REVIEW ARTICLE

Definitive Radiotherapy to the Primary Tumor in Stage IV NSCLC: A Consensus Statement From the International Association for the Study of Lung Cancer Advanced Radiation Technology Subcommittee

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ABSTRACT

The role of radiotherapy (RT) in stage IV NSCLC has traditionally been palliative; however, with advancements in systemic therapies and insights into the evolutionary processes underpinning advanced disease, the rationale for aggressive primary-tumor control has received renewed interest. This International Association for the Study of Lung Cancer (IASLC) consensus statement evaluates the current evidence for the role, timing, dosing, target volumes, and safety of primary-tumor RT in both actionable genomic alterations (AGA) and non-AGA metastatic NSCLC populations. The IASLC Advanced Radiation Technology

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subcommittee convened a multidisciplinary, international expert panel including radiation oncologists and medical oncologists from the IASLC Multidisciplinary Clinical Sciences Committee. Randomized studies published from 2010 to 2025 evaluating RT to the primary lung tumor in metastatic NSCLC populations (AGA and non-AGA) were identified through PubMed, and relevant published and presented abstracts were included. Evidence was synthesized and discussed to achieve consensus recommendations. In *EGFR*-mutant oligometastatic NSCLC, randomized phase III evidence supports early delivery of RT, conveyed as consolidation after induction systemic therapy, as a promising life-prolonging approach. In non-AGA populations, direct randomized evidence isolating the impact of primary irradiation remains limited. Emerging randomized data suggest dose escalation of definitive thoracic RT regimens may improve locoregional control compared with lower-dose approaches. Fractionation should be individualized to the primary tumor location to mitigate cardiopulmonary adverse events. Optimal target volumes remain uncertain, and the benefit of excluding involved thoracic lymph nodes has not yet been formally investigated in large, randomized trials. Safety data indicate toxicity is generally additive when RT is integrated with systemic agents; however, careful monitoring and recording of adverse events are important to ensure the addition of RT does not affect systemic therapy discontinuation rates. Definitive-dose RT to the primary lung tumor in metastatic NSCLC is supported by a growing biologic rationale and emerging trial data, with the strongest evidence in EGFR mutant populations. For patients without AGAs, preliminary findings are encouraging but insufficient for definitive treatment recommendations. The paucity of data necessitates prospective trials that isolate the contribution of primary-tumor RT, confirm its safety, and define the optimal RT sequencing, dose, and target volumes.

Keywords: Radiation therapy; TKI; Immunotherapy; Chemotherapy; Non-small cell lung cancer; Targeted therapy

Introduction

Advanced NSCLC encompasses a diverse spectrum of disease states. Patients are stratified and managed on the basis of histologic diagnosis, genomic profile, and burden of disease. Traditionally, the role of radiotherapy (RT) in metastatic NSCLC has been reserved for palliation of symptoms, including shortness of breath, cough, hemoptysis, and pain. In contrast, patients with a limited number of metastatic lesions are generally considered to have oligometastatic disease and are managed more aggressively.[1] Radiation is often used between cycles of systemic therapy with varying regimes depending on the location of the lesion treated, class of systemic therapy, the patient's performance status, and treatment intent. Experience in other cancer types, notably, nasopharyngeal and prostate cancer, has found a survival benefit in treating the primary tumor with higher "radical" radiation doses upfront to prevent the potential of further metastatic spread (Fig. 1).[2–4] Given that the primary tumor is a common source of symptomatology and a common site of first progression, early higher radiation doses may serve both treatment goals.

The distinction between management strategies for nonmetastatic and metastatic lung cancer has become less clear in the modern era, with the advent of more sensitive functional imaging such as positron emission tomography. In addition, advancements in systemic therapies have significantly improved survival in stage IV disease. In this context, there has been a shift toward integrating local therapies, particularly RT, with higher dose moving away from conventional low-dose palliative approaches. This evolving treatment paradigm is supported by emerging evidence on tumor progression and metastatic spread. For example, a longitudinal evolutionary analysis in patients with recurrent NSCLC provided valuable insight. Tissue samples from 19 patients were analyzed, with matched specimens from primary lymph node metastases and subsequent recurrence or progression. In 13 of these cases, dissemination originated solely from the primary tumor, highlighting its role as a driver of metastatic spread.[5]

The cytoreductive potential of radical RT is particularly important for patients with better prognoses, including those with tumors harboring actionable genomic alterations (AGA) and those responding to immunotherapy. A retrospective analysis of 143 patients with stage IV NSCLC receiving immunotherapy identified the lung primary as the site of first progression in 61% of cases, suggesting that there may be a role for proactive local control.[6] In patients whose best response was only stable disease, rates of progression can reach upward of 75%.[7] In patients with metastatic *EGFRm* NSCLC who develop resistance to first-line osimertinib, the lung is the initial site of disease progression in more than 60% of cases.[8]

Despite its increasing use in routine clinical practice, evidence supporting the use of radical doses of RT in metastatic NSCLC remains limited. To date, trials evaluating the potential benefit of radical lung irradiation in the metastatic setting have reported significant heterogeneity in design. Most of the evidence comes from the oligometastatic setting, in which many cases also receive local RT to all visible sites of disease. Despite

variations in trial design and clinical context, valuable insights can be drawn from the expanding body of literature. These developments highlight the need for further discussion and evaluation of the role of primary tumor RT in advanced NSCLC.

