



Translational and basic science opportunities in palliative care and radiation oncology

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Abstract: Radiation therapy is commonly used in the metastatic setting to palliate pain, neurological deficits, bleeding and other complications of metastatic disease, allowing patients to live longer and have better quality of life. Despite the effective use of radiation and other palliative treatment modalities, many patients continue to experience poorly controlled pain and other serious sequelae of their disease, underscoring the need for additional research in this area. In this review we highlight recent developments impacting the fields of palliative care and radiation oncology and describe opportunities for research and innovation including studies of tumor microenvironment, identification of effective biomarkers of tumor response and combinatorial treatments with new systemic agents. It is our hope that progress in these fields will improve the lives of patients living with advanced malignancies.

Keywords: Palliative; radiation; oligometastases; translational; microenvironment

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Introduction

Palliative radiation oncology comprises almost 30% to 40% of radiation treatments and involves tailoring treatment recommendations to the context of a patient's life expectancy and goals of care in the continuum of their illness. The line between curable and metastatic disease has historically established a framework for the treatments that clinicians can offer and the toxicities that patients are prepared to experience in the hope of cure as opposed to focusing only on alleviating suffering. This line has become increasingly blurred as new therapies and methods of detection in oncology have altered the natural history of cancer across multiple disease sites, creating new inflection points at which radiation therapy can impact outcomes. An exciting body of recent randomized data has validated the existence of a transitional state of "oligometastatic" or "oligoprogressive" disease as originally proposed by

Hellman and Weichselbaum in 1995, where local therapy delivered to limited sites of metastatic progression with curative intent may translate into a long-term survival benefit (1-4).

Whereas much effort has been invested into improving palliative care through improving assessment of quality of life and end of life care and communication, enhancing the cost-effectiveness of treatment, or identifying predictors of prognosis, there remains much to be explored as far as clinical and translational research for the metastatic patient population in radiation oncology. With novel advances in systemic treatment, the importance of achieving local control has become even more vital to maintaining good quality of life. Technological advances in radiation have further enabled the delivery of ablative doses of radiation with minimal toxicity, improving the therapeutic ratio.

Advances in radiation oncology delivery and practice, medical oncology, and radiology have transformed the

cancer landscape to create fertile opportunities for basic science investigations into the mechanisms underlying treatment response. Similarly, opportunities for translational research, or investigations that directly advance how scientific and clinical trial knowledge is applied in practice, has had tremendous growth in palliative radiation oncology, some of which we will now attempt to outline.

Biological impacts of radiotherapy on tumor microenvironment

While radiation is designed to primarily exert its effects on tumor cells, it has long been recognized that radiation also has complex and important effects on surrounding normal tissues as well, including components of the tumor stroma, blood vessels and the immune system. These effects may play a critical role in determining the fate of the tumor itself through intracellular signaling and communication, recruitment of tumor-killing machinery and establishing environmental conditions that either are supportive or unfavorable for tumor growth. We will examine the contributions of each component of tumor microenvironment on tumor biology and point out key unanswered questions that are currently under investigation or present opportunities for future research.

Immune system

In the metastatic disease setting, radiation has traditionally been reserved for palliation of symptomatic lesions, helping to alleviate pain and prevent local progression and neurological compromise. While radiation is regarded as primarily a local treatment, it was recognized over 60 years ago that in rare instances radiation can have impact on systemic disease burden as well (5,6), resulting in tumor shrinkage outside of the radiation portal. This phenomenon has been referred to as the abscopal effect. Although the exact mechanism by which radiation exerts anti-tumor effects at distant sites is not completely understood, studies over the years have established that the effect is mediated by the immune system. For instance, studies in syngeneic mouse models of fibrosarcoma showed that the radiation dose required to control tumor 50% of the time was lower in the T cell-competent mice compared to T cell-deficient counterparts (7). It is generally thought that following irradiation, stress response or death of tumor cells leads to the release of tumor-specific antigens that are recognized by the specialized antigen presenting cells (APC)

leading to activation of cytotoxic CD8⁺ T cells that then go on to attack and kill the tumor at both irradiated and unirradiated metastatic sites. However, because the tumor microenvironment contains a number of immunosuppressive factors [TGF- β and other immunosuppressive cytokines released by tumors), M2 macrophages, myeloid-derived suppressor cells (MDSC) and CD4⁺ T cells with regulatory function (Tregs)] (8), abscopal effects are quite rare at baseline. Because of the rarity of this response, delivering radiation therapy with the primary purpose of inducing a systemic disease response rather than palliation of local symptoms was not considered clinically appropriate.

