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ORIGINAL ARTICLE – MELANOMA

Impact of Effective Systemic Therapy on Metastasectomy in Stage IV Melanoma: A Matched-Pair Analysis

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ABSTRACT

Background. Although resection historically played a prominent role in the treatment of metastatic melanoma, recent advances have altered the therapeutic landscape, and potentially the role of surgery. We examined surgical selection and metastasectomy outcomes before and after the onset of the effective drug therapy era.

Methods. Patients with stage IV melanoma were identified and characterized by treatment era (either 1965–2007 or 2008–2015) and by systemic therapy agents. BRAF and/or MEK inhibitors, as well as checkpoint inhibitors, were included as modern agents. Selection factors for metastasectomy were examined by era. A matched-pair analysis of outcomes of surgical and non-surgical patients receiving modern systemic agents was performed.

Results. Among 2353 eligible patients, 1065 (45.2%) underwent surgical treatment. Factors associated with selection for metastasectomy in the early era included female sex, no prior stage III disease, single-organ involvement, and M1a (vs. M1c) disease (all $p < 0.007$). In the current era, the proportion of surgically treated patients increased modestly (54.5% vs. 44.7%, $p = 0.02$) and age was the only independent selection factor ($p < 0.01$). Surgery followed by modern therapy in 47 matched pairs was associated with higher 5-year melanoma-specific survival (MSS) versus modern therapy alone (58.8% vs. 38.9%, $p = 0.049$). Multivariable regression showed single-organ involvement (hazard ratio [HR] 0.43, 95% confidence interval [CI] 0.21–0.90, $p = 0.02$) and first-line surgery (HR 0.47, 95% CI 0.23–0.98, $p = 0.04$), as well as use of modern agents (HR 0.29, 95% CI 0.21–0.40, $p < 0.001$), were independently associated with improved MSS.

Conclusions and Relevance. While modern systemic agents have improved outcomes in stage IV melanoma, metastasectomy remains associated with favorable survival. Resection remains a viable therapeutic approach, possibly worthy of prospective evaluation.

Treatment of metastatic melanoma represents one of the most rapidly evolving fields of oncology. Historically, stage IV melanoma had a dismal prognosis, with median survival measured in months.[1] Due to the lack of effective drugs, metastasectomy in appropriately selected patients was a major component of the metastatic melanoma treatment. Numerous single-institution experiences, as well as multicenter series, demonstrated favorable outcomes associated with metastasectomy in the oligometastatic setting.[2–8] In a recently published phase III randomized trial evaluating an adjuvant allogeneic whole-cell vaccine in stage IV melanoma, complete resection was associated with 5- and 10-year overall survival rates of more than 40% and 30%, respectively.[9]

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In 2011, the US FDA approved two agents for the treatment of metastatic melanoma—the cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) inhibitor ipilimumab and the BRAF inhibitor vemurafenib.[10–12] Since then, additional checkpoint inhibitors and molecularly targeted agents have been developed and approved in the metastatic setting.[13–15]

In light of these recent, rapid improvements in systemic treatment, the objective of this study was to re-examine the role of metastasectomy in stage IV melanoma in the modern era to determine how recently approved therapies have influenced patient selection for metastasectomy and outcomes associated with combined surgery and modern systemic therapy.

METHODS

This study received Institutional Review Board (IRB) exemption after independent regulatory review. A prospectively maintained institutional melanoma database was queried for all patients with stage IV melanoma and treated with systemic therapy alone or in combination with metastasectomy between 1965 and 2015. Patients not receiving treatment were excluded.

Patients were evaluated for demographic (sex, age at primary diagnosis, age at stage IV diagnosis), disease (primary tumor characteristics, disease-free interval, M stage, number of organs involved), and treatment-related (type of systemic therapy, sequence of treatment) characteristics. Systemic therapies were categorized as either historical (chemotherapy, biologic therapy, biochemotherapy) or modern. Modern therapies included checkpoint inhibitors (anti-CTLA-4 and anti-programmed death-1 [PD-1]) and molecularly targeted therapies (BRAF and/or MEK inhibitors). Treatment sequences included systemic therapy alone, surgery followed by systemic therapy, or systemic therapy followed by surgery.

