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Omission of Completion Lymph Node Dissection in Sentinel Node Biopsy Positive Head and Neck Cutaneous Melanoma Patients

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Abstract

Background.—Recent studies evaluating patients with a positive sentinel lymph node biopsy (SLNB+) show no melanoma-specific survival difference between patients undergoing lymph node basin surveillance and completion lymph node dissection (CLND). This has been broadly applied, despite underrepresentation of head and neck (HN) cutaneous melanoma patients. We evaluated whether this was upheld in the HN melanoma cohort.

Methods.—Patients with HN melanoma with a SLNB+ were selected from the National Cancer Database (NCDB) from 2012 to 2019. Overall survival (OS) of patients who underwent SLNB only versus SLNB + CLND were compared. Subgroup analyses were performed based

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DISCLOSURE The National Cancer Database (NCDB) is a joint project of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society. The CoC's NCDB and the hospitals participating in the CoC's NCDB are the source of the de-identified data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

on pathologic N (pN) and receipt of immunotherapy. Adjusted hazard ratio (aHR) and 95% confidence interval (CI) were calculated.

Results.—Analysis of 634 patients with multivariable Cox regression showed no difference in OS in SLNB only versus SLNB + CLND cohorts (hazard ratio [HR] 1.13; 95% confidence interval [CI] 0.71–1.81; $p = 0.610$). Charlson–Deyo score (CDS) 1 versus 0 (HR 1.70; 95% CI 1.10–2.63; $p = 0.016$), pN2+ versus pN1 (HR 1.74; 95% CI 1.23–2.45; $p = 0.002$), and lymphovascular invasion (LVI) versus no (HR 2.07; 95% CI 1.34–3.19; $p = 0.001$) were associated with worse prognosis. Subgroup analysis by pN showed no OS benefit for CLND in either pN1 (HR 1.04; 95% CI 0.51–2.10; $p = 0.922$) or pN2+ (HR 1.31; 95% CI 0.67–2.57; $p = 0.427$) patients or in patients who received immunotherapy (HR 1.32; 95% CI 0.54–3.22; $p = 0.549$).

Conclusions.—This study of SLNB + HN melanoma patients showed no OS difference in SLNB only versus SLNB + CLND. Further studies need to be performed to better define the role of CLND.

The majority of melanomas are confined to the skin and have excellent 5-year survival rates of 99%.[1] Unfortunately, once melanoma spreads to lymph nodes, survival declines to an average 5-year survival rate of roughly 68%. While there is significant variability within this cohort of patients, ranging from 93% for Stage IIIA patients to 32% for Stage IIID, multiple studies have shown that prognosis is strongly associated with presence of regional nodal disease.[1] As such, knowledge of lymph node involvement significantly impacts treatment recommendations and follow-up. Sentinel lymph node biopsy (SLNB) is a staging procedure that allows for identification of lymph node metastasis in patients with clinically node-negative disease.[2]

For many years, if regional SLNs were involved with metastases, the recommendation was to proceed with completion lymph node dissection (CLND) followed by adjuvant systemic therapy.[3,4] Unfortunately, the morbidity of lymph node dissection can be quite high, resulting in lymphedema, neurovascular injury, and neck impairment and the systemic therapies which were available for melanoma only offered limited disease free survival.[3–5] In the past decade, the management of SLNB positive patients has dramatically changed. Patients with positive SLNB can either undergo CLND or lymph node basin surveillance with ultrasound. This is based on the results of two large randomized control trials (RCT), the German Dermatologic Cooperative Oncology Group—Selective Lymphadenectomy Trial (DeCOG-SLT) and the Multicenter Selective Lymphadenectomy Trial II (MSLT-II), both showing no survival difference when comparing these surgical approaches in patients with positive SLNs.[6,7] Based on these studies, the National Comprehensive Cancer Network (NCCN) guidelines currently include these recommendations for cutaneous melanomas of all primary sites, despite the fact that HN cutaneous melanoma patients were not well represented in these trials.[8] In fact, these patients were excluded from DeCOG-SLT and made up only 13.7% of the patients in MSLT-II. Additionally, melanoma of HN origin was the only factor in the multivariable analysis of the MSLT-II trial where there was a trend toward a survival benefit with CLND, although not statistically significant.[7] However, given the knowledge that cutaneous melanomas of HN origin are more aggressive and have a worse prognosis compared with those from other primary sites, one questions the utility of CLND in this population.[9]

From a systemic therapy standpoint, immunotherapy and targeted agents have been adopted as adjuvant treatment, based on several RCTs, which showed recurrence-free survival (RFS) benefit.[10–12] However, the majority of these trials were performed before the publication of MSLT-II and DeCOG-SLT and show the effect of treatment on patients who underwent CLND after a positive SLNB but not on patients who underwent nodal basin observation. Conversely, the aforementioned surgical trials were mostly performed before FDA approval of newer immunotherapy treatments. Hence, the impact of new immunotherapy regimens on these patients is unknown. Therefore, we examined a large cohort of HN cutaneous melanoma patients from a national clinical oncology database sourced from hospital registry data to evaluate the role of omission of CLND in patients with positive SLNs, with specific attention to the impact of more advanced nodal disease and immunotherapy on outcomes.

METHODS

Data Source

The National Cancer Database (NCDB) was utilized to perform the analysis. The NCDB is an American College of Surgeons Commission on Cancer and American Cancer Society supported nationwide hospital-based cancer registry, which gathers de-identified data on cancer cases from more than 1500 Commission on Cancer accredited facilities. Institutional Review Board approval was not required for this study, because data in the NCDB are de-identified.

Patient Selection

The study inclusion and exclusion criteria leading to the analytical final sample are outlined in Fig. 1. We included patients from 2012 to 2019 with invasive HN cutaneous melanoma who were aged 18–75 years with clinically negative lymph nodes (N0 disease) who underwent wide local excision (WLE) and SLNB, as was included in both MSLT-II and DeCOG-SLT. We excluded patients with more than one cancer diagnosis, clinically apparent nodal disease, and clinical or pathologic M1 disease. We also excluded patients who did not undergo WLE or SLNB and did not receive treatment at the reporting facility. Of note, even though we included patients through 2019, these patients were not included in our final sample, as the vital status was not reported. We then selected patients who had positive SLNs and stratified patients according to lymph node management, SLNB only, or SLNB + CLND.

Demographic and clinicopathologic characteristics were reported for the entire cohort and compared between groups (Table 1). We performed subgroup analysis based on extent of regional lymph node involvement (pN1 vs. pN2+) and receipt of immunotherapy. The NCDB Participant User Files (PUF) 2019 data dictionary describes other variables analyzed.[13]

Statistical Analysis

For demographic clinical characteristics, descriptive statistics were calculated by using frequencies with percentage for categorical data for overall sample as well as by groups. An analysis of the association of clinicopathologic factors among treatment groups was

performed by chi-squared (χ^2) or Fisher's exact tests to show differences in percentages in categorical variables across treatment groups. The variables evaluated included age at diagnosis, sex, race, Hispanic ethnicity, type of insurance, median income, year of diagnosis, Charlson–Deyo Score (CDS), pathologic T (pT) and N (pN) stage, ulceration, lymphovascular invasion (LVI), mitotic rate, receipt of immunotherapy, chemotherapy and/or radiation therapy, and vital status.

