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Review

Stereotactic body radiotherapy in the treatment of advanced non-small cell lung cancer patients with oligoprogression during immunotherapy

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ABSTRACT

Immune checkpoint inhibitors (ICIs) improve survival in patients with metastatic non-small cell lung cancer (NSCLC), but, unfortunately, only a minority clearly benefits from ICIs, and treatment options after progression to these agents are limited and not very effective. Patients with oligometastatic disease may benefit from local treatments such as radiotherapy, achieving better local control rates, delaying progression and improving survival. Stereotactic body radiotherapy (SBRT) allows to deliver high radiation doses, with much less toxicity. Furthermore, radiotherapy has several immunomodulatory effects that could enhance the activity of ICIs and this synergy seems to be improved with SBRT. Our aim was to review the evidence supporting the use of SBRT in patients with metastatic NSCLC with oligoprogressive disease after an initial benefit with ICIs.

KEYWORDS: NSCLC, immunotherapy, immune checkpoint inhibitors, oligoprogressive disease, stereotactic body radiation therapy.

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Introduction

Immune checkpoint inhibitors (ICIs) improve survival in patients with metastatic non-small cell lung cancer (NSCLC), achieving a significant percentage of long-term survivors [1-5].

Patients with driver mutations, who after an initial response to targeted therapies, show oligoprogressive disease, may benefit from local treatments for the progressing lesions, while maintaining the same systemic treatment [6]. However, this therapeutic approach is not defined in responders to immunotherapy (IO) who oligoprogress during treatment.

Evidence from prospective and retrospective studies support the use of local ablative therapies in patients with oligometastatic NSCLC, as this strategy can significantly increase survival in selected patients [7].

Radiotherapy (RT) is a widely used therapeutic option in the management of oligometastatic disease. In particular, stereotactic body radiotherapy (SBRT) allows the delivery of high biologic doses of radiation, with exquisite precision and low toxicity [7].

Currently, there is evidence that radiotherapy, in addition to its well-known direct antitumor

effects, also has immunogenic effects that may improve outcomes in patients treated with IO. This immunomodulatory role of RT seems to be dose-dependent, with higher doses per fraction being more efficient in promoting tumor immunogenicity. Therefore, SBRT could be more immunogenic than conventional RT [8].

A potential synergy for the combination of RT and IO is supported by the results of the PACIFIC trial, in which durvalumab increased progression-free survival (PFS) and overall survival (OS) in patients with unresectable NSCLC who had completed chemoradiotherapy [9-11].

The aim of this review is to study the evidence supporting the use of SBRT in NSCLC patients showing an initial benefit from IO but subsequently present oligoprogression during treatment.

Effects of RT on the antitumor immune response

RT has direct effects on tumor cells, causing irreparable damage to DNA, resulting in cell death and loss of replicative potential [12]. It is currently known that in addition to these direct antitumor effects, RT also has immunogenic effects [8, 12].

Radiation damage of tumor cells favors neoantigen presentation and the development of a specific T-cell-mediated anti-tumor response [13]. In addition, after damage to the tumor cell, cytokines are released [13, 14], which attract activated T lymphocytes towards the tumor.

Also, RT improves the recognition of tumor antigens through the activation of dendritic cells and by increasing the expression of molecules of the class I major histocompatibility complex (MHC) [15-17], which in turn lead to activation of CD8+ T lymphocytes [15, 17].

Finally, RT can modulate the tumor micro-environment by decreasing immunosupressive cells such as T-regulatory cells (Tregs) and myeloid-derived suppressor cells (MDSCs) and thereby induce long-lasting anti-tumor immune responses [18]. In summary, RT has immuno-modulatory effects, which can activate a local and systemic anti-tumor immune response [19].

Immunotherapy in combination with radiotherapy

RT has immunogenic effects, which can be enhanced by the administration of IO [20]. Besides the many effects already mentioned, RT can increase PD-L1 expression on the surface of tumor cells, turning cold tumors into warm tumors, and *a priori* IO non-responding tumors into responding ones [12, 21, 22].

Preclinical and clinical data suggest that the immunogenic effect of RT increases with a higher dose per fraction, and according to this, SBRT would be more immunogenic than conventional fractionated RT [20].

Preclinical evidence supports the synergistic effect of RT and IO [21]. Demaria *et al*., using mouse models of poorly immunogenic breast cancer, showed that the combination of local radiation and an anti-CTLA-4 antibody, achieved a CD8+ T lymphocyte-mediated tumor response that also improved survival [22]. In another study in mice [23], RT increased PD-L1 expression in the tumor microenvironment while the administration of an anti-PD-L1 agent increased the efficacy of RT through a mechanism dependent on cytotoxic T lymphocytes. Furthermore, it was found that the administration of RT and an anti-PD-L1 decreased the presence of immunosuppressive cells in the tumor microenvironment, which may favor the response to IO. This synergistic effect of RT and IO was also observed in a study conducted in mice by Twyman-Saint Victor *et al*. [24], in which the combination of RT, an anti-CTLA-4 and an anti-PD-L1, achieved tumor responses through non-redundant immune mechanisms.

