Consensus

International consensus on radiotherapy in metastatic non-small cell lung cancer

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Background: Lung cancer is the leading cause of cancer-related death worldwide, with non-small cell lung cancer (NSCLC) accounting for most cases. While radiotherapy has historically served as a palliative modality in metastatic NSCLC, considerable advances in its technology and the continuous development of cutting-edge therapeutic agents, such as targeted therapy and immune checkpoint inhibitors (ICIs), are increasing its role in the multi-disciplinary management of the disease.

Methods: International radiotherapy experts were convened to consider and reach consensuses on the clinical utilities of radiotherapy in metastatic NSCLC, with the aim to provide patient-focused, up to date, evidence-based, recommendations to assist cancer specialists in the management of patients with metastatic NSCLC worldwide.

Results: Timely radiotherapy can offer rapid symptom alleviation and allow subsequent aggressive treatment approaches in patients with heavy tumor burden and/or oncologic emergencies. In addition, appropriate incorporation of radiotherapy as concurrent, consolidation, or salvage therapy makes it possible to achieve long-term survival, or even cure, for patients with oligo-metastatic disease. Cranial radiotherapy plays an important role in the management of brain metastasis, potentially augmenting the response and prolonging survival associated with targeted agents and ICIs. However, key questions remain, such as the appropriate choice of radiation techniques, optimal sequence of systemic therapies and radiotherapy, and optimal patient selection for such combination strategies. Although a strong rationale for combining radiotherapy and ICIs exists, its optimal parameters in this setting remain to be established.

Conclusions: In the modern era, radiotherapy serves not only as a palliative tool in metastatic NSCLC, but also plays active roles in patients with oligo-focal disease, CNS metastasis and receiving ICIs.

Keywords: Non-small cell lung cancer; radiotherapy; oligo-metastasis; brain metastasis; immune checkpoint inhibitor

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide. It is estimated 2.2 million new lung cancer cases were diagnosed globally in 2021 and 1.8 million people will die from this disease (1). Non-small cell lung cancer (NSCLC) is the most common pathological type of lung cancer, accounting for approximately 85% of all cases (2), and as most patients are diagnosed at an advanced stage, the prognosis is poor (2). Systemic therapy is the main treatment of metastatic NSCLC, while radiotherapy is conventionally used to alleviate symptoms and mitigate oncological emergencies. However, with considerable advances in radiotherapy technology and the continued development of cutting-edge systemic therapies, such as targeting agents and immune checkpoint inhibitors (ICIs), the role and scope of radiotherapy in metastatic NSCLC

are evolving.

The last two decades have brought remarkable advances in the medical treatments of NSCLC, such as targeted therapy and immunotherapy. These methods not only greatly improve patient survival, but also increase the role of radiotherapy in metastatic disease (3). For example, timely radiotherapy may improve the general condition of patients with primary severe symptoms caused by tumor emergencies or metastases, rendering them eligible for subsequent aggressive therapeutic approaches.

Although the term "oligo-metastasis" was first coined by Hellman and Weichselbaum in the 1990s, a common definition for this clinical entity remains a matter of debate (4-7). Accumulating data has demonstrated superior survival in patients with oligo-metastatic disease compared to multi-metastatic disease (8-10). Consolidative stereotactic body radiotherapy (SBRT) following induction and prior to maintenance chemotherapy could triple progression-free survival (PFS) in patients with oligo-metastatic disease compared with maintenance chemotherapy alone (11). Similarly, in patients with three or fewer metastases, consolidative radiotherapy or surgery extended the median PFS from 4.4 to 14.2 months and median overall survival (OS) from 17.0 to 41.2 months (12). Although these results are appealing, the role of radiotherapy in oligo-metastatic NSCLC warrants validation in prospective clinical trials (13).

Radiotherapy has long been the standard of care for NSCLC patients with central nervous system (CNS) metastasis due its efficacy and the poor penetrance of cytotoxic agents through the blood brain barrier (BBB). The introduction of tyrosine kinase inhibitors (TKIs) and ICIs has resulted in impressive improvement in survival outcomes for patients with CNS metastasis (14-17), although the mechanisms underlying their synergistic anti-tumor effect with radiotherapy have not been elucidated (18-20). The clinical value, optimal timing, and technology of cranial radiotherapy (CRT) for CNS metastasis remains to be established.

The treatment paradigm for metastatic NSCLC has been rapidly transformed by the advent of ICI's, which have become a new standard of care in first-line settings (21-23). The synergistic anti-tumor effect of radiation and immunotherapy has formed the basis of several prospective trials evaluating the safety and efficacy of this combination therapeutic strategy (13,24-28). As different dose-fractionation regimens have been found to result in heterogeneous immunologic effects, it is of clinical importance to explore the optimal regimen to maximize the efficacy of combined radiotherapy and ICI therapy.

The role of radiotherapy has shifted from palliative care alone to therapy with curative intent in a subgroup of patients with metastatic NSCLC. In the era of precision medicine, the formulation of individualized radiotherapy strategies incorporating both clinical expertise and patient values poses a significant challenge to radiation oncologists. Herein, we invited multiple international lung cancer experts to weigh in and address these important issues. The resultant group consensuses are presented below and summarized in *Table 1*.

Palliative radiotherapy

Consensus 1.1: Palliative radiotherapy is a safe and effective approach for patients who present with oncologic emergencies or cancer-related severe symptoms

Radiotherapy is known to have beneficial effects in the palliative treatment of metastatic NSCLC, and some data suggest potential survival improvement (29). Despite the increasing use of chemotherapy in the palliative setting, local radiotherapy is an established option to achieve rapid, effective symptom control with few side effects and expedient improvement in overall patient status. Oncologic emergencies and cancer-related severe symptoms are two clinical scenarios in which the employment of timely radiotherapy is crucial.

Among patients diagnosed with malignancies, some will experience an acute condition caused by cancer or its treatment and require rapid intervention to avoid death or severe permanent damage, termed an oncological emergency (30,31). The manifestations are diverse, ranging from mechanical obstruction due to tumor growth to metabolic derangements due to abnormal tumor secretions. Local radiotherapy is conventionally employed in structural and obstructive oncologic emergencies, such as superior vena cava syndrome (SVCS), metastatic spinal cord compression (MSCC), hemoptysis, malignant airway obstruction (MAO), and brain metastases (BMs) with impending herniation. Previous data show a high incidence of oncological emergencies in metastatic NSCLC. At diagnosis, SVCS is present in 1.7% of NSCLC cases (32) and approximately 28% of patients with metastatic NSCLC develop MSCC (33). Hemoptysis and MAO are present in more than 20–30% of NSCLC patients, respectively (34,35). In addition to oncologic emergencies, the occurrence of cancer-related severe symptoms such as pain, cough, or

Table 1 The resultant group consensuses

No.	Item	Consensus
1	Palliative radiotherapy	Palliative radiotherapy is a safe and effective approach for patients presenting with oncologic emergencies or cancer-related severe symptoms
2	Oligo-focal disease	Oligo-focal disease states, which manifest as oligo-metastatic disease, oligo-residual disease, or oligo-progressive disease, are characterized by limited tumor lesions and relatively favorable oncologic outcomes
		PET/CT should be considered and encouraged in the process of identifying patients with oligo-focal disease states
		Concurrent radiotherapy in combination with optimal systemic therapy could provide additional survival benefit for NSCLC patients with oligo-metastatic disease
		Consolidative radiotherapy may improve survival for patients with oligo-residual disease after certain systemic therapy
		For patients who develop oligo-progressive disease after acquired resistance to targeted therapy or ICIs, salvage radiotherapy could prolong the time to treatment failure and may potentially improve OS
		Multisite SBRT targeting oligo-focal tumor lesions could provide additional clinical benefit for selected patients
3	CNS metastases	For oncogene-addicted NSCLC with baseline BMs, upfront CRT in combination with corresponding TKIs may provide additional survival benefit among selected patients with favorable profiles (especially oligo-metastatic BMs). Otherwise, next-generation TKIs with stronger potency against BMs should be preferred as first-line treatment and upfront whole brain radiotherapy may be deferred
		CRT in combination with ICIs could be safe and provide additional clinical values in selected patients with driver mutation negative NSCLC. However, evaluation on a case-by-case basis is warranted
		The decision to use SRS or WBRT should be individualized based on clinical expertise, patient values, and logistical considerations
		CRT is generally not recommended for patients with leptomeningeal metastasis for improving survival
4	Combining radiation and ICIs	Appropriate radiation therapy can enhance the efficacy of ICIs with manageable toxicities in patients with metastatic NSCLC
		Different dose-fractionation regimens can have diverse immunologic effects in modulation of the tumor microenvironment and could impact the treatment efficacy of combinational therapy

CNS, central nervous system; ICI, immune checkpoint inhibitor; PET/CT, positron emission tomography/computed tomography; NSCLC, non-small cell lung cancer; OS, overall survival; SBRT, stereotactic body radiotherapy; BMs, brain metastases; CRT, cranial radiotherapy; TKI, tyrosine kinase inhibitor; SRS, stereotactic radiosurgery; WBRT, whole brain radiation therapy.

hemoptysis, commonly due to loco-regional progression of primary or metastatic tumor burden, is another indication for radiotherapy (36). Once these oncologic emergencies or cancer-related severe symptoms occur, performance status (PS) is immediately adversely impacted, which prohibits the use of aggressive treatment for metastatic NSCLC. However, the timely intervention of palliative radiotherapy can prevent and reduce this barrier by offering fast, efficient symptom relief, after which the general condition of the patient can be optimized for subsequent treatment approaches.

A wealth of studies has evaluated the efficacy and safety of palliative radiotherapy (37-40). A recent meta-analysis including 14 randomized controlled studies and 3,576 patients assessed the effects of different regimens on improving thoracic symptoms and prolonging the survival of patients (36). The results showed a symptom response rate ranging from 43% to 86%, median OS ranging from 5.9 to 8.5 months, and 1-year survival rate ranging from 20.0% to 40.0%. In addition, a retrospective study reviewed the records of 140 patients treated with split-course palliative thoracic radiotherapy (PTR), and symptomatic relief was observed in 52–84% of patients, with no grade 3 to 5 toxicities (41). Pain relief was experienced by approximately 86% of patients treated with palliative radiotherapy for painful local recurrence (42), and this treatment has been proven to be cost-effective (43). In patients who developed SVCS, a symptom relief

rate could be achieved in 63.0% patients with palliative radiotherapy (44). For patients with MSCC, SBRT provided a significant rate of pain relief and objective local control of over 80%, with a low (<1%) incidence of myelopathy (45). A recent study evaluated the effect of palliative external beam radiotherapy (EBRT) on MAO in 75 patients with lung cancer and analyzed the influencing factors (46). Dyspnea was improved in 61.3% of the participants, and tumor size was partially decreased in 52%. Symptom improvement was observed in most participants and was significantly related to the time taken to initiate EBRT, which indicates the importance of timely radiotherapy intervention. In addition to short-term palliation, appropriate intervention with radiotherapy provided better survival by improving PS and allowing the viability of future aggressive treatment options. Despite the median survival of 4.6 months reported in patients treated with PTR near the end of life, a longer median survival of 9.8 months was observed in those with bone metastases also treated by radiotherapy. Additionally, timely radiotherapy for bone metastasis was identified as a significant, independent, and favorable prognostic factor (47,48). In a prospective study of short-course palliative radiotherapy, 73% of participants (including those with initially poor PS) experienced an improved PS score, which was the only factor influencing survival (P=0.0289) (49). In a large-scale retrospective study, over 2% (23/963) of cases survived at least 5 years after palliative radiotherapy, with approximately 74% free of disease (50). All these data suggest palliative radiotherapy may provide long-term survival or even cure in some cases.