The primary clinical endpoint was the overall survival (OS) for patients with SLN positive HN cutaneous melanoma who underwent SLNB only versus SLNB + CLND. Overall survival (OS) was defined as the time in years from cancer diagnosis to death from any cause or last follow-up. Event-free patients were censored at the date of last follow-up. OS were estimated by Kaplan–Meier method and associations with prognostic factors assessed by log-rank test. Univariable and multivariable Cox proportional hazard regression models were used to assess the association between treatment and OS for selected variables. Results were reported as hazard ratios (HR) with 95% confidence intervals (95% CI). Statistical significance was set at a threshold of $p < 0.05$. A post-hoc sensitivity analysis was performed by excluding the outliers of regional nodes examined. The findings were consistent with those from the primary analysis and lead to similar conclusions about cohort and regional nodes examined effects, meaning that the outliers of regional nodes examined had little or no influence or impact on the primary conclusions.

We found an interaction between treatment and pathologic N (pN) in the whole sample and performed a subgroup analysis on patients within pN1 versus pN2+ disease. Cox proportional hazards regression models were utilized to identify predictors of OS in all and both subsets of patients. All statistical analyses were performed by using SAS version 9.4 (SAS Institute Inc. Cary, NC).

RESULTS

Description of Study Population

A total of 634 patients were identified for analysis (Fig. 1). Table 1 displays the demographics and clinicopathologic features of our patient sample. The majority of patients were > 45 years (77.3%), male (72.8%), white (98.1%), had private insurance (56.4%), CDS of 0 or 1 (94.0%), pT2–4 (73.5%), and pN1 (62.3%). Immunotherapy was utilized in a minority of patients (33.9%), as was chemotherapy (4.9%) and radiation (11.7%). A total of 310 patients (48.9%) underwent SLNB only, and 324 patients (51.1%) underwent SLNB + CLND. In the SLNB only group, a median of 2.0 SLNs were removed, whereas the SLNB + CLND patients had a median of 30.0 lymph nodes removed. Over the study period, there was an increase in omission of CLND (7.1% vs. 29.7% in year 2012 vs. 2018, respectively). The median follow-up time was 3.19 years for the SLNB only group and 4.53 years for the SLNB + CLND patients in alive patients, 2.07 and 2.05 years in deceased patients, respectively. Compared with the SLNB + CLND population, the SLNB only cohort were more likely to be older (> 45 years) (80.3% vs. 74.4%, $p = 0.011$), Black/Asian/others (2.9% vs. 0.6%, $p = 0.028$), to have Medicare insurance (35.8 % vs. 26.2%, $p = 0.008$), to have CDS of ≥ 2 (8.1 vs. 4.0%, $p = 0.098$), and pN1 disease (74.5% vs. 50.6%, $p < 0.001$). The SLNB only group had slightly higher utilization of immunotherapy (33.9% vs. 31.2%,

$p = 0.140$), similar rates of chemotherapy (4.8% vs. 4.9%), and slightly less use of radiation (9.7% vs. 13.6%, $p = 0.126$) (Table 1).

Survival Analysis and Evaluation of Prognostic Factors

On univariable analysis (UVA), age > 65 versus 18–44 (HR 2.45; 95% CI 1.55–3.87; $p < 0.001$), male sex versus female (HR 1.45; 95% CI 1.01–2.08; $p = 0.047$), CDS of 1 versus 0 (HR 1.75; 95% CI 1.18–2.59; $p = 0005$), pT2–T4 versus pT1 (HR 2.96; 95% CI 1.21–7.20; $p = 0.017$), pN2+ versus pN1 (HR 1.90; 95% CI 1.41–2.57; $p < 0.001$), LVI (yes vs. no) (HR 2.25; 95% CI 1.56–3.25; $p < 0.001$), and receipt of radiation therapy (HR 1.62; 95% CI 1.10–2.39; $p = 0.015$) were associated with worse OS (Table 2; Fig. 2A, B). On multivariable analysis (MVA), we found that total CDS 1 (HR 1.70; 95% CI 1.10–2.63; $p = 0.016$), pN2+ (HR 1.74; 95% CI 1.23–2.45; $p = 0.002$), and LVI (HR 2.07; 95% CI 1.32–3.19; $p = 0.001$) were associated with worse prognosis.

Subgroup Analysis: Pathologic Nodal Stage

Because there was a statistically significant interaction between cohort and pathologic N, subgroup analysis by pN was performed to evaluate the cohort effect (Tables 3 and 4). When examining the pN status, 395 (62.3%) patients had pN1 disease and 239 (37.7%) patients had pN2+ disease (Table 3). In both groups, use of CLND decreased over time. Within the pN1 cohort, 164 patients (41.5%) underwent SLNB + CLND. On MVA, patients who underwent SLNB + CLND had similar OS compared with SLNB only patients (Table 4). Factors associated with worse OS in the pN1 cohort were age > 65 years (HR 2.69; 95% CI 1.28–5.64; $p = 0.009$) and LVI (HR 2.90; 95% CI 1.39–6.04; $p = 0.004$; Table 4). Within the pN2+ cohort, 160 (66.9%) patients underwent SLNB + CLND. There was no difference in OS between the two treatment arms ($p = 0.427$; Fig. 2D). Similar prognostic factors were associated with worse OS as in the pN1 group, in addition to median income $40,227–$50,353 (HR 4.16; 95% CI 1.31–13.22; $p = 0.016$) and CDS 1 (HR 2.16; 95% CI 1.15–4.06, $p = 0.017$; Table 4).

Subgroup Analysis: Immunotherapy

We also performed a subgroup analysis by receipt of immunotherapy (Table 5). A total of 215 patients received immunotherapy. Compared with the entire cohort, patients who received immunotherapy were younger (< 45 years 29.8% vs. 22.7%), had higher median income (≥ $63,333 34.9% vs. 32.5%), had private insurance (62.8% vs. 56.2%), more frequently had pN2+ disease (41.4% vs. 37.7%), had more tumors with LVI (19.5% vs. 14.8%), and were treated in later years (2017–2018, 50.7% vs. 2012–2016, 27.9%). Within the immunotherapy cohort, 114 (53.0%) underwent SLNB only and 101 (47.0%) underwent SLNB + CLND (Table 5). Patients receiving immunotherapy had comparable survival to the total cohort (Fig. 2E). Subgroup analysis of patients not receiving immunotherapy also was performed (Table 5). There was no significant difference in OS between SLNB alone and SLNB + CLND for both subgroups (Table 6). No prognostic factors were identified on multivariable models to be associated with worse survival in patients receiving immunotherapy.