However, for patients with advanced metastatic disease who have progressed through multiple systemic therapies, immune-mediated systemic responses may offer the best hope for prolonged survival. Abscopal responses may also be critically important in cases of local progression following irradiation, where cumulative normal tissue constraints limit the ability to deliver further local radiation therapy. Having the ability to treat a distant site and induce a meaningful response at a previously irradiated site would potentially avoid the development of irreversible damage to organs-at-risk or the need for surgical interventions in patients with poor prognosis.

Advent of immunotherapy in recent years allowed for the first time the ability to overcome certain immunosuppressive mechanisms employed by tumor cells. For instance, immune checkpoint blockade including CTLA and PD1/PD-L1 antagonists remove suppressive mechanisms on T cells, thus increasing their activity (9). It is thus reasonable to hypothesize that immunotherapy agents that remove immunosuppressive effects should synergize with radiation, increasing the frequency of abscopal effect following radiation therapy. Indeed, a number of preclinical and early phase clinical studies (10,11) have demonstrated that a combination of immunotherapy and radiation can potentially yield better local and systemic response than either therapy alone. While there was some concern about increased toxicity of concurrent administration of radiation and immunotherapy agents, recently published retrospective studies show that a combination of immune checkpoint blockade and radiation is not associated with increased toxicity across many disease sites (12). Nonetheless, further studies are needed to rigorously establish the safety profile of concurrent administration of radiation and immunotherapy. This is especially important because the half-life of immune checkpoint blockade agents is on the order of several weeks (13), making sequential

administration of radiation following washout of the drug frequently impractical due to the urgency of palliative radiation in many cases.

There are a number of challenges that require further investigation. First, even in combination with immunotherapy, abscopal effects are induced in the minority of cases. A number of newer agents aimed at either activating the immune system or inactivating immunosuppressive mechanisms are being developed, including agonists of CD28, CD137, OX40 and antagonists of TIM-3, LAG-3 and others (14). Clinical studies will be needed to establish the safety profile on concurrent use of these agents with radiation as well as to assess for potential synergy in inducing abscopal effect. Further studies are also needed to establish the optimal timing of immunotherapy administration relative to radiation therapy as well as optimal dose and fractionation. Some preclinical studies have suggested that use of 8 Gy \times 3 fractions or 6 Gy \times 5 commonly prescribed for SABR treatments may be optimal (15), but further research is needed. It also remains unclear whether subclinical doses of radiation may be sufficient to induce abscopal effect in certain cases when used in combination with immunotherapy agents. These may be considered in cases where local palliation of tumor is not needed potentially limiting treatment toxicity. Another challenge is that patients with metastatic disease frequently require dexamethasone for palliation of brain metastases, spinal cord or nerve compression, severe pain and other causes. Immunosuppressive effects of dexamethasone may render most immunotherapies ineffective. Alternative strategies are needed to be able to achieve palliation in this setting without antagonizing immunotherapy agents.

