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Synergizing radiotherapy and immunotherapy: Current challenges and strategies for optimization

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ABSTRACT

Numerous clinical studies are investigating the integration of radiotherapy and immune checkpoint inhibitors (ICI) in the management of advanced or metastatic solid cancers based on preclinical evidence demonstrating a synergistic interaction between these treatments. However, it remains unclear how to optimally integrate these therapeutic modalities in the treatment of cancer patients. Beyond disease-specific factors there exists numerous unanswered questions regarding optimal sequencing of radiation and ICI, as well as, radiation dosing and target selection. Here, we examine the available clinical evidence for combination radiation and ICI approaches and propose strategies to expand investigations of the potential synergy in cancer patients.

Introduction

Radiotherapy and immunotherapy are extensively utilized in the treatment of patients with advanced or metastatic malignancies, and there is growing enthusiasm to combine these treatment modalities based on the rationale that radiation-induced augmentation of local and systemic immunity and reduction of disease burden might enhance the efficacy of ICI. With extensive preclinical evidence demonstrating immunomodulatory effects of radiation, numerous clinical trials have evaluated combinatorial approaches in various clinical contexts, such as for primary versus metastatic disease and in the adjuvant versus concurrent setting. Disease and treatment characteristics have also varied with regards to radiation dose, fractionation, and treatment volume as well as the ICI agent administered. Although two trials investigating adjuvant ICI have shown promising results in the definitive setting, the majority of clinical trials on the combination of radiation and ICI have been negative. Here, we synthesize clinical data and preclinical evidence on combining radiotherapy with ICI and examine the challenges in integrating these treatments.

Biological rationale for combination radiation and ICI

The immune system plays an integral role in not only fighting pathogens, but also eliminating malignant cells. In general, the immune system attacks tumor cells through recognition and binding of tumor-associated antigens; however, tumor cells have evolved mechanisms to evade anti-tumor immunity and proliferate under conditions of immune suppression. Tumor evasion strategies are broad, but generally include mechanisms intrinsic to the function of tumor antigen presentation and those extrinsic to this process. The former primarily includes downregulation of receptors (MHC class I or II) that are important in the presentation of tumor antigens ultimately recognized by the immune system, whereas the latter mechanisms enhance immunosuppression, ranging from the release of suppressive cytokines to alterations of the tumor microenvironment and interactions with inhibitory immune checkpoint proteins on T cells [1,2]. The physiologic function of these immune checkpoints on T cells is to prevent over-activation of the immune system leading to autoimmune conditions. Immune checkpoint inhibitors (ICI) have been designed to primarily target cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death receptor 1 (PD-1) on T cells or programmed death-ligand 1 (PD-L1) on non-T cells to inhibit immunosuppressive interactions between lymphocytes and tumor cells [3–6].

By contrast, the immunomodulatory effects of radiotherapy can be both stimulatory and inhibitory [7]. The stimulatory effects of radiotherapy enhance the recruitment and activation of CD8+ T-cells through increased dendritic cell activation and T cell priming, release of damage-associated molecular patterns (DAMPs), and activation of pro-death signaling in tumor cells [8,15–17]. Immunosuppressive effects of radiotherapy are predominantly mediated by the infiltration of regulatory T cells (Treg), myeloid suppressor cells, and immunosuppressive cytokines [8,19]. In addition, preclinical evidence indicates that radiotherapy leads to upregulation of immune checkpoints, including PD-1 expression on tumor-infiltrating CD8+ T cells [20], which supports the use of ICI in combination with RT. Additional preclinical data show a dose response effect with higher RT-induced expression of PD-L1 on can-

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Table 1
Randomized trials combining radiotherapy with ICI in non-metastatic disease.