DISCUSSION

In this study, we analyzed the impact of the omission of CLND to SLNB on OS of patients with HN cutaneous melanoma with positive SLNs. When examining the entire cohort of patients, there was no significant difference in OS between those who underwent SLNB only compared with SLNB + CLND. This finding is consistent with the results of MSLT-II and DeCOG-SLT, which showed no statistically significant difference in melanoma-specific survival in patients with cutaneous melanoma of all sites when comparing SLNB only to SLNB + CLND.[6,7] These results also are consistent with a previous analysis of HN cutaneous melanoma patients from the NCDB 2012–2014 and a retrospective review of patients from the SEER database who were diagnosed with HN cutaneous melanoma from 1998 through 2007.[14,15] Both of these studies showed no OS benefit to the addition of CLND.[14,15] Our study is unique as it included a larger population, and it evaluated patients who were managed both before and after the publication of DeCOG-SLT in 2016 and MSLT-II in 2017.[7,16] This is reflected by the trend toward more frequent omission of CLND in the more recent years. The reports of these major studies impacted practice patterns as shown in our study with an increasing proportion of patients undergoing SLNB only from 2017 and beyond. Our study also highlights a longer follow-up of Huang et al.'s population and shows that the addition of CLND in the overall study group did not add an additional long-term survival benefit.[14] As previous studies have shown, roughly 75% of the time there are no non-SLNs with metastatic disease, and SLNB alone is providing durable regional control.[17]

In our analysis, CDS of 1, pN2+, and LVI were factors associated with worse OS. Given that the majority of patients had CDS of 0 (82.0%), the worse survival seen in patients with CDS of 1 may reflect additional comorbid conditions. The association of advanced nodal disease with worse OS is consistent with previously reported studies.[18] The association of LVI with OS is less consistent in the literature, although multiple studies have shown that LVI is associated with higher risk features and increased likelihood of identifying positive lymph nodes.[19]

Given the association of survival with nodal burden, we performed a subgroup analysis to further evaluate the role of CLND in patients depending on extent of nodal disease found on pathology. An OS benefit was not observed in those patients with either pN1 or pN2+ disease who underwent SLNB + CLND compared with those who had SLNB alone. This is consistent with the findings of both the MSLT-II and DeCOG-SLT trials.[6,7] A majority of patients in these two trials had low-volume nodal disease, with 71% of patients in MSLT-II and 92% of patients in DeCOG-SLT having only one positive node.[6,7] Therefore, the pN1 patients in our analysis are similar in terms of nodal burden to those included in MSLT-II and DeCOG-SLT, and as suggested by the recent follow-up study of MSLT-II, SLNB alone is playing a therapeutic role in controlling the regional nodal basin without the need for CLND.[17] For the patients with an even higher nodal burden (pN2), there is an increased risk of distant metastasis and poor overall prognosis. This likely explains the absence of a survival benefit with the addition of CLND in patients with pN2+ disease in our analysis. Furthermore, follow-up studies of the MSLT-II trial show that even when patients have regional recurrence, they are being effectively managed with CLND. This effect is likely

further enhanced with the addition of systemic therapy, such as immunotherapy or targeted agents.[17] Additional institutional studies that contain granular data on burden of lymph node disease are required to better characterize which patients may benefit from upfront CLND.

In our study, a total of 215 patients (33.9%) received immunotherapy and use of immunotherapy increased over time, particularly after 2017. This is an increase from the study by Huang et al. where only 22.3% of patients received immunotherapy.[14] This likely reflects that fact that current immunotherapeutic agents, which are utilized for treatment of advanced melanoma were approved by the FDA for use in the adjuvant setting during our study period (2012–2019), including the approval of ipilimumab in 2015 based on a large RCT showing a RFS benefit and the approval of Nivolumab in 2017 and of pembrolizumab in 2019 based on findings from CHECKMATE-238 (NCT02388906) and EORTC1325/KEYNOTE-054 (NCT02362594) respectively.[20–22] We showed that in patients who received immunotherapy, there was no difference in OS in patients who underwent SLNB alone compared with SLNB + CLND. In addition, unlike the entire cohort, there were no prognostic factors on MVA that were associated with worse OS, including pathologic nodal burden and LVI. This suggests that immunotherapy may help to overcome some of these poor prognostic factors.

There are several limitations to our study. Most significantly is the retrospective nature and the associated selection bias that comes from individual physician choices regarding extent of surgery and utilization of immunotherapy. It is notable that in our study the patients in the SLNB + CLND group had a longer median, follow-up time than the SLNB only group. While this may not have captured some of the patient deaths, recent studies have shown that the majority of melanoma recurrences occurred within the first 3 years of diagnosis.[17] Considering that most of the melanoma-specific deaths occur in patients with recurrences, one could extrapolate that this differential would not contribute substantially to an overall survival difference. While the NCDB is a great resource to provide a large population of patients with cancer, its shortcoming is the lack of specific features regarding characteristics of node positivity (including more specific data on size of nodal metastases, extranodal extension, number of sentinel vs. nonsentinel lymph nodes in the CLND, etc.), location or timing of recurrence, or cause of death, and in turn limits the ability to determine melanoma-specific survival. The NCDB also does not provide treatment data, such as the specifics of single-agent immunotherapy and how many cycles were delivered, both of which have been found to have an impact on survival. This population of patients also does not reflect patients who had neoadjuvant immunotherapy. Recent studies have shown this approach leads to an improvement in event-free survival.[23] Furthermore, the NCDB only includes patients from Commission on Cancer (CoC) accredited hospitals, which may not accurately reflect all stage III patients treated throughout the United States.

CONCLUSIONS

Our study shows that in a large population from the NCDB, there is no OS benefit for patients with HN cutaneous melanoma who undergo SLNB + CLND compared with SLNB only. This is consistent with the large, published studies of cutaneous melanoma of other primary sites. Larger studies that include more specific data on lymph node burden and

utilization of systemic therapy are needed to evaluate which patients may benefit from CLND.

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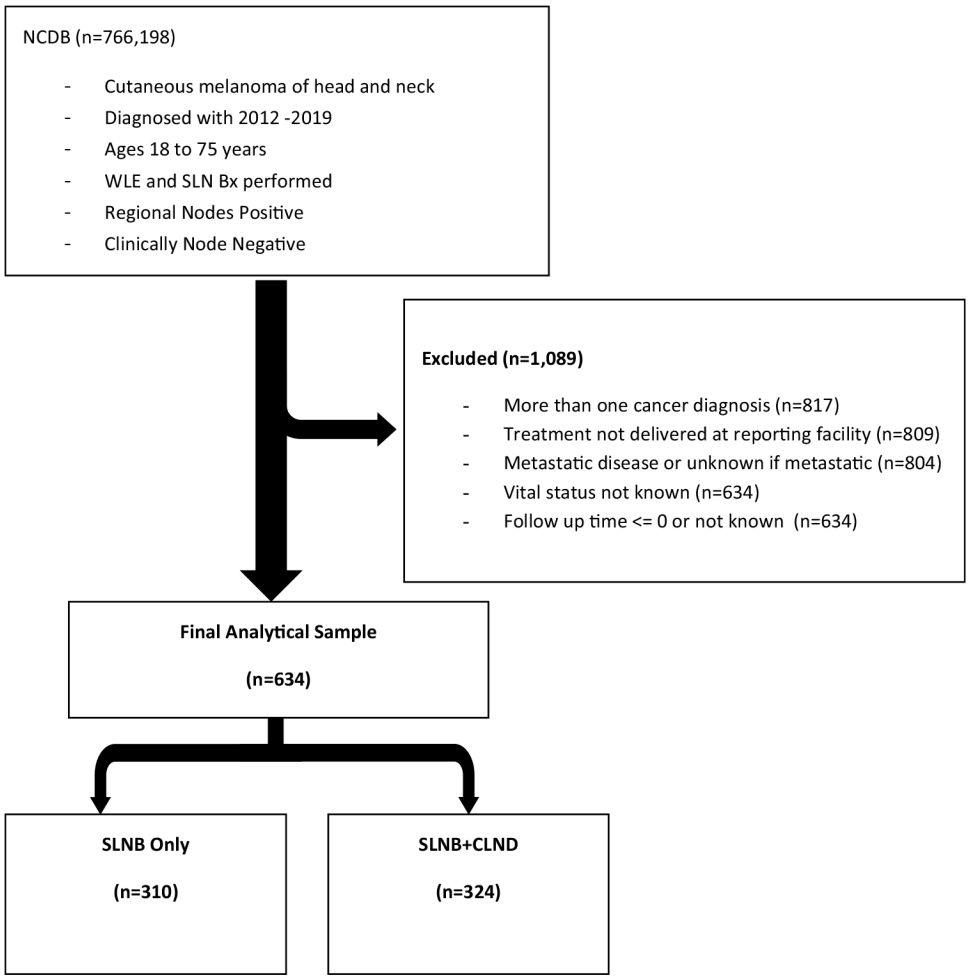

