



Michele R. Sassi. *Faces of Rajasthan, India*, #3. Photograph, 2007.

*Treatment options for metastatic melanoma are often limited, but select patients with isolated, resectable metastatic disease may benefit from surgery alone or a multidisciplinary approach.*

## Treatment Options for Limited or Symptomatic Metastatic Melanoma

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**Background:** Patients who develop metastatic melanoma often have limited effective treatment options. However, a select group of patients will benefit from aggressive surgery or a multidisciplinary approach, depending on the site of metastasis.

**Methods:** The current literature was reviewed and summarized regarding the collective recommendations for staging and treating patients with metastatic melanoma.

**Results:** A thorough preoperative staging includes positron-emission tomography, MRI of the brain, and CT of the chest, abdomen, and pelvis. Tumor biology ultimately determines the success of intervention. A long disease-free interval is a good indicator of potential benefit from resection of metastatic disease. If surgery is performed, no less than a complete resection will affect the overall survival of the patient. Surgery and other multimodality treatment options can be used for symptomatic palliation but will not affect survival. Chemotherapy and radiation are often used to control the symptoms of brain and bony metastases but have limited if any impact on survival.

**Conclusions:** A select group of patients with metastatic melanoma will benefit from aggressive surgery. Identifying which patients will benefit from treatment requires good clinical judgment and a thorough radiologic evaluation to identify the true extent of disease.

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### Introduction

Metastatic melanoma is a highly lethal malignancy with few good treatment options. Metastatic melanoma can present with a wide variety of symptoms and in almost any organ system in the body; however, most patients will have disease that is too extensive to resect or is unresectable by virtue of its location. Even potentially resectable regional disease (eg, in-transit disease) or isolated, distant metastases often harbor microscopic disease that precludes long-term disease control by surgery. Nonetheless, numerous retrospective studies

and some prospective trials have demonstrated improved survival rates in metastatic melanoma patients undergoing complete surgical resection.<sup>1-7</sup>

Advances in imaging technologies as well as improvements in surgical techniques and perioperative care raise the prospect that patients with truly isolated metastatic disease can be identified and safely subjected to surgery. A surgical approach requires an understanding of the disease process, adequate imaging, and careful patient selection.

Often the perspective of the treating physician influences the ultimate treatment choice. If there is an underlying assumption of a uniformly poor outcome in the absence of a surgical intervention, then a surgical approach may be chosen that might not actually alter the disease outcome. Alternatively, an overly pessimistic view of the likelihood of a beneficial outcome after resection may lead to pursuing untested adjunctive therapies, with any good outcomes subsequently used as justification to avoid surgery in the future. The literature includes multiple retrospective studies, analyses of prospectively acquired databases, and case reports supporting the potential value of resecting metastatic melanoma in properly selected cases.<sup>1,3,4,8-12</sup> However, there is a distinct lack of clinical trials that specifically evaluate patients with a clinically and radiographically resectable lesion randomized to resection vs nonoperative therapies. Nonetheless, it appears that carefully selected patients with isolated, resectable metastatic disease may derive long-term benefit from a complete resection of all identifiable tumor sites, even in the absence of any additional nonsurgical therapy. This subject has been extensively reviewed in several recent publications,<sup>4,7,13</sup> and several principles have emerged as guidelines in the evaluation of patients with potentially resectable metastatic melanoma.

## Preoperative Imaging

The first guiding principle is the need for adequate preoperative imaging. Advances in imaging provide the opportunity to exclude patients who are unlikely to be rendered disease-free by surgery. Most patients who are being considered for complete resection of metastatic melanoma should undergo a preoperative evaluation that includes a whole-body PET/CT scan and an MRI of the brain, as well as appropriate studies aimed at delineating the local extent of lesions to be resected.<sup>14,15</sup> Determining the appropriate radiologic evaluation is controversial due to a lack of reliable prospective studies. Routine preoperative imaging in stage I, II, and IIIA melanoma patients is likely to be unproductive because of an unacceptably high rate of false positive findings.<sup>16-21</sup> For patients with stage IIIB/C and IV melanoma, the rate of identification of clinically occult metastases is high enough to justify the risk of encountering false positive findings. Prospective data are surprisingly limited, but

the available evidence supports the routine use of a brain MRI as well as chest, abdominal, and (when appropriate) pelvic CT and whole-body PET scanning in the preoperative evaluation of stage IIIB/C and IV melanoma patients.<sup>14,22</sup>

