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Combined radio-immunotherapy: An opportunity to increase the therapeutic ratio of oligometastasis-directed radiotherapy

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Abstract

The utility of radiotherapy as a means of palliating symptoms due to metastatic cancer is well-accepted. A growing body of literature suggests that radiotherapy may play a role beyond palliation in some patients with low-burden metastatic disease. Recent data suggest that oligometastasis-directed radiotherapy may improve progression-free and even overall survival in select patients. Immunotherapy also has a growing role in the management of patients with metastatic cancer and, like radiotherapy, appears to be most effective in the setting of low-volume disease. Thus, the addition of immunotherapy may be a feasible means of increasing the therapeutic ratio of metastasis-directed radiotherapy, particularly among patients with oligometastatic cancer.

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Introduction

Metastatic cancer reflects a wide range of disease states in which cancer cells have disseminated from their primary location to distant sites. Metastatic disease is recognized as a significant cause of morbidity and mortality in cancer patients and has been estimated to account for up to 90% of cancer-related related deaths [1]. Historically, systemic therapies such as including cytotoxic chemotherapy and hormonal manipulation have been the mainstay of treatment for patients with metastatic cancer. Recent work has aimed to improve outcomes for patients across the metastatic spectrum with the introduction of new systemic therapies, including immunotherapy agents. Moreover a number of investigations of metastasis-directed local therapy have recently been completed with additional studies currently ongoing. A better understanding of the efficacy of these therapies, alone and in combination, may afford novel treatment strategies to improve the outcomes of patients with metastatic cancer.

The role of radiotherapy in the treatment of patients with metastatic cancer

Radiotherapy has been used as a means of treating patients with cancer for over a century [2]. Although radiotherapy is well-accepted as a key component of definitive therapy for many types of cancer, until recently radiotherapy was primarily reserved for palliation of disease-related symptoms in patients with metastatic disease. Emerging data suggest that radiotherapy may improve progression-free survival (PFS), and potentially even overall survival (OS; potentially a more accurate measure of efficacy than PFS in this population given that some patients may require a number of therapies) in select patients with metastatic cancer.

A number of studies (summarized in Table 1) have recently been conducted to better define the role of metastasis-directed radiotherapy in patients with low-volume metastatic cancer. Two randomized phase II studies of radiotherapy targeting all sites of active disease in patients with response following induction chemotherapy for metastatic non-small cell lung cancer (NSCLC) have been reported [3, 4]. Both studies were halted prematurely based upon interim analyses demonstrating a significant benefit in favor of the addition of local therapy over systemic therapy alone. In the study reported by Iyengar et al., which enrolled patients with ≤ 5 metastases following induction chemotherapy, primary tumor and metastasis-directed radiotherapy improved median PFS (9.7 months) compared to systemic therapy alone (3.5 months; $P = 0.01$) [3]. Similarly, patients with ≤ 3 metastases following induction chemotherapy derived a significant benefit from local consolidative therapy (23 of 25 patients randomized to local consolidative therapy received some form of metastasis-

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Table 1

Reported Randomized Trials Utilizing Metastasis-Diretcted Radiotherapy.

