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Impact of initial stage on metastatic melanoma survival

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Abstract

Background: Patients diagnosed with metastatic melanoma have varied clinical courses, even in patients with similar disease characteristics. We examine the impact of initial stage of melanoma diagnosis, *BRAF* status of primary melanoma, and receiving adjuvant therapy on post metastatic survival.

Methods: We studied melanoma patients presenting to Perlmutter Cancer Center at New York University (NYU) and prospectively enrolled in NYU's melanoma biospecimen database and followed up on protocol-driven schedule. Patients were stratified by stage at initial melanoma diagnosis as per AJCC 7th edition guidelines. Post-metastatic survival was determined using the Kaplan-Meier method, and Cox proportional hazards models were used to assess hazard ratios

Results: Three hundred and four out of 3204 patients developed metastatic disease over the time of follow up (median follow up 2.2 years, range 0.08–35.2 years). Patients diagnosed with stage I

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(n=96) melanoma had longer pmOS (29.5 months) than those diagnosed with stage II (n=99, pmOS 14.9 months) or stage III (n=109, pmOS 15.1 months) melanoma (p=0.036). Initial stage of diagnosis remained significant in multivariate analysis when controlling for LDH and site of metastases (primary diagnosis stage II (HR 1.44, p=0.046), stage III (HR 1.5, p=0.019)). Adjuvant treatment was associated with better survival but *BRAF* mutation status did not show an association.

Conclusion: Our data challenge the general assumption that primary melanomas converge upon diagnosis of metastatic disease and behave uniformly. Primary stage of melanoma at the time of diagnosis may be prognostic of outcome, similar to LDH and metastatic disease sites.

Keywords

metastatic melanoma; initial stage; prognosis; overall survival; clinical course

Introduction

Despite recent advances in treatment options, over 10,000 patients died of metastatic melanoma in 2016 in the US alone [1]. Systemic PD-1 inhibitors, combination CTLA-4/PD-1 immunotherapy, and combination BRAF/MEK dual targeted therapy offer the best survival benefit to patients, with clinical trials showing one-year survival rates of 60–75%, 85%, and 50–60%, respectively [2–6]. Predictive factors are needed to better identify patient outcomes.

According to 2009 AJCC 7th edition cancer staging guidelines, the only independent prognostic factors for stage IV melanoma are location of metastases and serum LDH levels.[7] The presence of visceral metastases (excluding lung metastases) has repeatedly been identified as a negative prognostic factor in studies of stage IV melanoma patients.[8–11] Presence of metastases in more than one visceral site as opposed to a single location has also been shown to be predictive of poor survival, however this distinction is not included in AJCC staging guidelines.[7–11]

Most metastatic melanoma patients present with disease history that predates stage IV diagnosis. The impact of initial cancer stage at the time of diagnosis has been studied in other tumor types but not adequately studied in melanoma.[12–15] It is unknown what impact disease history, including stage at initial diagnosis, and primary tumor characteristics have on prognosis following onset of metastatic disease. Observations regarding the relationship between stage at diagnosis and survival following stage IV diagnosis may be clinically relevant for predicting patient outcomes, and may in turn suggest that stage-dependent biological characteristics of disease at first intervention are persistent following recurrence at a later stage.

Here, we examine the association between stage of initial melanoma diagnosis and survival following the diagnosis of metastatic melanoma using our database of NYU patients enrolled within the last 14 years. We compared tumor and patient characteristics at time of initial diagnosis and at time of diagnosis of metastatic disease, in addition to association with survival. We assessed if presence of a *BRAF* mutation affected outcomes, as well as the effect of adjuvant therapy on survival outcomes.

Methods

Study Population

We studied melanoma presenting to Perlmutter Cancer Center, NYU Langone Medical Center from August 2002 to December 2015 and prospectively enrolled in the Interdisciplinary Melanoma Cooperative Group (IMCG) database[16]. Some patients were diagnosed with melanoma prior to their presentation to NYU. The study was approved by the Institutional Research Board at NYU and all patients provided informed written consent at the time of enrollment. All patients underwent surgical treatment of the initial primary tumor. *BRAF* and *NRAS* mutational status was determined directly, either for clinical purposes, including clinical trial enrollment, or research, by qPCR, sequencing, or targeted next generation sequencing, from tumor specimens, when available. Other clinical characteristics were extracted from patient charts. Date of diagnosis was defined as the biopsy date of the primary tumor and was used to calculate age at diagnosis, follow-up time, and time to recurrence. Recurrence and survival information were collected by active prospective follow-up every six months for all patients enrolled in the database.

Primary melanoma diagnosis refers to the time at which the patient was first diagnosed with melanoma—either Stage I, II, or III, as defined by AJCC cancer staging 7th edition. Metastatic disease refers to the time at which the patient was diagnosed with metastatic melanoma, stage IV disease. Characteristics recorded for each patient included age, gender, date of primary melanoma diagnosis, primary tumor thickness, ulceration, anatomic site, clinical stage at primary melanoma diagnosis, adjuvant therapy received, date of metastatic diagnosis, site of distant metastases, LDH level, *BRAF* and *NRAS* mutational status, systemic treatment received, and ECOG performance status. Adjuvant therapy was defined as treatment given after the initial surgery and before the date of metastatic diagnosis. Therapy included interferon, GM-CSF (Leukine®), and vaccine clinical trials.