The presence of brain metastases, while not an absolute contraindication to surgery, generally leads to a decision not to operate on a patient with non-CNS metastases until and unless the CNS disease can also be controlled. Hence, routine preoperative evaluation of the CNS is justified.<sup>15</sup> Gadolinium-enhanced MRI is the most sensitive test for detecting brain metastases from melanoma and should be routinely employed. CT is an alternative in patients with a contraindication to MRI. PET scans can be used for the brain, but standard <sup>18</sup>F-fluorodeoxyglucose (<sup>18</sup>F-FDG) PET is an insensitive test for identifying brain metastases due to the brain's high baseline glucose utilization. For the remainder of the body, the <sup>18</sup>F-FDG PET scan has emerged as a useful and sensitive study to identify unsuspected metastatic lesions. Glucose is readily concentrated in melanoma, but the PET scan does have limitations. As with all imaging studies, the sensitivity of PET scans for detecting tumors less than 1 cm in size diminishes. Because PET is a purely functional study, anatomic localization can be problematic. To improve the anatomic localization, PET is often combined with a CT scan to produce a study referred to as a PET/CT fusion. However, hypermetabolic areas on PET with no corresponding CT abnormality are commonly encountered and can be difficult, if not impossible, to categorize as true or false positive findings. The development of handheld probes capable of detecting <sup>18</sup>F-FDG intraoperatively may help overcome this problem in the future.<sup>23</sup>

Several prospective trials have evaluated PET in the preoperative setting. Brady et al<sup>14</sup> evaluated the role of preoperative imaging in 103 patients with stage IIC, III, and IV melanoma. They concluded that PET is better than CT in identifying distant disease, but the combination of the two studies is more accurate than each individually. The imaging findings of additional disease affected surgical decision making in their series, but false positive and indeterminate findings were common. In 36 of 103 patients, findings on imaging resulted in management changes. Of these 36 patients, 34 had a change in their management by findings exclusively seen on either PET or both PET and CT, whereas only 2 had a change in management based on CT findings in the absence of a PET abnormality. Ultimately, 19 of the 36 patients had their planned surgery canceled because of the extent of disease discovered by the imaging studies. False positive findings, however, were not uncommon. Among the 59 patients undergoing both CT and PET, 5 had false positive findings and 10 had false negative results. False negative results were defined as having a normal

PET and developing a metastasis within the following 4 months after surgery.

Fuster et al<sup>22</sup> retrospectively evaluated the role of PET scans as a surveillance tool in patients with known metastatic melanoma compared to standard screening techniques including physical examination, CT scans, MRI, ultrasound, liver function blood tests, and plain x-rays. They concluded that PET scanning alone was more accurate overall than all other standard screening techniques combined. The false negative rate for lung lesions was 12 of 89 with an overall sensitivity rate of 57%.

In the workup for in-transit disease, the presence of concomitant lymph node metastasis affects the surgical approach. Therefore, preoperative evaluation of the lymph node basin is an important consideration. While both PET and CT can identify nodal metastases, particularly those larger than a centimeter, ultrasound of the nodal basin has emerged as a more sensitive test that can also be used to provide localization if a needle biopsy is required.<sup>24,25</sup>

A chest x-ray is often used in the preoperative evaluation in stage III and IV patients. CT has a much higher sensitivity for small pulmonary metastases, including metastases below the threshold for detection by PET, but also identifies a large number of tiny and indeterminate lesions.<sup>21,22</sup> Blood tests are notoriously insensitive and nonspecific in metastatic melanoma patients, and no highly accurate melanoma-specific serologic markers exist. Mild elevations of serum lactate dehydrogenase (LDH) are nonspecific, but marked elevations usually indicate widespread disease.<sup>21,26</sup>

In summary, during the preparation to operate on patients with in-transit metastases or stage IV disease, PET combined with CT imaging can identify clinically significant disease that will likely change the management algorithm in a substantial number of patients, justifying the risk of encountering false positive findings.