Evidence-based recommendations from the International Association for the Study of Lung Cancer (IASLC) Advanced Radiation Technology subcommittee provide an international perspective on the impact of radiation timing, dosing, and safety of radical RT and concurrent systemic therapies when treating the primary lung tumor in metastatic NSCLC. The Advanced Radiation Technology is a subcommittee of internationally recognized radiation oncologists from North and South America, Europe, and Asia-Pacific. Expert medical oncologists from IASLC subcommittees were included in this consensus statement. All experts were volunteers and members in good standing with the IASLC. Published randomized studies from 2010 to 2025 in both AGA and non-AGA metastatic NSCLC populations with patients who underwent RT to the primary lung tumor were included and accessed through the PubMed database. Published and presented abstracts were also included. Relevant studies that provided insight and evidence for each question were then discussed, and a consensus was reached. Herein, we present a consensus statement from a multidisciplinary, international panel of experts selected by the IASLC to address these important questions.

Role of RT in the Primary and Optimal Timing

Actionable Genomic Alterations

The addition of radical RT has been found to improve survival in *EGFRm* oligometastatic NSCLC treated with tyrosine kinase inhibitors (TKIs). The strongest evidence comes from Sun et al.[9] a multicenter phase III trial that randomized 118 patients with *EGFRm* oligometastatic NSCLC. Patients were randomized 1:1 to receive upfront thoracic RT (TRT: 60 gray [Gy] to the lung primary and positive regional lymph nodes) concurrently with a first-generation TKI versus first-generation TKI alone. In this study, the oligometastatic state was defined as involvement of three or more organs. RT to metastases at other sites was left to the discretion of the treating clinician. The TRT plus TKI group reported significantly improved progression-free survival (PFS) (hazard ratio [HR] 0.57, $p = 0.004$) and overall survival (OS) (HR 0.62, $p = 0.029$), with median PFS of 10.6 months versus 17.1 months and median OS of 26.2 months versus 34.4 months compared with the TKI group. When assessing the pattern of failure, the TRT plus TKI group reported a significantly better

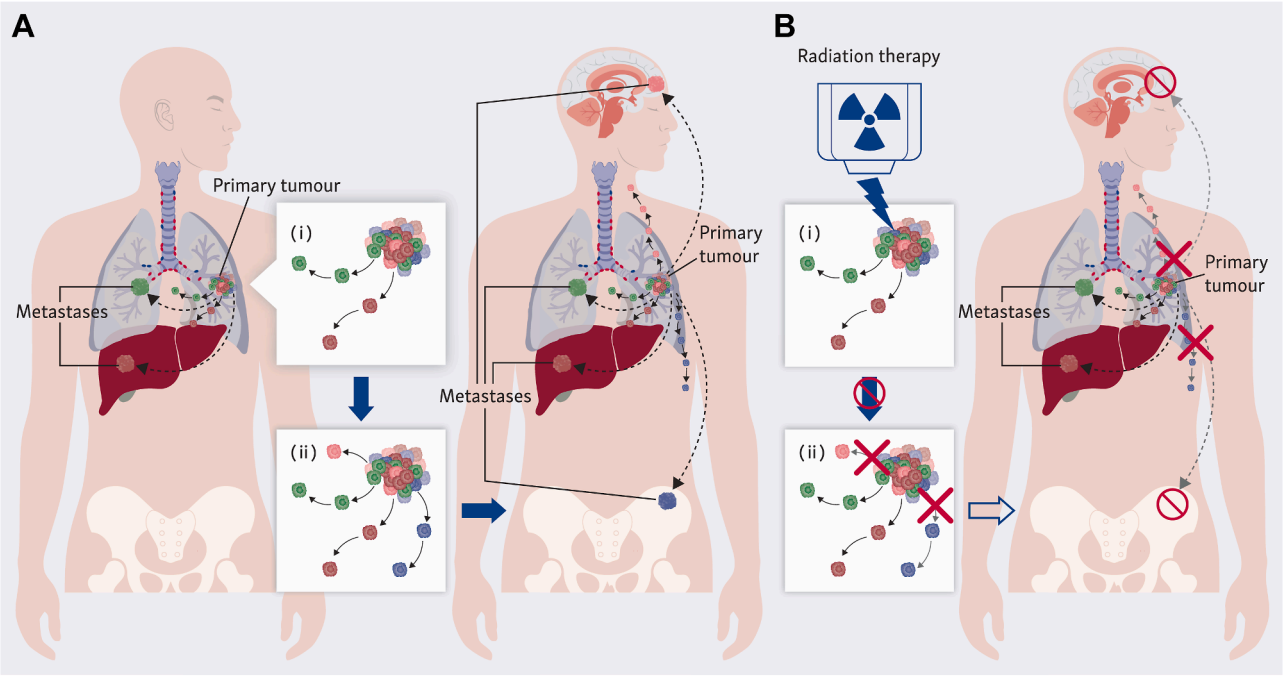

Figure 1. Clonal seeding and the cytoreductive role of radiotherapy in metastatic progression. *(A)* Schematic representation of clonal seeding from a heterogeneous primary lung tumor, indicating the way distinct subclones give rise to spatially and genetically diverse metastases. *(B)* Schematic representation illustrating cytoreductive potential of radiation therapy in limiting the seeding of distant metastasis.

locoregional PFS (HR 0.345, $p < 0.001$) but similar distant metastasis PFS and brain metastasis PFS. The survival benefits observed in the TRT plus TKI group were attributed to improved local control. Treatment was well tolerated; however, there was a higher incidence of severe treatment-related adverse events in the TRT plus TKI group (11.9% versus 5.1%, $p = 0.013$).