The immunogenicity of RT is clinically supported by a phenomenon known as the abscopal effect, which is the reduction or disappearance of tumor lesions located outside the field of irradiation [12, 25]. With the introduction of IO in cancer treatment, this phenomenon has been increasingly reported [26]. Several case reports and case series have described the occurrence of the abscopal effect in patients treated with RT and ipilimumab showing a greater benefit compared to that provided by ipilimumab alone [26-30]. The combination of

RT plus ipilimumab was evaluated in a phase II clinical trial including patients with metastatic NSCLC [31]. Patients received RT over a single tumor lesion (6 Gy for 5 days) with concomitant systemic ipilimumab 3 mg/kg every 3 weeks for 3 cycles. Of 12 evaluable patients, 7 showed an abscopal response (3 complete responses and 4 partial responses). Given the low activity demonstrated by Ipilimumab in NSCLC [32, 33], these encouraging results suggest that RT can enhance the antitumor activity of IO and generate responses away from the radiation field, acting as a vaccine.

The efficacy and good safety profile that anti-PD-1 and anti-PD-L1 drugs have shown in NSCLC [1-5, 34], make them attractive agents to be combined with other treatments, such as chemotherapy and RT.

In a secondary analysis of the phase I clinical trial KEYNOTE-001 [35], those patients with metastatic NSCLC treated with pembrolizumab who had previously received RT achieved significantly longer PFS (4.4 vs 2.1 months, HR 0.56, 95% CI 0.34-0.91, p = 0.019) and OS (10.7 vs 5.3 months, HR 0.58, 95% CI 0.36-0.94, p = 0.026) compared to those not receiving RT. In a retrospective study of metastatic lung cancer patients (95% NSCLC) treated with anti-PD-1/anti-PD-L1 drugs, patients previously treated with thoracic RT, showed a trend towards a better OS (HR 0.66, 95% CI 0.42-1.01, p = 0.06), compared to those who had not received it [36]. Luke *et al*. conducted a phase II clinical trial that included 79 heavily pretreated patients with solid tumors (7 patients with CPNCP). Patients received SBRT on 2-4 metastatic lesions with subsequent pembrolizumab. Treatment was well tolerated and response rate in the overall population was 13.2% [37]. In PEMBRO-RT and MDACC trials, the combination of pembrolizumab plus RT showed a numerically higher response rate compared to pembrolizumab alone; however neither study met their pre-specified criteria [38, 39]. Recently, a pooled analysis of these two randomized trials showed that addition of radiotherapy to pembrolizumab significantly increased abscopal response rate (41.7% vs 19.7%, p = 0.0039), which led to significantly higher PFS (9.0 vs 4.4 months, HR 0.67, 95% CI 0.45-0.99, p = 0.045) and OS (19.2 vs 8.7 months, HR 0.67, 95% CI 0.54-0.84, p = 0.0004) [40]. These results, once again, suggest a synergistic effect of these therapeutic strategies and support the observation that RT can increase the efficacy of IO.

In addition, the combination of RT and IO could trigger a powerful immune response directed not only at macroscopic disease, but also micrometastases [41]. This hypothesis is supported by the PACIFIC trial, which included patients with unresectable stage III NSCLC, who were randomized to durvalumab or placebo for one year after completing radical chemoradiotherapy. Adjuvant treatment with durvalumab significantly prolonged PFS (16.8 vs 5.6 months, HR 0.52, 95% CI 0.42-0.65, p < 0.001), time to death, time to distant metastasis (23.2 vs 14.6 months, HR 0.52, 95% CI 0.39-0.69, p < 0.001) and OS (Not reached vs 29 months, HR 0.69, 95% CI 0.55-0.86) [9-11].

SBRT for oligoprogressive disease during immunotherapy

PD-1 and PD-L1 inhibitors have shown to prolong survival in patients with metastatic NSCLC, but this benefit is limited to a subset of patients and many of the responders eventually progress [1-5, 34]. Therefore, new therapeutic strategies that allow to reverse both primary and acquired resistance to IO are urgently needed.

Preclinical evidence suggests that RT may reverse resistance to IO. Wang *et al*. conducted a study in a preclinical model of lung cancer resistant to anti-PD-1 therapy, finding that localized RT induces IFN-β production, thereby increasing MHC class I expression and restoring sensitivity to anti-PD-1 therapy [42].