FIG. 1.
Study flowchart

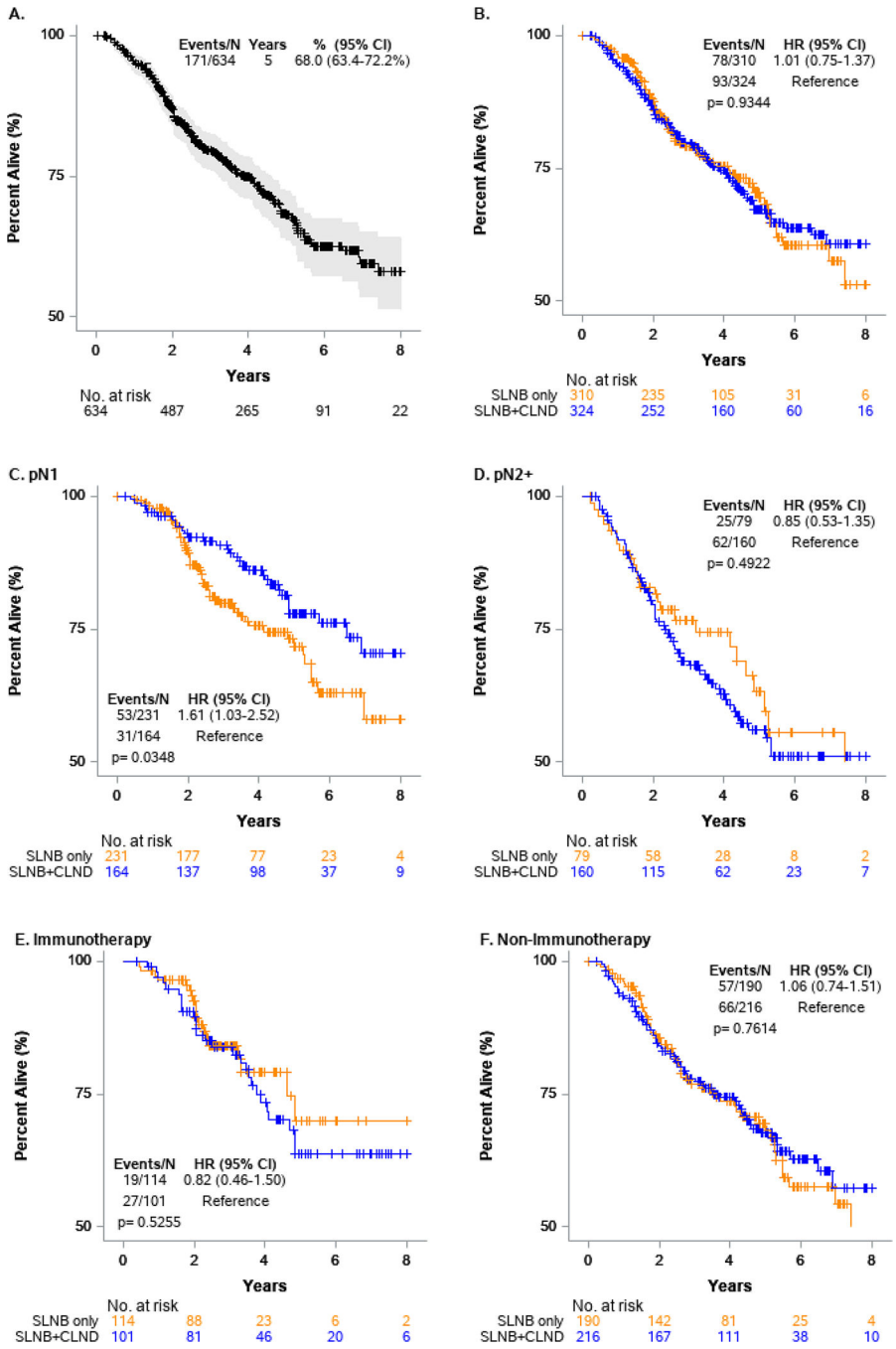

FIG. 2.
Kaplan–Meier survival analysis of overall cohort and subgroup analyses

TABLE 1

Patient, tumor, and treatment characteristics

Variable	All		Cohort				p [a]
			SLNB only		SLNB+CLND		
	N	%	*N*	%	*N*	%	
All	634	100.0	310	100.0	324	100.0	
Age at diagnosis (years)							
18–44	144	22.7	61	19.7	83	25.6	0.011
45–64	274	43.2	126	40.6	148	45.7	
65+	216	34.1	123	39.7	93	28.7	
Sex							
Female	173	27.3	88	28.4	85	26.2	0.533
Male	461	72.7	222	71.6	239	73.8	
Race							
White	622	98.1	301	97.1	321	99.1	0.028
Black/Asian/Other	11	1.7	9	2.9	2	0.6	
Unknown	1	0.2	–	–	1	0.3	
Insurance							
Medicaid	33	5.2	18	5.8	15	4.6	0.008
Medicare	196	30.9	111	35.8	85	26.2	
Other government	19	3.0	13	4.2	6	1.9	
Not insured	20	3.2	10	3.2	10	3.1	
Private	356	56.2	151	48.7	205	63.3	
Unknown	10	1.6	7	2.3	3	0.9	
Median income							
< $40,227	70	11.0	42	13.5	28	8.6	0.433
$40,227–$50,353	118	18.6	65	21.0	53	16.4	
$50,354–$63,332	110	17.4	54	17.4	56	17.3	
≥ $63,333	206	32.5	104	33.5	102	31.5	
Unknown	130	20.5	45	14.5	85	26.2	

