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Clinical Features and Response to Systemic Therapy in a Historical Cohort of Advanced or Unresectable Mucosal Melanoma

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Abstract

Background—There are little data available regarding pattern of first metastases in resected MM as well as the response of advanced MM to cytotoxic therapy.

Patients and Methods—A retrospective, single-institution cohort was assembled of all patients with advanced/unresectable MM between 1995 and 2012 who received systemic therapy with available imaging ($N=81$). Responses to first- and second-line systemic therapy were assessed using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. The relationship between response, OS, and clinical covariates was investigated using Cox proportional hazards regression.

Results—Primary sites included anorectal ($N=31$, 38%), vulvovaginal ($N=28$, 35%), head and neck ($N=21$, 26%), and gallbladder ($N=1$, 1%) mucosa. Seven percent of patients first relapsed in the brain. Cytotoxic therapy represented 82% and 51% of first- and second-line regimens. Best response achieved in the first-line setting was similar for single-agent (10%; 95% CI: 1–32%) and combination alkylator therapy (8%; 95% CI: 2–21%). Median OS from 1st-line treatment was 10.3 months (95% CI 8.7–13.9 months). Patients with elevated LDH (HR 1.87, 95% CI: 1.10–3.19, $p=0.020$) and ECOG performance status 1–2 (HR 1.69, 95% CI: 1.05–2.72, $p=0.030$) had a higher

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Disclosures

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risk of death, while patients with 12-week objective responses had a lower risk of death (HR: 0.12, 95% CI: 0.04–0.41, $p < 0.001$).

Conclusion—Cytotoxic systemic therapy has modest activity in advanced/unresectable MM, belying its adjuvant benefit. Patients whose tumors have an objective response to therapy have a lower chance of death. Brain imaging should be considered in routine surveillance.

Keywords

Mucosal melanoma; cytotoxic therapy; metastasis; prognosis

Introduction

Malignant melanoma is a heterogeneous group of melanocytic neoplasms diagnosed in approximately 76,000 people in the United States yearly [1]. Mucosal melanomas (MM) comprise 1–2% of all melanomas in the US and arise from non-hair bearing mucosal surfaces of the body, most commonly the head and neck, anorectal, or vulvovaginal regions [2]. MM is clinically and genetically distinct from cutaneous melanoma [3, 4]. Patients diagnosed with MM tend to be older than those with cutaneous or uveal primary sites, and their stage-matched prognosis is poorer [5, 6]. A retrospective review of survival from the time of metastasis in 2920 patients with melanoma of various primary sites demonstrated that those with MM lived a median (95% confidence interval (CI)) of 9.1 (7.6 – 9.8) months, versus 13.4 (11.6–15.6) and 11.7 (11.2 – 12.6) months for those with uveal and cutaneous disease, respectively [6]. It is not clear whether clinical factors such as site of first metastasis or a lower response to systemic therapy influence this poorer prognosis.

The most rigorous MM therapy study to date was a large, single-center randomized Phase 2 trial that enrolled 189 patients with resected MM in a 1:1:1 ratio to observation, adjuvant interferon alpha, or adjuvant cisplatin plus temozolomide [7]. Patients receiving adjuvant cisplatin plus temozolomide or high-dose interferon had a significant improvement in overall survival (48.7 vs 40.4 vs 21.2 months, respectively; $p < 0.01$ for both comparisons). All patients on the observation arm recurred within 2 years, and seventy-five percent recurred either regionally or in a distant site [7].

Given the significant benefit of adjuvant therapy with cytotoxic agents and interferon, there is a need to document the activity of cytotoxic therapy in the advanced setting. To our knowledge, there are only four published retrospective series reporting response of MM to cytotoxic or biochemotherapy. The largest included 28 patients receiving dacarbazine-based chemotherapy and reported a similar objective response rate (ORR) between non-cutaneous and cutaneous melanoma (CM) of 20 and 30%, respectively [8]. The other studies reported responses in 7/13 (54%) head and neck MM, 8/18 (44%) of anorectal MM, and 4/11 (36%) of vulvovaginal MM with biochemotherapy, which combines cytotoxic agents such as cisplatin, vinblastine, and dacarbazine (CVD) with immunomodulatory therapy such as interferon alpha and/or interleukin (IL)-2 [9–11].