Furthermore, the randomized phase 3 SINDAS trial[10] investigated upfront RT plus first-generation TKI versus first-generation TKI alone in 133 patients with synchronous oligometastases (≤five metastases) from *EGFR* mutant adenocarcinoma. RT (25–40 Gy in five fractions) was delivered to all sites of metastases including the primary tumor, and involved regional lymph nodes identified on imaging. In total, 133 patients were recruited. Median PFS in the TKI-only arm was 12.5 months versus 20.2 months in the TKI plus RT arm; ($p < 0.001$). Median OS was 17.6 months versus 25.5 months ($p < 0.001$), respectively. Treatment across both arms was well tolerated, with TKI dose reductions required in three of 65 patients (4.6%) in the TKI-only arm and five of 68 (7.4%) in the TKI plus RT arm. Rates of grade 3 to 4 pneumonitis were two of 65 (3.1%) in the TKI-only arm and five of 68 (7.4%) in the TKI plus RT arm, respectively. No grade 5 events were reported. Although this trial indicated a survival benefit with the addition of RT, it did not isolate the specific contribution of treating the primary tumor because RT was also delivered to sites of oligometastatic disease.

Although these two randomized trials investigated RT as an early intervention, the optimal timing of primary irradiation remains unclear, and direct evidence comparing early with delayed RT is limited. Theoretically, oligoprogression reflects tumor escape from the selective pressure of systemic therapy and may represent a more aggressive disease phenotype, potentially associated with concurrent metastatic seeding events. In a real-world study, Wei et al.[11] reported in 79 patients with widespread metastatic *EGFRm* NSCLC, suggesting that PFS may be improved with earlier receipt of RT. Patients received stereotactic ablative body radiotherapy (SBRT or SABR) to the primary lung lesion either at the point of maximal response of EGFR-TKI (pre-emptive RT, n = 45) or at the time of oligoprogression after initiating *EGFR* therapy (delayed RT, n = 34). The following two endpoints were assessed: PFS1, defined as the time from initiation of TKI to disease progression, and PFS2, defined as the time from TKI initiation to progression after SBRT. The pre-emptive RT group had significantly better median PFS1 than did the delayed RT group (22.3 mo versus 12.9 mo, $p = 0.0031$). However, no significant difference in median OS was observed between the two groups (46.6 mo versus 51.3 mo, $p = 0.54$).

Consolidative RT Across Non-AGA NSCLC Subtypes

The rationale for consolidative RT is that prior cytoreduction of tumors with systemic therapy may reduce tumor burden, allowing smaller RT target volumes and potentially improving treatment tolerability. Furthermore, consolidative RT may facilitate better patient selection because early progressors can be identified and excluded before initiating RT. Selective treatment of nonresponsive lesions may reduce the number of lesions requiring RT, thereby further improving safety and limiting adverse events (Fig. 2). The phase II CURB randomized controlled trial indicated a significant benefit of SBRT in patients with oligoprogressive disease versus standard of care, which involved no change in management. Median PFS was significantly longer in the SBRT group (10.0 mo versus 2.2 mo, $p < 0.001$). Notably, 51 of the 59 patients (85%) enrolled had NSCLC without an AGA.[12] Conceptually, although systemic therapy can be associated with cumulative toxicities, patients are often at their fittest at diagnosis. This raises the question of whether consolidative, rather than upfront, RT is always the optimal approach from a tolerability perspective. However, the counterargument is that early RT may introduce treatment-related adverse events that could disrupt systemic therapy and compromise overall disease control.

At present, when RT is delivered early in the treatment course, the optimal duration of "induction" systemic therapy remains undefined. Although not specifically addressing RT to the primary tumor alone, the phase II trials by Iyengar et al.[13] and Gomez et al.[14] reported a PFS benefit and acceptable tolerability when RT was delivered as consolidation approximately 3 months after the initiation of systemic therapy, in patients with oligometastatic disease whose disease had not progressed. This 3-month interval is frequently adopted in study designs of consolidative RT, likely for pragmatic reasons, given it typically aligns with the timing of the initial response assessment scan. For example, the ongoing SARON randomized phase III trial (trial ID: NCT02417662) evaluates consolidation RT to both the primary and one to three oligometastatic sites after four cycles of induction systemic therapy. Taken together, and acknowledging the limited availability of direct comparative data, current evidence suggests that RT delivered either upfront or as consolidation after induction therapy may be preferable to treatment reserved at the time of oligoprogression.

Summary of Recommendations From the IASLC

The role of radical RT and optimal timing of irradiation of the primary tumor remains uncertain in