Variable	All		Cohort				*p* [a]
			SLNB only		SLNB+CLND		
	N	%	*N*	%	*N*	%	
Year of diagnosis							
2012	69	10.9	22	7.1	47	14.5	< 0.001
2013	105	16.6	35	11.3	70	21.6	
2014	81	12.8	32	10.3	49	15.1	
2015	83	13.1	37	11.9	46	14.2	
2016	94	14.8	37	11.9	57	17.6	
2017	79	12.5	55	17.7	24	7.4	
2018	123	19.4	92	29.7	31	9.6	
Total Charlson–Deyo score							
0	520	82.0	248	80.0	272	84.0	0.098
1	76	12.0	37	11.9	39	12.0	
≥ 2	38	6.0	25	8.1	13	4.0	
Pathologic T							
pT1	5	0.8	3	1.0	2	0.6	0.784
pT2–T4	35	5.5	13	4.2	22	6.8	
Unknown	128	20.2	94	30.3	34	10.5	
Pathologic N stage							
pN1	395	62.3	231	74.5	164	50.6	< 0.001
pN2+	239	37.7	79	25.5	160	49.4	
Regional lymph nodes examined							
1–5	314	49.5	269	86.8	45	13.9	< 0.001
6–10	49	7.7	22	7.1	27	8.3	
11–15	31	4.9	7	2.3	24	7.4	
15+	240	37.9	12	3.9	228	70.4	
Ulceration							
No	68	10.7	51	16.5	17	5.2	0.734
Yes	43	6.8	31	10.0	12	3.7	
Unknown	523	82.5	228	73.5	295	91.0	

TABLE 2

Five-year overall survival using Cox proportional hazards regression models

Variable	Category	Univariable		Multivariable	
		HR (95% CI)	*p*	aHR (95% CI)	*p*
Cohort	SLNB only	Ref		Ref	
	SLNB+CLND	0.99 (0.73–1.34)	0.934	1.13 (0.71–1.81)	0.610
Age (years)	18–44	Ref		Ref	
	45–64	1.63 (1.02–2.59)	0.040	1.40 (0.85–2.30)	0.188
	65+	2.45 (1.55–3.87)	< 0.001	1.71 (0.91–3.19)	0.094
Sex	Female	Ref		Ref	
	Male	1.45 (1.01–2.08)	0.047	1.32 (0.91–2.01)	0.132
Year of diagnosis	2012	Ref		Ref	
	2013	0.98 (0.62–1.53)	0.917	0.72 (0.44–1.19)	0.201
	2014	0.83 (0.50–1.37)	0.466	0.72 (0.42–1.23)	0.235
	2015	0.35 (0.19–0.67)	0.001	0.23 (0.12–0.45)	< 0.001
	2016	0.71 (0.41–1.22)	0.217	0.67 (0.38–1.19)	0.174
	2017	0.69 (0.37–1.27)	0.229	0.60 (0.31–1.16)	0.129
	2018	0.38 (0.19–0.79)	0.010	0.16 (0.01–2.09)	0.163
Total Charlson–Deyo score	0	Ref		Ref	
	1	1.75 (1.18– 2.59)	0.005	1.70 (1.10–2.63)	0.016
	≥ 2	1.79 (0.97–3.32)	0.065	1.57 (0.79–3.10)	0.196
Pathologic T	T1	Ref		Ref	
	pT2–pT4	2.96 (1.21–7.20)	0.017	1.86 (0.74–4.867)	0.186
	Unknown	1.63 (0.57–4.65)	0.365	8.69 (1.58–49.72)	0.013
Pathologic N	pN1	Ref		Ref–	
	pN2+	1.90 (1.41–2.57)	< 0.001	1.74 (1.23–2.45)	0.002
Regional nodes examined	1–5	Ref		Ref	
	6–10	0.93 (0.51–1.70)	0.806	0.87 (0.44–1.72)	0.695
	11–15	1.60 (0.87–2.93)	0.130	0.90 (0.44–1.84)	0.774
	15+	0.89 (0.64–1.23)	0.467	0.69 (0.41–1.13)	0.140
Lymphovascular invasion	No	Ref		Ref	

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Variable	Category	Univariable		Multivariable	
		HR (95% CI)	*p*	aHR (95% CI)	*p*
	Yes	2.25 (1.56–3.25)	< 0.001	2.07 (1.34–3.19)	0.001
	Unknown	1.03 (0.65–1.63)	0.905	1.23 (0.76–1.98)	0.410
Immunotherapy	No	Ref		Ref	
	Yes	0.79 (0.57–1.12)	0.183	0.81 (0.56–1.18)	0.267
	Unknown	0.58 (0.14–2.34)	0.443	0.63 (0.14–2.74)	0.535
Radiation therapy	No	Ref		Ref	
	Yes	1.62 (1.10–2.39)	0.015	1.33 (0.86–2.04)	0.201

MVA without interactions, but when include interaction, we found that there is significant interaction between cohort and pathologic N, and no significant interaction between cohort and immune therapy. Therefore, the effect of cohort should be evaluated from subsample analysis by cohort

Additionally adjusted for race, ethnicity, median income, insurance, ulceration, mitotic rate, chemotherapy

HR Hazard ratio, *aHR* adjusted hazard ratio, *CI* confidence interval, *Ref* reference group

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TABLE 3

Patient, tumor, and treatment characteristics based upon pathologic N

Variable	All		Pathologic N									
			pN1				*p* [a]	pN2+				*p* [a]
			Cohort					Cohort				
			SLNB only		SLNB+CLND			SLNB only		SLNB+CLND		
	N	%	*N*	%	*N*	%		*N*	%	*N*	%	
All	634	100.0	231	100.0	164	100.0		79	100.0	160	100.0	
Age at diagnosis (years)												
18–44	144	22.7	45	19.5	42	25.6	0.319	16	20.3	41	25.6	0.001
45–64	274	43.2	102	44.2	70	42.7		24	30.4	78	48.8	
65+	216	34.1	84	36.4	52	31.7		39	49.4	41	25.6	
Sex												
Female	173	27.3	72	31.2	47	28.7	0.692	16	20.3	38	23.8	0.543
Male	461	72.7	159	68.8	117	71.3		63	79.7	122	76.3	
Insurance												
Medicaid	33	5.2	14	6.1	8	4.9	0.240	4	5.1	7	4.4	0.002
Medicare	196	30.9	73	31.6	46	28.0		38	48.1	39	24.4	
Other government	19	3.0	9	3.9	2	1.2		4	5.1	4	2.5	
Not insured	20	3.2	7	3.0	4	2.4		3	3.8	6	3.8	
Private	356	56.2	122	52.8	103	62.8		29	36.7	102	63.8	
Unknown	10	1.6	6	2.6	1	0.6		1	1.3	2	1.3	
Median income												
< $40,227	70	11.0	34	14.7	17	10.4	0.724	8	10.1	11	6.9	0.900
$40,227–$50,353	118	18.6	51	22.1	32	19.5		14	17.7	21	13.1	
$50,354–$63,332	110	17.4	39	16.9	30	18.3		15	19.0	26	16.3	
≥ $63,333	206	32.5	74	32.0	45	27.4		30	38.0	57	35.6	
Unknown	130	20.5	33	14.3	40	24.4		12	15.2	45	28.1	
Year of diagnosis												

