Review Article

Palliative extracranial radiotherapy in patients receiving immunotherapy for non-small cell lung cancer: a narrative review

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Background and Objective: Role of radiotherapy (RT) in the era of immuno-oncology (IO) in advanced non-small cell lung cancer (NSCLC) is rapidly changing. RT is not only intended for addressing palliation symptoms but also is considered as a potential tool potentializing an immunogenic effect of given drugs. However, the best timing, techniques, doses, volumes, and its use for asymptomatic patients is a subject of research. We performed a review on the role of palliative RT schedules in combination with IO for advanced NSCLC. Indications in symptomatic and asymptomatic patients, outcomes, toxicity, and possible developments are discussed.

Methods: A literature search was conducted in MEDLINE and PubMed databases and clinicaltrials.gov using the keywords 'lung cancer' AND "immunotherapy" AND 'radiotherapy' OR "palliative radiotherapy".

Key Content and Findings: Body of evidence indicate that palliative RT used in combination with IO is effective in terms of symptom management and safe; does not increase the risk of serious side effects, including serious pulmonary toxicity. We have limited data evidencing improvement of survival by addition of short ablative RT dose to one site of the disease to IO in oligometastatic NSCLC. Some data indicate that short ablative doses of stereotactic body radiation therapy (SBRT) are more effective with regard to treatment response and survival than protracted RT schedule with lower fractional doses. However, this may be a selection bias of better prognostic patients who underwent SBRT. The use of steroids being a potential concern during IO should not be prohibited if clinically indicated during palliative RT. Its detrimental effect shown in some studies may also be a result of selection bias, because steroids given for not cancer-related causes during IO did not decrease survival.

Conclusions: RT for symptom management may be used during, directly before or after IO. This has a potential to ease symptom burdens and improve performance status (PS). However, still more studies are needed to establish optimal guidelines in asymptomatic patients for appropriate timing, volumes, dose, and fractionation schedules of palliative RT use in combination with IO.

Keywords: Palliative radiotherapy; immuno-oncology (IO); non-small cell lung cancer (NSCLC)

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Introduction

Radiotherapy (RT) has an established role in managing non-small cell lung cancer (NSCLC). A systematic review of treatment guidelines on RT for lung cancer from nearly 20 years ago demonstrated that the proportion of lung cancer patients treated with RT is 76% (1). From that time, new developments in RT, as stereotactic body RT (SBRT) enabling the delivery of high (ablative) doses to small volumes with a fast dose falloff outside the tumor implying an adequate normal tissues sparing, have entered into clinical practice and established its place in the management of oligometastatic disease and early stage lung cancer. On the other hand, the development of targeted therapy and immunotherapy has opened new perspectives for prolonging life in advanced disease. Immunotherapy refers to treatments that use the body's own immune system to combat diseases; immuno-oncology (IO) specifically involves immunotherapy directed at cancer.

RT, including palliative RT though still commonly used, has its roles to be redefined in the context of new therapeutical strategies developed for NSCLC. Palliative RT has been used, when a no curative option was available, due to an advanced stage of the disease, volume of the disease, performance status (PS), or serious comorbidity. Although the palliative RT schedules have been sometimes used also for asymptomatic patients, a prerequisite for the use of palliative RT was a presence of symptoms caused by growth of the primary tumor or metastases. According to the World Health Organization (WHO) definition of the palliative care, this approach is not only directed to the alleviation of the symptoms in the incurable disease, which may be interpreted as a relegation of this care to the last stages of the disease, but it is extended from the early time in the trajectory of the disease, in order to prevent occurrence or aggravation of the symptoms. This differs from the end of life care, as it does not exclude a possibility of life prolongation by the modification of the disease course, even if it is not indicated as the goal of the palliative care (2). RT has a very high potential for the alleviation of the symptoms caused by the intrathoracic tumor growth. As many as 65–77% of patients who participated in the randomized trials had the symptom improvement following palliative thoracic RT (3). Another less studied potential of palliative RT is an improvement of patients' PS by mitigating bothersome or debilitating symptoms which gives selected patients a chance to get access to the modern systemic treatment strategies, like IO or targeted therapy, potentially prolonging overall survival (OS), but reserved only for patients in good PS.