Author(Institution/Study Name)	Cancer Type (Enrollment)	Eligibility(Disease Burden)	Trial Design	Selected Results
Iyengar et al. [3] (UTSW)	NSCLC (n = 29)	≤ 5 metastases with no PD after 1st-line systemic therapy	1st-line systemic therapy followed by maintenance ± RT[1]	Improved PFS in the RT arm; median 9.7 mo vs. 3.5 mo, $P = 0.01$
Gomez et al. [4, 5] (Multicenter)	NSCLC (n = 49)	≤ 3 metastases with no PD after 1st-line systemic therapy (65% of patients had 0-1 metastases following systemic therapy)	1st-line systemic therapy followed by maintenance ± LCT[2]	Improved OS in the LCT arm; median 41.2 mo vs. 17.0 mo, $P = 0.017$
Wang et al. [6] (SINDAS)	EGFRm NSCLC (n = 133)	≤5 metastases with ≤2 lesions in any one organ (53% of patients had ≤ 2 metastases at presentation)	1st-generation TKI ± RT[3]	Improved OS in the RT arm; median 25.5 mo vs. 17.4 mo, $P < 0.001$
Gore et al. [56] (RTOG 0937)	SCLC (n = 86)	≤ 4 extracranial metastases with PR/CR following 1st-line systemic therapy (40% of patients had 1 metastasis)	PCI ± RT[4]	1-yr OS not improved in the RT arm; 51% vs. 60%, NS
Ost et al. [7, 8] (STOMP)	Prostate (n = 62)	≤ 3 oligorecurrent extracranial metastases following definitive prostate-directed local therapy (44% of patients had 1 metastasis)	Surveillance vs. MDT[5]	Improved 5-yr ADT-free survival[6] in the MDT arm; 34% vs. 8%, $P = 0.06$
Phillips et al. [9] (ORIOLE)	Prostate (n = 54)	≤ 3 oligorecurrent metastases following definitive prostate-directed local therapy	Surveillance vs. RT[7]	Less PD[8] at 6 mo in the RT arm; 19% vs. 61%, $P = 0.005$
Palma et al. [10, 11] (SABR-COMET)	Multiple[9] (n = 99)	Controlled primary with ≤5 metastases (75% of patients had ≤ 2 metastases)	Standard palliative treatment ± RT[10]	Improved 5-yr OS in the RT arm; 42.3% vs. 17.7%, $P = 0.006$

UTSW = University of Texas Southwestern Medical Center, NSCLC = non-small cell lung cancer, PD = progression of disease, RT = radiotherapy, PFS = progression-free survival, mo = months, LCT = local consoldative therapy, OS = overall survival, EGFRm = epidermal growth factor receptor-mutated, TKI = tyrosine kinase inhibitor, SCLC = small cell lung cancer, PR/CR = partial or complete response, PCI = prophylactic cranial irradiation, yr = year, NS = non-significant, MDT = metastasis-directed therapy, ADT = androgen deprivation therapy

1. Ultra-hypofractionated RT (1-5 fractions) was utilized to treat all sites of active disease. In the event that normal tissue constraints could not be met with an ultra-hypofractionated regimen, 45 Gy was given over 15 fractions.
2. LCT consisted of RT and/or surgical resection of all sites of active disease.
3. RT consisted of 25-40 Gy in 5 fractions to all sites of disease as well as regional lymphatics.
4. RT consisted of 45 Gy in 15 fractions to all sites of active disease.
5. MDT consisted of ultra-hypofractionated radiotherapy (n = 25) or surgery (n = 6).
6. ADT was initiated in response to symptomatic progression, development of > 3 sites of metastatic disease, and/or radiographic progression of existing metastases.
7. RT consisted of 19.5-48.0 Gy in 3-5 fractions.
8. PD was a composite endpoint, which included PSA increase to ≥ 2 ng/dL and 25% above nadir, radiographic progression, symptomatic progression, ADT initiation, death, or study withdrawal.
9. Patients with multiple types of cancer were included. The most common primary tumors were breast (n = 18), lung (n = 18), colorectal (n = 18), and prostate (n = 16).
10. RT primarily consisted of 30-60 Gy in 3-8 fractions, depending on target size and location. Single fractions of 16-24 Gy were allowed for targets in the brain and spine.

directed radiotherapy) in the study reported by Gomez et al. [4]. The long-term outcomes from the study reported by Gomez et al. demonstrate that compared to systemic therapy alone, the addition of local consolidative therapy improved both PFS (14.2 months vs. 4.4 months; $P = 0.022$) and OS (41.2 months vs. 17.0 months; $P = 0.017$) [5]. These findings are further supported by a recently reported phase III study investigating the addition of metastasis-directed radiotherapy to tyrosine kinase inhibition (TKI) in patients with epidermal growth factor receptor-mutated (EGFRm) NSCLC with ≤ 3 metastases, which similarly demonstrated that metastasis-directed radiotherapy improved median PFS (12.5 months vs. 20.2 months; $P < 0.001$) and OS (17.4 months vs. 25.5 months; $P < 0.001$) compared to TKI alone [6].

