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Case Study

Dosimetric Characterization of an Abscopal Response in a Patient With Oligometastatic Melanoma Undergoing Concurrent Treatment With Pembrolizumab and Stereotactic Body Radiotherapy (SBRT)

Jennifer Sims-Mourtada, PhD[1*]; Serguei Casteneda, MD[2]; David Huang, MS[2], John McGlade, MS[2]; Sunjay Shah, MD[2]; Lindsay Romak, MD[2]; Adam Raben, MD[2]; Firas Mourtada, MSE, PhD[2]

[1]Center for Translational Cancer Research, Helen F. Graham Cancer Center, Christiana Care Health Services, Newark, DE, USA
[2]Department of Radiation Oncology, Helen F. Graham Cancer Center, Christiana Care Health Services, Newark, DE, USA

[*]***Corresponding author***
Jennifer Sims-Mourtada, PhD
Senior Clinical Scientist, Center for Translational Cancer Research, Helen F. Graham Cancer Center, Christiana Care Health Services, Newark, DE, USA
E-mail: jsimsmourtada@christianacare.org

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ABSTRACT

Recently, preclinical and clinical evidence has shown that a synergy may exist between radiation and immune check-point therapies such as pembrolizumab. Radiation has been shown to activate the immune system, and in combination with immunotherapy may lead to systemic anti-tumor responses. However, the exact dose regimens needed to induce synergistic responses are unclear. Here, we report a dosimetric characterization of a patient treated with stereotactic radiation in combination with immune check-point therapy.

Keywords
Stereotactic body radiotherapy (SBRT); Dosimetric; Immunotherapy; Radiation.

Abbreviations
SBRT: Stereotactic Body Radiotherapy; GTV: Gross Tumor Volume; HI: Homogeneity Index; PTV: Planning Target Volume; TAMS: Tumor-associated Macrophages; CT: Computed Tomography; FDG: ^{18}F-fluorodeoxyglucose; HF: Hydrofluoric acid.

INTRODUCTION

Stereotactic Body Radiotherapy (SBRT) is a sophisticated form of radiation that allows high dose, conformal radiation delivery to solid tumors. In addition to providing local control, reports of abscopal (or out-of-field) effects indicate a possible systemic effect of SBRT.[1,2] Although, clinical reports of abscopal immune responses induced by SBRT are relatively rare,[2] recent advances in immunotherapy and the potential benefits of the combination of immunotherapy and SBRT have driven interest in radiation-induced anti-tumor immune responses. Several clinical studies are currently underway to determine the effects of combined radiationand check-point inhibition.[3] Although, results of clinical trials combining PD-1 inhibition and radiation are still forthcoming, clinical reports demonstrate that combination radio-immunotherapy may yield therapeutic advantage.[4,5] While reports suggest that hypofractionated regimens used in SBRT may induce superior immune priming, the optimal dose, and fractionation regimens are still to be determined.

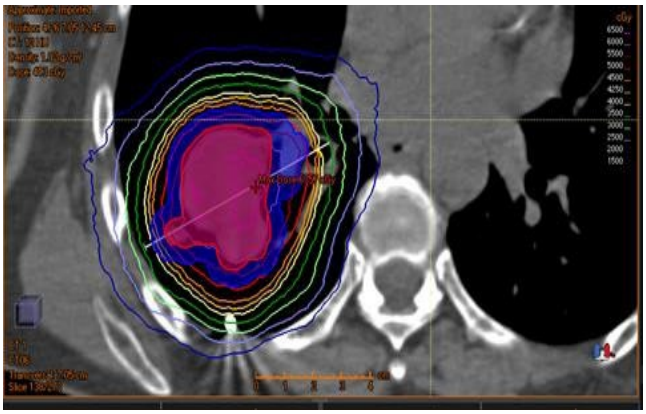
CASE STUDY

Patient History and Treatment

Here we report a dosimetric characterization of a possible abscopal response in a 57-year-old female with oligometastatic melanoma.

Patient data was obtained during a retrospective chart review under a protocol approved by the Institutional Review Board (IRB) of Christiana Care Health Services, Inc., Newark, DE, USA. Previously, the patient received intensity modulated radiation therapy treatment in the management of her metastatic melanoma to the left orbit. She underwent surgical resection followed by post-operative radiation therapy to the orbit. She completed a dose of 375 Gy in 15 fractions at 25 Gy per fraction. She was also diagnosed at that time with right lateral temporal metastasis and underwent radiosurgery. The patient received a dose of 20 Gy to the single right temporal metastasis. The patient was placed on maintenance pembrolizumab with good response but had a single-site progression one year later evidenced by increase in size to a right lower lobe centrally located oligo-metastasis for which she received palliative CyberKnife® (AccurayInc, Sunnyvale, CA, USA) SBRT. She received a dose of 50 Gy in 5 fractions prescribed to the 74% isodose line, determined using a Monte Carlo dose calculation (Figure 1). At this time, the patient also presented with a rapidly enlarging palpable right supraclavicallymph node which demonstrated asymmetry with focal hypermetabolic activity on positron emission tomography/computed tomography (PET/CT).

