Advances in radioimmunotherapy 3

Integration of radiotherapy and immunotherapy for treatment of oligometastases

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Metastasis is the leading cause of cancer-related mortality and remains one of the prevailing challenges in cancer treatment. Most patients with metastatic disease are treated with systemic agents, which prolong survival and improve symptoms but are typically not curative. The oligometastatic hypothesis challenges the perspective that metastasis is an invariably disseminated process, and proposes a biological spectrum of metastatic virulence. Mounting evidence supports the idea that patients with numerically and spatially restricted sites of metastases, termed oligometastases, can achieve prolonged survival following metastasis-directed therapies, such as surgery or radiotherapy. Improvements in clinical and molecular staging of metastatic disease, as well as integration of effective systemic therapies with localised interventions, might achieve better outcomes for patients with diverse metastatic states. In this Series paper, we propose a rationale for the integration of immune checkpoint inhibitors with radiotherapy to advance the potential for effective treatment along the spectrum of disease, with emphasis on how immunotherapy can potentiate radiotherapy treatment in the oligometastatic setting.

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Introduction

Most patients with metastatic disease are unable to achieve long-term survival with systemic treatments. Notable exceptions exist, including subsets of patients with metastatic melanoma,[1] non-small-cell lung cancer (NSCLC),[2] or renal cancer[3] treated with immunotherapy, or those with germ cell tumours treated with chemo-therapy.[4] The high mortality for many patients with metastases has led to the prevailing view that metastatic disease is invariably widespread and incurable. However, the oligometastatic hypothesis proposes that metastases can vary in biological virulence, from a single metastatic site to widely disseminated disease.[5,6] This concept suggests that personalised cancer treatment should reflect an individual's metastatic state. In this context, localised interventions, such as radiotherapy or surgery, can be highly effective for patients with few metastases to limited organ sites. Prospective randomised trials have shown promising improvements in survival for patients with oligometastatic disease with the use of metastasis-directed therapies when compared with standard-of-care systemic therapy alone.[7–12] However, systemic disease progression remains a substantial challenge, and strategies to predict and treat subclinical disease are needed.

Emerging evidence has identified the tumour and host factors that can influence the biological heterogeneity in the virulence of metastatic disease. In this context, molecular subtyping of clinical metastases and considerable experimental data have shown that innate and adaptive immunity are central to the restriction of metastatic dissemination that is associated with improved clinical outcomes after localised therapies. Thus, immunosuppression that underlies widespread metastatic dissemination represents a therapeutic oppor-tunity to potentially improve outcomes for patients with metastatic disease. In this regard, strategies that augment systemic immune responses, such as immune check-point inhibition, will potentially be critical in the curative management of metastatic disease. The addition of radiotherapy to immunotherapy for patients with predominantly widespread metastases has gained substantial interest, based on the concept that radiotherapy will improve immunotherapeutic response.[13–18] By contrast, in this Series paper, we propose a rationale for integrating immunotherapy into the framework of potentially curative radiotherapy for oligometastatic disease whereby immunotherapy potentiates radiotherapy. Extending the central concepts of the oligometastasis hypothesis, we propose that the integration of immune checkpoint inhibition with localised radiotherapy will improve local and distant metastatic control and, ultimately, clinical outcomes in patients with oligometastatic cancer.

Metastasis-directed therapies to extend patient survival

Metastasis-directed interventions have shown favourable local control and prolonged progression-free survival in the oligometastatic setting.[6–12,19–22] Three prospective randomised phase 2 trials[8,9,12] have investigated the integration of radiotherapy with systemic treatments for patients with clinically defined oligometastatic disease. In the SABR-COMET trial,[12] 99 patients with a range of tumour histologies (including breast, colorectal, lung, and prostate cancers) were randomly allocated to receive standard-of-care systemic therapy with (n=66) or without (n=33) stereotactic ablative radiotherapy (SABR) to all known sites of metachronous metastases. Radiation doses varied by metastatic site, but were generally regarded as ablative (biologically effective dose$_{10}$ ≥100 Gy

for lung, liver, and adrenal metastases and 60 Gy for bone metastases). SABR was delivered to five or fewer metastases with no more than three metastases in any single organ system; 93% of patients had one to three metastases. In addition, all patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, a life expectancy of at least 6 months, and previously treated primary tumours. After a median follow-up of about 2 years, median overall survival (the primary outcome) was increased in the group that received SABR (41 months [95% CI 26 months–not reached]) compared with that in the control group (28 months [19–33 months]; hazard ratio [HR] 0·57 [0·30–1·10]; p=0·090). Median progression-free survival was also improved in the SABR group when compared to controls (12 months [6·9–30·4 months] *vs* 6 months [3·4–7·1 months]; HR 0·47 [0·30–0·76]; p=0·0012). 46% of patients treated with SABR were alive after 5 years, compared with 24% in the control group. However, the number of patients with grade 2 or higher treatment-related toxicities was increased to 29% following the use of SABR compared with 9% in the control group.