In addition to NSCLC, randomized phase II studies investigating metastasis-directed local therapy have been conducted in patients with metastatic prostate cancer. Ost et al. reported the results of a study which randomized men who were previously treated with definitive local therapy

for prostate cancer and subsequently developed ≤ 3 metastases to observation versus metastasis-directed local therapy (radiotherapy was utilized in 25 of 31 patients randomized to local therapy) [7]. With long-term follow-up, 5-year androgen deprivation therapy (ADT)-free survival was 34% among men treated with metastasis-directed therapy compared to only 8% in men not receiving metastasis-directed therapy [8]. (ADT was initiated in this study in response to symptomatic progression, development of > 3 sites of metastatic disease, and/or radiographic progression of existing metastases.) Similarly, metastasis-directed radiotherapy significantly reduced biochemical progression at 6 months in patients with ≤ 3 prostate cancer metastases in the study reported by Phillips et al. (61% vs. 19%; $P = 0.005$) [9].

Finally and perhaps most notably, the long-term results of SABR-COMET, a phase II screening trial which randomized patients with a variety of cancer types, ≤ 5 distant metastases, and a controlled primary tumor to receive standard of care therapy with or without metastasis-directed radiotherapy in a 2:1 ratio demonstrated a significant benefit with the addition metastasis-directed radiotherapy. As reported by Palma et al., 5-year PFS was not reached in patients treated with standard of care therapy alone (3.2% 4-year PFS with the final patient in this arm censored prior to 5 years) while the addition of metastasis-directed radiotherapy resulted in a 5-year PFS of 17% ($P = 0.001$) [10]. Moreover, 5-year OS was significantly higher among patients treated with metastasis-directed radiotherapy (42.3%) compared to patients treated with standard of care therapy alone (17.7%; $P = 0.006$) [10].

Although the results of ongoing confirmatory studies are needed to better define the role of metastasis-directed radiotherapy in patients with metastatic cancer, preliminary data suggest that a select group of patients are likely to benefit from this therapeutic approach. While preliminary studies are largely heterogeneous in nature, it is notable that these studies exclusively focus upon patients with relatively limited metastatic burden and primarily enrolled patients with only a few sites of metastatic disease. (For example although SABR-COMET included patients with ≤ 5 metastases, 75% of patients had ≤ 2 metastases and 93% of patients had ≤ 3 metastases [11]). Although the results of number of ongoing studies, which investigate the role of metastasis-directed local therapy in patients with few and several metastases separately are likely to better define the impact of metastatic burden on the efficacy of metastasis-directed local therapy (NCT03862911, NCT0372134, NCT02364557, NCT03137771), the results of preliminary randomized [3–11] and non-randomized [12, 13] studies support the idea that disease volume is an important predictor of outcome in this population. Moreover, extensive data from metastatic colorectal cancer patients treated with hepatic metastasectomy support both number and size of hepatic tumors as being predictors of long-term survival in this population [14]. Thus, patients with oligometastatic cancer may be the most likely to benefit from metastasis-directed radiotherapy.

Originally described in 1995 by Hellman and Weichselbaum, the oligometastatic hypothesis predicts that some patients with metastatic cancer have a low-volume of metastatic disease at the time of presentation that is unlikely to progress rapidly [15]. Given the inherently low burden of metastatic disease in oligometastatic patients, these patients are ideally suited to benefit from local therapy and may in some instances experience long-term survival [12, 13]. However, most patients eventually experience disease progression following metastasis-directed radiotherapy, underscoring the need to identify ways to increase the efficacy of this treatment [16]. Given that long-term rates of distant failure following oligometastasis-directed radiotherapy approach 70% [16], systemic therapy is likely to play an important role in improving outcomes in patients with oligometastatic cancer. The addition of immunotherapy to radiotherapy may represent an opportunity to improve upon the therapeutic ratio of both of these modalities as monotherapies in patients with oligometastatic cancer.

