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REVIEW ARTICLE

# Integrating stereotactic radiotherapy and systemic therapies

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## ABSTRACT

This paper focuses on stereotactic radiotherapy (SRT) interactions with targeted therapies and immune system modulating agents because SRT inevitably interacts with them in the treatment of oligometastatic patients.

Radiation oncologists need to be aware of the advantages and risks of these interactions which can, on one hand, enhance the effect of therapy or, on the other, potentiate reciprocal toxicities. To date, few prospective studies have evaluated the interactions of SRT with new-generation drugs and data are mainly based on retrospective experiences, which are often related to small sample sizes.

**Key words:** stereotactic radiotherapy; oligometastasis; targeted therapies; immune system modulating drugs; immunotherapy; radiosurgery

## Introduction

Since stereotactic radiotherapy (SRT) plays a major role in the treatment of oligometastatic patients [1], one direct consequence is that it will inevitably interact with new-generation drugs such as targeted therapy and immune system modulating drugs [2]. Interactions between SRT and new drugs may, on one hand, enhance the effect of therapy [3] or, on the other, potentiate toxicities of the two therapeutic modalities [4]. To date, few prospective studies have evaluated the interaction between targeted therapies and SRT and available data are mainly based on retrospective experiences, often related to small sample sizes. Our purpose is to describe data on SRT and targeted therapies and immune system modulating drugs.

## State of the Art

### SRT and targeted therapies

Single-dose SRT causes apoptosis of vascular endothelial cells [5] and, therefore, theoretically, could be associated with anti-angiogenic drugs to improve results. This therapeutic association was evaluated in both preclinical and clinical studies. Anti-angiogenic drugs are monoclonal antibodies or tyrosine kinase inhibitors of the Vascular Endothelial Growth Factor Receptor (VEGFR). Bevacizumab, a monoclonal antibody binding to the Vascular Endothelial Growth Factor (VEGF), the main VEGFR-2 ligand, inhibits its receptor thus eliminating the enzymatic cascade that increases pro-mitotic signals. The effect of bevacizumab combined with SRT was mainly evaluated in patients

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with primary brain tumors. In oligometastatic disease, encouraging clinical results were reported in patients with brain metastases from lung cancer who were treated with single-dose SRT and subsequently bevacizumab (under four weeks between treatments). At a median follow-up of 7.8 months, 75% volumetric reduction of treated lesions was observed; the intracranial progression free survival was 12.7 months (95% CI: 9–20 months), with no grade 3 or greater toxicity [6]. Another retrospective study, which, however, evaluated only five patients, showed that the association of SRT and bevacizumab is feasible in selected cases, even in pretreated patients with brain metastases [7].

Bevacizumab was also tested in association with SRT in patients with recurrent high grade gliomas. The combined treatment seemed to improve OS, especially in patients with IDH wild-type tumors (median OS 10.9 months for SRT and Bevacizumab *vs* 8.2 months for bevacizumab alone). There was no grade 3 or greater toxicity [8].

Finally, although some reports indicated that bevacizumab had a role in improving SRT-induced radionecrosis [9] the potential toxicity of the combination should not be underestimated. In fact, esophageal fistulas and intestinal perforation were described in patients with metastatic abdomen lesions who received bevacizumab and SRT [10]. Accordingly, concomitant administration of the two therapeutic modalities is not recommended. Extreme caution is advised in their sequential use, which must take into account the bevacizumab half-life of about 20 days (range 11–50 days).

There are some promising data on sunitinib and sorafenib, which are VEGFR tyrosine kinase inhibitors derived from phase I and II clinical studies. Sunitinib was used after SRT in patients with brain metastases [11] and concomitant with SRT in oligometastatic patients with abdominal lesions [12]. Although clinical results were favorable, grade 3 or greater toxicity was recorded in 33% of patients according to Kao et al. [12], particularly when abdominal or pelvic irradiation was delivered. Fatal toxicities were also recorded in 4% of patients. A review of sorafenib [10] reported that cases of grade ≥ 3 toxicity (gastric ulcers, bleeding, intestinal obstructions) occurred in patients who also received SRT. Combined with single-dose SRT to the brain, sorafenib was recently used in a phase I study without showing relevant toxicity [13]. One case of "radiation recall dermatitis" was described in a patient treated for a vertebral metastasis [14]. As in the case of bevacizumab, current data suggest avoiding concomitant administration of sunitinib/sorafenib and SRT, especially if the treated volume is near the airways or intestines.