In a parallel study, Gomez and colleagues[8] randomly allocated 49 patients with oligometastatic NSCLC to receive standard maintenance systemic therapy or surveillance with (n=25) or without (n=24) local consolidation therapy, including surgery or radiotherapy (eg, conventionally fractionated radiation with concurrent chemotherapy, SABR, hypofractionated radiotherapy, or palliative radiotherapy regimens).[8] Eligible patients had an ECOG performance status of 0–2 and three or fewer non-progressing lesions after first-line systemic therapy, which consisted of four or more cycles of standard platinum doublet chemotherapy or at least 3 months of treatment with drugs targeting EGFR mutations (eg, erlotinib) or *ALK* rearrangements (eg, crizotinib). After a median follow-up of 38·8 months, median progression-free survival was improved in the local consolidation therapy group (14·2 months [7·4–23·1 months]) compared with the control group (4·4 months [2·2–8·3 months]; p=0·022), as was median overall survival (41·2 months [18·9 months–not reached] *vs* 17·0 months [10·1–39·8 months]; p=0·017). 82% of patients with metastatic progression in the control group progressed at existing sites of metastasis compared with only 15% in the local consolidative treatment group. Consistent with the SABR-COMET study,[12] the proportion of patients with grade 3 or higher treatment-related toxicity increased from 8·3% in the control group to 20% in the experimental group.

In a similar study, Iyengar and colleagues[9] randomly allocated 29 patients with oligometastatic NSCLC to receive standard maintenance systemic therapy with (n=14) or without (n=15) radiotherapy (SABR or hypofractionated radiotherapy consisting of one to 15 fractions with biologically effective dose$_{10}$ ranging from 42 Gy to 100 Gy) to all sites.[9] Patients were included if they had a Karnofsky performance status of at least 70% and up to six non-progressing lesions after first-line systemic therapy (four to six cycles of platinum-based chemotherapy). Median progression-free survival was increased in the group treated with radiotherapy compared with the maintenance chemotherapy group (9·7 months *vs* 3·5 months; p=0·01), after a median follow-up period of 9·6 months. Of the patients with disease progression, 70% had recurrence within the original sites of disease in the control group, whereas none of the irradiated sites in the experimental group progressed after treatment. In addition, the incidence of treatment-related toxicity was similar in both groups.

These three studies[8,9,12] were the first completed randomised trials to corroborate the better-than-expected outcomes observed in previous retrospective reports of patients with clinically defined oligometastatic disease treated with systemic therapy plus consolidation therapy. Although radiation dose, fractionation, and target sites (metastases with or without primary tumour) varied across studies, there was a consistent improvement in progression-free survival. The ongoing US National Cancer Institute-sponsored trials NRG-BR002 (NCT02364557) and NRG-LU002 (NCT03137771) and the international studies SABR-COMET 10 (NCT03721341) and CORE (NCT02759783) are investigating whether radiotherapy delivered to all sites of metastases improves survival in the phase 3 setting for patients with limited metastatic disease from NSCLC, breast, prostate, and other cancers (table). Because disease progression remains a considerable barrier to improved outcomes from localised interventions, characterisation of the clinical and biological features associated with increased risk of metastatic failure are essential for risk stratification and, potentially, treatment intensification for patients with oligometastatic disease.

Heterogeneity of clinically defined metastatic states

Although the metastatic state is anatomically defined by the number and locations of clinically detectable metastases, additional factors influence the risk of metastatic progression and clinical outcomes of patients following localised interventions for limited metastatic disease. These factors include the interval between treatment of the primary tumour and development of metastasis (ie, synchronous *vs* metachronous metastasis), the volume of disease, the rate of metastatic dissemination, and the presence of lymph node metastasis. For example, in a meta-analysis[23] of 757 patients with NSCLC treated with curative-intent surgery or radiotherapy (or a combination) of the primary and all metastatic sites (one to five lesions), 5-year overall survival was lower in patients who presented with synchronous metastases and lymph node involvement (13·8%) than in patients with lymph node-negative disease and metachronous metastases (47·8%).

