

## Critical Review

# Toxicity of radiation and immunotherapy combinations

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### Abstract

**Purpose:** Although immunotherapy is a rapidly emerging modality for cancer care, there have been multiple reports of fatal toxicities. There have also been cases of treatment-related deaths with combined non-immunotherapeutic biologic compounds with radiation therapy. Thus, provision of summative information appraising the safety of combinatorial immunotherapy and radiation therapy (iRT) is imperative. Because this has not been well characterized, this review summarizes the available evidence to date.

**Methods and materials:** Owing to the heterogeneity and relatively low quantity of published reports, this review was conducted in a narrative rather than systematic format.

**Results:** The results of combined iRT, both concurrent and sequential, are discussed for oncologic therapy of the brain, lung, liver, and prostate. Most evidence is from small samples and shorter follow-up but does consist of multiple prospective publications. Most data exist for ipilimumab, with programmed cell death -1 inhibitors emerging in more recent years. With 2 large phase 3 trials as exceptions, there were no instances of iRT-related deaths across all discussed studies. Altogether, grade 3 to 4 toxicities were relatively low in frequency; of the studies that compared iRT with an “immunotherapy only” or “RT only” cohort, none documented a clear increase in high-grade adverse events with combined-modality management.

**Conclusions:** Despite the low quantity of data, combined iRT offers encouraging safety profiles. There is no evidence that iRT produces an overt increase in high-grade toxicities. Further data, especially on concurrent iRT, are anticipated from numerous iRT trials that are currently ongoing worldwide.

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## Introduction

Although the immunology of cancer has been studied for decades, the current decade has been marked by a sharp increase in corroborative clinical evidence displaying the efficacy of immunotherapies for oncologic management.<sup>1–4</sup> Phase 3 data have displayed superior survival with several agents over standard therapies for multiple neoplasms, such as melanoma<sup>5,6</sup> and lung cancer.<sup>7,8</sup> These practice-changing findings have resulted in the rapid creation and implementation of numerous prospective trials to evaluate the safety and efficacy of combination immunotherapy with standard therapies for nonmetastatic disease.<sup>9</sup>

The safety of combinatorial therapy is an unquestionably important one to evaluate, because there are mechanistic bases for increased toxicity with combined immunotherapy and radiation therapy (iRT).<sup>1–4</sup> Namely, because radiation therapy (RT) creates a proinflammatory milieu (some of which leads to known RT-related adverse events) and because of the combined delivery of agents that augment the immune system (ie, immunotherapy), there is a theoretical concern for increased toxicities. This concern is exemplified by the aforementioned randomized data largely not using combinatorial therapy with standard therapies, including RT. Although RT carries toxicity risks that are independent of immunotherapy, the delivery of multiple concurrent immunotherapeutic agents (without RT) has been known to cause fatal adverse events.<sup>10,11</sup> This cautiousness in administering iRT has also been exemplified by randomized trials that often mandate the completion of RT well in advance of immunotherapy.<sup>12,13</sup> Some trials have deemed patients ineligible if they received higher than palliative doses within several months of immunotherapy.<sup>8</sup>

Multiple reports have documented grade 5 toxicities in patients receiving concurrent targeted therapies (which are not generally categorized as immunotherapies) with RT (reviews encompassing targeted therapies and RT are described elsewhere).<sup>14</sup> Two phase 2 studies (N = 48 and N = 56) observed 1 case each of fatal toxicity in patients receiving stereotactic reirradiation with concurrent cetuximab.<sup>15,16</sup> One case of fatal cerebral hemorrhage 3 months after stereotactic radiosurgery (SRS) with sunitinib for intracerebrally metastatic renal cell carcinoma was reported in a series of 106 patients,<sup>17</sup> along with a case of fatal upper gastrointestinal hemorrhage in 16 patients in a phase 1 trial of sorafenib with stereotactic RT for hepatocellular carcinoma.<sup>18</sup> Lastly, in a phase 2 study of erlotinib with stereotactic RT for oligometastatic disease (N = 24), 1 fatal case of acute respiratory distress syndrome was possibly attributed to the protocol treatment.<sup>19</sup>

Hence, iRT may risk incurring excess toxicities, which may limit further receipt of oncologic therapy and sharply diminish quality of life. Because clinical reports detailing

toxicities with such regimens have not been well characterized to date, an appraisal of the safety of combined iRT in a variety of clinical settings to justify its continued use going forward is essential. The goal of this review is to summarize existing data regarding the safety of combined iRT and to address areas in need of further clarity with future research, which have implications for ongoing trials as well as those under design.