Study	Cancer Type (n)	Disease Stage	Treatment Setting	ICI Agent	Radiation Details (Gy / fractions)	Trial Design	Selected Results
Spigel et al. (PACIFIC)	NSCLC (n = 709)	III	Adjuvant	Durvalumab	60-66 Gy in 30-33 fractions to primary tumor and involved nodes	Durvalumab following no PD[1] after definitive CRT[2]	mOS[3] 47.5 ICI vs. 29.1 mo placebo mPFS 16.9 mo vs. 5.6 mo placebo 5OS[4] 42.9% vs. 33.4% placebo 5PFS[4] 33% vs. 19% placebo
Kelly et al. (Checkmate-577)	Esophageal/GEJ (n = 794)	II/III	Adjuvant	Nivolumab	Definitive RT dose (not specified) to primary tumor and nodes (involved and elective)	Neoadjuvant CRT with PR followed by R0 resection of stage II/III cancer	mPFS 22.4 mo ICI vs. 11.0 mo placebo
Lee et al. (JAVELIN)	HNSCC (n = 697)	HPV-/Non-Opx[8] HPV+: III/IVA/IVB OPx HPV+: T4/N2c/N3	Definitive	Avelumab	70 Gy in 35 fractions to primary tumor and nodes (involved and elective)	Locally advanced SCC[5] treated with CRT with concurrent ICI vs placebo	mPFS not reached (95% CI 16.9 mo – not reached for ICI vs. 23.0 mo – not reached for placebo)
Bourhis et al. (PembroRad)	HNSCC (n = 131)	III/IVA/IVB	Definitive	Pembrolizumab	69.96 Gy in 33 fractions to primary tumor and nodes (involved and elective)	Non-operable SCC receiving CRT (cetuximab) vs. ICI + RT	15mo LRC 59% CRT vs. 60% ICI-RT (NS) 2PFS[7] 40% CRT vs. 42% ICI-RT (NS) 2OS[7] 55% CRT vs. 62% ICI-RT (NS)
Lim et al. (Checkmate-548)	MGMT methylated GBM (n = 320)	-	Definitive	Nivolumab	60 Gy in 30 fractions to primary tumor	RT + TMZ + placebo vs. RT + TMZ + ICI	mPFS 10.6 mo ICI vs. 10.3 mo placebo mOS 28.9 mo ICI vs. 32.1 mo placebo

1. PD = progressive disease
2. CRT = chemoradiation
3. mOS = median overall survival
4. 5OS/5PFS = 5 year overall survival/5 year progression free survival
5. SCC = squamous cell carcinoma
6. TRAE = treatment-related adverse effects
7. 2OS/2PFS = 2-year overall survival/ 2-year progression free survival
8. OPx = Oropharynx

cer cells following 10 Gy of irradiation as compared to 5 Gy [21]. The increase in PD-L1 expression on tumor cells was found to occur over several days, peaking at 3 days following radiation therapy [22]. As described below, these counteracting effects of radiotherapy observed in preclinical models might pose a significant obstacle in actualizing the potential synergy between radiotherapy and ICI in cancer patients [9–14].

Combining radiation and ICI in the definitive management of non-metastatic disease

Several clinical trials have reported on the combination of radiotherapy with ICI in the definitive treatment of non-metastatic disease. Two recent phase III randomized clinical trials demonstrated benefits of ICI in the adjuvant setting (sequential administration) following definitive radiotherapy.

The PACIFIC trial investigated adjuvant durvalumab, a PD-L1 inhibitor, in unresectable stage III non-small cell lung cancer (NSCLC). Patients received chemoradiation therapy to a dose of 60-66 Gy in 2 Gy fractions targeting the primary tumor and radiographically involved regional lymph nodes and were randomized to adjuvant durvalumab or placebo if there was no evidence of disease progression following chemoradiation. At five years, the addition of durvalumab significantly improved both progression-free survival (PFS 33% [95% CI, 28-38%] vs. 19% [95% CI, 14-25%]) and overall survival (OS 43% [95% CI, 38-47%] vs. 33% [95% CI, 27-40%]) compared to placebo [23].

Similarly, the CheckMate-577 trial investigated the role of adjuvant nivolumab, a PD-1 inhibitor, in stage II-III esophageal and gastroesophageal junction (GEJ) cancer [24]. Patients with residual disease after chemoradiation therapy delivered to primary disease and regional nodal regions followed by surgery were randomized to receive either nivolumab or placebo. The study demonstrated an improvement in median disease-free survival with adjuvant ICI of 22.4 months versus 11.0 months with placebo. Improved outcomes related to nivolumab held across subgroups stratified by PD-L1 status, lymph node status, and tumor histology.