Figure 1. *Lung Cyberknife case (50 Gy in 5 fractions) with suboptimal tumor coverage with (8 o'clock) clinical intent to spare the adjacent ribs to reduce risk of bone fracture. PTV: blue line*



Patient Response

A partial response was noted, approximately 3 months after CyberKnife® treatment, in the irradiated lesion, identified decreased hypermetabolic activity and a 50% reduction in size by PET/CT. The patient also developed a systemic response in the previously enlarged cervical lymph node which was located out of the radiation field. The patient reported resolution of the palpable cervical lymph node shortly after radiation treatment. This node was no longer clinically palpable when the patient presented for staging three months after treatment. A radiological response was also noted. By PET/CT, there was no evidence of lymphadenopathy with the previously enlarged hypermetabolic lymph node now showing a reduction in size and no ^{18}F-fluorodeoxyglucose (FDG) activity.

Dosimetric Characterization

Upon review of the CyberKnife® SBRT plan dosimetric parameters, we realized that the dose of 50 Gy in 5 fractions is slightly lower than the standard dose for lung lesions of 55 Gy in 5 fractions. Additionally, the planning target volume (PTV) was atypically colder (89.9% of PTV covered by the 100% prescription dose) with the clinical intent to decrease chances of bone fracture in the ribs. There was also a relatively high value of gross tumor volume (GTV) and a homogeneity index (HI) of 1.35. HI, defined as max dose/prescribed dose, is a factor to indicate the degree of uniformity of dose within the target. These findings suggest that higher HI may be associated with enhanced immunologic effects of SBRT.

DISCUSSION

Meta-analysis of preclinical studies has shown that the probability of an abscopal immune response intensifies with increasing biological effective doses. Furthermore, preclinical studies have suggested that ablative or hypofractionated radiation is superior to conventional fractionation schemes for release of immunostimulatory cytokines such as interferon gamma, upregulation of MHC and the activation of effector CD8$^+$ T-cells.[8-13] However, hypofractionated regimens may also have immunosuppressive effects. Hydrofluoric acid (HF) induces severe damage to vasculature and is associated with increased hypoxia. Hypoxia not only decreases the biological effects of radiation, but may also promote immunosuppression through alterations of cytokine gradients, recruitment of tumor-associated macrophages (TAMS) and increased functions of Tregs.[14-16] Likewise, radiation has been shown to induce changes in macrophage polarity. While conventional fractionation regimens have been shown to promote anti-tumor M1 macrophage polarity, HF may result in immunosuppressive M2 differentiation.[15,17-18] Additionally, there is concern that high doses used in HF may have a detrimental effect on existing or infiltrating T-cells as a reduction in TILs has been observed following single doses higher than 7-10 Gy.[16,19-22] Thus, although SBRT may promote enhanced CD8$^+$ T-cell responses, efficacy may be diminished by the death of infiltrating lymphocytes and other microenvironmental changes that increase immunosuppression. In contrast, conventional doses of ≤2 Gy per fraction may preserve endogenous and infiltrating tumor reactive T-cells. While conventional fractionation schedules may overcome some of the drawbacks of HF, doses may not be high enough to induce a robust immuneresponse.

Although, current planning objectives strive for PTV coverage over 95% of the dose prescription with HI <1.2, this case study suggests that abscopal effects may be enhanced in patients treated SBRT with sub-optimal PTV dose coverage and undergoing concurrent immunotherapy. The inherent high dose gradient of CyberKnife® beam profile (due to the steep dose gradient from beam center to edge) might be an important contributing factor to the possible response observed here and may contribute to the advantage of CyberKnife® SBRT over standard radiation therapy in combination with immunotherapy. The effects of dose heterogeneity on biological attributes such as hypoxia and the immune response are unknown. Moreover, the optimal dose and fractionation schedule for synergistic effects of CyberKnife® with immunotherapy are not yet well-defined. In our case, it is unclear if the

slight decrease in dose (50 Gy *vs.* 55 Gy) had an impact on immunological response patterns. However, the lower dose combined with supoptimal tumor coverage may have helped limit hypoxia and promote immune responses leading to an abscobal effect in this case. Further investigation on the impact of heterogeneous dose delivery on activation of anti-tumor immune responses is needed. Dosimetric characterization of radiotherapy may help to provide information about optimal radiation doses for interactions with immunotherapeutics.

CONFLICTS OF INTEREST

The authors report no conflicts of interest with this work.

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