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Surgical Resection for Bulky or Recurrent Axillary Metastatic Melanoma

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Abstract

Introduction—Metastatic melanoma has few FDA approved treatments, and aggressive surgical resection has to be considered for management of bulky axillary metastases. We hypothesized that axillary resection in this setting is well tolerated and improves symptoms in the majority of patients.

Methods—We reviewed a prospectively collected database and identified 47 stage IIIC and IV patients with axillary nodal disease greater than 5 cm (68%), recurrent disease (36%), or disease adherent to axillary neurovascular structures (45%). Paresthesias, pain, and bleeding were present in 40% of patients, and were stable or improved after surgery in 75%. Most patients were asymptomatic prior to resection, and underwent resection for prevention of potential symptoms.

Results—Most patients underwent outpatient surgery. Postoperative complications included lymphedema (34%), range of motion limitation (23%), wound infection (17%), and neuropathic pain (17%). Among symptomatic patients, average time to progression was 3 months, compared to 9.5 months in asymptomatic patients ($P = 0.08$). Five-year survival was lower (16%) in symptomatic patients than in asymptomatic patients (35%, $P = 0.001$).

Discussion—Surgery for bulky axillary melanoma metastases is well tolerated, and should be considered in the management of Stage III or IV melanoma. Resection prior to symptoms may improve quality of life and is associated with longer survival.

Introduction

Melanoma remains, at its essence, a surgical disease. One of the ten most commonly diagnosed cancers, the incidence of melanoma is rising by 2.4% each year and is currently responsible for 8600 deaths annually in the United States [1]. While there are currently numerous adjuvant treatments offered to patients, most are in the context of experimental protocols, reflecting the lack of effective, tolerable, approved treatments, particularly for patients with advanced disease. Currently, interferon is the only FDA-approved adjuvant treatment for Stage III melanoma. The side effect profile of interferon creates a significant burden on the patient's health and well-being in exchange for limited benefit [2]. Even with promising new therapies available for advanced melanoma, no therapy offers durable control for more than a subset of patients. Thus, aggressive surgical resection has to be considered for management of advanced melanoma in appropriate settings [3–7].

Reduction of tumor burden by resection of metastatic melanoma may offer either survival benefit or palliation [7]. Resection of solitary lymph node metastases can achieve five year survival rates of approximately 50% [8,9]. Extensive axillary adenopathy, (N3 or Stage IIIC) has a five year survival of 39% [9]. It is largely unknown whether an aggressive surgical approach in these patients offers survival advantage. Furthermore, resection of extensive axillary disease, involving the brachial plexus or axillary vasculature may carry added risk. In patients who have had previous axillary surgery, particularly complete axillary node dissection, resection may be technically challenging. The benefit of reducing tumor burden, alleviating symptoms, and potential for cure must be balanced against possible risks and anticipated morbidity that may impact the patient's quality of life. With movement toward conservative management of positive sentinel nodes, as seen in MSLT-II, there is an increased likelihood of bulky axillary recurrent disease management.

The practice at our institution has been to attempt resection of bulky axillary disease in all Stage III patients, even those who are asymptomatic at presentation. We have also considered surgical resection in stage IV patients who have symptomatic sequelae of their disease, either present or imminent. Additionally, systemic therapy, either FDA approved, or within a clinical trial, was considered in all patients. Anecdotal experience suggests that this is an acceptable approach, but the true effect of aggressive surgical resection is largely unknown. In patients without symptoms, there is concern that resection will offer no benefit while exposing patients to surgical risks. However, we hypothesized that axillary resection of bulky disease is well tolerated in all patients, and improves symptoms in those with symptomatic disease. Furthermore, we hypothesized that patients with symptomatic metastases would have increased postoperative complications, due to increased disease burden and consequent increased scope of resection. Primary endpoints were postoperative resolution of symptoms, length of stay, and postoperative complications. Secondary endpoints included evaluating disease free survival and overall survival of patients undergoing resection of bulky axillary metastases.