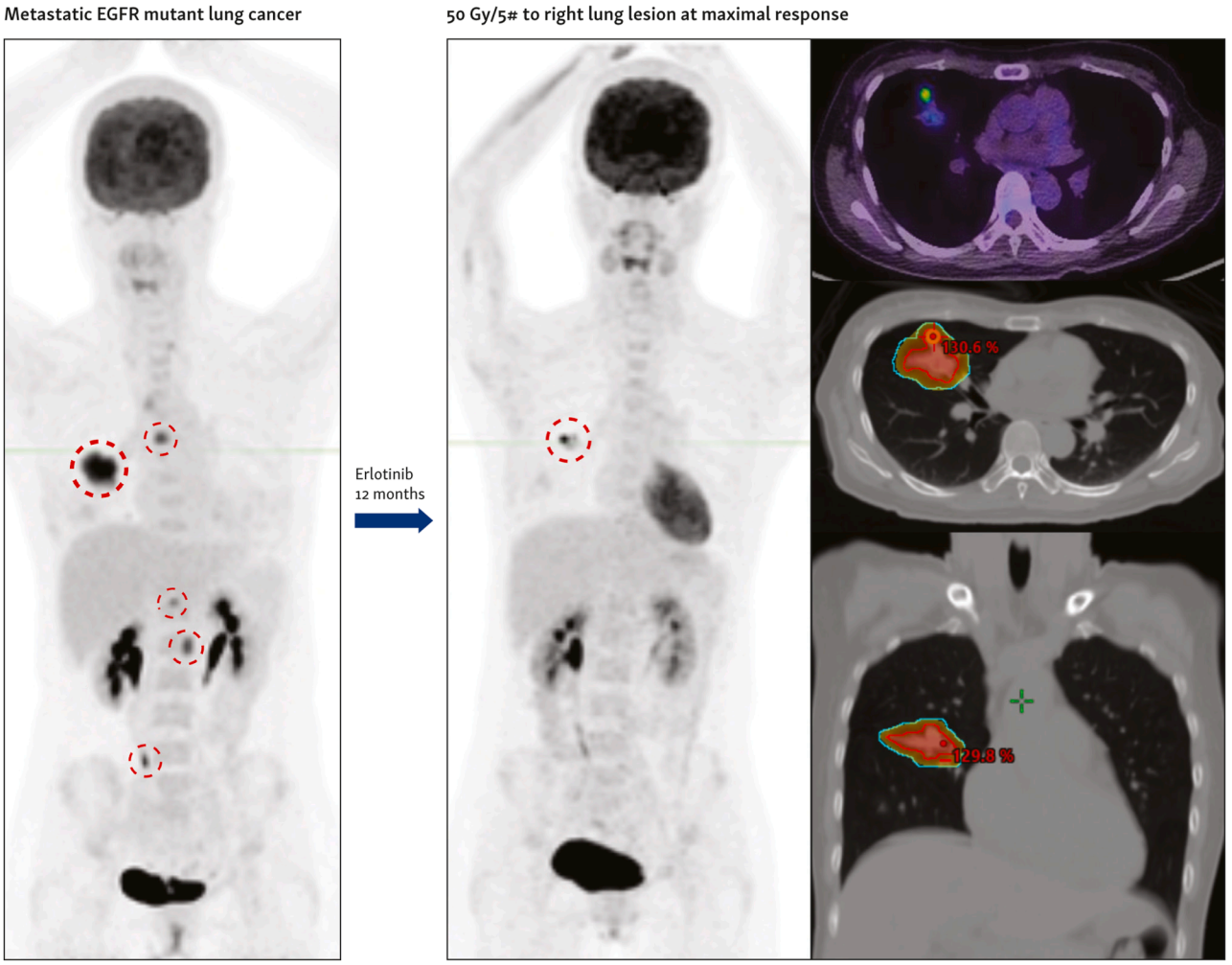

Figure 2. Schema of a patient with de novo metastatic *EGFRm* lung cancer who underwent TKI therapy (erlotinib) followed by SBRT (50 Gy/ five fractions) to residual right lung primary disease. Gy, gray; SBRT, stereotactic body radiotherapy; TKI, tyrosine kinase inhibitor.

patients without AGA. Although cross-trial comparisons should be interpreted with caution owing to variations in study design and patient populations, early RT, delivered as consolidation after induction systemic therapy, seems to be a promising approach, particularly in patients with AGA.

Optimal Radiation Dose and Target Volumes

NSCLC includes a spectrum of histologic diagnoses, primarily comprising adenocarcinoma and squamous cell carcinoma. Each histologic diagnosis has a distinctive disease pattern, with the propensity of squamous histologic diagnosis to manifest as centrally located thoracic primaries. RT dose delivery is location-dependent, with peripheral lung lesions typically amenable to hypofractionated regimens, whereas central or ultracentral lung lesions often require more conventionally fractionated schedules to minimize cardiopulmonary toxicities.

Jie et al.[15] provide the most compelling evidence to date supporting definitive doses to the primary tumor. In a recently published abstract, this randomized phase III study compared two doses of RT delivered upfront to patients with newly diagnosed oligometastatic NSCLC involving three or more metastatic organs. Patients were randomized 1:1 to receive either 63 Gy or 45 Gy, both administered concurrently with chemotherapy. A total of 340 patients were enrolled across 14 cancer centers; *EGFRm* status was wild-type or unknown. Median loco-regional PFS was improved in the 63 Gy group (18 mo; 95% confidence interval: 13.0 mo–23.0 mo), compared with the 45 Gy group (13 mo; 95%

confidence interval: 10.13 mo–15.87 mo). Loco-regional PFS rates at 1, 2, and 5 years were 62.9%, 36.9%, and 20.5%, respectively, in the 63 Gy arm versus 50.4%, 24.0%, and 5.5%, respectively, in the 45 Gy arm ($\times 2 = 9.997$, $p = 0.002$). OS at 1, 2, and 5 years was also improved in the higher-dose group: 70.2%, 41.3%, and 16.2% versus 52.2%, 30.7%, and 11.3%, respectively ($\times 2 = 3.874$, $p = 0.049$). However, higher rates of radiation esophagitis and grade 3 to 4 radiation pneumonitis were observed in the 63 Gy group ($p < 0.05$).

Despite growing evidence supporting the use of more intensive radiation doses in stage IV NSCLC, considerable debate remains regarding the optimal treatment volumes for the primary disease. When local control is the primary objective, inclusion of the adjacent mediastinal lymph nodes may be justified, particularly when the aim is to prevent the extrinsic compressive effects on critical structures, such as the local vasculature and the esophagus. However, in the context of RT combined with immunotherapy either in the first-line or subsequent treatment settings, emerging preclinical evidence suggests that preserving the immune axis between the tumor and its draining lymph nodes may be important for maximizing the efficacy of systemic immunotherapy and facilitating abscopal responses,[16,17] an area that remains under active investigation.

Furthermore, radiation-induced lymphopenia, a recognized consequence of radical thoracic irradiation, has been associated with inferior survival outcomes in NSCLC.[18–20]

This raises important considerations when deciding whether to exclude elective nodal volumes, particularly in patients receiving immunotherapy. If regional lymph nodes are deliberately spared to preserve immune function, the potential difficulty of re-irradiating the thorax or mediastinum in the event of symptomatic progression must also be weighed. To date, few trials have explicitly mandated exclusion of nodal volumes, often leaving treatment volume decisions to the discretion of the treating clinician (Fig. 3).

