8 Radiation Therapy for Melanoma

WENYIN SHI

Department of Radiation Oncology, Sidney Kimmel Medical College, Thomas Jefferson University, Philadelphia, PA 19107, USA

Author for correspondence: Wenyin Shi, Department of Radiation Oncology, Sidney Kimmel Medical College, Thomas Jefferson University, 111 S 11 ST, Suite G301, Philadelphia, PA 19107, USA. E-mail: Wenyin.shi@jefferson.edu

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Abstract: Although melanoma is a relative radioresistant tumor, radiation therapy (RT) remains a valid and effective treatment option for the management of melanoma. RT as a primary treatment is often offered in well-defined situations, such as medical inoperability, lentiginous melanoma, mucosal melanoma, and ocular melanoma. Adjuvant RT following lymphadenectomy in node-positive melanoma patients prevents local and regional recurrence; however, the role of adjuvant RT remains controversial and underutilized due to lack of overall survival benefit. On the other hand, RT is highly effective in providing symptom palliation for metastatic melanoma and is widely used. Advanced RT technologies such as stereotactic radiosurgery (SRS) and stereotactic body radiotherapy (SBRT) can achieve excellent local control with minimum toxicities. They are commonly used in the management of brain, lung, spine, and liver metastases. Most recently, it is under active investigation on combining RT with new systemic options, such as targeted therapy, or immunotherapy. The advancements in the treatment of patients with melanoma highlight the importance of multidisciplinary management in this disease. Radiation therapy will continue to be one of the key therapeutic options.

Key words: Melanoma; Radiation treatment; Stereotactic body radiation treatment; Stereotactic Radiosurgery

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Introduction

In the United States, in 2016, there were 76,380 new cases of melanoma and 10,130 deaths (1), and the incidence and mortality have been steadily increasing over the past decades (1, 2). Surgery remains the mainstay of treatment for most patients, particularly for patients with early stage disease. Radiation therapy, on the other hand, plays an active role in the management of patients with advanced stages of the disease. Definitive radiation therapy is suited for certain well-defined situations, including medical inoperability, lentigo maligna melanoma (LMM), mucosal melanoma, and ocular melanoma. For patients with node-positive disease, adjuvant radiation therapy (RT) following lymphadenectomy effectively prevents local and regional recurrence. For patients with advanced stage and metastatic disease, RT is highly effective in providing symptom palliation. Radiation therapy also plays a role in conjunction with systemic therapy, such as BRAF inhibitor, or immune therapy to achieve additive or even synergistic benefit. The comprehensive management of patients with melanoma warrants a multidisciplinary approach. Radiation therapy will continue to be one of the key therapeutic options.

Historical Perspective

RT works by inducing DNA damage in cancer cells. Historically, melanoma had been deemed a radioresistant tumor. This notion is derived from *in vitro* clonogenic cell death assay demonstrating a broad shoulder. Based on linear quadratic model, the broad shoulder in cell survival curves indicates high repair efficacy at low dose. The high repair capacity of melanoma cells is due to efficient enzymatic system, high proliferation capacity, poor cell differentiation, hypoxia-induced radioresistant stem cells, and abnormal apoptosis due to p53 functional attenuation (3–5). This broad shoulder in cell survival curve also indicates an increased sensitivity to higher dose per fraction (6, 7). Conflicting initial clinical experience with varying doses per fraction prompted a multicenter randomized Phase III study through the Radiation Therapy Oncology Group (RTOG). This study (RTOG 8305) directly compared two dose schemes. In this trial, 137 patients with measurable metastatic melanoma were randomized to 32 Gy in 8 Gy per fraction weekly versus 50 Gy in 2.5 Gy daily fractions. No difference in clinical response rate was observed (8). There have been multiple additional retrospective studies evaluating various hypofractionated regimens, which showed similar outcomes in all the regimens (9–12). Nonetheless, hypofractionated radiation with 2.5 Gy or higher per fraction has become commonplace in the treatment of melanoma given its tolerability, convenience, and low risk of late effects.