Methods

This study was approved by the Human Investigation Committee of the University of Virginia Institutional Review Board (IRB). We have previously established a large, IRB-approved, prospective database; using this, we were able to identify a total of 2040 patients with melanoma who were seen at the University of Virginia by a single surgeon (CLS) between 1995 and 2009. These included patients who underwent their index surgery at other institutions. A retrospective review of prospectively collected data was performed. Criteria for inclusion included axillary nodal metastatic melanoma that met one or more of the following characteristics: bulky disease, (defined as measuring 5 centimeters or more), recurrent disease (defined as recurring after a previous complete lymph node dissection), or invasive disease, (defined as disease which was invading or strongly adherent to the axillary neurovascular bundle or thoracodorsal nerve). Patients who had non-lymphatic metastases to the axillary skin or subcutaneous tissue were excluded. Patient demographics, histologic information about the primary tumor, details of axillary surgery, and clinical followup data were obtained from database review, hospital chart records, and Social Security Death Index searches.

Wound infection was defined by the use of antibiotics for cellulitis or presence of purulent discharge postoperatively. Prolonged drain use was defined as >30 days postoperatively. Seroma was defined as a palpable subcutaneous fluid collection requiring percutaneous drainage. Wound necrosis and breakdown is defined as prolonged separation of the wound lasting longer than 2 weeks. Lymphedema was defined as such if there was documented upper extremity swelling no less than 3 months following axillary dissection.

Descriptive and comparative statistical analyses were performed using the chi-square test of association and the Wilcoxon rank-sum test. Kaplan-Meier survival functions were calculated for overall survival and disease-free survival. The log-rank test was used to assess statistical significance. Statistical analyses were performed in SPSS-17 (International Business Machines, Somers, NY).

Results

Demographic Data

Forty-seven patients met the inclusion criteria. The median age of the patients was 52 ± 2 years, and 66% were male. Thirty-two patients (68%) presented with bulky disease, 17 patients (36%) had recurrent disease in the axilla, and 21 (45%) had neurovascular invasion. All patients underwent resection of their axillary disease. Forty-three percent of patients had symptoms related to their axillary disease at the time of their operation (Table I). Brachial plexus symptoms, ranging from occasional paresthesia to severe pain, were seen in 17 patients (36%). Two patients (5%), both of whom underwent palliative surgery, had skin erosion with bleeding and/or open wounds (Fig. 1). Preoperative lymphedema was seen in two patients: one with lymphedema from a prior axillary lymphadenectomy, and another with extremity edema from tumor burden. The majority of patients did not have symptoms prior to resection, but instead underwent resection for prevention of potential future symptoms.

Of the 47 patients, 33 (70%) had no additional evidence of disease, and were resected with intent to cure. The remaining 14 patients had distant disease at the time of surgery. Four of these patients had resection of all metastatic disease, and 10 had an isolated axillary lymphadenectomy primarily for palliation of established symptoms or prevention of anticipated symptoms. In all cases, surgical resection followed oncologic principles with attempts to resect all visible disease; however, in 2 cases an R₀ resection was curtailed to avoid damaging vital structures and increasing postoperative morbidity.

The most common sites of primary tumor were the torso (n = 20, 43%) and upper extremity (n = 14, 30%) [Table 2]. Breslow depth of the primary melanoma averaged 3.65mm (0.52–17). Ten patients (21%) had unknown primary tumor sites and presented initially with bulky axillary disease with or without other distant metastases. The majority of the patients presented at the time of initial diagnosis with late stage melanoma, with 25 (53%) presenting at Stage III or above.

Operative Data

On average, 16 (1–60) lymph nodes were identified in the surgical specimens, and 6 (1–26) contained metastatic melanoma. Intraoperatively, 17 patients (36%) had adherence of tumor to the axillary vein (Table I). A major branch of a bifid or trifid axillary vein was sacrificed in four cases. One case involved partial resection of the wall of the axillary vein. The entire axillary vein was taken in four cases without reconstruction. The axillary vein was reconstructed in one case with a Gore-Tex patch. Thirteen patients (28%) had adherence to major nerves, most commonly the thoracodorsal nerve. In eight cases, when tumor was adherent only to the thoracodorsal nerve, the nerve was resected. One patient required resection of both the thoracodorsal and the long thoracic nerves. In five patients, the tumor was carefully dissected off the nerve with preservation. In one patient undergoing surgery with initially curative intent, gross tumor had to be left to preserve the brachial plexus. The majority of patients (55%) underwent outpatient surgery. Drainage with Jackson Pratt drains was standard postoperatively to prevent seroma.