Oligo-focal disease states

The "oligo-metastatic disease" hypothesis describes an intermediate state between loco-regionally confined disease and diffuse metastatic disease. This idea has gained significant traction over the decades following its proposal by Hellman and Weichselbaum in 1995 (51), and supported by data and evidence from numerous clinical trials, the term has been incorporated into the American Joint Committee on Cancer (AJCC) 8th edition staging system for NSCLC (52). Systemic therapy remains the mainstream treatment, while local therapy (LT) is playing an increasingly important role in combination therapy. At present, there is great interest in defining which patient subgroups can be expected to benefit most from radiotherapy, optimal radiotherapy timing, and the appropriate radiotherapy technology. Taking inspiration from "oligo-metastatic disease", the terms "oligo-residual disease" and "oligo-progressive disease" have generally been used to describe stage IV patients harboring limited residual and progressive disease after a period of active systemic therapy, respectively.

Consensus 2.1: Oligo-focal disease states, which manifest as oligo-metastatic disease, oligo-residual disease, or oligo-progressive disease, are characterized by limited tumor lesions and relatively favorable oncologic outcomes

Since the "seed and soil" hypothesis was first postulated, much has been learned about the distant metastatic process (53). The metastatic cascade has various steps, including loss of cellular adhesion, increased motility and invasiveness of the primary tumor, entry into and survival in the circulation, and adhesion to the blood vessel wall followed by extravasation and colonization of new organs (54). Numerous studies have demonstrated primary tumors consist of heterogeneous subpopulations of clonogens with varying metastatic potential that can give rise to further metastases (54-57). This evidence supports the *de novo* phenotypes of oligo-metastatic, oligo-residual, and oligo-progressive disease, and provides a theoretically sound rationale for local radiotherapy.

Oligo-metastatic NSCLC was first defined as a maximum of five metastases and three organs, and mediastinal lymph nodes were not considered a metastatic site (58). However, the inclusion criteria across different clinical trials have been heterogenous, and based on an ESTRO-ASTRO consensus document, oligo-metastatic disease is currently defined as one–five metastatic lesions, with a controlled primary tumor being optional, but all metastatic sites must be safely treatable (5). For these patients, radiotherapy plays a role of synchronous therapy. Slightly distinct from the concept of oligo-metastatic disease, oligo-residual disease refers to the persistence of polymetastases at the onset rendered oligo-metastatic (generally one–three lesions remaining) by a period of treatment (59). In patients with oligo-residual disease, local consolidation radiotherapy may treat the remaining lesions before any progression occurs, and importantly, such treatment can be delivered safely, with minimal toxicity, in carefully selected patients (60). The term oligo-progressive disease was first introduced to describe a clinical scenario where only a few tumor lesions progressed and most of the disease was under control, with an upper limit for the number of progressive lesions instead of that of metastases (61). In this setting, the utility of radiotherapy as salvage therapy may eradicate the drug-

resistant lesions and extend the duration of systemic therapy, resulting in better survival outcomes.

Consensus 2.2: PET/CT should be considered and encouraged in the process of identifying patients with oligo-focal disease states

Positron emission tomography/computed tomography (PET/CT) is a well-established molecular imaging platform enabling non-invasive quantification of the relevant biological tumor characteristics (62). Technological improvements combined with the development of new radiotracers over the past decades have extended the possibilities for disease characterization using PET/CT.

Fluorodeoxyglucose PET/CT (FDG-PET) is recommended as a first-line staging modality due to its excellent diagnostic accuracy (63). For patients with oligo-metastatic NSCLC, PET/CT can offer a higher sensitivity for global disease assessment at baseline, and evidence indicates primary tumor and oligo-metastatic lesions can be detected at an earlier stage using FDG-PET as compared with CT measurements (64). According to the European Organization for Research and Treatment of Cancer Lung Cancer Group survey on questions involving synchronous oligometastatic (sOM) NSCLC, 98% of physicians completed sOM staging with PET/CT, highlighting its role in the process of identifying patients in an oligo-metastatic state (65). Presently, clinical trials conducted in the setting of an oligo-metastatic disease state frequently require participants to undergo PET/CT before randomization and contrast-enhanced CT-scans on follow-up (66-70). It is generally believed that, compared to CT, PET/CT with its superior diagnostic accuracy will more accurately filter patients not meeting the inclusion criteria and enable better stratification of oligo-metastatic and polymetastatic disease (71). A systematic review focusing on sOM NSCLC found PET/CT was used for accurate disease staging in 81% (17/21) of the eligible articles (72).

Currently, FDG-PET using traditional standardized uptake value (SUV)-derived indices is used for early response assessment to chemotherapy and radiotherapy. Several studies have demonstrated the potential to monitor treatment effects based on SUVs on serial FDG-PET imaging of the primary tumor, and recently, the efficacy of the initial response to nivolumab was compared in metastatic NSCLC patients between CT-based criteria and ^{18}F-FDG PET response criteria in a clinical trial (NCT02475382) (73). Despite a low concordance between the two criteria, the PET-based response demonstrated prognostic significance in patients classified as having progressive disease, indicating its potential in improving therapeutic decision making, especially in the setting of oligo-residual and oligo-progressive disease.

Consensus 2.3: Concurrent radiotherapy in combination with optimal systemic therapy for suitable patients could provide additional survival benefit for NSCLC patients with oligo-metastatic disease

A single-center retrospective study showed approximately 26% of patients with stage IV NSCLC present with oligo-metastatic disease at diagnosis as detected by PET/CT and brain magnetic resonance imaging (MRI) (74). For such patients, concurrent radiotherapy in combination with appropriate systemic therapy could provide additional survival benefit. Based on previous studies, SBRT, a metastatic radiotherapy technique with high local tumor control rates and low toxicity, boosted the 2-year local control rate to over 90% in malignancies with limited metastatic burden (75,76). A meta-analysis of 21 studies with a total of 924 oligo-metastatic NSCLC patients found both OS [hazard ratio (HR) =0.44, 95% confidence interval (CI): 0.32 to 0.6, P<0.001] and PFS (HR =0.42, 95% CI: 0.33 to 0.55, P<0.001) were significantly improved with the addition of concurrent thoracic radiotherapy to the primary tumor (77). Similarly, a survival benefit has been observed from the addition of concurrent radiotherapy to TKIs in epidermal growth factor receptor (EGFR)- or anaplastic lymphoma kinase (ALK)-mutated patients with oligo-metastatic disease (78).

In addition to the findings of retrospective studies, the results of several prospective clinical trials have provided convincing evidence demonstrating the efficacy of radiotherapy in oligo-metastatic NSCLC (79). According to Gomez *et al.*, local consolidative radiotherapy or surgery could offer an obvious survival benefit in patients with three or fewer metastases, extending median PFS from 4.4 to 14.2 months and improving median OS from 17.0 to 41.2 months (12,80). The interim reports of a randomized phase III, open-label clinical trial (SINDAS) showed the combination of EGFR-TKI and concurrent SBRT significantly extended the PFS (20.2 *vs.* 12.5 months) and OS (25.5 *vs.* 17.4 months) in patients harboring EGFR mutation when compared to EGFR-TKI alone (81). In a phase II study where most (17/29) participants received SBRT after induction chemotherapy, the overall metabolic

response rate was 60%, with a median PFS and OS of 11.2 and 23 months, respectively (68). All these results demonstrate the critical role of concurrent radiotherapy in combination with proper systemic therapy in oligo-metastatic NSCLC.

Consensus 2.4: Consolidative radiotherapy may improve survival for patients with oligo-residual disease after systemic therapy

Despite the favorable response rate and survival outcomes produced by TKIs in oncogene-addicted patients, progression inevitably develops in most cases after 1–2 years of treatment (82-87). For patients who receive initial systemic therapy and have oligo-residual disease, local consolidative radiotherapy outside the CNS is strongly suggested for several reasons. Firstly, disease progression at the original site is the predominant pattern of failure for patients treated with first-line systemic therapy (88). Secondly, as tumor growth follows a sigmoidal pattern and the effect of systemic therapy is proportional to the rate of tumor growth, consolidative radiotherapy may move the tumor growth curve back to a state of exponential growth and augment the antitumor activity of systemic therapy (89). Thirdly, local consolidative radiotherapy might serve as a means of eliminating an evolutionary reservoir of resistant subclones and help extend the use of systemic therapy (90). The results from a pattern of failure analysis in metastatic NSCLC indicated approximately 20% of patients were considered consolidative SBRT candidates based on the extent of disease at the time of maximum response to TKI therapy (91). Similarly, Guo *et al.* analyzed the serial imaging of patients with TKI-treated oligo-residual NSCLC and identified 26.8% patients as candidates for consolidative SBRT at the time of maximal response (92).

Accumulating evidence suggests local consolidative radiotherapy could improve survival in patients with metastatic NSCLC (93). A multicenter, retrospective study reviewed 84 cases of stage IV NSCLC treated with systemic therapy and found the OS was significantly higher in patients undergoing local consolidative radiotherapy than in those who did not (13 *vs.* 7 months, P=0.002) (94). The survival benefit of consolidative radiotherapy is more apparent in highly selected patients, and in patients with limited metastatic NSCLC without EGFR- or ALK-mutations, SBRT prior to maintenance chemotherapy nearly tripled PFS to 9.7 months compared with maintenance therapy alone, with no difference in toxic effects (11). Similar results have been reported by several prospective studies, including the ATOM trial, where the efficacy of preemptive SBRT was assessed in patients with oligo-residual disease after TKI therapy, and a 1-year PFS rate of 68.8% and median OS of 43.3 months were reported, with no occurrence of grade 3 or higher SBRT-related toxicities (67). In the same trial, the risk of progression was lower in participants receiving preemptive SBRT compared with those unfit for SBRT due to screen failure (HR =0.41, P=0.0097). More recently, prolongation of PFS and OS by local consolidative SBRT was seen in patients with oligo-metastatic NSCLC without progression after front-line therapy (70).

