Review Article

A narrative review of evolving roles of radiotherapy in advanced non-small cell lung cancer: from palliative care to active player

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Abstract: Radiotherapy, along with other loco-regional interventions, is conventionally utilized as a palliative approach to alleviate symptoms and mitigate oncological emergencies in advanced non-small cell lung cancer (NSCLC). Thanks to the ongoing improvement of medical treatments in the last decade, such as targeted therapy and immunotherapy, the survival of patients with advanced NSCLC has been considerably prolonged, making it feasible and clinically beneficial for radiotherapy to play a more active role in highly selected subpopulations. In this review, we will focus on the evolving roles of radiotherapy in advanced NSCLC. First of all, among patients who are initially unable to tolerate aggressive treatment due to severe symptoms caused by metastases and/or tumor emergencies, timely radiotherapy could significantly improve their performance status (PS) and general condition, thus giving them a chance for intensive treatment and prolonged survival. The efficacy, potential candidates, and optimal dose-fractionation regimens of radiotherapy in this clinical scenario will be discussed. Additionally, radiotherapy can play a curative role as a concurrent therapy, consolidation therapy, and salvage therapy for patients with oligo-metastatic, oligo-residual, and oligo-progressive disease, respectively. Accumulating evidence from recent clinical trials, basic research, and translational investigations regarding the potentially curative roles of radiotherapy in NSCLC patients with oligo-metastatic disease will be summarized. Moreover, with the advent of various small molecular tyrosine kinase inhibitors (TKIs), the treatment efficacy and overall survival of oncogene-addicted NSCLC with brain metastases have been significantly improved, and the clinical value and optimal timing of cranial radiotherapy have become topics of much debate. Finally, synergistic antitumor interactions between radiotherapy and immunotherapy have been repeatedly demonstrated. Thus, the immune sensitizing role of radiotherapy in advanced NSCLC is also highlighted in this review.

Keywords: Non-small cell lung cancer (NSCLC); radiotherapy; palliative cancer; performance status (PS)

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Introduction

According to GLOBOCAN (1), there was an estimated 18.1 million new cancer cases and 9.6 million cancer deaths in 2018. Lung cancer is the most commonly diagnosed cancer (11.6% of total cases) and the leading cause of cancer death (18.4% of total cancer deaths), and the 5-year survival varies from 4–17% depending on stage and regional differences (1,2). Among the common histological subtypes

of lung cancer, non-small cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases. Over half of the patients with NSCLC are diagnosed with locally advanced (stage III) or metastatic (stage IV) disease (3). The mainstream treatment for patients with advanced NSCLC is systemic therapy, and loco-regional interventions such as radiotherapy are conventionally recognized as palliative approaches to alleviate symptoms and mitigate oncological emergencies (4,5). Radiotherapy uses ionizing radiation to target tumor tissue, but normal tissues that are exposed to radiotherapy can also be affected, leading to off-target toxic effects, such as radiation-induced lung injury, radiation-induced brain injury, and pathologic fracture (6). Despite the radiation toxicity, the advantage of radiotherapy in advanced NSCLC cannot be neglected.

Thanks to the continuous innovation and advancements in medical treatments such as targeted therapy and immunotherapy in the last decade, the survival of patients with advanced NSCLC has been prolonged, making it feasible and clinically beneficial for radiotherapy to play a more active role in highly selected subpopulations (7). For some patients who are initially unable to tolerate aggressive treatment due to severe symptoms caused by metastases (including lung, bone, and brain) and/or tumor emergencies [such as superior vena cava syndrome (SVCS), malignant spinal cord compression (MSCC), and hemoptysis], timely radiotherapy could significantly improve their general condition and performance status (PS) score, giving them a chance at more aggressive treatment and prolonged survival (8).

Additionally, a wealth of research has demonstrated the essential role of radiotherapy in improving survival among NSCLC patients with oligo-metastatic disease, which refers to an intermediate state between localized and widespread metastatic disease (9). It generally has 3 clinical scenarios: oligo-metastasis at diagnosis, oligo-persistence at the maximal response to systemic therapy, and oligo-progression upon treatment failure. A multi-institutional, phase II, randomized study showed that local therapy (LT) with radiotherapy or surgery significantly prolonged progression-free survival (PFS, 11.9 *vs.* 3.9 months) and overall survival (OS, 41.2 *vs.* 17.0 months) compared to maintenance therapy in patients with oligo-metastatic NSCLC (10,11). More recently, the interim results of the randomized phase III, open-label SINDAS trial showed that upfront stereotactic radiotherapy (SBRT) in combination with first-line epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) significantly prolonged PFS and OS, compared with EGFR TKI alone in patients with EGFR-mutant NSCLC with *de novo* oligo-metastatic disease (12). These results highlight the potential role of radiotherapy as a cornerstone in the treatment of oligo-metastatic NSCLC.