	Histology	Treatments		Estimated enrolment	Inclusion criteria	Primary endpoint
		Experimental group	Control group			
NRG-BR002 (NCT02364557)	Breast cancer	Systemic treatment with metastasis-directed treatment (SBRT or surgery or both)	Systemic treatment	402 patients	≤2 metastases (maximum diameter ≤5 cm); controlled primary tumour; ECOG status ≤2	Overall survival
NRG-LU002 (NCT03137771)	NSCLC	Systemic chemotherapy with localised treatment (SBRT to metastases and SBRT or hypofractionated radiotherapy to primary tumour)	Systemic chemotherapy	300 patients	≤3 metastases without progression after first-line systemic treatment; ECOG status ≤2	Overall survival
SABR-COMET 10 (NCT03721341)	Any cancer	SBRT plus standard of care treatment (chemotherapy, immunotherapy, hormones, or observation, at the discretion of the treating oncologist)	Standard of care treatment (chemotherapy, immunotherapy, hormones, or observation, at the discretion of the treating oncologist)	159 patients	4–10 metastases (maximum diameter ≤5 cm); controlled primary tumour; Karnofsky performance status >60; life-expectancy >6 months	Overall survival
CORE (NCT02759783)	Breast, prostate, or NSCLC	Systemic treatment with localised treatment	Systemic treatment with or without palliative radiotherapy	245 patients	≤3 metastases (maximum diameter <5 cm in lung, <6 cm in all other tissues); controlled primary tumour; ECOG status ≤2; life-expectancy >6 months	Progression-free survival

SBRT=stereotactic body radiotherapy. ECOG=Eastern Cooperative Oncology Group. NSCLC=non-small-cell lung cancer.

Table: **Prospective randomised phase 3 trials of localised therapy for oligometastatic disease**

Additionally, Pastorino and colleagues[24] showed that patients with pulmonary metastases could be stratified on the basis of the disease-free interval (between treatment of the primary tumour and the diagnosis of metastasis), number of metastases, and resectability of pulmonary metastases. Among 4572 patients, median overall survival was 61 months for patients with a single, resectable pulmonary metastasis and a disease-free interval of 3 years or more, but was only 14 months in patients with unresectable disease, and 24 months in those with multiple pulmonary metastases and a disease-free interval of less than 3 years.

Lussier and colleagues[25] showed that the incidence of metastatic progression of subclinical disease after resection of all clinically evident pulmonary metastases per year was also predictive of survival. In a population of 63 patients, median overall survival was 18·0 months for patients (n=16) with more than 3·6 new metastases per year compared with 63·5 months in patients (n=32) with fewer than 0·6 new metastases per year (p<0·0001).

Consistent with these findings, Fong and colleagues[26] showed that a disease-free interval of less than 12 months, more than one hepatic metastasis, largest metastasis of more than 5·0 cm in diameter, lymph node involvement, and carcinoembryonic antigen concentration of more than 200 ng/mL were independently predictive of overall survival after resection of all clinically evident colorectal liver metastases (typically one to three lesions) in patients (n=1001) without extrahepatic disease. Patients with none of these clinical factors had a 5-year overall survival of 60%, compared with 14% in patients who had all five factors (p<0·0001). Similarly, multi-institutional analyses of 361 patients with various primary tumour histologies treated with radiotherapy for limited metastatic disease showed that 3-year overall survival was 75% in patients with breast, prostate, or kidney cancers, and 85% in patients with a disease-free interval of more than 75 months, compared with 13% in patients who were older than 62 years, had a disease-free interval of less than 75 months, had non-breast, prostate, or kidney histologies, and had three or more metastases (p<0·01).[21] In addition, higher radiation doses (biologically effective $dose_{10}$ ≥75 Gy) were associated with improved irradiated tumour control, as well as progression-free survival and overall survival.

Taken together, evidence from these studies indicate that patients with oligometastatic disease at presentation represent a heterogeneous population, predominantly defined by clinical features. The features underlying clinical heterogeneity might define additional metastatic states that reflect disease burden (eg, number and size of metastases) and biology (eg, lymph node involvement), and could inform potential therapies.

