Immunotherapy Mythbusters in Head and Neck Cancer: The Abscopal Effect and Pseudoprogression

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Overview

Atypical patterns of response to immunotherapy have been observed, including the abscopal effect and pseudoprogression. Although both are infrequent in head and neck squamous cell carcinoma, the synergism between radiation and checkpoint blockade therapy has generated excitement for exploitation of the abscopal effect. However, robust abscopal tumor regression observed in preclinical models has not translated to clinical experience. The optimal sequencing of radiotherapy with immunotherapy and dosage of radiation to target lesions to elicit this effect is being explored in clinical trials. Predictive markers of efficacy must be studied further to identify patients who may benefit from an abscopal effect and continued checkpoint inhibitor blockade beyond initial signs of radiologic progression. Given the rarity of pseudoprogression in head and neck squamous cell carcinoma, patients should be carefully selected to continue on immunotherapy, despite early radiologic signs of progression, given the risk of aggressive true progression and clinical deterioration that may result in missed opportunities for alternate treatments.

ABSCOPAL EFFECTS OF RADIOTHERAPY

The Phenomenon

Radiotherapy (RT) represents a cornerstone in the management of head and neck squamous cell carcinoma (HNSCC) and is clinically implemented in different treatment regimens. For locally advanced HNSCC, definitive and postoperative settings of classically fractionated intensity-modulated RT (daily doses of 1.8–2.0 Gy) are used, alone or in combination with concomitant chemotherapy or cetuximab treatment.[1,2] In recurrent and metastatic disease, the EXTREME chemotherapy protocol, involving cisplatin/carboplatin, 5-fluorouracil, and cetuximab, represents the standard first-line treatment,[3] but stereotactic body RT (SBRT), with three to five fractions of 8 to 15 Gy, is increasingly being used.[4] Meanwhile, RT exhibits a high degree of spatial precision[5]; however, there is accumulating evidence that local RT can induce systemic responses occasionally resulting in the regression of nonirradiated distant tumor lesions. This phenomenon has been termed "abscopal effects of RT,"[6] and preclinical studies have shown that the underlying driving force is a stimulation of systemic antitumor immune mechanisms (Fig. 1).[7-9]

Although the first clinical reports about abscopal tumor regression upon RT date back to the beginning of the 20th century,[10] it still remains a rather rare event in the clinical routine.[11] Nevertheless, the numbers of reported cases are increasing, particularly since the clinical introduction of immune checkpoint inhibiting agents targeting CTLA-4 or the PD-1/PD-L1 axis.[12-14] For recurrent or metastatic HNSCC, immune checkpoint inhibition has shown promising therapeutic efficacy[15]; however, response rates remain limited to 10% to 20%,[16,17] clearly indicating the need for biomarkers of response prediction and combined modality approaches for response improvement. In view of the abscopal immunostimulating effects of RT, immunotherapy appears to be a promising partner in this regard.

The Underlying Mechanisms

Historically, RT has been considered to be immunosuppressive. Lymphocytes are highly radiosensitive, and RT reportedly leads to lymphopenia.[18,19] Furthermore, RT can interfere with T lymphocyte priming via downregulation of costimulatory molecules on antigen-presenting cells (APCs).[20] On the contrary, RT can activate immune responses and, thus, may contribute to reprogram the tumor microenvironment.[21]

RT induces DNA damage which, if not repaired properly, results in cell death or senescence. Apoptosis, necrosis, mitotic catastrophe, and/or senescence can be observed upon RT, and the major determinants appear to be the irradiation dose, the cellular origin, the genetic repertoire of the cell, and the functionality of cell cycle checkpoints.[22,23] Importantly, different modes of cell death have different immunologic consequences. Preclinical studies have shown

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PRACTICAL APPLICATIONS

- Abscopal tumor regression in response to radiotherapy remains a rare clinical event, but its incidence is increasing as a result of the clinical implementation of immune checkpoint inhibition.
- Critical parameters, such as treatment sequence of radiotherapy and immunotherapy and dosing of radiotherapy per established clinical protocols, must be reconsidered when using a combination strategy.
- Observations of abscopal tumor regression in response to radiotherapy, with or without immunotherapy, appear to be particularly rare in HNSCC. It needs to be examined whether this is as a result of unique aspects of HNSCC biology and/or immunology.
- Pseudoprogression is rare in HNSCC, and, therefore, patients who continue on checkpoint blockade therapy despite early radiologic signs of progression should be carefully selected based on the absence of clinical deterioration, the presence of modest tumor growth, and the lack of alternative treatment options.
- There is no standard imaging method that predicts for pseudoprogression. Methods to identify pseudoprogression are being developed to prevent premature treatment discontinuation in patients who may clinically benefit from immunotherapy.