Considering the poor prognosis for patients with MM, the magnitude of OS benefit with cytotoxic therapy, and the relative paucity of published data, we sought to assess the patterns

of first metastasis, response rates, and overall survival for patients with MM treated with any systemic agents at our institution.

Methods

After obtaining IRB approval, we used institutional databases to identify patients who were diagnosed with metastatic or unresectable MM between 1/1/1995 and 12/31/2012, received 1 non-adjuvant systemic therapy, and had CT, MRI, or PET imaging available for radiological evaluation.

We collected standard demographic data, such as age, gender, race, ECOG performance status, tumor stage, prior receipt of adjuvant therapy, and systemic therapies received in the first- and second-line settings for advanced or unresectable disease. Patients were classified by primary disease site: anorectal, vulvovaginal, head/neck, and gallbladder.

CT and/or MRIs were collected at baseline and during the course of treatment for advanced or unresectable disease. Initial sites of metastatic disease were identified using radiographic or pathologic reports and categorized by organ system. Multiple nodules in an organ were counted only once. Responses to first- and second-line regimens were determined using RECIST 1.1 by radiologists (MB and RL) blinded to treatment.

Patients with metastatic disease were staged using American Joint Committee on Cancer 7th edition guidelines [12] for cutaneous melanoma (M1a, M1b or M1c). Therapies were categorized into the following groups: single-agent alkylator (e.g., temozolomide or dacarbazine); combination alkylator (e.g., cisplatin, vinblastine and temozolomide [CVT]); non-alkylating cytotoxic; immunotherapy; biochemotherapy; targeted agents; and other.

Statistical Methods

Patient characteristics were summarized using medians and ranges for continuous variables and frequencies and percent for categorical variables. Differences between site and adjuvant therapy rates were tested using Fisher's exact test. Twelve week response rate was defined as partial (PR) or complete (CR) response using RECIST 1.1 by 12 weeks after the commencement of line 1 systemic therapy. For all response proportions, percent of response was provided along with exact 95% confidence intervals.

Overall best response (BR) was defined as PR or CR using RECIST 1.1 during any point of the chemotherapy regimen. BR was measured separately for each line of therapy. Patients without scans during the duration of therapy were excluded from the analysis. Twenty-four week disease control rate (DCR) was defined as RECIST 1.1 PR, CR, or stable disease (SD) at or after 24 weeks of treatment in all patients evaluable for response. If a patient stopped or changed regimens before 24 weeks or did not have a scan available, they were considered not controlled.

Overall Survival (OS) was defined as the time interval between chemotherapy line 1 commencement and death or last follow up. Patients alive at last follow up were censored. Factors associated with overall survival were evaluated using Cox proportional hazards regression and twelve week response was modeled as a time dependent covariate. OS

stratified by response rate was plotted by Kaplan Meier methods landmarked at 12 weeks. P values <0.05 were considered statistically significant. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R 3.1.1 (The R Foundation).

Results

Patient Characteristics

Patient characteristics and demographics are shown in Table 1. Overall, 81 patients met the inclusion criteria. The median age at diagnosis was 63 years (range: 33–89 years). Seventy-three percent of patients were female (59/81) and 82% were Caucasian (66/81). Thirty-eight percent had disease arising from the anorectal (31/81) mucosa, 26% from the head and neck (21/81), 35% from the vulvovaginal mucosa (28/81), and 1% from the gallbladder (1/81). Eighty-four percent underwent resection of the primary disease (68/81).

Mutation status of KIT, BRAF, and NRAS genes was available for a subset of tumors. Nine of 43 (21%) were found to harbor KIT mutations, with 8 affecting exon 11 (6 L576P, 1 V560D, 1 deletion) and 1 affecting exon 13 (V654A). Three of 38 (8%) harbored BRAF mutations, with 2 D594 missense mutations and 1 T599I mutation identified. Five of 36 (14%) harbored NRAS mutations, with 3 Q61 mutations and 2 G12D mutations observed.

Pattern of Initial Metastases

At time of first non-adjuvant systemic treatment, 84% of patients had metastatic disease identified on imaging and 16% had locally advanced unresectable disease. LDH was elevated in 33% of cases.