Statistical Analysis

Patients were categorized based on clinical stage at primary melanoma diagnosis, as defined by AJCC cancer staging 7th edition criteria. Protocol based follow-up of disease status was used to identify melanoma patients who developed metastatic disease and assess disease course and response to treatment. Time to metastatic recurrence was defined as the time from primary melanoma diagnosis until diagnosis of metastatic disease. Post metastatic OS (pmOS) was defined as the time from diagnosis of metastatic disease until death or date of last follow up. The Kaplan-Meier method was used to calculate survival curves based on clinical stage at primary melanoma diagnosis, adjuvant therapy, systemic treatment types, and *BRAF* mutational status. The p-values for the difference of survival curves are calculated based on log-rank test. Cox Proportional hazards models were used to assess hazard ratios, 95% confidence intervals, and p-values for pmOS. The univariate and multivariate Cox model was used to assess the associations of clinical stage at primary melanoma diagnosis, primary tumor characteristics, adjuvant therapy, other clinical characteristics of metastatic disease, and systemic treatment types with survival outcomes.

Results

Primary Diagnosis of Stage I Melanoma Associated with Improved Post-Metastatic Survival

In our cohort of 3204 melanoma patients presenting to NYU between 2002 and 2015, 304 patients (11%) developed metastatic disease during follow up. The median time to diagnosis of metastatic disease from time of initial diagnosis was 2.2 years (range 0.08 to 35.2 years). Median follow-up was 25 months post diagnosis of metastatic disease (range 0.5 to 167.8 months) for surviving patients. Patient characteristics at the time of primary melanoma diagnosis are summarized in Table 1.

The majority of patients were male (66.4%, 202/304) and the median age at the time of primary melanoma diagnosis was 59.5 years (range 17.7 to 93.6 years), reflective of the general worldwide melanoma distribution. Fifty patients (17.2%) presented with primary tumors ≤1.0 mm in thickness, 78 (26.9%) with tumors between 1.01 and 2.0 mm, 81 (27.9%) between 2.01 and 4.0 mm, and 81 (27.9%) greater than 4 mm. Primary tumor ulceration was assessed in 88.5% (269/304) of the cohort, of which 50.2% (135/269) were ulcerated. The median time to diagnosis of metastatic disease from time of initial diagnosis was 26.6 months (range 0 to 422.8 months).

When categorized by the initial stage of primary melanoma diagnosis, 96 patients (31.6%) presented with stage I disease, 99 (32.6%) with stage II disease, and 109 (35.8%) with stage III disease. Survival analysis of patients stratified by clinical stage at the time of primary melanoma diagnosis demonstrated a significant difference in pmOS among the groups (p=0.036; Figure 1). Patients diagnosed with stage I melanoma had better pmOS (29.5 months) than patients diagnosed with stage II or III disease (pmOS 14.9 and 15.1 months, respectively). No significant differences in post metastatic OS were found when comparing substages of each clinical stage (e.g. stage IA vs. IB) at the time of primary melanoma diagnosis (Supplemental Figure 1). Univariate analysis revealed that primary melanoma diagnosis of stage II (HR 1.42, p=0.041) or stage III (HR 1.51, p=0.015) were associated with worse post metastatic OS than those initially diagnosed with stage I disease (Table 2). The association between initial stage II and stage III diagnosis and pmOS (adjusted HR 1.42, p=0.046 and adjusted HR 1.56, p=0.010, respectively) remained statistically significant in multivariate analysis adjusting for LDH, age, gender, and presence of brain metastases.

Elevated LDH and Stage M1c Disease at Metastatic Recurrence Associated with Worse Survival

Patient characteristics at the time of diagnosis of metastatic disease were also analyzed (Table 1). LDH levels were available for 171 patients (56.3%, 171/304), and 52 (30.4%, 52/171) of these patients had elevated LDH levels. Approximately 77 percent of patients (235/304) were classified as having substage M1c disease at the time of metastatic disease (Table 1). Two hundred and seventeen (71.4%) patients were confirmed deceased at the time of publication. The pmOS of all patients was 14.4 months (range 0 to 167.8 months). The median age of patients at the time of diagnosis of metastatic disease was 64 years (range 22.0 to 97.1 years). We next investigated the association between known prognostic factors and initial stage of melanoma diagnosis. In multivariate analysis, male gender is associated

with worse prognosis, but is not statistically significant (adjusted HR 1.20, p=0.225, Table 2).. Increasing age at primary diagnosis, however, was prognostic of pmOS (adjusted HR 1.16 per 10 year increase in age, p=0.001, Table 2). High LDH level was associated with significantly worse OS in multivariate analysis (adjusted HR 1.65, p=0.001).