Historically, with palliative care as the main objective, local treatment including surgery and radiotherapy was the standard of care for NSCLC patients with brain metastasis due to the poor ability of chemotherapeutic drugs to penetrate the blood brain barrier (BBB). Stereotactic radiosurgery (SRS) and whole-brain radiation therapy (WBRT) are performed according to the number and size of brain metastases (13). With the advent of various small molecule TKIs exhibiting enhanced penetrance across the BBB, promising survival outcomes have been reported in patients with brain metastases harboring anaplastic lymphoma kinase (ALK) rearrangements or EGFR mutations (14-16). Pre-clinical studies have uncovered the rationale for the synergistic anti-cancer effect of TKIs combined with radiotherapy (17). Accumulating data suggests that cranial radiotherapy, when performed on a selected subgroup of oncogene-addicted NSCLC patients with brain metastasis using an appropriate radiation technique at the right time, can not only contribute to symptom control, but can also lead to extended survival.

Furthermore, the last decade has seen substantial progress in immunotherapies for NSCLC, such as the development of immune checkpoint inhibitors (ICIs, e.g., anti-CTLA-4 antibodies and anti-PD-1/PD-L1 antibodies), cytokines and cytokine blockers (e.g., GM-CSF, IL-2, and TGF-β blockade), oncolytic viruses (e.g., ADV/HSV-tk), and other targeted immunotherapies (e.g., OX-40 antibodies, toll-like receptor (TLR) agonists, and IOD1 inhibitors) (18-20). To date, PD-1 inhibitors (such as pembrolizumab and nivolumab), PD-L1 inhibitors (such as atezolizumab) and CTLA-4 blockade with ipilimumab, have been approved by the Food and Drug Administration (FDA) for the treatment of advanced NSCLC, as monotherapy or in combination with other agents (21-23). Based on data from previous studies, radiotherapy has immunomodulatory qualities capable of augmenting antitumor immune responses, making the integration of radiotherapy with immunotherapy a new therapeutic option in advanced NSCLC (24,25).

This review will focus on the roles of radiotherapy in advanced NSCLC. The transition from palliative care to more proactive participation of radiotherapy will be discussed. In addition, the combination of radiotherapy with

systemic therapy in oligo-metastatic, oligo-progressive, and oligo-persistent advanced NSCLC, the role of radiotherapy in oncogene-addicted NSCLC with brain metastases, and the synergistic interaction between radiotherapy and immunotherapy will also be discussed.

A literature search was conducted in Embase, MEDLINE databases, and clinicaltrials.gov using the keywords 'lung cancer' AND 'radiotherapy' OR 'radiation'. We present the following article in accordance with the Narrative Review reporting checklist (available at http://dx.doi.org/10.21037/tlcr-20-1145).

Radiotherapy as a bridge from palliative care to aggressive treatment

Palliative care is defined by the World Health Organization as "an approach that improves the quality of life (QOL) of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual (26)". Unlike "hospice care" which is specifically intended for the end of life, palliative care also encompasses care during progression and the advanced stages of disease (27). Palliative care as a special medical care is an important treatment in advanced NSCLC, especially for those with high symptom burden (28). Despite an increasing use of chemotherapy in the palliative setting, the role of radiotherapy should not be disregarded.

Palliative radiotherapy is an upfront treatment for those who present with oncological emergencies or severe symptoms caused by loco-regional growth of the tumor, and could serve as a bridge from palliative care to aggressive treatment. The major advantage of radiotherapy is that it is noninvasive, safe, and simpler than other methods such as bronchoscopy, laser ablation and intraluminal brachytherapy (29). The most common oncological emergencies include hemoptysis, malignant airway obstruction (MAO), MSCC, SVCS, and increased intracranial pressure due to brain metastasis (30). Data from previous literature shows a high incidence of oncological emergencies in lung cancer. Hemoptysis and MAO occur in upwards of 20% and 30% of patients, respectively (31,32). Approximately 28% of patients develop MSCC during their disease course (33). SVCS is present in 1.7% of NSCLC at diagnosis (34). Once oncological emergencies or tumor-related symptoms occur in the course of advanced NSCLC, the general condition of the suffering patient will deteriorate immediately, and the PS score will reduce greatly. In this situation, the immediate intervention of appropriate palliative radiotherapy can offer quick, efficient palliation and improve the PS score, thus making it possible for subsequent aggressive treatment approaches. To a certain degree, radiotherapy not only plays a role as a palliation therapy, but may also function as a bridge across the gap between poor general condition with worsening prognosis, and a much more stable and tolerable condition.

With ongoing advances in radiotherapy techniques and accumulating knowledge, as well as the increasing recognition of the role of palliative radiotherapy, widespread attention has been drawn to questions regarding its efficacy and clinical outcomes in advanced NSCLC patients experiencing oncological emergencies or serious symptoms. There is also ongoing debate as to how to precisely identify the candidates for such "bridging radiotherapy", thus prolonging their survival significantly. The optimal dose-fractionation regimen is another issue of concern, given that maximal antitumor effects and minimal toxicity cannot be achieved simultaneously.