that the induction of antitumor immune mechanisms requires distinct forms of cell death that are sensed by the immune system as dangerous. This involves the exposure of damage-associated molecular patterns (DAMPs).[24,25] Briefly, extracellular DAMPs stimulate attraction of monocytic cells and favor their maturation into APCs. Upon tumor antigen uptake, activated APCs present and cross-present tumor antigens to naive T cells, resulting in the stimulation of adaptive antitumor responses that can counteract tumor cells in the irradiated tumor volume, as well as in distant out-of-field metastases (Fig. 1). Molecularly, this is orchestrated by an intratumoral cascade of type I and type II interferons (IFNs). After ingestion of dying tumor cell material, tumor cell–derived DNA escapes into the cytosol of APCs and triggers activation of the cytosolic DNA sensor cyclic GMP-AMP synthase, ultimately leading to stimulator of interferon genes–dependent transactivation of type I IFN genes.[26,27] This may also happen in the irradiated tumor cell itself. Type I IFNs favor antigen cross-presentation and improve T-cell priming in the draining lymph nodes.[26,28,29] Once activated, T cells and natural killer cells can attack tumor cells and produce type II IFNs, enforcing major histocompatibility complex class I expression on tumor cells, shaping the tumor vasculature for improved T-cell trafficking, and stimulating chemokine secretion for T-cell recruitment.[30,31]

During immunoediting, developing tumors adopt various strategies of immune evasion.[32] Immunologically "cold" tumors, which appear histologically to exhibit an absence of immune infiltrate or an essential immune cell subpopulation, including $CD8^+$ T cells, are far more frequent than immunologically "hot" tumors, with well-detected $CD8^+$ T-cell infiltration and an intratumoral IFN signature.[21] This is orchestrated by a complex mixture of tumor-intrinsic (e.g., tumor mutational burden), host-intrinsic (e.g., overall immune status, gut microbiome), and environmentally dictated factors (e.g., infections, exposure to sunlight). RT reportedly can turn "cold" tumors into "hot" ones, at least in preclinical model systems.[33] By engaging the described intratumoral IFN cascade, RT enhances the presentation of an expanded major histocompatibility complex class I ligandome on tumor cells and favors the recruitment and activation of APCs and T cells.[26,28,34,35] Very recently, RT has also been shown to promote the exposure of immunogenic mutations.[36] Accordingly, RT can be considered a means of in situ cancer vaccination, providing all elements of a classic vaccination approach: tumor-specific (neo-) antigens and adjuvants represented by exposed DAMPs[9] (Fig. 1). However, in the monotherapy setting, these effects appear to be limited, and it remains questionable whether RT alone can stimulate long-lasting immunologic memory. Accordingly, a combination with immunotherapy, such as immune checkpoint inhibition, seems tempting.

Clinical Experiences and Ongoing Clinical Trials

Clinical reports of abscopal effects of RT remain largely limited to case reports and retrospective analyses. Nevertheless, the first cases were described with the clinical implementation of RT, and the numbers are increasing, particularly since the advent of cancer immunotherapy.[8,10,14] Comprehensive analyses of the published data are challenging, yet common features can be extracted. The majority of patients with RT-induced abscopal effects were of advanced age, received high doses of RT in the definitive setting, or had metastatic cancer. Although various cancer entities can be found, some occur more frequently, particularly malignant melanoma, lymphoma, renal cell carcinoma, and hepatocellular carcinoma.

Several retrospective analyses underline the synergism between immune checkpoint inhibition and RT and report increased occurrence of abscopal effects, as well as improved overall survival (OS) with this combination approach.[37-39] Interestingly, the treatment sequence appears to be crucial.[40] Although secondary analysis of KEYNOTE-001 revealed that patients with advanced non–small cell lung cancer