On the other hand, there have been significant advancements in RT with evolution of imaging techniques, such as high-resolution computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), as well as advances in radiation delivery techniques. Two-dimensional techniques

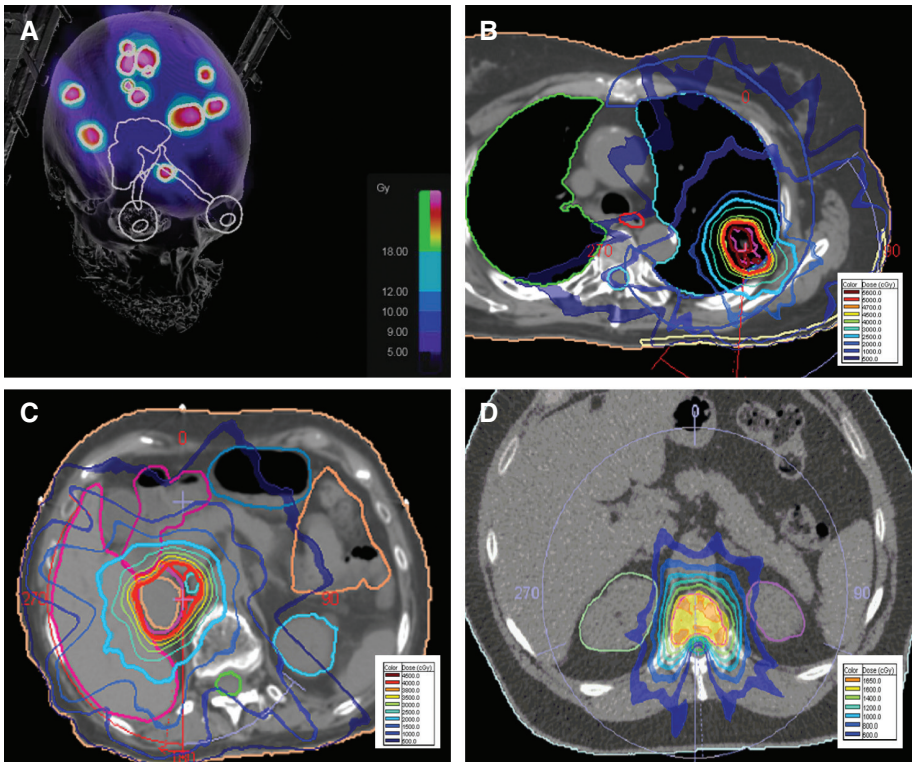

Figure 1 **Examples of SRS and SBRT treatment plans for melanoma metastasis: A) stereotactic radiosurgery (SRS) for multiple brain metastases; B) stereotactic body radiotherapy (SBRT) for lung metastasis; C) SBRT for adenral metastasis; and D) SBRT for spine metastasis.**

evolved to three-dimensional techniques with implementation of CT planning scans. The development of inverse planning such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT) have allowed for even more precise RT delivery while sparing normal tissues and decreasing associated toxicity (13). High precision with patient immobilization, imaging guidance, and steep dose gradient allows for high-dose treatment delivery, which is most suitable for melanoma. Stereotactic radiosurgery (SRS) and stereotactic body radiation therapy (SBRT) are two examples of high-dose radiation therapy with high precision delivery (Figure 1). SRS refers to a precisely delivered single large dose of radiation achieved by multiple noncoplanar beams converging on a radiographically defined target (14). For this type of RT delivery, there is a steep decline of radiation dose just outside the target volume, thereby limiting the dose to normal critical structures. It is commonly used for treating melanoma brain metastasis. SBRT refers to high dose per fraction precise RT over approximately 2–5 treatment sessions. This dose fractionation scheme is particularly useful for patients with oligometastatic disease, such as lung, bone, liver, or adrenal metastasis.

Definitive RT for Lentiginous Patients

Lentigo maligna (LM) is the most common melanocytic malignancy of the head and neck. It has the potential for dermal invasion and development into invasive LMM (15). LM and LMM have slow growth rates and are associated with less potential for metastatic disease. While surgery is generally the treatment of choice for these lesions, the population most frequently affected are elderly patients who may not be optimal surgical candidates (16). To confound this, surgical option may also be limited due to the location and size of the lesion. Definitive RT has been used as a primary treatment modality for these patients with good long-term local control with acceptable cosmetic and functional outcomes (17–21). A recently published pooled analysis of eight studies with 349 patients with LM treated with definitive RT showed a 5% local recurrence rate (22). A majority of the patients who recurred were successfully salvaged with further RT, surgery, or other treatments. Another analysis of 454 patients from 10 studies demonstrated a mean recurrence rate of 11.5%, with the majority of studies having follow-up of more than 20 months (23). The side effects of radiation treatment are commonly mild, including pigment change, telangiectasia, and erythema (22). Definitive radiation therapy is a safe, well-tolerated, and effective treatment for LM and LMM.