The efficacy of palliative radiotherapy and clinical outcomes

In advanced NSCLC patients experiencing oncological emergencies or severe symptom burden, achieving symptom relief at the shortest expense of time and resources remains the main objective of palliative radiotherapy. A prospective study of short-course radiotherapy in NSCLC found that clinical palliation was achieved in 77% of patients, and PS improved in 73% of patients (35). Clinical data of 78 patients with metastatic NSCLC treated with palliative thoracic radiotherapy (PTR) for painful local failure showed significant pain relief in 67 (85.9%) patients (36). As the mainstay of PTR, external beam radiotherapy (EBRT) is a common and effective treatment for symptomatic advanced NSCLC, leading to thoracic symptom relief and improvements in QOL in 66% and 33% of irradiated patients, respectively (34). In patients with SVCS, the symptom relief rate was 63.0% for radiotherapy alone versus 31.3% for combined chemoradiotherapy (37). For spinal and bone metastasis, a pain relief rate of over 80% and a similar objective local control rate were observed in patients treated with SBRT (38).The result of a large-scale study evaluating the impact of radiation refusal in the palliative setting in metastatic NSCLC showed palliative radiation was recommended in 42% and refused by 3.1%

of patients. The median survival was 3 months for patients refusing radiation, and 5 months for those receiving radiation (39).

In addition to achieving quick palliation, intervention with radiotherapy provides promising local control and makes aggressive treatment tolerable by improving PS, thus making it possible to achieve better survival in patients with high symptom burden or oncological emergencies. A retrospective analysis of PTR near the end of life in 1,584 patients with lung cancer found that the median survival was 20 weeks (40). Nonetheless, many clinical studies have reported a much longer median survival in patients receiving palliative radiotherapy. In 78 metastatic NSCLC patients receiving PTR, the median OS was 7.7 months, and the 1-year OS rate was 26.5% (36). The 6- and 12-month OS rates were 76.7% and 47.2%, respectively, in patients with bone metastases treated with radiotherapy (41). More recently, the results from a retrospective study of 202 patients diagnosed with skeletal metastasis from lung cancer found that the mean skeletal metastasis survival was 9.8 months, and radiotherapy for skeletal metastasis was a significant, independent, and good prognostic factor (P=0.007) (42). A retrospective study of 963 patients who received palliative radiotherapy found that 23 patients survived at least 5 years, with approximately 74% being free of disease (43), suggesting that palliative radiotherapy utilizing appropriate doses may bestow long-term survival and possibly a cure.

To summarize, palliative radiotherapy has demonstrated efficacy for symptom relief and PS improvement, making it possible to achieve longer survival in patients with advanced NSCLC. However, data remains insufficient on the proportion of patients who become eligible for more aggressive treatment after palliative radiotherapy.

Identifying the candidates for "bridging radiotherapy"

As palliative radiotherapy has played an increasingly proactive role, how to select the appropriate population so as to maximize the potential survival benefits of "bridging radiotherapy" has become a hot spot of research. Clinicopathological characteristics such as histology, N and M stage, number of metastatic lesions, and tumor-relative symptoms have been widely investigated. The results from a retrospective study of 159 patients treated with PTR showed that squamous cell carcinoma (SCC) was associated with better prognosis (44). Similarly, a trend toward improved OS was observed when using radiotherapy for any metastatic sites in NSCLC patients with SCC (45). A retrospective study which aimed to validate a prognostic score based on PS and N and M stage classified 232 patients into 3 subgroups according to the prognostic score (46). The low-score group, the intermediate-score group, and the high-score group consisted of 56 (24%), 137 (59%), and 39 (17%) patients, respectively. The median survival for the 3 groups was 1.2, 5.3, and 8.2 months, respectively. Absence of anemia and fewer metastatic sites were identified as independent prognostic factors for longer OS in a previous study by Topkan *et al.* (36). In a retrospective review of 102 patients treated with PTR, the results from univariate and multivariate analyses indicated that stronger pain while not moving and reduced appetite predicted significantly shorter survival (47). A similar result that appetite loss appeared the most powerful independent prognostic indicator was obtained from the multivariate analysis of 301 patients in a randomized trial (48).

Taken together, histology is a prognostic factor favoring SCC in advanced NSCLC treated with palliative radiotherapy. Patients with other clinicopathological characteristics, such as fewer metastases, and absence of symptoms, including appetite loss and anemia, are predicted to achieve improved PS and extended survival. From our point of view, patients with younger age, indolent tumor behavior, less tumor burden and symptom burden, and availability of molecular targeted therapies with high potency, are expected to get rid of local compression, obstruction, bleeding and other emergencies through radiotherapy, with or without systemic therapies. However, due to the retrospective nature of most studies, randomized controlled trials (RCTs) are warranted to validate the efficacy of these variables, thus helping to precisely identify the appropriate candidates for "bridging radiotherapy".