Currently, there is little evidence establishing the best therapeutic strategy in patients with NSCLC who oligoprogress after a response to IO.

Data from prospective and retrospective studies support the use of aggressive local therapies in oligometastatic NSCLC. SBRT is an increasingly used technique to treat oligometastatic disease, since it delivers high doses of radiation to the tumor lesion, with high precision, less fractionation and lower toxicity [7].

Data in lung cancer and other malignancies, such as melanoma, suggest that RT to one or more metastatic lesions may reverse resistance to IO. Postow *et al*. reported the case of a patient with metastatic melanoma treated with Ipilimumab, with slow progression of the disease, requiring RT (28.5 Gy in 3 fractions) over a paraspinal mass that caused pain, and subsequently continued with Ipilimumab. Three months after receiving RT, tumor response was observed in the irradiated lesion and in other metastatic lesions outside the radiation field [27]. Yuan *et al*. reported the case of a patient with a PD-L1-negative metastatic squamous cell lung cancer, showing progression of a left perihilar mass with bronchial obstruction during second-line treatment with nivolumab, for which he received palliative RT to the left perihilar mass (30 Gy in 10 fractions), achieving an almost complete response of the irradiated mass and a partial response of metastatic disease outside the radiation field [43]. A patient with lung adenocarcinoma who relapsed after surgery, with a large single liver metastasis and a single lung metastasis and progressed to first-line platinum-based chemotherapy, received treatment with nivolumab with progression of the liver mass. The patient received RT (40 Gy in 20 fractions) over the liver metastasis, achieving, only 3 weeks later, a striking response both in the irradiated liver mass and in the lung metastasis distant from the radiation field [44]. Finally, we previously reported the case of a patient with PD-L1-negative metastatic lung adenocarcinoma, who received second-line treatment with nivolumab achieving a complete response, but after one year of treatment, received SBRT over a monotopic right adrenal metastasis and continued with subsequent nivolumab. The patient achieved a durable complete response that lasts for more than 4 years [45]. In a retrospective study that included patients with advanced tumors that showed progression during treatment with nivolumab or pembrolizumab and who had received local palliative RT, there were 7 abscopal responses after RT among 24 evaluable patients [46]. Metro *et al*. conducted another retrospective study that included patients with advanced NSCLC with high PD-L1 expression who had progressed to first-line pembrolizumab. Of the included patients, 9 presented oligoprogression, being treated with ablative RT to the progressing lesions, and subsequently continued with pembrolizumab, achieving a 12-month post-progression survival rate of 71% [47]. All this clinical evidence suggests the potential capacity of RT to reverse resistance in patients who progress during IO treatment, and may be a therapeutic option in this setting.

Furthermore, there are data that support the hypothesis that local RT treatments of oligometastatic disease delay the appearance of new lesions, suggesting the activation of an antitumor immune response against micrometastatic disease. Gomez *et al*. conducted a phase II clinical trial in which patients with oligometastatic NSCLC, who did not progress after first-line treatment, were randomized to local treatment of metastatic lesions or maintenance/observation. The time to the appearance of new lesions was longer among patients who received local treatments compared to patients who randomized to maintenance/observation (11.9 vs 5.7 months, $p = 0.0497$) [48]. A lower tumor burden has been associated with a less immunosuppressive tumor microenvironment and this may favor the response to IO [49, 50]. SBRT can be useful in reducing tumor burden and therefore in improving the response to IO. In patients with oligometastatic disease, reducing tumor burden with SBRT would favor the activation of T lymphocytes and the elimination of micrometastases [51]. This hypothesis is supported by a phase II study conducted by Bauml *et al*. [52], in which 51 patients with oligometastatic NSCLC who received ablative RT to all lesions followed by pembrolizumab, achieved a median PFS of 19 months with a 24-month OS rate of 78%, improving the results of historical controls.

On the other hand, several studies and retrospective series have reported on the activity of anti-PD1 therapy alone or combined with stereotactic radiosurgery (SRS) for the treatment of melanoma brain metastases. However, little evidence exists on the efficacy and safety of combining IO and SRS for the treatment of brain metastases in patients with NSCLC, an issue which is being studied in currently ongoing trials (NCT02696993, NCT02858869, NCT02886585, NCT02669914) [53].

Table 1. Studies evaluating the combination of SBRT and immune-checkpoint inhibitors in metastatic NSCLC.