RT in Mucosal Melanomas

Mucosal melanomas are rare, as compared to cutaneous melanomas. Primary sites of origin include the head and neck, anorectum, and vulvovaginal regions. It is uniquely different from cutaneous melanoma with respect to epidemiology, etiology, pathogenesis, and prognosis (24). They are clinically aggressive; even with aggressive surgical interventions, local recurrence can occur in 29–79% of patients (25–27). Therefore, adjuvant treatment, in particular radiation therapy, has been investigated with mixed results. A majority of the data pertains to head and neck mucosal melanomas and the addition of postoperative RT offers a local control benefit. The local recurrence rates with adjuvant radiation ranges from 15 to 30% (27–29). Despite the local control benefit of adjuvant radiation, there is no impact on overall survival, likely due to the high risk of systemic relapse (28–33).

Many patients present with unresectable lesions due to location and proximity to critical structures, particularly in the head and neck. Definitive radiation has been investigated in such setting. In a retrospective series of 28 patients with mucosal melanoma of the nasal cavity and paranasal sinuses, definitive RT was given to a dose of 50–55 Gy in 15–16 fractions and initial complete regression was observed in 22 out of 28 patients (79%). Local control of 49% at 3 years was observed in these patients (31). A similar report on 31 patients from multiple institutions treated with definitive RT showed a local control of 58.1% (33). The authors also noted that there was an increase in the local control and survival in patients who received a hypofractionated regimen with a dose per fraction greater than 3 Gy (33). Based on these findings, patients with unresectable mucosal melanoma, primary RT should be attempted for patients with localized disease.

Definitive RT for Ocular Melanomas

Ocular melanoma is a rare but potentially devastating malignancy arising from the melanocytes of the uveal tract, conjunctiva, or orbit; it represents less than 5% of all melanoma cases in the United States (34). Historically, enucleation of the eye has been the definitive treatment for patients with ocular melanoma. Over the past several decades, RT has become a crucial part of the successful treatment of ocular melanoma while preserving the eye and vision. Local control is exceptionally good with RT delivered by either external beam radiation therapy (EBRT) or episcleral plaque brachytherapy (35).

Brachytherapy has been used to treat intraocular tumors since 1930 (36). The custom-designed plaque is temporarily sutured to the sclera overlying the tumor. The plaque remains in place for 2–5 days, depending on the type of radioactive source. Preliminary experiences of episcleral brachytherapy used the high-energy isotope, cobalt-60 (^{60}Co) (37). Currently, iodine-125 (^{125}I) is the most commonly used isotope, but other low-energy isotopes, such as iridium-192, cesium-131, protactinium-103, and ruthenium-106/rhodium-106, have also been used (ABS-OOTF 2014) (38). The Collaborative Ocular Melanoma Study established the role of plaque brachytherapy in the management of ocular melanoma (39). This is a 12-year study that demonstrated relative equivalence of ^{125}I plaque (85 Gy) compared with enucleation in the prevention of metastatic melanoma for medium-sized choroidal melanoma. Plaque brachytherapy was effective in sterilizing the gross tumor, with local control being achieved in approximately 90% of patients. Only 5% of the patients require enucleation due to radiation-induced toxicities (39). Radiation-induced ocular injury is dose dependent and therefore lower doses have also been investigated to reduce toxicity. Doses as low as 69 Gy are capable of achieving similar rates of local control, distant metastasis-free survival, and overall survival as compared with 85 Gy (40). Specific dose constraints for tumors close to the macula have been suggested in order to minimize the potential of visual acuity loss. For such tumors, a dose less than 70 Gy to the tumor apex should be considered (41).