Optimal dose-fractionation regimens

Much work has been done to determine the optimal dose-fractionation regimen of PTR. In a meta-analysis of 14 RCTs, the dose of radiotherapy investigated ranged from 10 Gy in 1 fraction (10 Gy/1F) to 60 Gy/30F over 6 weeks, with a total of 19 different dose/fractionation regimens. There was no strong evidence that any regimen gave greater palliation (49). Another meta-analysis of 13 RCTs involving 3473 patients found that for patients with good PS, the 2-year OS was better in the higher-dose group (35 Gy or more) compared to the lower-dose group (26.5% *vs.* 21.7%); whereas no advantage of high dose schedules was observed for patients with PS 3–4 (4). This finding

indicates that a small survival benefit is provided by increased dose and fractionation, but this schedule only suits patients with limited disease. Consistent with these results, the Scottish Intercollegiate Guidelines Network (2014) guidance recommends 39 Gy in 13 fractions for patients with good PS, and a lower dose regimen of 1 or 2 fractions for those with poor PS. Similarly, the American Society for Radiation Oncology (ASTRO) consensus is in agreement with the better survival and symptom relief in patients with a favorable PS, and suggests 30 Gy/10 F or greater for good PS patients and those with sufficient life expectancy (50). For patients with poor PS, shorter regimens are recommended such as 20 Gy/5 F, 10 Gy/1 F, and 17 Gy in 2 weekly fractions. The updated 2018 guidelines retain these recommendations (51).

Despite the consensus regarding the dose-fractionation regimen of PTR for advanced NSCLC, there are many studies investigating on the optimal regimen of palliative radiotherapy in oncological emergencies. Recently, a median dose of 39 Gy (range, 24–59 Gy), 2–3 Gy per fraction was found to be well-tolerated and effective in a retrospective analysis of 75 patients with MAO in lung cancer treated with palliative EBRT (52). Similarly, a median dose of 30 Gy (range, 8–45 Gy), 3 Gy per fraction achieved a satisfactory palliative response rate of 78.9% in 95 MAO patients with lung cancer (53). According to Armstrong *et al.*, compared to conventional dose fractionation (2 Gy), high dose fractions (3–4 Gy) yielded symptom relief in less than 2 weeks in a larger proportion of patients with SVCS (70% *vs.* 56%) (54). More recently, an accelerated hyper-fractionation (tumor dose of 30 Gy/20 F/2 week followed by a boost to 36–40.8 Gy/30–34 F/3–3.5 week) was shown to be tolerable in the treatment of SVCS caused by NSCLC (55). For patients with MSCC, many regimens are prescribed worldwide, with 20 Gy in 5 daily fractions or 30 Gy in 10 daily fractions the most commonly used regimens in patients with a good prognosis (56). For those with a poor prognosis, a single dose of 8 Gy is indicated focusing on pain relief based on the results of a secondary analysis from the National Cancer Institute of Canada (NCIC) Clinical Trials Group Symptom Control Trial SC.23 (57).

Taken together, guidelines for the PTR dose-fractionation regimen are mainly based on the PS and life expectancy of the patients. Hypofractionation acts as the main approach, with individualized regimens based on the type of oncological emergencies and the patients' overall condition.

Radiotherapy with curative intent in patients with oligo-metastatic disease

Oligo-metastatic disease, which can manifest as oligo-metastasis, oligo-persistence, or oligo-progression, is characterized by limited tumor lesions and relatively indolent tumor biology. A series of studies have been performed to redefine the treatment approaches and the therapeutic outcomes for these historically "incurable" patients. Systemic therapy remains the mainstream treatment, while LT, such as radiotherapy, plays a role in synchronous therapy, consolidation therapies, and salvage therapy. With radiotherapy involved, significantly better PFS and OS have been observed in several studies (58,59), making it possible for some patients to achieve clinical cure.

Oligometastases

The term "oligo-metastasis" was first coined by Hellman *et al.* in an editorial in 1995. It refers to an intermediate state between limited primary and polymetastatic cancers, in which LT, including radiotherapy, can achieve long-term survival or cure, with no restrictions on primary lesions (60). Generally, oligo-metastasis is defined as 1–5 metastatic lesions, a controlled primary tumor being optional, but all metastatic sites must be safely treatable (61). However, the inclusion criteria differ across clinical trials. Consistent definitions remained warranted until a consensus report regarding the definition of oligo-metastatic NSCLC was first published (62), where a maximum of 5 metastases and 3 organs were proposed, and mediastinal lymph nodes were not counted as a metastatic site.