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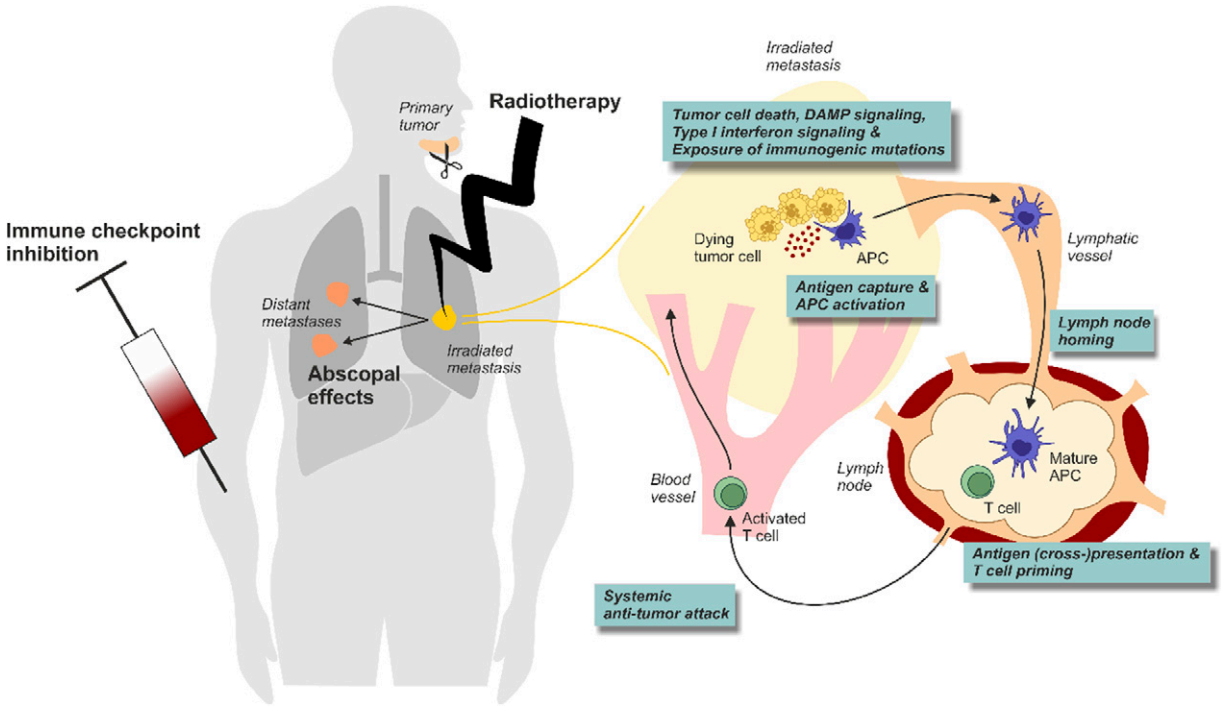


FIGURE 1. Abscopal Effects and Out-of-Field Lesion Regression Induced by Radioimmunotherapy

In recurrent or metastatic HNSCC, abscopal antitumor immunity is induced by RT of a pulmonary metastasis combined with systemic immune checkpoint blockade. RT generates an in situ cancer vaccine which, in the presence of immune checkpoint inhibition, stimulates the induction of systemic antitumor immune mechanisms. (Right part of the scheme): tumor antigens and adjuvant DAMPs are released by dying tumor cells and are ingested and processed by APCs, which (cross-)present these tumor antigens to naive T cells in a tumor-draining lymph node. Systemic antitumor immunity is achieved by activated T cells that leave the lymph node and subsequently attack metastatic tumor nodules at distant nonirradiated sites.

Modified from Brix et al.[8]

(NSCLC) who had previously received RT showed longer progression-free survival (PFS) upon pembrolizumab treatment,[41] systematic analyses of the treatment sequence suggest that initiating immune checkpoint inhibition before RT is associated with superior outcomes.[42,43] Clearly, detailed prospective clinical evaluation is needed in this regard (Tables 1 and 2).

The Persisting Gap Between Preclinical and Clinical Experiences

Preclinical investigations with heterotopic xenograft models have fundamentally contributed to our mechanistic understanding of RT-stimulated abscopal responses. With this setup, RT-mediated abscopal tumor regression can be observed very robustly across different cancer entities, yet preferred tumor models include melanoma, breast cancer, colorectal cancer, and lung cancer. Studies with HNSCC tumors are rare,[44] and orthotopically transplanted or autochthonous tumors have been used even less often.[8] This robust abscopal effect in heterotopic transplantation models is one major difference compared with the clinical situation. The stimulation of antitumor immune responses may be easier in subcutaneous situations than in orthotopic situations, because the strength of an immune response, as well as the class of the responsible effectors, is clearly shaped by the respective tissue.[45]

Another issue is the irradiation regimen. Preclinical reports commonly use high single doses with up to 60 Gy or hypofractionated protocols with 3 to 5 x 6 to 12 Gy, whereas, in the clinical routine, classic fractionation with daily doses of 1.8 to 2.0 Gy is used for the majority of patients. Importantly, most case reports of RT-induced abscopal responses are associated with higher doses, and retrospective analyses also support the notion that increased doses are beneficial for immunostimulation.[11,37] This has been considered for ongoing clinical trials in which immune checkpoint inhibition is combined with SBRT (Tables 1 and 2).