Consensus 2.5: For patients who develop oligo-progressive disease after acquired resistance to targeted therapy or ICIs, salvage radiotherapy could prolong the time to treatment failure and potentially improve OS

Oligo-progression is a common phenomenon in TKI-treated oncogene-addicted NSCLC (95-97), and is increasingly encountered in patients treated with ICIs (98-100). Once acquired resistance (AR) is identified, systemic treatment options include next generation TKIs or other ICIs, introduction of other biological agents targeting bypass signaling pathways leading to AR, and chemotherapy. Although a subset of patients might benefit from these approaches, further development of resistance or lack of tolerability eventually results in discontinuation of treatment. In this instance, the use of radiotherapy as a salvage approach to eradicate TKI- or ICI-resistant subpopulations, extend the duration of systemic therapy, and result in improved OS, is of great clinical significance.

Clinical observations suggest a growing role of salvage radiotherapy in the treatment of oligo-progression. The proportion of oligo-progression cases ranged from 15% to 47% during first-generation TKI treatment and increased to approximately 70% with third-generation TKI (101-103). Intracranial oligo-progression is a frequent and serious phenomenon in patients treated with TKIs due to their inadequate ability to penetrate the BBB. A retrospective study of 232 patients treated with first-generation TKIs showed the site of first disease progression was the CNS in 16% of patients (104), and among those with ALK rearrangements, 20–46% developed isolated CNS metastases at the time of progression after TKI treatment (105). In a study of patients with extra-cranial oligo-progression, 49% were considered suitable for local

radiotherapy or surgery (106). In terms of survival benefit, the results from a retrospective study showed the addition of LT to TKIs resulted in a significantly longer median PFS (13.9 *vs.* 9.2 months, P=0.007) and OS (28.3 *vs.* 17.1 months, P=0.011) in the oligo-progressive cohort and locoregional recurrence was the major pattern of failure in the switching chemotherapy group (107).

A growing body of evidence demonstrates the efficacy of radiotherapy in oligo-progression after ICI treatment. In a retrospective study of 26 patients with AR to programmed cell death protein-1 (PD-1) axis inhibitor therapy, 88% of cases had recurrence limited to one (54%) or two (35%) sites of disease, and among the 15 patients who went on to receive salvage systemic therapy, the median survival time and 2-year survival rate from AR were 27 months and 69% (95% CI: 0.48 to 1), respectively (108). A total of 15 patients received LT to sites of AR, 11 of whom continued respective PD-1 axis inhibitor after LT, and among the 15, the median survival time from AR was not reached, and the 2-year survival rate from AR was 92% (95% CI: 0.77 to 1). The superior survival in patients who received LT (including radiotherapy) indicates local radiotherapy to oligo-progression with continuation of ICIs should be considered. Similarly, a significantly longer PFS (12.9 *vs.* 10.0 months, P=0.006) and OS (26.3 *vs.* 18.5 months, P=0.001) with local radiotherapy plus continued immunotherapy were seen in patients with oligo-progression from ICI treatment, compared with the survival in patients not receiving local radiotherapy (109). All these data indicate the potential role of salvage radiotherapy in oligo-progressive NSCLC from ICI treatment, and an ongoing study by Alliance (USA; NCT04929041) will directly address the role of SBRT in programmed death ligand 1 (PD-L1)-negative patients.

Consensus 2.6: Multisite SBRT targeting oligo-focal tumor lesions could provide additional clinical benefit for selected patients

Although the oligo-metastatic phenotype may arise *de novo* in patients with NSCLC, it may also be rendered by tailored systemic therapies, in which it is termed oligo-residual disease. Additionally, advances in diagnostic imaging have led to greater sensitivity in identifying patients with oligo-focal disease states. These factors predict a future increase in the incidence of oligo-metastatic, oligo-residual, and oligo-progressive NSCLC, and it is of great importance to administrate the optimal therapeutic strategy in this highly selected group of patients.

The SBRT procedure is an advanced radiotherapy technique which precisely delivers high radiation doses over a limited number (fraction) of treatments. With the accurate delivery of multiple small radiation fields, radiation damage can be minimized outside of the target lesions (organs at-risk). Although the precise dose-response relationship at high doses per fraction is controversial, the proportion of cells killed appears to increase at least exponentially with dose and may involve destruction of the vascular endothelium (110,111). Thus, the dose-fraction relationship of SBRT may be far more effective at killing tumor cells than the equivalent total dose conventionally given over many smaller fractions. A wealth of clinical studies have demonstrated SBRT can produce high tumor control rates along with a favorable toxicity profile delivered to one–three metastatic sites (75,112-114). However, it can still be a significant challenge to deliver SBRT to patients with more than three metastases or those with two metastases in close proximity. As the number of metastases increases, treatment-related toxicity may increase because of the interval and the cumulative radiation dose to the surrounding organs. Additionally, the prior radiotherapy may limit further dosing to surrounding normal tissues, magnifying the difficulty in delivering multiple courses of SBRT.

Due to the rapid refinement of SBRT techniques, there is growing interest in exploring its utility in patients with multiple metastases. The NRG-BR001 phase I trial was performed to evaluate the safety of SBRT in patients with three–four metastases or two metastases in close proximity (≤5 cm) to each other. The starting dose schedule was 50 Gy in five fractions (central lung and mediastinal/cervical lymph node), 45 Gy in three fractions (peripheral lung, abdominal-pelvic, and liver), and 30 Gy in three fractions (bone and spinal/paraspinal). Among the 39 patients evaluable for dose-limiting toxicity (DLT), no protocol-defined DLTs were observed, and the safety profile of SBRT treatment for multiple metastases was shown to be similar to that reported from the treatment of single metastases and primary tumors (11,80,115-117). These findings suggest up to four separate metastatic sites can be safely treated with curative-intent SBRT doses. Ongoing phase II/III National Cancer Institute-sponsored trials (NRG-BR002, NRG-LU002) will further assess the efficacy of treatment with SBRT for multiple metastases.

CNS metastases

Approximately 20–40% of patients diagnosed with NSCLC

develop BMs during the course of the disease (118), and the management of BMs is an age-old problem in real-world clinical practice. Due to the presence of the BBB and the poor passage of traditional cytotoxic agents across it, limited therapeutic options have been available beyond LT, including surgical resection and radiotherapy. However, in recent years, the role of systemic therapy in the management of BM has been dramatically reinforced due to the advent of new-generation highly CNS-penetrant TKIs (e.g., osimertinib and alectinib) and immunotherapeutic agents, which have demonstrated promising activity in the CNS. The ever-growing therapeutic armamentarium for BM also raises key questions about the role of CRT in multidisciplinary care, including the appropriate choice of radiation techniques, optimal sequence of systemic therapy and radiotherapy administration, and ideal candidates for this combination treatment strategy.

Consensus 3.1: For oncogene-addicted NSCLC with baseline BM, upfront CRT in combination with corresponding TKIs may provide additional survival benefit among selected patients with favorable profiles (especially oligo-metastatic BM). Otherwise, next-generation TKIs with stronger potency against BM should be preferred as first-line treatment, and upfront whole brain radiotherapy may be deferred

In the era of first-generation TKIs, the role of CRT for patients with oncogene-driven NSCLC with BM has been investigated in numerous studies (119-122). In a retrospective analysis of 93 patients with metastatic ALK-rearranged NSCLC treated with crizotinib, Ni *et al.* observed CRT before crizotinib could alter the disease recurrence patterns and prolong PFS for patients with baseline BM (119). A meta-analysis of published studies also reported a longer PFS among patients with BM harboring EGFR or ALK mutations treated with the combination of TKIs plus radiotherapy compared with TKI alone (18.6 *vs.* 13.6 months, P=0.06). However, no significant OS benefit was observed with the addition of CRT to TKIs (120). In contrast, a retrospective study involving 571 patients with EGFR-mutated NSCLC-BM treated with TKIs reported a significant difference in OS between patients treated with and without intracranial local radiotherapy (23.6 *vs.* 17.0 months, P=0.0008) (121). The divergent conclusions derived from various studies on combination TKIs and CRT in oncogene-driven NSCLC may be attributable to the heterogeneity of the patient populations and treatment modalities across studies.

Further studies with more detailed patient stratification and classification of LT have lent credence to the crucial role of CRT for patients with oncogene-driven NSCLC with BMs. A retrospective analysis of patients with ALK-rearranged or EGFR-mutant NSCLC with multiple (≥4) BM reported single and multiple courses of radiosurgery without whole brain radiation therapy (WBRT) were well tolerated and could be an effective treatment strategy for these patients (123). Another retrospective analysis of patients treated with WBRT+TKI, stereotactic radiosurgery (SRS) +TKI, or TKI alone for ALK-rearranged or EGFR-mutant NSCLC suggested a prolongation of time to intracranial progression in those treated with WBRT+TKI, with no significant differences in OS between the three groups (124). This study provided preliminary evidence for the use of TKI+SRS or TKI alone in selected patients on active surveillance for intracranial recurrence. Yomo *et al.* investigated the impact of concurrent or post-SRS EGFR-TKI use on the efficacy and toxicity of SRS for lung adenocarcinoma with BM in propensity score-matched cohorts, and found the use of TKIs was associated with a longer median OS (25.5 *vs.* 11.0 months, HR 0.60, 95% CI: 0.48 to 0.75, P<0.001). Moreover, previous literature has suggested the safety profile of combined EGFR-TKI and SRS is acceptable, with no significant increase in severe adverse event rates observed in relation to this combination treatment (125-127). Of note, the risk of radiation necrosis was found to increase when SRS was performed after development of TKI resistance (128).

The appropriate sequence of TKIs administration and CRT has also been explored in various studies. A retrospective analysis using data from a multi-institutional cohort of 351 patients with EGFR-mutant NSCLC reported those who received SRS followed by TKI had a longer OS than those who underwent WBRT followed by TKI or TKI followed by SRS or WBRT (129). Similarly, Lee *et al.* reported the median survival times for patients with brain-metastatic EGFR-mutant NSCLC treated with immediate WBRT, immediate SRS, delayed radiotherapy upon intracranial progression, and no CRT were 18.5, 55.7, 21.1, and 18.2 months, respectively (P=0.008). Moreover, immediate SRS and fewer extracranial lesions have been associated with improved survival (130). Miyawaki *et al.* evaluated the clinical value of upfront LT in a retrospective study involving 176 patients with EGFR-mutant NSCLC, with a particular focus on the efficacy of upfront cranial radiotherapy (uCRT) in subgroups of patients stratified

by the number of BM (1–4 *vs.* >4) (131). Among all participants, 107 (61%) received upfront TKI and 69 (39%) received upfront LT, and of the latter group, most (82%) of those with >4 BM received WBRT, while all patients with 1–4 BMs received SRS. The beneficial effects of upfront LT in terms of PFS and OS were more prominent in patients with 1–4 BMs (median PFS, 14 *vs.* 9.1 months; HR, 0.57; 95% CI: 0.34 to 0.91; P=0.02; median OS, 35 *vs.* 23 months; HR 0.54; 95% CI: 0.32 to 0.90; P=0 .02) than in patients with >4 BM, among whom no significant benefit was observed in PFS and OS (median PFS, 8.4 *vs.* 7.4 months; HR 1.13; 95% CI: 0.70 to 1.80; P=0.61; median OS, 22 *vs.* 27 months; HR 1.08; 95% CI: 0.64 to 1.81; P=0.76). These findings suggest personalized therapeutic strategies should be carefully tailored to individual patients depending on their general condition and characteristics of BM.

