Stereotactic radiosurgery and immunotherapy for metastatic spinal melanoma

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The management of metastatic spinal melanoma involves maximizing local control, preventing recurrence, and minimizing treatment-associated toxicity and spinal cord damage. Additionally, therapeutic measures should promote mechanical stability, facilitate rehabilitation, and promote quality of life. These objectives prove difficult to achieve given melanoma's elusive nature, radioresistant and chemoresistant histology, vascular character, and tendency for rapid and early metastasis. Different therapeutic modalities exist for metastatic spinal melanoma treatment, including resection (definitive, debulking, or stabilization procedures), stereotactic radiosurgery, and immunotherapeutic techniques, but no single treatment modality has proven fully effective. The authors present a conceptual overview and critique of these techniques, assessing their effectiveness, separately and combined, in the treatment of metastatic spinal melanoma. They provide an up-to-date guide for multidisciplinary treatment strategies. Protocols that incorporate specific, goal-defined surgery, immunotherapy, and stereotactic radiosurgery would be beneficial in efforts to maximize local control and minimize toxicity.

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METASTATIC melanoma poses an onerous clinical burden. Its incidence is rising rapidly in the US and abroad,³⁸ and the median survival time of patients with advanced melanoma is less than 10 months.²⁶ This trend derives from myriad factors that render melanoma difficult to treat. Melanoma has demonstrated a propensity for early metastasis,⁶ and its vascular characteristics amplify the difficulty of surgical excision.^{29,42} Both of these factors contribute to the high recurrence rates observed following resection.⁵ Additionally, data demonstrate that metastatic melanoma is relatively resistant to both conventional external-beam radiation therapy (cEBRT)^{13,14,28,47,49} and chemotherapy.^{49,92} Finally, melanoma is capable of downregulating proliferation pathway gene expression to

assume a more invasive phenotype.⁵⁵ This property, known as dynamic phenotype switching, enables melanoma to metastasize rapidly in response to specific environmental stimuli, such as hypoxia. This adaptation complicates treatment decisions because its onset is difficult to predict. Dynamic phenotype switching, a feature of highly malignant neoplasms, allows the tumor cells to alternate between proliferative and invasive phenotypes in response to external challenges (such as hypoxia, radiation, or chemotherapy), contributing to its ability to resist chemotherapy and radiation therapy. Additionally, hypoxia-induced alterations in tumor cell genotype can influence response to immunotherapeutic techniques, including BRAF and ERK inhibitors.

ABBREVIATIONS cEBRT = conventional external-beam radiation therapy; CTLA-4 = cytotoxic T-lymphocyte antigen-4; IFN = interferon; IL-2 = interleukin-2; LINAC = linear accelerator; MHC = major histocompatibility complex; NK = natural killer; NOMS = Neurological deficits, Oncological features, Mechanical spinal instability, and Systemic disease progression; PD-1 = programmed death-1; PD-L1, -L2 = programmed death-1 ligands 1 and 2; SRS = stereotactic radiosurgery; Th1 = helper T cell Type 1; TIL = tumor-infiltrating lymphocyte.

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When metastatic melanoma presents in the spine, these obstacles become more prominent. The spinal cord can tolerate maximal, single-fraction radiation doses of approximately 14 Gy to a point dose on the spinal cord (cord Dmax)⁹⁴ which is substantially lower than the tolerance of surrounding normal tissue. Considering melanoma's radioresistant histology and the spinal cord's increased susceptibility to radiation damage, cEBRT lacks the precision required to deliver a dose that is both safe and therapeutic, whereas radiosurgery offers the ability to deliver a higher therapeutic dose with the precision necessary to spare adjacent critical structures.²⁸ Surgical excision of metastases also requires great caution and conveys operative risks and rehabilitation needs for patients who already have systemic disease. These treatment limitations prove particularly relevant, considering that the incidence of melanoma has substantially increased over the past 40 years,⁶⁷ and the spine is the most common site for melanoma metastases.^{29,81}

This review is designed to evaluate the efficacy of surgical therapy, radiosurgery, and immunotherapy for metastatic spinal melanoma, separately and in combination. For the purpose of this review, we focus our analysis on treatment of extramedullary paraspinal melanoma metastases. In our experience, intramedullary metastases, or metastases that demonstrate leptomeningeal spread, are not suitable candidates for traditional surgical or radiosurgical intervention. We provide a conceptual overview of recent developments in melanoma immunotherapy, and we devote particular attention to the application of the concept of "separation surgery" and stereotactic radiosurgery (SRS) to treat extramedullary metastatic spinal melanoma.