BRAF Mutation Status is not associated with Survival Outcomes

Genomic characterization of melanoma tumors has become standard practice, used to as characterize melanoma tumors, as well as identify suitable treatments with targeted therapies. We next assessed the association between *BRAF* mutation status and prognosis in this cohort. *BRAF* mutation status was available for 240 patients (79.0%, 240/304). Of the patients for whom data was available, 115 out of 240 (47.9%) had *BRAF* mutations. Analysis of time to metastatic disease based on *BRAF* status revealed no significant difference in progression free survival between patients with *BRAF* mutations and those who were wild-type (median time to recurrence 31.3 vs. 24.9 months, p=0.51; Figure 2A). Survival analysis based on *BRAF* mutation status showed no significant difference in pmOS between the two groups (pmOS 16.8 months vs. 18.9 months, *BRAF* mutant vs wild-type, respectively, p=0.81; Figure 2B).

Adjuvant Therapy associated with longer Post-Metastatic Survival

We investigated the impact of additional interventions at the time of primary melanoma diagnosis on post metastatic survival outcomes. One hundred seventeen patients were eligible for adjuvant therapy prior to diagnosis of metastatic disease, and 91 patients (29.9%, 91/304) received adjuvant therapy. Twenty-five patients (8.2%, 25/304) received interferon, 21 (6.9%, 21/304) received GM-CSF (Leukine®), and 41 (13.4%, 41/304) were treated with a vaccine clinical trial; one patient received an unclassified adjuvant therapy; ten patients received more than one adjuvant treatment. Fifteen patients received combination adjuvant and systemic therapy and were not included for analysis. Survival analysis of patients stratified by receipt of adjuvant therapy demonstrated that those who had received specified adjuvant treatment had significantly better post metastatic OS than those who did not (median pmOS 24.3 vs. 15.7 months, p<0.01; Figure 3). Receipt of adjuvant therapy was also associated with significantly better post metastatic OS in multivariate analyses (adjusted HR 0.66, p=0.012; Table 2).When stratified by the specific type of adjuvant therapy received, there was no significant difference in post metastatic OS among the treatments (Interferon median OS 2.6 years vs. GM-CSF median OS 2.1 years vs. vaccine median OS 2.3 years, p=0.43; Supplemental Figure 2).

Immunotherapy Improves Survival of Patients with Metastatic Disease

At the time of diagnosis of metastatic disease in the 304 patients, 144 patients (47.4%) received immunotherapy, 76 (25%) received targeted therapy, and 141 (46.4%) received chemotherapy as systemic treatment for their metastatic disease. Ninety six patients (31.2%) received more than one type of systemic therapy. Survival analysis of patients stratified by treatment demonstrated that patients who were treated with immunotherapy had significantly better pmOS than those who were not treated with immunotherapy (median OS 24.6 months vs. 10.8 months, respectively; p<0.01; Figure 4A). There was no significant difference in OS between patients treated with targeted therapy and those who were not treated with targeted

therapy (median OS 17.6 months vs. 15.7 months, respectively; p=0.51; Figure 4B). Similarly, no difference was observed between those who received chemotherapy and those who did not receive chemotherapy (median OS 16.4 months vs. 19.6 months, respectively; p=0.85; Figures 4C). Treatment with immunotherapy was also associated with significantly better OS multivariate analysis (adjusted HR 0.57, p<0.001; Table 2). Treatment with either targeted therapy or chemotherapy was not associated with significant differences in pmOS (Table 2).

Discussion

Our investigation suggests that initial stage at primary melanoma diagnosis impacts survival after developing metastatic disease. Initial diagnosis of stage II and Stage III melanoma was associated with significantly worse pmOS compared to initial diagnosis of stage I disease. In addition, elevated LDH and Stage M1c disease at the time of diagnosis of metastatic disease continue to negatively impact on metastatic melanoma survival.

There are limited studies investigating the prognostic role of initial tumor stage on post metastatic survival. A study of 58 patients with recurrent Hodgkin's lymphoma found initial stage of disease to be the most important predictor of survival following relapse.[14] Patients who initially presented with stage IA-IIIA$_{S+N-}$ disease had a 4-year post-relapse survival rate of 81% compared with those originally diagnosed with stage IIIA$_{S\pm N+}$-IIIB disease who had a survival rate of 42% (p<0.05).[14] Similarly, a Danish study of 2427 women with breast cancer demonstrated decreased survival in patients diagnosed with breast cancer at a more advanced disease, indeed, mortality was nearly doubled for patients diagnosed with Stage III breast cancer compared to Stage 1.[12] In contrast a study of 598 patients with stage IV colorectal cancer did not find a significant difference in post metastatic OS between patients who initially presented with stage 0-III disease compared with those who presented with distant metastases (HR 0.92, p=0.680).[15] The discordance of results is possibly due to the population being studied and study design, retrospective versus prospective. Moreover, it is possible that disease specific factors, such as hormonal factors or other cellular cofactors, can influence tumor biology and disease prognosis.

