# Role of Surgery in Stage IV Melanoma

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**KEYWORDS**

• Melanoma • Cutaneous malignancy • Metastasectomy • Stage IV melanoma
• Metastatic melanoma

**KEY POINTS**

- Historically, stage IV melanoma carried a poor prognosis and surgery was the only potential for cure.
- New targeted therapies, systemic immune therapies, and oncolytic viruses have achieved durable responses in advanced melanoma.
- In the era of modern systemic therapy, metastasectomy can be associated with good long-term survival.
- With effective targeted and systemic therapy, response to treatment helps appropriately selected patients who would likely benefit from metastasectomy.

## INTRODUCTION

Melanoma remains the most fatal form of skin cancer and will account for more than 7000 estimated deaths in 2019.[1] Most melanomas are early stage and remain highly treatable, but up to 4% of patients present with stage IV disease and 20% of surgically treated patients will develop distant recurrences.[2,3] Historically, patients with stage IV disease have had poor overall survival, with an estimated 5-year survival rate of 6% and a median survival of less than 1 year.[4]

Metastasectomy historically has been associated with modest outcomes at best, owing to the inherent aggressive underlying biology and lack of effective systemic therapy.[5,6] The median disease-free interval (DFI) after metastasectomy for stage IV melanoma was 8 months in the era before effective systemic therapy.[6] Outcomes for resection of metastatic melanoma depended on the location and volume of the metastases. In very well-selected patients, metastasectomy was associated with a 5-year overall survival rate of 22% for patients with M1a disease consisting of subcutaneous metastases.[5] The 5-year survival rate after resection of lung metastasis was

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14% in the era before high-quality cross-sectional imaging.[5] The Southwest Oncology Group intergroup trial (S9430) of resection of stage IV melanoma for multiple sites of metastases reported a 4-year overall survival of 29%.[7] Recent data have shown improvements in outcome. The MMAIT-IV trial analysis compared adjuvant Bacillus Calmette-Guérin and Canvaxin to Bacillus Calmette-Guérin (+) placebo for metastatic patients who underwent complete resection of up to 5 metastatic lesions. No improvements in survival were seen with this adjuvant therapy; however, it was noted that placebo patients attained a 60.6-month median overall survival for M1a disease, a 37.6% 5-year overall survival after lung metastasectomy, and a 5-year overall survival of 43% among all groups after metastasectomy.[8] Certainly, the 5-year survival rate for highly selected patients can be improved with metastasectomy.[5,9,10]

Improvement in outcomes for operative resection of metastatic melanoma have been achieved not from improvements in surgery, but rather from improvements in systemic therapy. Before the widespread availability of effective immunotherapy, operative resection in highly selected patients with limited metastatic disease was probably more effective than the therapeutic agents in use at the time. Data from the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) showed metastasectomy was associated with improvement in 4-year survival to 21% versus 7% for systemic medical therapy alone.[3,11] Systemic medical therapy at that time largely consisted of dacarbazine or other cytotoxic chemotherapy drugs, either alone or in combination. Some patients with excellent performance status received high-dose IL-2 or biochemotherapy (regimens containing $\geq$1 cytotoxic agent along with IL-2 and interferon) with limited response rates and high toxicity. The treatment of metastatic melanoma, and the role of surgical resection, would evolve as the systemic therapies evolved. Currently, both BRAF/MEK inhibitors and immune checkpoint inhibitor therapies have improved survival and led to high response rates. Immunotherapy provides reasonable durable complete response rates, whereas BRAF/MEK inhibitors have very high response rates that are less durable.[12,13] Importantly, not all patients respond to therapy and not all responses are durable,[14] raising new questions regarding the appropriate role of surgery for stage IV disease.

- Metastasectomy can offer improvements in overall survival in highly selected patients.