Primary Outcomes

Only two patients required hospitalization longer than 2 days, at 4 and 5 days, respectively; one patient had postoperative arm weakness and mental status changes that ultimately resolved, and the other had a delayed discharge due to pain management. The median length of JP drainage was 14 days (2–34 days, intraquartile range 14), with three patients (6%) drained for longer than 30 days.

Overall postoperative complication rate was 47%. Lymphedema was the most common postoperative complication, occurring in 12 (26%) of patients. Eleven patients (23%) also experienced range of motion limitations, most (63%) of which were classified as mild and did not interfere with activities of daily living. Neuropathic pain occurred in a total of eight patients (17%). In four patients, this was an improvement from preoperative pain levels, two had no change in their preoperative pain, and two patients had new neuropathic pain after surgery. Wound infections occurred in eight patients (17%), and all but one was treated with oral antibiotics with complete resolution (Table 1).

Eighteen patients (38%) received postoperative radiation, and radiation therapy was considered for all patients. Reasons for declining radiation included presence of distant metastases (10) and patient preference. Thirty-three patients (70%) received other adjuvant systemic therapy: 11 received systemic chemotherapy (Taxol or DTIC), 10 received systemic immune therapy (IFN or IL-2), and 21 received treatment as part of a clinical trial (vaccine therapy or targeted therapy). Some patients received multiple types of therapy.

Secondary Outcomes

Axillary recurrences occurred in nine patients (19%), and median time to recurrence was 5 months (1–22 months). Five patients who recurred underwent a second axillary operation [Table 3]. 68% of patients had distant progression of disease after surgery. Median time to progression was 4 months. Median survival was 12 months. Five-year survival was 27%. Average followup was 24 months.

Among symptomatic patients, average time to progression was 3 months, compared to 9.5 months in asymptomatic patients ($P = 0.08$). Recurrence rates in the ipsilateral axilla were comparable in symptomatic (16%) and asymptomatic patients (22%) ($P = 0.74$) (Fig. 2). Symptomatic patients had a median survival of 12 months following axillary surgery, while asymptomatic patients had a median survival of 34 months ($P = 0.009$). Similarly, 5-year survival was lower (16%) in symptomatic patients than in asymptomatic patients (35%, $P = 0.001$) (Fig. 2). Six (33%) of patients receiving radiation therapy had nodal recurrence, while three (10%) of those who did not have radiation recurred in their axilla ($P = 0.068$).

Among the 33 patients resected for cure, distant progression of disease occurred in 19 patients (58%). Patients in this curative intent group had a median time to progression of 8 months. Their median survival was 30 months, with a five-year survival rate of 39% [Figure 2]. Among the 14 patients resected for palliation, 13 (93%) experienced tumor progression, and patients in the palliative group had mean and median survival of 7 months. Median followup was 12 months. One patient resected with palliative intent survived 3½ years after surgery. A second patient lived over 2 years after his palliative resection and died of other causes with apparent spontaneous regression of his remaining melanoma. He received no adjuvant therapy.