Variable	All		Pathologic N									
			pN1				*p* [a]	pN2+				*p* [a]
			Cohort					Cohort				
			SLNB only		SLNB+CLND			SLNB only		SLNB+CLND		
	N	%	*N*	%	*N*	%		*N*	%	*N*	%	
2012	69	10.9	16	6.9	30	18.3	< 0.001	6	7.6	17	10.6	0.009
2013	105	16.6	24	10.4	34	20.7		11	13.9	36	22.5	
2014	81	12.8	23	10.0	23	14.0		9	11.4	26	16.3	
2015	83	13.1	27	11.7	24	14.6		10	12.7	22	13.8	
2016	94	14.8	27	11.7	26	15.9		10	12.7	31	19.4	
2017	79	12.5	44	19.0	14	8.5		11	13.9	10	6.3	
2018	123	19.4	70	30.3	13	7.9		22	27.8	18	11.3	
Total Charlson–Deyo score												
0	520	82.0	187	81.0	133	81.1	0.253	61	77.2	139	86.9	0.127
1	76	12.0	26	11.3	24	14.6		11	13.9	15	9.4	
≥ 2	38	6.0	18	7.8	7	4.3		7	8.9	6	3.8	
Pathologic T stage												
pT1	40	6.3	15	6.5	19	11.6	0.353	1	1.3	5	3.1	0.675
pT2–pT4	466	73.5	144	62.3	130	79.3		56	70.9	136	85.0	
Unknown	128	20.2	72	31.2	15	9.1		22	27.8	19	11.9	
Regional lymph nodes examined												
1–5	314	49.5	210	90.9	26	15.9	< 0.001	59	74.7	19	11.9	< 0.001
6–10	49	7.7	13	5.6	16	9.8		9	11.4	11	6.9	
11–15	31	4.9	5	2.2	13	7.9		2	2.5	11	6.9	
15+	240	37.9	3	1.3	109	66.5		9	11.4	119	74.4	
Lymphovascular invasion												
No	444	70.0	157	68.0	136	82.9	0.008	47	59.5	104	65.0	0.701
Yes	94	14.8	29	12.6	9	5.5		19	24.1	37	23.1	
Immunotherapy												
No	406	64.0	145	62.8	116	70.7	0.103	45	57.0	100	62.5	0.341

Variable	All		Pathologic N								
			pN1				*p* [a]	pN2+			*p* [a]
			Cohort					Cohort			
			SLNB only		SLNB+CLND			SLNB only		SLNB+CLND	
	N	%	*N*	%	*N*	%		*N*	%	*N*	%	
Yes	215	33.9	81	35.1	45	27.4		33	41.8	56	35.0	
Unknown	13	2.1	5	2.2	3	1.8		1	1.3	4	2.5	
Chemotherapy												
No	585	92.3	211	91.3	154	93.9	0.645	72	91.1	148	92.5	0.756
Yes	31	4.9	12	5.2	7	4.3		3	3.8	9	5.6	
Unknown	18	2.8	8	3.5	3	1.8		4	5.1	3	1.9	
Radiation therapy												
No	560	88.3	214	92.6	150	91.5	0.668	66	83.5	130	81.3	0.664
Yes	74	11.7	17	7.4	14	8.5		13	16.5	30	18.8	
Unknown	96	15.1	45	19.5	19	11.6		13	16.5	19	11.9	
Vital status												
Alive	463	73.0	178	77.1	133	81.1	NA	54	68.4	98	61.3	NA
Dead	171	27.0	53	22.9	31	18.9		25	31.6	62	38.8	

NA not applicable statistical test due to censored observations

[a] Chi-square/Fisher's exact test excluding unknown

TABLE 4

Five-year overall survival using Cox proportional hazards analysis of subgroup based upon pathologic N

Variable	Category	pN1, *n* = 395				pN2+, *n* = 239			
		UVA		MVA		UVA		MVA	
		HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Cohort	SLN only	Ref		Ref		Ref		Ref	
	SLNB+CLND	0.62 (0.40–0.97)	0.036	1.04 (0.51–2.10)	0.922	1.18 (0.74–1.87)	0.493	1.31 (0.67–2.57)	0.427
Age (years)	18–44	Ref		Ref		Ref		Ref	
	45–64	1.70 (0.83–3.47)	0.144	1.77 (0.85–3.69)	0.128	1.69 (0.91–3.13)	0.094	1.57 (0.82–3.01)	0.175
	65+	3.01 (1.51–5.99)	0.002	2.69 (1.28–5.64)	0.009	2.19 (1.18–4.06)	0.013	2.06 (1.05–4.01)	0.035
Sex	Female	Ref		Ref		Ref		Ref	
	Male	1.83 (1.06–3.16)	0.029	1.77 (0.98–3.20)	0.058	1.07 (0.66–1.76)	0.776	0.91 (0.52–1.58)	0.732
Median income	< $40,227	Ref		Ref		Ref		Ref	
	$40,227–$50,353	0.65 (0.33–1.25)	0.194	0.66 (0.31–1.37)	0.263	2.91 (0.98–8.66)	0.055	4.16 (1.31–13.22)	0.016
	$50,354–$63,332	0.53 (0.25–1.13)	0.099	0.53 (0.23–1.18)	0.120	2.52 (0.85–7.50)	0.096	2.86 (0.91–8.99)	0.071
	≥ $63,333	0.40 (0.21–0.79)	0.008	0.43 (0.21–0.88)	0.021	1.55 (0.54–4.45)	0.413	1.74 (0.58–5.27)	0.324
	Unknown	0.62 (0.31–1.24)	0.175	0.77 (0.37–1.64)	0.333	2.08 (0.72–6.03)	0.176	2.98 (0.97–9.17)	0.057
Year of diagnosis	2012	Ref		Ref		Ref		Ref	
	2013	0.79 (0.43–1.45)	0.443	0.82 (0.43–1.58)	0.560	1.10 (0.55–2.18)	0.785	0.59 (0.26–1.32)	0.200
	2014	0.73 (0.37–1.44)	0.361	0.65 (0.32–1.32)	0.234	0.88 (0.41–1.89)	0.744	0.56 (0.25–1.27)	0.163
	2015	0.13 (0.04–0.45)	0.001	0.08 (0.02–0.29)	< .001	0.61 (0.27–1.39)	0.242	0.36 (0.14–0.89)	0.027
	2016	0.44 (0.19–1.01)	0.052	0.35 (0.14–0.83)	0.018	1.01 (0.47–2.18)	0.973	0.78 (0.35–1.77)	0.559
	2017	0.63 (0.28–1.41)	0.260	0.51 (0.22–1.20)	0.122	0.93 (0.36–2.38)	0.875	0.72 (0.27–1.90)	0.505
	2018	0.70 (0.30–0.59)	0.388	0.41 (0.16–1.02)	0.056	0.08 (0.01–0.64)	0.017	0.06 (0.01–0.52)	0.010
Total Charlson–Deyo score	0	Ref		Ref		Ref		Ref	
	1	1.82 (1.05–3.15)	0.034	1.69 (0.90–3.18)	0.102	1.80 (1.03–3.14)	0.040	2.16 (1.15–4.06)	0.017
	≥ 2	2.80 (1.27–6.16)	0.011	2.09 (0.86–5.08)	0.105	1.04 (0.38–2.85)	0.941	1.64 (0.54–4.98)	0.382
Regional nodes examined	1–5	Ref		Ref		Ref		Ref	
	6–10	0.76 (0.33–1.78)	0.533	0.63 (0.24–1.67)	0.348	0.97 (0.40–2.36)	0.952	0.93 (0.33–2.64)	0.896
	11–15	1.90 (0.86–4.17)	0.111	1.34 (0.51–3.53)	0.557	1.14 (0.44–2.96)	0.789	0.74 (0.23–2.39)	0.612