Recently, the approach to the management of the advanced stage of NSCLC has been completely changed in the way that a choice of the treatment strategy in the PS 1–2 patients is no longer guided only by a histology of the tumor, but the molecular characteristic of the disease has become a determinant of the therapy. In the absence of the driver mutations, the PD-L1 expression in cancer cells guide a choice of the treatment; the IO using immune checkpoint inhibitors (ICIs) with or without chemotherapy is a first choice treatment for appropriately selected patients (4). As the main prospective trials on the use of palliative thoracic RT were conducted before the introduction of IO in the routine management of patients with metastatic NSCLC, a question about the role of palliative RT in a new treatment era arises. The findings on the symptom management demonstrated in these trials are probably valid. However, new issues related to palliative RT with the introduction of the ICIs into the therapeutic arsenal appear: what is the role of palliative RT in the mitigation of the disease course during IO, how does this impact on OS, what are the possible immunomodulatory effects of RT, and what is the role of palliative RT schedules in asymptomatic patients. Radiation oncologists are aware of the palliative potential of RT in NSCLC patients, however, its use in combination with IO is not standardized and many issues related to the timing of the use of these two treatment modalities, radiotherapy dose, fractionation, and volume are still debatable. All these uncertainties as to the use of RT with IO were reflected in two recently published surveys (5,6). In the German survey, 51 participants of 1,291 invited radiation oncologists completed on-line questionnaires. They had to assess their knowledge on ICIs therapy; on the scale from 1 to 10 where 1 referred to "very limited knowledge" and 10 to "excellent knowledge"; 49% of responders scored their knowledge below 6. Major diversity on the pausing ICIs administration during RT was also observed, reflecting no standards in this regard (5). In the similar survey conducted among 27 Dutch radiation oncologists, 10 medical oncologists, and 17 pneumonologists, the major diversities in the combination of ICIs with RT and concerns of participants about their knowledge on these issues were demonstrated. More than half of the participants declared not to have sufficient knowledge on the issue of combination of targeted therapy or IO with RT. Moreover, such knowledge, resources, multidisciplinary protocols did not exist in their

Table 1 Methodology of the search for the review

Items	Specification
Date of search	2022: June 15th–July 15th
Databases and other sources searched	MEDLINE and PubMed databases and clinicaltrials.gov
Search terms used	'lung cancer' AND "immunotherapy" AND 'radiotherapy' OR "palliative radiotherapy"
Timeframe	1980–2022
Inclusion and exclusion criteria	Restricted to articles published in English; without predefined restriction as to the study type
Selection process	Conducted by the author of this study: Lucyna Kepka

institutions. No respondent declared to refuse patient RT during IO, but 37% and 22%, modified their fractionation scheme and RT technique, respectively (6). These variations reflect the lack of evidence-based guidelines on the safety and outcomes of these new combinations.

Short RT schedules used in advanced NSCLC have undergone a huge evolution, from the strictly palliative use, when some standards where available (7) to the new applications as a bridge from palliative care to aggressive treatment by its consolidative, salvage or immunomodulatory effect in combination with IO (8,9). However, still it is a gap between rapid development of the IO in clinical practice and the evidence-based knowledge on the incorporation of the palliative RT schedules into the treatment strategies based on IO.

Currently, we have evidences that local therapy with radiation may prolong survival in conjunction with effective systemic treatment for oligometastatic disease, especially in oligometastatic setting. This was extensively discussed in a recent consensus of international experts on the use of RT in metastatic NSCLC. However, this was agreed that the evidences on the impact of RT on survival come from the trials in which IO was not used (10). Thus still being aware of the impact of IO on survival in metastatic NSCLC, we cannot yet consider these cases as curable. Thus we will consider all types of RT schedules (shorter or longer, with higher or lower dose, covering all sites of the disease or only some parts of the tumor extension) used in combination with IO, as palliative schedules, not excluding the potential of RT for prolongation of survival in this setting.

We performed a review on the role of palliative RT schedules in combination with IO for advanced NSCLC. Indications in symptomatic and asymptomatic patients, outcomes, toxicity, and possible developments will be discussed. We present the following article in accordance with the Narrative Review reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-22-1969/rc).

Methods

A literature search was conducted in MEDLINE and PubMed databases and clinicaltrials.gov using the keywords 'lung cancer' AND "immunotherapy" AND 'radiotherapy' OR "palliative radiotherapy". The secondary references cited in articles obtained from the MEDLINE and PubMed search were also retrieved. Methodology of the search is summarized in the *Table 1*.

Palliative RT for NSCLC: the state of the art before an era of IO

Thoracic RT

There are numerous indications for the use of palliative RT in NSCLC; first of all, the symptoms caused by the growth of the primary tumor and metastases to the regional lymph nodes, which encompasses a large field of the thoracic RT issues. Extracranial metastases, mainly to bone, but also to any organ, may cause bothersome symptoms and are often amenable to management by RT. RT for brain metastases represents a complex and distinct problem which is outside the scope of this review.

Palliative thoracic RT is used for palliation of various symptoms: dyspnea, hemoptysis, cough, and pain are the most often reported. As mentioned above, a meta-analysis of 13 randomized trials including 3,473 patients evaluating different doses and fractionation schedules (single or two fractions *vs.* multi-fractional regimens) of palliative thoracic RT demonstrated that 65–77% of patients had a symptom improvement. This palliative effect was independent of the type of fractionation used, i.e., shorter and more

protracted RT schedules were equally effective for symptom management (3). In the randomized trials, RT was the most efficacious for hemoptysis and chest pain, 72–95% and 50–88%, respectively, whilst the lowest effect was for cough and dyspnea, 20–80% and 37–66%, respectively (7). The etiology of these two later would be multifactorial, not only caused by the tumor. Patients with superior vena cava syndrome (SVCS) were not included into the prospective trials on dose, fractionation in RT. A systematic review on the treatment of SVCS showed that 60% of patients with SVCS caused by NSCLC obstruction had a symptom relief after RT alone (11).

