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Real world experience with omission of therapeutic lymph node dissection in clinical stage III malignant melanoma treated with checkpoint or kinase inhibition systemic therapy

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Abstract

Background: Management of clinical stage III melanoma, which historically was treated with surgical therapeutic lymph node dissection (TLND), has changed significantly due to the introduction of effective systemic therapies including immune checkpoint and BRAF/MEK inhibitors. We asked how surgical interventions changed progression free survival and overall survival in this population.

Methods: The Flatiron Health electronic health records database for Advanced Melanoma was queried for patients with clinical stage III melanoma treated between 2018 and 2022 with systemic therapy. Patients were stratified by receipt of TLND.

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Ethics statement

None

Declaration of Competing Interest

Dr. Stewart is a consultant for Merit Medical. Dr. Medina reports Institutional Principal Investigator (institutional funding) for the following: Bristol Myers Squibb, Genentech, Inc., Iovance pharmaceuticals, Merck & Co., Inc., Agenus, Other-Anaveon, Other-Bioatla, Inc, Other-Infla-Rx, Other-Moderna, Other-Replimune, Other-TriSalus, Other-Ultimovacs, Pfizer Inc., Regeneron Pharmactcls, SeaGen, and Immatics. All other authors had nothing to report.

Results: There were 533 patients with clinical stage III melanoma treated with systemic therapy identified; 235 (44.1 %) underwent TLND prior to systemic therapy, 17 (3.2 %) underwent TLND after receipt of systemic therapy, and 281 (52.7 %) received systemic therapy alone and did not have surgery. There were 38.1 % (n = 203) who experienced disease progression at 2 years. Patients in the no surgery group had the best 2-year progression free survival (67.3 %) compared to the upfront surgery (58.3 %) and surgery after systemic therapy groups (23.5 %, p = 0.001), and there was no difference in 2-year overall survival (82.2 % vs 80.0 % vs 82.3 %, p = 0.81). These findings persisted on multivariable analysis.

Conclusions: In this modern era dataset, more than half of patients with clinical stage III melanoma were treated with systemic therapy alone, despite guideline recommendations for TLND. They had superior progression free survival and similar overall survival compared to those also treated with potentially morbid surgery. Randomized data are needed to evaluate appropriate omission of surgery in this patient population.

Keywords

Stage III melanoma; Lymphadenectomy; Therapeutic lymph node dissection; Immunotherapy; Immune checkpoint inhibitors

Introduction

The management of clinically node-positive stage III malignant melanoma has changed significantly in the last decade, due to use of immune checkpoint inhibitors and BRAF/MEK inhibitors (systemic therapy) and surgical care[1]. The standard of care for this disease has traditionally been surgical treatment with wide local excision (WLE) of the primary lesion and therapeutic lymph node dissection[2,3]. Therapeutic lymph node dissection, however, is associated with significant morbidity including wound infections and chronic lymphedema in up to 30 % of patients[4–7]. The development of effective systemic therapies in recent years, has thus led to a paradigm shift in the treatment of this disease.

With systemic therapy response rates from 33 % to 68 %[8–14], interest in neoadjuvant treatment and de-escalation of surgical care has increased[15]. Most recently, the prospective randomized phase II Southwest Oncology Group Cancer Research Network S1801 trial found that patients with stage III and IV melanoma who received pembrolizumab peri-operatively had longer event-free survival than patients who received pembrolizumab after therapeutic lymph node dissection[16]. Recently presented data from the phase III NADINA trial of patients with clinical stage III melanoma echoed these results with longer event-free survival in the neoadjuvant ipilimumab-nivolumab arm[17]. Further, the phase II PRADO trial evaluated omission of therapeutic lymph node dissection in patients with clinical stage IIIB-D melanoma with a major pathologic response to neoadjuvant ipilimumab-nivolumab, and found that this protocol enabled treatment de-escalation in 59 % of subjects, with 93 % recurrence free survival at 24 months[18]. Outside of these trials, and prior to any public presentation of these trial results, the authors have also observed changes in practice patterns, with omission of therapeutic lymph node dissection in an increasingly larger percentage of these patients.

Given these recent developments, we sought to compare the outcomes of patients with clinically node-positive stage III melanoma who were treated with modern systemic therapies alone without surgery, compared to those treated with therapeutic lymph node dissection and modern systemic therapies. We hypothesized that surgical interventions would change progression free survival but would not change overall survival. To answer this question, we leveraged a large, real-world clinical database of patients with advanced melanoma that included detailed descriptions of the systemic and surgical therapies patients received.