## EVOLUTION OF THERAPY

Dacarbazine, an alkylating agent, was the principle cytotoxic systemic agent historically used for the treatment of melanoma. Response rates were at best 20% and the majority of responses were partial, with fewer than 5% complete responses.[15,16] Combination therapy, such as the multiagent Dartmouth regimen (dacarbazine, cisplatin, 1.3-bis[2-chloroethyl]-1-nitrosourea, and tamoxifen) did not show any improvement over dacarbazine alone.[17] To date, there is no convincing evidence that cytotoxic chemotherapy improves overall survival in melanoma.

Improvements in response rates were ultimately demonstrated with the transition to immune-modulating agents. High-dose IL-2, a proinflammatory cytokine that activates lymphocytes, had response rates similar to cytotoxic chemotherapy on the order of 15% to 20%, but strikingly 40% of responders demonstrated durable response beyond 5 years.[18] Other agents, including Interferon-$\alpha$2b and pegylated interferon- $\alpha$, were of more limited benefit.[19–22]

Immune checkpoint inhibitor therapy became the first modality to demonstrate promising improvements in overall survival. Ipilimumab, a cytotoxic T-lymphocyte-associated

antigen 4 inhibitor, improved median overall survival to 10.1 months in stage IV malignant melanoma.[23] Newer agents targeting the programmed death protein-1 molecule, such as nivolumab, demonstrated improved adverse event profiles compared with ipilimumab, with durable objective responses approaching 40% and the 12-month recurrence-free survival of 70.5% versus 60.8% with ipilimumab.[24–26] These response rates were further improved with combination cytotoxic T-lymphocyte-associated antigen-4 and programmed death-1 therapy; objective responses were 61% in combination nivolumab and ipilimumab therapy versus 11% with monotherapy ipilimumab.[12] This effect is not without a high incidence (54%) of grade 3 or 4 toxicity.

Targeted therapies to BRAF V600 mutant melanomas, which are present in at least 40% of cutaneous melanomas, have shown an overall response rate of 48% in patients with stage IV disease, whereas combination BRAF inhibition with a MEK inhibitor such as trametinib may improve the overall response rate to 68% to 87%.[27–30] Despite an excellent objective response, the duration of response is limited and the median progression free survival is 5.1 months for BRAF inhibitor monotherapy.[31]

Talimogene laherparepvec (T-VEC) is an oncolytic virus expressing granulocyte-macrophage colony-stimulating factor derived from type 1 herpes simplex virus.[32] This process leads to the release of tumor-specific antigens and expression of granulocyte-macrophage colony-stimulating factor, which has been shown to activate T cells for an antitumor response and induce dendritic cell maturation.[33] T-VEC has been modified to selectively replicate within tumor cells, leading to tumor cell lysis and immune cell recruitment.[34,35]

T-VEC oncolytic immunotherapy was first trialed in patients with unresectable stage IIIb or IV melanoma and provided a durable response rate of 16.3% (95% confidence interval, 12.1%–20.5%).[36] Several studies have evaluated T-VEC alone or in combination with systemic immunotherapy and have shown promising results with an overall response rate approaching 50% and an 18-month overall survival rate of 67%.[32,37,38] Oncolytic virotherapy with T-VEC provides an additional strategy for treatment of patients with advanced melanoma.

Before the advent of effective treatments for advanced melanoma, surgical resection was considered the standard-of-care treatment for resectable stage IV disease. However, the advent of modern melanoma therapy has ushered in a whole new set of questions regarding the most appropriate role of surgery for metastatic melanoma.

- Early systemic therapies were largely toxic with low response rates.
- BRAF/MEK inhibition has shown objective response rates in 68% to 87% of patients, and durable objective responses have been found with immunotherapy.
- These improvements alter the landscape for the role of surgery in metastatic melanoma.

