



Immunotherapy orchestrates radiotherapy in composing abscopal effects: A strategic review in metastatic head and neck cancer

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Abstract: The treatment of metastatic head and neck squamous cell carcinoma (HNSCC) with a combination of radiotherapy (RT) and immunotherapy can augment treatment response and symptomatic relief. Combination therapy can also trigger a non-targeted tumor control event called the abscopal effect. This effect can be demonstrated by treatment with anti-programmed death 1/programmed death ligand 1 (PD-L1) and anti-cytotoxic T-lymphocyte-associated antigen 4 antibodies in combination with hypofractionated RT. Individual studies and clinical trials have revealed that combination radio-immunotherapy improves overall treatment response by successful initiation of the abscopal effect, which extends the treatment effects to non-targeted lesions. Growing attention to the abscopal effect may inspire innovations in current RT toward more effective and less toxic radiobiological treatment modalities for advanced HNSCC. We review the latest findings on the abscopal effect with emphases on therapeutic modalities and potential applications for treating metastatic HNSCC.

Keywords: Abscopal effect; Checkpoint inhibitor; Head and neck cancer; Immunotherapy; Radiotherapy

1. HEAD AND NECK SQUAMOUS CELL CARCINOMA EPIDEMIOLOGY AND CLINICAL FEATURES

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common malignancy. Among 630,000 patients diagnosed with HNSCC each year, >350,000 die.¹ HNSCC is the third most common cause of cancer death and the fifth leading cause of overall mortality worldwide.² HNSCC is more common in males than in females, and the incidence rate is estimated at 20 per 100,000 people in the regions of Central and Eastern Europe, Spain, Italy, France, Hong Kong, the Indian subcontinent and Brazil, and among African Americans in the United States.³ Tobacco use, betel leaf and nut chewing, alcohol consumption, poor oral hygiene, and ultraviolet radiation are widely considered to be risk factors of HNSCC.² The human papilloma virus, Epstein-Barr virus, and p53 malfunction are also associated with HNSCC occurrence.^{4,5} Notably, autopsy data show that distant metastasis is found in up to 46.7% of HNSCC patients.⁶ Lungs, bones, mediastinal lymph nodes,

brain, liver, skin, and peritoneum are common metastatic sites, among which the lungs are the most common.^{6,7}

Clinically, radiotherapy (RT), surgical resection, chemotherapy, and targeted therapy are treatment approaches for HNSCC. RT was considered the primary treatment in the first half of the last century due to limited availability of antibiotics and anesthesia. As availability of these increased, surgery and chemotherapy became preferred first-line treatments due to the adverse effects and poor outcomes of RT.⁸ The introduction of intensity-modulated RT and image-guided RT helped to improve response rates and reduce toxicity. Recently, immune checkpoint targeted therapy became an effective treatment choice.⁸ Advanced laryngohypopharyngeal squamous cell carcinoma, a type of HNSCC, was routinely treated by surgery with adjuvant RT in past decades;^{9,10} however, this had the potential to cause serious impairment of laryngeal function, which compromised patients' quality of life and led to social isolation.¹¹⁻¹³ RT combined with chemotherapy and immunotherapy is therefore considered an attractive method for treating HNSCC patients with advanced and/or unresectable tumors.¹⁴

2. RADIATION THERAPY AND THE ABS COPAL EFFECT IN CANCER THERAPY

The therapeutic effect of RT is mediated not only by direct energy deposition to the exposed target but also by the so-called abscopal effect wherein distal lesions respond to the local treatment. The specific pathway of the abscopal effect is still under debate despite documentation of a similar RT-driven bystander effect associated with cytokines, immunogenic signals, and extracellular vesicles.^{15,16} Putative mechanisms that involve

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cytokines, the immune system, and pseudo-abscopal effects have been described.¹⁷ Faguet et al¹⁸ reported that clastogenic factors are secreted from the irradiated cells and subsequently cause chromosomal destruction to the unirradiated cells. This tumor-suppressing effect has been shown to last in irradiated animals for up to 10 weeks. Asur et al¹⁹ revealed that tumor necrosis factor alpha, ceramide, and tumour necrosis factor-related apoptosis-inducing ligand are induced by RT and are associated with apoptosis in the epithelial and endothelial portions of the cancer microenvironment. Peters et al²⁰ suggested that the use of high-dose spatially fractionated radiotherapy (GRID) may contribute to both bystander and abscopal effects. Similar outcomes shown by Kanagavelu et al²¹ indicated that lattice RT led to abscopal effects in syngenic Lewis Lung Carcinoma animal models. Indeed, GRID is effective in the treatment of advanced massive tumors.²² Lattice RT translates GRID therapy into advanced 3D conformational RT with the help of modern radiation oncology instruments.²³ To date, the mechanism of communication between primary and metastatic lesions remains unknown, but it is generally agreed that the immunogenic effect of radiation exposure is the primary component.²⁴