Finally, the treatment sequence is different between preclinical studies and the majority of clinical cases. RT can function as a means of in situ vaccination, enforcing the antigenicity and the adjuvanticity of a tumor. However, if the gross tumor mass has been removed by preceding surgery,

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TABLE 1. Clinical Trials Involving RT and Immune Checkpoint Inhibition for Locally Advanced HNSCC

NCT Number	Phase of Trial	Irradiation Regimen	Intervention	Outcome Measure and Comments
NCT03799445	II	Definitive IMRT	RT + immune checkpoint inhibition (nivolumab + ipilimumab)	Primary endpoints: dose-limiting toxicity (postcompletion), complete response rate (6 months), PFS (2 years) Secondary endpoints: grade 3 treatment-related adverse events, acute and chronic adverse events (3 months), OS (1 and 2 years)
NCT03673735	III	Postoperative RT	RT + chemotherapy (cisplatin) vs. RT + chemotherapy (cisplatin) + immune checkpoint inhibition (durvalumab)	Primary endpoint: DFS (2 years) Secondary endpoints: OS (5 years), distant metastasis (5 years), locoregional recurrence (5 years), secondary cancers (5 years), toxicity (5 years), quality of life (5 years)
NCT03635164	I	Preoperative SBRT	RT + durvalumab	Primary endpoint: maximum tolerated dose and dose-limiting toxicities Secondary endpoints: pathologic response (2 years), OS (2 years), LRPFS (2 years), toxicity profile, immune cell infiltration
NCT03618134	I/II	Preoperative SBRT	RT + immune checkpoint inhibition (durvalumab) + TORS + neck dissection vs. RT + immune checkpoint inhibition (durvalumab + tremelimumab) + TORS + neck dissection	Primary endpoints: adverse events and grade, PFS (2 years) Secondary endpoints: OS (2 years), primary tumor control (2 years), locoregional control (2 years), distant recurrence (2 years), quality of life
NCT03529422	I	Postoperative IMRT	RT + immune checkpoint inhibition (durvalumab + tremelimumab)	Primary endpoints: safety (12 weeks), acute toxicity (12 weeks) Secondary endpoints: chronic toxicity (12 weeks), DFS (5 years), OS (5 years), PD-L1 expression (12 weeks)
NCT03509012	I	RT	RT + chemotherapy (cisplatin) + immune checkpoint inhibition (durvalumab)	Primary endpoints: dose-limiting toxicity (28 days after therapy), adverse events (90 days after therapy) Secondary endpoints: PFS (1 year), OS (4 years), response rate (4 years), DFS (4 years)
NCT03426657	II	Definitive IMRT	RT + chemotherapy + immune checkpoint inhibition (durvalumab + tremelimumab)	Primary endpoints: feasibility, intratumoral $CD8^+$ T cells, dose-limiting toxicity Secondary endpoints: PFS (12 weeks after therapy), pathologic response (12 weeks after therapy), OS (12 weeks after therapy)
NCT03247712	I/II	Preoperative SBRT	RT (5× 8 Gy) + immune checkpoint inhibition (nivolumab) + surgery vs. RT (3× 8 Gy) + immune checkpoint inhibition (nivolumab) + surgery	Primary endpoints: safety and tolerability Secondary endpoints: Decrease in tumor size or number of lymph nodes involved
NCT03051906 DUCRO-HN	I/II	Definitive IMRT	RT + cetuximab + immune checkpoint inhibition (durvalumab)	Primary endpoint: PFS (2 years) Secondary endpoints: adverse events (90 days after treatment), locoregional control (2 years), OS (2 and 5 years), quality of life (2 weeks after treatment)

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TABLE 1. Clinical Trials Involving RT and Immune Checkpoint Inhibition for Locally Advanced HNSCC (Continued)

NCT Number	Phase of Trial	Irradiation Regimen	Intervention	Outcome Measure and Comments
NCT02999087 REACH	III	Definitive IMRT	RT + chemotherapy (cisplatin) vs. RT + chemotherapy (cisplatin) + immune checkpoint inhibition (avelumab)	Primary endpoint: PFS (6 years) Secondary endpoints: OS (6 years), safety (6 years)
NCT02764593	I	Definitive IMRT	Cisplatin + immune checkpoint inhibition (nivolumab) vs. cisplatin (high dose) + immune checkpoint inhibition (nivolumab) vs. cetuximab + immune checkpoint inhibition (nivolumab) vs. RT + immune checkpoint inhibition (nivolumab)	Primary endpoint: Dose-limiting toxicity (28 days after therapy)
NCT03623646* CITHARE	II	Definitive IMRT	RT + chemotherapy (cisplatin) vs. RT + immune checkpoint inhibition (durvalumab)	Primary endpoint: progression (1 year) Secondary endpoints: PFS (2 years), OS (2 years), safety (2 years), quality of life (2 years)
NCT03383094* KEYCHAIN	II	Definitive IMRT	RT + chemotherapy (cisplatin) vs. RT + immune checkpoint inhibition (pembrolizumab)	Primary endpoint: PFS (3 years) Secondary endpoints: OS (3 years), acute toxicity (3 years), late toxicity (3 years), patterns of failure (3 years)

Data are from www.clinicaltrials.gov.