Thickness is a main determinant of initial stage in primary melanoma. Our data are in concordance with a recent study evaluating the prognostic value of primary tumor characteristics in stage IV melanoma patients. The study included 227 patients diagnosed with stage IV melanoma, though the total melanoma population is not indicated, and demonstrated increasing thickness to be an independent predictor of worse post metastatic survival (HR 1.09, 95% CI 1.02–1.06, p<0.01)[13], but the analysis was limited to tumor thickness. Additional characteristics, including ulceration, lymph nodes, and in transit/satellite metastases, also contribute to staging information. The authors hypothesize that thicker tumors have distinct biologic attributes that not only contribute to their aggressive nature but persist throughout disease progression as well.[13]

In our study, M1c stage, a surrogate for location of metastases, was independently prognostic of worse OS, consistent with previous studies.[8–11] Similarly, our study found high LDH levels to be an independent marker of worse OS, which is consistent with

previous reports.[7,17] Our study also contributes to the ongoing debate of the prognostic significance of a *BRAF* mutation. [18–20] Our analysis demonstrated that the presence of a *BRAF* mutation had no effect on the development of metastatic disease and no effect on overall survival once diagnosed with metastatic disease. Our results are consistent with recent findings demonstrating no difference in OS between *BRAF*-mutant and WT populations from the time of stage IV diagnosis.[18] Importantly, *BRAF*-mutant disease was not predictive of survival on in our study. In our study, we also observed that patients who received adjuvant therapy had improved pmOS. Our patient cohort does represent a smaller sample size than large multicenter studies, and could be reflective of the patient population at our institution, as well as the fact that this is an observational study. Moreover, patients were treated with agents prior to the use of immune checkpoint inhibitors in the adjuvant setting. Adjuvant therapy is used to reduce the risk of recurrence in patients with high-risk local or regional melanoma with a 5-year risk of recurrence greater than 30%.[21] Previous clinical trials of adjuvant treatments have shown little benefit with high toxicity[22–25], though recent randomized studies demonstrated improvement in disease-free survival when treated with high dose ipilimumab[26] and nivolumab.[27]

Our analysis cannot be appreciated without considering our study's limitations. This is a single-center study at a large, academic medical center, which may bias the patient population. It is highly likely that patients treated with immunotherapy, targeted therapy, and certain adjuvant treatments received treatment as part of a clinical trial, most of which have strict inclusion criteria related to performance status, metastatic sites, and treatment history, which could influence outcomes. In addition, it is possible that patient-related factors—for example, frequency of routine medical visits—might affect diagnosis of primary and metastatic melanoma. Patients with high risk stage II and III disease are seen more often by oncologists in follow-up and receive more frequent whole body imaging as compared to stage I melanoma patients. Stage I melanoma patients do not require oncology follow up and do not undergo surveillance imaging unless there are symptoms that necessitate scans. This has potential for contributing towards a lead-time bias in the detection of metastatic disease (in the form of asymptomatic metastases) for patients presenting at stage II or III. We do not believe, however, that our results have been affected in this way; our results suggest longer survival for patients diagnosed with stage I disease, where a lead-time bias would presumably influence survival calculations towards longer survival for patients undergoing vigilant disease monitoring.

In conclusion, we found initial stage, in particular stage I disease at primary diagnosis, to be a positive prognostic factor following diagnosis of metastatic disease, as well as receipt of adjuvant treatment prior to metastatic diagnosis. Our results highlight the need for further investigation of metastatic disease behavior based on initial stage, both clinically and biologically. Vigilant, early detection and adjuvant treatment of disease may be of benefit to patients and should continue to be evaluated.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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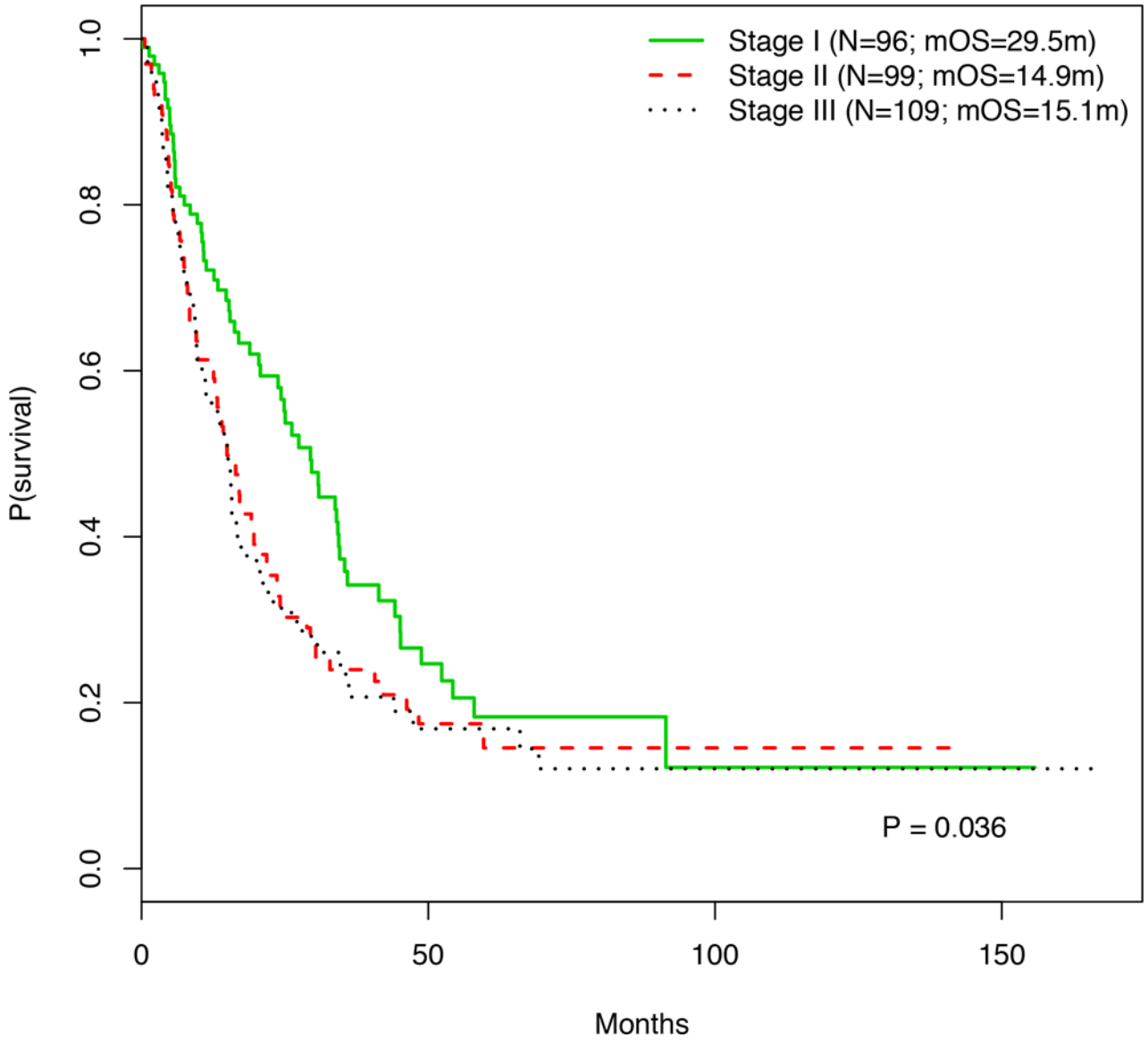