Methods

We performed this study using the Flatiron Health electronic health records database for Advanced Melanoma (Flatiron Health Inc., New York, NY, USA). Flatiron Health is a health data company that aggregates electronic health records data from more than 280 community cancer centers and 8 major academic cancer centers across the United States. Patients were included if they were 18 years or older, presented with newly diagnosed stage III melanoma with N stages N1b, N2b, N2c, N3b, or N3c between 1/2018 and 8/2022, and were treated with either immune check point inhibitors or BRAF/MEK inhibitors at some point during their treatment. Patients with AJCC stage IIIA disease, and with N stages N1a, N1c, N2a, and N3a were excluded. Dual immune therapy was defined as treatment with any two immune check point inhibitors at the same time. This study was approved by the Colorado Multiple Institutional Review Boards (COMIRB 23–0876).

Patients were classified into three groups: those who underwent therapeutic lymph node dissection prior to systemic therapy (upfront surgery group), those who underwent therapeutic lymph node dissection after receipt of systemic therapy (surgery after systemic therapy group), and those who did not undergo therapeutic lymph node dissection at any time during their treatment (no surgery group). Systemic therapy was divided by duration of treatment < 3 months, 3 months – 1 year, and > 1 year. Eastern Cooperative Oncology Group (ECOG) performance status was categorized as either 0–1 or 2 + [19].

Descriptive statistics of the cohort were generated. Kaplan-Meier survival analysis was performed to generate overall survival and progression-free survival curves and account for censoring and missing data. Cox proportional hazard models were generated to adjust for confounding variables. Confounders were accounted for using backward elimination of prespecified patient demographic variables. Duncan's correction was used to adjust for multiple comparisons and the likelihood ratio test was performed for comparison of survival curves. Statistics were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Demographics and treatment

Patient demographics, disease characteristics, and treatments are presented in Table 1. There were 533 patients with clinical stage III cutaneous melanoma who met the inclusion criteria, with a median follow up time of 21.6 (IQR 12.4–35.1): 235 (44.1 %) who underwent

therapeutic lymph node dissection prior to systemic therapy (upfront surgery group), 17 (3.2 %) who underwent therapeutic lymph node dissection after receipt of systemic therapy (surgery after systemic therapy group), and 281 (52.7 %) did not undergo therapeutic lymph node dissection during the study period (no surgery group). Demographics between the groups were similar regarding age (mean 64 years old, SD (14.5), gender (30.4 % female), race (81.4 % Caucasian), body mass index (29.9), ECOG status (81.4 % 0–1), and health insurance (64.2 % commercial). Differences were detected between groups regarding T and N staging, BRAF mutation status, and resectability, which are presented in detail in Table 1. Notably, patients in the upfront surgery group were more likely to have N3b and N3c disease (36.2 % vs 17.4 % in the no surgery group), to have BRAF mutations (43 % vs 31.3 % in the no surgery group), and to be considered resectable (91.9 % vs 61.9 % in the no surgery group). Of note, only 4 % of patients in the no surgery group were categorized as "unresectable," but 33.8 % had this variable listed as "unknown."

Systemic treatment was categorized by both type (BRAF/MEK inhibitors, immune check point inhibitors with further sub-stratification for dual immune check point inhibitor therapy), and by duration of treatment. Nearly all (94.7 %) patients were treated with immune check point inhibitors, and 20.4 % were treated with BRAK/MEK inhibitors. Duration of treatment was not statistically different between groups. Most patients received immune check point inhibitor treatment for a duration between 3 months and 1 year. Only 30.6 % of patients in the no surgery group received immune check point inhibitors for > 1 year.

Progression free survival

Data regarding treatment and oncologic outcomes are presented in Table 2. For the entire cohort, there were 38.1 % (n = 203) of patients who experienced disease progression at 2 years. Patients in the no surgery group were more likely to have local progression, but less likely to have distant progression compared to the upfront surgery group. Patients in the no surgery group had the best progression free survival at 2 years (67.3 %) compared to the upfront surgery (58.3 %) and surgery after systemic therapy groups (23.5 %, p = 0.001, Table 2, Fig. 1). This finding persisted in multivariable analysis adjusted for age, ECOG status, T-stage, BRAF mutation status, and type of systemic therapy delivered, each of which were independently associated with progression free survival (Table 3). Of patients in the surgery after systemic therapy group, 9/17 (52 %) experienced progression prior to undergoing therapeutic lymph node dissection (Table 2).

Overall survival

The 2-year overall survival of the entire cohort was 81.2 % (n = 433). There was no difference in 2-year overall survival identified when comparing the no surgery (82.2 %) upfront surgery (80.0 %), and surgery after systemic therapy groups (82.3 %, p = 0.81, Table 2, Fig. 2). This finding persisted on multivariable analysis adjusted for age, ECOG status, T-stage, and type of systemic therapy delivered, each of which were independently associated with overall survival (Table 4).