These seminal phase III trials established the role of adjuvant ICI following the definitive treatment of primary stage III NSCLC and stage II-III esophageal/GEJ cancers. While these studies do not conclusively indicate a synergistic interaction with radiotherapy, they suggest that the favorable outcomes reported in these studies was potentially related to the reduction in primary tumor volume by localized therapy, which is consistent with emerging evidence that tumor burden is a critical determinant of ICI efficacy [24].

Despite the practice-changing results of the PACIFIC and CheckMate-577 trials, other studies evaluating the combination of radiation and ICI in the treatment of non-metastatic cancers have been negative (summarized in Table 1). For example, the phase III JAVELIN trial investigated the role of ICI in unresectable locally advanced head and neck squamous cell carcinoma (HNSCC) of the oral cavity, oropharynx, hypopharynx, and larynx [25]. Avelumab, a PD-L1 inhibitor, was administrated concurrently with chemoradiation to 70 Gy in 2 Gy fractions with cisplatin [25]. Unfortunately, the trial failed to show a PFS benefit with multimodal therapy.

Similarly, the PembroRad trial investigated the role of pembrolizumab (a PD-1 inhibitor) administered concurrently with radiation in stage III-IVa/b HNSCC in patients unfit for standard-of-care cisplatin [26]. Again, no synergistic effect of pembrolizumab and radiation was found with 15-month locoregional control of approximately 60% and 2-year PFS of approximately 40% in both arms. This study included

patients with significant burden of disease with approximately half of patients exhibiting advanced lymph node involvement (i.e. N2c-N3 disease). Taken together, these studies demonstrated that concurrent administration of ICI failed to improve clinical outcomes for patients with HNSCC.

Importance of lymph node irradiation

Patients with advanced HNSCC often receive elective radiotherapy to tumor-draining cervical lymph node regions that are at risk for malignant involvement. By contrast, in NSCLC, only grossly involved lymph nodes are irradiated. Draining lymph nodes are sites of T-cell priming and activation. In preclinical murine models, irradiation of tumor-draining lymph node basins not only decreased local tumor control but also suppressed immune cell infiltration [27]. It is thought that regional nodal irradiation inhibits the effects of ICI subsequently. Models demonstrate that CD8+ T cells in the draining lymph nodes are more sensitive to radiation as compared to tumor resident CD8+ T cells [28].

In murine studies, the inclusion of draining lymph nodes in the radiation field with concurrent administration of ICI was found to be associated with decreased overall survival [27]. In addition, murine melanoma models have demonstrated that tumor draining lymph nodes are critical in mediating abscopal, or distant, effect of local irradiation [29]. Using a flank tumor model, radiation was delivered to the tumor alone or to the tumor and it's draining lymph nodes. Local irradiation of the tumor alone resulted in stimulation of CD8+ T cells which was found to mediate abscopal responses. When both the tumor and draining lymph nodes were irradiated, however, there was a reduction in the abscopal effect as well as in the number of stem-like CD8+ T cells in the tumor and draining lymph nodes [29]. Taking these factors into account, it is possible that irradiation of draining lymph nodes might adversely affect local and systemic immune responses by dampening T-cell priming and suppressing adaptive immune activation. On the other hand, radiation of regional nodes can be associated with immune upregulation, primarily associated with CD8+ effector T-cell infiltration of tumors in addition to an increase in Tregs. Survival outcomes in murine models, treated with a combination of SBRT and ICI, were found to be associated with the ratio of CD8+ effector T-cells to Tregs and the density of CD8+ cells within the tumor [30]. Taken together, the effect of irradiation to draining lymph nodes in the setting of combination radioimmunotherapy is complex.