Biological evidence for oligometastasis

Emerging evidence suggests the existence of distinct biological determinants associated with oligometastatic disease. In 2018, Pitroda and colleagues[27] published an integrative molecular analysis of liver metastases from colorectal cancer, combining mutation, somatic copy number, mRNA, microRNA, and microsatellite instability data, to identify a subset of patients who experienced long-term survival presenting with clinically limited metastatic disease. 134 patients with metastatic colorectal cancer who received perioperative fluorouracil-based systemic chemotherapy and curative treatment of primary tumours as well as surgical resection of all hepatic metastases (typically one to three lesions) were examined.

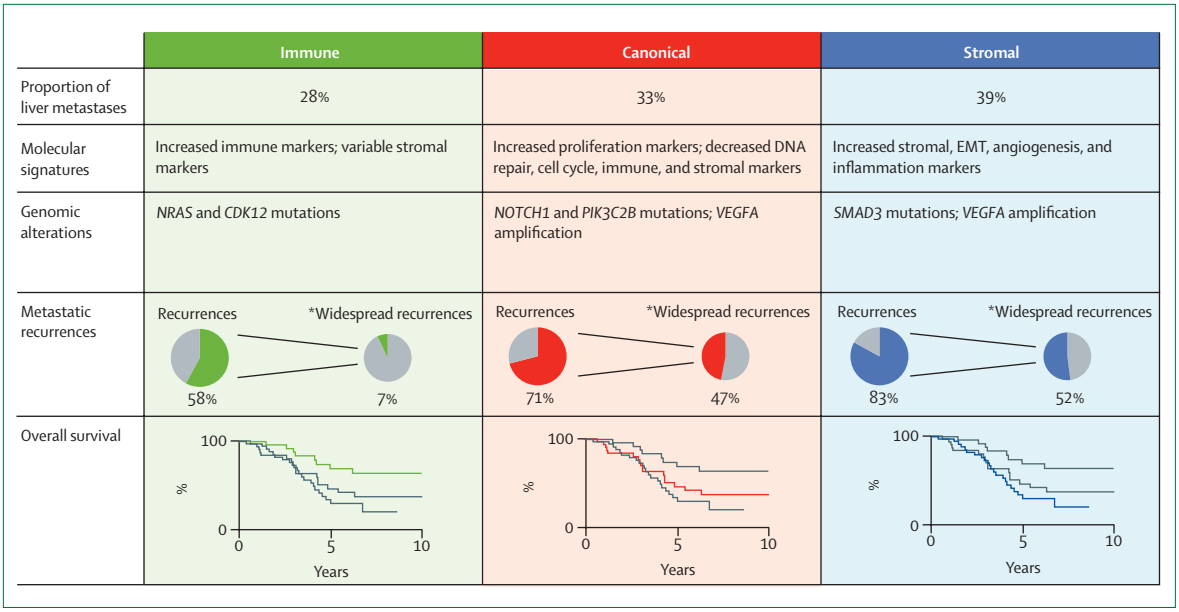

Figure: **Integrated molecular subtypes of liver metastases from colorectal cancer**
Adapted from Pitroda et al. (2018),[27] with permission. EMT=epithelial–mesenchymal transition. *Widespread recurrences refers to the proportion of recurrences involving four or more metastatic sites.

Patients with extrahepatic disease or previously treated metastases were excluded. Through an integrated transcriptional analysis, three robust, biologically distinct molecular subtypes of colorectal liver metastases were discovered, which predicted clinical outcomes after metastasis-directed surgery, independently of established clinical risk factors (figure).

A microsatellite instability-independent molecular subtype, characterised by upregulation of immune-related genes (designated as the immune subtype), was present in 28% of metastases and was associated with the most favourable 10-year overall survival (64%). Although 58% of patients with this immune subtype developed metastatic recurrences after surgery, 93% of recurrences were limited to one to three additional sites, many of which underwent a subsequent localised treatment. Metastases with this subtype were characterised by elevated expression of T-cell activation markers and antigen presentation and IFN-inducible genes, which was associated with increased cytotoxic T-cell infiltration on histological analysis and was consistent with a robust adaptive immune response.[27] These findings are congruent with the seminal works of Angelova and colleagues[28] and van den Eynde and coworkers,[29] who showed that the adaptive immune response plays a central role in restricting metastatic development. Mlecnik and colleagues[30] reported that an elevated Immunoscore, which reflects intratumoral cytotoxic T-lymphocyte infiltration, predicted favourable clinical outcomes and decreased metastatic virulence after resection of colorectal liver metastases. In addition, the metastasis with the lowest Immunoscore within an individual was the strongest prognostic factor for survival and complemented clinical risk factors.