Fibroblasts and tumor-associated fibroblasts

Fibroblasts are commonly found in the microenvironment of many tumor types and have been implicated in promoting pro-tumorigenic phenotype through intercellular signaling and remodeling of extracellular matrix (16). Compared to most other cell types, fibroblasts are quite radioresistant, surviving single radiation doses of 50 Gy or more in cell culture (17-20). Upon exposure to radiation, fibroblasts undergo complex long-term changes in gene expression profile including genes involved in DNA damage response, cell cycle regulation, proliferation, growth factor signaling, inflammatory response, programmed cell death and others (21). The nature of the response appears to depend on fraction size and the number of fractions. For

instance, some studies have shown that extracellular matrix remodeling and reactive oxygen species scavenger pathways are induced most significantly by larger total doses delivered using fractionated regimens (22). Upon exposure to doses above 10 Gy, fibroblasts undergo induction of irreversible DNA-damage response leading to permanent arrest by cellular senescence. Senescent cells remain metabolically active, releasing soluble paracrine pro-inflammatory factors that can have important effects on neighboring proliferating tumor cells (23). Called senescence-associated secretory phenotype (SASP), this phenomenon leads to the secretion of inflammatory mediators, proteases, growth factors and extracellular matrix proteins that have been suggested to exert pro-tumorigenic effects on surrounding cells (24,25). However, the effects of SASP are complex and not completely understood, with some studies proposing tumor inhibitory effects instead (26). In addition to the effects on tumor itself, fibroblasts have been implicated in both acute and long-term side effects of radiation, including acute inflammation and fibrosis. Additional studies are needed to understand the effects of fibroblasts on tumor biology following exposure to radiation and the role of dose and fractionation in this process, leading to interventions that can enhance efficacy of radiation and reduce its side effects.

Blood vessels

It has long been recognized that tumors possess abnormal, leaky and fragile blood vessels, serving the basis for Judah Folkman's proposal in 1971 to target tumor cells indirectly by attacking endothelial cells of blood vessels (27). This led to the development of anti-angiogenesis drugs targeting VEGF (28), an important growth factor regulating endothelial proliferation. In addition, it has been recognized that radiation can have important effects on tumor vasculature, which is highly dose-dependent. At lower fraction sizes used with conventional radiation, the vasculature is generally preserved and even normalized in some cases, leading to improved tumor perfusion later in radiation course and tumor re-oxygenation (29-31). However, at higher single fraction doses >10 Gy, such as those used for stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT), radiation can lead to ablation of vasculature. This vascular effect has been proposed to contribute significantly to overall tumor killing effects of these treatments by computer modeling (32). However, it is unclear at this time whether this vascular effect is uniform across many tumor and tissue types, or

heterogeneous. If the latter, it may be possible to use MRI and other functional imaging modalities to select a subset of patients with tumors that may benefit the most from these vascular effects of large single doses of radiation. In other instances, it may be more efficacious to treat tumors with standard fractionation regimens in order to preserve and normalize vasculature.

Bone

Bone metastases are common across many cancer types, frequently causing pain and other complications including pathologic fractures, neurological deficits and hypercalcemia requiring hospitalizations, surgeries and other invasive procedures. Bone metastases are becoming an increasingly challenging problem as systemic therapies continue to improve and patients live longer with their disease. Bone metastases form following hematogenous dissemination and extravasation of a metastatic cell. In order to survive in the new microenvironment, the cell must be able to interact with the surrounding tissue. This is accomplished by complex signaling that is incompletely understood. Another important signaling occurring in some tumor types involves release of parathyroid-hormone related protein (PTHrP) by the tumor, which in turn leads to activation of receptor activator of nuclear factor KB ligand (RANKL) by osteoblasts and their precursors. RANKL, in turn, binds to receptor activator of nuclear factor KB (RANK) on osteoclasts and their precursors, leading to their recruitment and increase in bone resorption. Bone resorption, in turn, leads to release of growth factors that further stimulates tumor growth, resulting in “vicious cycle” of tumor growth (33–36). Interestingly, increased osteoclast activity is a universal problem shared by all bone metastases types, both osteolytic and osteoblastic. While osteolytic lesions undergo almost exclusively bone resorption without new bone deposition, osteoblastic lesions also undergo abnormal bone formation in regions surrounding tumor cells. Nonetheless, all bone metastatic lesions have highly dysfunctional bone remodeling, leading to increased fragility and risk of fracture.

