local ablation' for oligoprogression avoids premature escalation to next-line agents, preserving the activity of subsequent TKIs.

5.2 ALK-Rearranged and ROS1-Rearranged Oligometastatic NSCLC

ALK gene rearrangements occur in approximately 3–7% of NSCLC and, like EGFR mutations, confer sensitivity to highly active TKIs (crizotinib, alectinib, brigatinib, lorlatinib). The evidence base for SBRT in ALK-positive OM-NSCLC is predominantly retrospective, but the concept of local ablative therapy for oligoprogression during TKI therapy is well established.

Gan et al. (2014) published a seminal retrospective study evaluating stereotactic radiation therapy (SRT) for extra-CNS oligoprogressive disease in ALK-positive NSCLC patients on crizotinib. SRT was found to be safe and effective, enabling continued crizotinib therapy beyond the point of oligoprogression, with a median time to second progression of 6.5 months from SRT and an acceptable safety profile [24]. This approach continuing the same TKI with local ablation of resistant sites has become an accepted strategy for ALK-positive oligoprogression in the absence of systemic resistance mechanisms.

For ROS1-rearranged NSCLC, there are no dedicated randomised trials of SBRT in the oligometastatic/oligoprogressive setting, though the same principles of local ablation with TKI continuation are applied by analogy. The critical caveat is that identification of systemic resistance mechanisms (e.g., secondary EGFR T790M mutation, ALK bypass mutations) should guide whether TKI switching is warranted rather than local ablative therapy (Table 2).

6. Radiotherapy and Immunotherapy: A Synergistic Combination?

The integration of immune checkpoint inhibitors (ICIs) with radiotherapy represents one of the most promising and scientifically compelling frontiers in thoracic oncology. Radiotherapy promotes the release of tumour-associated antigens and damage-associated molecular patterns (DAMPs), induces immunogenic cell death, and stimulates innate immune activation collectively functioning as an 'in situ cancer vaccine'. At ablative SBRT doses, these immunostimulatory effects are particularly potent [25].

The abscopal effect the phenomenon of tumour regression at distant, unirradiated sites following local radiotherapy has been attributed to radiation-induced systemic immune activation. While historically rare with radiation alone, the combination of SBRT with ICIs may potentiate abscopal responses. The PEMBRO-RT trial demonstrated that pembrolizumab combined with SBRT induced superior cytotoxic T-cell infiltration in non-irradiated tumour sites compared to pembrolizumab monotherapy, providing evidence for an immunological abscopal effect in the tumour microenvironment [26].

However, the optimal dose, fractionation, and timing of SBRT to maximise immune synergy with ICIs remains an open question. Preclinical data suggest that hypofractionated regimens (e.g., 3×8 Gy) may be more immunogenic than single high-dose fractions, due to cGAS-STING pathway activation and reduced type I interferon suppression. Conversely, very high single doses may generate immunosuppressive effects. Compared with conventionally fractionated radiation therapy, SBRT is associated with less lymphopenia and better clinical efficacy [29].

It is in this context that the negative NRG-LU002 trial must be interpreted. With 90.7% of patients receiving ICI-based regimens, the incremental benefit of LCT may have been attenuated by already-activated systemic immune responses. The possibility that adding local radiotherapy may even disrupt established immune equilibria at residual disease sites needs further investigation in correlative biomarker studies embedded within prospective trials.

7. Site-Specific Considerations in OM-NSCLC

7.1 Brain Metastases

Brain metastases are common in advanced NSCLC, occurring in 20–40% of patients, with particularly high rates in EGFR-mutant and ALK-rearranged disease. Stereotactic radiosurgery (SRS) has largely replaced whole brain radiotherapy (WBRT) as the preferred modality for patients with limited brain metastases (typically 1–4, with some centres extending to up to 10 lesions), owing to superior preservation of neurocognition and equivalent or superior OS. Randomised trials and meta-analyses have confirmed that for patients with 1–4 brain metastases from NSCLC, SRS alone provides equivalent OS to WBRT with SRS boost, with significantly better neurocognitive outcomes [30].

In EGFR-mutant and ALK-positive NSCLC, the high CNS penetration of newer-generation TKIs (osimertinib, alectinib, brigatinib, lorlatinib) has led to debate about whether upfront SRS is necessary for asymptomatic brain metastases or whether TKI alone suffices. Current consensus, reflected in NCCN and ESMO guidelines, generally supports early SRS for symptomatic brain metastases or those posing risk, while deferring radiation in asymptomatic patients on effective TKI therapy with close CNS surveillance in selected cases.