Clinical studies have shed light on the potential influence of lymph node irradiation on the tumor response to radiation and ICI. A recent phase II trial investigated the role of pre-operative durvalumab (PD-L1 inhibitor) with or without radiotherapy to the primary tumor in potentially resectable stage I-IIIA NSCLC. Lymph nodes were intentionally left unirradiated. Patients received either two cycles of durvalumab alone or radiation (24 Gy in 3 fractions over consecutive days) followed by durvalumab [31]. The authors demonstrated a significant increase in the major pathological response rates with SBRT + ICI vs. ICI alone of 53.3% vs. 6.7%. Notably, pathologic down-staging of biopsy proven mediastinal lymph nodes occurred in 14% following ICI vs. 66% following SBRT + ICI. Although it is unclear whether enhanced local response to combination therapy improved survival, these data suggest that radiation target selection might be of importance when considering interactions with ICI.

Selectivity of the blood-brain barrier

The central nervous system (CNS) is considered to lack major lymphatic involvement due to the blood-brain barrier's selectivity of cells and molecules that are permitted entry into the brain. Nonetheless, the CNS harbors microglial cells which act as the brain's resident immune cells. In addition, the dura and meninges of the brain contain small lymphatic vessels that drain into the cervical lymph nodes. T-cells can enter cerebrospinal (CSF) fluid from these cervical lymph nodes once activated by antigens that travel from the brain to these nodes. Both the microglial cells and the cervical lymph node drainage route provide potential avenues of investigation of immunotherapy.

In this context, in patients with newly diagnosed glioblastoma multiforme (GBM) the CheckMate-548 (MGMT promoter methylated) and CheckMate-498 (MGMT promoter non-methylated) phase III trials evaluated the benefit of nivolumab to the standard-of-care treatment of radiation (+/- temozolomide [TMZ]) [32–34]. Unfortunately, the trials demonstrated that the addition of nivolumab failed to improve survival when administered concurrent with radiation therapy.

Summary

Taken together, these studies of non-metastatic disease demonstrated survival benefits with adjuvant ICI following definitive treatment of NSCLC and esophageal/GEJ cancers, but not with the concurrent administration of ICI with radiation therapy for HNSCC and GBM [25,26,32,33]. The lack of interaction between radiation and ICI could be related to disease-specific factors, but also treatment-related features such as the timing of radiation and ICI as well as the volume of irradiated tissue. Specifically, adjuvant ICI following definitive treatment of the primary tumor might have enhanced efficacy in the context of a smaller burden of disease at the time of ICI administration as opposed to concurrent ICI where gross disease is typically present. Moreover, the elective irradiation of tumor-draining lymph nodes might have potentially adverse consequences on local and systemic adaptive immune activation in patients with HNSCC.

Combining radiation and ICI in the treatment of metastatic disease

In the metastatic setting, the majority of trials to-date have not demonstrated a clear improvement in survival with combination radiation and immunotherapy [35–38]. However, the diversity of these studies in terms of trial design, disease sites, disease burden, and treatment characteristics provides an opportunity to investigate the potential contexts in which radiation therapy might augment clinical outcomes for patients with metastatic disease (Fig. 1).

Radiation dose and fractionation

Initial preclinical studies investigating the combination of radiation and anti-CTLA-4 antibodies demonstrated increased efficacy of hypofractionated radiation as compared to single fraction radiation with regards to induction of an abscopal effect [39]. Radiation dose greater than 24 Gy in 3 fractions is thought to lead to downregulation of key immunostimulatory pathways through the suppression of interferon [18]. Although SBRT is associated with immunosuppressive effects in the irradiated tumor, it could potentially amplify the response to ICI [40]. For example, in highly aneuploid NSCLC, the administration of ablative doses of radiation concurrently with ICI was found to upregulate key immune pathways and lead to enhanced local and distant tumor responses, whereas SBRT alone downregulated adaptive immune pathways [40].

Reoxygenation and the total duration of radiation treatment are also important factors when evaluating the optimal radiation dose-fractionation in combination with ICI. Reoxygenation occurs primarily in the setting of conventionally fractionated radiation that is associated with increased radiosensitivity and tumor response. In the setting of ablative doses of radiation, delivery of multi-fraction treatment might allow for reoxygenation and improved local tumor response [41]. Moreover, hypoxia has been associated with radioresistance which can have a pronounced effect in the setting of combination therapy with ICI by compromising the efficacy of both therapies.