Discussion

Current literature advocates that surgery should be the treatment of choice for bulky nodal melanoma in the absence of systemic metastases [10]. Our data support this, and further suggest that resection of bulky melanoma is well tolerated and may have clinical benefit even in the presence of distant metastatic disease, especially as a palliative procedure. Though palliative surgery is controversial, it is a useful means for symptomatic control and may even provide a survival benefit for select patients [11]. Bulky axillary disease may lead to pain, lymphedema, or skin breakdown, which can significantly affect quality of life. The preoperative rate of severe symptoms (brachial plexus symptoms and bleeding) was 40%, while postoperative rate was only 17%. The majority of patients in this study with bulky axillary disease were asymptomatic at presentation however, and nearly half of patients had some postoperative complication. These were typically more tolerable symptoms (range of motion limitation or lymphedema) or limited in duration (wound infection). Because we have shown that resection of bulky axillary disease is well tolerated, the anticipated morbidity from progressive disease warrants surgical resection in these patients. Since many of the symptoms experienced in the axilla reflect neurovascular or skin invasion, delay of surgery until there are symptoms may be associated with a higher risk of unresectability or postoperative morbidity. Thus, an early surgical approach should be considered, and may be justified even in the absence of clinical symptoms. Early intervention is further supported by the fact that the cohort with symptomatic disease had shorter overall survival than those with asymptomatic disease, and a trend toward a shorter time to disease progression. Symptomatic patients were evenly distributed between those resected for palliation and those resected for cure, and thus stage is not likely to account for the survival difference seen between symptomatic and asymptomatic resections for cure.

Because goals of axillary dissection in these cases are to prevent or to manage symptoms, it was important that the operation was well tolerated with low morbidity. Postoperative incidence of pain or paresthesia was reduced by 50%, and in most cases pain level reflected maintenance or improvement of preoperative symptoms. Infection rates were low and treatable with oral antibiotics. Our study found rates of wound infection (17%) and lymphedema (34%) comparable to published rates [12–14]. Overall, patients commonly underwent outpatient surgery and had JP drainage for an average of two weeks postoperatively. Surgical recovery time was short and thus supports the value of resection even if there is no clear survival advantage.

Surgical treatment of macroscopic nodal disease improves local disease control. The rate of nodal basin recurrence is 13% [15], but can increase to 30–50% when lymph nodes are large (>3cm), contain extracapsular extension, or melanoma is found in 4 or more nodes [12,16,17]. This is consistent with the recurrence rate of 24% for patients who underwent curative resection in this study. Radiation therapy after resection of nodal melanoma metastases provides excellent local control [18,19], though there is no overall survival benefit [13,15,20,21]. Only a portion (38%) of our patients received radiation, and perhaps consistent use of postoperative radiation in these patients may reduce axillary recurrence further. The recurrence rate among patients receiving radiation was higher, and approached significance, but this likely is due to selection of patients for radiation who had neurovascular involvement or close margins of resection. There is insufficient data in the present study to draw any conclusions about the use of radiation in this patient population.

Most studies have found that lymphadenectomy will improve local disease control; controversy remains over whether local control improves overall survival. Some studies suggest no improvement in overall survival [10,15]. However, overall survival is greater for patients who have complete resection of metastases, compared to those with only palliative resection or nonsurgical management [22]. Our study findings do show prolonged survival in a large subset of patients with bulky axillary adenopathy, and leaves open the possibility of a survival benefit with this surgery for some patients. The five-year survival among stage IIIC patients, resected for cure, in our study was 39%. This is comparable to American Joint Committee on Cancer (AJCC) five-year survival rate of 39% in Stage IIIC patients. However, stage IIIC includes patients with 4 or more positive sentinel nodes or one positive sentinel node and a microscopic satellite. The current studied population had much more bulky disease and arguably may be expected to have had a worse outcome. In this study, median survival for patients resected with curative intent was 2.5 years, compared with 2 years for a similar cohort of patients Stage IIIC or above in the AJCC database. Also, in the 14 patients with stage IV disease undergoing resection, median survival of 12 months exceeds the national cooperative group experience with systemic therapy for stage IV melanoma [23].

There are several limitations to this study. The small sample size and nonrandomized design hinder objective comparisons, particularly with regard to mortality and recurrence rates. However our data do support that aggressive surgical resection is safe and well tolerated, and may, in fact, offer survival and disease-free survival benefits. Patient selection for palliative surgical intervention likely favors patients that are healthier and have other

favorable disease characteristics. Additionally, this study may be limited by confounding factors such as use of experimental vaccines, utilized by 45% of our subjects. With a small sample size, controlling for this can pose a challenge, but this study and others suggest that reduction of tumor burden may partly contribute to this survival advantage.