## Clinical evidence

### Brain

Combinatorial iRT for intracerebral disease is associated with the largest quantity of published experiences thus far, most of which studied patients with metastatic melanoma and brain metastases receiving ipilimumab. One such series described 33 patients, of whom 16 underwent whole brain RT (WBRT; 30-37.5 Gy) and 17 received SRS (14-24 Gy).<sup>20</sup> Although the duration and timing of both modalities were not explicitly reported other than treatment being delivered concurrently, 1 patient experienced intratumoral hemorrhage and there were no cases of radiation necrosis at a median of 20 months of follow-up.

A larger series of 58 patients undergoing SRS, of whom 25 received concurrent ipilimumab, was also reported in 2013.<sup>21</sup> The median SRS dose was 20 Gy (range, 15-20 Gy) delivered to a median of 3 lesions (range, 1-9). The investigators noted, with a median follow-up of 6 months, 7 cases (28%) of intracranial hemorrhage, not statistically different from those receiving SRS alone (30%). There were no cases of treatment-related radiation necrosis.

A study from Memorial Sloan-Kettering Cancer Center evaluated 46 patients receiving SRS and ipilimumab (n = 15 concurrent; n = 19 SRS first; and n = 12 ipilimumab first).<sup>22</sup> Most lesions were small, with a median of 2 metastases treated (range, 1-6) at a median dose of 21 Gy (range, 15-24 Gy). There were 6 instances of grade 3 toxicities (n = 2 brain hemorrhage; n = 2 seizure; n = 1 skin; and n = 1 hepatitis) in patients receiving concurrent iRT and 4 instances (n = 2 brain hemorrhage and n = 2 hepatitis) in the remainder. However, not all grade 3 toxicities were specifically attributed to iRT (eg, hepatitis). There was 1 case each of grade 4 adverse events in patients receiving concurrent iRT (cardiopulmonary) and in the remainder (brain hemorrhage).

Another series from the Medical University of South Carolina assessed 10 patients receiving SRS before or concurrently with ipilimumab as part of a larger cohort analysis.<sup>23</sup> There was a median of 2 lesions treated with SRS, with specific doses not reported. At a median follow-up of 33 months, grade  $\geq 3$  toxicities were limited

to 1 patient with diarrhea/colitis, without occurrences of neurologic adverse events.

A large experience of 88 cases, half of which received iRT, has been reported from Duke University.<sup>24</sup> However, standardization of RT regimens and doses from that study is difficult because the study encompassed a combination of ablative and nonablative RT. Additionally, although many patients received brain RT, the study also mixed patients treated to other unspecified body sites. Nevertheless, at a median follow-up of 18 months, there were few overall toxicities. In the iRT group, crude rates of nausea were 9%, dermatologic events 27%, gastrointestinal events 18%, and endocrine events 2%. In addition to the heterogeneity, a major limitation to that publication was the absence of toxicity assessment details such as the scale or grading technique.

The largest series to date, a 137-patient iRT series from MD Anderson Cancer Center, specifically evaluated radiation necrosis.<sup>25</sup> Eighty percent of patients received SRS (remainder WBRT), with a median of 2 treated lesions. Ipilimumab was delivered in 87% of patients, pembrolizumab in 9%, and both in 4%. The median follow-up was 10 months from RT, and the overall crude rate of radiation necrosis was 27%. In patients receiving ipilimumab, pembrolizumab, and both, the respective rates were 13%, 7%, and 27%. Of note, in addition to the lesion sizes not being reported, most patients did not receive concurrent iRT. In fact, the authors found a trend ( $P = .08$ ) toward lower radiation necrosis-free survival in patients who received immunotherapy and RT within 6 months of each other.

A recent experience by Patel et al. detailed their 20-patient experience of ipilimumab and SRS within 4 months of each other.<sup>26</sup> Most patients had 2 to 3 brain metastases, and doses were based on size-related cutoffs (15-21 Gy). The median follow-up was 7 months. The crude 1-year rates of radiation necrosis were 30% in patients receiving combined-modality therapy versus 21% with SRS alone ( $P = .08$ ). However, there were no statistical differences in symptomatic necrosis or hemorrhage (15% in both groups, for both parameters).