Abbreviations: IMRT, intensity-modulated RT; DFS, disease-free survival; LRPFS, locoregional progression-free survival; TORS, transoral robotic surgery.

*Not yet recruiting.

the availability of tumor (neo-)antigens is much more limited than in preclinical model systems in which the tumor receives a definitive RT dose. Moreover, the tumor-draining lymph nodes, which are sites of antigen presentation and T-cell priming, require attention.[29] The time of lymph node and bulk tumor removal relative to RT needs to be carefully optimized to increase the chance of abscopal tumor regression. Currently, this is addressed in several clinical trials utilizing definitive or neoadjuvant RT in combination with immune checkpoint inhibition (Tables 1 and 2).

Abscopal Effects in HNSCC

Although the first report of RT-induced abscopal effects was in a patient with head and neck cancer,[10] HNSCC is underrepresented in preclinical and clinical studies, and it remains unclear whether the immunogenicity of HNSCC makes head and neck cancer an appealing disease to exploit the abscopal effect.

HNSCC exhibits various mechanisms of immunosuppression that are known from other cancer entities. As such, suppressive immune cell populations, including tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells, have been observed in the HNSCC tumor microenvironment together with immunosuppressive cytokines, like transforming growth factor-beta or interleukin-10, and immune checkpoints.[46] This is of clinical relevance, because markers of immunologically "hot" tumors are associated with improved prognosis, whereas markers of "cold" tumors prognosticate impaired outcome.[47-50] Regarding this immune profile, HPV+ HNSCCs more commonly exhibit "hot" morphology compared with HPV– ones.[51] This is not associated with the tumor mutational burden, which is similar for HPV+ and HPV– HNSCCs and, overall, is lower than the mutational burden of other mutagen-associated cancer entities, such as melanoma and lung cancer.[52,53] Still, patients with HPV+ HNSCC have significantly better clinical outcomes and are suggested to have slightly better responses to immune checkpoint inhibition.[16,17] Combining immunotherapy with other treatment modalities may be beneficial. In this regard, RT has been reported to upregulate expression of the PD-1/PD-L1 axis, thus increasing the probability of responding to immune checkpoint inhibition.[54] Whether the in situ vaccination effects of RT can be achieved in HNSCC, as in other cancer entities, has not been systematically analyzed. Molecularly, HNSCC (particularly HPV– HNSCC) is considered a "loss-of-function" cancer, and inactivating mutations of *TP53* and *CDKN2A* dominate the genetic landscape.[55] This may affect the mode of RT-induced cell death, as well as its immunogenicity. Best abscopal responses upon RT have always been achieved with "gain-of-function" cancer models driven by activating mutations in *RAS*, such as melanoma, and there seems to be a link between *RAS* status and PD-L1 expression.[56,57] Moreover,

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TABLE 2. Clinical Trials Involving RT and Immune Checkpoint Inhibition for Recurrent or Metastatic HNSCC

NCT Number	Phase of Trial	Irradiation Regimen	Intervention	Outcome Measure and Comments
NCT03546582 KEYSTROKE	II	SBRT	RT vs. RT + immune checkpoint inhibition (pembrolizumab)	Primary endpoint: PFS (2 and 5 years) Secondary endpoint: OS (5 years)
NCT03522584	I/II	SBRT	RT + immune checkpoint inhibition (durvalumab + tremelimumab)	Primary endpoint: safety (2 years) Secondary endpoints: response rate (2 years), OS (2 years), PFS (2 years)
NCT03317327 REPORT	I/II	RT	RT + immune checkpoint inhibition (nivolumab)	Primary endpoints: adverse events Secondary endpoints: PFS (1 years), OS (5 years), response rate (3 years)
NCT03212469 ABBIMUNE	I/II	SBRT	RT + immune checkpoint inhibition (durvalumab + tremelimumab)	Primary endpoint: dose-limiting toxicity Secondary endpoint: -
NCT03085719	II	RT	RT (high dose) + immune checkpoint inhibition (pembrolizumab) vs. RT (high dose + low dose) + immune checkpoint inhibition (pembrolizumab)	Primary endpoint: response rate (1 year) Secondary endpoints: OS (1 year), PFS (1 year), adverse events (1 year), abscopal responses (1 year)
NCT02684253	II	SBRT	Immune checkpoint inhibition (nivolumab) vs. SBRT + immune checkpoint inhibition (nivolumab)	Primary endpoint: best overall response (2 years) Secondary endpoint: -
NCT03283605	I/II	SBRT	RT + immune checkpoint inhibition (durvalumab + tremelimumab)	Primary endpoints: acute toxicity (3 months), PFS (6 months) Secondary endpoints: local control (2 years), PFS (2 years), OS (2 years), abscopal events (2 years)
NCT03313804	II	Three-dimensional RT or SBRT	RT + immune checkpoint inhibition (nivolumab or pembrolizumab or atezolizumab)	Primary endpoint: PFS (6 months) Secondary endpoints: $PD1^+/CD4^+$, $PD1^+/CD8^+$, $CD8^+/IFN\gamma^+$, $PD\text{-}L1^+/CD4^+$ T cells