Approximately 10% of patients with advanced NSCLC present with oligo-metastatic disease (63), and large-scale data is still lacking for an exact proportion. For such patients, radiotherapy plays a role in synchronous therapy. In previous studies, the 2-year local control rate of radiotherapy exceeded 90% in malignancies with limited metastatic disease burden (64,65). The results from a recent meta-analysis of patients with oligo-metastatic NSCLC suggested that consolidation with radical radiotherapy to the primary tumor was associated with better survival (66). In a retrospective study of EGFR-mutant NSCLC patients with oligo-metastasis, survival benefit provided by the addition of LT was assessed. In the oligo-metastatic cohort, addition of LT showed a significantly longer PFS (12.9 *vs.* 7.9 months) and OS (36.8 *vs.* 21.3 months) compared to

EGFR TKIs alone (67). The same results were found in a multicenter retrospective study which explored the role of radiotherapy in the management of EGFR- or ALK-mutated metastatic NSCLC. SBRT was identified as an independent factor related to better OS (68). In addition to retrospective studies, the interim results of a randomized phase III, open-label clinical trial (SINDAS) provided more convincing evidence for the vital role of radiotherapy in oligo-metastatic NSCLC. Compared with EGFR TKI alone, the combination of EGFR TKI and SBRT significantly prolonged both PFS (20.2 *vs.* 12.5 months) and OS (25.5 *vs.* 17.4 months) (12). This finding suggests that SBRT should be explored further as a standard treatment option in this clinical scenario. Other similar RCTs are still in progress (69,70).

Oligo-persistence

The concept of "oligo-persistence", slightly distinct from oligo-metastasis, refers to a patient with polymetastases at the onset rendered oligo-metastatic by a period of treatment. In this patient, radiotherapy plays a role of local consolidation in order to treat the remaining lesions before any progression can occur. By analyzing complete serial imaging of 49 patients with advanced NSCLC, Al-Halabi *et al.* found that approximately 20% of patients transition to an oligo-persistent state, and were retrospectively classified as consolidation SBRT candidates at the time of best response to EGFR TKI therapy (71). Coincidentally, Guo *et al.* reviewed the serial scans of patients with oligo-persistent NSCLC treated with osimertinib, and found that 26.8% of patients were identified as candidates for consolidation SBRT at the time of maximal response (72).

A large-scale retrospective study classified 145 enrolled patients into 3 groups, with Group 1 receiving consolidation radiotherapy to all oligo-metastatic sites, Group 2 receiving consolidation radiotherapy to either the primary tumor or oligo-metastatic sites, and Group 3 receiving no consolidation radiotherapy. For the 3 groups, the median PFS was 20.6, 15.6, and 13.9 months, respectively (P<0.001), and the median OS was 40.9, 34.1, and 30.8 months (P<0.001) (73). The same PFS benefit (36.0 *vs.* 14.0 months, P=0.0024) with the addition of local consolidation therapy (mainly SBRT) was observed in another retrospective study (74).

Similar results have also been reported by several prospective studies. A phase II study (ATOM) assessing the efficacy of preemptive local ablative therapy (LAT) to residual oligometastases found that the 1-year PFS rate was 68.8% and median OS was 43.3 months. Compared with patients with screen failure who were unfit for LAT, the patients receiving preemptive LAT had a lower risk of progression (HR 0.41, P=0.0097) (75). In a multi-institutional, phase II, randomized study of patients with advanced NSCLC, 3 or fewer metastases and no progression at 3 or more months after systemic therapy, the survival benefits of local consolidation therapy over maintenance therapy or observation were observed in both PFS (14.2 *vs.* 4.4 months) and OS (41.2 *vs.* 17.0 months) (10,11).

Oligo-progression

The term "oligo-progression" was first introduced in 2012 to describe a clinical scenario where only few tumor lesions progressed (76). Unlike the concept of oligo-metastasis, there is an upper limit for the number of progressive lesions instead of that of metastases, while the majority of the disease is under control.

Oligo-progression is a common phenomenon in patients with oncogene-driven NSCLC treated with TKIs targeting EGFR or ALK due to inadequate BBB penetration of drugs in cases of central nervous system (CNS) progression, or biological change in the tumour (77-80). In this setting, SBRT, an advanced radiotherapy technique with high local tumor control rates and low toxicity, can be used to eradicate TKI-resistant subpopulations and extend the duration of targeted therapy, thus leading to prolonged PFS and OS (81).

Clinical observations suggest a growing role for SBRT in the treatment of oligo-progression. Data from published literature indicated that the proportion of patients progressing with an oligo-progressive disease ranged from 15% to 47% during first-generation TKI treatment (82,83), and the proportion increased to approximately 70% with osimertinib, a third-generation TKI (72,84). In a retrospective study of patients with extra-cranial oligo-progression, 49% of patients were deemed suitable for LT, which was defined as radiotherapy or surgery (85). Currently, several ongoing prospective clinical trials are exploring the use of SBRT as a method of aggressive local control whilst on TKI therapy. The single-arm phase II trial (NCT01573702) aims to evaluate PFS with the addition of SBRT and erlotinib in patients with no more than 5 progressed sites. Similarly, a single-arm phase I trial (NCT02450591) is assessing the addition of LT in EGFR-mutated patients with oligo-metastatic disease, with the primary endpoint of 5 patients completing LT. HALT, a

randomized, multicenter, phase II/III trial will directly compare the effect of the addition of SBRT and TKI alone.