Recently, the promising efficacy of new generation targeted therapies in patients with ALK rearranged or EGFR mutant NSCLC with BM has been reported in numerous prospective and retrospective studies, with impressive response rates and notable improvements in CNS-PFS and OS (132-134). The approval of new generation TKIs (e.g., osimertinib and alectinib) with better BBB penetration compared with earlier generations for oncogene-addicted NSCLC raises questions of immense clinical interest regarding the role of CRT. The results of the exploratory analyses of two phase II trials showed alectinib-treated patients with ALK-positive NSCLC and baseline BM progressed at a higher rate in the CNS, as suggested by a higher cumulative incidence rate of CNS progression than non-CNS progression at 24 months (43.9% *vs.* 31.0%) (135). Another exploratory analysis of CNS efficacy in the J-ALEX study of alectinib versus crizotinib in ALK-positive NSCLC also suggested patients were at a higher risk of CNS progression than non-CNS progression, even if they received a selective CNS-active ALK inhibitor (136). In a secondary analysis of the phase III ALEX study, the 12-month cumulative incidence of CNS progression was lower in patients with baseline BM treated with both radiotherapy and alectinib compared with those who had not received previous radiotherapy (8.6% *vs.* 20.5%, no P value given) (137). This suggests the addition of radiotherapy, especially SRS, to alectinib may provide long-term intracranial disease control compared with ALK-targeted therapy alone.

For patients with EGFR mutant NSCLC, subgroup analyses from a phase II trial of 160 mg osimertinib in EGFR T790M-positive NSCLC with BMs who progressed on prior TKI therapy demonstrated those who had previously undergone radiotherapy had a longer PFS than radiotherapy-naïve patients (138). A Bayesian network meta-analysis demonstrated the combination of TKIs (gefitinib/erlotinib) and SRS/WBRT ranked first in terms of OS, followed by third-generation TKIs (osimertinib), suggesting the addition of cranial radiation to targeted therapies may provide the greatest survival benefit (127). A recent retrospective study involving 135 first-generation EGFR-TKI-resistant NSCLC patients with an acquired EGFR T790M mutation included 54 patients with BM (139), and found those who received osimertinib combined with CRT had a median OS of 53 months versus 40 months for those treated with osimertinib alone (P=0.014). These findings suggest the combination of new generation TKIs and CRT could have a positive impact on patient outcomes over TKIs alone. Furthermore, a recent multi-institutional retrospective study of patients with NSCLC-BM conducted by Yu *et al.* provided valuable insight into the clinical value of uCRT via a detailed analysis of patterns of recurrence on osimertinib and the impact of uCRT on patient outcomes stratified by the number of BM (140). Patterns of recurrence analysis revealed 40.2% of the initial progression on osimertinib involved the brain and most (76.9%) of intracranial progression occurred at the original BM sites, providing a rationale for uCRT before progression occurs. Additionally, in the propensity-score matching oligo-BM cohort, the uCRT group demonstrated improved OS compared with the non-uCRT group, and no significant differences in OS were reported in the subgroup of patients with multiple BM. More mature data on the efficacy of this combination treatment strategy are needed to provide a benchmark for individualized treatment in the future.

Consensus 3.2: CRT in combination with ICIs could be safe and provide additional clinical values in selected patients with driver mutation-negative NSCLC. However, evaluation on a case-by-case basis is warranted

The advent of ICIs has revolutionized the treatment approach for metastatic lung cancer. The approval of PD-1/PD-L1 inhibitors for metastatic NSCLC also raises questions about the interaction of CRT in relation to anti-PD-1/PD-L1 therapy for patients with BM. The current body of clinical data suggest combining ICI treatment with CRT for the management of NSCLC-BM could be superior to radiotherapy alone or exclusively systemic therapy in terms of local tumor response and survival

outcomes, presumably due to the immunologic effects of radiotherapy in the tumor microenvironment (141-147). Shepard *et al.* observed the combination of ICI and SRS resulted in an increased rate of complete response (CR) in the CNS for NSCLC-BM treated with SRS according to the Response Assessment in Neuro-Oncology (RANO) criteria compared with SRS alone, with a shorter median time to BM regression (143). Chen *et al.* retrospectively analyzed the survival outcomes of patients with NSCLC, melanoma, and renal cell carcinoma (RCC) with BM treated with concurrent SRS and ICI (145), and reported a superior median OS relative to those who underwent non-concurrent SRS/SRT and ICI (24.7 *vs.* 14.5 months; P=0.006) or SRS/SRT alone (24.7 *vs.* 12.9 months; P=0.002). These observations echo those of other recent studies (148-150), which suggest concurrent SRS and ICI is the preferred therapeutic strategy to sequential SRS and ICI to maximize the synergy between ICI and radiotherapy for the treatment of patients with BMs. Schapira *et al.* reported patients who underwent concurrent SRS and anti-PD-1 therapy (defined as the receipt of SRS within 1 month of anti-PD-1 therapy) had improved local control and OS compared with those treated with SRS before or after anti-PD-1 therapy (150).

Clinical safety is an obvious concern when combining ICIs and CRT for the treatment of patients with NSCLC-BM. The short-term safety profile of combining the two seems to be acceptable, with no significant increase in immune- or radiotherapy-related adverse events (145,146,149-151). However, some studies have raised the concern that ICI treatment may increase the risk of radiation necrosis (152-154), and it is worth noting current data regarding the combination of ICI and CRT in the management of NSCLC-BM is limited to retrospective studies. The appropriate therapeutic index of combining CRT with ICI and the toxicities of this combination strategy, especially regarding long-term neurological and cognitive sequelae, remains to be clarified. The combination of CRT and ICIs seems to be safe, and holds promise to provide extra clinical values in selected patients. However, until more robust clinical trial data are published, caution is warranted with the addition of CRT. The decision regarding the use of CRT and timing relative to immunotherapy should be made by a multidisciplinary thoracic tumor board, on a case-by-case basis depending on the patient's PS, PD-L1 expression status, neurological symptoms, corticosteroid use, tumor location, number of lesions, and size characteristics of metastatic brain lesions.

Consensus 3.3: The decision to use SRS or WBRT should be individualized based on clinical expertise, patient values, and logistical considerations

Historically, WBRT has been the mainstay local treatment modality for BM. However, this treatment paradigm has been challenged over the past decade by growing concerns over neurocognitive dysfunction following treatment which have arisen from the results of prospective trials evaluating the safety and efficacy of SRS plus WBRT versus SRS alone for the treatment of BM (155,156). Due to the superior preservation of neurocognitive function with no compromise in survival outcomes with the use of SRS alone compared with WBRT, SRS has now become the most widely used local treatment modality for selected patients with limited [1–4] BM (157,158).

More recently, technological advances in SRS have enabled the management of patients with larger numbers of BMs, and the role of SRS for multiple (>4) BM is rapidly evolving (159). A multi-institutional prospective observational study from the Japanese Leksell Gamma Knife Society demonstrated no significant differences in OS among patients with 2–4 BM treated with SRS compared with those with 5–10 BM (160). Similarly, Hughes *et al.* reported patients undergoing initial SRS for 5–15 BM had similar OS compared to those with 2–4 BM (161). These findings suggest SRS may be an effective treatment modality in selected patients with multiple BM, and the decision to use SRS or WBRT should not depend solely on the number of BM. Another retrospective analysis of 64 patients undergoing SRS for ≥5 BM showed a Karnofsky performance scale (KPS) score of ≥80, rather than the number of metastatic brain lesions, was predictive of an improved survival outcome (160). Several other studies have shown cumulative intracranial tumor volume might have more prognostic impact than the total number of BM (162,163). Therefore, the choice of SRS or WBRT should be individualized to each case based on clinical expertise, patient values, and logistical considerations. Several ongoing randomized clinical trials (NCT03550391, NCT01592968, NCT03775330, NCT03075072) are investigating the efficacy of SRS in patients with ≤20 BM.

Consensus 3.4: CRT is generally not recommended for improving survival in patients with leptomeningeal metastasis

Leptomeningeal metastasis (LM) is another serious CNS complication whereby cancer cells spread to the

subarachnoid space. It remains a devastating clinical problem historically associated with poor prognosis, with a median survival of 3.0 months (164).

Management of LM includes approaches such as WBRT, craniospinal irradiation (CSI), and the elimination of focal lesions by SRS and SRT, although controversy exists regarding the efficacy of WBRT for LM. In a retrospective analysis of 149 NSCLC patients with LM conducted by Lee *et al.*, WBRT was one of the positive prognostic factors for OS on multivariate analysis (165). However, studies have also suggested WBRT provides no benefit in OS. Morris *et al.* reported data from 125 NSCLC patients with LM, of whom 46 received WBRT, and observed no significant differences in survival between patients treated with and without WBRT (164). Similarly, Li *et al.* retrospectively analyzed a series of 109 consecutive EGFR-mutant NSCLC patients with LM and reported that compared with TKIs alone, TKIs plus WBRT did not confer any survival benefit (166).

For most patients with LM, multiple lines of treatment can weaken the immune system and affect overall PS. Thus, caution is warranted with CSI for LM, as the former can cause serious treatment-related side effects, leading to aggravation of clinical symptoms. The safety and efficacy of CSI in patients with LM from breast cancer (n=9), lung cancer (n=3), and other cancers (n=3) were investigated in a retrospective study in which patients with lung cancer experienced no improvement in neurological symptoms, the median OS added up to 3 months, and there were six cases of grades 3 and 4 toxicity and three treatment-associated deaths (167). While several studies have suggested SRS may be particularly useful in appropriately selected cases with focal lesions in the salvage setting (168,169), future studies are necessary to explore its safety and efficacy for patients with focal leptomeningeal disease.

In summary, while cranial radiotherapy (RT) is generally not recommended for patients with LM, WBRT can still be considered for symptom palliation. The efficacy of WBRT for NSCLC patients with LM is still uncertain, and caution is warranted for the use of CSI for LM. Identification of prognostic factors that predict patients likely to derive benefit from cranial RT, and the combination of cranial RT with immunotherapies and targeted therapies for the management of LM, are worthy of further clinical research.