Variable	Category	pN1, *n* = 395				pN2+, *n* = 239			
		UVA		MVA		UVA		MVA	
		HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
	15+	0.44 (0.25–0.77)	0.004	0.34 (0.14–0.79)	0.012	1.08 (0.68–1.73)	0.744	1.06 (0.53–2.12)	0.877
Lymphovascular invasion	No	Ref		Ref		Ref		Ref	
	Yes	2.14 (1.12–4.09)	0.021	2.90 (1.39–6.04)	0.004	1.81 (1.14–2.88)	0.012	1.84 (1.09–3.11)	0.022
	Unknown	1.09 (0.60–1.98)	0.784	1.18 (0.62–2.25)	0.610	0.96 (0.47–1.96)	0.918	1.36 (0.65–2.84)	0.420

Additionally adjusted for age, sex, chemotherapy, radiation

NE not estimable

TABLE 5

Patient and disease characteristics based upon receipt of immunotherapy

Variable	All		Immunotherapy									
			Yes				*p* [a]	No				*p* [a]
			Cohort					Cohort				
			SLNB only		SLNB+CLND			SLNB only		SLNB+CLND		
	N	%	*N*	%	*N*	%		*N*	%	*N*	%	
All	621	100.0	114	100.0	101	100.0		190	100.0	216	100.0	
Age at diagnosis (years)												
18–44	141	22.7	27	23.7	37	36.6	0.044	33	17.4	44	20.4	0.063
45–64	268	43.2	50	43.9	44	43.6		73	38.4	101	46.8	
65+	212	34.1	37	32.5	20	19.8		84	44.2	71	32.9	
Sex												
Female	169	27.2	31	27.2	21	20.8	0.274	54	28.4	63	29.2	0.869
Male	452	72.8	83	72.8	80	79.2		136	71.6	153	70.8	
Insurance												
Medicaid	31	5.0	10	8.8	5	5.0	0.066	8	4.2	8	3.7	0.020
Medicare	192	30.9	34	29.8	19	18.8		75	39.5	64	29.6	
Other government	19	3.1	2	1.8	1	1.0		11	5.8	5	2.3	
Not insured	20	3.2	6	5.3	2	2.0		4	2.1	8	3.7	
Private	350	56.4	62	54.4	73	72.3		86	45.3	129	59.7	
Unknown	9	1.4	–	–	1	1.0		6	3.2	2	0.9	
Median income												
< $40,227	66	10.6	11	9.6	10	9.9	0.301	30	15.8	15	6.9	0.169
$40,227–$50,353	114	18.4	26	22.8	13	12.9		36	18.9	39	18.1	
$50,354–$63,332	110	17.7	22	19.3	20	19.8		32	16.8	36	16.7	
≥ $63,333	202	32.5	36	31.6	39	38.6		67	35.3	60	27.8	
Unknown	129	20.8	19	16.7	19	18.8		25	13.2	66	30.6	
Year of diagnosis												

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Variable	All		Immunotherapy									
			Yes				*p* [a]	No				*p* [a]
			Cohort					Cohort				
			SLNB only		SLNB+CLND			SLNB only		SLNB+CLND		
	N	%	*N*	%	*N*	%		*N*	%	*N*	%	
2012	68	11.0	4	3.5	16	15.8	< 0.001	18	9.5	30	13.9	< 0.001
2013	103	16.6	4	3.5	20	19.8		31	16.3	48	22.2	
2014	78	12.6	5	4.4	8	7.9		27	14.2	38	17.6	
2015	82	13.2	8	7.0	14	13.9		28	14.7	32	14.8	
2016	91	14.7	11	9.6	16	15.8		23	12.1	41	19.0	
2017	77	12.4	19	16.7	11	10.9		35	18.4	12	5.6	
2018	122	19.6	63	55.3	16	15.8		28	14.7	15	6.9	
Total Charlson–Deyo score												
0	507	81.6	91	79.8	86	85.1	0.139	151	79.5	179	82.9	0.482
1	76	12.2	12	10.5	12	11.9		25	13.2	27	12.5	
2+	38	6.1	11	9.6	3	3.0		14	7.4	10	4.6	
Pathologic T stage												
pT1	38	6.1	2	1.8	10	9.9	0.131	13	6.8	13	6.0	0.565
pT2–pT4	457	73.6	49	43.0	73	72.3		148	77.9	187	86.6	
Unknown	126	20.3	63	55.3	18	17.8		29	15.3	16	7.4	
Pathologic N stage												
pN1	387	62.3	81	71.1	45	44.6	< 0.001	145	76.3	116	53.7	< 0.001
pN2+	234	37.7	33	28.9	56	55.4		45	23.7	100	46.3	
Ulceration												
No	67	10.8	34	29.8	8	7.9	0.659	16	8.4	9	4.2	1.000
Yes	43	6.9	23	20.2	7	6.9		8	4.2	5	2.3	
Unknown	511	82.3	57	50.0	86	85.1		166	87.4	202	93.5	
Lymphovascular invasion												
No	434	69.9	70	61.4	68	67.3	0.466	130	68.4	166	76.9	0.765
Yes	94	15.1	24	21.1	18	17.8		24	12.6	28	13.0	

Variable	All		Immunotherapy									
			Yes				*p* [a]	No				*p* [a]
			Cohort					Cohort				
			SLNB only		SLNB+CLND			SLNB only		SLNB+CLND		
	N	%	*N*	%	*N*	%		*N*	%	*N*	%	
Unknown	93	15.0	20	17.5	15	14.9		36	18.9	22	10.2	
Mitotic rate												
0–1	19	3.1	11	9.6	2	2.0	0.780	4	2.1	2	0.9	1.000
2–10	74	11.9	37	32.5	10	9.9		16	8.4	11	5.1	
11+	10	1.6	4	3.5	2	2.0		3	1.6	1	0.5	
Unknown	518	83.4	62	54.4	87	86.1		167	87.9	202	93.5	
Regional lymph nodes examined												
1–5	308	49.6	99	86.8	17	16.8	< 0.001	192	47.3	165	86.8	< 0.001
6–10	48	7.7	12	10.5	9	8.9		27	6.7	9	4.7	
11–15	30	4.8	1	0.9	4	4.0		25	6.2	6	3.2	
15+	235	37.8	2	1.8	71	70.3		162	39.9	10	5.3	
Chemotherapy												
No	575	92.6	109	95.6	95	94.1	0.737	170	89.5	201	93.1	0.703
Yes	31	5.0	4	3.5	5	5.0		11	5.8	11	5.1	
Unknown	15	2.4	1	0.9	1	1.0		9	4.7	4	1.9	
Radiation therapy												
No	548	88.2	101	88.6	86	85.1	0.453	174	91.6	187	86.6	0.109
Yes	73	11.8	13	11.4	15	14.9		16	8.4	29	13.4	
Vital status	121	29.8	99	86.8	17	16.8		111	58.4	10	4.6	
Alive	452	72.8	95	83.3	74	73.3	NA	133	70.0	150	69.4	NA
Dead	169	27.2	19	16.7	27	26.7		57	30.0	66	30.6	