Figure 1.
Kaplan-Meier curve displaying the post metastatic OS of patients stratified by their original clinical stage of their primary melanoma.

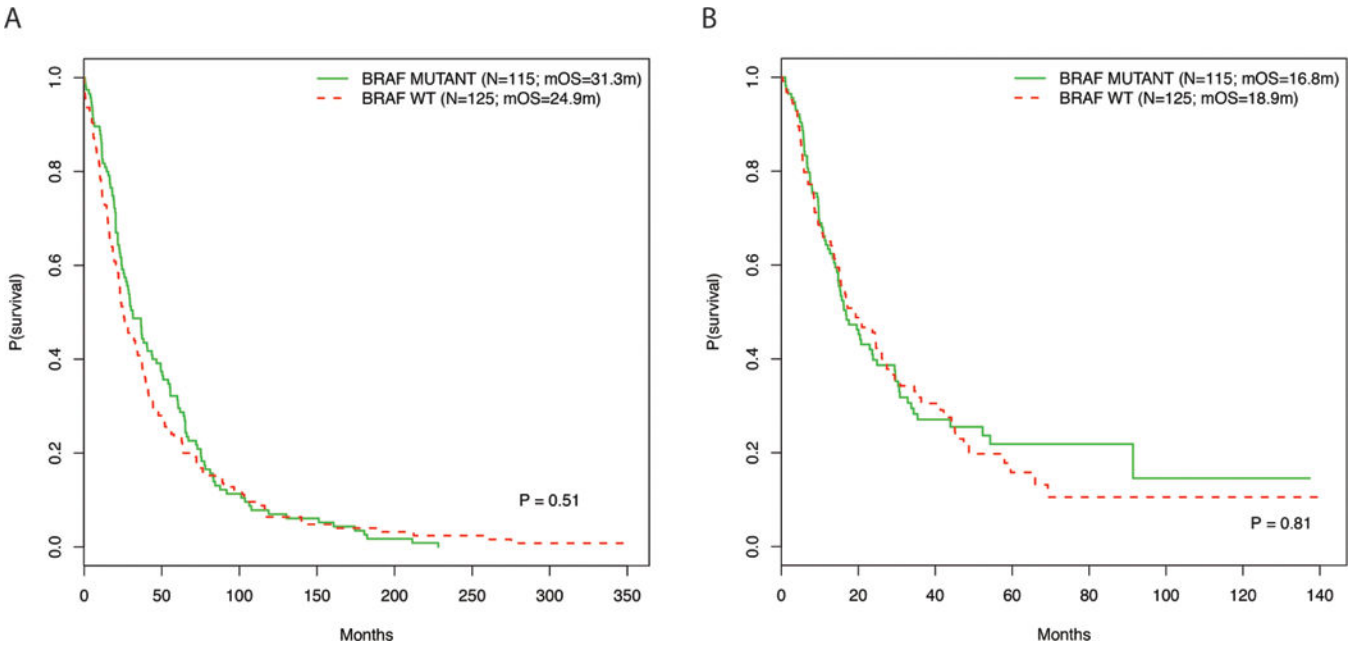

Figure 2.

Kaplan-Meier curves displaying the (A) time to metastatic recurrence from primary melanoma diagnosis and (B) post-metastatic OS and for patients stratified by BRAF mutation status.