7.2 Bone Metastases

Bone represents one of the most common sites of metastases in NSCLC. Historically, conventional palliative radiotherapy (e.g., 8 Gy × 1 or 30 Gy in 10 fractions) has been the standard for painful bone metastases. However, in the oligometastatic setting, spine SBRT (stereotactic body radiation surgery or SBRS) can deliver ablative doses to spinal metastases with high rates of pain control and durable local control exceeding 85–90% at 1 year, while minimising spinal cord dose. The randomised NRG/RTOG 0631 trial demonstrated superiority of single-fraction spine SRS (16–18 Gy) over conventional

Table 2. Studies Evaluating SBRT in Driver-Mutation-Positive Oligometastatic/Oligoprogressive NSCLC

Study	Design	N	Mutation	Intervention	Median PFS (months)	Median OS (months)	Notes
SINDAS (Wang et al. 2022, JAMA Oncol)	Phase III RCT	133	EGFR+	SBRT + TKI vs TKI alone	20.2 vs 12.5 (p<0.001)	25.5 vs 17.4 (p<0.001)	Upfront SBRT with TKI superior; landmark trial
Peng et al. 2023 (Radiother Oncol)	Phase II RCT	Multicenter	EGFR+	EGFR-TKI + SBRT vs TKI alone	17.6 vs 9.0 (p=0.016)	33.6 vs 23.2 (p=0.026)	No grade ≥3 toxicity in either arm
NORTHSTAR Trial (Phase II)	Phase II prospective	Single arm	EGFR+ (osimertinib)	Osimertinib + LCT	Pending	Pending	Well-tolerated; grade ≥3 AE 29% vs 16% (p=0.09)
Gan et al. 2014 (IJROBP)	Retrospective	Oligoprogressive	ALK+ (crizotinib)	SRT to oligoprogressive sites + continued TKI	Median TKI continuation: 6.5 months post-SRT	N/A	SRT can safely control extra-CNS oligoprogression in ALK+ NSCLC

Abbreviations: SBRT = stereotactic body radiotherapy; TKI = tyrosine kinase inhibitor; LCT = local consolidative therapy; EGFR = epidermal growth factor receptor; ALK = anaplastic lymphoma kinase; SRT = stereotactic radiotherapy; PFS = progression-free survival; OS = overall survival; AE = adverse events.

A pivotal secondary analysis of 98 metastatic NSCLC patients from the phase I KEYNOTE-001 pembrolizumab trial found that patients who had received any prior radiation therapy had significantly better PFS (HR 0.56; 95% CI 0.34–0.91) and OS (HR 0.58; 95% CI 0.36–0.94) compared to those who had not received prior radiation. This improvement was independent of PD-L1 expression status [27]. More recent translational work published in Nature Cancer (2025) demonstrated that SBRT sensitises immunologically 'cold' tumours (low TMB, null PD-L1 expression, or Wnt pathway mutations) to pembrolizumab, with significant T-cell clone expansion in both irradiated and distant tumour sites [28].

Table 3. Selected Ongoing Trials in Oligometastatic and Oligoprogressive NSCLC

Trial Name	Phase	Population	Comparison	Primary Endpoint	Status / Notes
SABR-COMET-3 (NCT03862911)	Phase III RCT	All solid tumors, ≤3 mets	SOC vs SOC + SABR	OS	Confirmatory of SABR-COMET; accruing
SABR-COMET-10 (NCT03721341)	Phase II/III RCT	All solid tumors, 4–10 mets	SOC vs SOC + SABR	OS	Exploring higher oligometastatic burden
NCT04970693 (Furmonertinib trial)	Phase II RCT	Stage IV NSCLC, oligoprogression after TKI	Furmonertinib ± RT	PFS	Evaluating 3rd-gen TKI + RT for oligoprogression
OligoCare (NCT03818503)	Prospective Registry	All OMD (ESTRO/EORTC)	Observational all OMD patterns	PFS, OS, patterns of care	International registry; heterogeneity characterization

Abbreviations: SOC = standard of care; SBRT/SABR = stereotactic body/ablative radiotherapy; OS = overall survival; PFS = progression-free survival; RT = radiotherapy; TKI = tyrosine kinase inhibitor; OMD = oligometastatic disease.

external beam radiotherapy (8 Gy × 1) for local control in spinal metastases [31]. For non-spinal bone metastases, SBRT to oligometastatic sites can be incorporated as part of definitive local therapy.