## Tumor Biology

The second guiding principle encompasses the individual behavior of the tumor. A long disease-free interval from primary diagnosis to the diagnosis of metastases, fewer metastatic lesions, and a limited number of organ systems involved by disease all help to identify patients who are more likely to have prolonged survival after surgical intervention as well as after systemic therapies.<sup>1-4</sup> In patients with a short disease-free interval, the concern for a more aggressive tumor may necessitate a trial of systemic therapy or a delayed surgical plan to identify patients with diffuse but yet undetected disease. More than any other factor, the inherent biology of the melanoma will determine the ultimate outcome. Long-term survival after an intervention may be as much a reflection of the natural history of the disease as a result of the intervention itself.<sup>2,11</sup> Reported survival rates for patients with metastatic melanoma vary widely, and it

has long been recognized that patients selected for more aggressive treatments tend to be those who would have lived longer even in the absence of therapy. Eventually, technologies that include high-throughput techniques for gene expression analysis may be used to reliably identify patients who will benefit from surgical intervention as well as those who will not. Currently, clinical predictors must be used in the selection of patients with metastatic melanoma for surgery.

## Complete Resection

The third guiding principle insists on a complete resection (R0) of all identifiable disease in patients with metastatic melanoma, as it is only after complete resection that patients have a significant chance for prolonged disease-free survival. Patients with isolated resectable metastatic melanoma in the absence of a known primary site are also appropriate candidates for an aggressive surgical approach.

When treating in-transit disease, surgery should be attempted first, if anatomically possible, with the goal of a complete resection. Attention should also be directed to the lymph node basin as survival is worse if lymph node metastasis is present.<sup>26-29</sup> Surgical approaches to in-transit disease are based on the feasibility of resection as well as minimizing morbidity. Patients with relatively few lesions can be treated with resection along with lymph node dissection if nodal basins are found to be positive. A skin graft may be needed for closure, and consideration should be given to radiating the region of in-transit disease to minimize the local recurrence.<sup>30,31</sup> A histologically negative margin is a sufficient goal when resecting in-transit metastases; unlike resection for a primary tumor, no predetermined margin of normal tissue is established.

After an initial resection of in-transit metastases, further recurrence in the same extremity is commonplace. Dong et al<sup>32</sup> reviewed 648 patients with recurrent melanoma in a locoregional distribution. Fifty-five of those surgically treated experienced a second relapse within 2 years, and by 5 years, 82% had a local recurrence. When recurrence is limited to 1 or a few nodules, repeat resection is an appropriate approach. Frequent recurrences after surgery, radiation, and systemic therapy or presenting with a larger numbers of lesions may require an alternative approach. Local therapies such as intralesional therapy or laser therapy<sup>33,34</sup> have been used but have not had the same local control success as isolated limb infusion (IL) or isolated limb perfusion (ILP).

Any isolated metastasis to the lung should first be considered for resection. The lungs are the most common visceral site of metastasis in melanoma. Anywhere from 12% to 36% of patients with metastatic melanoma will develop 1 or more pulmonary metastases. If a metastatic lesion is truly isolated to the lung, pulmonary resection is an acceptable treatment. The 2001 staging

system by the American Joint Committee on Cancer (AJCC) subdivides the metastatic lesions into three distinct categories.<sup>26</sup> Lung metastases are given a separate category of M1b since the 1-year survival rate is 57% compared with 40.6% for metastases to other visceral organs (M1c). However, by 2 years, the survival rates are similar: 23.1% and 23.6% for lung metastases and other visceral organ metastases, respectively. Despite these 2-year findings, several studies have reported a median survival between 10 to 28 months and a 5-year survival rate of 6% to 27% with pulmonary resection.<sup>10,35-39</sup> Even in the presence of multiple nodules, some patients will benefit from resection as long as a complete resection can be performed. The advent of video-assisted thoracotomy has increased the interest in resecting metastases of all types, including melanoma, although precisely how much advantage this approach provides is a matter of debate. Wedge resections are the appropriate procedure for most melanoma metastases; lobectomies should be rare and a pneumonectomy is almost never indicated.<sup>39</sup>

The abdomen is also a common site of metastasis in melanoma, but only splenic, adrenal, and gastrointestinal (GI) metastases are commonly approached surgically. Of all patients with melanoma, 1.5% to 4.4% will develop symptomatic metastasis to the GI tract. Typical symptoms, when present, include pain, GI bleeding, anemia, obstruction, weight loss, and a palpable mass. In the evaluation of metastases to abdominal organs, surgery should be considered if all disease can be removed. The ability to resect all disease has consistently proven to be the most important factor in prolonging survival. Ollila et al<sup>4</sup> reviewed 124 patients evaluated for melanoma metastatic to the GI tract. Of the 69 patients who underwent resection, 46 were treated for cure and had a 48.9-month median survival, while 23 patients were treated for palliation of symptoms and had a 5.4-month median survival. The remaining 55 patients were treated nonoperatively and had an overall survival of 5.7 months.