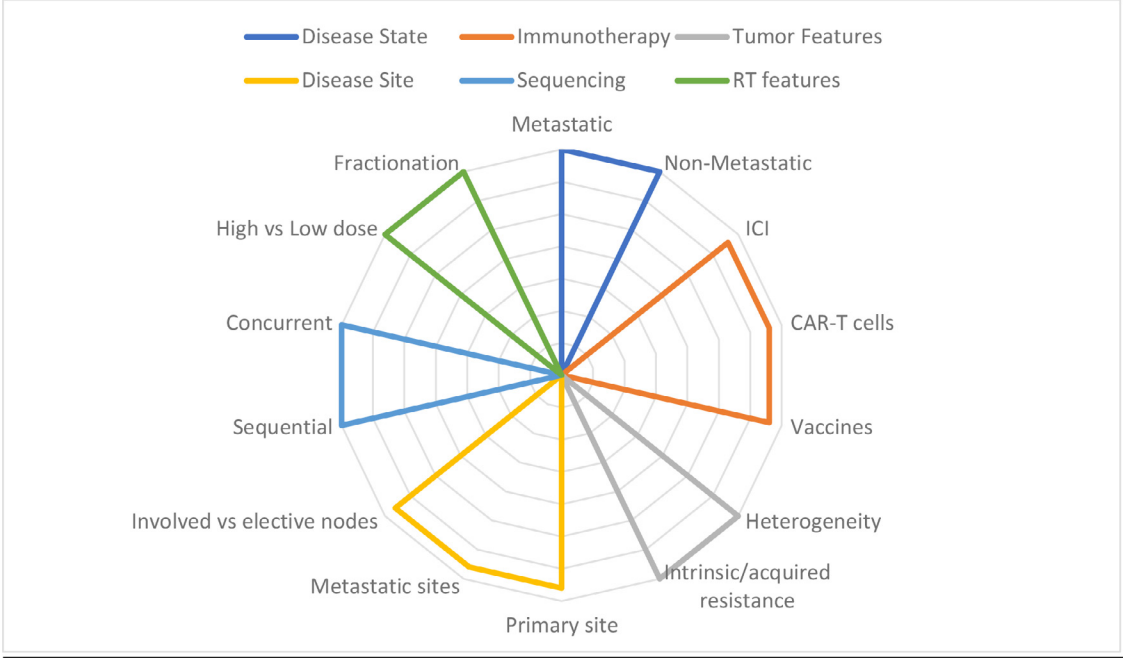

Fig. 1. Factors associated with efficacy of radio-immunotherapy
Abbreviations: CAR-T, chimeric antigen receptor-T cell; ICI, immune checkpoint inhibitor; RT, radiotherapy.

Impact of tumor burden and number of irradiated sites on ICI response

As discussed above, ICI improves survival for patients with NSCLC and esophageal/GEJ cancers following definitive curative-intent treatment of the primary tumor when disease burden is smallest. Importantly, tumor burden is a critical determinant of the response to ICI. A number of approaches have been used to quantify tumor burden, including CT and PET [42] imaging, circulating biomarkers such as ctDNA [42–44], and serum lactate dehydrogenase (LDH) [42,45,46]. In general, a higher tumor burden is associated with inferior clinical outcomes following ICI. For example, in a cohort of patients with advanced melanoma treated on KEYNOTE-001, pembrolizumab improved ORR and OS in those with tumors with less than the median baseline tumor size [47]. In addition, retrospective studies have demonstrated negative correlations between imaging- and liquid-biopsy defined tumor burden and response to ICI [42,48–53].