Immunotherapy may increase the therapeutic ratio of radiotherapy in patients with oligometastatic cancer

Immunotherapy plays a growing role in the management of patients with metastatic cancer. The utility of immunotherapy is perhaps best illustrated by the outcomes it achieves in the treatment of patients with metastatic melanoma and NSCLC. Patients with metastatic melanoma were recently reported to have a 5-year OS in excess of 50% following treatment with nivolumab and ipilimumab, which represents a significant improvement over historical outcomes [17]. Likewise, treatment for metastatic NSCLC with pembrolizumab monotherapy has been shown to achieve impressive results relative to historical controls, including a 5-year OS of 30% in treatment-naïve patients with a programmed death-ligand 1 (PD-L1) tumor proportion score ≥ 50% [18]. Much like local therapy, immunotherapy is seemingly most efficacious in patients with low-volume metastatic disease. Secondary analysis of KEYNOTE-001, in which patients were treated for advanced melanoma with pembrolizumab, demonstrated that patients with a baseline tumor size less than the median (summed diameter < 10.2 cm) had improved overall objective response rate (ORR) (44% vs. 23%; P < 0.001) and OS (HR 0.38; P < 0.001) [19]. Likewise, volume of metastatic disease has been shown to have significant prognostic and predictive value among patients with metastatic NSCLC treated with programmed cell death protein 1 (PD-1) blockade [20] [21].

In addition to studies investigating the role of immunotherapy alone in patients with metastatic disease, a number of studies of combined radio-immunotherapy in patients with metastatic disease have been conducted. A study reported by Golden et al. in which patients with ≥ 3 metastases were treated with radiotherapy to one metastasis (35 Gy in 10 fractions) in combination with granulocyte-macrophage colony-stimulating factor (GM-CSF) investigated the ability of this treatment regimen to produce abscopal responses at unirradiated metastases [22]. (Abscopal responses were defined in this study as a decrease in the longest diameter of any measurable non-irradiated lesion by ≥ 30%.) Abscopal responses were observed in 11 of 41 enrolled patients; however, the majority of abscopal responses were rather small. Moreover, consistent with data supporting radiotherapy and immunotherapy to be most effective as monotherapies in the setting of low-volume disease, of the 11 patients with out-of-field responses, 8 had 3 metastases and 3 patients had 4-6 metastases, while no patients with > 6 metastases experienced abscopal responses [22]. Additionally, in a non-randomized prospective study of metastatic NSCLC reported by Bauml et al., patients with ≤ 4 metastases were treated with a variety of locally ablative therapies to all sites of distant metastasis and subsequently received pembrolizumab [23]. (Stereotactic radiotherapy, chemoradiotherapy, and conventionally fractionated radiotherapy were utilized in 76%, 51%, and 33% of patients, respectively). This regimen yielded impressive results including a 2-year OS of 77.5%; moreover, consistent with additional data which demonstrate that radiotherapy and immunotherapy are most effective in the setting of low-volume metastatic disease, 61% of patients had 1 metastasis and 93% had ≤ 2 metastases [23].

In contrast to the select prospective studies in which radio-immunotherapy has yielded impressive outcomes, randomized studies of immunotherapy with and without radiotherapy in metastatic patients have largely failed to meet their primary endpoint. These studies, which have included patients with a variety of cancer types, including NSCLC [24–27], melanoma [26], adenoid cystic carcinoma (ACC) [28], and head and neck squamous cell carcinoma (HNSCC) [29], have typically paired an anti-PD-1/PD-L1 agent [24, 25, 27-29] or interleukin-2 (IL-2) [26] with metastasis-directed radiotherapy. Radiotherapy in these studies largely consisted of 24-30 Gy given over 3-5 fractions [24, 25, 28, 29] to 1-5 metastases, with the exception of the study reported by Curti et al., in

which patients received either one or two fractions of 20 Gy, and the study reported by Welsh et al., in which patients were treated with 48 Gy in 4 fractions if deemed clinically feasible (n=19) and otherwise received 45 Gy in 15 fractions (n=21) [27]. Notably, patients in these studies generally had considerable metastatic burden and all patients had at least one metastasis that did not receive any local therapy.