At the initial diagnosis of metastatic disease, 143 organ sites were involved (Figure 1). Forty-eight percent of patients had metastasis limited to 1 organ site. The most common sites of initial metastasis were the liver (57%), lung (41%), non-regional LN (38%), and soft tissue (22%). Bone metastases were observed in 9 cases (12%): six from head and neck, 3 from anorectal, and none from vulvovaginal MM. Brain metastases were relatively uncommon, but were observed as an initial metastatic site in 5 cases (7%), including 2 vulvovaginal (1 vulvar, 1 vaginal) melanomas and 1 each from rectal, nasal cavity, and gallbladder.

Treatment

Seventy-four and 43 patients were evaluable for response to first- and second-line systemic therapy, respectively (Table 2). Sixty-one (82%) first-line regimens and 22 (51%) second-line regimens included cytotoxic agents. Of these, 38 (62%) and 15 (68%), respectively, were combination alkylator regimens; 20 (33%) and 2 (5%), respectively, were single agent alkylators; and 3 (5%) and 5 (12%), respectively, were non-alkylator regimens

Immune-based therapy was utilized in 7 (10%) first-line and 13 (30%) second-line regimens, with the most common agent being ipilimumab ($N=4$ and $N=6$, respectively). Three patients received PD-1 inhibitors, all in the second-line setting ($N=2$ nivolumab; $N=1$ pembrolizumab). Targeted therapy was given to 4 patients (5%) as first-line therapy and to 6

patients (14%) as second-line therapy. Imatinib ($N=3$ for both first- and second-line) and nilotinib ($N=2$ second-line) were the most common targeted agents.

Overall Best Response and 24 Week Disease Control Rate

Overall, 14% of patients (10/74; 95% CI: 7–23%) responded to first-line and 23% (10/43; 95% CI: 12–39%) responded to second-line treatments (Table 3). Responses from first-line therapy lasted a median of 12 months (range: 5.3 – 53 months) and from second-line therapy a median of 6 months (range: 3.1 – 64 months). At 24 weeks, disease control rates for first- and second-line therapy were 14%; (10/74; 95% CI: 7–23%) and 7% (3/43; 95% CI: 1–19%), respectively. Best response achieved in the first-line setting was similar for single-agent (2/20, 10%; 95% CI: 1–32%) and combination alkylator therapy (3/38, 8%; 95% CI: 2–21%). By primary site, best response to first-line therapy was 5% for head and neck (1/21; 95% CI: 0–24%), 15% for anorectal (4/27; 95% CI: 4–34%), and 20% for vulvovaginal (5/25; 95% CI: 7–41%) disease. Best response to first-line therapy was 10% (4/39; 95% CI: 3–24%) for patients with liver metastases and 20% (6/30, 95% CI: 8–39%) for those without. Based on cutaneous AJCC M staging, response was 11% (5/47, 95% CI: 4–23%) for M1c, 33% (5/15, 95% CI: 12–62%) for M1a/M1b, and 0% (0/12, 95% CI: 0–26%) for M0. Best response was 16% (3/19, 95% CI: 3–40%) for patients who received adjuvant therapy, 11% (5/44, 95% CI: 4–25%) for patients who did not, and 18% (2/11, 95% CI: 2–52%) for patients who were never free of disease.

Overall Survival

Median overall survival (OS) from initiation of 1st-line treatment was 10.3 months (95% CI 8.7–13.9 months). OS did not differ by melanoma site (Figure 2), treatment in the first -line setting, sex, race, stage, or age ($p=0.10$ – 0.94). However, patients with elevated LDH (HR 1.87, 95% CI: 1.10–3.19, $p=0.020$) and ECOG 1–2 (HR 1.69, 95% CI: 1.05–2.72, $p=0.030$) had a higher risk of death. Patients with objective responses by 12 weeks had significantly lower risk of death (HR: 0.12, 95% CI: 0.04–0.41, $p<0.001$); see Table 4.

Discussion

To our knowledge, this historical series is the largest to report the effects of cytotoxic therapy in patients with MM. Reporting the initial sites of metastases provides guidance for metastatic surveillance in the post-operative setting. Regardless of primary site, the most common initial sites of metastasis were the lungs, liver, and non-regional lymph nodes. The rate of brain involvement as an initial site of metastasis was 7%, and no primary site was free of risk. Given these data, any surveillance imaging for MM should include the chest, abdomen, and pelvis, and brain imaging could be justified.