In terms of EBRT, proton therapy is most commonly used for the treatment of ocular melanoma. Compared to plaque therapy, proton therapy has advantages in treating larger tumors. A large, single institution study comparing proton beam with enucleation showed no apparent difference in long-term survival (42, 43). Favorable 5-year and 10-year local failure rates of 3.2% and 4.3%, respectively, were observed (43). For uveal melanoma, doses of 60 Gy delivered in four daily fractions of 15 Gy have been highly effective (44). Based on an analysis of 2069 patients treated at Harvard Cyclotron Laboratory and Proton Therapy Center at Massachusetts General Hospital between 1975 and 1997, a 15-year local control rate is 95% and the rate of eye preservation is 84%. A meta-analysis of 8809 patients with uveal melanoma included 7457 patients treated with charged particle therapy and 1352 patients with brachytherapy or enucleation. The rate of local recurrence was significantly lower with charged particle therapy than with brachytherapy (odds ratio 0.22) (45). However, there was no advantage with respect to mortality or enucleation when comparing particle therapy and brachytherapy (45). Dose reduction may be important for toxicity reduction in particle therapy as it is in brachytherapy, and a prospective randomized trial of lower-dose

(50 Gy) versus standard dose (70 Gy) proton radiation for small-to-moderate sized uveal melanoma showed no differences in a 5-year local or systemic recurrence or visual acuity loss, suggesting lower dose may be acceptable moving forward (44). In the past decade or two, linear accelerator (LINAC) stereotactic RT (SRT), or SRS with either LINAC or gamma knife has been investigated for its potential as an alternative option to proton beam (46–53). The initial experiences showed that SRT and SRS offer a noninvasive alternative to enucleation and brachytherapy in the management of uveal melanoma, with similar outcome to proton beam therapy (46–53).

Adjuvant RT for Cutaneous Melanomas

The role of RT in patients following surgical excision of cutaneous melanoma is multifaceted. With respect to adjuvant RT to the primary lesion, this is typically offered to patients who are at high risk for recurrence. Adjuvant RT to the primary site plays a role in the management of patients with desmoplastic neurotropic melanoma (DNM) as well as patients with lesions of the head and neck. Other indications for adjuvant radiation include tumor thickness >4 mm, ulceration, satellitosis, positive surgical margins, and mucosal origin (54).

There is a long history of adjuvant radiation after surgery to reduce local recurrence rate. The initial experience dated back to 1950s when patients thought to be at high risk of relapse were treated with brachytherapy or orthovoltage x-rays to the primary site (55). Subsequently, multiple retrospective studies further defined the role of adjuvant radiation. In 1981, Princess Margaret Hospital published a retrospective experience with 37 patients who underwent surgical resection of head and neck melanoma followed by adjuvant RT (56). This study provided an insight into the importance of radiation dose fractionation, as they found patients who received fractions greater than 4 Gy had improved local control (71% vs. 25%). A report from Sydney Melanoma Unit suggested that there may be an advantage in local control in patients with microscopically positive margins and/or adverse pathologic features who were offered postoperative RT (57). RT was delivered in a hypofractionated fashion to a total dose of 30–36 Gy in 5–7 doses over 2.5 weeks. The recurrence rate at 6 months was 11% in this cohort of 174 patients; this was compared with surgical data from the same time period which suggested that RT may have superior local control. However, there is no overall survival benefit due to high rate of distant failure (57).

With respect to patients with desmoplastic or neurotropic histology, data suggest that RT may offer a significant local control benefit. A retrospective analysis from Moffitt Cancer Center examined 277 patients with nonmetastatic desmoplastic melanoma who were treated with surgery with and without RT (58). At a median follow-up of 43.1 months, RT was associated with improved local control (HR, 0.15; 95% confidence interval, 0.06–0.39 [$P < 0.001$]), and this was particularly evident in patients with negative pathologic features (such as Breslow depth >4 mm, perineural invasion, or positive resection margins). Additional prospective data are needed to further clarify the role of adjuvant RT in desmoplastic or high-risk melanoma patients.

The role of adjuvant RT to the primary site in patients with a completely resected melanoma with neurotropic features is the question of a current clinical trial being run by Trans-Tasman Radiation Oncology Group (TROG) (www.ClinicalTrials.gov, NCT00975520). This is a 2-arm, randomized controlled trial in which patients are treated with surgical excision alone or surgical excision followed by adjuvant radiation to a dose of 48 Gy in 20 fractions over 4 weeks. The primary outcome of this trial is time to local relapse with the hypothesis that RT will improve local control in this select patient cohort.