Discussion

Here we present an analysis of a large real world multicenter clinical database to evaluate clinical outcomes of patients with clinical stage III melanoma treated with modern systemic therapy, with and without therapeutic lymph node dissection from 2018 to 2022. This is the first study to our knowledge that examines outcomes of patients with clinical stage III melanoma who received modern systemic therapy without surgical intervention. We found that when upfront surgery was the standard of care/guideline recommendation for management of clinical stage III melanoma, remarkably, less than half of patients underwent this treatment initially, with few undergoing surgery after receipt of systemic therapy. The majority of patients never underwent therapeutic lymph node dissection for their disease despite 61.9 % of patients in the no surgery group being categorized as “resectable”, and only 33 % of these subjects progressed at 2 years. These data clearly demonstrate that despite guidelines recommending surgery, clinicians were strongly inclined to omit therapeutic lymph node dissection when systemic therapy was available to these patients. This may have been justified by the option of classifying patients as borderline resectable by National Comprehensive Cancer Network guidelines (potentially in-appropriately), and/or related to the de-implementation of therapeutic lymph node dissection in patients with occult metastatic lymph node disease after dissemination of the results from MSLTII, which were reported in 2017[20]. These findings, showing that most patients treated with systemic therapy alone did not experience progression at 2 years, and that overall survival at 2 years was the same regardless of which treatment group they were in, suggest omission of therapeutic lymph node dissection in this patient population may be considered a reasonable treatment strategy. This, however, is contrary to the current guideline recommendations for neoadjuvant systemic treatment followed by therapeutic lymph node dissection for patients with resectable clinical stage III melanoma, based on the results of the recently published SWOG1801 study, as mentioned in the introduction above[16]. In SWOG 1801, event free survival at 2 years in the neoadjuvant-adjuvant arm was 72 % (CI 64–80 %), which is comparable to the 67.3 % progression free survival reported in this study.

It is important to recognize that in this patient population and during this time period therapeutic lymph node dissection after systemic therapy did not appear to be given with a true neoadjuvant intent. In this relatively small cohort (only 3.2 % of the total cohort), surgery was most often performed in the setting of progression at a median time of 9 months after diagnosis. The median time to surgery was 6 months after diagnosis, which is distinctly different than the manner in which neoadjuvant systemic therapy was given prior to therapeutic lymph node dissection in SWOG1801 and may explain the poor progression free survival in the surgery after systemic therapy group. It seems somewhat expected that when surgery is reserved for patients with poor biologic response to systemic therapy, that these patients will have worse outcomes. It does however highlight that most patients in this population were not likely considered borderline resectable by the treatment team, since surgery was most often several months after initiating systemic treatment and/or performed after progression.

The improvement in progression free survival in the no surgery group compared to the upfront surgery group is more challenging to understand. Given that neoadjuvant systemic

therapy is now known to improve event free survival in clinical stage III melanoma compared to upfront surgery in this patient population, the same rationale may potentially be applied here; that in subjects who respond to systemic therapy, efficacy is greatest when there is a larger tumor burden. This does beg the question of if there are patients in whom surgery can safely be omitted, and how they can best be identified. This was partially answered by the PRADO trial, which used the pathologic response of an index lymph node to drive decisions regarding further surgery and systemic therapy, and reported a 93 % 2-year recurrence free survival in patients who had a major pathologic response[18].

This study's inclusion of real-world clinical data supports the relevance of these findings but does have limitations. The observational nature of the data introduces significant selection bias, and limits inference of causality. There may be unmeasured differences between the populations not captured in the clinical database that confound the results. The database used in this study is intended for the study of advanced cancers; while patients with AJCC stage IIIA disease, and with N stages N1a, N1c, N2a, and N3a were excluded with the intention of excluding patients who underwent sentinel lymph node biopsy, the surgical treatment listed as "lymph node biopsy" in the database did not further indicate if this represented an excisional sentinel lymph node biopsy or needle biopsy.

We also do not know why different patients were treated with different regimens. This lack of intention-to-treat does not allow us to assess which patients planned for surgery ended up receiving it. This is further confounded by the low number of patients categorized as "unresectable" (only 3.2 %), and the relatively high number of patients categorized as "unknown" resectable status (21.2 %). In addition, we do not know which patients experienced drug induced toxicity or were unable to tolerate systemic treatment. Similarly, we do not know whether patients who underwent lymphadenectomy following disease recurrence were planned to undergo lymphadenectomy prior to recurrence. We do not know if patients who underwent surgery had a true therapeutic lymph node dissection or a more selective lymph node dissection (number of nodes examined was not available), and we also did not examine patients who underwent surgery alone, without systemic therapy treatment. Lastly, we did not perform a cost analysis in the present study. This was outside the scope of our clinical question, and data related to cost were not available to us. High cost has been noted to be an issue specifically for immune check point inhibitors[21]. Of note, findings from the updated OpACIN and OpACIN-neo trials, in which neoadjuvant check-point inhibitors were given for 2 cycles, followed by lymph node dissection, with omission of adjuvant systemic therapy for patients with clinical stage III melanoma, reported only a 4 % recurrence rate after > 2 years[22], potentially representing a major cost savings with surgery in this patient population. It should be noted however, that only a minority of patients in the no surgery group in this study received immune check point inhibitors for > 1 year.