As previously reviewed, currently reported trials of radio-immunotherapy in the treatment of patients with metastatic disease vary in a number of important ways, which along with the potentially immunosuppressive effects of radiotherapy may contribute to the negative results of the majority of these studies [30, 31]. However, given that the aforementioned prospective studies include patients with extensive metastatic burden with at least one metastasis not treated with local therapy, it is likely that, as is the case when radiotherapy and immunotherapy are used as monotherapies, combined radio-immunotherapy is most effective as a treatment for metastatic cancer in patients with low-volume disease, thus explaining the negative results of currently reported studies.

The hypothesis that radio-immunotherapy is most effective in the setting of low-volume disease is further supported by recent data from patients treated definitively for non-metastatic lung and esophageal cancer. In the PACIFIC trial, which randomized patients to receive adjuvant durvalumab or placebo following definitive chemoradiation for unresectable, stage III NSCLC [32], durvalumab significantly improved 5-year PFS (33.1% [95% CI, 28.0-38.2%] vs. 19.0% [95% CI, 13.6-25.2%]) and OS (42.9% [95% CI, 38.2-47.4%] vs. 33.4% [95% CI, 27.3-39.6%]) [33]. Similarly, the CheckMate-577 trial, which randomized patients to receive adjuvant nivolumab or placebo after neoadjuvant chemoradiotherapy followed by R0 resection for stage II-III esophageal and gastroesophageal junction cancer, demonstrated improved median disease-free survival (DFS) among patients treated with nivolumab (22.4 months [95% CI, 16.6-34.0 months] vs. 11.0 months [95% CI, 9.3-14.3 months]) [34]. It is of note that although the results of PACIFIC and CheckMate-577 support the benefit of adding immunotherapy following definitive local therapy, other studies combining radiotherapy and immunotherapy in the definitive setting have failed to improve outcomes. Among patients with locally advanced HNSCC, the addition of avelumab [35] and pembrolizumab [36] to definitive local therapy has failed to improve outcomes. Similarly, the addition of nivolumab to radiotherapy in patients with O6–methylguanine–DNA methyltransferase (MGMT)-unmethylated glioblastoma multiforme (GBM) and combined temozolomide/radiotherapy in patients with MGMT-methylated GBM, failed to improve outcomes in recently conducted trials [37–41]. While several differences exist in the design of currently reported randomized studies that investigate the role of immunotherapy in combination with definitive local therapy, it is of note that unlike trials in patients with HNSCC and GBM, PACIFIC and CheckMate-577 utilized immune checkpoint blockade (ICB) in the adjuvant setting. Thus, the inherent low burden of disease present following definitive local therapy may explain the success of the PACIFIC and CheckMate-577 trials in contrast to studies pairing ICB with definitive local therapy for HNSCC and GBM.