Higher radiation dose with more protracted RT schedule gave similar symptom relief than single or two fractions in prospective randomized trials (12-20). This was confirmed by a Cochrane systematic review of 14 randomized trials; the higher dose, more fractionated palliative thoracic RT regimens did not provide better or more durable palliation (21). Intuitively, higher radiation dose has for a goal a prolongation of survival. However, the randomized trials gave conflicting results concerning correlation of better survival with higher biological dose. Some demonstrated that higher dose was related to the improved survival (14,16,19), others demonstrated no difference of survival in relation to the dose (12,13,15,17,18,22-25), and in one, lower radiation dose was related to better survival (20). As mentioned above, Cochrane systematic review of 14 randomized studies did not find evidence of better survival rates with the higher dose regimens in the whole population of included patients. However, in patients with good PS the higher biological dose was related to improvement of survival at the expense of higher esophageal toxicity (21). Another systematic review of 13 randomized trials draw similar conclusions, despite symptom rate similar for lower and higher doses independently of patients PS, patients in good PS had an improvement of survival with higher radiation dose. For doses equal to and higher than the biologically equivalent dose (BED) of 35 Gy, there was an improvement of about 5% for 1-year survival compared with the lower doses (P=0.002). Similarly, as in Cochrane review (21), the oesophageal toxicity was significantly higher in higher dose (more than 35 Gy BED) than in lower dose regimens, 20.5% *vs.* 14.9%; P=0.01 (3). As esophagitis is a common RT-related toxic effect, a randomized phase III trial was designed to examine if the use of IMRT may reduce esophageal toxicity of palliative thoracic RT. Ninety patients receiving 20 Gy in 5 fractions (36 patients), or 30 Gy in 10 fractions (54 patients) were randomized to standard RT or esophagus-sparing (ES)-IMRT. Although ES-IMRT did not demonstrate a significant improvement in esophageal QoL measured two weeks after RT, the incidence of symptomatic esophagitis was significantly lower in ES-IMRT arm, 2% *vs.* 24% in the control arm. The reduced esophagitis was higher in patients receiving higher dose (30 Gy). These findings show that new radiation techniques are beneficial in patients receiving higher doses of palliative RT (26).

A debatable issue is the use of palliative RT in asymptomatic patients for whom curative RT is not an option. The possible indications for the use of palliative RT schedules in such patients would be the prolongation of survival, prevention of the occurrence of serious symptoms, or preservation of acceptable quality of life. In one study, 230 asymptomatic patients were randomized to receive immediate RT with a single fraction of 10 Gy or two fractions of 8.5 Gy versus delayed RT until symptom progression. Patients did not receive a systemic treatment at baseline. No difference in survival, QoL, symptom control was found between study arms. In addition, 56% of patients in the delayed RT arm did not need any form of thoracic RT until death (27). Similar findings on the futility of immediate RT for symptom prevention were brought by a Norwegian trial. Patients were randomized to three different palliative RT dose schedules and were stratified according to the presence of thoracic symptoms for palliation. Compared with symptomatic patients, those with no symptoms at baseline did not benefit from immediate RT in terms of improved long-term symptom control and their QoL worsened in the weeks following RT. It was concluded that delaying RT until symptoms occurrence is justified in asymptomatic patients (28). Although these two trials demonstrate no benefit of palliative RT in symptom prevention in asymptomatic patients, in the light of data indicating a possible impact on survival of higher radiation doses in good PS patients (3,21), a protracted RT schedule may be considered in such patients if they are unable or refusing to receive any form of systemic treatment. Also the use of modern RT techniques, like IMRT, may be beneficial in such patients to reduce a risk of esophagitis as demonstrated by a randomized trial (26).

Patients in PS 3 or 4 are not candidate for systemic treatment according to any guidelines (4,29), however if a deterioration of the PS is caused by a suffering from the symptoms that may be alleviated by a short RT schedule, palliative RT may reverse a disease course, and consequently an improvement of PS may enable the patient to get a

systemic treatment with a chance on prolongation of survival. A short course RT is frequently considered and indicated to a patient with very bothersome symptoms that could be potentially amenable by radiation, even though improvement of PS is not highly likely. However, a caution should be paid in such patients in order to avoid the useless RT at the end of life. Patients dying shortly following palliative RT are unlikely to have any benefit and may experience harm caused by the procedures related to the RT preparation and delivery. The 30-day mortality rate after palliative RT is an important quality metric. In the meta-analysis, 42 studies contributing 88,516 patients with advanced cancer of any primary who received palliative RT were evaluated in this regard. The overall 30-day mortality rate after palliative RT was found to be 16%. Patients in PS 3–4 were more likely to die within 30 days after RT (30). In order to minimize 30-day mortality after RT, an accurate estimation of disease related survival is imperative to know.