Patient selection for surgical therapy was based on resectability and the clinical judgment of a multidisciplinary team. In general, this was affected by patient comorbidities, pace of disease (e.g. disease-free interval[5] and/or tumor volume doubling time[16]), and extent of disease (number of involved organs[3] and resectability[17]). Patients who were not fit candidates for surgery or whose disease could not be completely removed were generally not considered for metastasectomy.

Stratification by Treatment Era

The first modern agent for the treatment of metastatic melanoma was approved by the FDA in 2011; however, patients in this series first began to receive modern therapies in the context of clinical trials in 2008. We therefore stratified by treatment era based on the date of stage IV diagnosis, using 2008 as the start of the modern era. These era definitions were not used for survival analyses, which were based on actual treatment received. The historical era (1965–2007) featured only older agents (chemotherapy, biologic therapy, biochemotherapy). Although not all patients in the modern era received modern drugs, surgical selection may have been affected by the availability of those agents, whether they were used for an individual or not.

Matched-Pair Analysis: Initial Surgery Versus Modern Therapies Alone

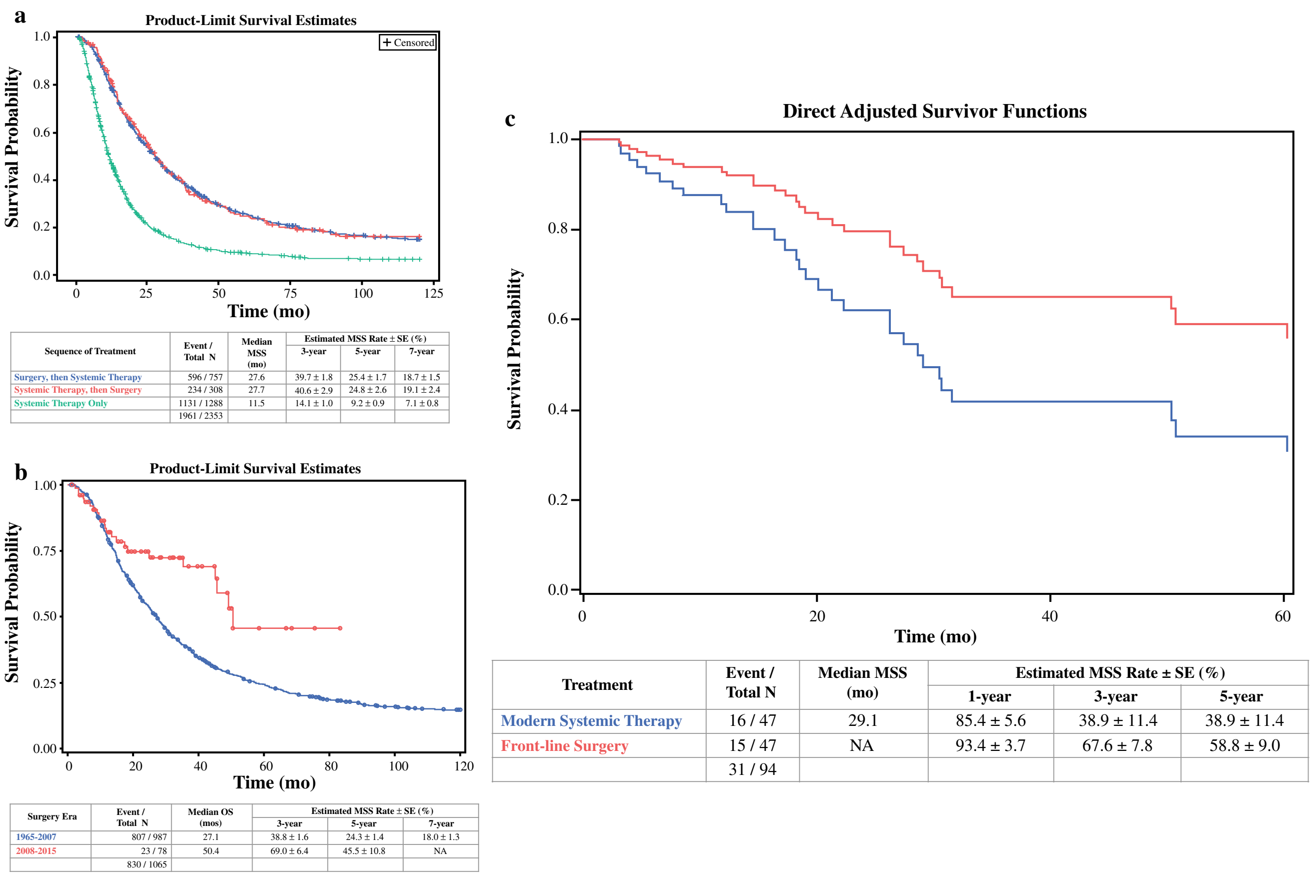
Selection bias is a common concern with retrospective metastasectomy studies. We attempted to diminish the effects of selection bias using matched-pair methodology. Matching was 1:1 (surgically treated:non-surgically treated) for factors associated with surgical selection: disease-free interval ($<$ 12 vs. $>$ 12 months) and number of organs involved by metastatic disease (1 vs. $>$ 1 organs). More restrictive matching using three categories for disease-free interval (DFI), and excluding brain metastases, are presented in the electronic supplementary figures. Patient demographics, tumor- and treatment-related characteristics, and outcomes between groups were compared. Modern agents were specifically defined as checkpoint inhibition or BRAF inhibition with or without MEK inhibition. Clinical trial patients were included if they were known to have received a modern agent in the trial.