Lastly, we do not know what proportion of the patients in this study who did not undergo lymph node dissection were considered truly borderline resectable/unresectable by a surgeon. Per current National Comprehensive Cancer Network guidelines, unresectability can be defined as technically unresectable (involvement of major neurovascular structures) or clinically unresectable (distant nodal disease)[23,24]. "Borderline resectable" however, is

not defined. It is difficult to glean from prior reports what percentage of patients with clinical stage III disease were historically considered resectable vs borderline/unresectable. The WHO international cooperative trial published in 1982 randomized to wide local excision and elective lymph node dissection or wide local excision and therapeutic lymph node dissection if clinical stage III disease developed later; in this study, no patients with unresectable clinical stage III disease were described[25]. Later research out of John Wayne Cancer Center from the early 1990s reported "all patients with lymph node metastases were treated with regional lymphadenectomy"[26]. While these older studies likely do not account for patients with distant lymph node metastases, they do suggest that historically the number of patients with truly borderline/unresectable disease is low.

To conclude, this is the first study reporting outcomes of patients with clinical stage III melanoma treated with modern systemic therapy without therapeutic lymph node dissection. These patients had improved progression free survival and similar overall survival at 2 years when compared to patients who underwent therapeutic lymph node dissection either before or after delivery of modern systemic therapy. These results highlight that a substantial number of patients with clinical stage III melanoma were not undergoing therapeutic lymph node dissection, which for those with resectable disease, was still the standard of care during the study period. We speculate that patients were also being classified as "borderline resectable" in name only to justify omission of therapeutic lymph node dissection when systemic therapy was being given. As such, our results strongly support prospective randomized studies focused on omission of therapeutic lymph node dissection, with emphasis on identification of responders to systemic therapy, either through gene expression profiling, clinical response, radiographic response, and/or pathologic response of a more limited specimen, to determine which patients may avoid the potentially life-altering morbidities of therapeutic lymph node dissection. Without such studies, clinical practice will likely continue to follow the above findings, but without the requisite data needed to support it.

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Synopsis

In a database including 533 clinical stage III melanoma patients from 2018 to 2022, 52 % received systemic therapy alone without lymphadenectomy; they had superior progression free and similar overall survival at 2 years compared to those who underwent lymphadenectomy.

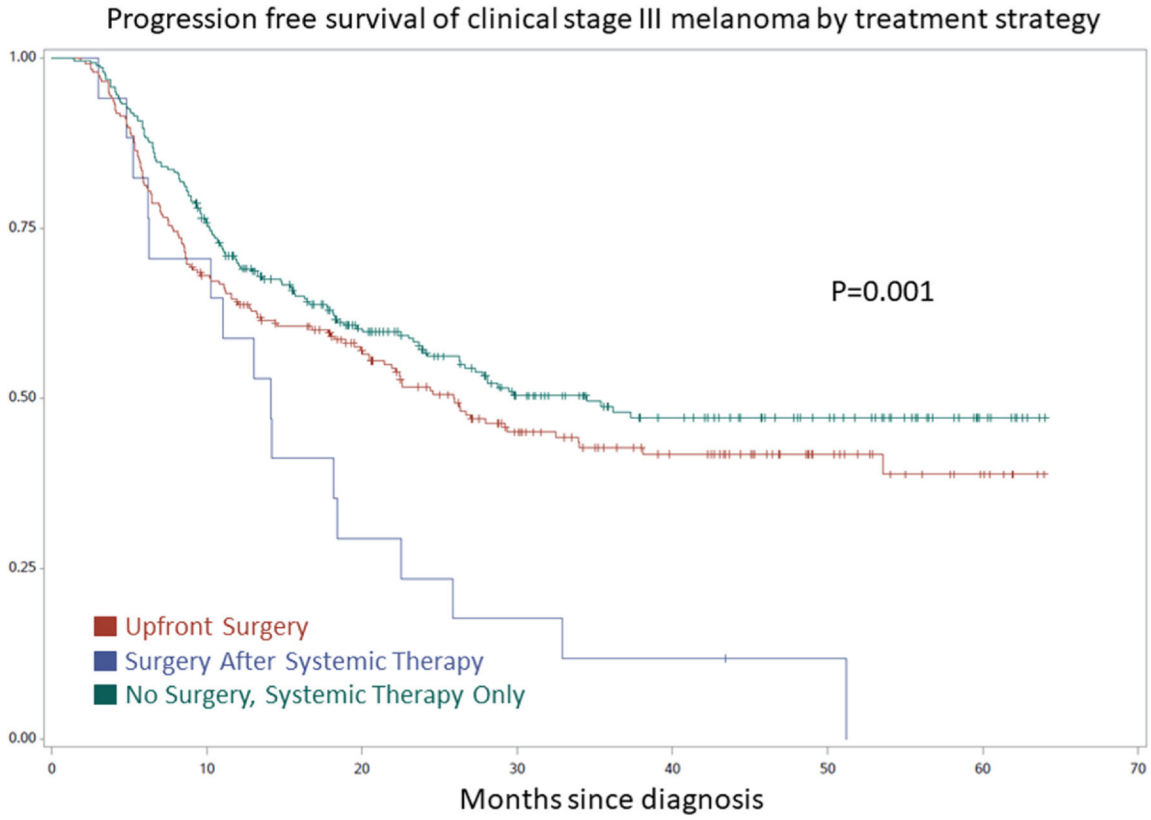

Fig. 1.