Use of bisphosphonates or antibodies targeting RANKL significantly decreases both the development and growth of bone metastases, thus lowering risk of complications (37,38). Despite the addition of these therapies in recent years, bone metastases remain a common problem occurring in nearly half of cancer patients. Additional research is clearly needed to understand complex signaling interplay between tumors

and bone microenvironment in order to develop new therapies aimed at preventing bone metastases and their complications. It is known that bone microenvironment produces many growth factors (TGF- β , BMP, PDGF, FGF, IGFs and others) that can promote tumor growth. In addition to stimulating tumor growth, many of these factors lead to secretion of additional factors by the tumor, including factors that promote further bone resorption and dissemination of tumors by hematogenous spread and recruit inhibitory immune cells that prevent recognition of the tumors by the immune system. Detailed understanding of the bone microenvironment and complex signaling interplay is critical in order to develop effective therapeutic strategies.

Radiation therapy is frequently used to treat bone metastases in the palliative setting, greatly improving pain and reducing the risk of neurological compromise and other complications. While effective in stopping tumor growth and allowing some resumption of bone remodeling in the long run, radiation does not by itself lead to improved bone stability or reduce the risk of pathologic fractures in the short term. Higher rates of vertebral compression fracture have been reported after single fraction spine SBRT with doses equal or exceeding 20 Gy (39). While prior work has shown that radiation of normal bone can affect bone growth and remodeling (40), our understanding of how radiation affects bone microenvironment in metastatic setting is very limited. Additional work is needed to understand the impact of different fractionation schemes used in the palliative setting (conventional doses of 2–4 Gy per fraction *vs.* SBRT fractions of 5–20 Gy or more). Detailed understanding of how radiation effects not only tumor cells, but also other cells in bone microenvironment will facilitate development of effective combinatorial strategies aimed at effectively controlling tumors both locally and systemically and improving bone stability. Understanding how radiographic findings observed following bone SBRT translate into a clinicopathologic correlate will help distinguish treatment response from radiation-related treatment effects such as necrosis or fibrosis and help define subsequent treatment strategy (41,42).

Identification of biomarkers of treatment response and toxicity

Life expectancy

The accurate prediction of survival is vital to decision-

making in palliative radiotherapy. Models that help clinicians predict life expectancy help tailor the fractionation and technical delivery of radiation to maximize the benefit achieved. The benefit of radiation may take weeks to months based on the palliative experience with bone metastases (43,44), yet many patients are still receiving palliative radiotherapy within the past few weeks to months of life (45). Clinicians are frequently inaccurate in estimating survival and tend to be overly optimistic, even in patients with limited life expectancy (46). In turn, patients can be overly optimistic in their perception of their illness such that they are willing to proceed with aggressive care even with end stage disease (43,47,48).

There are a number of prognostic models that exist for patients with advanced cancer (49) that would be applicable across different cancer types and clinical scenarios and highlight both patient and tumor specific factors predictive of survival, including Karnofsky Performance Status (KPS), symptoms of anorexia, dyspnea, nausea, or confusion, and serum markers including lactate dehydrogenase, C-reactive protein, albumin, leukocytosis or leukopenia.

Two models have specifically been applied to patients with advanced cancer referred for palliative radiotherapy. The Chow “number of risk factors” method analyzed a cohort of 395 patients referred for palliative radiotherapy and identified 6 among the 16 examined that were predictive, including: primary cancer site, metastasis site, KPS, fatigue, appetite, and dyspnea [all measured with the Edmonton Symptom Assessment Scale (ESAS)]. Based on the number of risk factors, one could then discriminate survival at 3-, 6-, and 12- months as validated by applying to the general population in their validation cohort (50,51). Krishnan and colleagues performed a similar type of analysis by reviewing retrospectively a cohort of 862 patients referred for palliative radiotherapy and created the TEACHH (Type of cancer, ECOG PS, Age, prior Chemotherapy, prior Hospitalizations, Hepatic metastases) model, which is capable of predicting patients with short (less than 3 months) and long life expectancy (greater than 1 year) (49).