Categorical variables were compared using the χ^2 test. For comparison of means, the t test or Wilcoxon rank-sum test were used. Kaplan–Meier melanoma-specific survival (MSS) curves were generated and compared using the log-rank test. Common prognostic variables and type of systemic therapy used were included in multivariable analysis using a stepwise Cox proportional hazards model. All statistical analyses were performed using SAS version 9.3 (SAS Institute, Inc., Cary, NC, USA). A p value < 0.05 was considered significant.

RESULTS

Demographics and Treatments Received

During the study period, 2353 patients were treated for stage IV melanoma, most (64.3%) of whom were male. Median age was 47.2 years at primary diagnosis and 51.4 years at stage IV diagnosis. The most common primary site was the trunk (39.2%), followed by extremity (26.5%) and head/neck (20.9%). There was no known



Sequence of Treatment	Event / Total N	Median MSS (mo)	Estimated MSS Rate ± SE (%)		
			3-year	5-year	7-year
Surgery, then Systemic Therapy	596 / 757	27.6	39.7 ± 1.8	25.4 ± 1.7	18.7 ± 1.5
Systemic Therapy, then Surgery	234 / 308	27.7	40.6 ± 2.9	24.8 ± 2.6	19.1 ± 2.4
Systemic Therapy Only	1131 / 1288	11.5	14.1 ± 1.0	9.2 ± 0.9	7.1 ± 0.8
	1961 / 2353				

Surgery Era	Event / Total N	Median OS (mos)	Estimated MSS Rate ± SE (%)		
			3-year	5-year	7-year
1965-2007	807 / 987	27.1	38.8 ± 1.6	24.3 ± 1.4	18.0 ± 1.3
2008-2015	23 / 78	50.4	69.0 ± 6.4	45.5 ± 10.8	NA
	830 / 1065				

Treatment	Event / Total N	Median MSS (mo)	Estimated MSS Rate ± SE (%)		
			1-year	3-year	5-year
Modern Systemic Therapy	16 / 47	29.1	85.4 ± 5.6	38.9 ± 11.4	38.9 ± 11.4
Front-line Surgery	15 / 47	NA	93.4 ± 3.7	67.6 ± 7.8	58.8 ± 9.0
	31 / 94				