Overall, the best response and 24-week disease control rates to systemic therapy were modest in both the first- and second-line settings and are lower than those seen in cutaneous disease. Notably, this historical cohort was weighted toward cytotoxic therapy. Alkylator-based cytotoxic therapy resulted in first-line ORRs of approximately 10%. This ORR is lower than the 16–27% reported in cutaneous melanoma [13, 14] and somewhat lower than the 20% ORR for MM reported in a smaller cohort [8]. This analysis provides an estimate

for a historical “non-promising” response rate that can be used to power future clinical trials in mucosal melanoma. Furthermore, this modest activity of cytotoxic therapy in the advanced setting belies the magnitude of survival benefit seen in the adjuvant randomized trial of MM [7], especially given the fact that an adjuvant trial of dacarbazine did not benefit patients in cutaneous melanoma [15]. A second, multicenter randomized trial is needed to confirm the benefit of adjuvant cytotoxic therapy for patients with MM.

We did not detect a significant association between response and single agent versus combination cytotoxic therapy. This analysis could not control for selection bias due to its retrospective design, and the sample size limited our ability to control for other factors in the response analysis. This study nonetheless represents the largest cohort of patients to date receiving these therapies. Given the historically higher toxicity rates of combination cytotoxic regimens [16] and the lack of difference in response rate in this cohort, single agents such as temozolomide or dacarbazine may be preferable for patients with MM who lack other clinical trial options.

In regards to immune checkpoint blockade, the 10 patients receiving ipilimumab in this report were part of a previously reported cohort [17] that reported a 7% RR. Only three patients in our report received anti-PD1 agents, and none derived clinical benefit. Thus, this analysis did not provide additional insight into clinical activity with these standard first-line agents that recently demonstrated ORRs of 23% with nivolumab (95% CI: 15 – 34%) and 37% with nivolumab plus ipilimumab (95% CI: 22 – 55%) [18].

Overall survival from time of initiation of systemic therapy was less than 1 year in this cohort, with no significant differences between MM primary sites. Increased LDH and poor ECOG performance status predicted a higher risk of death, consistent with findings in cutaneous melanomas. While class of cytotoxic therapy was not associated with improved OS, the risk of death was significantly lower in the select group of patients whose tumors have an objective 12 week response to systemic therapy compared to those whose tumors did not respond (HR: 0.12, 95% CI: 0.04–0.41). Further investigation is needed to identify the molecular and/or immunologic mechanisms of mucosal melanoma initiation and progression that will allow us to better select immune-based and other treatments that will benefit these patients.