There is currently no consensus on the role of surgery for patients with stages IIIC and IV melanoma [4]. In light of this, many patients do not undergo surgery and are instead treated with standard or experimental chemotherapy or immunotherapy. Promising new therapies with antibodies to CTLA-4 or with inhibitors of mutant BRAF may also provide palliation or survival benefit, but response rates to CTLA-4 antibodies remain low, and median duration of response to BRAF inhibitors is 7–9 months [24,25]. We have found that an aggressive surgical approach to patients with advanced or bulky axillary adenopathy is well tolerated and may offer a survival advantage for some patients. Aggressive resection of axillary disease may even be used in combination with metastasectomy for patients with concomitant distant metastatic disease [4]. In order to better define the role of surgery for patients with advanced stage melanoma, further studies should be performed to characterize outcomes, preferably in a randomized, controlled format. However, because of the limited armamentarium against metastatic melanoma, we propose that surgical resection for bulky axillary melanoma should be considered in the patient with Stage IIIC or IV melanoma where symptoms from the axillary disease are likely to be problematic before other systemic disease.

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Figure 1.
Bulky axillary metastasis can lead to complications including skin involvement and bleeding, leading to considerable morbidity.

Figure 3.

Overall survival of patients undergoing bulky axillary surgery. A).As predicted, those undergoing surgery for palliative reasons had lower overall survival. Notably, 5-year survival of those with curative intent was 39%, similar to published survival rates. B). Patients with axillary symptoms (neurologic, pain, or bleeding) had a significantly shorter overall survival than those without symptoms.

Table 1**Surgical details**

	All No. (%)	Curative intent No. (%)	Palliative Intent No. (%)
	N = 47	N = 33	N = 14
<i>Preoperative</i>			
Brachial plexus symptoms	17 (36)	12 (36)	5 (36)
Skin erosion	2 (4)	0	2 (14)
Lymphedema	2 (4)	1 (3)	1 (7)
<i>Operative</i>			
Vascular adherence	17 (36)	11 (33)	6 (43)
Nerve adherence	13 (28)	10 (30)	7 (50)
LOS (days) ^a	0 (0–5)	0 (0–4)	1 (0–5)
JP drain (days) ^b	14 ± 1	12 ± 1	19 ± 3
<i>Postoperative</i>			
Lymphedema	17 (36)	15 (45)	2 (14)
Limited range of motion	11 (23)	7 (21)	4 (29)
Neuropathic pain	7 (15)	5 (15)	2 (14)
Wound infection	8 (17)	7 (21)	1 (7)

^aMedian (range)^bMedian ± SE

Table 2

Patient demographics

	All	Curative Intent N=33	Palliative Intent N=14	P value
Male	27 (68)	19 (58)	12 (86)	0.09
Age at resection (median $\pm$ SE)	52 $\pm$ 2	50 $\pm$ 3	61 $\pm$ 5	
Location of primary				0.66
Upper extremity	14 (30)	12 (36)	2 (14)	
Torso	20 (43)	14 (42)	6 (42)	
Other	3 (6)	1 (3)	2 (14)	
Unknown	10 (21)	6 (18)	4 (29)	
Stage at initial diagnosis				0.10
I	8 (17)	6 (18)	2 (14)	
II	5 (10)	4 (12)	1 (7)	
III	18 (38)	15 (46)	3 (21)	
IV	7 (15)	2 (6)	5 (35)	
Not documented	9 (19)	6 (18)	3 (21)	

Table 3

Recurrence patterns

	All	Curative intent No. (%)	Palliative Intent No. (%)
Axillary Recurrence, no.(%)	9 (19)	8 (24)	1 (7)
Reoperations, no.(%)	5 (11)	3 (9)	1 (7)
Distant Progression, no.(%)	27 (57)	14 (42)	13 (93)
Disease free survival, median (range)		9 (1–113)	N/A