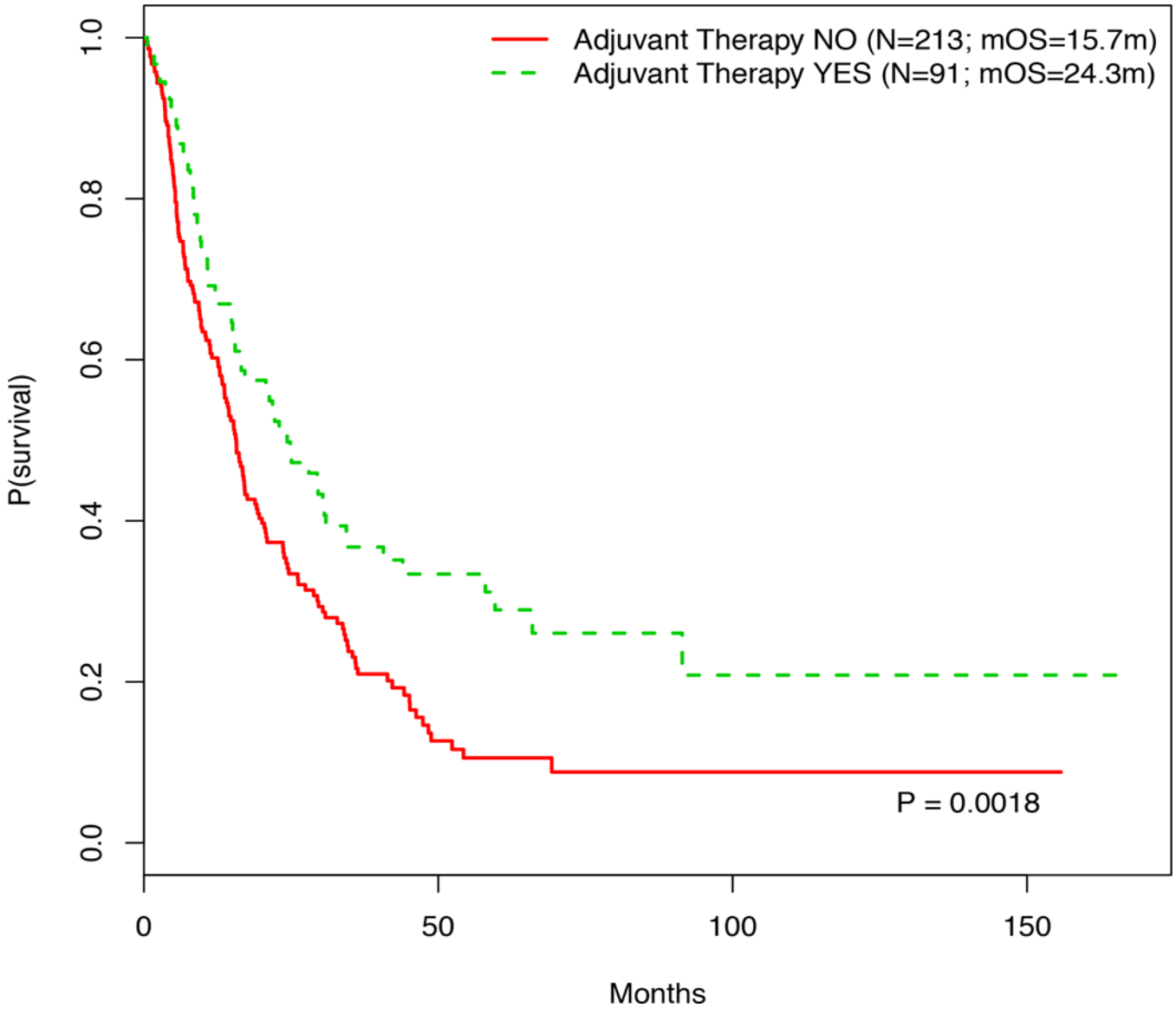

Figure 3.
Kaplan Meier curve showing the post metastatic OS of patients based on receipt of adjuvant therapy at the time of primary melanoma diagnosis.