Radio-immunotherapy in the treatment of cancer: future directions

Given that both radiotherapy and immunotherapy are seemingly most effective, both as monotherapies and when used in combination, in the setting of low-volume disease, future studies of radio-immunotherapy should focus upon patients with oligometastatic disease. Not only does the inherent low burden of metastatic disease in patients with oligometastatic cancer provide an opportunity to maximize the therapeutic ratio of this combined treatment modality, additionally, this patient population is unlikely to require large, potentially immunosuppressive elective radiotherapy treatment volumes, which may undermine the efficacy of immunotherapy. Draining lymph nodes have been shown to help facilitate anti-tumor immune response by serving as crucial sites of T-cell accumulation and priming [42] and likely mediate the effects of ICB agents given following radiotherapy. Unlike tumors, which have been shown to harbor radioresistant resident T-cells [43–45], circulating T-cells that populate lymphoid organs are known to be quite radiosensitive [44]. As such, radiotherapy targeting regional lymph nodes may inhibit the effects of subsequently given ICB agents. Accordingly, the addition of the draining lymph nodes to the radiotherapy target volume has been shown to decrease OS in murine models treated with concurrent radiotherapy and ICB [46]. The immunosuppressive effects of elective nodal radiation provide an additional potential explanation for the failure of studies of radio-immunotherapy in the definitive treatment of HNSCC compared to the success of this treatment strategy in the PACIFIC and CheckMate-577 trials. Given data which support that radio-immunotherapy is likely to be an effective treatment strategy for patients with oligometastatic disease, future studies of radio-immunotherapy should focus on this population Table 2 summarizes ongoing and future phase III trials investigating the addition of metastasis-directed radiotherapy to ICB, including whether the volume of metastatic disease is considered as an inclusion criterion and/or stratification factor in the study design.

Further investigations are also needed to identify novel means of maximizing the efficacy of radio-immunotherapy in patients with oligometastatic disease. Currently, a number of factors including the ideal radiotherapy dose, immunotherapy agents, and sequencing of radiotherapy and immunotherapy in patients with metastatic disease remain poorly defined [30]. Additionally, a number of ongoing studies are investigating immunomodulatory agents capable of overcoming ICB resistance; given that the majority of currently utilized immunotherapies are forms of ICB, these agents may help maximize the therapeutic ratio of radio-immunotherapy in patients with oligometastatic cancer [47]. Furthermore, recent studies demonstrating that the microbiome modulates anti-tumor immune responses induced by ICB [48, 49] and radiotherapy [50, 51] suggest that agents aimed at altering the microbiome may be able to improve the efficacy of radio-immunotherapy.

Future studies are also needed to better define the subset of oligometastatic cancer patients most likely to benefit from radio-immunotherapy. Among other cancer types, currently reported and ongoing studies of metastasis-directed radiotherapy largely include patients with oligometastatic prostate cancer [7–11], NSCLC [3-5, 10, 11] (NCT03137771), and breast cancer [10, 11] (NCT02364557); however, the types of oligometastatic cancer most likely to benefit from radio-immunotherapy remains largely undefined. Additionally, an increasingly nuanced understanding of the oligometastatic state may help to identify patients most likely to benefit from radio-immunotherapy. The oligometastatic state is defined by the presence of a low volume of metastatic disease that is unlike to progress rapidly [15], though additional features including cancer type, lymph node status, and the timeline of metastatic progression are also prognostic in this patient population [14, 52, 53]. Additionally, recent work has delineated molecular features associated with oligo- versus poly-metastatic progression in patients with low-volume metastatic disease [53] and has demonstrated the ability to stratify patients by risk of failure following metastasis-directed local therapy [54]. Thus, a variety of clinicopathologic and molecular factors are likely to be important considerations in future studies that aim to identify a subset of patients with metastatic cancer that benefit from radio-immunotherapy. Novel diagnostic tests such as circulating tumor DNA (ctDNA), which has been shown to correlate with disease burden [55], and functional imaging, which may more accurately characterize metastatic burden and improve the ability to target all sites with metastasis-directed radiotherapy [9], are also likely to play a major role in increasing the therapeutic ratio of radio-immunotherapy for patients with oligometastatic cancer.

Table 2

Ongoing and Future Phase III Trials Investigating the Addition of Metastasis-Directed Radiotherapy to Immune Checkpoint Blockade.