Summary of Recommendations From the IASLC

When considering RT for the primary lung tumor in stage IV NSCLC, current randomized data suggest that higher doses of radiation may confer improved outcomes. Fractionation schedules should be tailored to tumor location to minimize adverse events. Preclinical studies indicate that omitting involved lymph nodes from the RT field may enhance immunotherapy efficacy by preserving immune function; however, this approach has not yet been validated in prospective clinical trials.

The Optimal "Partnership" for Primary RT and Systemic Therapy

Systemic therapy options for patients with metastatic NSCLC are rapidly expanding. Immune checkpoint inhibitors (ICIs) are the current standard first-line therapy for patients without AGA, either alone or in combination with platinum-based chemotherapies.[21–24] For patients harboring AGA, the treatment landscape is far more complex, including monotherapy TKI and TKI plus chemotherapy. Extensive preclinical research has reported the potential synergistic effects of radiation and immune checkpoint inhibition when ICI is given as consolidation treatment, primarily through proinflammatory (antigen presentation) effects and mitigation of myeloid immunosuppression. This synergy has been clinically validated in phase III trials, most notably the PACIFIC trial,[25] which established the benefit of consolidative immunotherapy after chemo-RT in locally advanced NSCLC.

In contrast to preclinical studies suggesting synergy, clinical outcomes with concurrent chemo-RT and ICIs have been disappointing.[26,27] RT delivered during single-agent immunotherapy seems generally safe and tolerable,[28] but adverse events tend to be higher when delivered with concurrent rather than sequential administration.[27,29] This observation holds true even when using SBRT and smaller-volume radical RT. A systematic review and consensus recommendations from the EORTC-ESTRO OligoCare consortium,[30] comprising an international and interdisciplinary expert group in stereotactic RT, identified a clinically relevant risk of toxicity when SBRT is combined with dual-agent immunotherapy (nivolumab plus ipilimumab). Safety concerns were raised in the phase 1 COSINR study,[31] which evaluated 50 Gy/5# to patients with centrally located lung tumors, followed by dual checkpoint inhibition (ipilimumab and nivolumab). Two patients (two/19) experienced grade 4 pneumonitis, prompting dose de-escalation. Notably, such high-grade toxicity was not observed in the central tumor cohort when therapy was delivered concurrently. In peripheral lung tumors, the combination of SBRT and concurrent immunotherapy seems more tolerable, although additive in toxicity. In SWOG/NRG S1914,[32] a regimen combining neoadjuvant, concurrent and adjuvant atezolizumab caused grade 3 or higher adverse events in 12%, compared with 2% with SBRT alone. Similarly, in KEYNOTE-867,[33] concurrent and adjuvant pembrolizumab was associated with a grade 3 or higher adverse event rate of 20.4% versus 3.7% with SBRT alone. Neither trial improved oncological outcomes. Taken together, these findings suggest that the optimal sequencing of SBRT and immunotherapy may ultimately depend on tumor location and patient tolerability, highlighting the need for