## METASTASECTOMY

Metastasectomy, or operative resection of metastatic disease, may play an important role in the multidisciplinary, comprehensive treatment plan for patients with stage IV melanoma. Some, but not all, patients may benefit from surgery to render them disease free. In some cases, metastasectomy may result in durable recurrence-free survival. However, many factors must be considered when selecting patients for resection of metastatic melanoma. A true multidisciplinary discussion must be held to consider the timing of surgery in relation to systemic therapy and the goals of operative resection.

### *Prognostic Factors to Select Suitability for Resection*

An evaluation of the extent of metastatic disease is essential. Patients with a new diagnosis of metastatic melanoma, whether they present with metastatic disease at initial presentation or they develop metastatic disease as a recurrence, should be thoroughly investigated by high-resolution cross-sectional imaging of the chest, abdomen and pelvis either by computed tomography scan or PET/computed tomography scan and brain MRI.[39] High-quality imaging can detect early, otherwise clinically inapparent resectable metastatic disease and provide a baseline for evaluation of response to therapy. The full extent of disease is an important consideration for treatment planning purposes.

The ideal candidates for metastasectomy have a single site of metastasis and a long DFI before metastasis.[40,41] Overall survival is better for patients with a limited number of metastatic sites. In an early, preimmunotherapy study, patients who underwent metastasectomy for a single metastatic tumor had a 5-year survival rate of 29%, compared with a 5-year survival rate of 11% for those with 4 metastatic sites.[40] The DFI has been shown to predict survival. Patients who present with metastases within 1 year from the initial diagnosis have a worse outcome than those who present with a longer DFI.[42] Collectively, these prognostic factors are surrogates for tumor biology; patients with more indolent tumors and oligometastatic burden have favorable prognosis.

Response to systemic therapy is an important consideration when selecting patients for metastasectomy. The ability to assess the patient's response to therapy and to make sure that no additional metastatic disease develops on treatment is the rationale for starting with systemic therapy rather than a surgery first approach, even with oligometastatic disease. He and colleagues[43] performed metastasectomy for isolated residual foci of metastatic disease, isolated progressive disease in the setting of stable disease elsewhere, or for symptomatic disease in patients who were treated with vemurafenib within 30 days of surgery. Patients who had a longer duration of treatment had improved survival compared with those who underwent surgery in a more urgent fashion (hazard ratio, 2.93). Faries and colleagues[44] recently showed improved overall survival among patients who had an objective response or stable disease on systemic therapy before hepatic metastasectomy. As a general principle, with effective immunotherapy and targeted agent utilization, surgical resection for metastatic disease can be considered for stable or responding oligometastatic lesions or isolated progressive lesions with stable disease elsewhere when curative resection is feasible.

- A long DFI, isolated sites of progressive disease, and objective response to modern therapy are important considerations for metastasectomy.

### *Metastasectomy by M1 Classification*

The eighth edition of the American Joint Commission for Cancer guidelines contains 4 categories of M1 disease and is subclassified by serum lactate dehydrogenase levels[39](**Table 1**). M1a classification defines distant metastases to skin, soft tissue, or distant lymph nodes and represents 20% of all stage IV disease.[45] Data from the MSLT-1 showed that, among the 32 patients who underwent treatment of M1a metastases, patients with complete surgical resection had a median overall survival rate of 60 months compared with 12.4 months among those who underwent medical therapy alone.[11] Patients with nodal involvement, however, had worse outcomes compared with skin and soft tissue involvement.[5,46] Microscopically negative resection margins are acceptable for metastasectomy of M1a disease, as opposed to the gross 1- to

**Table 1**
**Four categories of M1 disease and is subclassified by serum lactate dehydrogenase levels**

| Classification | Site | Lactate Dehydrogenase Value |
|---|---|---|
| M1a | Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node | Not recorded or unspecified |
| M1a (0) | | Not elevated |
| M1a (1) | | Elevated |
| M1b | Distant metastasis to lung with or without M1a sites of disease | Not recorded or unspecified |
| M1b (0) | | Not elevated |
| M1b (1) | | Elevated |
| M1c | Distant metastasis to noncentral nervous system visceral sites with or without M1a or M1b sites of disease | Not recorded or unspecified |
| M1c (0) | | Not elevated |
| M1c (1) | | Elevated |
| M1b | Distant metastasis to central nervous system with or without M1a, M1b, or M1c sites of disease | Not recorded or unspecified |
| M1d (0) | | Not elevated |
| M1d (1) | | Elevated |

*Data from* Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(6):472-92.