Adjuvant RT for Regional Nodal Metastases

Adjuvant radiation after surgery decreases the risk of local recurrence for patients at high risk of regional failure after lymph node dissection. The high-risk factors include multiple positive nodes, large clinically palpable lymph nodes, extracapsular extension, and recurrence after prior lymph node dissection (54, 59–63). The largest retrospective analysis was performed by Agrawal et al. in which 615 patients who met the "high-risk" criteria for nodal relapse were offered adjuvant RT (60). The 5-year local recurrence rate was 10% in patients who received adjuvant radiation versus 41% in those patients who did not receive RT ($P < 0.0001$). High level of evidence was provided by Phase III trial run by the Australia and New Zealand Melanoma Trials Group and Trans-Tasman Radiation Oncology Group. In this trial, 250 patients with positive nodes who were deemed high risk were randomized following surgery to RT (48 Gy in 20 fractions) or observation. The criteria established for increased risk of regional recurrence were as follows: extracapsular extension, multiple positive nodes (>1 for parotid, >2 for neck and axilla, and >3 for groin location), and large lymph node (>3 cm for parotid, neck, and axilla, and >4 cm for groin location). After a mean follow-up of 73 months, lymph node recurrence in the RT arm was significantly lower as compared with observation (18% vs. 33%), but no benefit was observed with respect to relapse-free survival or overall survival (64).

Role of Palliative RT for Melanomas

Radiation therapy is highly effective for symptom palliation for melanoma distant metastasis. Common indications for palliative RT include pain, mass effect, tumor-related hemorrhage, and local irritation from skin or subcutaneous lesions (65). New RT techniques, such as SRS and SBRT, can achieve high probability of local control with very limited toxicity. SRS and SBRT are also preferred due to the relatively radioresistant nature of melanoma, and as a result improved efficacy can be achieved with higher dose per fraction. Ablative doses of RT such as those used in SBRT or SRS can be quite effective in the treatment of patients with limited number of metastases, or oligometastasis (66). Observed 5-year survival in patients with resectable metastases can be as high as 15 to 41% in the setting of few sites of distant metastases (67–70). In two series of patients from the University of Rochester, patients with 1–5 metastases (mainly breast, lung, and colon primary)

were treated with SBRT and the local control rate was reported to be 77% at 2 years (71). Duke University reported on a similar protocol and demonstrated a 2-year local control rate of 52.7% (72). SBRT for oligometastatic disease is a reasonable consideration for melanoma patients. There are currently eight open clinical trials investigating the use of SBRT in metastatic melanoma, most of which use a combination of an immune checkpoint inhibitor (www.ClinicalTrials.gov). This area of study is expected to significantly evolve in the coming decade.

Melanoma is the malignancy with the highest rate of brain metastasis, which occurs in more than 50% of patients with advanced melanoma (73). Intracranial disease progression is the cause of death in 20–54% of patients with disseminated melanoma (74). Despite advances in systemic therapy and surgical and radiation techniques, the prognosis of patients with brain metastasis remains poor. The median survival of these patients is 4.4 months and the 5-year survival rate is approximately 3% (75). Overall survival may be extended by effective locoregional treatment. Surgery, whole brain radiation therapy (WBRT), and SRS are all used in the treatment of brain metastasis; nonetheless, the best treatment remains controversial and many patients receive more than one modality (76, 77). Historically, WBRT is the *de facto* treatment for brain metastases. It can improve intracranial disease control and delay neurological decline (78). The most commonly prescribed dose schedule is 30 Gy in 10 fractions. Melanoma is considered a less radiosensitive tumor, and the local control with WBRT is poor. The estimated local control rate with WBRT at 6 months and 12 months are 37 and 15%, respectively (79), and the overall survival is unsatisfactory at 2–5 months (80). Besides dismal prognosis, WBRT is also associated with significant side effects, particularly high risk of neurocognitive decline (81, 82). Recently, there has been a paradigm shift toward more focused radiation treatment. For patients with limited brain metastases, SRS can be used as an alternative to WBRT without compromising overall survival, and with reduced neurocognitive impairment (83–86). Due to better response of melanoma to large radiation fraction dose, SRS treatment significantly improved the local control rate of melanoma brain metastases compared to those that were treated with WBRT (87, 88). The 12-month local control rate with SRS is about 65% (85–88). More impressively, SRS also contributes to improved overall survival from 4 months to 6–8 months as compared to WBRT (85, 89, 90). As a result, SRS alone should be considered the standard of care for patients with limited brain metastases (up to 10 brain metastases) and size suitable for SRS (usually ≤4 cm in diameter). Evaluation is ongoing as to whether the maximum number of lesions can be safely and effectively treated with SRS alone (91–93).