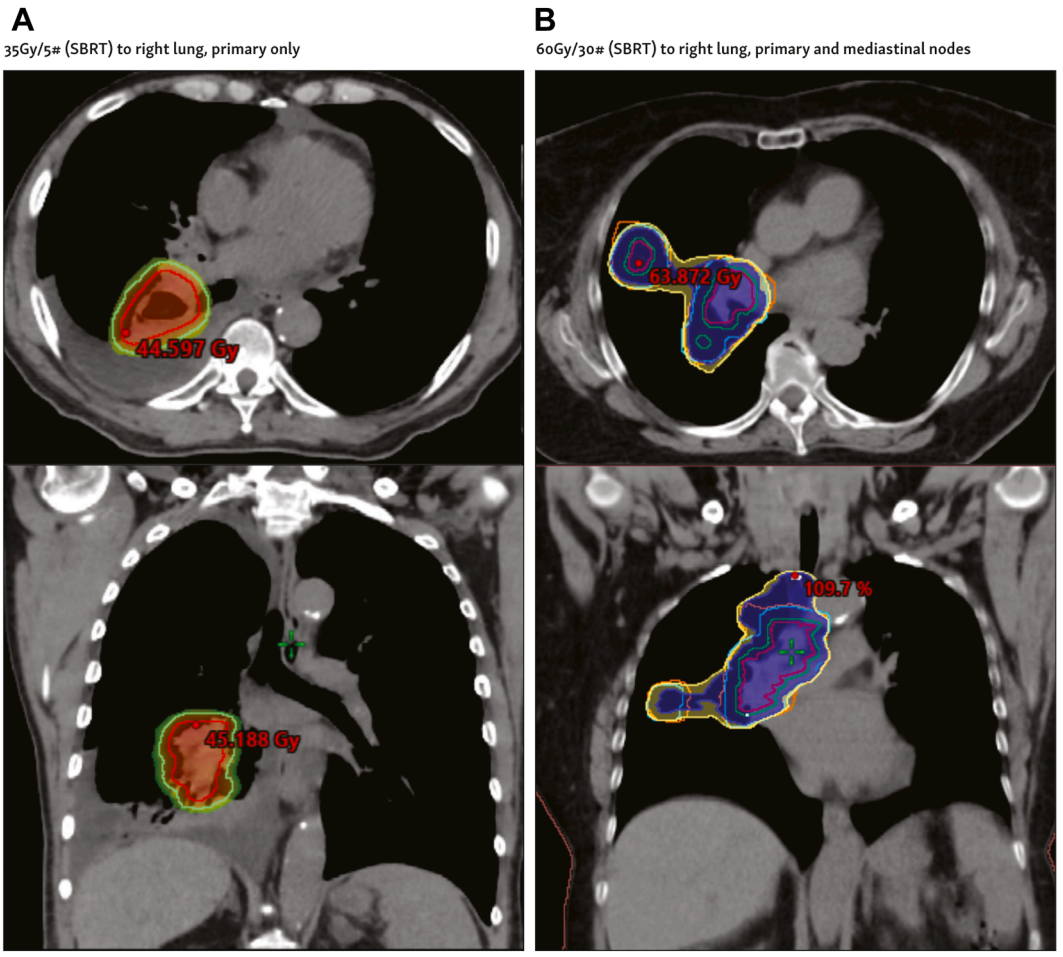

Figure 3. Planning CT comparison illustrating variations in radiotherapy dose and target volume in metastatic NSCLC. Planning CT scans from two patients with metastatic NSCLC receiving radiotherapy was planned to the primary tumor. The patient in panel *(A)* received 35 Gy/5# to the lung primary, and the patient in panel *(B)* received 60 Gy/30# to the lung primary and adjacent mediastinal lymph nodes. The comparison highlights that when radiotherapy is confined to the primary tumor, incidental dose to the mediastinal lymph nodes is limited. CT, computed tomography; Gy, gray; SBRT, stereotactic body radiotherapy.

careful patient selection and further prospective evaluation.

TKIs, either as monotherapy or in combination with other agents such as platinum-based chemotherapy or novel agents such as amivantamab, a bispecific antibody targeting *EGFR* and MET, form the backbone of treatment for patients with AGAs such as *EGFRm*.[34] Unlike checkpoint inhibitors, the mechanism of interaction between radiation and TKIs remains poorly defined. Preclinical studies have found the immune-modulatory role of *EGFR* signaling, including the downregulation of MHC class I and II expression, upregulation of PD-L1, increased activity of regulatory T cells, and suppression of cytotoxic T cells function.[35]

The clinical benefit of combining RT with TKIs, as indicated in the SINDAS trial[10] and the study by Sun et al.[9] is promising and seems to be associated with an acceptable adverse event profile. In these studies, the rates of radiation-induced pneumonitis were additive rather than synergistically amplified.[9] However, interpretation is limited by the predominant use of earlier generation TKIs, which are less likely to cause pneumonitis than are third-generation drugs. In addition, a retrospective analysis of an international multicenter database[36] of 158 patients with metastatic cancer treated with SBRT and concurrent targeted therapies (TT) found no significant difference in OS or PFS between patients who had temporary interruption of TT during SBRT and those who did not. Importantly, no differences were observed in the rates of grade 3 or higher acute or late SBRT-related toxicity.

Although not addressing the use of radical RT to the primary tumor specifically, consensus recommendations from the EORTC-ESTRO OligoCare consortium[30]

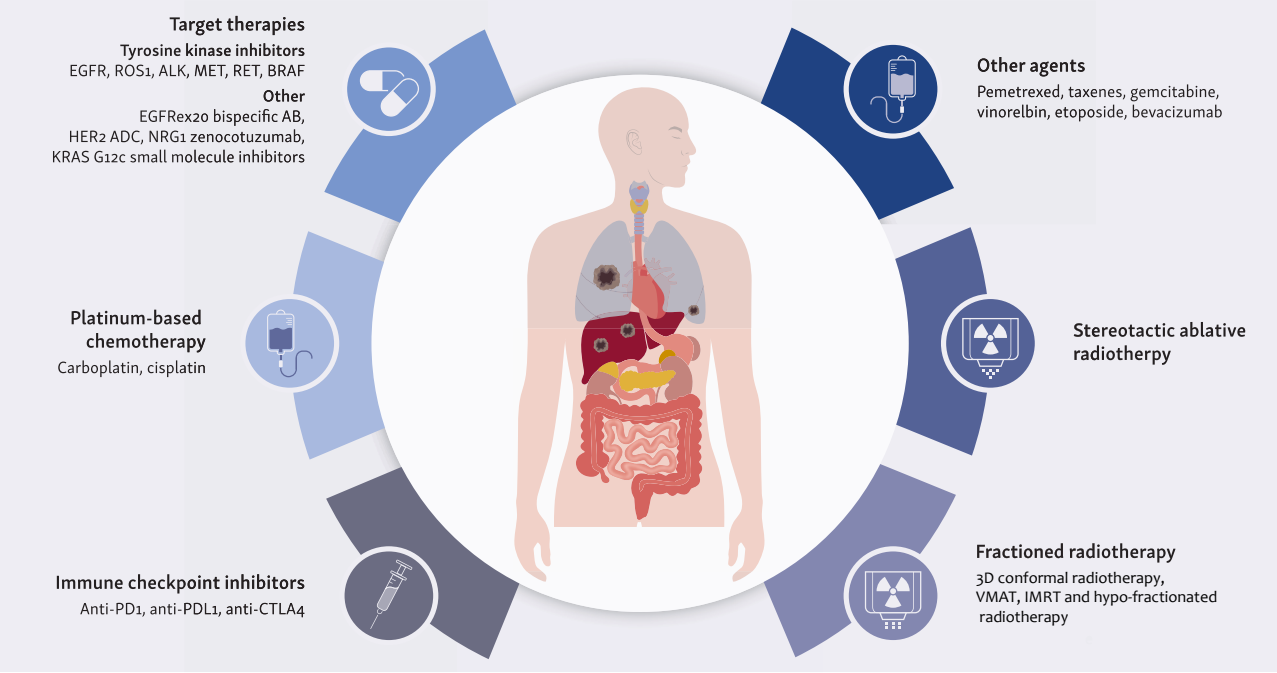

Figure 4. Overview of approved systemic therapies and their potential interactions with radiotherapy in metastatic NSCLC. ADC, antibody-drug conjugate; IMRT, intensity-modulated radiation therapy; RT, radiation therapy; VMAT, volumetric modulated arc therapy.