Identifying additional clinical and molecular correlates that could be layered onto these clinical prognostic models, such as albumin and white blood cell count, could help to refine our ability to focus palliative treatment towards those who would live long enough to benefit from it. Through prospectively enrolling patients onto protocols that would permit the collection of accurate information on staging, the patient’s history, diagnosis, treatment, and response,

the power of medical informatics could be implemented to more powerfully identify factors associated with increased survival and quality of life. Webb and Pass eloquently review aspects of translational research (52) including the need to establish infrastructures to robustly collect and analyze data or procure tissue specimens at different stages of treatment response to allow for genotype-phenotype to be identified. Such an approach could have a powerful impact in identifying key factors in determining survival or quality of life for patients with incurable disease; however, rather than viewing genetic or lab values as the only potential data to be discovered via “omics” research, the power of early palliative care consult, goals of care discussion, could be other means of improving survival.

With the discovery of actionable targets that guide targeted therapies, factors such as prior chemotherapy are likely too generic a descriptor to capture the heterogeneous biological response to systemic treatment. Incorporating molecular information such as PD-L1 status, tumor mutational burden could help predict likelihood of synergy of radiation treatment with immunotherapy; whereas, the presence of EGFR mutations in lung cancer or BRAF V600 mutations in melanoma could be game changers as far as dictating whether or not palliative radiation is indicated or whether it could be deferred in anticipation of a good response to targeted therapy, even in patients with metastatic disease. Incorporating genetic and molecular information into our ability to predict survival would thus help ensure patients are guided to the appropriate treatment at any time in their cancer trajectory.

Spine fractures

The skeleton is the most common site of metastases in advanced cancer, and skeletal-related events, including pain, pathologic fracture, cord or cauda equina compression, can significantly impact quality of life (53). The Spinal Instability Neoplastic Score (SINS) was a tool developed by the Spine Oncology Study Group that incorporates radiologic and clinical factors to guide referral for surgical evaluation as appropriate (54). The SINS score has been found to be highly reproducible with minimal inter or intra-observer variability (55) and SINS criteria have been found to be predictive of greater risk of vertebral compression fracture after SBRT (39) and has been applied to assess fracture risk after conventional palliative radiation as well (56,57).

The use of serum markers has been proposed as a

potential mechanism to assess the tempo of osseous metastatic growth. In addition to correlating biochemical markers of bone resorption, such as albumin or collagen-related matrix markers, with bone remodeling after spine radiation, applying high throughput methods to the analysis of radiographic changes after radiation would also be a translational opportunity to investigate the effectiveness of treatment response as radiologic phenomenon such as increased mineralization of lytic lesions or demineralization of blastic lesions on CT have been observed after SBRT (42). These are some of the findings that might be able to be analyzed through the analytic power of radiomics to more optimally determine the effectiveness of radiation in achieving local control or the risk of fracture.

Similar radiomic approaches could be applied to estimate risk of fracture after radiation for bone metastases, in calculating dosimetric volume histograms to predict risk of fracture, especially in the context of re-irradiation. This data would ultimately also be valuable in comparing the relative benefit of using conventional radiation compared to SBRT and could help generate hypotheses for better understanding what is happening at a biologic level with each type of treatment.

Brain metastases

The evolution in clinical management of brain metastases demonstrates how improved biomarkers in an era of improved systemic therapy could significantly improve quality of life for many patients by identifying patients who would benefit from alternate therapies other than whole brain radiation for treatment of their brain metastases. Brain metastases are a significant cause of morbidity and mortality for patients with metastatic cancer and most commonly arise from lung, melanoma, renal, breast, or colorectal cancer (58). The management of brain metastases with radiation treatment, including whole brain radiotherapy (WBRT) or SRS or hypofractionated stereotactic radiotherapy (SRT), has long been a mainstay to achieve local control for non-operative patients, as the brain has long been conjectured to be a sanctuary site for cancer possibly due to the inability of chemotherapy to effectively penetrate through the blood-brain barrier though other hypotheses abound (59).