3. THE ROLE OF PALLIATIVE RADIOTHERAPY IN METASTATIC HNSCC

RT is the usual adjuvant modality for curative and palliative treatment of metastatic HNSCC (mHNSCC).²⁵ An accumulating number of studies reveal that although the prognosis of mHNSCC is poor, some patients benefit from prolonged disease-free survival after RT to either the metastatic site or the primary lesion.²⁶ RT has thus been increasingly applied to patients with mHNSCC in recent years,²⁷ with a variety of available treatment regimens (Table 1).

Generally, the prescription for stage III or IV HNSCC is 70 Gy in 35 fractions for curative treatment; however, a range of 20–30 Gy in five fractions is often used for palliative cases. Mohanti et al²⁸ recommended a total dose of 20 Gy in five fractions, resulting in average outcomes of 37% tumor response and symptom relief between 47% and 59%. A split course was introduced by Stevens et al, which was composed of two cycles of 25 Gy in 10 fractions, reaching a total of 50 Gy. The tumor response and symptom relief were apparently enhanced to 82% and 85%, respectively.²⁹ Corry et al circulated the outcomes of the “Quad Shot regimen,” which comprised three courses of *bis in die* (BID, meaning twice a day),

giving 3.7 Gy per fraction for two successive days to achieve a total of 44.4 Gy in 12 fractions. The Quad Shot regimen contributed to clinical outcomes of 50%–70% tumor response and 80% symptom relief.³⁰ Porceddu et al²⁵ described a regimen of 30–36 Gy in five to six twice-weekly fractions, where an overall response of 80% and symptom response of 62% were achieved. Agarwal et al³¹ described an intensive palliative RT regimen delivering 40 Gy in 16 fractions, which demonstrated a treatment response rate of 73% and symptom relief of 75%. Case reports in palliative care therefore show that a higher total dose with a hypofractionated dosing regimen may produce favorable outcomes in terms of overall response and symptom relief.

4. COMBINED RADIO-IMMUNOTHERAPY IS ESSENTIAL FOR THE ABS COPAL EFFECT

The abscopal effect is a desired but rare event in radiation oncology.³² Checkpoint inhibitory target therapy and the abscopal effect return to focus with the combination of anti-programmed death 1 (PD-1), anti-programmed death ligand 1 (PD-L1), and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) treatments. Ipilimumab (a CTLA-4 checkpoint inhibitor) and Nivolumab (a PD-1 checkpoint inhibitor) have been shown to have complementary functions in the treatment of metastatic melanoma.³³ Ipilimumab is effective for cancer patients with overexpression of antitumor immunity molecules and has been identified as the primary agent contributing to overall survival (OS) in metastatic melanoma patients.^{34,35} Nivolumab has been approved as a second-line therapy for mHNSCC by the Food and Drug Administration.³⁶ Anti-PD-1/PD-L1 monotherapy is associated with greater clinical benefit in tumors expressing PD-L1. The addition of anti-CTLA-4 therapy has the potential to enhance antitumor activity of anti-PD-1/PD-L1 agents in both PD-L1 positive and PD-L1 negative tumors.³⁷

Radiotherapy plays a role in the recruitment of T cells in the tumor microenvironment,³⁸ secretion of cytokines, enhanced tumor antigen presentation,^{39,40} and increased expression of PD-L1 in irradiated tumors.⁴¹ Induction of the abscopal effect has been published in both pre-clinical and clinical data.^{41–43} In animal experiments, concurrent RT and anti-CTLA-4 antibody therapy can successfully induce the abscopal effect.^{44,45} In addition, PD-1 blockade after completion of RT has been reported to initiate elimination of retained tumors.⁴¹ Dual checkpoint blockade (anti-CTLA-4 and anti-PD-L1) in combination with RT has