Immunotherapy

Introduction to Melanoma Immunotherapy

The FDA approvals of interleukin-2 (IL-2) in 1998 and ipilimumab in 2011 were major breakthroughs in the development of immunotherapy for melanoma.⁷⁸ These treatments exemplify 2 important classifications of immunotherapy, cytokine based and checkpoint blockade based. Although checkpoint blockade-based therapy demonstrates improved tumor control and reduced toxicity compared with cytokine-based therapy, clinical trials are still being conducted to evaluate the efficacy of both treatments. Cytokine-based therapy involves administration of recombinant cytokines to potentiate the activity of endogenous immune cells and to drive immune differentiation toward the helper T cell Type 1 (Th1) cytotoxic subgroup. Checkpoint blockade-based therapy impairs regulatory pathways to amplify the immune response to tumors. Table 1 summarizes important studies for each of these 2 classes of immunotherapy.

Although we have limited our focus to the above strategies, it is worth noting that specific targeted antibody therapies also show great promise.⁷⁸ A popular subject of targeted therapy is BRAF, a serine/threonine kinase that up-regulates MEK kinase activity in the Ras-Raf-MEK-ERK pathway. Melanoma cells with BRAF V600E mutations have a worse prognosis than melanoma cells with wild-

TABLE 1. Studies of immunotherapy for metastatic melanoma

Authors & Year	Mechanism of Immunotherapy	No. of Patients	% Response Rate
Atkins et al., 1999	IL-2	270	16
Legha, 1997	IFN- α + IL-2 + chemo	62	60
Itzhaki et al., 2011	Adoptive cell transfer	31	48
Prieto et al., 2012	Ipilimumab + IL-2	36	25
Topalian et al., 2014	Nivolumab	107	31
Hamid et al., 2013	Lambrolizumab	135	38
Brahmer et al., 2012	Anti-PD-L1 antibody	55	17

Chemo = chemotherapy; ipilimumab = anti-CTLA-4 antibody; lambrolizumab, nivolumab = anti-PD-1 antibodies.

type BRAF.⁴⁸ Therefore, targeted antibodies have been developed to inhibit the proliferation of BRAF V600E mutation-positive melanoma cells. Two of these antibodies, vemurafenib and dabrafenib, are FDA approved for the treatment of Stage IV metastatic melanoma.⁹ Vemurafenib obstructs the adenosine 5'-triphosphate-binding site of the active form of the BRAF kinase.^{8,87} Therefore, its effects are restricted to melanoma cells with BRAF V600E mutations that promote constitutive BRAF activation. At this time, BRAF inhibitors are the primary example of personalized medicine in melanoma immunotherapy; cytokine-based and checkpoint blockade-based therapy do not involve consideration of a patient's genetic profile. In later sections we outline a clinical multidisciplinary treatment approach to metastatic melanoma, which includes these immunotherapeutic advances.

Cytokine-Based Therapy

Cytokine-based therapy proves to be advantageous because it stimulates a potent immune response with a cytotoxic effect specific to metastatic cells.