provide guidance on the integration of systemic therapies with metastases-directed SBRT. The panel recommended that certain systemic agents, including anti-*EGFR* antibodies, the combination of nivolumab plus ipilimumab, BRAF and MEK inhibitors, and multikinase inhibitors should not be administered on the same day as SBRT. Specifically, multikinase inhibitors and BRAF and MEK inhibitors should be withheld for a maximum of 2 weeks. To allow pharmokinetic biodistribution, antibodies such as anti-*EGFR* or ipilimumab plus nivolumab should be interrupted for a minimum of 1 week before or after SBRT. Importantly, there was a strong consensus that SBRT dose and fractionation should not be modified on the basis of the type of TT or immunotherapy used, regardless of the anatomical location of the lesion or proximity to organs at risk. Prospective data from ongoing registry studies, including the EORTC-ESTRO OligoCare study (NCT03818503) and the multi-institutional TOaSTT prospective registry,[37] are eagerly awaited to inform clinical practice and future trial design (Fig. 4)

Finally, as with any combination treatment involving RT, there is uncertainty whether the observed benefit arises from a true synergistic interaction between modalities or simply from the cytoreductive activity of radiation. Given the natural history of mutation-driven and non–mutation-driven lung cancers and the suggestion that irradiation of the primary tumor may confer benefit in both patient populations, it is possible that no universally "optimal" combinational strategy exists. Instead, treatment approaches may need to be tailored to individual tumor biology, disease burden, and patient-specific factors.

Summary of Recommendations From the IASLC

Several phase II and phase III trials have observed a benefit from adding RT to the primary tumor during or after TKI. However, concerns have emerged regarding the combination of large volumes of radical RT with concurrent immunotherapy or chemo-immunotherapy. RT should ideally be delivered without causing significant delays or interruptions to systemic treatment. Pneumonitis rates seem additive rather than synergistically amplified by combined drug and radiation effects; however, these risks should be carefully considered when combining multiple treatment modalities.

Summary and Future Directions

The potential benefit of radical RT to the primary lung tumor in metastatic NSCLC is supported by an evolving and growing body of evidence. Although current data remain limited, emerging results are encouraging. Evidence from several phase II and phase III randomized trials in other malignancies, including nasopharyngeal and prostate cancer, have reported a survival benefit of radical doses of RT to the primary tumor in stage IV disease.[2–4] Patients included in the

Table 1. Summary of Consensus Statements for Radiotherapy to the Primary Lung Cancer in Stage IV Disease

Clinical Question	Consensus Statement
Optimal primary RT timing	Early RT, delivered as consolidation following induction systemic therapy, appears to be a promising approach, particularly in patients with AGA. Optimal timing of irradiation of the primary tumour remains uncertain in patients without AGA.
Optimal RT dose and treatment volumes	Higher doses of RT may confer improved outcomes. Fractionation schedules should be tailored to tumor location to minimize adverse events. RT volumes, in particular omitting involved lymph nodes (to enhance immunotherapy efficacy), has not yet been validated in prospective clinical trials.
Partnering primary RT and systemic therapies	RT should be delivered without causing significant delays or interruptions to systemic treatment. Pneumonitis rates appear additive rather than synergistically amplified by combined drug and radiation effects. Risks must be carefully considered when combining multiple treatment modalities.

AGA, actionable genomic alteration; RT, radiotherapy.

studies, both in NSCLC and other tumor types, that indicated benefit had moderately good performance status and low volume of disease burden (≤three organ systems involved). A summary of the consensus statements is listed in Table 1.

The biological rationale underlying the observed benefit of irradiating the primary tumor in metastatic disease is increasingly supported by insights into the evolutionary history of metastatic disease. In several cancer types, polyclonal seeding of metastases from the primary tumor is now recognized as a common mechanism of disease progression. Intratumoral genetic diversity within tumors can act as a substrate for natural selection and tumor evolution.[38] In lung cancer specifically, this implies that polyphyletic dissemination can continue over time, contributing to disease spread and therapeutic resistance.[38,39] Whole genome sequencing studies have documented both mono- and polyclonal patterns of metastatic seeding in cancer of the lung,[40] pancreas,[41] prostate,[42] and breast.[43] The TRACERx study[5] provides the most comprehensive evidence to date in NSCLC. Among 126 tumors profiled, 25% exhibited early clonal divergence of metastasis from the primary tumor. Early divergence was more common in those who were smokers at diagnosis, potentially highlighting a rationale for early RT to the primary tumor in mutation-negative populations. In addition, 32% of patients revealed polyclonal tumor spread from the primary, which was associated with extrathoracic dissemination and worse survival outcomes. The authors hypothesized that the genetic diversity underpinning polyclonal dissemination confers a fitness advantage, enabling adaptation of metastasis clones to diverse microenvironments. Interestingly, platinum-based chemotherapy was also found to act as a mutagenic driver, an observation consistent with findings in other studies.[44–46] Radical irradiation of the primary tumor may therefore reduce the potential polyclonal metastatic dissemination and mitigate the mutagenic effects of systemic therapy.[38,39]

Tumor heterogeneity is a key contributor to variable responses to systemic therapy. Given the logistical and clinical challenges of performing serial on-treatment biopsies, noninvasive monitoring techniques such as circulating tumor DNA sequencing may provide critical insights. Tracking the dynamics—or disappearance—of circulating tumor DNA after RT to the primary tumor could serve as a surrogate for assessing the biological efficacy of local control. In parallel, advances in circulating cell-free DNA methylation profiling offer additional promise. Emerging in silico deconvolution techniques now enable the mapping of methylation signatures to specific tissue types, potentially allowing the inference of the anatomical origin of treatment-resistant clones.[47] These tools may collectively help indicate the systemic impact of RT to the primary tumor and guide future strategies for managing metastatic NSCLC.