The optimal timing of radiotherapy

The optimal intervention time of radiotherapy in advanced NSCLC is under debate. Theoretically, there is an advantage of consolidation radiotherapy for oligo-persistence over salvage radiotherapy for oligo-progression. With the lowest tumor burden and fewest metastatic lesions at the time of maximal response to systemic therapies, there are a larger number of patients who are suitable for SBRT. Moreover, progression most frequently occurs in original sites of gross disease (9,86). Hypothetically, the oligo-persistent sites serve as the seeds of future progression. When the oligo-persistent sites progress, the lesions may develop in size and number above critical levels, making it impossible for such patients to receive SBRT. In some patients, their general condition may deteriorate rapidly after disease progression, leaving only a few possibilities for them to receive further treatment. Furthermore, higher efficacy and less toxicity are expected after consolidation radiotherapy for oligo-persistence because of the smaller and fewer lesions. Taken together, consolidation radiotherapy for oligo-persistence can eradicate the resistant clone, remove the seeds of future progression, and delay the time to switch to other therapies, thus making extended OS possible.

Radiotherapy for oncogene-addicted patients with brain metastasis

Bain metastasis is a frequent complication with poor prognosis in NSCLC, with 20–40% of patients developing brain metastasis during the course of the disease (87). Before the advent of TKIs, treatment strategies for NSCLC with brain metastasis mainly focused on LT including WBRT, SRS, and surgical resection due to the inability of chemotherapeutic drugs to cross the BBB (88). In contrast to traditional cytotoxic agents, newly developed TKIs with improved penetration, such as osimertinib for EGFR and alectinib for ALK, have demonstrated robust BBB penetrability. With the extended survival owing to newer generation drugs, the goal of radiotherapy has transformed from palliation to promoting treatment efficacy. Current studies are mainly focusing on identifying the suitable population, the appropriate technical approach, and the right intervention time of local radiotherapy.

In the era of the first-generation TKIs, the clinical value of LT in oncogene-addicted NSCLC with brain metastasis has been explored by many retrospective and prospective studies. In a retrospective study of patients with ALK-rearranged NSCLC, brain radiotherapy before TKI altered the disease failure patterns and improved PFS among patients with baseline brain metastasis (89). A multi-institutional study sought to determine the optimal management of EGFR-mutant NSCLC with brain metastasis (90). Patients enrolled were treated with SRS followed by TKI, WBRT followed by TKI, or TKI followed by SRS or WBRT. The results showed that SRS followed by TKI led to the longest OS. By contrast, a recent meta-analysis of multidisciplinary approaches in 2,649 patients with ALK rearrangements or EGFR mutations from 30 studies found that patients treated with TKIs and radiotherapy had a higher median PFS compared to TKIs alone (18.6 *vs.* 13.6), but no OS benefit was observed (91). The heterogeneity of the enrolled population and the diversity of therapeutic approaches contribute to the conflicting conclusions.

However, thanks to recent studies with larger sample sizes, and balanced characteristics and detailed classification of LT, similar conclusions have been drawn. Meanwhile, the role of LT in oncogene-addicted NSCLC with brain metastasis is becoming increasingly clear. The results from a retrospective analysis of patients with EGFR-mutant and ALK-rearranged NSCLC and 4 or more brain metastases supported radiosurgery without WBRT for these patients (92). Doherty *et al.* evaluated the impact of first-line WBRT, SRS, and TKI alone on the outcomes of patients with brain metastases from EGFR/ALK-driven NSCLC. In that study, although first-line WBRT was associated with longer time to intracranial progression than SRS or TKI alone, no difference was seen in OS among the 3 groups, supporting deferral of WBRT until intracranial progression in a selected population under close surveillance (93). According to a retrospective analysis by Miyawaki *et al.* (94), the number of brain metastases plays a vital role in the choice of LT. In the study, 176 patients were enrolled, with 107 (61%) receiving upfront TKI and 69 (39%) receiving upfront LT. Among the 69 patients, most who had 1–4 brain metastases were treated with SBRT, whereas most who had ≥5 brain metastases were treated with WBRT. In patients with 1 to 4 brain metastases, the LT group showed significantly better OS compared with the TKI group [median OS, 35 *vs.* 23 months; hazard ratio, 0.54; 95% confidence interval (CI), 0.32–0.90], while no difference was seen in OS between the

LT and TKI groups for patients with ≥5 brain metastases. A similar retrospective study was performed by Lee *et al.* (95), where 198 patients with EGFR-mutant NSCLC and brain metastases were enrolled and categorized into 4 groups: immediate WBRT, immediate SRS, delayed radiation upon progression of cranial lesions (DRT), and never cranial irradiation (NRT). The median survival was 18.5, 55.7, 21.1 and 18.2 months for the WBRT, SRS, DRT, and NRT groups, respectively. In the multivariate analysis, immediate SRS and fewer extra-cranial lesions were associated with longer survival. Taken together, these findings suggest that TKI combined with SRS is recommended as first-line treatment for patients with CNS oligometastases, with a good general condition and high Graded Prognostic Assessment (GPA) score, while TKI alone is preferred for patients with multiple brain metastases, poor general condition or low GPA score. This requires validation in future RCTs.

