Article type: Original article

Title: Sentinel lymph node biopsy vs observation in high-risk cutaneous squamous cell carcinoma in immunosuppressed and immunocompetent patients: an inverse probability of treatment weighting study

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Abstract.

Background: The survival benefit of sentinel lymph node biopsy (SLNB) in immunocompetent and immunosuppressed patients with high-risk cutaneous squamous cell carcinoma (cSCC) has not been established.

Objective: To determine whether SLNB improves disease-specific survival (DSS) in high-risk cSCC. Secondary objectives were to analyze disease-free survival, nodal recurrence–free survival, and overall survival.

Methods: Multicenter, retrospective, observational cohort study comparing survival outcomes in immunosuppressed and immunocompetent patients treated with SLNB or

watchful waiting. Inverse probability of treatment weighting was used to adjust for possible confounding effects.

Results: We studied 638 tumors in immunocompetent patients (SLNB n = 42, observation n = 596) and 173 tumors in immunosuppressed patients (SLNB n = 28, observation n = 145). Overall, SLNB was positive in 15.7% of tumors. SLNB was associated with a reduced risk of NR (hazard ratio [HR], 0.05 [95% CI, 0.01-0.43]; *P* = .006), DSM (HR, 0.17 [95% CI, 0.04-0.72]; *P* = .016), and all-cause mortality (OS) (HR, 0.33 [95% CI, 0.15-0.71]; *P* = .004) only in immunocompetent patients.

Conclusions: SLNB was associated with improvements in NR, DSS, and OS in immunocompetent but not in immunosuppressed patients with high-risk cSCC.

INTRODUCTION

Cutaneous squamous cell carcinoma (cSCC) is the second most common malignant tumor in the world.[1] Approximately 5% of patients develop metastasis, largely via lymphatic spread.[2]

Classic factors associated with high-risk cSCC include tumor diameter and thickness, poor cell differentiation, and perineural invasion,[3,4] but immunosuppression has also been linked to an increased risk of recurrence and mortality.[5,6] Some authors have even recommended stratifying by immune status to predict prognosis in cSCC.[7,8] Although sentinel lymph node biopsy (SLNB) is well established in cutaneous melanoma,[9] consensus is lacking on its role in cSCC, as no randomized clinical trials have assessed its value as a staging or prognostic marker.[10,11]

The main aim of this study was to determine the effects of SLNB on disease-specific survival (DSS) in patients with high-risk cSCC stratified by immune status (immunosuppression and immunocompetence). Secondary aims were to compare disease-free survival (DFS), nodal recurrence–free survival (NRFS), and overall survival (OS) between patients who underwent SLNB and those managed with observation only.

METHODS

Participants and study design

We designed a multicenter, retrospective, observational cohort study of patients with high-risk cSCC selected from clinical databases at eight tertiary care hospitals participating in the SQUAMATA project. This project aims to analyze prognostic factors in high-risk cSCC and has been described elsewhere.[12] Seven of the participating hospitals are in Spain: Hospital Universitario de Salamanca, Salamanca; Instituto Valenciano de Oncología, Valencia; Hospital Germans Trias i Pujol, Badalona; Hospital Clínic, Barcelona; Hospital Universitari Vall d'Hebron, Barcelona; Hospital Universitario Central de Asturias, Oviedo; and Hospital San Cecilio, Granada. The eighth hospital is Italian (Azienda Ospedaliero-Universitaria Città della Salute e della Scienza di Torino, Turin).

Patients diagnosed with a primary or recurrent high-risk cSCC clinically N0, between January 1, 2000, and December 31, 2020, were included. A tumor was considered to be high-risk if it had any of the following characteristics: diameter ≥ 2 cm, thickness ≥ 6 mm, perineural or lymphovascular invasion, poor histologic differentiation, invasion beyond the subcutaneous fat, an ear or lip location. Patients were deemed to be immunosuppressed if they were on long-term immunosuppressive therapy or had a solid organ transplant, chronic lymphatic leukemia, HIV-infected patients, or chronic renal failure. In the case of multiple synchronous cSCCs, the tumor with the highest risk (i.e., with the most risk factors) was selected. Patients with missing data for any of the outcome variables were excluded.

SLNB was performed using a similar procedure in all the participating hospitals. A radioactive tracer was injected to obtain a preoperative lymphography (with or without preoperative computed tomography [CT] or positron emission tomography-CT) to identify the SLN(s) to be excised for biopsy. The histologic procedure was similar among hospitals (see protocol in supplementary material). The decision to perform SLNB was based on individualized assessment of tumor and patient characteristics. This evaluation was conducted by a multidisciplinary committee at each hospital. The study was approved by the ethics committee at Hospital Universitario Reina Sofía (registry no. 3958).