Patients with metastases to the GI tract may present with bleeding or obstruction that often requires a surgical intervention for palliation. However, many times the focus of bleeding is difficult to identify on exploration and the patients have multiple intestinal lesions, which even if not currently symptomatic will soon cause symptoms. Palliation may require resection of multiple loops of bowel or an intestinal bypass to achieve symptomatic relief. Several studies, including the above-mentioned Ollila study, have demonstrated that palliative surgery does not prolong survival, and in some studies survival is worse than with a nonoperative approach.<sup>6,40,41</sup> However, symptomatic relief can be achieved in carefully selected patients when treated by an experienced surgical team.

Occasionally, metastases to the adrenal gland may be the only site of disease. Several studies have demonstrated that resection can lead to prolonged survival

when no other site of disease is encountered.<sup>6,42-44</sup> If technically feasible, a laparoscopic adrenalectomy can be performed as long as a negative margin can be achieved. Laparoscopy has the advantage of evaluating the abdomen for intra-abdominal metastases that can be missed on preoperative imaging. Many times the adrenal metastases are locally invasive or incite an inflammatory response that necessitates an open approach to safely achieve negative margins. Bilateral adrenal metastases do occur and can be resected laparoscopically. Adrenal preservation may be considered, but long-term corticosteroid replacement is preferred to leaving a positive margin. Haigh et al<sup>6</sup> demonstrated that survival was significantly longer when adrenal metastases were treated for cure rather than for palliation. The median survival was 25.7 months for the curative group, 9.9 months for the palliative group, and 7.7 months for those patients treated nonoperatively. Metastases to the spleen should also be considered for resection if no other evidence of disease is identified. Laparoscopic and open procedures have been described; either approach is satisfactory if complete tumor excision can be accomplished.<sup>41</sup>

Metastases to the liver often present with multiple lesion or in unresectable locations. Patients with hepatic metastases rarely, if ever, achieve long-term disease-free status after liver resection and are considered poor candidates for a resection approach.<sup>13,45</sup> However, in select patients who have resectable disease, surgery may be considered. Intraoperative ultrasound is useful in identifying additional lesions not seen preoperatively. Surgical resection can be performed with an anatomic or nonanatomic approach and may require the addition of radiofrequency ablation to achieve negative margins. Ablative techniques can be used as a sole treatment method as well. Overall, the outcomes tend to be poor. Pawlik et al<sup>45</sup> demonstrated a median survival of 23.6 months in 24 patients with cutaneous melanoma metastatic to the liver, with no patient surviving longer than 45 months. It remains unclear why the outcomes for resection of apparently isolated liver metastases are worse than for other isolated visceral melanoma metastases, but at present liver resection should be employed for the treatment of metastatic melanoma only in highly selected cases, if at all, and only after a thorough search for other intra- and extrahepatic disease.

## Palliative Surgery

Palliative surgery also has an important role in the management of symptomatic patients with distant melanoma or disease that has spread beyond the regional nodes or recurred "in transit" between the primary and the regional nodal basin. Careful consideration is required before any surgical intervention is undertaken for metastatic melanoma. A presumed dismal outcome in the absence of surgical intervention or the lack of good treatment

alternatives does not justify the use of a heroic surgery in the absence of a well-thought-out treatment plan and an adequate understanding of the disease process.