FIG. 1 **a** Comparison of MSS stratified by treatment sequence. **b** Comparison of MSS stratified by era. **c** Adjusted comparison of MSS between first-line surgery versus modern systemic therapy alone. *MSS* melanoma-specific survival, *SE* standard error, *OS* overall survival

primary melanoma in 13.3% of patients, and primary lesions were most commonly of intermediate thickness (1.0–3.99 mm; 37.0%). Median DFI (time between primary and stage IV diagnoses) was 27.8 months. Most patients (55.7%) had no history of prior stage III disease. At the time of stage IV diagnosis, the median number of organs involved was 1.0, with 71.2% of patients having single-organ involvement and 1.8% with more than four organs involved.

Regarding treatment of stage IV disease, 54.7% of patients received systemic therapy alone. Of the 45.3% of patients treated with metastasectomy, 71.1% underwent first-line surgery followed by subsequent systemic therapy, and 28.9% received preoperative systemic therapy followed by surgery. Among patients undergoing first-line surgery, 65.9% initiated systemic therapy after subsequent recurrence. Overall, systemic therapy consisted of chemotherapy (59.1%), biologic agents (24.4%), or biochemotherapy (11.1%). A minority of patients received modern immunotherapy ($n = 118$, 5.0%) or targeted therapies ($n = 11$, 0.5%). Surgically treated patients had a more than twofold longer median MSS (27.6 months with first-line surgery; 27.7 months with preoperative systemic therapy vs. 11.5 months for systemic therapy alone; $p < 0.0001$) (Fig. 1a).

Factors Associated with Selection for Surgery by Treatment Era

Among all patients evaluated for stage IV melanoma during the two treatment eras, a larger percentage of patients underwent metastasectomy in the modern era ($n = 78/143$, 54.5%) compared with previous years ($n = 987/2210$, 44.7%, $p = 0.02$).

Patients in the modern era were older (initial diagnosis 50.7 vs. 46.3 years, $p = 0.02$; stage IV diagnosis 55.4 vs. 50.7 years, $p < 0.001$) (Table 1). The two groups were similar in primary Breslow thickness ($p = 0.94$). In the modern era, prior stage III disease was less common (24.4% vs. 39.7%, $p = 0.007$), but median DFI (31.7 vs. 31.0 months, $p = 0.27$) and the median number of organs involved at stage IV diagnosis were similar (1.0 vs. 1.0, $p = 0.16$). With the introduction of novel immune and targeted therapies, the frequency of utilization of historical

TABLE 1 Characteristics of patients treated with metastasectomy for stage IV melanoma, by treatment era