WBRT, which treats the whole brain over the period of 1 to 3 weeks, can be associated with significant fatigue, neurocognitive changes, and impacts on learning and memory that can significantly impact quality of life (60).

Indeed, the Quality of Life after Treatment for Brain Metastases (QUARTZ) trial recently demonstrated the potential detriment of utilizing WBRT in patients with a very limited prognosis. This multicenter phase III trial randomized patients with NSCLC unsuitable for surgery or stereotactic treatment to optimal supportive care (including dexamethasone) plus WBRT or optimal supportive care alone and found no difference in overall survival, quality of life, or dexamethasone use between the two groups with a median survival of 2 months among the entire cohort and 10% of patients assigned to WBRT dying before receipt or completion of therapy (61).

In contrast, SRS, which delivers focally ablative doses of radiation with high precision, offered the benefit of not only improved local control but also the potential to mitigate the neurocognitive impact of treating the entire brain. The associated benefit of achieving durable local control with SRS was initially demonstrated for patients with a limited number of brain metastases in three randomized control trials in the context of using SRS in addition to WBRT (60,62-64). The most recent trial presented by Brown and colleagues incorporated neurocognitive assessments to compare outcomes for patients with 1 to 3 brain metastases up to 3 cm in size treated with SRS versus SRS plus WBRT and demonstrated no difference in median overall survival and better neurocognitive outcomes with SRS alone at 3 months, such that SRS alone has now become the clear standard of care for patients with limited brain metastases (47). Current consensus guidelines from the ASTRO Choosing Wisely campaign recommend against routinely adding adjuvant WBRT to SRS for the management of brain metastases (65).

What counts as “limited brain metastases” remains a moving target, and stereotactic radiation may still be a viable approach for a larger population. Whereas the classic cut off has been fewer than 4 brain metastases, Yamamoto and colleagues recently showed in a nonrandomized, prospective study of stereotactic radiation no difference in overall survival, neurologic function, local recurrence, new lesions, use of salvage radiation or surgery, or use of systemic treatment between patients with 2 to 4 or 5 to 10 brain metastases, though total tumor volume had to be less than 15 mL (66,67). Randomized studies of SRS versus WBRT are needed, and one ongoing study by Aizer and colleagues at the Brigham and Women’s/Dana-Farber Cancer Center is actively addressing this question for patients with multiple brain metastases (NCT03075072).

The dogma regarding CNS penetration for systemic

agents is also being turned on its head as there is growing evidence showing CNS activity in multiple contexts, including alectinib, a next-generation ALK inhibitor for patients with ALK-positive lung cancer (68,69). Tucatinib has been approved on trial in setting of brain metastases from HER-2 positive breast cancer, and the use of tyrosine kinase inhibitors (TKIs) for patients with brain metastases from HER2 positive cancer is an active area of research (70).

How brain-directed radiation treatment may synergize with systemic treatment, particularly those with greater than four metastases has opened up many novel areas of research in an era where it may become increasingly less appropriate to define a role for radiation treatment based on number of lesions or tumor volume without factoring in molecular or histologic status. In patients with small volume disease who may be a candidate for one of the few systemic therapies with demonstrated CNS benefit, a decision whether to pursue brain radiation upfront versus systemic therapy with close observation has become significantly more nuanced. Prognostic models capable of factoring in histology, the burden of systemic versus intracranial disease and other factors would facilitate optimal decision making in this palliative setting as well. The use of “liquid biopsy” in patients with brain metastases may facilitate non-invasive characterization of tumor biology distinguishing the competing risks of intracranial and extracranial disease and providing insight into the evolution of tumor response or resistance.