2-cm margins required for primary site wide local excision. Currently, FDA approval is granted for T-VEC oncolytic therapy for unresectable M1a disease. Neoadjuvant therapy trials using T-VEC are underway,[47] which may help to downstage tumor and improve resectability, ultimately improving surgical selection and outcomes for M1a disease. Neoadjuvant approaches using immune checkpoint inhibitors and BRAF/MEK inhibition are also being evaluated.[48,49]

Pulmonary metastasis (M1b) is the most common category of M1 disease, representing up to 42% of patients with stage IV melanoma, and has a better prognosis than visceral involvement.[40,45] When clinical factors reflective of tumor biology are considered and complete resection of pulmonary involvement is feasible, the median survival after pulmonary metastasectomy ranges from 11 months to 40 months, with up to a 31% overall survival rate at 5 years.[46,50] Patients who do not undergo resection have median survivals of 6 to 13 months and a 0% to 4% overall survival rate at 5 years.[9] Patient selection is critical, with particular consideration given for DFI, the number of pulmonary lesions, and presence of extrathoracic disease.[9] Fortunately, high-resolution imaging has allowed for improved surveillance and staging of the burden of disease, which has been associated with improved outcomes after metastasectomy.[51] Durable long-term survival is possible, but is predicated on complete resection of metastatic disease.[52]

Under the current American Joint Commission for Cancer guidelines, M1c disease includes distant metastases to non–central nervous system visceral sites with or without M1a or M1b sites of disease. Before immunotherapy, 5-year overall survival rates of 38% to 41% have been reported for M1c disease.[9,53] When appropriately selected, adrenal metastasectomy has shown improved median survival of 20 to 25 months.[54,55] Similar outcomes have been reported for hepatic metastasectomy.[44] Central nervous system involvement, or M1d disease, occurs in up to 50% of patients with stage IV disease and results in up to 54% of the deaths from melanoma.[56,57] Most commonly, these lesions are symptomatic,[57] and surgery is often combined with whole-brain radiation or stereotactic radiotherapy because it may improve neurologic symptoms and improve survival.[56,57] Patients who underwent surgery and radiation

had a median overall survival of 8.9 months, whereas the median survival for supportive care alone was 2.1 months.[58]

### *Outcomes in the Modern Era*

Although data regarding metastasectomy in the current immunotherapy era are sparse, a recent study from Memorial Sloan Kettering evaluated patient outcomes after metastasectomy after immune checkpoint therapy.[59] This valuable study included a cohort of 237 highly selected patients with advanced stage III and stage IV melanoma. For all patients, among whom 88% had stage IV disease, the estimated 5-year survival was 75%. Of those who had stable disease or disease responsive to immune checkpoint therapy (n = 12), survival approached 90%. Those with isolated sites of progression who underwent resection (n = 106) had a 60% 5-year overall survival rate. The median survival was not reached in either group. Those who had multifocal progression (n = 119) and underwent palliative resection did significantly worse, with a median overall survival of 7.8 months.[9] This study provides promising evidence for the role of metastasectomy with effective and durable systemic immunotherapy treatments.

- In the era of modern effective therapy, the 5-year overall survival has been estimated at 75% in a cohort study using immune checkpoint therapy and selective metastasectomy.