Combining radiation and ICIs

The use of ICIs has revolutionized oncology practice for metastatic NSCLC, with responses often durable to several years in a subset of patients. Currently, PD-1/PD-L1 inhibitors, such as pembrolizumab, nivolumab, and atezolizumab, have demonstrated impressive efficacy in prospective randomized trials and are approved by the Food and Drug Authority (FDA) for patients with metastatic NSCLC (170-172). However, despite the encouraging outcomes achieved with ICIs, the objective response rate (ORR) of ICI monotherapy is still unsatisfactory, and AR inevitably occurs in most patients. Given the profound immune-modulatory effects of radiation, combining radiotherapy and ICIs to improve the therapeutic ratio for metastatic NSCLC is currently a burgeoning area of preclinical and clinical research.

Consensus 4.1: Appropriate radiation therapy can enhance the efficacy of ICIs with manageable toxicities in patients with metastatic NSCLC

To date, pre-clinical and clinical evidence have provided a strong rationale for the combination of radiotherapy and ICIs. Mechanistically, radiation can, via various mechanisms, increase tumor cell susceptibility to immune-mediated killing. For example, radiation can induce immunogenic cell death (ICD) and trigger the release of tumor antigens and the production of type I interferons (IFN) (173). Moreover, the radiation-induced local release of pro-inflammatory cytokines [e.g., tumor necrosis factor (TNF) and interleukin-1β (IL-1β)] and damage-associated molecular patterns trigger the infiltration and activation of immune cells, resulting in a favorable tumor microenvironment for anti-tumor immunity (174-176). Apart from the local immunologic effects in the tumor microenvironment, radiation also enhances a systemic anti-tumor response, which manifests as an out of field "abscopal" effect (177), and growing evidence suggests an *in situ* vaccine effect of radiation underscores this effect (178). Notably, radiation-induced upregulation of PD-L1 on tumor cells also triggers detrimental immunologic effects (179), and targeting these with the addition of ICIs can overcome adaptive immune resistance and augment the efficacy of radiotherapy.

The current body of clinical data suggests radiotherapy can enhance the efficacy of ICIs with an acceptable safety profile in patients with metastatic NSCLC (26,142,180). A secondary analysis of the KEYNOTE-001 trial conducted by Shaverdian *et al.* suggested a prolongation of PFS and OS in patients who received both thoracic radiotherapy and pembrolizumab compared with those with no previous

thoracic radiotherapy, and no statistically significant differences in the incidence of pulmonary toxicity of any grade were observed between the two groups (63% *vs.* 40%, P=0.052) (142). A recent retrospective study involving 269 metastatic NSCLC patients treated with nivolumab or pembrolizumab included 102 patients who underwent radiotherapy within 3 months of initiation of anti-PD-1 therapy or subsequently during anti-PD-1 therapy (180), and the addition of radiotherapy to anti-PD-1 therapy was not associated with increased toxicity. The efficacy and safety of ICIs in combination with radiation has also been explored in several prospective trials. The results from recently published safety run-in data of a multicenter, single-arm, phase II trial of sintilimab, SBRT, and granulocyte-macrophage colony stimulating factor as second-line therapy for metastatic NSCLC have demonstrated this combination strategy was safe, with manageable treatment-related adverse events (181). In addition, the results of a phase I/II study, the MDACC trial, demonstrated concurrent pembrolizumab and radiotherapy was safe, with few high-grade adverse events (182). Moreover, exploratory findings have demonstrated that for patients with low PD-L1 expression, median PFS was significantly improved with the combination of radiotherapy and pembrolizumab versus pembrolizumab alone (20.8 *vs.* 4.6 months, P=0.004). The phase II PEMBRO-RT study randomized patients with metastatic NSCLC to receive pembrolizumab either alone or after radiotherapy to a single tumor site. This study demonstrated no significant increase in treatment-related toxicity between the two arms, and ORR at 12 weeks and median PFS and OS were improved with the addition of radiotherapy (26). The results from a pooled analysis of the PEMBRO-RT trial and the MDACC trial demonstrated both OS (median 19.2 *vs.* 8.7 months, P=0.0004) and PFS (median 9.0 *vs.* 4.4 months; P=0.045) were improved with the addition of radiotherapy (27), and adding radiotherapy to pembrolizumab significantly increased the best abscopal response rate compared with pembrolizumab alone (41.7% *vs.* 19.7%, P=0.0039). Additionally, in a phase II study of 64 patients with 1–4 oligometastases from NSCLC, all participants underwent locally ablative therapy (resection and/or radiotherapy), with many receiving systemic chemotherapy, followed by a course of pembrolizumab. The median PFS (19.1 months) and 2-year OS (91%) were markedly better than those of the historic controls (183). These encouraging results suggest ICIs may have their greatest clinical impact in combinatorial regimens, and further support for systematic investigation of the combination of ICIs and radiotherapy is urgently required.

Consensus 4.2: Different dose-fractionation regimens can have diverse immunologic effects in the modulation of the tumor microenvironment and could impact the treatment efficacy of combined therapy

An increasing body of eloquent preclinical work indicates different dose-fractionation regimens can have diverse immunologic effects in the tumor microenvironment. On the one hand, radiation exposure to single fraction doses of just 1–3 Gy can have destructive effects on lymphocytes (184), and radiation dose per fraction and fraction number are among the factors correlating with radiation-induced lymphopenia (185). There is emerging evidence indicating radiation-induced lymphopenia is linked with poorer outcomes in patients with NSCLC (186,187), and the absolute lymphocyte count is a predictive factor of the response rate to ICI treatment (188,189). On the other hand, radiotherapy can be immune-activating through enhanced antigen presentation (190), and different radiation doses in a single fraction or short-course fraction regimen may induce diverse immunogenic effects. For example, Reits *et al.* reported that in irradiated tumor cells, radiation induced a dose-dependent increase in MHC-1 (191), which is essential for T-cell-mediated tumor cell killing. In addition, Vanpouille-Box *et al.* demonstrated high doses above 12–18 Gy may attenuate radiation-driven anti-tumor immunity through inducing Trex1 exonuclease expression and degrading cytosolic DNA (192). Thus, moderately fractionated doses (e.g., 8–12 Gy) below the dose threshold for Trex1 induction may be optimal for IFN-stimulatory DNA accumulation, cGAS/STING pathway activation, and induction of anti-tumor T cell responses.

Additionally, substantial work over the past decades has expanded understanding of the great difference in the immune response after irradiation with varying fractionation schedules. In a mouse model of ovalbumin (OVA)-expressing B16–F0 tumors, researchers observed enhanced antigen presentation and T-cell priming in draining lymph nodes after single (1×15 Gy) or fractionated (5×3 Gy) doses of localized radiation. Notably, compared with a 5×3 Gy fractionated schedule, 1×15 Gy irradiation led to greater numbers of host immune cells infiltrating the irradiated tumors (193). In another murine study by Schaue *et al.*, antitumor responses were evaluated in mice bearing B16-OVA melanoma treated with up to 15 Gy radiation in various sized fractions (194), and found single-dose radiation

of 7.5 and 10 Gy were successful in stimulating an effective antitumor immune response, but not 5 Gy. Compared with other fractionation schedules (5×3, 3×5, 1×15 Gy), two fractions of 7.5 Gy gave the maximal tumor control and antitumor immunity while maintaining low regulatory T cell (Treg) numbers. The diverse immunologic effects of varying dose-fractionation regimens on the tumor environment were further highlighted in a preclinical study showing the use of 30 Gy single-dose irradiation transformed the immunosuppressive tumor environment by decreasing the infiltration of myeloid-derived suppressor cells, while the addition of 10×3 Gy to the single dose of 30 Gy resulted in significantly increased infiltration of myeloid-derived suppressor cells (195). Overall, these findings suggest different dose-fractionation regimens of radiation can have diverse immunologic effects in the modulation of the tumor microenvironment and could significantly impact treatment efficacy when combined with ICIs.

Increasingly, studies suggest hypo-fractionated radiation, especially SBRT, may induce more potent antitumor immunity than conventionally fractionated radiotherapy. Using SBRT allows a high-dose per fraction to be delivered to the tumor with an exceedingly high level of conformality and limited exposure of adjacent critical structures. Thus, SBRT has the potential to better preserve lymphocyte function and induce more potent antitumor immunity compared with conventional fractionation regimens. Indeed, an increasing body of preclinical work suggests hypo-fractionated radiation may be more immunogenic than standard fractionation (196-198). Lan *et al.* reported that compared with conventional daily low-dose fractionated radiotherapy, hypo-fractionated schemes reduced vascular endothelial growth factor expression and inhibited recruitment of myeloid-derived suppressor cells into tumors (199). Grapin *et al.* investigated the effect of different fractionation schemes (3×8, 18×2, 1×16.4 Gy) on the immune response in an *in vivo* murine model (198). They found each fractionation protocol induced different lymphoid and myeloid responses with standard fractionation inducing a predominantly myeloid response and hypo-fractionated radiation inducing an intense and predominantly lymphoid response which may be more favorable for anti-tumor adaptive immunity.

While these studies explored the immunologic effects of hypo-fractionated radiation, the potential synergy of hypo-fractionated radiation in combination with ICIs has also been reported. In a mouse model, researchers demonstrated 3×8 Gy was the most effective scheme compared with other fractionation protocols (18×2, 1×16.4 Gy) when combined with anti-PD-L1 therapy (198). Dewan *et al.* explored the effects of different SBRT fractionation schemes (1×20, 3×8, 5×6 Gy) combined with anti-CTLA-4 antibody on tumor growth in a murine model of TSA mouse breast carcinoma (197), and found the combination treatment led to enhanced or complete primary tumor regressions compared with the use of an anti-CTLA-4 antibody alone. Intriguingly, researchers noted substantial growth inhibition of the tumor outside the radiation field (abscopal effect) when an anti-CTLA-4 antibody was added to the fractionated radiotherapy but not the single-dose regimen. There have also been several case reports describing the abscopal effect in patients with metastatic NSCLC treated with the combination of ICIs and SBRT (200). Furthermore, the results from a pooled analysis of the PEMBRO-RT trial and the MDACC trial showed a striking improvement in abscopal response rate for patients treated with pembrolizumab plus SBRT at either 50 Gy in four fractions or 24 Gy in three fractions, compared with those treated with pembrolizumab plus IMRT at 45 Gy in 15 fractions or pembrolizumab alone (27).

Collectively, the current body of preclinical and clinical data suggests hypo-fractionated radiation, especially SBRT, may induce more potent antitumor immunity than conventionally fractionated radiotherapy. The optimal dose-fractionation regimen remains a controversial quandary, with a growing body of preclinical evidence favoring 3×8 Gy, and several ongoing clinical trials (NCT04081688, NCT03801902, NCT03589547, NCT03237377) are investigating the efficacy of the combination of ICIs and non-conventional fractionation regimens.