High-Dose IL-2 and Interferon

Interleukin-2 is a cytokine that functions as a growth factor for T cells and natural killer (NK) cells. Administration of IL-2 can activate the Ras/MAPK and Jak/STAT pathways, both of which promote cytotoxic lymphocyte proliferation and differentiation.⁵⁴ When given to melanoma patients with good performance status, IL-2 therapy elicited a response in 16% of patients, with 6% achieving a complete response.³

Interferons (IFNs) can be divided into 3 primary subtypes: IFN- α , IFN- β , and IFN- γ . Therapy with IFN- β is becoming an integral part of hepatitis B and multiple sclerosis therapy,^{12,62,80} and IFN- γ , an immune effector involved in Th1 response, has been shown to induce major histocompatibility complex (MHC) expression in malignant melanoma cells.⁶⁶ However, IFN- α , a cytokine that is produced in response to viral infection, is the primary focus of the majority of melanoma clinical trials.^{15,54} In addition to promoting apoptosis and inhibiting the growth of melanoma cells,^{4,15,35,76} IFN- α stimulates the development of cytotoxic NK cells and CD8+ T cells.⁷ Treatment of metastatic melanoma with IFN- α alone resulted in a 15% response rate, which is comparable to data from IL-2

studies. The response rate grew to 60% when IFN- α was administered in combination with chemotherapy.⁴⁵ As in IL-2, the potential for neurotoxicity may limit its use in metastatic melanomas with CNS involvement.³⁹

Traditionally, administration of IL-2 has been discouraged for CNS metastases, due to heightened risk of increased intracranial pressure and neurotoxicity.^{51,64} The concern for neurotoxicity also applies for IFN treatment.³⁹ However, recent studies of melanoma brain metastases suggest that these risks are not absolute.^{16,34,64} Additionally, these precautions prove less restrictive when treating extramedullary spinal metastases. Because these lesions impinge on but do not directly involve the spine, CNS penetration is a less relevant concern.

Adoptive Cell Transfer

The unique mechanism of adoptive cell transfer warrants special distinction from the previously mentioned forms of cytokine-based therapy. Adoptive cell transfer involves identification, *ex vivo* amplification, and readministration of tumor-infiltrating lymphocytes (TILs) to precipitate a robust cytokine response specific to metastatic melanoma.⁶¹ The readministration of TILs necessitates lymphodepletion through chemotherapy or whole-body radiation therapy.^{23,61,71} Administration of TILs in combination with IL-2 resulted in an overall response rate

of 34%–40% and increased progression-free survival in patients with metastatic melanoma.^{36,71,90} These rates were similar in patients who were IL-2 naïve and in patients who had not responded to isolated IL-2 administration during previous therapy.⁷¹ Although this therapy showed some success, checkpoint blockade–based therapy and other targeted agents have demonstrated preferable tumor control and toxicity profiles.

Checkpoint Blockade–Based Therapy

Checkpoint blockade–based therapy targets pathways that promote self-tolerance and dampen immune response to prevent excessive inflammatory damage in surrounding tissue.⁵⁸ Figure 1 depicts the fundamental steps in T cell–mediated immune response and illustrates the mechanisms of prominent checkpoint-based therapeutic mechanisms.

Cytotoxic T-Lymphocyte Antigen–4 Blockade With Ipilimumab

Efficient T-cell activation occurs in a 2-signal system. Signal 1 is the recognition of a foreign antigen presented in the frame of MHC-I by the T-cell receptor. Signal 2, a costimulatory signal, involves the B7 ligand on the antigen-presenting cell binding to CD28, a costimulatory receptor expressed by naïve T cells. Cytotoxic T-lympho-

FIG. 1. Checkpoint blockade–based immunotherapy. The T-cell proliferation, differentiation, and cytokine release require 2 separate signal mechanisms. The Signal 1 involves T-cell receptor–mediated recognition of tumor antigen presented by MHC-I, which is located on the tumor cell. A second, costimulatory signal (Signal 2) involves B7 ligand, located on the tumor cell, binding to CD28, a receptor on the T cell. Both of these signals stimulate a variety of intracellular signaling pathways, which lead to upregulated activity of regulator proteins such as NF- κ B, Bcl-2, and PI3K. These signals promote T-cell activation. However, other ligand-receptor binding pairs can inhibit these cascades and restrict T-cell activation. These inhibitory checkpoints include B7 binding to CTLA-4 and B7-H1 (PD-L1) binding to PD-1. Anti-CTLA-4 antibodies (ipilimumab) and anti-PD-1 antibodies facilitate T-cell activation by obstructing inhibitory checkpoint processes. Ab = antibody; TCR = T-cell receptor.