Progression free survival of clinical stage III melanoma by treatment strategy. Patients treated with systemic therapy alone and no surgery (green) had superior progression free survival compared to patients who underwent upfront therapeutic lymph node dissection followed by systemic therapy (red), and therapeutic lymph node dissection after treatment with systemic therapy (blue) (p = 0.001).

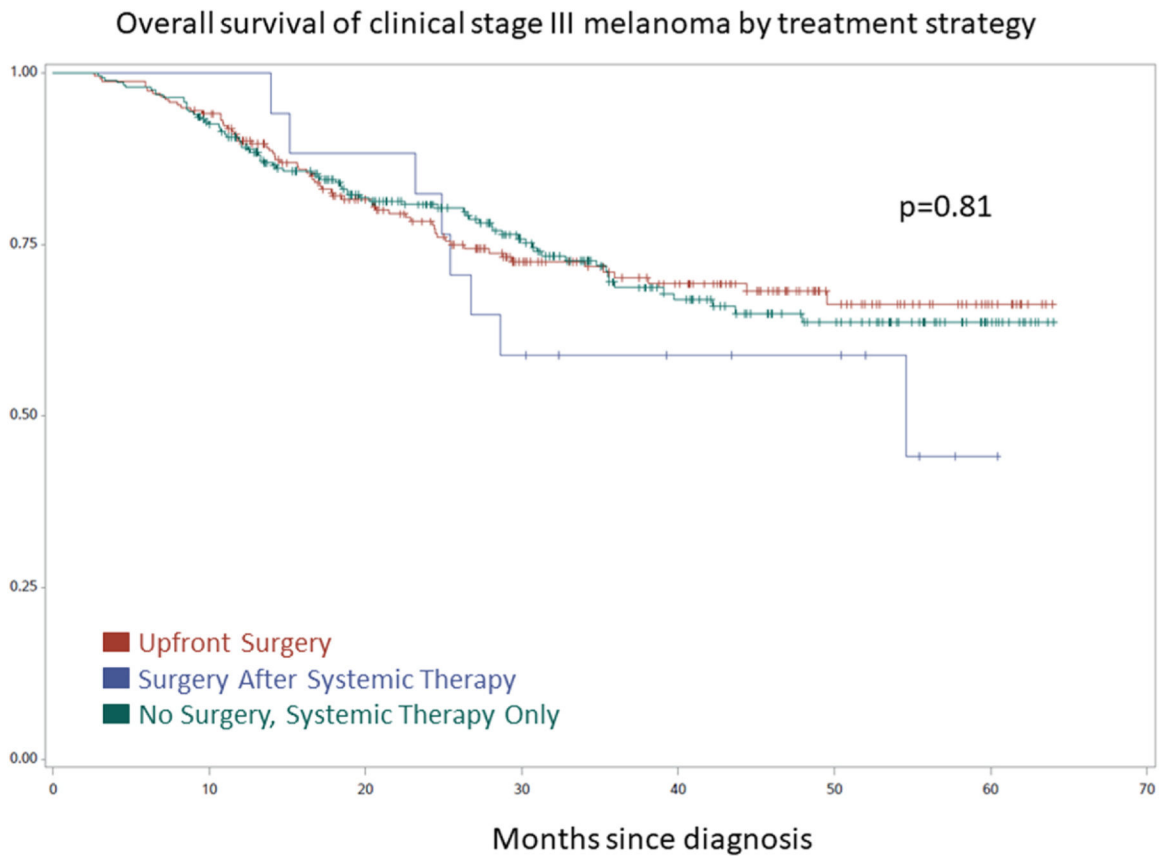

Fig. 2.

Overall survival of clinical stage III melanoma by treatment strategy. Overall survival did not differ if patients were treated with systemic therapy alone and no surgery (green), upfront therapeutic lymph node dissection followed by systemic therapy (red), or therapeutic lymph node dissection after treatment with systemic therapy (blue) (p = 0.81).

Table 1

Patient demographics, disease characteristics, and treatments of patients with clinical stage III melanoma treated with systemic therapy. Statistical significance is indicated in bold. BMI = body mass index; ECOG = Eastern Cooperative Oncology Group. Immune=Immune check point inhibitor; BRAF = BRAF/MEK inhibitor; Dual immune= treatment with any two immune check point inhibitors at the same time.