7.3 Adrenal Metastases

The adrenal gland is a recognised site of distant metastasis in NSCLC. Ablative SBRT to adrenal metastases can achieve local control rates of 70–90%, and in carefully selected patients with isolated adrenal oligometastatic disease, durable disease-free survival has been reported. Typical SBRT doses range from 40 Gy in 5 fractions to 60 Gy in 3 fractions, with careful attention to proximity of the stomach, bowel, and kidney.

7.4 Hepatic Metastases

Liver metastases from NSCLC are less common than from colorectal or other primaries, but occur in approximately 10–30% of patients. SBRT to liver metastases can achieve local control rates comparable to surgical resection in selected patients, with typical dose schedules ranging from 45–60 Gy in 3–6 fractions. The constraints on the liver (mean liver dose, V15, V20) and proximity to the bile duct, bowel, and stomach must be carefully respected.

8. Management Of Oligoprogressive Disease

Oligoprogression defined as radiological progression at a limited number of sites (typically ≤3) while other sites remain controlled under ongoing systemic therapy is a clinically distinct and increasingly recognised entity. Approximately 15–47% of patients on TKI therapy for EGFR-mutant or ALK-positive NSCLC will develop oligoprogressive rather than systemic progression, and a similar phenomenon is observed in patients on ICIs.

For TKI-treated patients, the rationale for SBRT to oligoprogressive sites is to ablate the resistant subclone (s) at the site (s) of progression while continuing the TKI, which maintains control of the remainder of the disease burden. By eradicating resistant clones before they can seed further sites, this approach may significantly prolong TKI efficacy. Multiple retrospective series and some prospective data support the feasibility and benefit of this approach, with extension of TKI use by a median of 6–22 months depending on the series [23, 24].

A critical caveat in EGFR-mutant oligoprogressive disease is the need to exclude systemic resistance mechanisms particularly T790M emergence (which dictates switch to osimertinib) or bypass pathway activation before committing to a local ablation strategy. Re-biopsy (tissue or liquid biopsy) of the progressing lesion is strongly recommended to guide this decision.

For ICI-treated patients with oligoprogression, the evidence is more limited and the biology is less well understood. The STOP trial (Stereotactic Ablative Radiation for Oligoprogressive Cancers), a randomised phase II study published in 2024, evaluated SBRT for oligoprogressive disease refractory to systemic therapy and reported promising outcomes. However, the interaction between ongoing ICI therapy and SBRT to oligoprogressive sites including potential disruption of immune equilibrium requires further study.

9. Technical Aspects of Radiotherapy Delivery in OM-NSCLC

The technical delivery of SBRT in OM-NSCLC demands a high level of departmental infrastructure, expertise, and quality assurance. Key technical elements include:

Dose and Fractionation: Dose-fractionation schedules vary by anatomic site. For pulmonary lesions, common regimens include 54 Gy/3 fractions (peripheral), 48–50 Gy/4 fractions, or 50 Gy/5 fractions. Central (perihilar) lesions require modified fractionation (e.g., 60 Gy/8 fractions or 50 Gy/5 fractions) to comply with dose constraints for the bronchial tree, oesophagus, and major blood vessels. For extrathoracic sites, dose-fractionation is tailored to site-specific constraints.

Motion Management: Intrafraction and interfraction tumour motion must be accounted for, particularly for lung and liver lesions. Respiratory gating, abdominal compression, breath-hold techniques (active breathing coordinator or deep inspiration breath-hold), and 4D-CT simulation are standard approaches.

Image Guidance: Daily online image-guided radiotherapy (IGRT) is mandatory, typically using cone-beam CT (CBCT) for setup verification. Fiducial markers may be implanted for lesions with poor soft-tissue contrast.

Planning Margins: Internal target volumes (ITV) are constructed to encompass the range of motion, and planning target volumes (PTV) incorporate setup uncertainties. Stereotactic setup with ≤5 mm PTV margins is standard in accredited SBRT programmes.

These technical requirements underscore that SBRT for OM-NSCLC should be delivered in experienced centres with dedicated expertise, advanced linac technology (preferably with kV-CBCT or MRI-guidance), and robust quality assurance programmes.

10. Ongoing and Future Trials

Despite the accumulating evidence, several critical questions remain unanswered, and numerous trials are ongoing to address them. These are summarised in Table 3.

SABR-COMET-3 (NCT03862911): A confirmatory phase III RCT across all solid tumour histologies enrolling patients with ≤3 metastatic lesions, designed to validate the SABR-COMET phase II results with OS as the primary endpoint.