Another recent publication was a phase 1 trial of concurrent iRT ( $n = 16$ ).<sup>27</sup> Five patients received WBRT (30 Gy) and the remainder received SRS (median 2 metastases; 15-30 Gy). The median follow-up in both arms was 8 and 11 months, respectively. There were no grade 4 toxicities, and grade 3 neurotoxicities were limited to headache ( $n = 1$ ) and hypophysitis ( $n = 1$ ).

Two series of programmed death-1 (PD-1) inhibitors in conjunction with cerebral RT have been reported. The first was a 2-patient series.<sup>28</sup> The first patient had prior SRS and received SRS for a new melanoma metastasis (22 Gy), followed by pembrolizumab 5 months thereafter. The patient experienced seizures and had the lesion surgically removed. The second patient had newly diagnosed metastatic non-small cell lung cancer (NSCLC) and

underwent SRS (20 Gy) to a single brain lesion, followed by nivolumab/ipilimumab, with an increase in perilesional edema, and similarly required surgical craniotomy for further control.

The second publication was an impactful experience of 73 cases treated with SRS (16-24 Gy in 1 fraction, or 20-30 Gy in 5 fractions) in 26 patients.<sup>29</sup> Of note, concurrent nivolumab was delivered for just 5 metastases, with most delivered before (48%) or after (45%) SRS. At a median follow-up of 9 months, no neurologic symptomatic grade  $\geq 3$  toxicities were reported; along with 4 cases of hemorrhage, there were 2 cases of grade 3 edema.

## Lung

In addition to a well-known case report of a patient with melanoma and a pleural-based paraspinal mass treated with ipilimumab followed by RT (28.5 Gy in 3 fractions) that did not develop RT-related toxicities,<sup>30</sup> there are studies evaluating iRT for lung disease. A publication from Duke University reported on 16 patients with prospective nonmetastatic NSCLC undergoing neoadjuvant chemotherapy and ipilimumab, which was followed by surgery and postoperative RT ( $n = 9$ ; median 50 Gy) or definitive chemoradiation ( $n = 7$ ; median 60 Gy).<sup>31</sup> Although toxicities were not reported in detail, there were no grade  $\geq 3$  events.

A phase 1 trial described 35 patients receiving stereotactic RT (50 Gy in 4 fractions or 60 Gy in 10 fractions) concurrently or sequentially with ipilimumab to lung and/or liver metastases.<sup>32</sup> The median follow-up was 9 months. There were no grade 4 or 5 events. A total of 12 patients (34%) experienced any grade 3 toxicity (4 of 13 patients receiving concurrent iRT and 8 of 22 patients sequential iRT). This included 6 patients undergoing liver RT and 4 patients lung RT ( $n = 2$  in both liver/lung). Of the 12 grade 3 toxicities, 2 were dose limiting (pancreatitis in a patient receiving concurrent iRT to the liver; elevated the liver function test results in a patient receiving sequential iRT to the liver). Importantly, no patient experienced grade  $\geq 2$  pneumonitis.

Transitioning to data on PD-1 inhibitors, in addition to a recently reported unpublished abstract showing a 14% rate of grade 3 toxicity (0% grade 4-5) in 21 patients with metastatic NSCLC who were treated with stereotactic or hypofractionated RT to the lung or liver with concurrent pembrolizumab,<sup>33</sup> the results from a secondary analysis of a phase 1 investigation will be described.<sup>34</sup> The phase 1 trial therein was designed to evaluate the safety of pembrolizumab for metastatic NSCLC, and the publication stratified patients by receipt of prior irradiation versus lack thereof. In patients who underwent previous thoracic RT ( $n = 24$ ) compared with those who did not ( $n = 73$ ), there was a statistical increase in pulmonary toxicities (3 patients [13%] vs 1 patient [1%]), but there was no

statistical difference in grade  $\geq 3$  events (1 patient in each group). These associations were also true for any pulmonary toxicity (regardless of association with protocol treatment).