Very few data are available on SRT in association with epidermal growth factor receptor inhibitors (EGFR), gefitinib and erlotinib, which are tyrosine kinase inhibitors. Such data, deriving from "case reports" or retrospective studies, provided anecdotal information on clinical results and toxicity [15, 16].

Vemurafenib and dabrafenib, V-raf murine sarcoma viral oncogene homolog B1 (BRAF) kinase inhibitors, which are widely used in melanoma patients, displayed a major radiosensitizing effect in preclinical studies [17, 18]. Since unexpected toxicities were described when these drugs were combined with radiotherapy [19, 20], the Eastern Cooperative Oncology Group (ECOG) reviewed the literature in 2016 [19]. Although an increased risk of bleeding was reported in some series, data on increased toxicity were not conclusive. As a precautionary measure, the ECOG suggested suspending BRAF inhibitor administration at least on the day before and the day after single dose SRT and for at least 3 days before and after fractionated SRT [19].

Anti-HER2 drugs had a clear radiosensitizing effect in preclinical studies [21]. Even though few clinical data are available, some cases of radionecrosis and cerebral edema were described after single dose SRT was combined with trastuzumab emtansine (T-DM1) [22, 23], especially when the drug was given during radiation treatment [24]. Therefore, we advise against T-DM1 administration concomitant with SRT to the brain.

Since cyclin-dependent kinase (CDK) 4/6 inhibitors have an effect on the cell-cycle, their association with SRT seems to be a promising treatment option. It was tested in few studies, appearing to be safe and feasible [25]. Ongoing randomized phase II/III clinical trials on SRT and concomitant administration of target therapies are reported in Table 1, key literature data regarding the association of SRT and target therapies are summarized in Table 2.

## SRT and immune system modulators

Interest is growing in combining SRT and immunotherapy given its recent success, particularly with drugs that block immune system checkpoints

**Table 1.** Ongoing randomized phase II/III clinical trials involving stereotactic radiotherapy (SRT) and concomitant administration of target therapies and/or immunotherapy

| NCT number | Study title | Drug | Primary outcome | Phase | Recruitment status |
|---|---|---|---|---|---|
| NCT02364557 | Standard of care therapy with or without stereotactic radiosurgery and/or surgery in treating patients with limited metastatic breast cancer | Standard of care including anti HER2 (Trastuzumab, Pertuzumab, Lapatinib) | PFS, OS | II/III | Recruiting |
| NCT03727867 | A randomized phase III trial of efficacy of epidermal growth factor receptor tyrosine kinase inhibitor combined with early stereotactic body radiation therapy to the primary tumor in advanced non-small cell lung cancer patients harboring epidermal growth factor receptor mutation | EGFR-TKI | PFS | III | Not yet recruiting |
| NCT04563507 | CIMER: Combined immunotherapies in metastatic ER+ breast cancer | Palbociclib | PFS | II | Recruiting |
| NCT04074096 | Binimetinib encorafenib pembrolizumab ± stereotactic radiosurgery in BRAFV600 melanoma with brain metastasis (BEPCOME-MB) | Binimetinib Encorafenib Pembrolizumab | Intracranial PFS | II | Not yet recruiting |
| NCT03115801 | A phase II randomized controlled trial of programmed death —1/Programmed Death Ligand-1 (PD-1/PDL-1) axis blockade Versus PD-1/PDL-1 axis blockade plus radiotherapy in metastatic genitourinary (renal/urothelial) malignancies | Nivolumab, Atezolizumab, Pembrolizumab | Best overall response rates, difference in best overall response | II | Not yet recruiting |
| NCT02843165 | Randomized phase II study of checkpoint blockade immunotherapy combined with stereotactic body radiation therapy in advanced metastatic disease | Anti-PD-1/PD-L1 immunotherapy | Objective response rate | II | Recruiting |
| NCT03795207 | Prostate cancer with oligometastatic relapse: combining stereotactic ablative radiotherapy and Durvalumab (MEDI4736) (POSTCARD) | Durvalumab | Two-years PFS | II | Recruiting |
| NCT03548428 | Stereotactic body irradiation of oligometastase in sarcoma (Stereosarc) | Atezolizumab | PFS | II | Recruiting |
| NCT04830267 | The efficacy of camrelizumab plus stereotactic body radiotherapy in R/M HNSCC | Camrelizumab | Best overall response | II | Recruiting |