NCT number	Phase	N	Setting	Design	RT regimen	Status
NCT03825510	Interventional	100 (NSCLC)	Stage IV	Nivolumab/Pembrolizumab + SBRT	SBRT (3-5 fractions in up to 3 lesions)	Recruiting
NCT03223155	I	80 (NSCLC)	Stage IV	Ipilimumab + Nivolumab + Sequential/concurrent SBRT (over 2-4 sites)	SBRT 3 or 5 fractions as determined by the location	Recruiting
NCT03158883	I	26 (NSCLC)	Stage IV (non-responders and progressors to PD-1 inhibitors)	Avelumab + SBRT	SBRT 50 Gy (10 Gy x 5)	Recruiting
NCT03812549	I	29 (NSCLC)	Stage IV	Sintilimab + SBRT + LDRT	SBRT 30 Gy (10 Gy x 3), LDRT 2-10 Gy	Recruiting
NCT04081688	I	15 (NSCLC)	Stage IV	Atezolizumab + Varlilumab + SBRT	SBRT (4-5 fractions)	Recruiting
NCT03275597	Ib	21 (NSCLC)	Stage IV (oligometastatic)	Durvalumab + Tremelimumab after SBRT (over all disease sites)	30 and 50 Gy in 5 fractions	Recruiting
NCT02444741	I/II	104 (NSCLC)	Stage IV	Pembrolizumab + SBRT/RT	SBRT (4 fractions), RT (15 fractions)	Recruiting
NCT02831933	II	25 (NSCLC and Uveal Melanoma)	Stage IV	Nivolumab after ADV/HSV-tk + Valaciclovir + SBRT	SBRT 30 Gy (6 Gy x 5)	Recruiting
NCT03511391	II	97 (NSCLC, UC, Melanoma, RCC and HNSCC)	Stage IV	Nivolumab/Pembrolizumab +/- SBRT	SBRT (8 Gy x 3 in up to 3 lesions)	Recruiting

Table 1 continued..

NCT number	Phase	N	Setting	Design	RT regimen	Status
NCT03693014	II	60 (NSCLC, UC, Melanoma, RCC and HNSCC)	Stage IV	Ipilimumab/Nivolumab/Pembrolizumab /Atezolizumab + SBRT (at progression, over 1-3 lesions)	SBRT 27 Gy (3 fractions)	Recruiting
NCT03313804	II	57 (NSCLC and HNSCC)	Stage IV	Nivolumab/Pembrolizumab /Atezolizumab + SBRT/RT (over single lesion)	SBRT to achieve BED > 100 Gy, or RT 30 Gy 3-D	Recruiting
NCT02839265	II	29 (NSCLC)	Stages III-IV	CDX-301 + SBRT (over 1 pulmonary lesion)	SBRT 34 Gy (1 or 3 fractions) or 50 Gy (10 Gy x 5)	Active, not recruiting
NCT03644823	II	30 (NSCLC)	Stages III-IV	Atezolizumab + SBRT (over 1-2 lesions)	SBRT (6 Gy x 3)	Recruiting
NCT03965468	II	47 (NSCLC)	Stage IV (oligometastatic)	Durvalumab + CHT + SBRT (over metastatic lesions), followed by Surgery/RT over primary tumor, followed by Durvalumab maintenance	SBRT (up to 10 fractions)	Recruiting
NCT04238169	II	48 (NSCLC)	Stage IV	Toripalimab + SBRT (over 2-4 lesions) +/- Bevacizumab	SBRT 30-50 Gy (5 fractions)	Not yet recruiting
NCT03867175	III	110 (NSCLC)	Stage IV	Pembrolizumab +/- SBRT	SBRT (3-10 fractions)	Recruiting

RT = Radiation therapy, NSCLC = Non small cell lung cancer, SBRT = Stereotactic body radiation therapy, UC = Urothelial cancer, RCC = Renal cell carcinoma, HNSCC = Head and neck squamous cell cancer, BED = Biological equivalent dose, CHT = Chemotherapy, LDRT = Low dose radiotherapy.

Given the available evidence, in those patients with metastatic NSCLC who obtain an initial benefit with IO but then present with oligoprogressive disease, irradiation of the progressing lesions [19], while subsequently maintaining the same systemic treatment, should be considered as an effective and safe approach. In this regard, SBRT could play a fundamental role, as it seems to be more immunogenic and less toxic than conventional fractionation external RT [20].

Multiple currently ongoing clinical trials in metastatic NSCLC, are evaluating the combination of SBRT plus IO (See Table 1). These studies will provide relevant information regarding the dose, sequence, efficacy and safety of this therapeutic strategy.

Conclusions

Both preclinical and clinical evidence demonstrate that radiotherapy appears to enhance the activity of immunotherapy by reversing primary and acquired resistance. Based on the existing evidence and while we await results from currently ongoing prospective studies, in those patients with prolonged responses or stabilizations under immunotherapy who eventually develop oligoprogressive disease, delivering SBRT to the progressing lesions while maintaining immunotherapy after SBRT may be considered as a potentially effective and safe therapeutic option.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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