RT for bone metastases

Bone metastases are the most common distant extracranial metastases amenable to palliation by RT. In 17,431 patients deceased from lung cancer, identified from the nationwide Swedish Cancer Registry, the bone was the most common metastatic organ in NSCLC (39%). Bone metastases also featured the worst survival compared to other sites (31). In the systematic review and meta-analysis of 29 randomized trials, RT brought a pain relief in 61% of cases of bone metastases. No difference in response rates were found with multiple (20 Gy in 5 fractions or 30 Gy in 10 fractions) *vs.* single (8 to 10 Gy) fractions, 62% *vs.* 61%, respectively, but a significant 2.5 folds increase in re-irradiation need was seen after a single fraction, 20% in the single dose arm, *vs.* 8% in multiple fraction arm, P<0.01 (32). Nowadays, conventional palliative RT for bone metastases is often replaced by SBRT, with one or a few fractions, providing the local control rate exceeding 80% in most studies with a very low grade of serious toxicity. Data on the pain control with the use of SBRT compared with conventional palliative RT are conflicting. Some studies showed a higher pain relief with SBRT than with conventional RT (33-36), others did not demonstrate any difference (36,37).

Changing role of RT in stage IV NSCLC

Historically, RT used for stage IV NSCLC had a palliative intent. Disseminated disease was considered as practically being out of scope of curative local treatment. However, in the context of technological progress in RT, i.e., a development and rapid propagation of SBRT techniques, an irradiation of a few separate disease sites has become possible. A concept of oligometastatic disease, as a disease stage, intermediate between localized and diffusely disseminated state has gained an acceptance as a category of stage IV disease amenable for more aggressive local treatment even without symptoms for palliative care. This notion in NSCLC, rather intuitive varies from a trial to trial in regard to a number of metastases or metastatic sites including or not a control of the primary, as well as regional metastases, and a time in the disease course when it is evaluated (synchronous or metachronous metastases; at baseline or after systemic treatment). Oligo-metastatic NSCLC was first defined as a maximum of 5 metastases and 3 organs involved, and mediastinal lymph nodes were not considered a metastatic site. Fluorodeoxyglucose F18 PET-CT and brain imaging were considered mandatory for a definition (38). Based on an ESTRO-ASTRO consensus, oligo-metastatic disease is currently defined as 1–5 metastatic lesions, with a controlled primary tumor being optional, but all metastatic sites must be safely treatable (39). Although consensus among experts was obtained, several issues remain unresolved and will require further research to agree on a definition of oligometastatic disease.

A systematic review and meta-analysis of 21 randomized and retrospective studies including 924 synchronous oligometastatic NSCLC that compared an addition of radical RT for primary tumor to management without RT demonstrated the improvement of progression free survival (PFS) [hazard ratio (HR) =0.42, 95% CI: 0.33–0.55; P<0.001] and OS (HR =0.44, 95% CI: 0.32–0.6; P<0.001) with addition of thoracic RT (40). We have two randomized trials that demonstrated a benefit of using consolidative RT in oligometastatic NSCLC. Both these trials were prematurely closed, when the interim analyses showed that PFS is significantly better with local treatment arm. In one study, 29 NSCLC without driving mutations patients with 1–5 metastases after 4–6 cycles of chemotherapy were randomized to RT with maintenance chemotherapy (14 patients) or maintenance chemotherapy alone (15 patients). In RT arm, seven patients received SBRT and seven hypofractionated RT 45 Gy in 15 fractions. A significant improvement in PFS in the RT-plus-maintenance chemotherapy arm of 9.7 *vs.* 3.5 months in the maintenance chemotherapy-alone arm was demonstrated, P=0.01 (41). Another randomized trial, also prematurely

closed after enrollment of 49 patients, included patients with up to 3 metastases after 4–6 cycles of chemotherapy or three months of targeted therapy; 25 were assigned to local treatment (mainly RT) with or without maintenance systemic treatment and 24 to maintenance therapy or observation alone. Survival benefit was demonstrated in patients who were treated with local consolidative RT or surgery, with an extension of median PFS from 4.4 to 14.2 months (P=0.022), and median OS from 17.0 to 41.2 months, P=0.017 (42). Recently, a randomized clinical trial (SINDAS) closed after inclusion of 133 NSCLC harboring epidermal growth factor receptor (EGFR) mutation patients with up to 5 metastases (excluding brain metastases) showed that the combination of EGFR tyrosine kinase inhibitors (TKI) and up-front concurrent RT (5× 5–8 Gy) improved the PFS (20.2 *vs.* 12.5 months, P<0.001) and OS (25.5 *vs.* 17.4 months, P<0.001) when compared to EGFR-TKI alone (43). In the SABR-COMET trial, 99 patients including 18 NSCLC with up to 5 metastases were randomized to SBRT directed to all metastases *vs.* palliative standard of care. Patients who received SBRT had longer OS than patients who did not, the 5-year OS rate was 42.3% in the SBRT arm *vs.* 17.7% in control arm, P=0.006) (44). These promising results support the use of short course, however, high (ablative) dose RT for oligometastatic NSCLC. RT in stage IV disease has been using not only in purely palliative role. However, none of randomized trials evaluated the role of consolidative RT in stage IV disease patients who were under management using IO. The benefit of adding RT to IO in stage IV disease remains to be demonstrated. Combinations of short course RT with IO with emphasis on short course RT will be discussed in details below.