PFS — progression-free survival; OS — overall survival; TKI — tyrosine kinase inhibitor; PD-1 — targeting programmed death-1; PD-L-1 — targeting programmed death ligand-1

(checkpoint inhibitors). By the 1950s, palliative radiotherapy was known to result in disease regression outside of the irradiated field in the absence of other systemic therapies. This "abscopal effect" [26] suggested that ionizing radiations somehow stimulated activation of anticancer immunity [27, 28]. Consequently, local radiation may trigger systemic effects that can be harnessed in combination with immunotherapy to induce responses outside the radiation field [29].

Radiotherapy causes immunogenic cell death (ICD) by inducing calreticulin translocation to the cell surface as well as release of ATP and other endogenous proteins, such as High Mobility Group Box 1 (HMGB1), uric acid and heat shock proteins [30]. These events are critical for dendritic cell (DC) activation and T cell priming. Additionally, radiotherapy facilitates effector T-cell recruitment to tumors by inducing chemokines [31] and cell adhesion molecules like the intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 which mediate lymphocyte adhesion to the vascular endothelium [32]. On the tumor cell surface the pro-immunogenic effect of radiotherapy includes MHC class 1 molecule upregulation and peptide repertoire modulation. Thus, cytotoxic CD8 T cells recognize tumor cells and counteract tumor immune evasion [33, 34]. Radiotherapy also increases expression of NKG2D receptor stress ligands, thus activating Natural Killer (NK) cell clearance of tumor cells [35]. Radiotherapy therefore transforms the irradiated tumor site into a true

**Table 2.** Summary of literature data regarding the association of stereotactic radiotherapy (SRT) and targeted therapies or immune system modulators

| | |
|---|---|
| **SRT and targeted therapies** | **Anti-VEGFR:** (moAb, TKI) theoretical synergism, but the concomitant association is not recommended especially if the treated volume is near the airways or intestines [5–14] |
| | **Anti-EGFR TKI**: very few data available [15, 16] |
| | **BRAF kinase inhibitors:** theoretical synergism, but the concomitant association is not recommended [17–20] |
| | **Anti-HER2 drugs:** proven radiosensitizing effect, T-DM1 administration concomitant with SRT to the brain is not recommended due to high rate of radionecrosis and cerebral edema [21–24] |
| | **CDK 4/6 inhibitors:** theoretical synergism, few data available, in breast cancer patients with brain metastases resulted safe and feasible [25] |
| **SRT and immune system modulators** | **CTLA-4 antagonist:** proven radiosensitizing effect**,** in patients brain metastases from melanoma excellent responses [45] associated with high radionecrosis risk [47, 48] |
| | **PD-1/PDL-1 axis antagonists:** theoretical synergism and "abscobal effect" induction [52], positive effects on disease control, without severe toxicities [53–55]; optimal timing, dose and fractionation have to be defined [56] |

VEGFR — vascular endothelial growth factor receptor; moAb — monoclonal antibody; EGFR — epidermal growth factor receptor; TKI — tyrosine kinase inhibitor; T-DM1 — trastuzumab emtansine; CDK — cyclin-dependent kinase; PD-1 — targeting programmed death; PDL-1 — targeting programmed death ligand-1

endogenous anticancer vaccine which may, in turn, stimulate a poly-antigenic T lymphocyte cytotoxic response [36].

These data provide the rationale for therapeutic strategies that combine Radiotherapy with immunotherapy and/or monoclonal antibodies that inhibit "immuno-checkpoints". Unfortunately, this approach seems counterproductive in large volume irradiation as it may be associated with massive release of necrotic material, inflammatory cells (Myeloid-Derivative-Supressor-Cells, MDSC) and strongly immunosuppressive cytokines. Indeed, prolonged irradiation of large volumes using conventional fractions, with irradiation of a significant amount of blood vessels, reduced the number of T lymphocytes which are highly radiosensitive and crucial in establishing an immune response against cancer [37, 38].