Although radical lung RT is generally well tolerated, its toxicity is additive to that of systemic therapies. Given that not all primary lesions are accessible for biopsy and that tumor heterogeneity and sampling limitations pose a challenge, noninvasive imaging biomarkers are emerging as promising tools to guide patient selection for RT to the tumor. This is particularly relevant in patients with NSCLC with PD-L1 expression of 50% or higher, who may experience durable responses to ICIs. Sun et al.[48] developed a CD8 radiomic score based on computed tomography-based tumor features, trained on a large pan-tumor data set with matched computed tomography scans and RNA sequencing data. The score estimates the degree of CD8 T-cell infiltration within the tumor microenvironment at an individual lesion level. Results revealed that both the entropy of lesion distribution and extreme minimum values of the score were associated with PFS and OS.[49] These findings suggest that CD8 radiomic scoring could aid in stratifying immunotherapy

responsiveness and identify patients who may derive additional benefit from RT to the primary tumor. However, calculating radiomic scores is time-consuming, requiring the contouring of lesions within RT planning software and extraction and calculation of radiomic features from third-party platforms. The emergence of positron emission tomography-labeled tracers that provide a functional and quantitative visualization of CD8+ T cells may impart a streamlined workflow; however, it remains to be tested and validated in large prospective studies.[50]

Limitations

The clinical adoption of radical RT to the primary tumor in metastatic NSCLC remains an evolving and actively investigated area. The most significant limitation in providing strong, actionable recommendations is the paucity of high-quality randomized controlled trials, especially in non-AGA settings. Furthermore, when multiple metastases are irradiated alongside the primary tumor, it is inherently problematic to determine the contribution of primary tumor irradiation to tumor control and toxicity, especially in the non-AGA cohort of patients. As such, high-quality data from the oligometastatic setting (where all disease sites were irradiated) were excluded from this consensus statement. Given the complexity of extrapolating data across multiple heterogeneous studies and the potential toxicities involved, these cases should be discussed at a multidisciplinary tumor board review.

Future studies should seek to isolate the impact of radical RT on the primary tumor, ideally by randomizing patients to receive radical RT to the primary tumor versus standard-of-care systemic therapy alone. Comprehensive toxicity monitoring, including rates of systemic therapy discontinuation or dose reduction, should be recorded. Currently, several phase I to III trials are actively investigating the role of primary RT in metastatic NSCLC. There is, however, considerable heterogeneity in terms of the timing of radiation, dose, and fractionation, and whether additional metastases are also irradiated (Table 2).

Conclusion

At present, the role of radical RT to the primary tumor in stage IV NSCLC is well established for palliation in patients with symptomatic disease. However, its use with the intent of achieving oncological benefits beyond those of systemic therapy alone is still evolving. The most robust evidence to date supports its role in patients with AGA. Preliminary data in patients without AGAs are encouraging, but definitive conclusions await the results of ongoing phase III trials specifically addressing this subgroup. This IASLC consensus statement provides practical guidance on key aspects of integrating RT to the primary tumor in stage IV NSCLC, including appropriate sequencing with systemic therapies, optimal radiation dosing and target volumes, and anticipated safety considerations.

CRediT Authorship Contribution Statement

Ryan McMahon: Conceptualization, Methods, Writing - original draft, Writing - review and editing.

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Table 2. Ongoing Clinical Trials Investigating Radiotherapy to the Primary Lung Tumor in Stage IV NSCLC

Trial Name	Phase	Patients (no.)	Actionable Mutations	Randomized	Primary Radiation Dose(s)	Primary Tumour (RT)	Other Metastasis (RT)	RT Timing	Systemic Therapy	Completion Date	Trial ID
NIRVANA-Lung	III	460	No	Yes	18Gy/3#	Yes	Yes	Upfront	Chemotherapy Immunotherapy	Dec-26	NCT03774732
PRIME-Lung	I	40	No	Yes	36Gy/12# 40Gy/15# 35-50Gy/5#	Yes	No	Upfront	Chemotherapy Immunotherapy	Mar-26	NCT05222087
PRIME-Lung	III	420	No	Yes	36Gy/12# 40Gy/15# 35-50Gy/5#	Yes	No	Upfront	Chemotherapy Immunotherapy	Jan-29	NCT07135882
TOURIST (PRINCE)	III	472	No	Yes	36Gy/12# 39Gy/13#	Yes	No	Upfront	Chemotherapy Immunotherapy	Dec-27	ISRCTN17123858
DRO2301	II	48	No	No	Not Stated	Yes	No	Upfront or within 6 months	Chemotherapy Immunotherapy	Feb-29	NCT06262321
MARS	III	162	No	Yes	36Gy/12#	Yes	No	3 Mo post Chemo/IO	Chemotherapy Immunotherapy	Feb-26	NCT04530708
salVage	III	128	Yes	Yes	Surgery or Radiotherapy (SBRT)	Yes	Yes	Patients responding post 3 cycles of SoC systemic therapy	Targeted therapy or Chemo/IO	Nov-27	NCT06114108
CHESS	II	96	No	No	Surgery or Radiotherapy 60-66Gy/30-33#	Yes	Yes	Patients responding post 3 mo of systemic therapy	Chemotherapy Immunotherapy	Dec-26	NCT03965468
HALT	II	113	Yes	Yes	SBRT: Site Dependant	Yes (not mandated)	Yes	Oligoprogression	TKI	Dec-26	ISRCTN53398136

RT, radiotherapy; SBRT, stereotactic body radiotherapy; SoC, standard of care; TKI, tyrosine kinase inhibitor.

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