Patient groups, study variables, and inverse probability of treatment weighting

We analyzed the effects of SLNB on NRFS, DFS, DSS, and OS in immunocompetent and immunosuppressed patients by their received treatment (SLNB *vs* observation).

Since the decision to perform SLNB was not randomized, we used a statistical technique called inverse probability of treatment weighting (IPTW) to adjust for any potential confounding factors and to analyze all patients in the study.[13] Briefly, IPTW involves calculating the probability of each patient being assigned to a given treatment group.[13] This probability, also known as a propensity score, was calculated by performing logistic regression analysis of predictors of SLNB, tumor progression, and mortality (sex, age, year of diagnosis, and American Joint Committee on Cancer 8th Edition [AJCC8] and Brigham Women's Hospital [BWH] tumor stages). Two weighting approaches were used: one targeting ATE (average treatment effect) and the other targeting ATT (average treatment effect among the treated population). The former assumes that all patients undergo SLNB, while the latter

estimates the effect for all patients actually treated. Stabilized weights were used to prevent extreme weights and improve stability of the estimates. IPTW and all additional analyses were carried out separately for immunocompetent and immunosuppressed patients.

As sensitivity analysis, we adjusted using other methods, such as propensity score matching (with different matching ratios), full optimal matching, doubly robust propensity score adjustment methods, and classic multivariate covariate adjustment.[14,15]

Statistical analysis

Descriptive statistics were computed using parametric and nonparametric tests for normally and non-normally distributed variables, respectively. Bivariate analyses were performed to compare clinical and histologic characteristics by immune status and treatment (SLNB vs observation). The Kruskal-Wallis rank sum test was used to assess statistically significant differences for quantitative variables, and the Fisher exact test to ascertain differences in proportions.

To compare survival between the treatment groups, IPTW-adjusted Kaplan-Meier curves with ATE weights were computed for each survival outcome of interest.[16] The adjusted log-rank test described by Xie and Liu[16] was used to test differences between curves. We compared survival at 5 years after diagnosis and computed the following measures to assess the absolute magnitude of the effect of SLNB on clinical outcomes: absolute risk reduction (ARR), number needed to treat (NNT), and differences in restricted mean survival time (RMST).[17] RMST is a measure of the average time free from an event up to a given time point and provide clinicians with an intuitive absolute measure of how long a given treatment delays an

event in those treated.[18,19] The relative effect of SLNB in treated patients, was analyzed with an IPTW-weighted Cox regression model. We also explored the effect of SLN positivity on nodal recurrence and disease-specific mortality using a multivariate Cox regression model including both immunocompetent and immunosuppressed patients.

All tests were two-tailed and statistical significance was set at $P < .05$. All analyses were performed from July to October 2022 using R software and the additional packages "tidyverse", "survival", "MatchIt", "IPWsurvival", "WeighIt", "cobalt", and "arsenal". The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were applied to report our findings.[20]

RESULTS

Clinical and demographic characteristics by treatment

In total, 1439 patients met the inclusion criteria. Of these, 628 were excluded due to missing tumor, clinical, or follow-up data (Supplementary Fig I; available via Mendeley DOI: 10.17632/88p28c9b23.2)

Most of the patients (n = 638) were immunocompetent, and 42 had undergone SLNB. The remaining 173 patients were immunosuppressed, and 28 of these had undergone SLNB (Table I). For tumors with associated SLNB, surgery was synchronous in 78.6% of cases, adjuvant radiotherapy was performed in 18.6% and complications were reported in 17.2% of SNLB procedures with a number needed to harm of 5.8. Computed tomography was the most common pre-operative imaging test, used in 65.7% of cases, with no difference between those with negative and positive SLNB (Supplementary table II). Median follow-up was 2.9 years in the immunocompetent group and 2.7 years in the immunosuppressed group. Most patients were men aged over 70 years. Immunocompetent patients in the SLNB group were younger and had larger, more advanced tumors and a higher frequency of desmoplasia and bone invasion (Table I and Supplementary table I, available via Mendeley DOI: 10.17632/88p28c9b23.2). Immunosuppressed patients in the SLNB group had a significantly higher BWH stage, a lower frequency of differentiated tumors, and a higher frequency of desmoplasia and recurrent tumor. Cause of immunosuppression and immunosuppressive treatment are detailed in table III supplementary. No significant differences were observed

for sex, tumor location, tumor thickness, or perineural invasion between immunocompetent and immunosuppressed patients in the analysis stratified by SLNB performance (Table I).