The inverse relationship between tumor burden and ICI response may be related to the fact that individual metastases within a patient can exhibit differential responses to ICI depending on the involved organ sites. Emerging evidence indicates that tumor microenvironmental heterogeneity can interfere with immune-mediated clearance of disease [8,54]. Theoretically irradiation of multiple metastatic sites within a patient might improve immunological exposure by upregulating MHC receptors, promoting antigen presentation, and eliminating immune suppressive cells, thereby minimizing pre-existing or acquired treatment resistant clones [55]. Several ongoing phase I and II trials are testing multisite radiation in combination with ICI, in some cases to determine the optimal ablative radiation dose and in other cases to assess clinical endpoints such as objective response rate (ORR) and survival [55] (NCT03431948, NCT03223155, NCT03464942, and NCT03283605).

Combination therapy was tested in a phase III trial evaluating ipilimumab, a CTLA-4 inhibitor, following palliative radiation in patients with metastatic castration-resistant prostate cancer that progressed after docetaxel chemotherapy [56]. Radiation (8 Gy in 1 fraction) was delivered to 1-5 osseous metastases followed by sequential ipilimumab or placebo. The median OS was 11.2 months in the ICI arm versus 10.0 months in the placebo arm ($p = 0.053$) [56]. In addition, a post-hoc analysis demonstrated a larger benefit of ipilimumab (22.7 months vs. 15.8 months; $p = 0.0038$) for the subset of patients with favorable prognostic factors indicative of lower disease burden.

In addition, a single-arm phase II study of NSCLC demonstrated an improvement in median PFS of 19.1 months in patients receiving adjuvant pembrolizumab after SBRT to up to four metastatic lesions compared to 6.6 months for historical controls receiving SBRT alone [57]. Pre-clinical data support this finding by showing that combination therapy with ICI is more effective when all sites of distant metastases are targeted with radiation. For example, in a murine model, radiating two sites of disease produced a more rapid abscopal effect in a third non-irradiated site as compared to radiating a single site of disease [58]. In another study, mice that received combination therapy with radiation to a single site and sequential ICI were more likely to exhibit immune-mediated tumor regression at irradiated and non-irradiated sites as compared with mice that received monotherapy. The response was greater with adjuvant ICI following irradiation as compared to neoadjuvant therapy [8,10,12]. Consistent with these findings, a phase I trial of advanced solid tumors in which patients were treated with SBRT to 2-4 metastatic sites followed by pembrolizumab found that interferon-γ associated genes from post-radiation biopsy specimen correlated with tumor response in non-irradiated sites [59]. These findings suggest that multisite radiation in concert with ICI could improve disease outcomes over single site radiation.

In addition, in metastatic melanoma, Curti et al. evaluated the benefit of SBRT to interleukin-2 (IL-2) immune therapy [35]. SBRT was delivered to 1-3 metastatic sites, primarily in the lung, liver, and lymph nodes, to a dose of 20 Gy in one fraction or 40 Gy in two fractions. The trial demonstrated higher ORR of 54% with the addition of SBRT compared to 35% with IL-2 monotherapy with complete response (CR), partial response (PR), and progressive disease (PD) in 21% vs. 15%, 33% vs. 15%, and 25% vs. 40% of patients.

Despite these promising studies, numerous other trials have failed to demonstrate significant improvements in clinical outcome with combination therapy. For example, in patients with widely metastatic adenoid cystic carcinoma treated with pembrolizumab [60], radiation therapy

(30 Gy in 5 fractions to ≤ 5 lesions) failed to meet its primary endpoint of response outside the irradiation field. Similarly, a recent study [61] evaluated durvalumab and tremelimumab (CTLA-4 inhibitor) alone or in combination with radiotherapy in patients with PD(L)-1 refractory metastatic NSCLC. Radiation was delivered to 1-2 lesions to a dose of 24 Gy in 3 fractions or 0.5 Gy twice daily for two days during the first four cycles of ICI. Unfortunately, the trial did not meet its primary endpoint of improved ORR with combination therapy.