Treatment regimen	1965–2007 [*n* = 987]	2008–2015 [*n* = 78]	*p* value
Sex			0.05
Female	387 (39.2)	22 (28.2)	
Male	600 (60.8)	56 (71.8)	
Age at diagnosis of melanoma (years)			0.02
≤ 60	794 (80.4)	54 (69.2)	
> 60	193 (19.6)	24 (30.8)	
Mean [SD]	46.9 [14.5]	51.0 [14.4]	
Median [IQR]	46.3 [36.3–57.3]	50.7 [41.4–62.9]	
Age at stage IV diagnosis (years)			0.01
≤ 60	714 (72.3)	46 (59.0)	
> 60	273 (27.7)	32 (41.0)	
Mean [SD]	51.2 [14.0]	56.3 [13.3]	
Median [IQR]	50.7 [41.3–61.2]	55.4 [47.4–67.2]	
Primary site			0.32
Extremity	264 (26.7)	20 (25.6)	
Head/neck	195 (19.8)	23 (29.5)	
Trunk	384 (38.9)	24 (30.8)	
Unknown primary	143 (14.5)	11 (14.1)	
Clark level			0.23
I/II	58 (5.9)	2 (2.6)	
III	178 (18.0)	11 (14.1)	
IV	309 (31.3)	20 (25.6)	
V	54 (5.5)	6 (7.7)	
Clark unknown	245 (24.8)	28 (35.9)	
Unknown primary	143 (14.5)	11 (14.1)	
Breslow thickness (mm)			0.94
< 1	117 (11.9)	9 (11.5)	
1–3.99	368 (37.3)	27 (34.6)	
≥ 4.0	99 (10.0)	7 (9.0)	
Breslow unknown	260 (26.3)	24 (30.8)	
Unknown primary	143 (14.5)	11 (14.1)	
Race			< 0.001
White	597 (60.5)	67 (85.9)	
Other/unknown	390 (39.5)	11 (14.1)	
Disease-free interval (months)			0.27
< 12	285 (28.9)	18 (23.1)	
≥ 12	702 (71.1)	60 (76.9)	
Mean [SD]	50.3 [61.3]	64.4 [99.3]	
Median [IQR]	31.0 [9.1–69.0]	31.7 [12.6–59.8]	
Prior stage III disease			0.007
Yes	392 (39.7)	19 (24.4)	
No	595 (60.3)	59 (75.6)	
Number of organs involved			0.02
1	748 (75.8)	55 (70.5)	
2	190 (19.3)	13 (16.7)	
3	39 (4.0)	6 (7.7)	
4+	10 (1.0)	4 (5.1)	
Mean [SD]	1.3 [0.6]	1.5 [0.8]	
Median [IQR]	1.0 [1.0–1.0]	1.0 [1.0–2.0]	

TABLE 1 continued

Treatment regimen	1965–2007 [n = 987]	2008–2015 [n = 78]	p value
M stage			< 0.001
M1a	271 (27.5)	14 (17.9)	
M1b	317 (32.1)	20 (25.6)	
M1c	291 (29.5)	22 (28.2)	
M1d	108 (10.9)	22 (28.2)	
Prior BCG therapy			0.23
Previous BCG	76 (7.7)	9 (11.5)	
No previous BCG	911 (92.3)	69 (88.5)	
Prior vaccine therapy			< 0.001
Previous vaccine	222 (22.5)	2 (2.6)	
No previous vaccine	765 (77.5)	76 (97.4)	
Type of systemic therapy			< 0.001
Biochemotherapy	119 (12.1)	4 (5.1)	
Biologic	324 (32.8)	9 (11.5)	
Chemotherapy	518 (52.5)	12 (15.4)	
Immune	26 (2.6)	46 (59.0)	
Targeted	0 (0.0)	7 (9.0)	

Data are expressed as *n* (%) unless otherwise specified

SD standard deviation, *IQR* interquartile range, *BCG* Bacillus Calmette–Guerin

TABLE 2 Clinical selection factors associated with metastasectomy in stage IV melanoma, by treatment era

	1965–2007 [n = 2210]			2008–2015 [n = 143]		
	OR	95% CI	p value	OR	95% CI	p value
Sex						
Female	1.00			1.00		
Male	0.78	0.66–0.93	0.007	2.00	0.89–4.48	0.09
Age at stage IV diagnosis (years)						
> 60	1.00			1.00		
≤ 60	1.15	0.95–1.39	0.16	2.86	1.30–6.30	0.009
Disease-free interval (months)						
≥ 12	1.00			1.00		
< 12	1.00	0.82–1.20	0.96	1.37	0.54–3.44	0.51
Prior stage III disease						
Yes	1.00			1.00		
No	1.49	1.25–1.77	< 0.001	1.72	0.77–3.84	0.18
Number of organs involved						
> 1	1.00			1.00		
1	1.36	1.11–1.66	0.003	0.60	0.25–1.45	0.25
M stage						
M1a	1.00			1.00		
M1b	0.95	0.75–1.20	0.66	1.16	0.37–3.64	0.80
M1c	0.69	0.54–0.87	0.002	0.40	0.14–1.17	0.09
M1d	0.82	0.60–1.12	0.20	1.71	0.46–6.42	0.42

OR odds ratio, *CI* confidence interval systemic therapy options decreased significantly ($p < 0.001$).