Observed outcomes, SLNB positivity, and clinical management

Significantly fewer overall recurrences were observed in immunocompetent patients who had a SLNB performed (14.3% vs 32.2% for observation, *P* =.01). The differences in immunosuppressed patients undergoing SLNB were nonsignificant (Table I). A similar pattern was observed for nodal recurrence (2.4% for immunocompetent patients who had undergone SLNB vs 24.8% for those who had not, *P* =<.001). Again, the differences in immunosuppressed patients were nonsignificant. Immunosuppressed patients that underwent SLNB had shorter NRFS, DSS, and OS (Supplementary Table I).

A higher, albeit nonsignificant, rate of SLNB positivity was observed in immunosuppressed patients (7/28, 25% vs. 4/42 immunocompetent patients, 9.5%; *P* = .102). The overall SLN positivity rate was 15.7% (11/70). Ten of the 11 SLN-positive patients underwent lymph node dissection, which detected additional diseased nodes in five cases (50%). Four of the SLNB-positive patients were also treated with adjuvant radiotherapy. Three patients experienced lymph node recurrence during follow-up despite having a negative SLNB (false negative rate, 21.4%; 3/14). All three patients received radiotherapy, with one also undergoing chemotherapy. This compares with the observed nodal recurrence in four of the 11 patients (36.4%) with a positive SLNB (*P* = .010), out of the four patients, three received chemoradiotherapy, and one received chemotherapy.

Following adjustment for age, sex, BWH stage, and immune status, SLNB positivity was associated with a 12-fold increased risk of nodal recurrence (hazard ratio, 12.2 [95% CI, 1.54-96]; *P* = .02) and a 12-fold increased risk of disease-specific mortality (hazard ratio, 11.9 [95% CI, 1.01-140]; *P* = .04).

Effect of SLNB on NRFS, DFS, DSS, and OS

The IPTW-adjusted analyses showed a significantly lower risk of nodal and overall recurrence in immunocompetent patients who had undergone SLNB (Figure IA and Table II). DSS at 5 years from diagnosis was also significantly higher in the SLNB group (Table II). SLNB in immunocompetent patients was associated with a 29.5% (95% CI, 25-34) absolute risk reduction in nodal recurrence and a 17.4% (95% CI, 12-22) reduction in disease-specific mortality 5 years after diagnosis. The NNT was 3.4 patients to prevent nodal recurrence and 5.7 patients to prevent death due to cSCC at 5 years. Performance of SLNB in immunocompetent patients was associated with an average delay to nodal recurrence of 15 months (95% CI, 12-18) and a mean improvement in DSS of 6 months (95% CI, 3-9) (Table II). Immunocompetent patients who underwent SLNB had a statistically significant improvement in 5-year OS rates (Fig IA and Table II).

SLNB in immunosuppressed patients was not associated with a significant improvement in absolute risk of nodal recurrence, overall recurrence, DSS, or OS (Figure IB and Table II).

The relative risk reduction for SLNB in the treated population was analyzed by IPTW-weighted Cox regression. Exchangeability between treatment groups was evaluated by visually

assessing the distributional balance of propensity scores and covariate balance. The graphs (Supplementary Fig II; available via Mendeley DOI: 10.17632/88p28c9b23.2) indicated good overall balance. Performance of SLNB was associated with significant reductions in the risk of nodal and overall recurrence, disease-specific mortality, and all-cause mortality, but only in immunocompetent patients (Table III). In this group, the greatest protection was observed for nodal recurrence followed by disease-specific mortality. To test the robustness of our findings, we estimated the same risk reductions using different adjustment and matching methods and observed very similar results (Supplementary Figure III; available via Mendeley DOI: 10.17632/88p28c9b23.2). As expected, risk of local recurrence was not reduced by SLNB (Supplementary Figure III; available via Mendeley DOI: 10.17632/88p28c9b23.2). Additional sensitivity analyses limited to AJCC8 T3 and T4 stages or using other prognostic factors, such as perineural invasion and lymphovascular invasion showed similar findings (data not shown). To explore whether the risk reductions observed were due to SLNB alone or possibly to different clinical management strategies after a positive or negative biopsy, we further adjusted the main model by SLN status, and again found no major changes in our estimates (Table III).