Data are from www.clinicaltrials.gov.
Abbreviation: DFS, disease-free survival.

p53-dependent signals appear to be of importance for RT-dependent abscopal tumor regression,[58,59] and the question arises whether differences in *TP53* and *RAS* status can determine differences in abscopal tumor regression between HPV+ and HPV– HNSCCs. Accordingly, further mechanistic studies in this context are needed, as well as prospective clinical evaluation. Pioneering results from a randomized phase II trial with nivolumab plus SBRT versus nivolumab treatment alone in metastatic HNSCC did not show enhanced abscopal tumor regression or improved outcome at the 2018 ASCO Annual Meeting.[60] Updated results, as well as subgroup and biomarker analyses, are pending publication. Finally, it is worth considering multimodality approaches with additional immunostimulating agents, because, for instance, intratumoral Toll-like receptor stimulation, in combination with immune checkpoint inhibition, has proven convincing abscopal tumor regression in HNSCC, at least in preclinical model systems.[61]

Conclusions

Abscopal effects of RT have become appreciated phenomena that warrant prospective evaluation in specifically dedicated clinical trials. There is growing interest to exploit the (re)activation of systemic antitumor immune responses by RT systematically, particularly in combination with immunotherapy. Nevertheless, there remains a gap between clinical and preclinical experiences. Established treatment protocols must be reconsidered with specific focus on dosing and treatment sequences, and resilient biomarkers must be identified. The increasing number of ongoing clinical trials for HNSCC and other malignancies will reveal whether the combination of RT and immunotherapy can really change oncological standards.

PSEUDOPROGRESSION

The Phenomenon

Pseudoprogression is the radiologic appearance of an increase in tumor burden with subsequent tumor regression or response. Biologically, pseudoprogression is not actual tumor growth, but rather results from infiltration of inflammatory cells, edema, and necrosis generated by immunotherapy.[62] Tumor biopsies performed at the time of initial radiologic progression in patients with melanoma treated with ipilimumab showed inflammatory reactions,

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suggestive of activated T-cell recruitment to the tumor site prior to antitumor activity that led to an artificial increase in tumor size.[63] Although there may appear to be tumor growth on initial imaging and physical examination, pseudoprogression should not be accompanied by clinical deterioration.

Radiologic Assessment of Response

Pseudoprogression on immune checkpoint inhibitor therapy was initially described in patients with melanoma, first in the early studies of the anti-CTLA4 inhibitor ipilimumab[64] and later in studies of anti–PD-1 therapy with nivolumab and pembrolizumab.[65,66] Given this atypical pattern of response, the use of RECIST criteria in clinical trials could result in premature discontinuation of immune checkpoint inhibitors in patients who derive a delayed clinical benefit; therefore, immune-related Response Criteria (irRC) were developed in 2009 to account for the potential for pseudoprogression. irRC specified that new or enlarged lesions become incorporated into total tumor volume and that disease progression requires an increase in tumor volume to be confirmed by two consecutive imaging studies a minimum of 4 weeks apart.[67] A disadvantage of irRC is that it uses bidimensional measurements, which are more subject to variability in response compared with unidimensional measurements.[68,69]

Immune-related RECIST was created, which uses unidimensional measurements while requiring confirmation of progression.[70] Despite irRC and immune-related RECIST, many immunotherapy trials used traditional RECIST criteria; thus, comparison of data between different trials was imprecise. This led to a consensus modification of RECIST 1.1 named immunotherapy RECIST (iRECIST) in an effort to standardize data collection concerning radiologic response (Table 3).[71] iRECIST defines immune unconfirmed progressive disease (iUPD) and immune confirmed progressive disease (iCPD). Progressive disease (PD) per RECIST 1.1 is synonymous with iUPD. However, per iRECIST, iUPD must be confirmed (iCPD) to be considered true progression, with repeat imaging performed at least 4 weeks, but not more than 8 weeks, following iUPD. iCPD is confirmed when there is an increase of at least 5 mm in total target lesion measurements. During the assessments following iUPD, response can be categorized as immune complete response, immune partial response, or immune stable disease, as well as iUPD multiple times, assuming iCPD has not been reached. Adoption of iRECIST has ensured a uniform approach to the conduction of clinical trials involving immunotherapeutics.