Bone metastases are common in patients with advanced melanoma. Bone metastases are important causes of morbidity and mortality in clinical practice and impair quality of life by causing pain, pathological fracture, spinal cord compression, bone marrow failure, and severe hypercalcemia. Approximately, 70% of bone metastases involve vertebrates, with thoracic and lumbar levels being the most common involvement sites. EBRT is a well-established treatment for vertebral metastases. Multiple prospective studies showed a pain response rate of 50–90% (94–98). RT achieves improvement in pain control in more than 65% of cases and re-calcification is observed in the areas with bone destruction on radiographs obtained a few months after treatment. There is no consensus on dose and fraction of palliative RT and many studies have been conducted to compare total dose and fraction (e.g., 8 Gy times 1, 10 Gy times 3, or 5 Gy times 4).

No difference was detected between longer and shorter therapies in any of the randomized studies including larger series (97, 99). As a result, 8 Gy in single-fraction RT was suggested as the standard of care for the palliation of uncomplicated painful bone metastases in the recent American Society for Radiation Oncology (ASTRO) guidelines (98, 100). However, conventional RT is limited by the low tolerance of the spinal cord and cauda equina, leading to subtherapeutic dose delivery for tumor control, particularly for melanoma. Local control for bone and/or spine metastasis treated with SRS and/or SBRT is also very favorable (70–90%) (101–106). SBRT treatment also has the advantage of better and more durable pain control for bone metastasis. A large series of 500 patients (including melanoma patients) with spinal metastasis who received single-fraction SRS treatment showed a long-term tumor control of 90%, and long-term pain control of 85% (107). A study focused on melanoma patients also showed axial and radicular pain improved in 27 of 28 patients (96%) treated with radiosurgery (99).

Melanoma has a marked predilection for the liver, particularly, ocular melanoma. Liver metastasis can occur in 15–20% of metastatic cutaneous melanoma (108, 109), and up to 95% of metastatic ocular melanoma (110, 111). With either type of melanoma, liver metastasis is attributed to a grim prognosis and is often the cause of death (112, 113). For those with chemorefractory liver metastases, liver-directed therapy is a preferred approach to reduce tumor burden and prolong overall survival. Unfortunately, only a very small subset (~9%) of patients are eligible for resection (114, 115). Treatment options for unresectable hepatic metastatic melanoma have historically been poor. Recent studies utilizing Yttrium-90 (^{90}Y) radioembolization have led to encouraging results (114, 116–118). This is a special form of radiation that was initially established for the treatment of hepatocellular carcinoma and liver metastasis (119–121). The first study in 2009 by Kennedy et al. on 11 uveal melanoma patients reported a strikingly high response rate of 77% with a 1-year survival of 80% (119). Further experiences suggest that it is an effective and safe option for managing hepatic metastasis from melanoma, with a high response rate (partial response and stable disease) in 80–90% (116–118, 122, 123). Given the hypervascular and aggressive nature of melanoma liver metastases, locoregional treatment with selective internal radiation therapy (SIRT) appears to be a reasonable approach at reducing disease progression. Median overall survival ranges from 7.6 to 10.1 months, substantially improved over the expected >3 month historical benchmark (124). However, large, randomized trials are warranted in order to validate radioembolization for melanoma liver metastasis.

RT with Concomitant Agents

There have been substantial recent advancements in the management of advanced stage melanoma, such as BRAF inhibitor and immunotherapy (125–127). This stimulates the interest of combining such agents with radiation.