Combination of IO with RT: survival outcome and toxicity

Many stage IV NSCLC patients are receiving IO based on ICIs given either in monotherapy or in combination with chemotherapy. Radiotherapy given in combination with ICIs concurrently or sequentially may be delivered in palliative intent when it is urgent to alleviate patients' symptoms or in asymptomatic patients in case of oligoprogressive or oligorecurrent disease, or in oligometastatic patients with theoretical goal of improvement of PFS and OS. RT for purely palliative purposes is given as a short course hypofractionated RT, whilst in asymptomatic patients ablative doses with SBRT are given whenever it is feasible. Theoretically, to have a benefit from a combination of RT with IO, these two treatment modalities should interact by spatial, temporal, and biological cooperation, as well as a cytotoxic enhancement and no meaningful toxicity is the prerequisite of the clinical use of this combination (45-47). All these properties supported by strong preclinical evidence, were driving clinical studies (47). We have already some evidence on the clinical benefit of the combination of RT with ICIs in NSCLC. The first suggestion that RT preceding treatment with ICIs may improve treatment outcome resulted from a secondary analysis of the phase I KEYNOTE-001 trial in which safety and anti-tumor activity of pembrolizumab were evaluated in advanced NSCLC. In 97 included patients, 38 received prior extracranial RT. PFS and OS with pembrolizumab were significantly higher in patients who previously received any RT than in patients without previous RT (48). Single studies on the combination of RT with ICIs did not demonstrate improvement of PFS compared with ICIs alone. In the retrospective study including 269 metastatic NSCLC receiving nivolumab or pembrolizumab, 102 patients received RT for symptom control during or within 3 months of starting anti-PD-1 therapy. RT revealed to be efficacious for symptom relief, however, did not improve PFS, nor OS (49). Similarly, two small, prospective phase II studies that evaluated the safety and response rate after addition of RT to one disease site of metastatic NSCLC to pembrolizumab did not demonstrate a significant improvement of PFS with addition of RT (50,51). The phase II PEMBRO-RT study randomized 76 patients with metastatic NSCLC to receive pembrolizumab either alone or one week after RT (3×8 Gy) to a single tumor site. Despite that overall response rate, PFS, and OS were numerically higher, this not reach statistical significance, probably because of a small size of the study (50). In the phase I/II MDACC trial, 72 patients were randomized to RT (50 Gy in 4 fractions) to one site of metastatic NSCLC concurrent to administration of pembrolizumab *vs.* pembrolizumab alone. Addition of RT did not bring a significant improvement of PFS (51). However, a pooled post-hoc analysis of the PEMBRO-RT trial and the MDACC trial demonstrated that both PFS (median 9.0 *vs.* 4.4 months; P=0.045) and OS (median 19.2 *vs.* 8.7 months; P=0.0004) were improved with the addition of RT to pembrolizumab (52). A meta-analysis of 6 studies (4 randomized; 2 retrospective from National Cancer Database) including 8,435 patients; locally advanced [810] and metastatic [7,574] NSCLC evaluated the impact of RT added to ICIs on survival. ICIs-RT significantly increased

the 1- and 3-year OS relative risk by 0.75 (P=0.0003) and 0.85 (P=0.0006), respectively, compared to ICIs or RT alone (53).