SABR-COMET-10 (NCT03721341): Exploring whether the benefits of SABR extend to patients with 4–10 metastatic lesions, an expanded definition of oligometastatic disease.

OligoCare (NCT03818503): An international prospective observational registry under the EORTC-ESTRO RADiation InfrAstrucTure for Europe (E2-RADIatE) platform. This registry aims to characterise the heterogeneity of OMD, standardise reporting, and generate large-scale outcomes data to inform future patient selection.

NCT04970693 (Furmonertinib ± RT): A randomised phase II study evaluating furmonertinib (a third-generation EGFR TKI) as monotherapy versus combined with radiotherapy for oligoprogressive stage IV NSCLC patients following first-line TKI treatment.

11. Patient Selection: Who Benefits Most?

Identifying the ideal candidate for local ablative therapy in OM-NSCLC remains one of the most important and unresolved challenges. Several factors are associated with improved outcomes following LCT:

Performance status and comorbidities: ECOG 0–1 is generally required for entry into clinical trials. Significant comorbid pulmonary disease, prior chest irradiation, or poor organ reserve may limit technical feasibility and increase toxicity risk.

Metachronous versus synchronous OMD: Multiple analyses suggest that patients with metachronous OMD (arising after a disease-free interval) have more favourable outcomes than those with synchronous OMD at initial presentation, likely reflecting more indolent biology.

Response to systemic therapy: Patients achieving a partial or complete response to systemic therapy prior to LCT appear to derive greater benefit. The NRG-LU002 experience heavily weighted toward stable disease after immunotherapy highlights the importance of not offering LCT to patients with suboptimal systemic disease control.

Number and sites of metastases: Fewer metastatic sites are generally associated with better outcomes. The presence of CNS metastases, mediastinal nodal disease burden, and contralateral thoracic involvement may influence treatment decisions. All lesions should be technically amenable to ablative radiotherapy doses with acceptable organ-at-risk constraints.

Molecular profile: Driver-mutation-positive status particularly EGFR mutation appears to predict greater benefit from the combination of TKI plus SBRT based on SINDAS and supportive data. Routine molecular testing (EGFR, ALK, ROS1, KRAS, BRAF, MET exon 14, RET, NTRK) is essential prior to treatment planning.

Biomarkers for predicting benefit from LCT remain an active area of research. Circulating tumour DNA (ctDNA) dynamics, tumour mutational burden (TMB), PD-L1 expression, and circulating immune cell profiling are being explored as potential predictive tools in correlative studies embedded within ongoing trials.

In conclusion, the oligometastatic state in NSCLC represents a biologically and clinically distinct entity in which aggressive local ablative therapy most effectively delivered as SBRT can meaningfully improve progression-free and overall survival in carefully selected patients. The evidence base has evolved dramatically over the past decade, progressing from hypothesis and retrospective data through phase II randomised trials (Gomez et al., Iyengar et al., SABR-COMET) that demonstrate compelling OS benefits, to the first phase III positive randomised trial in the EGFR-mutant subgroup (SINDAS).

The provocative negative results of NRG-LU002 the largest trial to date, predominantly enrolling patients receiving immunotherapy serve as a sobering reminder that the oligometastatic paradigm is not universally applicable in the modern systemic therapy era. The interaction between radiotherapy and immunotherapy is complex and may be either synergistic or antagonistic depending on the clinical context, the immune status of residual disease, and the patient's overall immune phenotype.

Looking forward, the field must answer several critical questions: (i) Who are the ideal candidates for LCT in the immunotherapy era? (ii) Can biomarkers reliably identify patients most likely to benefit? (iii) What is the optimal dose-fractionation schedule and sequencing with systemic agents? (iv) Can the benefits of LCT extend beyond 5 metastatic lesions? (v) How should oligoprogression during ICI therapy be managed?

In the meantime, SBRT should be considered and discussed in a multidisciplinary tumour board setting for OM-NSCLC patients, particularly those with driver mutations, metachronous OMD, partial/complete response to systemic therapy, limited metastatic burden, and all lesions amenable to safe ablative radiotherapy. For driver-mutation-positive patients, especially EGFR-mutant disease, the combination of SBRT with TKI represents a high-level evidence-based strategy. For driver-mutation-negative patients receiving immunotherapy, the decision must be individualised, acknowledging the absence of clear benefit in the contemporary randomised evidence.

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Statement of Transparency and Principles

• The authors declare no conflict of interest.

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