Limitations

Although the current consensus was reached by an international multidisciplinary team centering around radiotherapy-based treatment for metastatic NSCLC, limitations are inevitable since phase III clinical studies were not available in every clinical scenario discussed and considerable heterogeneity existed in terms of methodology and patient characteristics among the studies providing the crucial supporting evidence.

Furthermore, besides oligo-metastasis, CNS metastasis, and synergic effects between radiotherapy and immunotherapy, the current consensus also included palliative radiotherapy, with the main purpose of presenting a comprehensive view of the clinical utilities of radiotherapy

in the management of metastatic NSCLC.

Questions to be further discussed and considered

(I) To maximize the synergy between ICIs and radiotherapy, should all sites of disease be targeted by radiotherapy? If not, which is the optimal site of metastases to be targeted by radiation (lung vs. liver vs. lymph node vs. bone vs. others)?

Arturo Navarro-Martin: In my opinion, it depends on which kind of patient we are referring to. In an oligometastatic patient, we can treat all metastatic locations to increase the local control. However, in the poly-metastatic setting, I think we must choose the most immunogenic dose and the most immunogenic location to increase the PFS. Given the choice of which location will be the most immunogenic, some authors (201) suggest this will be lung metastases, as liver metastases are less immunogenic. In addition, Chicas-Sett *et al.* (202) suggest irradiation should be performed over visceral lesions instead of bone and lymph nodes. Therefore, in my opinion, lung lesions should be targeted first.

Dirk De Ruysscher: We do not know what the optimal sites for irradiation are in the context of synergy of radiotherapy and immune therapy. Theoretically, irradiating all sites with a detectable tumor would lower the tumor burden to an extent that immune therapy may be more efficient. On the other hand, too large a volume of the body, including the bone marrow, and/or the circulating pool of lymphocytes and stem cells may then receive a significant radiation dose, which may cause lymphopenia and immune suppression. This is topic of ongoing research (203).

Ben G. L. Vanneste: In my opinion, not all sites should be targeted by radiotherapy, as the goal is to obtain a systemic effect with LT in combination with the ICI. Although the optimal effect for choice of site is not known, and is part of investigations, it should be a site where no/the lowest side-effects are expected, taking into account the surrounding organs to avoid stereotactic ablative radiotherapy (SABR) with overlap of the intestines, and avoiding the use of large fields on bone marrow.

J. Isabelle Choi: This is very much an area of active investigation. Oncologically, all sites should be targeted to maximize local tumor control, but it may be possible that intentionally not targeting one or more sites can increase immunogenicity and lead to better outcomes. More research is needed in this field, but for now, the more common approach would be to target all sites in a patient with oligometastatic NSCLC. If intentionally not targeting one or more sites, it is likely the primary tumor should most optimally be targeted, as this may be more likely to induce an immune response compared with a bone metastasis or liver metastasis. This is because it is often larger and potentially harder to control with an abscopal response, and is likely to have the highest ability to itself metastasize to additional sites.

Jacek Jassem: There is no simple answer to this question, this is highly dependent on the clinical situation and should be individualized.

Joe Y. Chang: Based on translational and clinical data, comprehensive targets coverage with radiotherapy should be considered if it is safe to do so. While tolerance and other clinical data must be considered, lung and liver, and not weight bearing bone, are optimal sites for ablative radiotherapy.

Lucyna Kepka: We have no evidence from randomized trials on the number of metastases to be treated with the addition of radiotherapy for oligometastases in cases where ICIs are used. Many trials on this issue are ongoing, and most are dedicated to the local treatment of oligometastatic disease (OMD) include all sites of the disease into the radiation field (or surgery). However, the definition of OMD varies between trials, with some including a primary in the count and others not so, which is similar for BMs. Some also include baseline metastases, and some, residual metastases (so-called "induced oligometastases"). For these reasons, it is certainly conceivable in some clinical instances for patients outside of clinical trials to receive radiation to only some metastases, whilst others might only be observed during treatment with ICIs (+/– chemotherapy). A rationale for including only some portions of the disease into a radiation volume in cases of combined immunotherapy is that too large a radiation field may lead to the depletion of lymphocytes, which reduces the immunomodulatory effect of the drugs. Additionally, in treating only a minority of lesions, theoretically it is still possible to cause a systemic anti-tumor effect via the so-called abscopal effect, described elsewhere in the article. Obviously, it is common practice to treat only progressive sites of the disease ("oligo-progression"). For baseline oligometastases, a priority for radiation is given to BMs, which are commonly managed before or at the beginning of ICI use, when the extracranial metastases are left to the action of the systemic treatment only. In addition, large

volume of oligometastases +/– primary may be a reason not to perform radiotherapy. Symptomatic bone metastases are often a priority of treatment, and lung oligometastases +/– primary are sometimes not treated with radiation if the patient has concomitant lung disorders such as interstitial lung disease or a very low respiratory reserve. Concluding, we may formulate such a consensus on the radiation volume in OMD of patients treated with ICIs outside of clinical trials. If a decision on the use of radiotherapy in patients with OMD treated with ICIs is made, all accessible sites of the disease should be targeted, providing the risk of the use of radiotherapy related to the volume and location of the disease does not surpass the potential benefit of treatment. If it is not the case that all sites of the disease are targeted with radiotherapy, the choice of site should be individualized, taking into account the symptoms and characteristics of the disease.

Lukas Käsmann: The irradiated site may play a pivotal role in inducing ICD and durable antitumor immunity by radiotherapy (204). We recommend targeting all active sites of disease if safe radiation treatment constraints for organs at risk (OAR) can be achieved. However, we assume SBRT of bone and brain lesions may have a less synergistic effect on the establishment of an antitumor immune response compared with SBRT of the pathological lymph nodes and pulmonary lesions, including primary tumor and metastases (204-206). This could be explained by an attenuated antitumor response in the bone and intracranial compartment due to the insufficient recruitment of certain immune cell subsets from peripheral blood (207).

Michael T. Milano: When feasible, all sites should be treated. In my opinion we do not know which sites are best treated.

Paul Van Houtte: If we are looking for a synergy with ICI, all sites of metastatic disease should not be irradiated except in the presence of OMD. The site I would prefer will depend on the toxicity profile, and the lung is a good candidate because of its location and immunologic profile.

Rafal Suwinski: In my opinion, to maximize synergy between ICIs and radiotherapy, it is not necessary to treat all sites of disease. In our institutional practice, if multiple lesions exist, we select for radiotherapy the two lesions with the largest volumes. The aim of this is to release as many antigen targets as possible, while minimizing the toxicity of therapy. If multiple lesions of similar volume exist in diverse organs, we select those in organs with higher radiation tolerance doses (e.g., better lung than liver, better bone than kidney, etc.). There is weak evidence for this, the best of which comes from experience with melanoma (208-210).

Alberto Traverso: According to recent results, even if many studies come from pre-clinical models, there seems to be benefit in irradiating all site of disease for patients with >two lesions. Nevertheless, it is important to maintain consideration of the heterogeneity found within different metastatic lesions. The immune response elicited will only be efficacious for lesions sharing the same antigenic profile and sites secreting appropriate chemokines to traffic effector T-cells from the peripheral circulation.

Hiroshi Doi: I would suggest bone > liver > lung for treatment sites in terms of the synergy between ICIs and radiotherapy because it is necessary to minimize toxicities due to radiotherapy. Lymph nodes might also be avoided because of the effect on the immune reaction.

Yang-Gun Suh: I have not observed an abscopal effect in patients with NSCLC, and suspect it is very rare. Therefore, I am of the view radiation should be delivered to all active disease sites (if before the use of ICI, then for all sites, and if during the use of ICI, then for all active sites including progressing or persistent lesions).

Georges Noël: Notably, the efficacy of the combination of ICI and radiotherapy should be studied according to at least four prisms; the efficacy in terms of local control, the impact on OS, the tolerance of combination, and the immunologic reaction of this combination.

Importantly, because of difficulties of recruitment, publications are more often retrospective or prospective trials with oligometastases in several locations without specific analysis.

Finally, the delivery of ICI and irradiation is an important issue as there appears to be variation in the focus of studies to date. Since some studies have analyzed their concurrent or non-concurrent use (145), while others have investigate drug use before, after, or currently with irradiation (26,211).

Combining ICI and stereotactic irradiation (SRS) for brain metastasis, Chen *et al.* reported for SRS alone, SRS plus nonconcurrent ICI, and SRS plus concurrent ICI, and found a median OS of 12.9 months, 14.5 months, and 24.7 months, respectively (145).

Theelen *et al.* reported a phase two trial in 76 patients receiving SRS alone (40 pts) or SRS followed with pembrolizumab (36 pts). The main irradiated locations in the experimental arm were the lung or nodes, in 24 patients. In the control arm, 21 of 40 patients (53%) showed progressive disease as best ORR compared with 14 partial responses of 36 (39%) as best ORR in the experimental group. In the overall population, significant

improvement (64% *vs.* 40%; P=0.04) was observed in the 12-week disease control rate in favor of the experimental arm. Hence, an increase of medians of survival were 7.6 and 15.9 months, respectively, but OS was not significantly different between both groups (26).

In their series of 68 patients with 151 metastases in different location and from several primitive tumors treated with SRS and at least one pembrolizumab cycle, Luke *et al.* showed the mean percent change in tumor diameter was –21.7% for irradiated metastases versus –1.7% for nonirradiated metastases (P=0.0008). However, the authors did not report a difference in response according to the kind of metastases (212). In a recent review focusing on immunotherapy stereotactic irradiation and liver metastases in NSCLC, Corrao *et al.* failed to retrieve publications (213). However, a list of arguments led them to propose an association of ICI and SRS. On one hand, the activity of radiotherapy on vessels, the liver immune-reaction to irradiation, and the efficiency of irradiation on liver metastasis, and on the other hand, the vessel activity of bevacizumab and the activity of Checkmate 017/057 trials (214). While the specific results of nodes irradiation with ICI are rarely reported, two notable case reports presented results of the abscopal effect after the irradiation of nodes, one with the response of an unirradiated node and the other with unirradiated bone metastases (215,216).

SRS is efficient in adrenal metastasis (217-219). Arcidiacono *et al.* showed results were better for metachronous-oligoprogressive patients, with a 2-year LR-FS rate of 100% compared with 53% for synchronous and 45% for metachronous-oligorecurrent patients. However, metachronous-oligoprogressive patients received target therapy and/or immunotherapy. The reasons for these differences of results could be conditioned by the time of appearance of the metastases as well as the combined treatment (217).

Toxicity is relatively low in series with SBRT. A retrospective review of patients treated with palliative irradiation and ICI retrieved a 4% grade three or higher immune-related side-event rate, and the authors showed toxicity was not related to the anatomic location of irradiation (220). Although in the series by Luke *et al.*, toxicity was generally low, when it appeared, it was often in the irradiated region. Hence, it difficult to discriminate toxicity from combination therapy and this from radiation alone (212). Bang *et al.* did not show any correlation between time of irradiation accord and time of checkpoint blockade, before, during, or after, or in the 14 days after the beginning of checkpoint blockade. Analysis according to dose or EQD2 showed no correlation with complications (220).