ClinicalTrials.gov Identifier	Cancer Type	Trial Design	Metastasis Details (Upper Limit; Stratification)	Projected Enrollment	Date Open -Est. Completion	Primary Endpoint
NCT03867175	NSCLC	Pembrolizumab ± RT	≤ 8; 1-3 vs. 4-6	112	Jun. 2019 - Dec. 2027	PFS
NCT04944914	NPX	Camrelizumab ± RT	≤ 5, ≤ 3 in one organ; –	188	Jun. 2021 - Jun. 2026	PFS
NCT04402788	SCLC	Atezolizumab ± RT	≤ 10, ≤ 3 hepatic; high vs. low burden[1]	138	Aug. 2020 - Aug. 2027	PFS, OS[2]
NCT04929041	NSCLC (PD-L1 < 1%)	Chemo-IO[3] ± RT	–; –	100	Jan. 2022 - Dec. 2027	PFS, OS[2]
NCT03391869	NSCLC	Ipilimumab, nivolumab ± LT[4]	–; oligometastatic[5]	360	Dec. 2017 - Dec. 2022	OS
NCT04747054	HNSCC	Pembrolizumab ± RT	–; –	130	Jun. 2021 - Jun. 2029	PFS
NCT03827577	NSCLC	Chemo-IO[6] ± LT[7]	–; 1 vs. 2-3, 1-3 vs. > 3	195	Oct. 2019 - Sep. 2022	OS
NCT03774732	NSCLC	Chemo-IO[8] ± RT	–; –	460	Mar. 2019- Sep. 2024	OS

NSCLC = non-small cell lung cancer, NPX = nasopharyngeal carcinoma, SCLC = small cell lung cancer, PD-L1= programmed death-ligand 1, HNSCC = head and neck squamous cell carcinoma, RT = radiotherapy, Chemo-IO = chemotherapy-immunotherapy, PFS = progression-free survival, OS = overall survival

1. High vs. low tumor burden defined using ≥ 4, 5, and 6 metastases, as well as the median radiographic tumor volume as cutoffs. (Also stratified by complete vs. partial local consolidation of metastases.)
2. Phase II/III study where PFS is the primary endpoint of the phase II portion and OS is the primary endpoint of the phase III portion.
3. Several systemic therapy options permited including pembrolizumab, ipilimumab, nivolumab, and a number of cytotoxic chemotherapy agents.
4. Options for metastasis-directed local therapy include surgery and radiotherapy.
5. A pre-specified subgroup analysis is the impact of metastasis-directed local therapy on survival in the oligometastatic group.
6. Treatment with a platinum doublet, targeted agent, or immune checkpoint blockade allowed.
7. Options for metastasis-directed local therapy include surgery, radiotherapy, and radiofrequency ablation.
8. Several systemic therapy options permited including pembrolizumab and number of cytotoxic chemotherapy agents.

Conclusion

In conclusion, preliminary studies suggest that metastasis-directed radiotherapy benefits select patients with low-volume metastatic disease. However, a substantial proportion of metastatic patients eventually experience disease progression despite aggressive local therapy, necessitating novel means of improving the therapeutic ratio in this population. Immunotherapy represents a promising systemic therapy option that improves outcomes in some patients with metastatic cancer. Although the results of preliminary studies of radio-immunotherapy in patients with metastatic disease are largely underwhelming, further investigations are needed to determine whether radio-immunotherapy has a role in the management of patients with oligometastatic disease. Given that radiotherapy and immunotherapy, both as monotherapies and in combination, are seemingly most effective in the setting of minimal disease burden, oligometastatic cancer patients may be uniquely positioned to derive the greatest benefit from radio-immunotherapy. Thus, future studies should focus upon the role of radio-immunotherapy in patients with oligometastatic cancer and means of improving the efficacy of this therapeutic approach as well as ways to identify the subset of oligometastatic patients most likely to benefit from radio-immunotherapy.

Declaration of Competing Interest

R.R.W. has stock and other ownership interests with Boost Therapeutics, Immvira LLC, Reflexion Pharmaceuticals, Coordination Pharmaceuticals Inc., Magi Therapeutics, Oncosenescence. He has served in a consulting or advisory role for Aettis Inc., Astrazeneca, Coordination Pharmaceuticals, Genus, Merck Serono S.A., Nano proteagen, NKMax America Inc, Shuttle Pharmaceuticals, Highlight Therapeutics, S.L.

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CRediT authorship contribution statement

William Tyler Turchan: Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Sean P. Pitroda:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing. **Ralph R. Weichselbaum:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review & editing.

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