The largest experience of PD-L1 inhibitors for NSCLC comes from the PACIFIC trial, which randomized stage III unresected NSCLC undergoing definitive chemoradiation to durvalumab ( $n = 476$ ) versus placebo ( $n = 237$ ).<sup>35</sup> In addition to the landmark finding of a large progression-free survival benefit in the durvalumab group, the rates of any grade 3 and 4 events were 30% and 26%, respectively. Durvalumab also did not seem to appreciably increase pneumonitis (3% in both groups). Death from adverse events occurred in 6% in the durvalumab cohort and 4% in those receiving placebo.

The most recently available study was a combined analysis of iRT for various types of lung cancers, which was a pooled analysis of three phase 1/2 trials.<sup>36</sup> RT consisted of stereotactic radiation therapy in 60 patients with NSCLC, twice-daily RT (for small cell lung cancer [SCLC]) in 22 patients, and hypofractionated (45 Gy in 15 fractions) RT in 53 patients with NSCLC/SCLC. In the first group, 15 patients experienced a total of 34 grade 3 events, just 9 of which were pulmonary-specific (no grade  $\geq 4$  events). In the twice-daily cohort, 8 patients experienced a total of 16 grade 3 events, and 3 patients had a total of 5 grade 4 toxicities. In the hypofractionated population, just 1 patient suffered 2 grade 4 toxicities, and 10 patients had 17 instances of grade 3 events (2 were pulmonary-specific).

## Liver

In addition to the aforementioned study of both liver and lung iRT,<sup>32</sup> a highly cited case report from 2013 described a patient with metastatic, chemotherapy-refractory NSCLC who was started on ipilimumab together with RT to a large liver lesion (30 Gy in 5 fractions).<sup>37</sup> In addition to no treatment-related toxicities, the patient experienced a notable abscopal response and had no evidence of disease 1 year after iRT.

Another case report from Stanford University described similar findings in a patient (melanoma primary) treated with stereotactic RT to 2 of 7 liver lesions (54 Gy in 3 fractions) sandwiched between 2 cycles of ipilimumab.<sup>38</sup> A successful abscopal response was discerned, also without noted therapy-related toxicities.

## Prostate

The first of 2 prospective studies was a phase 1/2 multicenter trial of ipilimumab with or without RT in metastatic hormone-resistant prostate cancer.<sup>39</sup> RT was delivered (single-fraction 8 Gy) in up to 3 bone lesions, followed within approximately 1 week by

immunotherapy. Seventy-one patients received protocol treatment, 41 of whom received RT. The median follow-up was 16 months. Grade 3 and 4 events (colitis, hepatitis, diarrhea, and fatigue) occurred in 16 of 41 patients (39%) receiving iRT and 15 of 30 patients (50%) receiving ipilimumab alone. A total of 11 patients (27%) and 10 patients (33%) in the respective groups experienced toxicities that led to study discontinuation.

A phase 3 randomized study investigated bone-directed RT (single-fraction 8 Gy in up to 5 sites) followed by ipilimumab versus placebo for metastatic hormone-resistant prostate cancer.<sup>40</sup> Of the 399 patients in the iRT arm (initiated within 2 days of each other), the most common grade 3 event was diarrhea (16%), followed by fatigue and anemia (9% each). Nonhematologic grade 4 toxicities were limited to fatigue (2%), dyspnea, pain, colitis, and failure to thrive (1% each), along with diarrhea, asthenia, urinary tract infection, and pneumonia (<1% each). Seven patients (2%) had grade 5 events (4 patients with pneumonia and 3 with general health deterioration). There were no overt numerical differences in higher-grade toxicities between the arms.

## Discussion

Justifying the ongoing use of combined iRT by continually demonstrating the safety of such approaches is imperative. This is especially true not only because fatal toxicities have been reported, but also because existing randomized trials are wary of combining immunotherapy and RT. Summarizing the available evidence to date, we observe that iRT results in few severe toxicities. When conservatively interpreting the data, there is no evidence to suggest that adverse events are overtly higher than those with single-modality therapy. These data have implications for the continued use of iRT in clinical trials that are accruing or under development.

As a general summary across all studies, the rate of observed toxicities varied markedly for several reasons, including patient selection and clinical characteristics, follow-up time, categorization/definition of adverse events, and heterogeneity of therapies. For instance, based on the limited data, the rates of hemorrhage or brain necrosis in iRT patients ranges from 0% to 30%, but there was little evidence to suggest an exacerbation with combined iRT compared with RT alone. Likewise, pulmonary/pneumonitis events in lung iRT patients were up to 15%, which admittedly means little given the diverse RT techniques, dose/fractionation schemes, and treatment volumes within the lung cohort.