Variable	Total (n = 533)	Upfront Surgery (n = 235)	Surgery After Systemic Therapy (n = 17)	No Surgery (n = 281)	P-Value
Age at Diagnosis	64.0 (14.5)	63.4 (14.0)	61.8 (14.4)	64.6 (15.0)	0.54
BMI	29.9 (7.0)	29.4 (6.3)	30.2 (6.5)	30.4 (7.5)	0.32
Female Gender	162 (30.4 %)	79 (33.6 %)	3 (17.7 %)	80 (28.5 %)	0.23
Caucasian	434 (81.4 %)	192 (81.7 %)	15 (88.2 %)	227 (80.8 %)	0.74
Insurance					
Commercial	342 (64.2 %)	150 (63.8 %)	10 (58.8 %)	182 (64.8 %)	0.89
Medicaid	15 (2.8 %)	6 (2.6 %)	0 (0.0 %)	9 (3.2 %)	
Medicare	53 (9.9 %)	24 (10.2 %)	3 (17.7 %)	26 (9.3 %)	
Other/Missing	110 (20.6 %)	48 (20.4 %)	3 (17.7 %)	59 (21.0 %)	
Self-Pay	13 (2.4 %)	7 (3.0 %)	1 (5.9 %)	5 (1.8 %)	
Follow up period (median, IQR)	21.6 (12.4–35.1)	22.5 (12.2–38.2)	27.0 (21.4–50.6)	20.6 (12.4–33.3)	0.06
ECOG					
0/1	434 (81.4 %)	199 (85.5 %)	15 (88.2 %)	220 (78.3 %)	0.31
2–4	27 (5.1 %)	8 (3.4 %)	0 (0.0 %)	19 (6.8 %)	
Missing	72 (13.5 %)	28 (11.9 %)	2 (11.8 %)	42 (15.0 %)	
T-Stage					**< .0001**
T0	40 (7.5 %)	27 (11.5 %)	1 (5.9 %)	12 (4.3 %)	
T1	12 (2.3 %)	5 (2.1 %)	0 (0 %)	7 (2.5 %)	
T2	43 (8.1 %)	12 (5.1 %)	1 (5.9 %)	30 (10.7 %)	
T3	124 (23.3 %)	40 (17.0 %)	8 (47.1 %)	76 (27.1 %)	
T4	214 (40.2 %)	90 (38.3 %)	4 (23.5 %)	120 (42.7 %)	
Missing	100 (18.8 %)	61 (26.0 %)	3 (17.7 %)	36 (12.8 %)	
N-Stage					**< .0001**
N1b	179 (33.5 %)	78 (33.2 %)	4 (23.5 %)	97 (34.5 %)	
N2b	92 (17.3 %)	51 (21.7 %)	2 (11.8 %)	39 (13.9 %)	
N2c	123 (23.1 %)	21 (8.9 %)	6 (35.3 %)	96 (34.2 %)	

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Variable	Total (n = 533)	Upfront Surgery (n = 235)	Surgery After Systemic Therapy (n = 17)	No Surgery (n = 281)	P-Value
N3b	53 (9.9 %)	40 (17.0 %)	2 (11.8 %)	11 (3.9 %)	
N3c	96 (16.1 %)	45 (19.2 %)	3 (17.7 %)	38 (13.5 %)	
AJCC Stage					0.16
III	119 (22.3 %)	55 (23.4 %)	3 (17.7 %)	61 (21.7 %)	
IIIB	95 (17.8 %)	42 (17.9 %)	2 (11.8 %)	51 (18.2 %)	
IIIC	274 (51.4 %)	110 (46.8 %)	12 (70.6 %)	152 (54.1 %)	
IIID	45 (8.4 %)	28 (11.9 %)	0 (0.0 %)	17 (6.1 %)	
Resectability					
(AM)	403 (75.6 %)	216 (91.9 %)	13 (76.5 %)	174 (61.9 %)	**< .0001**
Resectable	17 (3.2 %)	4 (1.7 %)	1 (5.9 %)	12 (4.3 %)	
Unresectable	113 (21.2 %)	15 (6.4 %)	3 (17.7 %)	95 (33.8 %)	
Unknown					
BRAF Mutation					**0.004**
Negative	231 (43.3 %)	101 (43.0 %)	11 (64.7 %)	119 (42.4 %)	
Positive	191 (25.8 %)	99 (42.1 %)	4 (23.5 %)	88 (31.3 %)	
Missing	111 (20.8 %)	35 (14.9 %)	2 (11.8 %)	74 (26.3 %)	
Treatment					
BRAF only	28 (5.3 %)	14 (6.0 %)	0 (0.0 %)	14 (6.0 %)	0.51
Any Immune	323 (60.6 %)	138 (58.7 %)	8 (47.1 %)	177 (63.0 %)	
Dual Immune	101 (19.0 %)	44 (18.7 %)	4 (23.5 %)	53 (18.9 %)	
Both	81 (15.2 %)	39 (16.6 %)	5 (29.4 %)	37 (13.2 %)	
Duration of Treatment – Immune,	28 (5.3 %)	14 (6.0 %)	0 (0.0 %)	14 (5.0 %)	0.60
months	82 (15.4 %)	36 (15.3 %)	1 (5.9 %)	45 (16.0 %)	
None	271 (50.8 %)	126 (53.6 %)	9 (52.9 %)	136 (48.4 %)	
< 3 months	152 (28.5 %)	59 (25.1 %)	7 (41.2 %)	86 (30.6 %)	
3–12 months					
> 1 year					
Duration of Treatment - BRAF	424 (79.6 %)	182 (77.5 %)	12 (70.6 %)	230 (81.9 %)	0.34
(months)	22 (4.1 %)	11 (4.7 %)	2 (11.8 %)	9 (3.2 %)	
None	55 (10.3 %)	24 (10.2 %)	2 (11.8 %)	29 (10.3 %)	
< 3 months	32 (6.0 %)	18 (7.7 %)	1 (5.9 %)	13 (4.6 %)	