On the other hand, since SRT irradiates much smaller volumes, it may optimize the immunomodulating effect of immunotherapy and/or monoclonal antibodies. Recent data showed that SRT altered the tumor microenvironment, facilitating lymphocyte infiltration, inflammatory cytokine release and macrophage activation [2, 27]. SRT treatment of oligometastatic disease is, therefore, ideal for being combined with immunological drugs [39]. Preclinical data and reports of "abscopal responses" in patients undergoing SRT and immunotherapy showed that single doses of 6–8 Gy delivered for 3–5 fractions effectively determined an immune response [40–42]. Single doses over 12–18 Gy induced exonuclease Trex1, an enzyme that removes cytosolic DNA after radiotherapy. Thus, interferon production, as induced by ionizing radiation was prevented, which is a key step in dendritic cell migration [43].

Immunotherapy includes cancer vaccines and immune-checkpoint inhibitors (ICI). Many data are available on the association of SRT with monoclonal antibodies directed to antigen 4 on cytotoxic T lymphocytes (CTLA-4), and antibodies directed against the PD-1/PDL-1 axis. Although preclinical data are very promising, clinical information derives from case reports and phase I and II studies. In several preclinical studies ipilimumab, the CTLA-4 antagonist, acted synergistically with radiotherapy [44]. In clinical practice, when associated with SRT, it elicited excellent responses in patients with brain metastases from melanoma, as median survival was 21.3 months *vs.* 4.9 months in patients who received only SRT [45]. In particular, survival seemed better when SRT was performed before or during ipilimumab administration, rather than afterwards [46]. A single-centre retrospective study [47] on 137 melanoma patients (1094 lesions) who were treated with single fraction SRT and anti-CTLA-4 and/or anti-PD1 showed that, unlike chemotherapy, SRT was not associated with worse radiation-necrosis free survival, and the temporal proximity of immunotherapy to SRT was not clearly associated with differing radionecrosis risk. A recent review reported that treatment-related necrosis tended to occur 2.4 times more frequently when SRS and ICI were combined, compared with SRS alone in melanoma patients with brain metastasis (16.0% *vs.* 6.5%; $p = 0.065$) showing a high cumulative incidence within the first year [48].

In preclinical studies PD-1/PDL-1 axis antagonists in combination with SRT also demonstrated great therapeutic potential [49, 50]. Clinical experience showed good disease control in the ab-

sence of relevant toxicities. A recent phase I study evaluated SRT in association with pembrolizumab (initiated within 7 days of completing RT) in 73 oligometastatic patients with ovarian, lung, breast, endometrial, rectal, head-neck and biliary neoplasms. Outcomes were favorable with excellent toxicity profiles as only 6/63 patients who were evaluated for toxicity, had grade 3 toxicity. Lesion size was reduced in 13.2% of the 68 patients who were evaluated. Complete response was achieved in 9/68 patients and partial response in 8 [51]. An "abscopal effect" was described in a patient with lung cancer who was treated with Nivolumab and SRT [52]. Furthermore, current data suggested the association of SRT and immunotherapy seemed to exert positive effects on disease control, without clearly demonstrating severe toxicities [53–55]. Although the combination of SRT and immunotherapy is currently being investigated in several phase I and II trials, many questions persist about timing, dose and fractionation [56]. Ongoing randomized phase II/III clinical trials on SRT and concomitant administration of immune system modulators are reported in Table 1, key literature data regarding the association of SRT and immune system modulators are summarized in Table 2.

## Conclusions

In conclusion, although SRT in association with targeted therapies plays a role in the treatment of oligometastatic disease, concerns about the toxicity of combined treatments still need to be addressed. Furthermore, regarding SRT and immune system modulators potential side effects and toxicities need to be assessed as data are insufficient, and cannot, at present, provide definitive indications [57–59]. Ii is worth of notice that in the most relevant ongoing randomized phase III trial (i.e. SABR-COMET 3 [60], SABR COMET 10 [61], CORE trial [62],) which compares standard of care (SOC) *vs* SOC and SRT in oligometastatic patients, no immunotherapeutic or molecularly target agents are allowed from two weeks before SRT until one week after SRT. Therefore, prospective studies are needed to evaluate safety and efficacy of SRT and systemic therapies association, and data collection in large databases is particularly recommended [63].

### Conflicts of interest

The authors have no conflict of interest to declare.

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