In addition to the studies discussed, a few series (all in melanoma) did not uniformly deliver RT to a specific body site and instead reported results as an aggregate. These will be briefly mentioned under the caveat that with nonuniform disease sites, fractionations, and/or

techniques, conclusions are difficult to ascertain regarding toxicity outcomes.

First, a series from Australia evaluated 35 patients treated with sequential or concurrent RT with pembrolizumab (n = 27), nivolumab (n = 7), or both (n = 1); nearly all patients had had prior ipilimumab at a median of 1 month between immunotherapies.<sup>41</sup> The only grade 3 and 4 RT-related adverse events were 2 cases of radiation dermatitis and 1 case of radiation necrosis. Another prospective trial of 22 patients treated with concurrent iRT (ipilimumab) demonstrated no grade  $\geq 3$  toxicities pertaining to the irradiated regions.<sup>42</sup> Lastly, a recent study from France of 59 patients (n = 28 pembrolizumab, n = 31 nivolumab), 17 of whom were treated with palliative RT, showed no statistical differences in grade  $\geq 3$  events in the irradiated and unirradiated groups (7% vs 12%).<sup>43</sup>

Of note from the assembled data, increased toxicities directly related to iRT may generally relate to larger treatment volumes and/or anatomically sensitive areas (eg, the PACIFIC trial). This is similar to observations with RT alone, implying that existing dosimetric parameters and dose/fractionation considerations should very much still be exercised in the iRT setting. Presently, there are no data-driven indications to alter dosimetric objectives or dose constraints based on the receipt (prior, concomitant, or future) of immunotherapy. Nevertheless, this notion needs to be formally studied, along with several other factors, including well-matched prospective analyses of concurrent versus sequential iRT. Many RT regimens delivered in this setting and/or to induce the abscopal effect involve 1 or a few fractions (thus limiting the assessment of true concurrent therapy); however, a major confounding factor for toxicities in the available data was timing between immunotherapy and RT. This is important to address in future work to better select patients at higher risk of iRT-induced toxicities.

Likewise, it is reasonable to surmise that patients often at higher risk of iRT toxicities are the very same patients at higher risk for RT toxicities. Hence, the safety of iRT in patients with collagen vascular diseases, history of irradiation, and such circumstances must also be reported, recognizing that even case reports can provide substantial information of these rare situations. These high-risk patients can also include those with autoimmune diseases and those receiving multiple concurrent immunotherapies. The safety of other newer agents such as atezolizumab with RT is also important; even small retrospective experiences are noteworthy, especially in light of the overall dearth of PD-L1 iRT as compared with ipilimumab in this review.

There are several ways to enhance and streamline the toxicity reporting of ongoing prospective iRT trials. First, strong efforts to include homogeneous patient populations is crucial to evaluating toxicities with distinct clarity. Although many ongoing studies evaluate heterogeneous

populations, a subgroup analysis for the purpose of uniform toxicity reporting can substantially augment interpretation.

Second, factors that influence toxicities (including both patient- and treatment-related variables) must be thoroughly reported, especially in patients who experience higher-grade adverse events. Dosimetric analysis (including size of RT volumes) is also important to this extent. Third, in efforts to accurately attribute toxicities to iRT (as opposed to immunotherapy alone or other therapies), precisely categorizing time-related details of iRT toxicities is crucial because many patients receive other therapies before or after iRT. Lastly, reporting on quality of life and patient-reported outcome results are also extremely important in evaluating the net result of iatrogenic toxicities on patients and should ideally be incorporated in every prospective trial of iRT. Collectively, these details, as well as others, are imperative to shape clinicians' willingness to deliver iRT to patients with borderline tolerability and/or at high risk of toxicities.

## Conclusions

Justification for the use of combined iRT going forward by demonstrating its safety is essential. After a review of the available published evidence to date, combined iRT offers encouraging safety profiles. When conservatively interpreting the data, there is no evidence that iRT produces an overt increase in high-grade toxicities. Recognizing the limitations of these studies, further prospective experiences are greatly needed to corroborate the findings herein.

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