Variable	Total (n = 533)	Upfront Surgery (n = 235)	Surgery After Systemic Therapy (n = 17)	No Surgery (n = 281)	P-Value
3–12 months					
> 1 year					
Duration of Treatment – Both	63 (11.8 %)	29 (12.3 %)	0 (0.0 %)	34 (12.1 %)	0.36
(months)	275 (51.6 %)	127 (54.0 %)	8 (47.1 %)	140 (49.8 %)	
< 3 months	195 (36.6 %)	79 (33.6 %)	9 (52.9 %)	107 (38.1 %)	
3–12 months					
> 1 year					

Table 2

Clinical Outcomes of patients with clinical stage III melanoma treated with systemic therapy. Statistical significance is indicated in bold. * =not reached; N/A=not applicable.

Variable	Total (n = 533)	Upfront Surgery (n = 235)	Surgery After Systemic Therapy (n = 17)	No Surgery (n = 283)	P-Value
Progression	228 (42.7 %)	110 (46.8 %)	16 (94.1 %)	102 (36.3 %)	< **0.0001**
Local	92 (17.3 %)	29 (12.3 %)	12 (70.6 %)	51 (18.0 %)	< **0.0001**
Distant	136 (25.5 %)	81 (34.5 %)	4 (23.5 %)	51 (18.0 %)	**0.0001**
Time to progression (months)	37.4 (8.9-*)	28.0 (7.8-*)	14.2 (6.3–22.6)	* (10.2-*)	0.20
% Progressed in 2 years	203 (38.1 %)	98 (41.7 %)	13 (76.5 %)	92 (32.7 %)	**0.001**
Death	145 (27.2 %)	63 (26.8 %)	8 (47.1 %)	74 (26.3 %)	0.17
% Death in 2 years	100 (18.8 %)	47 (20.0 %)	3 (17.7 %)	50 (17.8 %)	0.81
Diagnosis to any treatment (months)	1.6 (1.0–2.3)	1.5 (1.0–2.2)	1.8 (1.4–3.5)	2.6 (1.9–4.0)	< **.0001**
Diagnosis to surgery (months)	1.6 (1.0–2.3)	1.6 (1.0–2.2)	6.2 (2.7–14.3)	N/A	< **.0001**
Surgery following progression	12 (2.3 %)	3 (1.3 %)	9 (52.9 %)	N/A	< **.0001**

Table 3

Cox proportional hazard coefficients for progression free survival of patients with clinical stage III melanoma treated with systemic therapy. ECOG = Eastern Cooperative Oncology Group. Statistical significance is indicated in bold.

	Univariate		Multivariate	
Variable	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
Treatment Group				
No Surgery	Ref	0.11	Ref	**0.007**
Upfront Surgery	1.22 (0.95–1.56)	**0.001**	1.42 (1.10–1.84)	**0.002**
Surgery After Systemic Therapy	2.49 (1.48–4.19)		2.38 (1.38–4.12)	
Age at Diagnosis	1.01 (1.00–1.02)	**0.01**	1.02 (1.01–1.03)	**0.001**
ECOG				
0/1	Ref	**< .0001**	Ref	**0.005**
2–4	2.60 (1.67–4.03)	0.69	1.97 (1.23–3.17)	0.19
Missing	0.93 (0.65–1.33)		0.78 (0.53–1.13)	
T-Stage				
T0	Ref	0.07	Ref	**0.01**
T1	2.49 (0.92–6.72)	0.28	3.57 (1.31–9.77)	0.06
T2	1.51 (0.71–3.19)	**0.006**	2.10 (0.97–4.51)	**0.003**
T3	2.46 (1.30–4.65)	**0.006**	2.73 (1.42–5.23)	**0.0003**
T4	2.90 (1.57–5.37)	0.11	3.19 (1.70–5.95)	**0.05**
Missing	1.71 (0.88–3.33)		1.95 (0.99–3.82)	
BRAF Mutation				
Negative	Ref	**0.02**	Ref	0.33
Positive	1.35 (1.05–1.75)	**0.001**	0.85 (0.62–1.18)	**0.001**
Indeterminate	0.54 (0.37–0.79)		0.59 (0.40–0.87)	
Treatment				
BRAF only	Ref	**0.004**	Ref	**0.001**
Immune only	0.44 (0.26–0.77)	0.18	0.38 (0.21–0.69)	0.53
Dual Immune	1.47 (0.84–2.56)	**0.001**	1.22 (0.66–2.22)	**0.01**
Both	2.50 (1.43–4.36)		2.20 (1.25–3.89)	
BMI	1.00 (0.98–1.01)	0.67		0.61