cyte antigen–4 (CTLA-4) interrupts this costimulatory signal and restricts T-cell activation.^{22,46,58,59,69,74,75} Ipilimumab, a monoclonal antibody that targets CTLA-4, interrupts this inhibitory checkpoint process and facilitates T-cell activation. In patients with unresectable Stage III or IV melanoma, administration of ipilimumab resulted in a 47.2% 1-year survival rate.⁵⁶ A long-term follow-up of 177 patients with metastatic melanoma treated with ipilimumab revealed an 88-month median duration of objective response, which suggests that complete remission is possible in some patients.⁶⁵ Additionally, Weber et al. demonstrated that ipilimumab is considered safe for patients with metastatic melanoma in whom there was CNS involvement.⁹¹

Programmed Death–1/Programmed Death–1 Ligand 1 Blockade

The programmed death–1 (PD-1) receptor is a T-cell receptor that negatively regulates immune response following interaction with certain ligands. Tumor ligands produced by melanoma cancer cells (programmed death–1 ligands 1 and 2 [PD-L1, PD-L2]) bind the PD-1 receptor and exploit this checkpoint. The PD-1/PD-L1 interaction inhibits T-cell proliferation, T-cell differentiation, and Th1-type cytokine release⁸⁸ while increasing tumor resistance to cytotoxic T-cell activity.⁵⁷ Therefore, disruption of the PD-1/PD-L1 interaction can promote cytokine production and enhance immune response.^{84,85} Nivolumab and lambrolizumab are 2 examples of monoclonal antibodies that target PD-1. Nivolumab is associated with a 43% 2-year survival rate in metastatic melanoma,⁸⁶ and lambrolizumab has demonstrated a response rate as high as 52%³¹ in patients with metastatic melanoma. Monoclonal antibodies that target PD-L1 have also shown promising efficacy, with stable disease rates as high as 27% in patients with metastatic melanoma.¹⁰

Open and Separation Surgery
En Bloc Resection

En bloc resection involves total excision of a tumor in 1 piece without violating the tumor margin and contaminating surrounding tissue.¹⁷ The goal of this therapy is to achieve wide negative margins in the setting of solitary or oligometastatic disease, but the procedure carries a risk of significant morbidity. Surgeons may determine whether a patient qualifies for en bloc resection by using the Tomita score. Lower Tomita scores indicate a better prognosis and correspond with treatment strategies that promote long-term local control, such as en bloc resection.⁸³ Additionally, clinicians may use the van der Linden score to determine a patient’s prognosis. Lower van der Linden scores suggest a poorer prognosis, which precludes the rigors of en bloc resection in favor of a more palliative approach.⁸⁹ Table 2 provides the methodology for calculating a patient’s Tomita and van der Linden scores. However, considering the aggressive profile of metastatic melanoma and the risks of spinal cord and nerve root injury associated with aggressive surgery, en bloc resection of metastatic spinal melanoma is becoming a less favored intervention.¹⁷

Separation Surgery

In contrast to more invasive measures, “separation surgery” does not require total resection of the metastasis or the vertebral body, but relies on SRS to provide local tumor control.⁵⁰ The goal of separation surgery is to decompress epidural tumor from a posterolateral approach to circumferentially decompress the spinal cord and reconstitute the thecal sac, followed by long posterior segmental fixation (e.g., with pedicle screws) to provide immediate stability.⁴³ Following surgery, patients undergo high-dose single-fraction or hypofractionated radiation to

TABLE 2. Tomita and van der Linden scoring systems for surgical treatment recommendations based on outcome prediction