Incidence of Pseudoprogression

Trials that report immune-related response distinctly from RECIST response invoke that the rate of pseudoprogression in the treatment of solid tumors with checkpoint blockade therapy is low, likely less than 10% across tumor types.[62,63] In patients with melanoma who received anti–PD-1 monotherapy with nivolumab and pembrolizumab on study, pseudoprogression was observed in 4.6% to 8.3% of patients who experienced a partial response (PR) per RECIST following PD.[72-75] In patients with NSCLC, pseudoprogression was reported in 1.9% to 6.9% treated with anti–PD-1/PD-L1 inhibitors.[76-80] Pseudoprogression was more broadly defined in NSCLC trials as the appearance of (1) a new lesion, followed by a decrease from baseline of at least 10%, in the sum of target lesions; (2) an initial increase from nadir of at least 20% in the sum of target lesions, followed by a reduction from baseline of at least 30%; or (3) an initial increase from nadir of at least 20% in the sum of target lesions or appearance of new lesions, followed by at least two tumor assessments that showed no additional progression, defined as at least a 10% additional increase in the sum of target lesions and new lesions. In patients with renal cell carcinoma treated with nivolumab[81,82] or urothelial carcinoma treated with atezolizumab,[83] PR according to RECIST following PD was observed in 4.9% to 7.1% and in

TABLE 3. Comparison of RECIST 1.1 Versus iRECIST

	RECIST 1.1	iRECIST
Complete Response	Disappearance of all target lesions	Disappearance of all target lesions
Partial Response	Greater than 30% decrease in tumor size, no new lesions	Greater than 30% decrease in tumor size, no new lesions
Stable Disease	Does not meet criteria for objective response or PD	Does not meet criteria for objective response or PD
PD	Greater than 20% increase in the sum of the products of diameters of target lesions, with an absolute increase of more than 5 mm; new lesions	Requires confirmed PD (iCPD) 4 to 8 weeks following unconfirmed progressive disease (iUPD) that is equivalent to RECIST 1.1 PD
New Lesions	Results in PD	Results in iUPD and subsequently, iCPD if additional new lesions appear or an increase in the size of new lesions is seen at the next assessment
Confirmation of PD	Not required	Required
Consideration in Clinical Status	Not included in assessment	Considered in whether treatment can be continued after iUPD

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1.6%, respectively. Overall, the rates of pseudoprogression are low, although many studies evaluating checkpoint inhibitors did not include immune-related response criteria, potentially underestimating the rates of pseudoprogression.

In HNSCCs, which have shown a more modest response to checkpoint inhibitor blockade compared with melanoma, NSCLC, and renal cell carcinoma, pseudoprogression has been reported, although it is rare.[84] In KEYNOTE-012, a phase Ib study of pembrolizumab in patients with recurrent or metastatic HNSCC, one patient of 45 was noted to have an "atypical response," with an initial "tumor flare," followed by a complete response.[85] It is unclear whether the "tumor flare" represented true radiographic pseudoprogression consistent with iUPD, followed by immune complete response, or occurred clinically before study imaging was completed. Further, in CheckMate 141, a randomized phase III study of nivolumab versus the investigators' choice standard single-agent chemotherapy, 1.3% (3/240) of patients in the nivolumab arm experienced growth in target lesions, followed by subsequent response, although the specifics were not reported in the article.[17] In this study, patients could be continued on nivolumab "beyond disease progression, as assessed clinically or radiographically, if the investigator felt that the study drug was providing clinical benefit." In a similar design to CheckMate 141, KEYNOTE-040, a phase III randomized trial of pembrolizumab versus the investigators' choice single-agent chemotherapy, did not report the response rate for RECIST compared with iRECIST. However, per the swimmer's plot, nine patients who were assigned to pembrolizumab continued on treatment following PD, and at least two patients remained on pembrolizumab for longer than 8 weeks after iUPD, suggesting that 7.7% (2/26) of patients with confirmed response and 0.8% (2/247) of total patients exhibited pseudoprogression.[86] Lastly, in a study of 100 patients with advanced HNSCC that showed that lower tumor burden was associated with a clinical benefit to immune checkpoint blockade, there was one patient with pseudoprogression.[87] In these large studies of patients with recurrent/metastatic HNSCC, the rates of pseudoprogression with PD-1 inhibitors, although not explicitly discussed, were exceedingly rare.