Importance of sequencing therapies

As discussed above, sequential but not concurrent ICI following definitive treatment of the primary tumor improves outcomes in non-metastatic disease. Moreover, as previously demonstrated, concurrent durvalumab, tremelimumab and radiotherapy in metastatic NSCLC showed no difference in ORR between the ICI alone arm and combination therapy arms [61]. Similarly, Welsh et al. demonstrated no significant difference in ORR outside the radiation field with the addition of radiation to pembrolizumab in metastatic NSCLC, specifically with lung or liver metastases with at least one non-contiguous metastasis [38]. In this case, PD-L1 status was not considered, and radiation was delivered to either a dose of 50 Gy in 4 fractions or 45 Gy in 15 fractions. Another trial in metastatic NSCLC in which cemiplimab, a PD-1 inhibitor, was administered with or without radiotherapy to a dose of 27 Gy in 3 fractions demonstrated similar findings. ICI monotherapy was shown to have significantly better ORR and antitumor activity than concurrent radiotherapy and ICI [62]. Similarly, phase II trials in other disease sites demonstrated a lack of benefit in disease control with administration of concurrent therapies. For instance, McBride et al. evaluated the combination of nivolumab with single-site SBRT in metastatic HNSCC [36]. The authors found no improvement in ORR with the addition of concurrent ICI to SBRT.

The sequencing of RT and ICI therapy has also been demonstrated to play a role in the efficacy of treatment. In a murine model of bilateral leg tumors, administration of both ICI and radiation was found to have a larger effect on tumor regression as compared to the administration of either therapy alone [63]. The administration of ICI following radiation was associated with abscopal responses whereas administration of ICI prior to radiation resulted in increased radiosensitivity of CD8+ T cells and ultimately apoptosis of tumor-associated CD8+ T cells. In preclinical models there was no significant difference in efficacy between concurrent administration of ICI with radiation or administration of ICI preceding radiation [64]. By contrast, other preclinical data show concurrent administration of therapies is more efficacious than sequential administration [22,40]. Recently, concurrent therapy was found to exhibit superior outcomes relative to sequential therapy for patients with highly aneuploid NSCLC [40]. It is possible that concomitant administration of ICI might have increased efficacy than sequential administration in blocking the induction of the PD-1/PD-L1 pathway by radiotherapy [22,40]

Treatment factors related to immunotherapy

Numerous immune checkpoint inhibitors have been employed in combination with radiotherapy; however, relatively little is known regarding combinations with novel immunotherapeutic agents, such as chimeric antigen receptor T-cells and dendritic cell vaccines. In the current oncologic landscape, one of the primary challenges in the evaluation of response to immunotherapy is the heterogeneity of tumor cells and the tumor microenvironment (TME) that make it difficult to define biomarkers of response and survival. While PD-L1 status, tumor mutational burden, and CD8+ T cell presence predict differential outcomes in the context of ICI, these biomarkers are imperfect and little is known as to whether these biomarkers predict outcome following combination radiation therapy and ICI. Also, additional novel predictive factors remain to be identified [65]. Importantly, Spurr et al. demonstrated a novel biomarker of tumor aneuploidy that predicted benefit from the addition of radiotherapy to ICI in patients with metastatic NSCLC [40].

ICI treatment resistance remains a challenge and is mediated by pre-existing resistance in which tumor cells fail to respond to immunotherapy through adaptive immune suppression or acquired resistance in which tumor cells initially respond to ICI but progress at a later time. The mechanistic basis of resistance is complex, but at least involves defects in antigen presentation and interferon signaling. Studies have demonstrated that interferon-γ signaling upregulates PD-L1 expression and induces the release of inhibitory molecules. It has been shown that interferon-γ-mediated resistance is associated with Ripk1 expression, which diverts tumor necrosis factor (TNF) through an alternate path involving NF-kB. This pathway promotes immunosuppression and ultimately decreases T and NK cell infiltration into tumor cells [66]. Other immune checkpoints that induce immunosuppressive cytokines are also involved in this process [67]. Overcoming resistance to ICI remains an expanding and critical area of investigation.