The association of clinical and pathological factors with selection for metastasectomy was examined within each of the eras, by multivariable regression (Table 2). Prior to 2008, patients with metastatic melanoma were more likely to undergo surgery if they were female, had no prior history of stage III disease, had only single-organ involvement, and had M1a versus M1c disease (all $p < 0.007$). In contrast, in the modern era, only age < 60 years was independently related to selection for surgery ($p < 0.01$).

Melanoma-Specific Survival

Prior to 2008, patients treated with combination systemic therapy and metastasectomy achieved median and 5-year MSS rates of 27.1 months and 24.3%, respectively. Combined systemic therapy and metastasectomy in the modern era was associated with significantly improved survival (median and 5-year MSS rates of 50.4 months and 45.5%, respectively, $p < 0.001$) (Fig. 1b). On multivariable Cox proportional hazards modeling, the use of modern immune or targeted therapies (vs. historical systemic therapies) was the greatest independent prognostic factor for survival (hazard ratio [HR] 0.29, 95% CI 0.21–0.40, $p < 0.001$) (Table 3).

Matched-Pair Analysis: Upfront Surgery Versus Modern Therapies Alone

Matched-pair analysis comparing patients with metastatic melanoma treated with modern immune or targeted agents alone versus patients treated with first-line surgery followed by the subsequent use of these agents was performed. Patients were matched by DFI (< 12 vs. ≥ 12 months) and number of organs involved by metastatic disease (1 vs. > 1 organ). Forty-seven matched pairs were identified. Patient demographics, and tumor- and treatment-related characteristics were compared (Table 4).

Patients who underwent upfront metastasectomy were younger at initial diagnosis (48.5 vs. 65.5 years, $p = 0.002$) and at stage IV diagnosis (56.5 vs. 68.6 years, $p = 0.04$). Although historically the absence of prior stage III disease had been a predictive factor selecting patients for metastasectomy, in this case patients undergoing upfront surgery more commonly had a history of prior stage III disease (74.5% vs. 55.3%, $p = 0.05$). The two groups were similar with regard to sex, DFI, number of involved organs, and M stage.

Systemic treatment in most matched-pair patients consisted of modern immunotherapy ($n = 43$, 91.5%), while a minority received targeted therapy ($n = 4$, 8.5%).

TABLE 3 Multivariable Cox proportional hazards modeling for melanoma-specific survival in patients treated with surgery and systemic therapy

	HR	95% CI	p value
Sex			
Female	1.00		
Male	1.20	(1.09–1.31)	< 0.001
Age at stage IV diagnosis (years)			
> 60	1.00		
≤ 60	0.97	(0.88–1.07)	0.54
Disease-free interval (months)			
≥ 12	1.00		
< 12	1.04	(0.94–1.15)	0.46
Prior stage III disease			
Yes	1.00		
No	0.82	(0.75–0.90)	< 0.001
Number of organs involved			
> 1	1.00		
1	0.76	(0.68–0.84)	< 0.001
M stage			
M1a	1.00		
M1b	1.18	(1.04–1.33)	0.01
M1c	1.26	(1.11–1.42)	< 0.001
M1d	1.53	(1.30–1.79)	< 0.001
Type of systemic therapy			
Historical	1.00		
Modern	0.29	(0.21–0.40)	< 0.001

HR hazard ratio, *CI* confidence interval

Ipilimumab was the most frequently used agent. Among patients receiving systemic therapy alone, 68.1% received ipilimumab, whereas for those undergoing first-line surgery, 74.5% subsequently received ipilimumab. The median time to initiation of systemic therapy in the upfront surgery cohort was 4.0 months (range 0.4–106). Systemic recurrence occurred in 29.8% ($n = 14$) of patients prior to initiating systemic therapy. Median and 5-year MSS in the systemic therapy-alone cohort was 29.1 months and 38.9%, respectively. Initial surgery was associated with a significantly improved 5-year MSS of 58.8%, and median MSS was not reached (Fig. 1c). On stepwise multivariable Cox proportional hazards modeling, single-organ involvement (HR 0.43, 95% CI 0.21–0.90, $p = 0.03$) and first-line surgery (HR 0.47, 95% CI 0.23–0.98, $p = 0.04$) were independently associated with improved MSS.