In the study by Pitroda and colleagues,[27] two molecular subtypes of colorectal liver metastases were associated with unfavourable prognosis: the so-called canonical and stromal subtypes (figure). The canonical subtype was present in 33% of metastases and had marked depletion of innate and adaptive immune signatures, which was associated with histological evidence of absent or minimal intratumoral cytotoxic T-cell infiltration. Metastases of this subtype displayed increased expression of cell proliferation markers and altered cell cycle and DNA repair pathways. 71% of patients with canonical metastases developed metastatic recurrences, and 47% of these recurrences occurred in four or more sites. The 10-year overall survival for patients with the canonical subtype was 37%. 39% of patients harboured metastases with the stromal subtype, which recurred in 83% of patients (with 52% of these recurrences involving four or more sites) and was associated with a 10-year overall survival of 20%. Stromal metastases expressed pathways of epithelial–mesenchymal transition, angiogenesis, and extracellular matrix remodelling. Moreover, these metastases were found to have reduced intratumoral cytotoxic T cells and expressed pathways of non-immune inflammation. The lack of immunological features in canonical and stromal metastases could be because of tumour intrinsic properties, as well as immune escape caused by unsuccessful immunoediting, as described by Schreiber and colleageus.[31,32]

These three molecular subtypes of colorectal liver metastases augmented clinical risk stratification (clinical

risk scores)[26] and defined three integrated prognostic subgroups with substantially different overall survival: a low-risk subgroup (10-year overall survival 94%), comprising immune or canonical metastases with low clinical risk scores; an intermediate-risk subgroup (10-year overall survival 45%), consisting of immune metastases with high clinical risk scores, or stromal metastases with low clinical risk scores; and a high-risk subgroup (10-year overall survival 19%), including canonical or stromal metastases with high clinical risk scores.[27] Metastatic dissemination following treatment was highly variable across these integrated clinical molecular risk groups, with progression to four or more sites occurring in 57% of high-risk patients, compared with 0% in low-risk patients. These findings were the first to show that integrated molecular subtyping of clinical metastases can identify a subset of patients presenting with oligometastatic disease who might benefit most from localised metastasis-directed treatment, as well as subsets of patients who are at highest risk of metastatic progression after treatment. In addition, these data pointed to distinct biological mechanisms that contribute to the disparate outcomes of patients treated with metastasis-directed therapy, and suggested that modifying the host antitumour immune response might promote more favourable clinical outcomes in patients at high risk of metastatic recurrence following localised interventions.

Preclinical evidence for immunomodulatory effects of radiotherapy

Building on the emerging framework of radiotherapy for the treatment of oligometastatic disease, as well as biological data showing reductions in innate and adaptive immunity in metastases associated with poor prognosis, we hypothesise that immune checkpoint inhibitors could augment local and systemic immune responses to further improve clinical outcomes for these patients. In this regard, many laboratories have characterised the immunomodulatory effects of ionising radiation (panel). These investigations revealed that radiotherapy promotes antitumour responses through the activation of CD8-positive cytotoxic T lymphocytes, professional antigen-presenting cells (APCs), and macrophages, as well as cytokines, chemokines, and adhesion molecules that attract these immune cells to the irradiated microenvironment.[17] Radiation induces the release of the so-called eat me signals, such as calreticulin, and damage-associated molecular patterns[14] in a similar way to that seen following tissue injury or infection.[13] Additionally, radiation has been proposed to increase tumour antigen release and MHC class I expression on tumour cells. By contrast, radiation can generate tumour-promoting chemokines and other signals that attract FoxP3-positive CD4-positive regulatory T cells (Tregs), myeloid-derived suppressor cells, and immuno-suppressive cytokines, such as TGFβ. We and others have previously hypothesised that the immunostimulatory effects of radiation could be dampened at later timepoints by the immunosuppressive effects.[17,18]

Panel: **Immunomodulatory effects of ionising radiation in preclinical models**

Stimulatory effects

- Recruitment and effector function of CD8-positive T cells
- Dendritic cell activation and T-cell priming
- Activation of pro-death signalling in tumour cells
- Release of damage-associated molecular patterns and so-called eat me signals