Scores	Tomita	van der Linden
Score groupings		
0–3	Wide marginal excision for long-term control	3 mos MOS
4–5	Marginal or intralesional excision for local control	9 mos MOS
6–7	Palliative surgery for short-term palliation	18.7 mos MOS
8–10	Nonop supportive care	
Score determinants		
Primary tumor	1 = slow growth	3 = breast
	2 = moderate growth	2 = prostate
	4 = rapid growth	1 = lung
Visceral metastases		0 = other
	2 = treatable	1 = no
	4 = untreatable	0 = yes
Bone metastases (if present)	1 = solitary or isolated	
	2 = multiple	
KPS		2 = KPS 80–100
		1 = KPS 50–70
		0 = KPS 20–40

KPS = Karnofsky Performance Scale; MOS = median overall survival.

ablate the residual gross and microscopic tumor volume. The radiation treatments spare normal tissue tolerance to at-risk structures, such as the spinal cord, since the separation surgery establishes an adequate distance for dose fall-off between the tumor margin and the spinal cord.⁵⁰ Data show that spinal decompression surgery followed by cEBRT results in significantly better survival times and overall ambulation than cEBRT alone, with no significant difference in hospitalization time.⁶⁰ However, the radioresistance of melanoma to cEBRT results in high local recurrence rates when used as a postoperative adjuvant.⁴⁴

Laufer et al. demonstrated that local progression of spinal metastases was reduced in patients treated with separation surgery followed by high-dose single-fraction (24 Gy) or high-dose hypofractionated SRS (18–36 Gy in 3 fractions) compared with low-dose hypofractionated SRS (18–36 Gy in 5–6 fractions).^{43,44} All patients underwent separation surgery with the intent to establish sufficient distance between the residual tumor and the spinal cord, which facilitated the administration of radiosurgery.^{43,44} The 1-year recurrence rates were less than 10% in both high-dose cohorts. The responses are histology independent, indicating that even tumors that were radioresistant to cEBRT, such as melanoma, respond well to high-dose single-fraction or hypofractionated SRS.^{43,44} It is important to note that Laufer et al.'s study was not intended to assess the effects of separation surgery alone. Rather, it accents Patchell et al.'s observation that surgical decompression is beneficial for patients with paraspinous metastases.⁶⁰

Decision Making

The NOMS criteria assist in determining whether patients qualify for separation surgery. The NOMS criteria incorporate evaluations of a patient's neurological deficits (N), oncological features (O), mechanical spinal instability (M), and systemic disease progression (S) to clarify the ideal treatment plan.⁴⁴ Neurological and oncological assessments include evaluation of the degree of epidural spinal cord compression and of functional deficits such as radiculopathy, and determination of the tumor's radiosensitivity.⁴⁴ If a neurological assessment reveals that epidural spinal cord compression is high grade, and if systemic evaluation reveals that the patient can tolerate surgery, then separation surgery is recommended prior to radiosurgery.⁴⁴ For further clarification, Fig. 2 describes the management of a sample patient with metastatic melanoma who underwent separation surgery prior to SRS. Figure 3 provides an algorithm for a comprehensive multidisciplinary treatment approach.

Stereotactic Radiosurgery

The evolution of SRS underlies the utility of separation surgery and the decreasing reliance on aggressive resection. Stereotactic radiosurgery delivers single-fraction, high-dose radiation to a specific target.² From a biological perspective, the efficacy of SRS derives from its ability to simultaneously kill individual tumor cells and damage tumor vasculature, both of which contribute to the release of proinflammatory cytokines that perpetuate an intense antitumor immune response.⁷⁹ From a technical perspec-

FIG. 2. Neuroimages obtained in a patient with metastatic melanoma treated with separation surgery. A 68-year-old man presented with severe mechanical radiculopathy. He had no history of cancer. Preoperative MRI studies showed a destructive lesion at L-5 causing high-grade thecal sac compression (**A and B**). The patient underwent separation surgery with a posterolateral resection of the epidural disease and L3–S1 pedicle screw fixation (**C**). He underwent a CT myelogram for radiation simulation and received a 24-Gy single fraction (**D and E**). The patient had postoperative MRI studies showing patency of the spinal canal and maintained alignment (**F and G**).

tive, the capacity of SRS to precisely limit target volumes facilitates steeper fall-off dose gradients than those of conventional radiation therapy.³² This implies that tissue in the immediate vicinity of the target volume is less likely to suffer radiation-induced damage.