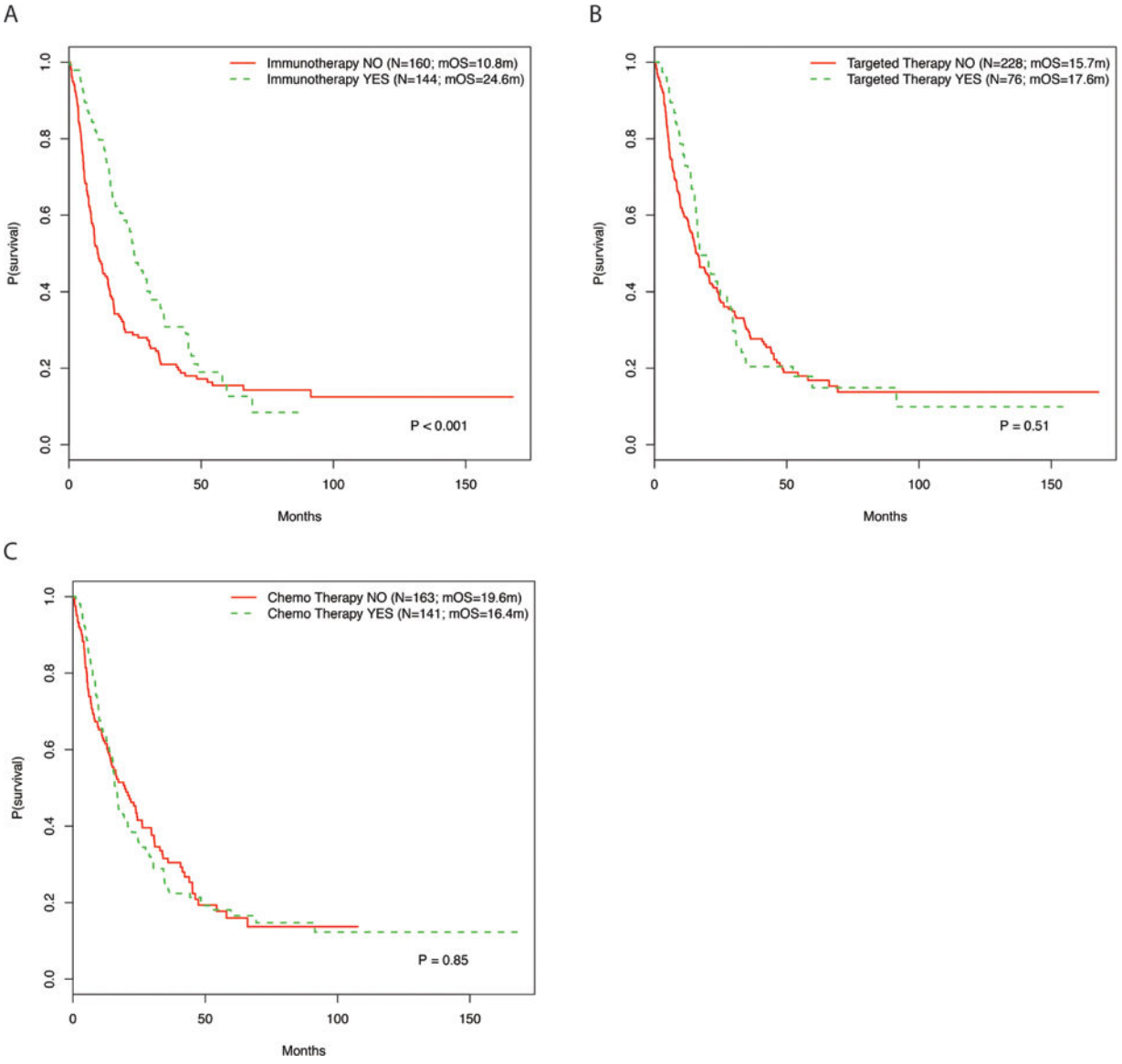

Figure 4.

Kaplan Meier curves showing the post-metastatic OS of patients based on receipt of (A) immunotherapy, (B) targeted therapy, and/or (C) chemotherapy for treatment of their metastatic melanoma.

Table 1.

Melanoma patient characteristics stratified by stage at diagnosis.

Patient/tumor characteristics		All (N=304)	Initial stage at diagnosis			P-value
			Stage I (N=96)	Stage II (N=99)	Stage III (N=109)	
Age (y) at primary diagnosis, median (range)		60 (18–93)	55 (18–82)	67 (31–93)	57 (20–84)	<0.001
Sex, n (%)	Female	102 (33.6)	32 (33.3)	30 (30.3)	40 (36.7)	0.81
	Male	202 (66.4)	64 (66.7)	69 (69.7)	69 (63.3)	
Primary tumor thickness (mm), n (%)	≤1.0	50 (17.2)	45 (47.9)	0 (0.0)	5 (5.1)	<0.001
	1.01–2.0	78 (26.9)	49 (52.1)	14 (14.3)	15 (15.3)	
	2.01–4.0	81 (27.9)	0 (0.0)	47 (48.0)	34 (34.7)	
	>4.0	81 (27.9)	0 (0.0)	37 (37.8)	44 (44.9)	
Primary tumor ulceration, n (%)	Absent	134 (49.8)	70 (90.9)	25 (26.0)	39 (40.6)	<0.001
	Present	135 (50.2)	7 (9.1)	71 (74.0)	57 (59.4)	
Primary tumor site, n (%)	Extremity	120 (40.3)	38 (39.6)	40 (40.4)	42 (40.8)	0.06
	Head/neck	76 (25.5)	22 (22.9)	37 (37.4)	17 (16.5)	
	Trunk	98 (32.9)	34 (35.4)	22 (22.2)	42 (40.8)	
	Many	4 (1.3)	2 (2.1)	0 (0.0)	2 (1.9)	
Clinical stage at primary diagnosis, n (%)	IA	25 (8.2)	25 (26.0)	0 (0.0)	0 (0.0)	<0.001
	IB	71 (23.4)	71 (74.0)	0 (0.0)	0 (0.0)	
	IIA	30 (9.9)	0 (0.0)	30 (30.3)	0 (0.0)	
	IIB	41 (13.5)	0 (0.0)	41 (41.4)	0 (0.0)	
	IIC	28 (9.2)	0 (0.0)	28 (28.3)	0 (0.0)	
	IIIA	29 (9.5)	0 (0.0)	0 (0.0)	29 (26.6)	
	IIIB	46 (15.1)	0 (0.0)	0 (0.0)	46 (42.2)	
	IIIC	34 (11.2)	0 (0.0)	0 (0.0)	34 (31.2)	
Primary tumor histologic subtype, n (%)	Acral lentiginous	19 (8.1)	5 (7.8)	4 (4.5)	10 (12.3)	<0.001
	Nodular	123 (52.6)	16 (25.0)	57 (64.0)	50 (61.7)	
	Superficial spreading	69 (29.5)	38 (59.4)	13 (14.6)	18 (22.2)	
	Other	23 (9.8)	5 (7.8)	15 (16.9)	3 (3.7)	
Adjuvant therapy received at primary diagnosis, n (%)	No	213 (70.1)	74 (77.1)	70 (70.7)	69 (63.3)	0.20
	Yes	91 (29.9)	22 (22.9)	29 (29.3)	40 (36.7)	
Time to metastatic recurrence (months), median (range)		26.7 (0.0–422.8)	65.1 (0.5–350.1)	22.6 (0.4–422.8)	16.2 (0.0–117.6)	<0.001
Clinical substage at metastatic recurrence, n (%)	M1a	25 (8.2)	9 (9.4)	6 (6.1)	10 (9.2)	0.78
	M1b	44 (14.5)	18 (18.8)	13 (13.1)	13 (11.9)	
	M1c	235 (77.3)	69 (71.9)	80 (80.8)	86 (78.9)	
Site of distant metastases, n (%)	Brain	32 (10.5)	12 (12.5)	8 (8.1)	12 (11.0)	0.97
	Visceral	176 (57.9)	56 (58.3)	58 (58.6)	62 (56.9)	
	Brain & visceral	96 (31.6)	28 (29.2)	33 (33.3)	35 (32.1)	
LDH, n (%)	High	52 (30.4)	21 (35.6)	15 (28.8)	16 (26.7)	0.75
	Normal	119 (69.6)	38 (64.4)	37 (71.2)	44 (73.3)	