[a] Chi–square/Fisher's exact test excluding unknown

TABLE 6

Five-year overall survival using Cox proportional hazards analysis of subgroup based upon receipt of immunotherapy

Variable	Category	Immunotherapy, *n* = 215				No immunotherapy *n* = 406			
		UVA		MVA		UVA		MVA	
		HR (95%CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Cohort	SLN only	Ref		Ref		Ref		Ref	
	SLNB+CLND	1.21 (0.67–2.20)	0.526	1.32 (0.54–3.22)	0.549	0.95 (0.66–1.35)	0.760	1.16 (0.65–2.07)	0.608
Age (years)	18–44	Ref		Ref		Ref		Ref	
	45–64	1.49 (0.71–3.11)	0.291	2.05 (0.92–4.60)	0.08	1.93 (1.02–3.63)	0.042	1.58 (0.81–3.06)	0.178
	65+	1.91 (0.87–4.16)	0.104	1.59 (0.59–4.25)	0.359	2.89 (1.56–5.36)	< 0.001	2.46 (1.27–4.77)	0.008
Sex	Female	Ref		Ref		Ref		Ref	
	Male	1.18 (0.59–2.39)	0.636	1.19 (0.50–2.83)	0.686	1.60 (1.04–2.47)	0.032	1.39 (0.87–2.22)	0.167
Median income	< $40,227	Ref		Ref		Ref		Ref	
	$40,227–$50,353	0.91 (0.33–2.51)	0.856	1.84 (0.57–5.88)	0.307	1.09 (0.57–2.09)	0.800	1.22 (0.60–2.46)	0.585
	$50,354–$63,332	0.58 (0.20–1.68)	0.319	0.73 (0.22–2.42)	0.610	1.24 (0.63–2.43)	0.541	1.14 (0.53–2.44)	0.737
	≥ $63,333	0.60 (0.23–1.56)	0.296	0.70 (0.24–2.01)	0.507	0.71 (0.37–1.33)	0.284	0.65 (0.32–1.32)	0.233
	Unknown	0.53 (0.18–1.57)	0.252	0.67 (0.20–2.20)	0.509	1.15 (0.61–2.15)	0.668	1.40 (0.70–2.80)	0.348
Year of diagnosis	2012	Ref		Ref		Ref		Ref	
	2013	0.48 (0.19–1.19)	0.114	0.35 (0.10, 1.20)	0.094	1.26 (0.74–2.15)	0.388	0.89 (0.50–1.60)	0.693
	2014	0.27 (0.07–0.97)	0.045	0.35 (0.08, 1.49)	0.156	1.10 (0.62–1.97)	0.747	0.95 (0.52, 1.75)	0.867
	2015	0.18 (0.05–0.64)	0.008	0.11 (0.02, 0.52)	0.005	0.46 (0.22–0.95)	0.036	0.29 (0.13, 0.63)	0.002
	2016	0.50 (0.19–1.29)	0.152	0.46 (0.14, 1.51)	0.200	0.73 (0.37–1.46)	0.374	0.78 (0.38, 1.61)	0.503
	2017	0.89 (0.36–2.21)	0.802	0.97 (0.30, 3.12)	0.959	0.54 (0.23–1.29)	0.164	0.46 (0.18, 1.16)	0.100
	2018	0.23 (0.08–0.70)	0.009	NE		0.71 (0.26–1.91)	0.496	0.44 (0.02, 8.73)	0.590
Total Charlson–Deyo score	0	Ref		Ref		Ref		Ref	
	1	1.46 (0.65–3.28)	0.362	1.11 (0.43, 2.89)	0.827	1.84 (1.17–2.88)	0.008	1.82 (1.11, 2.98)	0.017
	2+	0.95 (0.23–3.96)	0.944	0.49 (0.08, 2.86)	0.425	2.20 (1.10–4.37)	0.025	1.81 (0.83, 3.92)	0.133
Pathologic T	T1	Ref		Ref		Ref		Ref	
	pT2–pT4	4.55 (0.62–33.19)	0.135	3.74 (0.46–30.37)	0.216	2.41 (0.89–6.55)	0.083	1.38 (0.49–3.91)	0.541
1	Unknown	2.08 (0.24–17.61)	0.503	NE		2.12 (0.59–7.59)	0.248	NE	

Variable	Category	Immunotherapy, *n* = 215				No immunotherapy *n* = 406			
		UVA		MVA		UVA		MVA	
		HR (95%CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
Pathologic N	pN1	Ref		Ref		Ref		Ref	
	pN2+	1.57 (0.88–2.80)	0.127	1.91 (0.86, 4.22)	0.111	2.08 (1.46–2.96)	< 0.001	1.82 (1.20, 2.76)	0.005
Lymphovascular invasion	No	Ref		Ref		Ref		Ref	
	Yes	1.65 (0.84–3.24)	0.148	1.49 (0.67, 3.32)	0.332	2.83 (1.83–4.40)	< 0.001	2.49 (1.48, 4.19)	< 0.001
	Unknown	0.92 (0.38–2.22)	0.847	1.10 (0.41, 2.98)	0.851	1.16 (0.68–1.98)	0.590	1.21 (0.69, 2.14)	0.500
Mitotic rate	0–1	Ref		Ref		NA		NA	
	2–10	0.91 (0.09–8.79)	0.938	0.36 (0.03, 5.07)	0.453				
	11+	3.25 (0.20–52.08)	0.404	0.38 (0.01, 16.07)	0.611				
	Unknown	2.12 (0.29–15.63)	0.460	NE					
Regional nodes examined	1–5	Ref		Ref		Ref		Ref	
	6–10	1.34 (0.50, 3.59)	0.565	0.81 (0.24, 2.77)	0.741	0.83 (0.38, 1.82)	0.650	0.71 (0.28, 1.78)	0.461
	11–15	4.43 (1.30, 15.08)	0.017	4.91 (0.89, 27.02)	0.068	1.25 (0.62, 2.52)	0.530	0.70 (0.29, 1.66)	0.418
	15+	1.18 (0.62, 2.25)	0.608	0.59 (0.21, 1.68)	0.325	0.81 (0.55, 1.18)	0.273	0.58 (0.31, 1.07)	0.083
Chemotherapy	No	Ref		Ref		Ref		Ref	
	Yes	1.60 (0.49–5.17)	0.433	1.69 (0.40, 7.22)	0.476	0.65 (0.24–1.77)	0.403	0.77 (0.27, 2.22)	0.625
	Unknown	5.36 (0.73–39.43)	0.099	58.53 (3.15, 1088.88)	0.006	1.10 (0.41–2.99)	0.849	1.55 (0.54, 4.44)	0.413
Radiation therapy	No	Ref		Ref		Ref		Ref	
	Yes	0.95 (0.42–2.14)	0.904	0.53 (0.19, 1.48)	0.224	1.92 (1.22–3.02)	0.005	1.73 (1.04, 2.88)	0.034
	Unknown	3.42 (0.81–14.44)	0.094	NE		2.02 (0.49–8.22)	0.329	NE	