Inhibitory effects

- Infiltration of regulatory T cells
- Influx of myeloid-derived suppressor cells
- PD-L1 induction by inflammatory cytokines
- Activation of pro-survival mechanisms through prolonged IFN signalling

Numerous preclinical studies have explored a range of radiation regimens combined with immune checkpoint blockade; however, the radiation dose, fractionation, timing, and target organs to optimise synergy with immunotherapy are not well defined (extensively reviewed by Minn and colleagues).[13,33,34] Focusing on dose and fractionation, which are particularly relevant to the treatment of oligometastases, the effects of single-fraction, high-dose radiation (20 Gy) were modelled by Lee and colleagues,[35] who showed that CD8-positive T cells are essential for the antitumour effects of radiation.[35] In addition, high-dose irradiation improved antigen presentation by professional APCs and thereby induced CD8 positive T-cell priming. Using melanoma and breast cancer tumour models, Liang and colleagues[36] found that the spectrum of in-vivo tumour responses to radiotherapy was unrelated to intrinsic tumour cellular radiosensitivity. They showed that depletion of CD8-positive T cells led to regrowth of controlled tumours, suggesting that radiation-induced tumour equilibrium might be a balance between immunogenic cell death, which is regulated by CD8-positive T cells, and tumour cell proliferation.

DNA from tumour cells exposed to ionising radiation is taken up by professional APCs, which activates cGAS (cyclic GMP-AMP synthase) and results in the production of the secondary metabolite cGAMP. cGAMP binds to hSTING (downstream adaptor stimulator of interferon genes) and ultimately leads to type I IFN production—a critical event in effective antigen presentation following exposure to radiation.[37–39] In this way, radiation might function, in part, as a pathogen through the activation of hSTING by cytoplasmic double-stranded (ds)DNA, and connect the innate to the adaptive immune system. In contrast to high-dose single-fraction radiation regimens, Vanpouille-Box and colleagues[38] have suggested that radiation doses ranging from 12 Gy to 18 Gy cause

activation of TREX1 (three-prime repair exonuclease 1) in tumour cells, which degrades DNA and decreases IFN production, leading to immune suppression.[38] Supporting these findings, Diamond and colleagues[40] showed that radiation of 8 Gy per fraction causes accumulation of dsDNA within tumour-derived exosomes, which promotes a type I IFN response and recruits dendritic cells into tumours. This effect might promote antitumour T-cell responses in otherwise poorly immunogenic tumours. However, the role of IFNs in response to radiotherapy is complex and complicated by the fact that repeated irradiation of tumour cells induces type I IFN and IFN-stimulated gene expression, which mediates tumour cell radioresistance and metastatic dissemination through a STAT1-dependent pathway.[14,41–45]

Deng and colleagues[46] reported that irradiation of a localised tumour induced immunosuppressive PD-L1 expression on dendritic cells, macrophages, and tumour cells in the tumour microenvironment. However, when tumour-bearing animals were treated with PD-L1-neutralising antibodies, synergistic antitumour effects were observed within the irradiated tumour volume compared with the effects of treatment with radiation or anti-PD-L1 alone. When animals that responded completely to treatment were challenged with reimplantation of tumour cells, the injected tumour cells did not grow, suggesting that the animals had developed immunity against the tumour cells. In addition, Twyman-Saint Victor and colleagues[47] showed that immune checkpoint inhibitors activated non-redundant immune mechanisms in the context of radiotherapy. Whereas, treatment with anti-CTLA-4 predominantly inhibited Tregs, treatment with anti-PD-L1 reversed T-cell exhaustion, which increased the CD8-positive T cell to Treg ratio and facilitated oligoclonal T-cell expansion in melanoma models.

In separate experiments, animals were injected with tumour cells in the opposite leg to a tumour-bearing leg that was targeted with radiotherapy and anti-PD-L1. Although these non-irradiated tumours almost always regrew, they regrew more slowly in animals treated with radiotherapy and anti-PD-L1 than in untreated controls, which suggested an abscopal effect.[36,46] Radiotherapy might also promote extrinsic resistance through the hSTING–type I IFN pathway by recruiting myeloid-derived suppressor cells via the CCR2 pathway[48] and enhancing suppressive inflammation in tumours. The immune-suppressive effect of radiotherapy might abrogate the immune-stimulatory actions, making the effect unlikely to be clinically significant without extrinsic immune modulation. This notion is supported by the paucity of clinical studies that report abscopal effects with radiotherapy alone. Taken together, experimental data suggest several potential strategies to augment local and systemic antitumour immunity by the combined use of radiotherapy and immune checkpoint therapies.