From the perspective of palliative RT used in combination with ICIs, the evidences on the improvement of survival with addition of RT to ICIs in advanced NSCLC have less importance than the evidences on the safety of such combination. Available evidence suggests that combination of ICIs and RT does not increase the incidence of severe adverse effects. In the pooled analysis of patient-level data from prospective trials in the US Food and Drug Administration databases that included 16,835 patients, patients receiving ICIs within 90 days following RT had generally similar rates of adverse effects overall with no difference seen in high-grade adverse effects compared with those who had IO alone (54). Pneumonitis is a relevant side effect of both thoracic RT and ICIs. A meta-analysis of 16 phase II/III trials including 6,360 patients evaluated the risk of PD-1 inhibitors-related pneumonitis during IO alone. The incidence of pneumonitis during anti-PD-1 treatment was 2.9% for all-grade and 1.5% for high-grade pneumonitis. The lowest incidence of pneumonitis was reported for patients with melanoma (0.7%), but for patients with advanced NSCLC was the highest (4.7%) (55). Radiation pneumonitis depends mainly on dose, radiation volume, and the presence of concomitant lung disease and varies between studies from 5% to 50% of patients irradiated for lung cancer (56). A question arises on how the combination of the two treatment modalities potentially affecting the lung tissue will increase the incidence of pneumonitis. In the German survey on the pattern of practice in combining radiotherapy with ICIs, the participants were the most concerned about pulmonary toxicity of these combinations. Pulmonary toxicity during thoracic RT-IO was a potential concern for 59% of participants (5). In two randomized trials comparing Pembrolizumab alone *vs.* Pembrolizumab plus RT, there was no increase of high grade pneumonitis in the experimental arms (50,51). From available evidence, it appears that there is an increase in the occurrence of all grade pneumonitis, however, high grade pneumonitis is similar between patients who receive only ICIs and those who receive ICIs plus RT. This was demonstrated in KEYNOTE-001 trial in which all grade pneumonitis was higher in patients receiving RT before pembrolizumab without an increase of grade 4 and higher pulmonary side effects (48). In the phase-III PACIFIC trial studying consolidation therapy with durvalumab after concurrent radio-chemotherapy, an increased rate of all grade pneumonitis was observed in the durvalumab group without an increase of grade 3 and higher pneumonitis (57). However, still data on the safety of such an approach is accumulating. The increased risk of pneumonitis in 41 patients receiving thoracic RT (SBRT or hypofractionated RT) after previous occurrence of immune-related adverse effects (irAEs) defined as a need of receiving steroids after atezolizumab, nivolumab, pembrolizumab, durvalumab, or ipilimumab was reported; 61% developed grade 2 and higher radiation pneumonitis at a median of 4 months from thoracic RT and 11 months from onset of irAEs (58). Our knowledge about the dose constraints for lung tissue in thoracic RT come from era of RT alone or RT-CHT. A question arises, whether we may apply the same dose constraints for safe application of RT + IO as it was established before the use of ICIs with RT. Dose-volume-effect correlations for pneumonitis after combined SBRT with PD-1 or PD-L1 inhibitors given within a time frame of 50 days around thoracic RT of 13 patients were compared with data set of 29 patients receiving SBRT without ICIs administration. Three of 13 patients from SBRT + ICIs group had a large extent of pneumonitis, even bilateral and apart from the radiation volume. No such case was observed in the SBRT alone group. In general, a shift towards correlation of lower doses for a risk of pneumonitis was observed in SBRT + ICIs group compared to SBRT alone group (59). This suggestion of different correlation of dose-volume-effect for pneumonitis was not supported by the largest published series of thoracic SBRT and IO evaluating lung dose-volume parameters in patients receiving ICIs either sequentially (within 7 days after completion of SBRT) or concurrently (before or at the start of SBRT) in 123 patients participating in three phase I trials on combination SBRT and IO. The overall rate of grade 3+ pneumonitis was 8.1%, and its occurrence was correlated with established dose constraints for lung used in SBRT protocols, P<0.05 (60).

Summarizing, data on the efficacy and toxicity of RT-IO are still accumulating, however, the current evidence does not preclude the use of radiation for symptom management during IO whenever it is needed.

Evidence and current practice in the use of palliative RT with IO

Emergencies

In NSCLC emergencies include SVCS, massive

hemoptysis, airway obstruction causing major dyspnea, and spinal cord compression. In such indications, RT should be administered without delay. If this occurs during IO, the concurrent use is not a contraindication for starting RT, not only for a reason that we have already data about a safety of such an approach, but also because RT is a life-saving treatment at this moment. Emergencies are often cause of major deterioration of PS and this represents an obstacle for starting ICIs administration, because such a treatment is dedicated to PS 0–2 patients only according to the guidelines (4). Thus for some patients an appropriate use of RT may offer a quick symptom relief and subsequent improvement of PS enabling prescription of IO or other appropriate systemic treatment.

In most emergencies, as spinal cord compression, SVCS, or massive airway obstruction, the steroids are used jointly with RT to decrease symptom burden. The baseline use of corticosteroids is associated with poor outcomes in NSCLC patients receiving ICIs. The use of steroids during IO is debatable. One study evaluated an outcome in NSCLC patients receiving IO depending on whether corticosteroids were administered for cancer-related palliative reasons or cancer-unrelated indications, such as treatment of autoimmune disease, hypersensitivity reactions, COPD. Patients receiving 10 mg or more of prednisone within 24 hours of ICIs initiation had shorter PFS and OS than patients who received 0 to <10 mg of prednisone at that time. However, the detrimental effect of ≥10 mg prednisone was demonstrated only in patients who received steroids because of cancer-related palliative indications; steroids prescribed for cancer-unrelated indications had no negative impact on survival (61). Similar findings were found in a systematic review and meta-analysis of 16 studies including 4,045 patients that compared steroids and non-steroids users during treatment with ICIs. Patients taking steroids were at increased risk of progression and death compared to those not taking steroids, P=0.03. However, in sub-group analysis, the negative effect of steroids on PFS and OS was shown only in patients taking steroids for symptom management; steroids used to mitigate adverse events did not impact survival (62). It is very likely that this difference in survival are not related to the use of steroids but are driven by negative prognostic factors associated with a sub-group of patients treated with palliative RT in comparison with better prognosis of asymptomatic patients. Thus the use of steroids if clinically indicated should not be prohibited also during IO.