Independently of the antitumoral activity of ICI and radiation independently, their combination could lead to induced-ICD, not only at the irradiated site but also in non-irradiated locations; a reaction known as the abscopal effect. Käsmann *et al.* suggested the need to irradiate sites other than the brain and bone to stimulate this induced-ICD (204), because bone and the CNS are insufficiently efficient to recruit certain immune cell subsets from peripheral blood (207). By assessing the aggregation of the sum of response of non-irradiated lesions but receiving ICI also, another lesion was irradiated, Luke *et al.* concluded the response rate was consistent with preclinical models of the abscopal response (212). For the authors, a microenvironment characterizing the liver may help tumors escape from anti-tumor immune surveillance during immunotherapy (221,222).

In conclusion, literature cannot easily separate the different location of oligometastases and their response to stereotactic irradiation, alone or combined with ICI. Response rates with SRS are always high whatever the location of metastasis and are higher with ICI. This response of combined treatment likely increases OS, but the roles of ICI alone or the abscopal effect when combined with irradiation is impossible to discriminate. Finally, and notably, combined treatment is safe and well tolerated, and if side-effects appear, the causality of radiation therapy, ICI, or both is difficult to differentiate.

Natsuo Tomita: This is a difficult task. I think that for patients with between one and five oligometastatic tumors, all sites of disease should be targeted by stereotactic radiotherapy regardless of the regime of systemic therapy. However, if doses to the lung have a high risk of radiation pneumonitis, stereotactic radiotherapy for all sites is inadvisable. When patients with more than six oligometastatic tumors receive ICIs, stereotactic radiotherapy for one or two sites of disease may be reasonable in view of abscopal effects.

The optimal site of metastases targeted by radiation depends on doses to normal tissues. If patients can be treated with an acceptable range of doses to normal tissues, all sites may be optimal for targets of stereotactic radiotherapy.

Roman O. Kowalchuk: This is certainly a challenging topic, and clinical practice varies. In our practice, if the patient presents with limited (oligometastatic) disease, we may treat in a consolidative manner to all sites of disease.

If a patient presents with many sites of disease, another common practice at our institution would be to treat only the dominant lesion and/or any lesions threatening nearby organs or causing worsening of symptoms were the lesions to progress.

Terence T. Sio: This has been well addressed in the manuscript as well (see my comments). In RTOG 0937, for small-cell lung cancer, up to four extracranial sites were consolidated, and it did not seem to significantly improve clinical outcomes (older systemic therapy era). For NSCLC and the use of ICI's, clearly, there is no randomized and level one data to guide us on this topic. As a result, I do not believe all sites of disease should be targeted by radiotherapy. For a patient with good PS and systemic treatment options left for future consideration, I think it is reasonable to treat up to three subsites that are oligoprogressive, and that is regardless of anatomic location, although the lung should be controlled as first consideration if possible, which is extrapolated from Slotman's ESCLC trial for thoracic RT. However, there are certainly practice variation on this topic, at least among the American providers.

(II) For patients with oligo-metastatic disease, what is the optimal duration of systemic therapy after ablative radiotherapy covering all the metastatic lesions? (Should systemic therapy be used until disease progression or stopped at some time point?)

Arturo Navarro-Martin: This is also a good question. The problem of administering systemic therapy until progression or adverse event is that we may be treating patients who really do not need it, so we are espousing them of suffering unnecessary adverse events. However, we do not know the real benefit of this. In my opinion, after SBRT in all locations, if we do not know what systemic therapy is doing, it is better to hold off until disease progression.

Dirk De Ruysscher: The role is of maintenance immunotherapy after induction (chemo)-immunotherapy and radical LT is presently unknown. Systemic therapy remains the standard of care in polymetastatic disease to address as many as possible distant metastases that may be below detection thresholds. New trials are awaited to answer the questions of if and how long immune therapy should continue and the role of biomarkers such as circulating tumor (ct)DNA for patient selection.

Ben G. L. Vanneste: Systemic therapy could be continued until disease progression or unacceptable toxicity occurs, although a discontinuation after several years [1–2] of treatment may be a reasonable alternative to decrease the continuous risk of toxicity and the high costs of sustained therapy. While Waterhouse *et al.* revealed in a randomized trial that continuing nivolumab beyond 1 year improves outcomes (223), more research is needed to confirm this.

J. Isabelle Choi: While some providers administer four–six cycles of systemic therapy following LT for OMD, especially when delivering cytotoxic chemotherapy, in the era of immunotherapy I favor continuing immunotherapy until progression or patient intolerance to optimize PFS and OS.

Jacek Jassem: It depends on the type of systemic therapy. Chemotherapy is rarely used for more than six cycles, whereas targeted therapies and immunotherapy are frequently continued until progression or serious side effects occur.

Joe Y. Chang: Current data support continuing immunotherapy, targeted therapy, or maintenance chemotherapy until progression or issues of tolerance.

Lucyna Kepka: Obviously, it is of crucial importance to have an effective systemic treatment for micro-metastatic disease in cases of local treatment of OMD. However, I am a radiation oncologist, and not a medical oncologist. There are many controversies and new data on the duration and types of maintenance systemic therapy. This is a topic that is not in my professional area of interest.

Lukas Käsmann: Based on growing evidence, we recommend at least eight cycles of pembrolizumab (200 mg every 21 days) until disease progression with possible extension up to 16 cycles if the ICI treatment is well tolerated (183). Another phase II trial from Theelen *et al.* recommended a maximum duration of pembrolizumab treatment of 24 months (26).

Michael T. Milano: Again, I do not think we have an answer to this. For NSCLC, chemotherapy is usually given for four–six cycles and immunotherapy for up to 2 years. So even for widespread disease, it is stopped at some point. I think it makes sense to do so for oligometastases as well.

Paul Van Houtte: It may depend on the systemic treatment TKI, chemotherapy, or PD-L1 inhibitor. For chemotherapy, the duration is often limited by the toxicity, while TKI or PD-L1 inhibitors may be delivered until progression or toxicity.

Rafal Suwinski: In my opinion, for NSCLC, systemic therapy after radiotherapy for oligometastatic lesions should be used until disease progression. There is some evidence immunotherapy beyond progression may also be beneficial,

but this is highly controversial, mainly due to financial concerns.

Alberto Traverso: Systemic therapy should be used until disease progression.

Hiroshi Doi: I suggest systemic therapy might be used until disease progression.

Yang-Gun Suh: In the case of ICIs or targeted agents, these drugs can be administered until loss of clinical benefit such as experiencing toxicities or disease progression.

Georges Noël: The issue of the duration of systemic therapy could be considered globally equivalent for adjuvant therapy in localized or advanced disease requiring adjuvant therapy and oligometastases. The Pacific trial demonstrated the advantage of continuing targeted treatment 12 months after chemoradiation. The durvalumab added in the experimental arm led to an increase of OS (HR =0.68; 95% CI: 0.53 to 0.87; P=0.0025) with a median not reached versus 28.7 months, and an improvement of PFS (HR =0.52; 95% CI: 0.42 to 0.65; P<0.0001) with a median of 16.8 versus 5.6 months, respectively (224).

Continuation of systemic therapy is controversial and depends on several factors. It may be argued that its delivery could limit undetectable micrometastases to progress, keeping patients controlled. However, reverse arguments can be used. Postponement of systemic therapy can allow patients to maintain their quality of life and commence treatment only if new metastases appear and may avoid unnecessary treatment, although there is a risk of diminishing the activity of subsequent systemic therapy because of a larger burden of disease should it re-appear. Some authors propose postponing adjuvant hormonotherapy in prostate cancer (225) although in renal cell cancer systemic therapy and SRS seem additive (226).

In a retrospective series of brain metastasis from several primitive tumors, Guénolé *et al.* showed SRT delivered concurrently with systemic therapy and mainly immunotherapy seemed to be associated with improved local control, freedom for distant BMs, and OS, as well as with a higher rate of radionecrosis (227).

In a phase two trial, Iyengar *et al.* proposed stereotactic irradiation plus erlotinib in patients with limited progressive metastatic NSCLC and when progression of the disease was observed through at least one prior chemotherapy regimen (228). All metastases up to five were irradiated, and the main locations were the lung and mediastinum. No patients presented brain metastasis, and only three metastases of 47 progressed. Evolution of the disease was mainly new metastasis, and with a 6-month PFS at 69%, the authors considered the treatment worthy of further investigation. The median PFS at 14.7 months and OS at 24 months were considered longer than those observed in historical series (228). Collen *et al.* presented the results of a phase II trial studying chemotherapy and SBRT in 26 patients with oligometastatic NSCLC cancer, in which six patients presented with brain metastasis. Synchronous metastatic disease was diagnosed in 73% of the patients, and all metastases and the primitive tumor were irradiated, with a median PFS and OS of 11.2 and 23 months, respectively (68). Iyengar *et al.* led a two-arm randomized phase two trial comparing stereotactic radiation therapy plus maintenance chemotherapy with maintenance chemotherapy alone in the setting of limited metastatic NSCLC (11). The trial was stopped before the completion of accrual because intermediate analysis showed improvement of OS in the arm combining stereotactic radiation therapy plus maintenance chemotherapy, with a median OS of 9.7 *vs.* 3.5 months (P=0.01), respectively (11). Finally, a recent phase two randomized study included 49 patients with limited metastatic NSCLC, with or without targetable mutation positive disease. Patients were randomly assigned to LT with or without maintenance chemotherapy or observation versus maintenance chemotherapy or observation alone. Patients in the local consolidative therapy group had a longer median PFS at 11.93 months compared to 3.9 months for those not receiving local treatment. Furthermore, the 1-year PFS was 48% and 20%, respectively. The authors concluded that performing local aggressive treatment for all locations of oligometastatic NSCLC with or without maintenance therapy improved PFS compared to maintenance alone (80). The COMET randomized phase II trial included 99 patients with OMD to receive either standard-of-care (SOC) or SOC plus SABR. Eighteen patents had a primitive NSCLC. Overall, the 5-year and median OS rates were 17.7% and 28 months versus 42.3% 50 months, respectively (P=0.006) (229).

In conclusion, for patients with synchronous oligometastases, SBRT can be delivered in all metastases, and the primitive tumor can be treated with normofractionated RT or SBRT according to its size. Concurrent chemotherapy, ICI, or targeted treatment can be used, and maintenance treatment can be used for 12 months. For metachronous BMs alone accessible to an SRS, exclusive radiation treatment is acceptable. If other metastases are present, concomitant and maintenance systemic treatment is recommended. For oligoprogressive lesions, the same chemotherapy/ICI/

targeted treatment can be continued, and progressive lesions irradiated.