In the new era of the next and third- generation TKIs such as osimertinib, alectinib, and lorlatinib, the clinical value and intervention time of LT have attracted widespread attention. In a phase III AURA3 trial, the CNS objective response rate (ORR) was up to 70%, and the median CNS-PFS was 11.7 months in patients with measurable CNS lesions treated with osimertinib (96). In the phase III FLAURA study, the median CNS-PFS in patients with measurable lesions was not reached with osimertinib (95% CI, 16.5 months to not calculable), and the ORR was up to 91%. In a phase II trial (NCT01970865), 275 patients with ALK- or ROS1-positive metastatic NSCLC were enrolled into 6 different cohorts on the basis of ALK and ROS1 status, and therapy previous to lorlatinib (97). Overall response and intracranial response were 90% and 66.7%, respectively, in patients treated with first-line lorlatinib. A retrospective study on the CNS efficacy of alectinib in patients with untreated, symptomatic, large CNS metastases found a high CNS ORR of 73.3% (95% CI: 44.9–92.2%), a high CNS disease control rate of 100.0% (95% CI: 78.2–100.0%), and a long median CNS duration of response (19.3 months, 95% CI: 14.3 months-not evaluable) in patients with measurable CNS disease (98). As the next- and third-generation TKIs have demonstrated efficacy in controlling brain metastases and prolonging survival, the addition of radiotherapy in oncogene-addicted NSCLC with brain metastasis is debated. A recent evidence-based Bayesian network pooled study of multivariable survival analyses found that the combination of TKIs and SRS/WBRT was top ranking for OS followed by osimertinib. Both osimertinib and the combination of TKIs and SRS/WBRT achieved superior PFS [HR: 0.30 (0.15–0.59); HR: 0.47 (0.31–0.72)] compared with deferring SRS/WBRT (99). Since few studies have directly compared the efficacy between the next- and third-generation TKIs and the combination of radiotherapy and TKIs, vigorous clinical trials are in urgent need to establish the role of radiotherapy in oncogene-addicted NSCLC with brain metastasis in the era of the next- and third-generation TKIs.

Radiotherapy as a synergistic partner with immunotherapy

Platinum-based chemotherapy and molecular targeted therapy are the standard first-line treatment for advanced NSCLC (3). Nonetheless, the results of CheckMate 017 and CheckMate 057, 2 randomized phase III trials of PD-L1 blockade with nivolumab versus docetaxel in previously treated patients, have established the role of nivolumab in the second-line treatment in advanced NSCLC (100). Similarly, pembrolizumab and atezolizumab are approved as the second-line treatment based on results of the KEYNOTE-001, KEYNOTE-010, and the OAK trial (22,101,102). Furthermore, the encouraging results of KEYNOTE-024 and KEYNOTE-042, 2 randomized, open-label phase III trials of pembrolizumab in previously untreated patients, have revolutionized the treatment paradigm and established pembrolizumab as first-line monotherapy in advanced NSCLC (103,104). A series of RCTs have subsequently explored the combination of immunotherapy and chemotherapy or doublet immunotherapy. In the KEYNOTE-189 trial, compared to the placebo-combination group, improvement in OS was observed in the pembrolizumab-combination group regardless of PD-L1 tumor proportion score (TPS) (105). In the KEYNOTE-407 trial, the addition of pembrolizumab to chemotherapy resulted in significantly longer OS and PFS than chemotherapy alone in previously untreated metastatic, squamous NSCLC (106). The IMpower150 trial, an open-label phase III study, evaluated the efficacy of the combination of atezolizumab, bevacizumab, and platinum-based chemotherapy, in patients with metastatic nonsquamous NSCLC, and found that the addition of atezolizumab significantly prolonged the PFS and OS (107). The doublet immunotherapy, nivolumab and ipilimumab, was evaluated by the CheckMate 227 trial, where a longer duration of OS was observed in patients treated with first-line nivolumab plus ipilimumab compared to patients receiving

chemotherapy, independent of the PD-L1 TPS (23).

Despite the remarkable developments in ICIs in advanced NSCLC, several issues still remain. The results from recent clinical trials showed that the ORR of ICI monotherapies was not satisfactory. The ORR of pembrolizumab, nivolumab, and atezolizumab monotherapy in unselected advanced NSCLC were generally 15–20% (103,108,109). Furthermore, acquired resistance (AR) is unavoidable in most patients, despite an initial response to PD-1/PD-L1 blockade. In a large retrospective study of 1201 advanced NSCLC patients treated with ICIs, although complete response (CR) or partial response (PR) was observed in 243 patients, a total of 189 patients developed AR, with a 5-year rate of 74% (110). Encouragingly, 56% of patients with AR developed progression in no more than 2 lesions, which could be easily controlled by local treatment such as radiotherapy.