Rationale to integrate radiotherapy and immunotherapy

Through integration with radiotherapy, immunotherapeutic strategies have the potential to advance oligometastatic treatment, addressing both systemic and local disease. The safety of this combined approach has been extensively reviewed.[15] Emerging evidence suggests that systemic responses to immune checkpoint therapies are greatest when overall disease burden is smallest, which is potentially relevant following comprehensive localised treatment in the setting of oligometastatic disease. For example, in the PACIFIC trial, in which patients with non-metastatic, unresectable stage 3 NSCLC were treated with definitive chemoradiotherapy (54–66 Gy with conventional fractionation of 1·8–2 Gy per day), the addition of durvalumab improved the primary outcome of median progression-free survival from 5·6 months (n=236; 4·6–7·7 months) to 17·2 months (n=473; 13·1–23·9 months; HR 0·51 [0·41–0·63]) (median follow-up 25·2 months). 2-year overall survival improved from 55·6% (48·9–61·8%) to 66·3% (61·7–70·4%; p=0·005).[49] Consistent with these data, adjuvant ipilimumab increased recurrence-free survival from 30·3% to 40·8% and overall survival from 54·4% to 65·4% at 5 years following complete resection of stage 3 cutaneous melanoma.[50] Adjuvant pembrolizumab was also shown to improve 1-year recurrence-free survival from 61·0% to 75·4% in a similar setting.[51] These randomised phase 3 results in patients without metastasis represent some of the largest effects of immune checkpoint inhibitors on recurrence-free and overall survival observed among patients with NSCLC or melanoma.

Additional evidence regarding disease burden and immunotherapy response from a recent analysis of the KEYNOTE-001 trial showed that baseline tumour size was an independent prognostic factor for overall survival in patients with metastatic melanoma treated with pembrolizumab.[52] Additionally, a post-hoc analysis of patients with metastatic NSCLC treated in the KEYNOTE-001 trial also showed significantly prolonged survival among patients who had previously received any radiotherapy (6-month overall survival 73%) compared with patients who had not received previous radiotherapy (45%).[53] Moreover, abscopal responses in non-irradiated lesions might be more frequent in patients with a low disease burden. Golden and colleagues[54] investigated abscopal responses associated with granulocyte-macrophage colony-stimulating factor and single-site radiotherapy treatment (35 Gy in ten fractions) with concurrent chemotherapy in patients with three sites of metastatic disease or more. The authors reported that abscopal responses (defined as a ≥30% decrease in the longest dimension of the best responding non-irradiated lesion) were more likely to occur in patients with fewer disease sites, with 73% (8 of 11 patients) of abscopal responders having three metastases. Concordant findings were observed in a subgroup

analysis from a phase 3 trial of patients with metastatic castration-resistant prostate cancer treated with a single 8 Gy dose of radiation delivered to one to five osseous metastases or with radiation combined with ipilimumab.[55] The improvement in overall survival associated with the addition of ipilimumab to radiotherapy favoured patients with fewer bone metastases (one) when compared to those with more (two or more metastases; HR 1·38 [1·10–1·73]; p=0·0053). Importantly, data reported by Formenti and colleagues[56] showed that abscopal responses translate into improved clinical outcomes for patients with metastatic NSCLC following hypofractionated radiation (either five fractions of 6 Gy or three fractions of 9·5 Gy with ipilimumab). Overall survival at 3 years was 20·4 months (12·9 months–not reached) versus 3·5 months (3·1–7·4 months; p<0·0001) for responders (complete response, partial response, and stable disease) compared with non-responders (progressive disease).

Taken together, these findings suggest that systemic responses to immunotherapy against subclinical and clinically evident disease are more frequent when overall disease burden is smallest. Radiation therapy can be effective at reducing disease burden by debulking larger disease sites. Although, it is plausible that immunotherapy and radiotherapy might interact to promote antitumour immunity, combined radioimmunotherapies might also provide this benefit without direct interaction. The addition of immune checkpoint blockade to radiotherapy is particularly relevant to address micrometastatic disease in the oligometastatic setting, in which disease management involves comprehensive treatment of all clinically evident disease sites. Furthermore, integration of immunotherapy might have the largest benefit for patients with adverse clinical risk factors or poor immunogenic subtypes of metastatic disease who are at highest risk for metastatic recurrence.