Surgery for palliation is rarely effective in melanoma, but some exceptions are recognized as described below. Surgical palliation is a realistic goal for appropriately selected patients with symptomatic GI metastases, particularly when bleeding or intestinal obstruction occurs, provided only a few lesions are present.<sup>4,46</sup> Pulmonary metastases are rarely symptomatic, and when they cause dyspnea at rest, any palliative surgical effort comes too late. Symptomatic pleural effusions and ascites from melanoma metastases are also associated with a grave prognosis and are almost always best managed nonsurgically. When hemoptysis is caused by an endoluminal pulmonary metastasis, surgical palliation can be effectively achieved when other measures (such as endoscopic treatment) have failed.

Wornom et al<sup>47</sup> reported on 65 patients treated surgically for melanoma metastases and evaluated the nature of preoperative symptoms, if any, and the degree to which they were relieved by surgery. Of 17 patients undergoing resection of lung metastases, 2 were symptomatic (persistent cough), and both had resolution of their cough after surgery. Symptoms of intra-abdominal metastases were relieved by surgery in 100% of the patients. The abdominal surgeries were most commonly performed for small bowel obstruction or anemia. All patients developed progression of disease in other organs during follow-up. Among 17 patients with symptomatic brain metastases, 14 had complete relief of symptoms and 2 had partial relief, but 2 patients died of surgical complications. Among the survivors, more than two-thirds developed recurrent disease in the brain, and more than half developed non-CNS metastases. Patients with soft-tissue disease presented with symptoms of pain, itching, burning, or bleeding. Most palliative soft-tissue resections resulted in relief of symptoms (44 of 50 patients, 88%), but 92% subsequently developed disease in other organs.

Ollila et al<sup>4</sup> reported on 124 patients with metastases to the GI tract. Of the 69 patients who were operated on with either curative or palliative intent, 23 were treated for palliation. Symptoms requiring operation included crampy abdominal pain, anemia and/or acute GI bleeding, and high-grade obstruction. Overall, presenting symptoms were relieved by operative intervention in 67 of the 69 patients, indicating the palliative value of surgical resection in selected patients. Median survival was the same for patients treated nonoperatively compared with patients treated by palliative resection (5.7 months and 5.4 months, respectively), but it was noticeably better for those treated by complete resection (48.9 months). No patients survived beyond 25 months in the palliative or nonoperative group, whereas the 5-year survival rate in the complete resection group was 41%.

Haigh et al<sup>6</sup> evaluated 27 patients who underwent surgery for melanoma metastases to the adrenal gland. Of these, 9 underwent successful surgery solely for palliation of symptoms, such as adrenal hemorrhage and intractable pain. Again, no survival advantage was seen compared with nonoperative treatment. The median survival was 9.2 months, with 8 of the 9 patients developing additional metastases during follow-up.

Unresectable regional metastases can also cause significant symptoms, particularly from bleeding and ulceration. Isolated limb perfusion is a useful tool for loco-regional control in patients symptomatic from extremity disease.<sup>48,49</sup> Reported response rates are as high as 90%.<sup>50</sup> The duration of responses, however, may be shorter than previously appreciated.<sup>51</sup> Takkenberg et al<sup>52</sup> followed 8 patients treated with isolated limb perfusion for palliation of symptomatic limb disease. One patient had no response, 1 had a complete response, and 6 had partial tumor response. Six of the 8 patients experienced successful palliation of symptoms. A study performed by Fraker et al<sup>53</sup> followed 15 patients treated with isolated limb perfusion for palliation of symptoms. Nine of 11 patients with painful lesions had symptom resolution, whereas 6 of 6 patients with edema had symptom resolution. Bleeding was eliminated in 5 of 6 patients. Careful patient selection is required as the morbidity of the intervention is significant. Recently, a more minimally invasive technique of isolated limb infusion has gained popularity for treating patients with in-transit disease.<sup>54-56</sup> Catheters are placed percutaneously and the therapy is infused once an extremity tourniquet is applied. Clinical results have been similar to those with isolated limb perfusion.<sup>49</sup> The regional toxicity of isolated limb infusion is similar to isolated limb perfusion with respect to immediate skin and soft-tissue injury. However, the risk of deep vein thromboses, amputations, and compartment syndrome is greater with isolated limb perfusion than with isolated limb infusion.<sup>57,58</sup> Both procedures can be repeated; however, the severity of postprocedure side effects can be worse with subsequent applications.

Local therapies for in-transit disease have also been advocated. Intralesional interleukin 2 (IL-2) has been demonstrated to be effective in inducing a durable, local response in some patients.<sup>59,60</sup> Overall survival benefits have yet to be published. However, IL-2 is a potential treatment option for nonsurgical candidates.