TABLE 4 Matched patients treated with modern systemic therapy alone versus surgery followed by subsequent modern systemic therapy

Treatment regimen	Systemic therapy only [n = 47]	Surgery then systemic therapy [n = 47]	p value
Sex			0.66
Female	14 (29.8)	16 (34.0)	
Male	33 (70.2)	31 (66.0)	
Age at diagnosis of melanoma, years			0.002
≤ 60	20 (42.6)	35 (74.5)	
> 60	27 (57.4)	12 (25.5)	
Mean [SD]	60.6 [16.4]	49.1 [16.5]	
Median [IQR]	65.5 [49.1–71.3]	48.5 [39.0–60.9]	
Age at stage IV diagnosis, years			0.04
≤ 60	16 (34.0)	26 (55.3)	
> 60	31 (66.0)	21 (44.7)	
Mean [SD]	65.6 [14.6]	55.9 [14.6]	
Median [IQR]	68.6 [54.0–75.4]	56.5 [46.9–66.1]	
Disease-free interval, months			1.00
< 12	10 (21.3)	10 (21.3)	
≥ 12	37 (78.7)	37 (78.7)	
Mean [SD]	59.6 [75.9]	81.5 [111.5]	
Median [IQR]	34.7 [13.0–74.5]	42.7 [18.0–91.7]	
Prior stage III disease			0.05
Yes	26 (55.3)	35 (74.5)	
No	21 (44.7)	12 (25.5)	
Number of organs involved			0.82
1	33 (70.2)	33 (70.2)	
2	7 (14.9)	9 (19.1)	
3	4 (8.5)	2 (4.3)	
4+	3 (6.4)	3 (6.4)	
Mean [SD]	1.6 [1.0]	1.5 [0.8]	
Median [IQR]	1.0 [1.0–2.0]	1.0 [1.0–2.0]	
Number of organs involved			1.00
1	33 (70.2)	33 (70.2)	
> 1	14 (29.8)	14 (29.8)	
M stage			0.97
M1a	9 (19.1)	10 (21.3)	
M1b	13 (27.7)	13 (27.7)	
M1c	18 (38.3)	16 (34.0)	
M1d	7 (14.9)	8 (17.0)	
Type of modern systemic therapy			
Immune	43 (91.5)	43 (91.5)	1.00
Targeted	4 (8.5)	4 (8.5)	

Data are expressed as n (%) unless otherwise specified

SD standard deviation, *IQR* interquartile range

DISCUSSION

Throughout most of its history, systemic therapy for metastatic melanoma was associated with low response rates and short survival. Systemic chemotherapy demonstrated responses in one patient in five, response duration was generally only a few weeks, and median overall survival was approximately 6 months.[18] In that environment, surgical resection was a prominent consideration. Relatively recent reports of prospectively monitored clinical trial patients, including the SWOG registry study,[4] the first Multicenter Selective Lymphadenectomy Trial,[5] and the

CanVaxin stage IV study,[9] have demonstrated that a substantial subset of these carefully monitored patients experienced extended survival, even in the absence of good medical treatments. While there were undoubtedly numerous reasons for these favorable results, including patient selection, long-term survival of 20–45% for patients with stage IV melanoma was unmatched with any other options available then.[4,5,9]

The last several years have brought a raft of new therapies, eclipsing all prior medical options. These therapies generally fall into two categories—targeted and immune. These result in much higher rates of response, many of which are durable or even permanent.[10–15] There is now clearly documented survival benefit from medical treatment in the metastatic setting, which was not the case in the historical period. Our study examines the effects of this medical revolution on the role of surgery in stage IV melanoma.