BRAF mutations occur in approximately 40–70% of patients, leading to constitutive and uncontrolled cell proliferation, as well as deregulated apoptosis (128, 129). The development of BRAF inhibitors (i.e., vemurafenib, dabrafenib) has led to a significant improvement in the overall survival among patients who harbor

this mutation (125, 130, 131). Interestingly, BRAF inhibitor was found to have radio sensitization effect (132, 133). However, the radiosensitization effect of BRAF inhibitor also increased the risk of skin toxicities with radiation (133–136). Due to the minimum skin dose from SRS, several studies that evaluated BRAF inhibitor with SRS for patients with brain metastases reported favorable outcome (137–139). Studies that directly compared outcomes of patients treated with SRS alone and SRS with BRAF inhibitor suggest that there indeed may be a survival benefit of combination therapy (140–142). However, it seems that because of the radiosensitization effect, increased toxicity other than skin toxicity may also be induced, such as radionecrosis (141). As a result, consensus guidelines from the Eastern Cooperative Group (ECOG) were recently published documenting severe toxicities reported in 27 publications in which patients received a BRAF inhibitor in combination with RT. Based on this review, recommendations for combination therapy include holding BRAF inhibitor for at least 3 days before and after fractionated RT and at least 1 day before and after SRS. There were no fatal reactions documented with RT doses less than 4 Gy per fraction. More prospective trials are necessary to further clarify the optimal timing of BRAF inhibition with RT (143).

In recent years, there is great enthusiasm on the combination of RT with immunotherapy for patients with metastatic melanoma. Recent advances have demonstrated the efficacy of immunotherapy in the treatment of melanoma (126, 127). Several immune therapy strategies have achieved great clinical success in metastatic melanoma, resulting in overall survival improvement (126, 144–149). There are multiple rationales to support the combination of radiation with immunotherapy, and such a combination may lead to a synergistic effect. Radiation is a promising immunological adjuvant and a complex modifier of the tumor microenvironment. Radiation-induced damage in the tumor and normal tissue is affected by various regulatory immune mechanisms (150). Radiation, in particular hypofractionated radiation, can induce the expression of checkpoints, such as PD-L1, PD-L2, and CTLA-4 (151–153). Hence, removing the immune inhibition leads to enhanced tumor control effect. RT promotes tumor cell death, releasing tumor debris and tumor antigens. Radiation treatment has the capacity to prime an adaptive T-cell-mediated immune response, through mechanisms that enhance antigen presentation, activation of dendritic cells, and cross-presentation of tumor-associate antigens (154–156). Besides local effect, radiation may also impact systemic response. Abscopal effect refers to the infrequently reported tumor regression of a secondary site following RT to a separate primary site (157–161). One recent report analyzed 21 patients with advanced melanoma treated with ipilimumab followed by RT and observed an abscopal response in 11 patients (52%) with the median time of 1 month from RT to response. Median overall survival for those patients who had an abscopal response was 22.4 months versus 8.3 months for those without a response. Larger prospective studies are required to bolster this small but impressive report (160). This effect is believed mediate through immune response. Seromic analysis and immunologic correlates of the abscopal effect in a patient with melanoma showed antigenic targets with increased antibody responses following RT (159). Recently, Hiniker et al. reported the result from a prospective trial including 22 patients with Stage IV melanoma treated with palliative RT and four cycles of ipilimumab. The primary objective is assessing safety and efficacy of this combination (162). RT was delivered within 5 days following initiation of immunotherapy. The combination of treatments was well tolerated without

unexpected toxicities. Three patients had complete responses and three had partial responses, suggesting further investigation of the combination of RT with immunotherapy in patients with Stage IV melanoma (162). Similarly, early experiences also showed that dramatic responses have also been shown in the combination of RT with PD-1 or PDL-1 blockade in patients with advanced melanoma (163). Currently, sufficient evidence on the optimal RT dose, schedule, and temporal relationship with immune therapy is lacking. Great efforts are dedicated to address these questions; currently there are multiple open clinical trials evaluating various combinations of RT (EBRT, SRS, SBRT, or radiospheres) with immunotherapy (ipilimumab, nivolumab, atezolizumab, etc.) (www.ClinicalTrials.gov).

Perspectives and Conclusions

RT clearly will continue to play an important role in the management of melanoma. With the advances in the more effective systemic therapy and immune therapy, there is great enthusiasm for combining radiation with systemic therapy. Currently, only a few small studies reported the combination of radiation and immune therapy. Early data suggest that such strategies may improve treatment outcome but also increase adverse effects. There are currently several open clinical trials evaluating various combinations of RT with immunotherapy. The optimal combination, timing, and fractionation schedule of radiation will be further defined with the results of these ongoing trials. However, it is clear that further advances in the treatment of melanoma will be multidisciplinary.

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