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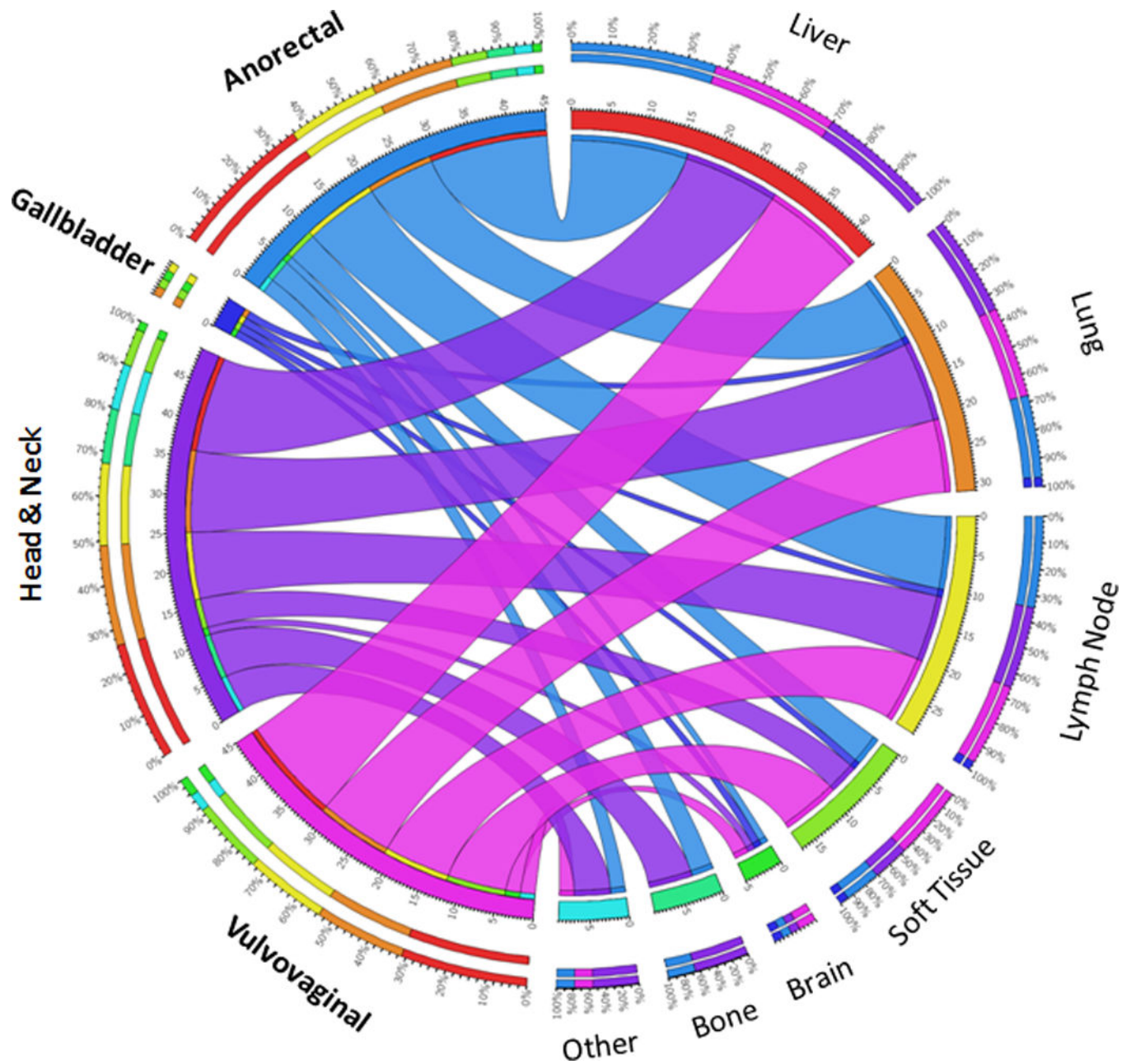


Figure 1.

Circos plot of all initial metastatic sites (n=143) for 76 patients. The 143 sites are broken down by primary site on the left half of the circle and the metastatic organ on the right half, with the segments representing the relative abundance of metastases by primary site and destination. Ribbons connect the primary site with the metastatic organ system, with the color corresponding to the primary site associated with that colored segment (e.g. anorectal, blue) and the width denoting the number of cases that metastasized to that site (e.g. anorectal spread to liver, n=16). Relative percentages of spread are represented on the outer segments; for example, 36% of anorectal metastases were to the liver (red, 11 o'clock) and 67% of bone metastases originated from the head and neck (purple, near 6 o'clock).