Stereotactic radiosurgery can be performed with a variety of systems that operate with the following fundamental components: imaging and planning systems, a source of ionizing radiation, and a localization and placement procedure.^{1,11} Historically, the Gamma Knife was used to deliver SRS, but the Gamma Knife cannot reach spinal targets beyond C-2. Linear accelerator (LINAC) systems have since been adopted to deliver spinal radiosurgery. The LINAC produces high-energy x-rays as the radiation source and has fewer positional restrictions to aid more refined target selection.¹¹ Most of today's systems do not

FIG. 3. Treatment algorithm for metastatic spinal melanoma based on the algorithms posited by Kaufman et al.⁴⁰ and Laufer et al.⁴⁴ This schematic incorporates elements of the NOMS criteria⁴⁴ with immunotherapeutic and molecular treatment schemes. Radiosurgery is necessary for treating extramedullary spinal melanoma metastases, because melanoma's radioresistant histology precludes cEBRT administration. If high-grade epidural spinal cord compression (ESCC) exists, decompressive separation surgery is required prior to radiosurgery. If patients present with mechanical instability, stabilization surgery is an independent surgical indication. Molecular typing of spinal melanoma metastases depends on whether the BRAF V600E mutation is present, because this influences the tumor's sensitivity to proteasome inhibitors and BRAF-kinase inhibitors, such as vemurafenib, dabrafenib, and trametinib.⁴⁰ In the absence of a BRAF V600E mutation, CTLA-4 inhibitors such as ipilimumab, are indicated. If melanoma cells are Kit mutation–positive, they are less responsive to ipilimumab and nonresponsive to BRAF inhibitors. These patients are referred to clinical trials for more suitable immunotherapeutic regimens. PS = prognosis.

require frame fixation and can adjust for patient movement.^{1,11} Compared with cEBRT, SRS is associated with superior pain relief, long-term control, and survival in patients with spinal metastases.^{14,72} However, SRS can result in complications such as radiation-induced myelopathy, vertebral compression fractures, esophageal toxicity, and radiculopathy.^{72,73}

Data for Treatment of Metastatic Spinal Melanoma With SRS

Although relatively few studies exist that specifically catalog the efficacy of SRS for treating metastatic spinal melanoma, the literature available reveals encouraging results. When malignant melanoma lesions were treated with CyberKnife radiosurgery (an image-guided and frameless LINAC system) and stereotactic body radiotherapy, local control was observed in 100% of patients with spinal lesions.³⁷ Of these patients, 50% demonstrated complete response to therapy and 50% demonstrated a stable disease state. A study of separation surgery and SRS reported 100% local control in a set of 9 patients with metastatic spinal melanoma.⁴³ Gerszten et al. also report 75% local

radiographic control and 96% long-term pain improvement following CyberKnife SRS in a group of patients with 38 metastatic spinal melanoma lesions.²⁷ Additionally, in a set of 9 patients with metastatic melanoma who were treated with the Elekta Synergy system (a frame-based LINAC system with 3D image guidance), 100% of patients with preoperative pain reported an improved or stable pain response at follow-up.³⁰ Eight patients (89%) demonstrated local control at last imaging follow-up. Two patients had undergone prior conventional radiation therapy, and 2 had undergone prior single-fraction radiosurgery. No patients suffered from radiation-induced acute dermatitis, dysphagia, myelopathy, or fracture at the treated vertebral body. Additionally, no patients required subsequent SRS, and only 1 patient required subsequent decompression surgery.