Table 1

Palliative radiotherapy prescriptions and outcomes for metastatic HNSCC

Study	RT regimen	Outcomes
Mohanti et al ²⁸	20 Gy as 4 Gy per day for 5 days	ORR: 37%, SR: 47%–59%
Stevens et al ²⁹	50 Gy as 25 Gy per cycle for 2 cycles, 2.5 Gy per fraction	ORR: 82%, SR: 85%
Corry et al ³⁰	44.4 Gy BID as 3.7 Gy per fraction for 2 days per course for 3 courses	ORR: 50%–70%, SR: 80%
Porceddu et al ²⁵	30–36 Gy as 6 Gy per fraction twice weekly for 3 weeks	ORR: 80%, SR: 62%
Agarwal et al ³¹	40 Gy as 2.5 Gy per fraction for 3 weeks	ORR: 73%, SR: 75%

ORR= Overall response rate; PS= Patient satisfaction; SR= Symptom relief; Gy= Gray; BID= twice a day

Table 2

The reported cases of combined radio-immunotherapy triggering the abscopal effect

Study	Radiotherapy	Immunotherapy
Shinde et al ⁵⁰	QUAD SHOT, 3.7 Gy BID for 2 days (total 14.8 Gy), with 2 additional courses in 1-month intervals, reaching 44.4 Gy	Anti-PD-1/PD-L1 and anti-CTLA-4 antibodies
Bahig et al ⁵¹	Patients received 3 to 5 SBRT fractions, with 15 Gy in 1 to 5 fractions	Durvalumab (1500 mg IV every 4 weeks) and tremelimumab (75 mg IV for a total of 4 doses)

also been shown to stimulate immune mechanisms.⁴⁶ Abscopal effects are increasingly being documented, particularly in the context of the combination of immune checkpoint blockade and radiation.^{47–49}

A case report by Shinde et al showed that the abscopal effect in HNSCC can be triggered when RT is combined with ipilimumab (anti-CTLA-4 monoclonal antibody). A regimen of ipilimumab and nivolumab administered concurrently every 3 weeks for four cycles, however, resulted in negative outcomes. An RT regimen, “QUAD SHOT” for palliation was then given with 3.7 Gy BID for 2 days (total dose 14.8 Gy) to the primary site and 3.3Gy BID for 2 days (total dose 13.2 Gy) to the microscopic areas at high risk for disease. No radiation was given to the lung, which was the secondary metastatic site of HNSCC. Two weeks after irradiation, the primary lesion and bulk left neck adenopathy had decreased by about 25%, and the metastatic pulmonary nodule had decreased by about 50%. The QUAD SHOT regimen was repeated two more times at one-month intervals, and finally the patient was cured.⁵⁰ Notably, the same QUAD SHOT dosage did not reflect any sign of the abscopal effect in the absence of ipilimumab administration.²²

Following the same strategy, Bahig et al initiated combined radio-immunotherapy to investigate its anticancer effects. Up to 15 Gy per fraction was given by stereotactic body radiotherapy (SBRT), accompanied by the systemic infusion of durvalumab and tremelimumab. Rather than demonstrating direct evidence of the abscopal effect, the OS and progression-free survival partially supported the point-of-view that the local SBRT may work synergistically with systemic anti-PD-L1 administration⁵¹ (Table 2).

5. DISCUSSION

The abscopal effect is described as the regression of metastatic tumor mass at a distant location from the radiation site. RT regimens delivered with higher total doses and hypofractionation show no evidence of the abscopal effect despite benefits in tumor control and symptom relief. Monotherapy using monoclonal antibodies is sometimes unable to control tumor growth, whereas combining it with RT leads to the non-targeted effect. Remarkably, immunotherapy with anti-PD-1/PD-L1 and anti-CTLA-4 antibodies in combination with RT shows enhancement of the abscopal effect in several tumor-bearing animal models for colon and colorectal cancers, mammary adenocarcinoma, and melanoma.^{41,45,46,52,53}

There is concern that the abscopal effect from radio-immunotherapy is actually a consequence of systemic administration of monoclonal antibodies. Accumulating evidence indicates that plenty of immunogenic markers are released after local RT, but few studies identify possible mediators involved in the communication between primary and metastatic lesions. Growing interest in extracellular vesicle-mediated biological effects will potentially draw more attention from researchers, but very limited information is available thus far. We believe that further investigation of radio-immunotherapy as well as the abscopal effect may improve clinical outcomes for patients.

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