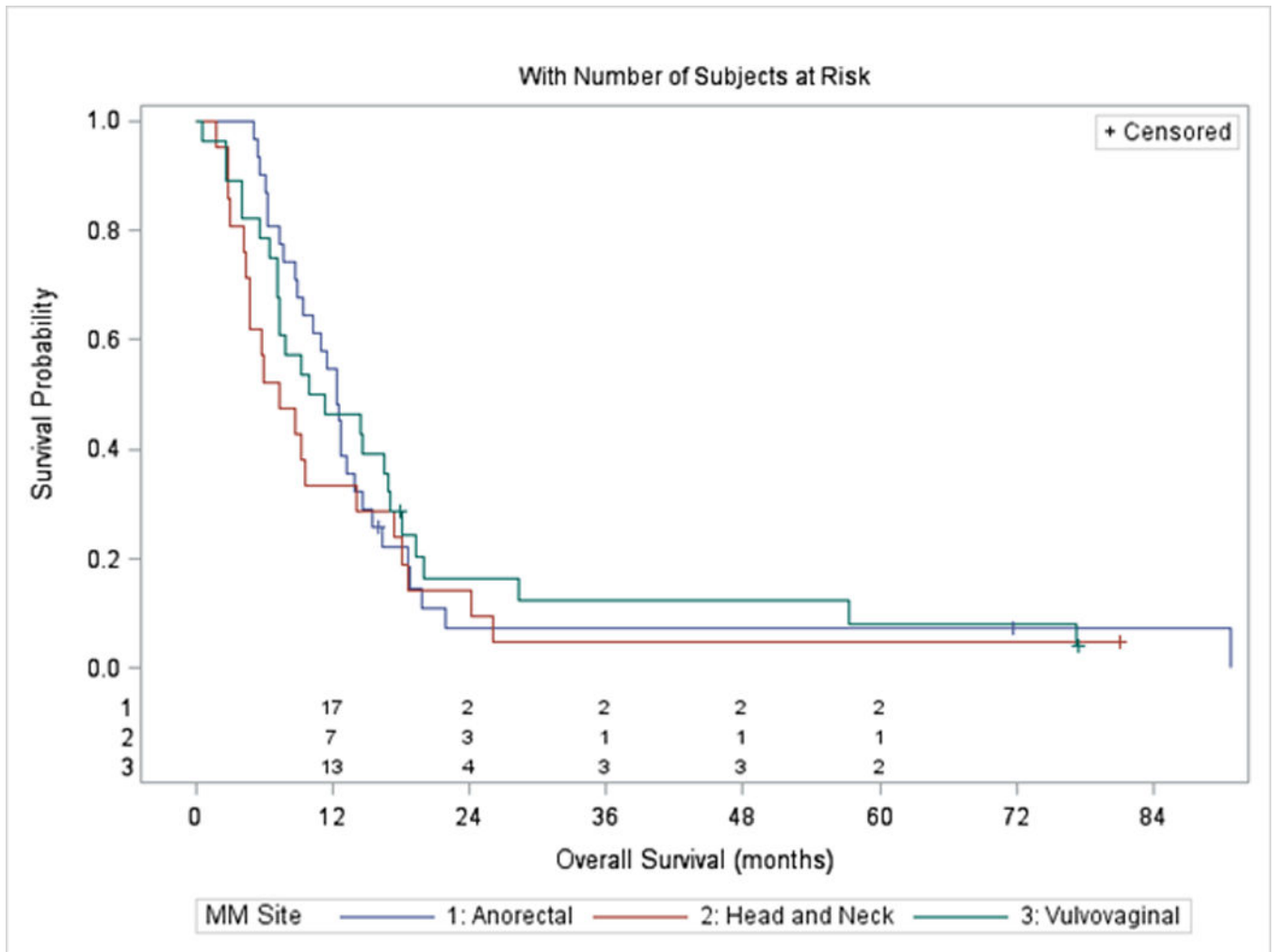


Figure 2.

Overall survival from initiation of first systemic treatment by primary site.

Overall OS was 10.3 months (95% CI 8.7–13.9 months). There was no significant difference in median OS for tumors arising from the anorectal, head and neck, and vulvovaginal regions ($p=0.57$, log-rank test).

Table 1

Patient Characteristics	Site			
	All (N=81)	Anorectal (N=31)	Head & Neck (N=21)	Vulvovaginal (N=28)
Gender				
	Male 22 (27.2)	8 (25.8)	14 (66.7)	0 (0)
	Female 59 (72.8)	23 (74.2)	7 (33.3)	28 (100)
Race				
	White 66 (81.5)	25 (80.6)	16 (76.2)	24 (85.7)
	Black 6 (7.4)	2 (6.5)	2 (9.5)	2 (7.1)
	Asian 8 (9.9)	4 (12.9)	3 (14.3)	1 (3.6)
	Unknown 1 (1.2)	0 (0)	0 (0)	1 (3.6)
Age at Diagnosis (years)	Median (range)	62.6 (32.9–89.4)	61.1 (35.7–82.1)	65.1 (39.9–89.4)
Mutation Status				
KIT				
	Wild Type 34 (42)	14 (45.2)	10 (47.6)	10 (35.7)
	Mutant 9 (11.1)	2 (6.5)	1 (4.8)	6 (21.4)
	Unknown 38 (46.9)	15 (48.4)	10 (47.6)	12 (42.9)
BRAF				
	Wild Type 35 (43.2)	12 (38.7)	9 (42.9)	14 (50)
	Mutant 3 (3.7)	2 (6.5)	1 (4.8)	0 (0)
	Unknown 43 (53.1)	17 (54.8)	11 (52.4)	14 (50)
NRAS				
	Wild Type 31 (38.3)	11 (35.5)	9 (42.9)	11 (39.3)
	Mutant 5 (6.2)	1 (3.2)	1 (4.8)	3 (10.7)
	Unknown 45 (55.6)	19 (61.3)	11 (52.4)	14 (50)
Surgery				
	No 13 (16)	3 (9.7)	4 (19)	6 (21.4)
	Yes 68 (84)	28 (90.3)	17 (81)	22 (78.6)
Adjuvant Treatment				
Chemotherapy				
	No 47 (58)	15 (48.4)	15 (71.4)	16 (57.1)
	Yes 21 (25.9)	13 (41.9)	2 (9.5)	6 (21.4)
	n/a 13 (16)	3 (9.7)	4 (19)	6 (21.4)
Radiation Therapy				
	No 43 (53.1)	27 (87.1)	1 (4.8)	14 (50)
	Yes 25 (30.9)	1 (3.2)	16 (76.2)	8 (28.6)
	n/a 13 (16)	3 (9.7)	4 (19)	6 (21.4)
At Treatment Start				