Timing of palliative RT

The preclinical studies indicate that RT in combination with IO should be administered concurrently to obtain the maximum synergistic effect by the increase of damaged cancer cells and the release of tumor-specific antigens exposed to the immune system and subsequent activation of cytotoxic T cells, as well as an adaptation of tumor micro-environment (63,64). However, the optimal timing of RT has not been investigated in prospective trials. No phase 3 randomized trials have been reported on the concurrent RT-IO. Thus for the palliative RT use we may recommend its delivery whenever a need for symptom relief occurs. Its use before IO may be especially beneficial in patients with a heavy symptom burden precluding the use of systemic treatment. For asymptomatic patients, we have no evidence from prospective studies on what the best combination is: sequential as consolidation, sequential preceding IO, or the concurrent use.

Outcome of palliative RT

As discussed above, before IO era, the efficacy of palliative thoracic RT in symptom relief was independent of the RT schedule used, i.e., single or 2 fractions *vs.* protracted, higher dose schedule. Contrarily, for patients in good PS, survival was longer with protracted and higher dose RT schedules (3,21). For asymptomatic patients, the use of palliative RT in terms of prolongation of survival or prevention of symptoms was ineffective in two prospective trials (26,27). All these findings may be challenged in the IO era. A pooled analysis of two randomized trials, in which 3×8 or 4×12.5 Gy were added to pembrolizumab in asymptomatic, oligometastatic patients demonstrated an improvement of PFS and OS (52). Thus we cannot exclude that apart of its palliative effect short or even very short course RT when used with IO prolongs survival via different mechanisms than RT alone i.e., promoting action of the immune system. However to prove that, we need more evidence from larger prospective trials. Asymptomatic oligometastatic stage IV NSCLC patients had a benefit from local consolidative RT following systemic treatment with chemotherapy or targeted RT (41,42), as well as up-front RT used in synchronous oligometastatic EGFR mutated NSCLC (43). However, these patients had no IO. The benefit from the use of short hypofractionated RT for asymptomatic patients receiving IO requires a confirmation

by larger randomized trials.

Technique, dose, and volume of palliative RT

Data are accumulating that contrarily, as before the use of IO, RT for stage IV NSCLC when combined with ICIs gives better outcome when used as short schedule of ablative doses as in SBRT techniques than conventionally fractionated protracted RT. An exploratory analysis of the phase I/II MDACC trial that randomized patients to pembrolizumab with or without RT revealed that abscopal effect was numerically higher in SBRT arm (38%) *vs.* conventional RT (10%) and this was translated in significant improvement of PFS in SBRT arm, 20.8 *vs.* 6.8 months, P=0.03. This may be related to lower reduction in lymphocyte count in SBRT group compared to conventional fractionation group demonstrated in this trial (51). Probably, larger radiation field and protracted RT schedule cause more lymphocytic depletion and by consequence reduce immunogenic effect. Two large retrospective studies based on National Cancer Database (NCDB) evaluated an outcome of combined RT-IO depending on the technique and fractionation schedule demonstrated that higher fractional doses combined with IO may be beneficial in metastatic NSCLC (65,66). In one study, patients receiving RT with doses 5 Gy and higher were designed as having hypofractionated RT (HRT) while those receiving doses <5 Gy were deemed standard fractionation (SFRT). Patients receiving IO had an improved OS regardless of fraction size compared to patients receiving RT alone. Patients receiving SFRT had worse OS than patients receiving no RT. HFRT improved OS, even though this difference was not significant (66). In another NCDB-based study patients receiving IO for metastatic NSCLC were further divided as those who received no RT, stereotactic RT (SRT), and non-stereotactic external beam RT (EBRT). For IO patients, the median OS for no RT, EBRT, and SRT was 14.5, 10.9, and 18.2 months, respectively (P<0.0001) (66). Obviously, in both these studies, an improvement of OS with ablative doses and small volumes may be related to the negative selection of patients for treatment with protracted schedules usually used in large tumor volumes and symptomatic patients, thus in cases carrying poor prognosis. One randomized phase II trial that evaluated different RT doses and techniques in metastatic NSCLC was prematurely closed after inclusion of 90 patients due to futility assessed at interim analysis. Patients who progressed at first line PD(L)-1 therapy were randomized to durvalumab plus tremelimumab alone *vs.* the same drugs plus high dose SBRT (3×8 Gy) *vs.* the same drugs plus low dose RT (0.5 Gy delivered b.i.d for 2 days during each of the first four cycles of IO). There was no difference as predefined by a study protocol in overall response rate between IO alone, IO plus SBRT, and IO plus low dose RT arms (67). In most palliative cases, the use of ablative doses with stereotactic techniques may not be feasible. Currently in Canada, a prospective, observational study NCT03705806 is recruiting patients with stage IV NSCLC, routinely treated with a PD-1 inhibitor for indications approved by Health Canada. All patients who are selected are referred for palliative thoracic RT with a standard dose prescription of 30 Gy in 10 fractions. The main end-point of this study is toxicity. No other trials investigating protracted palliative RT schedules in combination with IO were found by our search.