Natsuo Tomita: I think the optimal duration of systemic therapy after ablative radiotherapy covering all metastatic lesions depends on various factors such as efficacy, adverse effect, and cost of systemic therapy, patient status, and tumor burden at the times of recurrence. When patients receive molecularly targeted drugs or ICI after ablative radiotherapy, at least 2 years may be necessary if disease progression is not observed.

Roman O. Kowalchuk: This will depend on the underlying tumor characteristics, disease extent at presentation, duration of time to recurrence or development of metastatic disease, how well tolerated the systemic therapy regimen is, the patient's PS, and other factors.

Terence T. Sio: I follow the Gomez phase II (MDACC) and the UTSW (Iyengar) studies, which were also well discussed in this manuscript (11,12). The criteria per Gomez would be "no progression at 3 or more months after front-line systemic therapy". We do not routinely continue systemic therapy after giving ablative radiotherapy, which is consistent with how the two trials above were completed. Patients should be given a chance for remission (in some cases, it is very durable), and consider more treatment again at the earliest sign of clinical or radiographic progression.

(III) What is the optimal timing of ablative radiotherapy for patients with synchronic oligo-metastatic disease? (Should radiotherapy be performed concurrently with systemic therapy from the beginning, or should it be preferred as consolidation therapy after tumor response to systemic therapy?)

Arturo Navarro-Martin: This is a relevant question. The Gomez trial (80) and Iyengar (228), indicate SBRT or radiotherapy after induction chemotherapy it is a good strategy to select good responders for treatment. However, this is a question for active research.

Dirk De Ruysscher: The optimal timing of local treatments has not been investigated in randomized studies. The latter have given typically 3 months of systemic treatment in responders followed by radical LT. While none of the randomized trials included immune therapy, non-randomized studies suggest giving LT first may be an option in selected patients. However, this approach cannot be put forward as standard care in view of the paucity of data and unclear patient selection criteria for benefit (69,230).

Ben G. L. Vanneste: Radiotherapy could preferentially be performed concurrently with immunotherapy to obtain the maximum synergistic effect, including the possible upregulation of PD-L1 expression and adapting tumor micro-environment. However, this is mostly based on preclinical and small clinical research, and not on randomized clinical studies, which are needed to confirm this hypothesis (28,231).

J. Isabelle Choi: This is also an area of active investigation. The literature is conflicting on the most optimal timing. It also appears different ICIs are more optimally delivered in different sequences relative to radiation therapy. As radiation has been shown to increase PD-L1 expression, administering it early in the treatment course is likely the preferred approach, especially when performed with stereotactic body radiation therapy that is less immunosuppressive than conventionally fractionated radiation therapy and can even be immunostimulatory. However, that does not necessarily mean at the initiation of therapy, and I favor initial induction with immunotherapy followed shortly thereafter (i.e., 2–4 cycles) by stereotactic body radiation therapy in an attempt to maximize synergy between the modalities.

Jacek Jassem: There is no firm clinical data supporting either option. Intuitively, I would prefer the latter, as radiotherapy makes sense in patients responding to systemic therapies. In this scenario, treatment volume is much smaller than the initial dose.

Joe Y. Chang: Based on published data, consolidative radiotherapy after about 3 months of systemic treatment should be considered. More data is needed for concurrent systemic treatment with radiotherapy in oligo-metastases.

Lucyna Kepka: There is no evidence for the timing of radiotherapy from randomized studies. Currently, we have only one ongoing randomized trial (OITROLOC, NCT 02076477) trying to answer the question of the timing of ablative radiotherapy for patients with synchronic OMD. All patients received systemic treatment, but they are randomized to radiotherapy (to the primary and metastatic sites) given up-front or after completion of chemotherapy.

Among three fully published randomized trials, one which included patients with EGFR-mutated adenocarcinoma with synchronous, treatment-naïve oligometastases (≤five metastases excluding BMs), demonstrated a significant improvement of outcome with the use of up-front radiotherapy with TKIs versus TKIs only (70), and two demonstrated benefit from the use of local treatment (radiotherapy or surgery) after a course of systemic disease *vs.* systemic treatment only (11,12).

In the setting of immunotherapy, administering up-front ablative radiotherapy and following it with "pseudo-adjuvant" ICIs has a solid theoretical background. As described elsewhere in this article, radiation has a synergistic effect with the action of ICIs by releasing tumor antigens and proinflammatory cytokines, leading to activation of the immune system which is a target for ICIs. Apart from this local effect, radiation may also cause a systemic anti-tumor response (abscopal effect) by activation of the immune system. In the phase two trial, 51 oligometastatic patients received up-front ablative radiotherapy to all disease sites followed by pembrolizumab for eight cycles, with provision to continue to 16 cycles in the absence of progressive disease or untoward toxic effects. The median PFS from the start of radiotherapy was 19.1 months, significantly greater than the historical median of 6.6 months, P=0.005, and the median PFS from the start of pembrolizumab was 18.7 months. Giving pembrolizumab after radiotherapy was safe and did not reduce quality of life (183).

On the other hand, in two pivotal randomized trials that demonstrated a benefit of local treatment, patients with NSCLC without driver mutation in one and only with a small percentage of oncogene-addicted tumors in another were included after a course of systemic therapy regardless of the number of metastases at the beginning of treatment (11,12). Thus, patients with "induced" not "genuine" OMD were treated. This may be a selection test of tumors with less aggressive biological behavior, i.e., patients with a response to therapy may receive a greater benefit from ablative therapy. Patients who progress quickly with systemic therapy or their PS quickly deteriorates during such treatment probably have an inherently more aggressive tumor, and local treatment in the absence of amenable to alleviation by radiation symptoms cannot bring any benefit. Obviously, in the scenario of the symptomatic burden that may be decreased by radiation, any form of radiotherapy should be used before systemic treatment.

Thus, we may formulate a consensus on the timing of ablative radiotherapy for OMD treated outside clinical trials. In patients treated with chemotherapy, we have more data that radiotherapy should be used after a course of systemic treatment that may select patients with a less aggressive disease course and reduce radiation volume. However, some pre-clinical and clinical data incite the use of radiotherapy before the start or at the beginning of therapy with ICIs. In EGFR mutated tumors, the use of up-front radiotherapy combined with TKIs is supported by results from a randomized trial. Before gathering evidence from ongoing prospective trials, the sequence of treatment should be individualized for each patient, taking into account the molecular characteristics of the tumor, type of systemic treatment planned, the volume of the disease, PS, and symptoms of the disease.

Lukas Käsmann: In the case of synchronous oligo-metastatic disease, following Bauml *et al.* and Theelen *et al.* (26,183), we recommend performing radiation treatment at all active sites before the start of pembrolizumab therapy However, the number of treatment fractions and overall radiation treatment time must be considered because a prolonged radiation treatment regimen results in a significant risk of severe lymphocytopenia (205). Despite a controversial discussion with growing evidence based on preclinical data favoring 3×8 Gy, several ongoing clinical trials (NCT04081688, NCT03801902, NCT03589547, NCT03237377) are investigating the synergistic mechanisms of the combination of ICIs and altered fractionation regimens.

Paul Van Houtte: If we are looking to a possible enhancement of the PD-L1 effect, then radiotherapy should be given at the beginning of treatment to one or two sites. When chemotherapy is used, I would prefer to delay radiotherapy and use it as a consolidative approach.

Rafal Suwinski: In my opinion, ablative radiotherapy for patients with synchronic oligo-metastatic disease should be performed concurrently with systemic therapy from the very beginning, although symptomatic BMs requiring steroid therapy might be an exception (232).

Alberto Traverso: The decision should be based on identification of the prognostic factors of patients that will respond to systemic therapy. An example of a work in progress is: https://www.thegreenjournal.com/article/S0167-8140(22)00023-8/fulltext

Hiroshi Doi: I would suggest radiotherapy should be preferred as consolidation therapy after tumor response to systemic therapy.

Yang-Gun Suh: To avoid unnecessary treatment, physicians in our institution prefer consolidation or salvage treatment for local progression.

Georges Noël: This question is very important, and two points are of concern; the size of the lesion and whether the lesion is symptomatic. Symptomatic lesions should be treated at the beginning of treatment to avoid worsening and because radiation, mainly SRS, and other local treatments can control symptoms quickly. A recent PRISMA analysis concluded SRS led to a symptom improvement of 55%, and these results compared favorably

to trials of targeted or immunotherapy for BMs (233). Concerning painful metastasis, ablative radiotherapy is efficient but compared to conventional irradiation, comparisons have yielded contradictory results (234,235). In adrenal metastasis, Zhao *et al.* reported a 100% alleviation of symptoms after SBRT when patients received systemic treatment after SBRT (219). To our knowledge, comparison of the timing of SBRT in a symptom decreasing goal has not been addressed in trials, and only expert conclusions can propose SRS at the beginning of combined treatment.

The second point is the size of the lesion. The risk is that growth of the lesion during systemic therapy does not allow efficient SRS because of the reached size or because of the proximity to critical organs. Recently, Cao *et al.* showed the total volumetric burden of metastases at initial oligometastatic presentation to SBRT is strongly and independently prognostic for the risk of distant and widespread progression, with each twofold increase in total PTV conferring a 40.6% increased risk of distant progression (236). The same constatation was observed for survival, with twofold PTV change increasing the risk of death by 60.7% during the first 6 months and by 34% thereafter (236).

Another issue is the volume to irradiate at time of partial response, as this optimal volume (i.e., initial volume or volume at time of the best response) is unknown. Furthermore, limits of the volume can be blurred after the response to systemic treatment complicating delineation of the volume.

In conclusion, there is no definitive response to the question. Pragmatic management is proposed, leading to irradiation volume as soon as possible if the patient is symptomatic, if the volume could be non-sustainable for irradiation if it would grow. For the other cases, beginning the irradiation early will not increase any risk.

Natsuo Tomita: I think the optimal timing of ablative radiotherapy for patients with synchronic oligo-metastatic disease depends on various factors such as the range and organ of radiotherapy field, and the predicted effect of systemic therapy. I think the concurrent use of radiotherapy and systemic therapy may carry a risk of adverse effects. Either ablative radiotherapy → systemic therapy or neoadjuvant short-term systemic therapy → ablative radiotherapy → long-term systemic therapy may be feasible.

Roman O. Kowalchuk: This depends on whether or not the systemic therapy is also a radiosensitizer. Radiotherapy to metastatic sites can often be performed in a single fraction at our institution. In such cases, it is often given upfront.

Terence T. Sio: Pursuant to the answer to Question (II) above, I would typically wait to give radiotherapy based consolidation therapy after the patient has demonstrated a tumoral response to systemic therapy, including cases with synchronic presentation here, rather than metachronous. This is also a biologically sound approach, as it is more likely patients will benefit from radiotherapy if they can demonstrate they will not progress with more distant metastatic diseases while on best systemic therapies including ICI's.

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Footnote

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