Patient/tumor characteristics		All (N=304)	Initial stage at diagnosis			P-value
			Stage I (N=96)	Stage II (N=99)	Stage III (N=109)	
BRAF status, n (%)	Mutant	115 (47.9)	48 (56.5)	30 (41.1)	37 (45.1)	0.25
	Wild type	125 (52.1)	37 (43.5)	43 (58.9)	45 (54.9)	
NRAS status, n (%)	Mutant	32 (19.8)	8 (15.4)	13 (23.6)	11 (20.0)	0.76
	Wild type	130 (80.2)	44 (84.6)	42 (76.4)	44 (80.0)	
Chemotherapy received at metastatic recurrence, n (%)	No	163 (53.6)	53 (55.2)	56 (56.6)	54 (49.5)	0.76
	Yes	141 (46.4)	43 (44.8)	43 (43.4)	55 (50.5)	
Immunotherapy received at metastatic recurrence, n (%)	No	160 (52.6)	42 (43.8)	58 (58.6)	60 (55.0)	0.20
	Yes	144 (47.4)	54 (56.2)	41 (41.4)	49 (45.0)	
Targeted therapy received at metastatic recurrence, n (%)	No	228 (75.0)	65 (67.7)	79 (79.8)	84 (77.1)	0.24
	Yes	76 (25.0)	31 (32.3)	20 (20.2)	25 (22.9)	
ECOG performance status, n (%)	0	204 (77.9)	67 (80.7)	72 (79.1)	65 (73.9)	0.73
	>0	58 (22.1)	16 (19.3)	19 (20.9)	23 (26.1)	
Survival outcome, n (%)	Alive	75 (24.7)	29 (30.2)	23 (23.2)	23 (21.1)	0.76
	Deceased	217 (71.4)	62 (64.6)	73 (73.7)	82 (75.2)	
	Unknown	12 (3.9)	5 (5.2)	3 (3.0)	4 (3.7)	
Follow up time (months), median (range)		25 (0.5–167.8)	22 (5.1–155.8)	37.5 (5.5–141.3)	27.7 (0.5–167.8)	0.84

Table 2.

Univariate analysis and multivariate analysis of post-metastatic overall survival (pmOS) based on clinical stage of initial melanoma diagnosis and other clinicopathological characteristics.

Patient/tumor characteristics	HR (95% CI)	P-value
Univariate analysis		
Clinical stage at initial diagnosis (vs. stage I)		
Stage II	1.42 (1.15–2.00)	0.041
Stage III	1.51 (1.08–2.10)	0.015
Multivariate analysis		
Clinical stage at initial diagnosis (vs. stage I)		
Stage II	1.42 (1.01–2.01)	0.046
Stage III	1.56 (1.11–2.18)	0.010
LDH (high vs. normal)	1.65 (1.25–2.20)	0.001
Age at initial diagnosis (per 10 year increase)	1.16 (1.06–1.27)	0.001
Sex (male vs. female)	1.20 (0.89–1.60)	0.225
Site of metastasis (brain metastasis vs no brain metastasis)	1.61 (1.23–2.11)	0.001