	Univariate		Multivariate	
Variable	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
Female Gender	0.96 (0.74–1.25)	0.78		0.24
Caucasian	0.87 (0.64–1.17)	0.35		0.92
Insurance				0.06
Commercial	1.42 (1.01–1.98)	0.04		
Medicaid	1.15 (0.52–2.57)	0.73		
Medicare	1.99 (1.27–3.11)	0.003		
Self-Pay	2.58 (1.26–5.30)	0.01		
Other/Missing	Ref			
N-Stage				0.06
N1b	Ref	0.97		
N2b	1.01 (0.69–1.48)	**0.01**		
N2c	1.59 (1.15–2.21)	0.32		
N3b	1.26 (0.80–1.98)	< **.0001**		
N3c	2.60 (1.85–3.65)			
AJCC Stage				0.85
III	Ref	**0.04**		
IIIB	0.65 (0.43–0.98)	0.46		
IIIC	1.12 (0.83–1.52)	**0.001**		
IIID	2.10 (1.37–3.22)			

Table 4

Cox proportional hazard coefficients for overall survival of patients with clinical stage III melanoma treated with systemic therapy. ECOG = Eastern Cooperative Oncology Group. Statistical significance is indicated in bold.

	Univariate		Multivariate	
Variable	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
Treatment Group	Ref	0.90	Ref	0.73
No Surgery	0.98 (0.70–1.37)	0.34	1.06 (0.75–1.51)	0.20
Upfront Surgery	1.42 (0.69–2.95)		1.64 (0.78–3.44)	
Surgery After Systemic Therapy				
Age at Diagnosis	1.03 (1.02–1.04)	< **0.001**	1.03 (1.02–1.05)	< **0.001**
ECOG				
0/1	Ref	< **0.0001**	Ref	**0.01**
2–4	3.12 (1.82–5.26)	0.74	2.19 (1.23–3.90)	0.82
Missing	0.92 (0.55–1.53)		0.94 (0.56–1.59)	
T-Stage				
T0	Ref	0.61	Ref	0.57
T1	0.57 (0.07–4.76)	0.62	0.54 (0.07–4.52)	0.71
T2	0.75 (0.24–2.33)	0.08	0.81 (0.26–2.52)	0.14
T3	2.14 (0.90–5.06)	**0.03**	1.69 (0.70–4.07)	**0.045**
T4	2.51 (1.09–5.77)	0.26	2.36 (1.02–5.46)	**0.031**
Missing	1.67 (0.68–4.08)		1.59 (0.65–3.91)	
Treatment				
BRAF only	Ref	0.82	Ref	0.95
Immune only	1.02 (0.41–2.54)	0.16	0.97 (0.38–2.44)	0.23
Dual Immune	1.93 (0.77–4.85)	0.08	1.79 (0.69–4.67)	0.08
Both	2.39 (0.90–6.31)		2.33 (0.90–6.02)	
BMI	0.99 (0.97–1.02)	0.40		0.16
Female Gender	0.75 (0.51–1.09)	0.13		0.38
Caucasian	0.92 (0.61–1.39)	0.70		0.92
Insurance				0.84
Commercial	1.44 (0.91–2.28)	0.12		

	Univariate		Multivariate	
Variable	**Hazard Ratio**	**P-Value**	**Hazard Ratio**	**P-Value**
Medicaid	0.87 (0.26–2.90)	0.82		
Medicare	1.60 (0.86–2.99)	0.14		
Self-Pay	1.64 (0.57–4.76)	0.36		
Other/Missing	Ref			
NStage				0.58
N1b	Ref	0.34		
N2b	0.77 (0.45–1.32)	0.36		
N2c	1.23 (0.79–1.91)	0.76		
N3b	1.10 (0.59–2.05)	**0.01**		
N3c	1.82 (1.16–2.85)			
AJCC Stage				0.12
III	Ref	0.09		
IIIB	0.64 (0.37–1.08)	0.41		
IIIC	0.85 (0.57–1.26)	0.76		
IIID	1.10 (0.59–2.08)			
BRAF Mutation				0.11
Negative	Ref	0.44		
Positive	1.15 (0.81–1.64)	0.06		
Indeterminate	0.63 (0.38–1.02)			