Electroporation is another local therapy that can be used in patients with unresectable in-transit disease.<sup>61</sup> A local electrical impulse is applied to the tumor site in combination with local or systemic application of a chemotherapeutic agent. The electric impulse increases permeability of the cell membrane and induces vasoconstriction, allowing for increased exposure of the tumor to the chemotherapeutic agent. The chemotherapeutic agents shown to have the highest efficacy with electroporation are bleomycin and cisplatin.<sup>62-65</sup>

In addition to the above-mentioned local therapies, palliative surgery offers an alternative therapeutic approach for isolated or limited symptomatic cutaneous lesions, with relatively low morbidity and the promise of rapid resolution of symptoms. Although the duration of symptomatic relief is generally short, repeated resections are often practical.

The available data support the judicious use of palliative surgery for carefully selected patients with symptomatic melanoma metastases, but the actual magnitude of benefit patients derive is difficult to ascertain. Objective reports of outcome results for palliative surgery are notoriously difficult to find in the literature, especially for melanoma patients. The Palliative Surgery Outcome Score (PSOS) was devised to assess the impact and success rate of treatment in this setting.<sup>66</sup> The determination of success is based on the ratio of the number of symptom-free, nonhospitalized days compared with the number of days in the hospital. If 70% of the days are symptom-free, the palliative intervention is considered successful. Other useful measures include the Functional Assessment of Cancer Therapy (FACT) and the European Organization for Research and Treatment of Cancer (EORTC) questionnaires. Future studies of palliative surgery in melanoma patients should make use of these objective tools, which facilitate comparisons with other studies and with non-surgical modalities. Patient selection criteria should be defined as clearly as possible. Given the major limitations and inconsistent success rates of palliative surgery in melanoma, the decision to surgically intervene requires clear and realistic communication with the patient on therapy goals and potential outcomes.

### Adjunctive Therapy

The role of chemotherapy or immunotherapy after resection remains controversial. No adjuvant therapy has been proven to be useful after resection of metastatic melanoma beyond the regional nodes. While nonrandomized studies using historical controls have often suggested a possible benefit,<sup>47,67,68</sup> to date no prospective randomized trial data exist to document such benefit. Indeed, the intervention with the strongest nonrandomized data to support its use after resection of stage IV melanoma, the oncolytic virus (Canvaxin) allogeneic melanoma vaccine showed no benefit compared with placebo in a recently conducted randomized trial.<sup>69</sup> High-dose interferon alpha (IFN- $\alpha$ ) is the only adjuvant therapy approved by the US Food & Drug Administration (FDA) for "high-risk" melanoma patients, but it has never been prospectively tested in patients after resection of stage IV melanoma. Moreover, many patients who develop resectable stage IV melanoma have already received adjuvant IFN- $\alpha$  for stage IIB/C or stage III melanoma. Nonetheless, patients with resected stage IV melanoma who have not had adjuvant IFN- $\alpha$  previously may be considered for high-dose IFN- $\alpha$  therapy, and consideration

should be made to treat these patients within the auspices of a clinical trial. Kirkwood et al<sup>70</sup> summarized the Eastern Cooperative Oncology Group (ECOG) data from the E1684, E1690, and E1694 trials for high-dose IFN- $\alpha$  in patients who were at high risk for recurrence. These patients were stage IIB/C or III and were treated with high-dose IFN- $\alpha$  after resection. The overall survival was not impacted by IFN- $\alpha$  therapy; however, the relapse-free interval was significantly prolonged. Whether the ECOG data are applicable to complete resection of distant metastatic melanoma is currently unknown as no prospective data have demonstrated a benefit for IFN- $\alpha$  after a resection of stage IV melanoma.

### Radiation Therapy for Brain Metastases

Symptomatic patients with metastatic melanoma who are not amenable to surgery are often referred for consideration of radiation. The two most common conditions requiring palliative treatments with radiation therapy are for brain metastases and bone metastases. Unfortunately, there are few randomized trials specific to melanoma to guide appropriate palliative therapy. Symptomatic melanoma patients are often allowed in trials that are evaluating metastases from multiple primary sites. Thorough reviews of randomized trials on bone metastases have been published by Kachnic and Berk<sup>71</sup> and Chow et al,<sup>72</sup> and a summary article of brain metastases is available from Richards et al.<sup>73</sup> The following section focuses on the available literature relevant to metastatic melanoma.