	Site				
	All (N=81)	Anorectal (N=31)	Head & Neck (N=21)	Vulvovaginal (N=28)	
Stage	M1a/M1b 16 (19.8)	8 (25.8)	3 (14.3)	5 (17.9)	
	M1c 52 (64.2)	19 (61.3)	15 (71.4)	17 (60.7)	
	M0 13 (16)	4 (12.9)	3 (14.3)	6 (21.4)	
ECOG PS	0 51 (63)	23 (74.2)	11 (52.4)	17 (60.7)	
	1 24 (29.6)	6 (19.4)	9 (42.9)	8 (28.6)	
	2 5 (6.2)	2 (6.5)	1 (4.8)	2 (7.1)	
	Unknown 1 (1.2)	0 (0)	0 (0)	1 (3.6)	
L/DH Status	Normal 36 (44.4)	14 (45.2)	8 (38.1)	14 (50)	
	Elevated 27 (33.3)	12 (38.7)	8 (38.1)	7 (25)	
	Unknown 18 (22.2)	5 (16.1)	5 (23.8)	7 (25)	
Chemotherapy					
Line 1 Duration (weeks)	Median (range) 9 (0.9–65.2)	10.5 (3.6–43.1)	7.7 (3–24.9)	8.9 (0.9–65.2)	
Line 2 Duration (weeks)	Median (range) 9 (0.3–266.7)	8 (3–57.3)	9.8 (8.8–37.2)	11.3 (0.3–266.7)	
Follow up Time (months)	Median (range) 10.3 (0.5–90.8)	12.4 (5.1–90.8)	7.3 (1.8–81.1)	10.6 (0.5–77.5)	

* This table excludes 1 patient with gallbladder primary.

Table 2

Systemic Therapy Regimens Administered

	Total N (%)	Chemotherapy Line	
		1 N (%)	2 N (%)
Cytotoxic Therapy			
<i>Single Agent Alkylator</i>			
Dacarbazine	4 (3.4)	4 (5.4)	0 (0.0)
Temozolomide	18 (15.4)	16 (21.6)	2 (4.7)
<i>Combination Alkylator</i>			
Temozolomide + Cisplatin +/- other agent(s)	6 (5.1)	4 (5.4)	2 (4.7)
CVT/CVD	34 (29.1)	23 (31.1)	11 (25.6)
Other Alkylator Combination	3 (2.6)	2 (2.7)	1 (2.3)
Temozolomide + thalidomide	10 (8.5)	9 (12.2)	1 (2.3)
<i>Other Cytotoxic</i>			
Anthracycline based	2 (1.7)	1 (1.4)	1 (2.3)
Carboplatin + paclitaxel	4 (3.4)	0 (0.0)	4 (9.3)
FOLFIRI + flavopiridol	2 (1.7)	2 (2.7)	0 (0.0)
Immune Therapy			
<i>Immune checkpoint inhibitor</i>			
CD137 Agonist	1 (0.9)	0 (0.0)	1 (2.3)
Ipilimumab	10 (8.5)	4 (5.4)	6 (14.0)
Nivolumab	2 (1.7)	0 (0.0)	2 (4.7)
Pembrolizumab	1 (0.9)	0 (0.0)	1 (2.3)
<i>Biochemotherapy</i>			
CVT/CVD + IL-2, IFN α	5 (4.3)	2 (2.7)	3 (7.0)
Other	1 (0.9)	1 (1.4)	0 (0.0)
Targeted treatment			
Imatinib	6 (5.1)	3 (4.1)	3 (7.0)
Nilotinib	2 (1.7)	0 (0.0)	2 (4.7)
Other	2 (1.7)	1 (1.4)	1 (2.3)
Other			
High dose acetaminophen	1 (0.9)	0 (0.0)	1 (2.3)
Temozolomide + imatinib	1 (0.9)	0 (0.0)	1 (2.3)
Temozolomide + sorafenib	2 (1.7)	2 (2.7)	0 (0.0)
Total	117 (100.0)	74 (100.0)	43 (100.0)