Early clinical data suggest that immune checkpoint inhibitors might augment the local effects of radiotherapy. Luke and colleagues[57] tested this hypothesis in a phase 1 trial investigating the toxicity and feasibility of pembrolizumab following stereotactic body radiotherapy (SBRT) to two to four metastatic sites in 79 patients with widespread metastatic solid tumours, in whom previous treatment had been unsuccessful after a median of five previous systemic therapies. Findings showed that the combined treatment approach had acceptable toxicity profiles. In secondary analyses, no difference in control of irradiated tumours was found between patients who had received the full SBRT dose to the entire tumour when compared to those patients (25% of cohort) who had received a reduced radiation dose because of excessive tumour size or proximity to critical structures. Although these findings are constrained by the phase 1 trial design, the small number of patients recruited, and the unfavourable survival in this cohort, they suggest the possibility of a local antitumour interaction between radiotherapy and pembrolizumab, which warrants further investigation.[57]

Future directions

The oligometastatic hypothesis has affected clinical practice by challenging the perspective that metastases are always widespread and incurable. Results from emerging randomised, phase 2 clinical trials suggest improved outcomes with the use of ablative interventions in patients with limited metastatic disease; however, phase 3 randomised trials are needed to elucidate the potential overall survival benefit of metastasis-directed treatment. In addition, because metastatic recurrences are commonplace there is substantial interest in the combination of localised interventions with systemic therapies for patients with potentially curable oligometastatic disease. Immune checkpoint inhibitors have the potential to safely and effectively integrate with radiotherapy to augment local and systemic immunity and potentially reduce the risks for metastatic recurrences in patients with oligometastatic disease. However, additional clinical studies are needed to investigate optimal radiation dose, fractionation, and timing with regard to immune checkpoint inhibitors (as well as other immune therapies, such as adoptive T-cell therapy and cancer vaccines) to fully realise the potential of integrated radioimmunotherapies.

Conclusion

We suggest that integrated clinical and molecular staging of metastasis should serve as the foundation for future studies to best inform treatment decisions along the spectrum of metastatic disease. The inclusion of molecular correlatives in prospective clinical trials testing the role for localised interventions for metastatic disease will be of crucial importance. Advancements in the analysis of circulating tumour cells and cell-free nucleic acids, as well as novel imaging modalities, are likely to provide real-time characterisation of metastatic proclivity to complement molecular analyses in the prediction

Search strategy and selection criteria

We searched PubMed for articles published in English using the terms "immunotherapy" OR "immune checkpoint therapy" AND "stereotactic ablative body radiotherapy" OR "stereotactic body radiotherapy" OR "radiation therapy" OR "radiotherapy" AND "metastasis" OR "oligometastasis" OR "oligometastases". Articles that included these terms and were available on PubMed before Dec 31, 2018, were included for review. Relevant studies with results presented at the American Society of Clinical Oncology or American Society of Radiation Oncology 2018 annual meetings were also included. We also searched the ClinicalTrials.gov database for studies that included the terms "radiation" AND "immunotherapy".

of metastatic tropism, tumour vulnerabilities, and patient survival. Using the oligometastatic hypothesis as a framework, we propose that investigations into metastasis staging systems combining clinical, molecular, and host features will enhance our understanding of the metastatic state along the spectrum of disease and inform personalised treatment approaches, whether they are localised, systemic, or used in combination, to improve outcomes for patients with metastatic cancer.

Contributors

Individual sections of the manuscript were written by all authors in accordance with their specific expertise in each area. The manuscript was edited and finalised by all of the authors.

Declaration of interests

SPP reports a pending patent for Methods and Kits for Diagnosis and Triage of Patients with Colorectal Liver Metastases. SJC reports personal fees from Reflexion Pharmaceuticals, outside the submitted work; their spouse is employed as the medical director of Astellas Pharma Inc. RRW reports non-financial support from Aettis Inc, Genus, ImmunoVir, Nano Proteagen, Reflexion Pharmaceuticals, RiMO, Shuttle Pharmaceuticals, Boost Therapeutics Inc, and Oncosenescence, and personal fees from AstraZeneca and Merck Serono SA, all outside the submitted work. RRW also has a pending patent for Methods and Kits for Diagnosis and Triage of Patients with Colorectal Liver Metastases, and has participated as a guest speaker with sponsored industry travel for Boehringer Ingelheim.

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