For patients with brain metastases, Carella et al<sup>74</sup> reported on 60 patients culled from two prior Radiation Therapy Oncology Group (RTOG) trials comparing fraction size with survival from brain metastases. The Karnofsky Performance Status, neurologic status, and specific neurologic symptoms were also followed. The patients were divided among 6 fraction schedules. Unfortunately, there were too few patients allotted in each arm to make the resulting comparisons meaningful. Nevertheless, improvements in symptoms were noted in 76% of these patients, with 31% having a complete resolution of their symptoms. Neurologic function, as measured using a nonvalidated, ad-hoc scale, improved in 27% of the patients (Hendrickson<sup>75</sup> provides a discussion of the limitations of this ad-hoc scale). The median survival of these patients was 10 weeks on the first trial and 14 weeks on the second trial. Approximately 60% of the patients died of the brain metastases.

Choi et al<sup>76</sup> presented the results of 59 melanoma patients from a larger study of 194 patients that used twice-a-day radiation therapy for brain metastases. These 59 patients with melanoma metastatic to the brain underwent either a complete resection of the brain metastases followed by radiation or were treated with radiation alone. Seven twice-a-day fractionation schemes were tested, with the dose increasing from 30 Gy in

twice-daily 3-Gy fractions to 48 Gy in twice-daily 2.4-Gy fractions. Seventy percent of the patients with unresected brain metastases had stable or improved symptoms. They found a significant improvement in survival among these same patients using 1-week regimens (30 Gy to 37.5 Gy) compared with 2-week regimens (37.5 Gy to 48 Gy), with median survivals of 285 days and 187 days, respectively, and 1-year survival rates of 45% and 17%. The best response was seen in patients with a complete resection of the brain metastases or in patients where the brain was the only site of disease.

Ziegler and Cooper<sup>77</sup> retrospectively reported on 72 patients, of whom 52 received 30 Gy in 10 fractions and 20 received 30 Gy in 5 or 6 fractions. They found no difference in response or survival. Overall, about 60% of patients had an improved functional status on a 5-point scale, and the median survival was 5 months. Morris et al<sup>78</sup> reported on the outcome of 112 patients treated with doses from 20 Gy in 5 fractions to 30 Gy in 10 fractions. The median survival was 51 days. Using the RTOG recursive partitioning analysis characteristics,<sup>79</sup> they found that class 1 patients had a median survival of 151 days, class 2 patients 71 days, and class 3 patient 21 days. Patients with no extracranial metastases had a median survival of 105 days compared with 39 days for patients with extracranial metastases. Furthermore, Buchsbaum et al<sup>80</sup> performed a similar analysis of 74 patients. The median survival of this group was 5.5 months. The class 1 patients survived 10.1 months (310 days), the class 2 patients survived 5.9 months (180 days), and the class 3 patients survived 1.8 months (55 days). In addition, Konstadoulakis et al<sup>81</sup> reported on 136 patients treated with multimodality therapy for brain metastases. The median survival was 1 month and the mean survival was 8 months.

Several groups have reported on the outcome of stereotactic radiosurgery (SRS) when used for brain metastases from melanoma. For example, Selek et al<sup>82</sup> reported on 103 patients with a total of 153 intracranial metastases treated with SRS. The 1-year local control rate was 49%, with local control rates of 75% and 42% for patients with a less than or greater than 2-cm tumor focus, respectively. The 1-year overall survival rate was 25%. They found that the Score Index for Radiosurgery (SIR), which ranks patients based on age, performance status, status of systemic disease, size of the largest brain lesion, and number of lesions, also predicted for survival. Furthermore, Gaudy-Marqueste et al<sup>83</sup> reported on 221 melanoma brain metastases treated in 106 patients, of whom 61% had a single lesion. The median survival from the time of treatment was 5 months, and the local control rate was 84%. This control rate consisted of 43% stable disease, 42% partial response, and 14% complete response. Again, the SIR predicted for survival. Samlowski et al<sup>84</sup> reported on 44 melanoma patients who underwent SRS treatment for 156 lesions.