Oligometastatic disease and biomarkers of response

Initially proposed by Hellman and Weichselbaum in 1995, “oligometastatic” disease denotes an intermediate state in the spectrum of local and disseminated cancer where cure can still be attained with aggressive local therapy (71). This concept was initially empirically validated through the survival benefit seen with resection of lung and liver metastases in colorectal carcinoma and sarcoma (72,73). More recently, the first phase II randomized trial of local consolidative therapy (using surgery, radiation, or both) versus maintenance therapy or observation in patients with oligometastatic non-small cell lung cancer (NSCLC) demonstrated a progression-free survival of 11.9 *vs.* 3.9 months in favor of patients receiving local consolidative therapy and an overall survival benefit of 41.2 *vs.* 17 months with longer follow up (1,74). The SABR-COMET trial has further demonstrated a potential survival to metastatic-

directed therapy for multiple histologies (3).

A multicenter, phase II randomized control trial for 62 patients with oligorecurrent prostate cancer compared outcomes for patients treated with metastasis-directed therapy (MDT) compared to active surveillance and similarly identified a significantly delayed time to biochemical recurrence and a trend towards ADT-free survival with a median ADT-free survival of 13 months (80% CI, 12 to 17 months) with surveillance versus 21 months (80% CI, 14 to 29 months) with MDT [hazard ratio, 0.60 (80% CI, 0.40 to 0.90); log-rank $P=0.11$], though this difference was not statistically significant.

The addition of SBRT to the armamentarium of locally ablative therapies has therefore helped establish an exciting frontier in oncology, where efforts to assert local control over metastatic disease may translate into meaningful impacts on patient quality of life, survival, and even chance of cure. The use of SBRT in comparison to conventionally fractionated radiation for palliation of bone metastases could be analogous to the use of SRS versus WBRT for intracranial disease as far as advancing the ability to control disease while minimizing risk of toxicity.

There is a wealth of primarily retrospective and phase I/II single-arm prospective experiences that have demonstrated excellent tolerability and local control with SBRT for oligometastatic disease; however, the biological correlates for treatment response after SBRT are lacking. Biomarkers of treatment response following SBRT would have important clinical implications, including enabling the earlier detection of tumor relapse, facilitating risk-adaptive approaches towards radiation therapy, and also shed further insight into the biology underlying the superior effectiveness of SBRT compared to conventional fractionation and its potential synergy with targeted or immunotherapy through the activation of innate and adaptive immune responses. In addition, the identification of serum biomarkers that predict treatment response would permit a non-invasive method for interrogating mechanisms of tumor evolution and treatment resistance.

Translational research that enables the prospective and systematic collection of patient tumor, blood, or urine samples could allow for novel methods for tumor and mutation detection that could allow for detection of tumor abundance or mutational profiles in response to treatment, particularly in setting where no good biomarkers exist.

Tumors continually shed DNA into the blood where it can be detected as circulating tumor DNA (ctDNA). Markers such as ctDNA to track mutations or tumor

burden may enable analysis of treatment response in a way that would enable better understanding of the biology underlying SBRT and comparative efficacy of different fractionation approaches, including conventional radiation treatment. Among patients with EGFR-mutant NSCLC treated with osimertinib, cell free DNA (cfDNA) and circulating tumor cells (CTCs) were complementary, non-invasive assays for evaluation of acquired resistance to first line EGFR TKI (75). The use of liquid biopsy to detect KRAS or EGFR mutations for patients with advanced lung cancer (76) or to query CSF for actionable mutations in patients with leptomeningeal disease (77) are but a few examples of practical translational applications of this technology that is a topic of active investigation across multiple disease contexts. Utilization of such molecular correlatives may facilitate faster, non-invasive methods to determine patients who may benefit from early initiation of targeted therapy as opposed to urgent palliative radiotherapy.

Conclusions

As systemic treatment evolves, the management of common palliative indications, including brain metastases, cord compression, leptomeningeal disease with radiation treatment, must also evolve, as the thoughtful delivery of palliative radiation also involves consideration of prognosis, timing and toxicity of planned sequential or concurrent systemic treatments, and weighing the relative benefit of pursuing either treatment approach.

We are currently living in an exciting era where there remain far more questions than answers in oncology. Translational research may prolong the life of patients with advanced cancer by providing novel biomarkers and therapeutic targets, opportunities to assess treatment response and adapt therapy, and inform how better to couple radiotherapy and novel systemic agents.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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