Concerning optimal volume of RT in combination with IO, it is also a subject of debate with no clear guidelines on this issue. We are used to irradiate all detectable disease sites in radical RT. In symptomatic patients this was conceivable to treat only these parts of tumor extension that caused the symptoms, as an irradiation of mediastinum only in patient with SVCS and presence of other disease foci. However, for asymptomatic stage IV patients, a question of target volume, remains a pertinent issue. It may seem attractive for radiation oncologist to irradiate all accessible disease sites to control a disease. However, irradiation of too large volume may lead to the depletion of lymphocytes which reduces immunomodulatory effect of the used drugs. A reasonable choice should be an inclusion only of the site of recurring or progressing disease (oligo-recurrence or oligoprogression) or a choice of the lesion with no or minor risk of side effects.

Table 2 summarizes all differences and unresolved issues of the use of palliative RT for NSCLC without IO in comparison with its use in combination with IO.

Conclusions

Current body of evidence indicates that palliative RT may be used during, directly before or after IO. This has a potential to alleviate symptoms burden and in some cases lead to the improvement of PS and subsequently enable patient to get an appropriate systemic treatment which was inaccessible due to the poor PS. Palliative RT delivered concurrently with IO has also a promising potential of improving OS by promoting immune-dependent cell death

Table 2 Palliative RT for NSCLC without use of IO *vs.* palliative RT in combination with IO

Issue	Palliative RT without IO	Palliative RT with IO
Outcome for symptom relief (dose and fractionation)	65–70% in thoracic palliative RT; outcome independent of RT schedule used (1–2 fractions *vs.* protracted RT)	Not studied in this context; however, no rationale for questioning its efficacy for symptom relief
Outcome for OS (dose and fractionation)	In good PS patients OS was prolonged with protracted RT schedule compared to single fractions and lower RT dose; for poor PS patients no difference in regard to dose/fractionation	No randomized trial that compared OS depending on dose/fractionation; suggestions from preclinical and retrospective studies that shorter RT schedule using ablative techniques may be beneficial via lower depletion of lymphocytes and the enhancement of anti-tumor immune response
RT technique	Higher RT dose led to the increase of esophageal toxicity; one small randomized trial demonstrated that IMRT may reduce this risk in higher dose regimens (10×3 Gy)	SBRT indicated in preclinical and some clinical studies as more beneficial than standard RT; however, this may be a selection bias of better prognostic patients referred for SBRT
RT volume	No randomized studies on this issue: the usual practice was in asymptomatic patients to treat all amenable to radiation disease sites; in symptomatic patients to treat lesions causing symptoms	No randomized studies on this issue; current practice to treat in asymptomatic patients oligoprogressive or oligorecurrent lesion, or 1–3 amenable to radiation lesions with no or minor risk of serious side effects, if more lesions persist leaving them for abscopal effect of IO; for symptomatic patients as before IO era
Treatment of emergencies	RT to start without delay; in thoracic RT no randomized studies on dose/fractionation; for compression of spinal cord no difference in outcome for shorter/longer RT schedule	As before IO era; additional benefit may be an improvement of PS with palliative RT enabling to deliver appropriate systemic treatment
Use of steroids during palliative RT	Was not questioned if clinically indicated	Suggestions that steroids given for symptom management may reduce an effect of IO and decrease OS from some studies; however, this may be an effect of selection bias; patients needing steroids may have a worse prognosis. Thus, if clinically indicated steroids should be given with palliative RT
RT for asymptomatic patients	No impact on OS, no on prevention of symptoms occurrence of protracted RT schedules; in oligometastatic patients, small randomized trial demonstrated that SBRT prolongs PFS/OS (44) also as consolidation after systemic treatment (41,42) or as upfront treatment in targeted RT for EGFR (+) (43)	Short ablative courses may prolong OS in oligometastatic patients

RT, radiotherapy; NSCLC, non-small cell lung cancer; IO, immunotherapy; OS, overall survival; PS, performance status; IMRT, intensity modulation radiation therapy; Gy, gray; SBRT, stereotactic body radiation therapy; PFS, progression free survival; EGFR, epidermal growth factor receptor.

and abscopal effect. Some canons of palliative RT from pre-IO era, as the futility of using short RT schedules for asymptomatic patients are challenged in the era of IO. The preclinical and some clinical studies indicate that short, ablative RT schedules may improve treatment outcome in oligometastatic patients. Nevertheless, we need more studies to establish the new rules for volumes, dose, and fractionation schedules for palliative RT use in combination with IO.

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Footnote

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