Their median survival was 11 months, with 1-year and 2-year survival rates of 48% and 18%.

Chemotherapy has also been used concurrently with radiation therapy for the treatment of brain metastases from melanoma. Mornex et al<sup>85</sup> reported on a phase III trial of fotemustine vs fotemustine and radiation therapy for brain metastases from melanoma. Thirty-nine patients received fotemustine (100 mg/m<sup>2</sup> weekly for 3 weeks followed by a 5-week break) and 37 patients received concomitant whole-brain radiotherapy (37.5 Gy in 2.5-Gy fractions) and fotemustine. Patients in the first arm were allowed to receive salvage radiation therapy after day 50. The study was closed early after a futility analysis. The radiographic response rates of the metastases at day 50 were 7.4% on the fotemustine-only arm and 10.0% on the combined arm. The best responses (including those after day 50) were 30% and 47%, respectively. The median survivals were 86 days and 105 days, which were not significantly different. Margolin et al<sup>86</sup> reported on a phase II trial of temozolomide and whole-brain radiation therapy for melanoma brain metastases. Thirty-one patients received concurrent 75 mg/m<sup>2</sup> of temozolomide and 30 Gy in 10 fractions. Six weeks of 75 mg/m<sup>2</sup> of temozolomide was repeated every 10 weeks. There was 1 complete response lasting 4.5 months and 2 partial responses lasting 2 months and 7 months. The median survival was 6 months. A report from Boogerd et al<sup>87</sup> compared patients with brain metastases from melanoma on prospective studies of temozolomide (150 to 200 mg/m<sup>2</sup>) and no radiation therapy. The median survival of the patients was 5.6 months. There were 3 complete and 2 partial responses (9% response rate), and 6 had stabilization of the brain metastases (11%). These results are similar to the results of the Margolin study<sup>86</sup> of combined temozolomide and radiation therapy.

In summary, these reports suggest that whole-brain radiation therapy is moderately effective, at best, for the control of melanoma metastatic to the brain. The complete response rate is less than 20% and the partial response rate is about 50%. Patients with metastatic melanoma to the brain have a median survival of approximately 4 to 6 months. Adjunctive treatment may prolong survival but often for only a few additional months.<sup>88</sup> Chemotherapy has not significantly increased the local control rate. Stereotactic radiosurgery may increase the control rate in patients with limited disease. These select patients who might benefit from stereotactic radiosurgery can potentially be identified based on the SIR criteria.

## Radiation Therapy for Bone Metastases

The data for the treatment of bone metastases from melanoma are again sparse. Rate et al<sup>89</sup> reviewed 26 patients with 39 bone metastases. They reported an 85% response rate with no difference in response rates

between lower-dose (3 Gy or less) and higher-dose (4 Gy or more) fractionation. The definition of response, however, was not given in their report. They also looked at treatment of spinal cord compression and reported that among 17 patients, complete relief of neurologic symptoms was obtained in 8 patients and partial relief in 4 patients. Three of the 17 patients required palliation with a laminectomy.

Konefal et al<sup>90</sup> reported on 28 patients with bone metastases. Significant palliation, defined as considerable relief from symptoms for at least 2 months, was achieved in 19 of the 28 patients. The authors did not find an effect based on fraction size or total dose.

From these limited data, no conclusions can be reached about the effectiveness of radiation therapy for bone metastases from melanoma.

## Conclusions

In the treatment of limited metastatic melanoma, complete resection of disease is the best option for cure. However, the art of surgery relies on the ability to determine which patient will benefit from surgical intervention. In addition to a thorough history and physical examination, evaluation requires staging studies including a PET/CT scan, an MRI of the brain, and a lactate dehydrogenase (LDH) level. The literature for metastatic melanoma is limited in what can be proven with scientifically sound and reproducible data. However, it is evident that a select group of patients will have their disease process altered by an appropriate and aggressive surgical intervention. For those patients who have disease that cannot be completely resected and are symptomatic, palliative treatment options are available that include surgery, radiation, chemotherapy, and appropriate combination therapy. Multidisciplinary teams are often required in order to treat these patients adequately.

## Disclosures

*No significant relationship exists between the authors and the companies/organizations whose products or services may be referenced in this article.*

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