The rationale for the integration of radiotherapy and immunotherapy in patients with NSCLC has been widely explored, with increasing recognition of their complex interplay, and a greater appreciation of the ability of radiotherapy to influence systemic tumors. Mechanistically, radiotherapy up-regulates susceptibility to T cell-mediated attack of tumor cells by modulating the immune system (111). Moreover, radiotherapy triggers immunogenic cell death by means of promoting the release of tumor antigens from dying tumor cells, enhancing MHC class I expression, and up-regulating immunomodulatory cell surface molecules (112). Radiotherapy also triggers an inflammatory tumor microenvironment by initiating the production of pro-inflammatory cytokines (24,113). Additionally, the expression of PD-L1 is up-regulated in response to radiotherapy (114), thus, integrating radiotherapy with anti-PD-1/PD-L1 antibodies can overcome adaptive immune resistance. This synergistic antitumor effect of the combined therapy has been confirmed in mouse models of NSCLC (114-117). Besides, preclinical studies showed that the synergistic antitumor effect was affected by the types of immunotherapy drugs. For example, radiotherapy may elicit more effective antitumor immunity if administrated concurrently with anti-CTLA-4 therapy, whereas in other cases, radiotherapy may be more effective if administrated prior to anti-PD-1/PD-L1 therapy (118).

Despite the synergistic antitumor effect, the overlapping toxicity of the integration of radiotherapy and immunotherapy is an issue of clinical importance. The safety and efficacy of radiotherapy combined with immunotherapy has been investigated in several prospective clinical trials. In the phase I KEYNOTE-001 trial, 24 of the 97 patients enrolled with metastatic NSCLC received thoracic radiotherapy prior to pembrolizumab (119). The incidence of pulmonary toxicity of any grade was higher in patients with previous thoracic radiotherapy versus patients without previous thoracic radiotherapy (63% *vs.* 40%), however, no significant difference was found (P=0.052). The incidence of pembrolizumab-related pulmonary toxicity of any grade was significantly higher in patients with previous thoracic radiotherapy versus patients without previous thoracic radiotherapy (13% *vs.* 1%, P=0.046). Significantly longer PFS and OS were observed in patients who previously received radiotherapy versus those without previous radiotherapy (PFS, 6.3 *vs.* 2.0 months; P=0.008; OS, 11.6 *vs.* 5.3 months; P=0.034). More recently, in a multicenter, randomized phase II study (PEMBRO-RT), 92 patients were enrolled and treated with pembrolizumab either alone (control arm) or after radiotherapy (experimental arm) (120). No increase in treatment-related toxic effects, along with a promising ORR at 12 weeks (36% *vs.* 18%), median PFS (6.6 *vs.* 1.9 months), and median OS (15.9 *vs.* 7.6 months) were observed in the experimental arm versus the control arm.

In addition to the survival benefit of radiotherapy before ICI treatment, radiotherapy also plays a role after progression during ICI treatment. In a retrospective study aimed to evaluated subsequent outcome and management strategies for patients with AR to ICIs, 77% of patients experienced AR in lymph nodes and 88% of the patients had recurrence limited to no more than 2 sites (121). A total of 55% of the patients received LT to sites of AR, and the 2-year survival rate from AR in these patients was 92% (95% CI: 0.77–1). Similar results were found in the large retrospective study by Schoenfeld *et al.*, where 56% of patients with AR developed progression in no more than 2 lesions, which could be easily controlled by LT such as radiotherapy, thus making it possible to achieve longer survival (110). Significant tumor regression was also observed in metastatic melanoma patients who received combined radiotherapy and immunotherapy (122). In a small retrospective study of patients who had disease progression after ipilimumab who thus received subsequent radiotherapy, an abscopal response was observed in 52% of patients who exhibited a local response to radiotherapy, which correlated with prolonged OS (123).

Taken together, ICIs have resulted in impressive clinical responses, but optimal treatment requires combination with other therapies. The synergic antitumor interaction

of radiotherapy and immunotherapy makes it a promising therapeutic option either before or after progression during ICI treatment. However, many questions remain unanswered, such as the optimal sequence and timing of radiotherapy and immunotherapy, the appropriate choice of radiation techniques, the optimal radiation dose, schedule and field amongst others. More preclinical and clinical research is urgently needed to provide a clear direction on the questions above.

Conclusions

Local treatment including radiotherapy is mainly used for palliative care in advanced NSCLC. However, with new radiotherapy techniques and knowledge, the historic role of radiotherapy has transformed from pure palliation to more proactive participation. Radiotherapy, such as SBRT, has gained an increasing role in oligo-metastatic, oligo-progressive, and oligo-persistent advanced NSCLC for its excellent efficacy in local control. In oncogene-addicted NSCLC with brain metastasis, the combination of brain radiotherapy and TKIs provides clinical benefits. Furthermore, in the prosperous era of immunotherapy, encouraging results have been obtained to suggest the integration of radiotherapy and immunotherapy in advanced NSCLC. However, more clinical trials and prospective studies are warranted to explore the detailed use of radiotherapy in this setting.

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