## MESTASTASECTOMY AS AN ADJUNCT TO SYSTEMIC THERAPY: ADOPTIVE CELL THERAPY

Current systemic immunotherapies activate and enhance host immune responses. Adoptive cell therapy represents a new shift in highly personalized cancer therapy that directly delivers tumor-reactive lymphocytes into the host and can result in durable complete responses in melanoma.[60] Surgically resected melanoma tumor deposits are processed and cultured with high-dose IL-2 to expand tumor-infiltrating lymphocytes (TIL).[61] TIL with sufficient growth and antitumor reactivity are selectively expanded. This process may take 6 weeks, but will produce up to $10^{11}$ lymphocytes.[60] The patient is then lymphodepleted with aggressive chemotherapy and the expanded TIL are infused. TIL expansion is stimulated by high-dose IL-2.[61]

Unlike conventional forms of immunotherapy that rely on the host for production of sufficient immune cells, this therapy grows antitumor lymphocytes in vitro, selects cells with the highest avidity for tumor specific antigens, and can be activated in vitro so that these cells may overcome in vivo inhibition.[60] Until recently, this technique was not available outside of the National Cancer Institute, where objective response rates approached 55% with a 22% durable response.[60] The brain is not a sanctuary site with TIL therapy; therefore, patients with brain metastases are potentially eligible for this therapy and responses have been reported.[62]

The surgeon's role in an adoptive cell therapy program is to assist with resection of metastases for TIL harvest. The best TIL targets are those that can be safely resected with minimal risk of complications that allow the patient to undergo the aggressive immunoablative regimen necessary for TIL reinfusion and expansion. Superficial subcutaneous metastases or lymph node metastases in the cervical, axillary, or inguinal distribution are examples of good targets for TIL harvest. The operation should be as minimally invasive as possible. Brain metastases or hollow viscus metastases (ie, bowel metastases) are not ideal TIL harvest targets owing to issues related to recovery and contamination of the specimen.

- Surgery in metastatic patients can also be used to improve therapeutic options for systemic therapy.
- Obtaining tissue in a safe and reasonable manner allows patients to potentially undergo adoptive cell therapy.

## PALLIATIVE SURGERY

The typical focus of surgical oncology is related to long-term survival. However, relief of patient suffering remains a critical role for the surgeon, particularly for patients with metastatic disease. Patients with unresectable disease or unfavorable tumor biology have worse overall survival, but surgery can provide excellent palliation when the expectations of surgical goals are understood and met. Ultimately, providing patients with maintenance of their quality of life is imperative and patients may benefit from surgical palliation. Symptoms from locally advanced metastatic tumors may prevent a patient from undergoing systemic therapy, and palliation in this regard may ultimately provide an opportunity to receive effective systemic therapy. Surgery should be accomplished with minimal morbidity and length of hospital stay. The focus should be to alleviate specific symptoms such as bleeding or intestinal obstruction.[63] With these goals in mind, surgical palliation may provide relief in 77% to 100% of patients.[64] Ollila and colleagues[53] showed that 97% of patients had relief after resections of gastrointestinal obstructions. With the intent of palliation of symptoms, surgery will remain an integral component of management of the patient with advanced melanoma.

- Surgical palliation will always play a critical role in the management of metastatic patients to relieve suffering for symptoms such as bleeding or intestinal obstruction.

## SUMMARY

Before immune therapy and oncolytic therapy, only very modest survival gains were achieved with metastasectomy.[5] With more effective systemic therapies achieving durable responses approaching 40%,[24,25] surgery can be used in patients selected to have more favorable tumor biology. Indeed, in this setting, recent evidence has been very promising with 5-year overall survival of 75% in patients with advanced melanoma.[59] Optimal treatment sequencing remains to be defined and is a matter of current debate and investigation.[9,43,59] Surgery, however, will remain an essential component of the multidisciplinary management of metastatic melanoma.

## DISCLOSURE

K.M. McMasters: Scientific Advisory Board, Elucida Oncology. The remaining authors have nothing to disclose.

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