Role of ICI in the neoadjuvant setting

Biological rationale for neoadjuvant ICI prior to surgery

The utility of ICI in the neoadjuvant setting, preceding tumor resection, is the topic of several ongoing trials. The rationale for this approach emerges from the results of neoadjuvant chemotherapy paradigms, which in many cases leads to pathologic responses that are associated with improved long-term outcomes. ICI is thought to target micrometastatic disease and thereby, reduce the risk of tumor recurrence following surgery [68,69]. There are two primary mechanistic explanations for the utility of ICI given neoadjuvantly. First, ICI can activate tumor-specific cytotoxic T cells in the TME, triggering them to target micrometastatic sites. Second, ICI can enhance the presentation of tumor antigens to T cells in draining lymph nodes, which then migrate to the tumor sites [69]. These points are especially relevant when comparing the efficacy of ICI neoadjuvantly versus adjuvantly following resection in that neoadjuvant ICI when the tumor is intact might allow for a greater number of potential tumor antigens to be presented [68,69].

Ongoing trials employing neoadjuvant ICI

There are several completed and ongoing clinical trials investigating the efficacy of neoadjuvant ICI, including in NSCLC and HNSCC. The aforementioned phase II trial in resectable stage I-IIIA NSCLC, reported the rates of major pathologic response (MPR), defined as the presence of <10% viable tumor cells, in those who received neoadjuvant durvalumab alone versus those receiving durvalumab in combination with SBRT. Surgery was performed within 2-6 weeks following the completion of two cycles of durvalumab. The authors reported a significant difference in MPR between the two groups, with a 53.3% response in the combination group versus 6.7% response in the durvalumab alone group [31].

In HPV-negative HNSCC, the administration of durvalumab with SBRT in the neoadjuvant setting demonstrated a 75% MPR in a phase I/IB trial [70]. The SBRT dose ranged from 12 Gy to 24 Gy in 3 fractions with MPR up to 89% in those who received 24 Gy. There are several ongoing trials, such as in NSCLC investigating the efficacy of neoadjuvant ICI monotherapy or in combination with chemotherapy or radiation. Some of the phase III trials investigating ICI monotherapy or in combination with chemotherapy include AEGEAN, Checkmate 771, Checkmate 816, Impower 030 and KEYNOTE 671, with most evaluating the primary endpoint of pathologic response and event-free or overall survival (NCT03800134, NCT04025879, NCT02998528, NCT03456063, NCT03425643). There are also several ongoing trials in HNSCC employing neoadjuvant ICI (NCT 03708224, NCT04722523, NCT04922450).

Conclusion

Combination radiation therapy and ICI is a potentially promising treatment approach for patients with diverse cancers; however, further investigation is required to maximize the therapeutic ratio of this approach. Although favorable clinical outcomes have been demonstrated with the sequential administration of these therapies in the setting of definitive treatment, numerous tumor and host factors pose significant challenges in identifying the optimal ICI regimens and appropriate radiation dose and fraction.

Further investigation of potential biomarkers to guide the identification of patients most likely to benefit from combination radiation and ICI are critically needed. We propose that future trials should focus on multi-site over single-site radiotherapy and investigate the role of combination therapy in patients with oligometastatic disease where tumor burden is comprehensively treated with localized modalities. Novel diagnostic tests such as ctDNA and functional imaging could improve identification and targeting of all site of disease.

Recent work has demonstrated that biomarker screening can be beneficial in prognostication and prediction of treatment efficacy. Delineation of molecular features associated with oligometastatic vs. polymetastatic disease could further improve patient stratification and predict recurrence risk following treatment. In addition, multi-site radiation for the treatment of patients with oligometastatic disease has demonstrated efficacy and further improvements in survival might be achieved by combining radiotherapy with ICI in this setting. While institutional studies and randomized control trials demonstrate opportunities for incorporation of radiotherapy in the oligometastatic landscape, there is dearth of translational studies to identify factors predictive of treatment response. Translational studies, investigating the effects of radiotherapy on tissue samples or applying radiomics to identify predictors of immunologic response are potential avenues for future investigations. These studies are necessary in order to identify the optimal clinical context in which combination therapy can be utilized.

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Declaration of Competing Interest

None to disclose.

CRediT authorship contribution statement

Greeshma Rajeev-Kumar: Writing – original draft, Writing – review & editing. **Sean P. Pitroda:** Writing – original draft, Writing – review & editing.

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