Pseudoprogression Versus True Progression

There is no reliable assessment to help clinicians decipher between potential pseudoprogression and true progression. The time from initiation of therapy to pseudoprogression is not always consistent. Pseudoprogression is more frequently seen in the first weeks after treatment initiation but can be seen several months after treatment initiation.[88] Clinical deterioration should not be seen with pseudoprogression; rather, it should be an indication of true disease progression.[71] The presence of immune-related adverse events has been inferred to be associated with response to immunotherapy[89]; however, it is unknown whether immune-related adverse events in the setting of tumor growth increase the likelihood for pseudoprogression rather than true progression. Although obtaining a biopsy for histologic assessment of progressive lesions may clarify whether an increase in tumor size is a result of the inflammatory infiltrate or true progression,[90] it may not be feasible, especially prior to making a treatment decision regarding continuation of checkpoint blockade therapy.

Currently, there is no ideal imaging method to predict pseudoprogression. Given that ^{18}F-fluorodeoxyglucose tends to accumulate in cells with high metabolic activity, which includes neoplastic and inflammatory cells, ^{18}F-fluorodeoxyglucose positron emission tomography scans do not distinguish pseudoprogression from true progression well.[90] New radiotracers are being developed to specifically mark T cells that consist of monoclonal antibodies specific for T-cell antigens and radioactive elements.[91] CTLA-4, PD-1, PD-L1, and CD3 have been commonly studied targets preclinically. The first-in-human positron emission tomography study evaluated ^{89}Zr-atezolizumab, a radiotracer bound to a PD-L1 antibody in patients with bladder cancer, NSCLC, and triple-negative breast cancer treated with azetolizuamb.[92] Tumor uptake of the radiotracer was found to correlate with response to RECIST 1.1. It is hoped that "immuno–positron emission tomography" will become a tool used to identify patients who will respond to immunotherapy.

How Should Initial Radiologic Progression Be Managed?

Without tools to identify pseudoprogression, given that the occurrence of pseudoprogression in HNSCC is rare, the potential for delayed durable responses to checkpoint inhibitors following documented progression should be weighed with caution against marked disease progression on these agents. In studies evaluating pembrolizumab and nivolumab in recurrent or metastatic HNSCC, PD was seen as best response in more than 40% of patients.[17,93,94] Best overall response data from CheckMate 141 and KEYNOTE-040 revealed that 41.7% and 43.7% of patients receiving nivolumab and pembrolizumab, respectively, had PD compared with 34.7% and 39% of patients receiving investigator's choice chemotherapy on each study.[86,95] These data suggest that, compared with cytotoxic chemotherapy, which provides better cytostatic activity in the absence of an objective response, when the immune system fails to activate in the presence of these novel agents, the natural biology of untreated HNSCC is witnessed. Additionally, the phenomenon of hyperprogression has been described and identified as an increase in tumor growth rate after checkpoint inhibitor initiation by a factor or two,[96] which is thought to be a result of immunotherapy-induced acceleration of tumor growth rather than the natural biology.

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One should be selective about which patients are continued on treatment, despite early radiologic signs of progression. Patients with stable performance statuses and moderate, rather than marked, tumor growth can be considered for continued treatment until repeat confirmation scans are obtained. Further, per reported patterns of pseudoprogression,[62] there should be more enthusiasm about continuing patients with a decrease in target lesions in the presence of new lesions, rather than initial tumor enlargement in target lesions, on checkpoint blockade therapy.

The practice of treating through documented PD per RECIST 1.1 to allow for a delayed response should not be habitual, given the risk of aggressive true progression and clinical deterioration while awaiting confirmation imaging between 4 and 8 weeks. For patients with no remaining treatment options, this is an unfortunate reality of end-stage HNSCC, and treating through progression presents minimal risk in terms of missed opportunity for other treatments. On the other hand, for patients receiving checkpoint blockade therapy who have available therapeutic options, either standard or other investigational agents, treatment through progression may present harm by preventing receipt of further lines of therapy because of functional decline secondary to tumor growth. Additionally, given the long half-life of checkpoint inhibitors, patients who respond should experience a benefit beyond the duration of treatment; in the setting of pseudoprogression, a response can occur following discontinuation of treatment. Therefore, if response while on a further line of treatment is far better than expected, it is possible that pseudoprogression on checkpoint blockade had occurred, and rechallenge should be considered.

Conclusions

When treating patients with immunotherapy, the potential for remarkable durable responses that translate into a substantial overall survival advantage must be balanced with the prospect of a futile intervention that allows for unrestrained tumor growth. As we expand the indications for checkpoint inhibitors in the management of HNSCC and continue to investigate new ways to augment immunogenicity through novel combinations, we should continue to research predictive markers of efficacy and institute practices that optimize benefits and avoid harm. Therefore, the real, but rare, possibility for pseudoprogression should be weighed against the harm of continued treatment that can result in missed opportunities for alternate treatments, along with unwarranted toxicity and cost.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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