Table 3

Overall Best Response and Disease Control Rate by Type of Therapy and Melanoma Primary Site

Treatment	Line			
	1st Line		2nd Line	
	Overall Best Response	24 wk disease control	Overall Best Response	24 wk disease control
Single Agent Alkylator	2/20 10% (1–32%)	2/20 10% (1–32%)	0/2 0% (0–84%)	0/2 0% (0–84%)
Combination Alkylator	3/38 8% (2–21%)	4/38 11% (3–25%)	4/15 27% (8–55%)	1/15 7% (0–32%)
Other Cytotoxic	1/3 33% (1–91%)	2/3 67% (9–99%)	1/5 20% (1–72%)	1/5 20% (1–72%)
Immune Checkpoint Inhibitors	1/4 25% (1–81%)	1/4 25% (1–81%)	0/10 0% (0–31%)	0/10 0% (0–31%)
Biochemo	0/3 0% (0–71%)	0/3 0% (0–71%)	2/3 67% (9–99%)	0/3 0% (0–71%)
Targeted tx	1/4 25% (1–81%)	1/4 25% (1–81%)	3/6 50% (12–88%)	1/6 17% (0–64%)
Other	2/2 100% (16–100%)	0/2 0% (0–84%)	0/2 0% (0–84%)	0/2 0% (0–84%)
Total	10/74 14% (7–23%)	10/74 14% (7–23%)	10/43 23% (12–39%)	3/43 7% (1–19%)

Site	Line			
	1st Line		2nd Line	
	Overall Best Response	24 wk disease control	Overall Best Response	24 wk disease control
Anorectal	4/27 15% (4–34%)	5/27 19% (6–38%)	3/19 16% (3–40%)	1/19 5% (0–26%)
Head and Neck	1/21 5% (0–24%)	1/21 5% (0–24%)	3/8 38% (9–76%)	1/8 13% (0–53%)
Vulvovaginal	5/25 20% (7–41%)	4/25 16% (5–36%)	4/15 27% (8–55%)	1/15 7% (0–32%)
Total	10/74 14% (7–23%)	10/74 14% (7–23%)	10/43 23% (12–39%)	3/43 7% (1–19%)

Table 4

Univariate Cox Proportional Hazards Regression for Overall Survival

	HR	95% CI]	p-value
Age at Diagnosis	0.99	[0.97 – 1.01]	0.21
Site**			
Head and Neck	1.30	[0.73 – 2.33]	0.58
Vulvovaginal	0.98	[0.57 – 1.68]	
Anorectal	REF		
Gender			
Female	0.73	[0.44 – 1.22]	0.23
Male	REF		
Race			
White	0.78	[0.43 – 1.43]	0.43
Other	REF		
Stage			
M1c	1.07	[0.58 – 1.99]	0.10
M1a/M1b	0.55	[0.25 – 1.20]	
M0	REF		
LDH Status			
Elevated	1.87	[1.10 – 3.19]	0.020
Normal	REF		
ECOG PS			
0	REF		
1–2	1.69	[1.05 – 2.72]	0.030
Line 1 Subclass (2g)			
Combination	REF		
Single Agent	0.66	[0.37 – 1.16]	0.15
12 Week Response*			
Responder	0.12	[0.04 – 0.41]	<.001
Non-responder	REF		

* Modeled using time dependent covariate

** The single patient with a gallbladder primary was excluded from statistical analyses where site was a covariate.