In another study of 80 patients with metastatic spinal melanoma and renal cell carcinoma, Thiagaragan et al. reported an overall radiographic and symptomatic control rate of 92% following SRS.⁸² The patients were treated upfront with radiation doses ranging from 18 Gy to 24 Gy, and melanoma lesions treated with 24 Gy demonstrated a 97% local control rate. Data regarding concurrent or prior immunotherapy and chemotherapy were not available for

this cohort, but considering the recent advances of targeted immunotherapy, it is possible that these modalities may have provided additional advantage. These results demonstrate the promise of SRS in the treatment of metastatic spinal melanoma. The aforementioned studies are outlined in Table 3.

Combination Therapy

The benefits of immunotherapy, separation surgery, and SRS discussed earlier suggest that patients with metastatic spinal melanoma would benefit from individualized treatment regimens that combine these strategies. A study of 77 patients who underwent radiosurgery for melanoma brain metastases revealed that using ipilimumab as a supportive treatment was associated with a 27.5% increase in 2-year survival.⁴¹ However, a study of IFN therapy following SRS demonstrated no improvement in the outcomes of 39 patients with uveal melanoma.⁶⁸ Finkelstein et al. revealed that 3-year overall survival and disease-free survival in patients with Stage III cutaneous melanoma were 48% and 43%, respectively, following treatment with IFN and hypofractionated radiation therapy.²⁵ No cases of acute Grade III myositis and only 9 cases of Grade III radiation dermatitis were reported in this study, contrasting with previous evidence of excessive toxicity associated with combination IFN and hypofractionated radiation.^{18,33,53} Additionally, a Phase I trial of IL-2 and stereotactic ablative body radiation therapy demonstrated an overall response rate of 62.5% in 7 patients with metastatic spinal melanoma.⁷⁷

One of the benefits of combining ionizing radiation and immunotherapy is the induction of metastatic tumor regression at sites distant from the original radiation therapy location, a finding known as the abscopal effect.⁶³ This effect was shown in a case report⁶³ as well as in murine models,^{19–21} and it may be associated with hypofractionated rather than single-fraction radiation therapy.²¹ Additionally, elevated concentrations of activated CD4 T cells and reduced concentrations of suppressor cells were observed after the administration of ipilimumab and radiation therapy, which suggests that radiation therapy may have enhanced the expansion of the patient's activated T-cell population and contributed to the systemic metastasis regression.⁶³

TABLE 3. Studies of stereotactic radiosurgery for metastatic spinal melanoma

Authors & Year	No. of Patients	Separation Surgery	% Local Control	% Pain Relief
Jahanshahi et al., 2012	NR	No	100	NR
Laufer et al., 2013 ⁴³	9	Yes	100	NR
Gerszten et al., 2007	38	No	75	96
Guckenberger et al., 2014	9	No	89	100*
Thiagaragan et al., 2010	NR	No	97†	NR

NR = not reported.

* This applies only to 7 patients. The other 2 patients did not exhibit preoperative pain.

† Applies only to patients treated with high-dose (24 Gy) stereotactic radiosurgery. The local control for all patients with metastatic melanoma was not reported.

Future Directions

Focused ultrasound uses high-intensity sound waves to destroy tumors with high temperatures.⁹³ Following thermal ablation, the patient gradually reabsorbs the remaining tumor debris. Additionally, data show that focused ultrasound may function through immunomodulation to strengthen immune response to the remaining tumor cells via upregulation of Th1-type cytokine production and normalization of the CD4/CD8 T-cell ratio.^{24,52,70,93}

The burgeoning success and popularity of immunotherapy and radiosurgery signify promising treatment options for patients with metastatic spinal melanoma. Additional research is necessary to determine the utility of combining SRS and immunotherapy to treat metastatic spinal melanoma. However, recent data suggest that cytokine-based therapies such as IFN and IL-2, or checkpoint blockade-based therapies such as ipilimumab, represent promising complements to separation surgery and SRS. Strategic use of combination therapy should improve local control and survival while lessening the risk of neurotoxicity and alleviating the need for onerous and costly total resections.

Conclusions

Metastatic melanoma to the spine is a significant challenge for clinicians. Immunotherapy coupled with separation surgery and SRS appears to offer a favorable outcome for many patients. However, further clinical studies are required to optimize the treatment approach for individual patients.

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