We confirmed the previously established survival advantage with surgical treatment across eras, as well as the marked improvement in survival when modern therapies are used. The modern era demonstrated a more than 70% reduction in risk of death compared with the earlier era. We also found that the improvement in outcomes associated with surgical treatment persisted into the modern era. This did not appear to be the result of increased stringency of surgical selection in recent years. The fraction of patients who underwent surgical treatment *increased* over time, and fewer factors were related to surgical selection in the modern era.

Clearly, the surgical population is still a highly selected group, based on clinical judgment and identification of patients who are more likely to enjoy extended survival after resection. We worked to account for this bias with two strategies. First, a multivariable analysis incorporating standard prognostic variables found the association of surgery with improved outcome was independent of those other factors. Second, pairs of patients matched for surgical selection factors found substantially improved outcomes in those who underwent resection.

Is there a reasonable biological mechanism by which surgery would contribute to survival beyond the impressive effects of the new drugs themselves? There are emerging data from clinical trials of modern systemic therapies that the efficacy of new medications in the unresectable metastatic disease setting is greatest among patients with low-volume disease.[19] Additionally, improved MSS in adjuvant drug studies suggests they may be more effective when there is no clinically apparent residual disease.[20,21] Alternatively, this may reflect surgical removal of more aggressive or potentially treatment-resistant areas of disease, leaving more responsive sites to medical therapy remaining.

Long et al.[21] examined long-term outcomes in patients treated with combination BRAF and MEK inhibition and found that patients who had normal baseline lactate dehydrogenase (LDH) and fewer than three organ sites involved had better survival than those with higher-volume disease. Similarly, Nosrati et al.[22] demonstrated increased response to anti-PD-1 therapy among patients with normal LDH, while Huang et al.[23] found that melanoma patients with lower disease burden were more likely to respond to anti-PD-1 therapy. These data suggest that a reduction in tumor volume could also reduce tumor-derived immunosuppression or molecular resistance mechanisms. Weber et al. demonstrated improved relapse-free survival in the adjuvant setting with anti-PD-1 treatment beyond the benefits seen from CTLA-4 blockade.[10,20] Long et al. showed improved relapse-free and overall survival with combination BRAF and MEK inhibition, even at a time when those medications were available upon metastatic disease recurrence.[24] This evidence of improved drug efficacy with lower tumor burden, and the potential efficacy of surgical therapy if disease is detected when resectable, both argue for the utility of close follow-up and imaging of patients for those who are at substantial risk for disease recurrence.

Our series is retrospective and thus subject to uncertainty, and we do not intend to suggest this definitively demonstrates the superiority of resection in the first-line setting. In fact, we saw similar outcomes for patients who had initial medical therapy followed by surgery. This may occur in the setting of consolidation of a partial response or selective resection of a site of resistance. Recent practice pattern changes related the results of the second Multicenter Selective Lymphadenectomy Trial, and the approval of multiple systemic therapy in the adjuvant setting, may alter the use of metastasectomy in ways that are very difficult to predict at this time. The broader availability of these agents and other new agents and combinations are likely to continue to impact the use of surgery in ways that are difficult to predict. It is important to maintain a well-trained population of surgeons capable of performing both therapeutic lymph node dissections and metastatic resections. Although our study sample is relatively small, this remains the largest series to examine outcomes associated with the combination of upfront surgery and modern agents. The findings support the notion that metastasectomy remains an excellent therapeutic option for appropriately selected patients. Definitive therapeutic recommendations will require prospective evaluation of the utility of surgical resection for metastatic melanoma.

CONCLUSION

This report examines the outcomes of melanoma metastasectomy in a cohort of over 2000 patients. It not only confirms the previously established favorable outcomes associated with metastasectomy but also allows the examination of the impact of the first-generation of effective medical therapies. Although no retrospective analysis can definitively prove efficacy, this examination supports continued use of surgical resection of melanoma metastases in patients carefully selected in a multidisciplinary setting. A prospective evaluation of surgical resection in stage IV melanoma appears warranted.

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