DISCUSSION

Although Cabañas[21] first described the use of SLNB to treat penile SCC in the 1970s, no randomized controlled trials have assessed its role in cSCC. SLNB is widely used in other tumors that preferentially spread through the lymphatic system, such as cutaneous melanoma[11] and breast cancer. We are therefore currently in a state of clinical equipoise regarding the potential merits of SLNB in cSCC.[2,22]

In our study, SLNB was associated with a lower risk of nodal recurrence, overall recurrence, disease-specific mortality, and all-cause mortality in immunocompetent patients with cSCC. It showed no survival benefits, however, in immunosuppressed patients.

We believe that these findings in immunocompetent patients with high-risk cSCC are clinically relevant and promising. The procedure was associated with a 29% reduction in nodal recurrence and a 17% reduction in disease-specific mortality at 5 years after diagnosis. In immunocompetent patients, SLNB also delayed the onset of nodal recurrence by a mean of 15 months and extended overall 5-year survival by a mean of 6 months. Finally, immunocompetent patients who underwent SLNB experienced a 67% relative reduction in all-cause mortality rate.

To our knowledge, this is the first report of SLNB exerting a protective effect in cSCC. Maruyama et al.[23] observed no significant differences in metastasis-free or disease-specific survival in 49 patients who underwent SLNB vs 107 who did not. Immune status of participants, however, was not specified. In a retrospective study, Kofler et al.[24] found no differences in NRFS or metastasis-free survival between 101 patients treated with SLNB and 570 who did not receive this treatment. In this case, 23% of the patients in the SLNB group and 14% of those in the observation group were immunosuppressed, but the authors did not conduct a stratified analysis.

The available evidence would seem to justify stratifying SLNB results by immune status in high-risk cSCC. As we observed, immunosuppressed patients appear to have higher rates of SLN positivity.[25-27] They also tend to have smaller metastases and more high-risk features

than immunocompetent patients, as well as a higher risk of locoregional recurrence despite adjuvant radiotherapy.[29] Other authors, however, have attributed the worse prognosis observed in this setting to more advanced disease at diagnosis rather than immunosuppression[30]. Finally, in some series of cSCC, the majority of patients who developed distant metastasis, including immunosuppressed, were SLN negative.[31,24]

It is unclear why patients who undergo SLNB exhibit different biologic behavior depending on their immune status. Based on the current evidence, it could be hypothesized that the immune surveillance activities of SLNs[32] are suppressed in the absence of a competent immune system.

The results of our analysis adjusted for SLN status suggest that the survival benefits of SLNB in immunocompetent patients with cSCC are independent of the biopsy result. These findings indicate that selective treatment of regional lymph nodes might reduce the risk of recurrence and mortality in immunocompetent patients with high-risk cSCC. Amit et al.[33] compared elective neck dissection (END) (n = 173) with observation (n = 938) in patients with cSCC of the head and neck and observed no survival benefits or improvements in locoregional control. Approximately 25% of the patients analyzed were immunosuppressed, but again, a stratified analysis was not performed. Xiao et al.,[34] by contrast, in a prospective descriptive study, found that END plus superficial parotidectomy improved survival in patients with high-risk cSCC of the head and neck.

In a recent review, the success rate of SLNB in cSCC does not seem to be affected by the timing of the intervention[35]. This is important in a current context in which Mohs surgery is

an increasingly frequent procedure and therefore the performance of SLNB has to be carried out after the procedure[36].

The main limitations of our study are those inherent to its retrospective design and the use of data from multiple hospitals, which carries a risk of slight variations in the criteria used for the indication of SLNB and subsequent management. Its strengths include a large sample of patients with high-risk cSCC, stratification of results by immune status, and use of different sensitivity analyses to test the robustness of our findings.

In conclusion, SLNB was associated with improved DFS, NRFS, DSS, and OS in immunocompetent but not in immunosuppressed patients with high-risk cSCC. These findings suggest a promising role for SLNB in high-risk cSCC as a prognostic and therapeutic procedure especially with the possible coming advent of immunological adjuvant or neoadjuvant therapy[37].

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Table legend

Table I. Tumor data by patient immune status and SLNB biopsy

Table II. IPTW-adjusted five-year clinical outcomes by SNLB biopsy in immunocompetent and immunosuppressed patients.

Table III. Hazard ratios (HR) and 95%CI for the use of SNLB on different clinical outcomes by immune status.

Figure legend

Figure 1. Inverse probability of treatment weighting (IPTW)-adjusted survival curves by sentinel lymph node biopsy (SLNB) performance in immunocompetent patients.

Footnote Fig 1: Survival curves adjusted by age, sex, year of diagnosis, and American Joint Committee on Cancer 8th edition and Brigham and Women's Hospital tumor stages via stabilized IPTW average treatment effect weights. *P* value from the IPTW-adjusted log-rank test described by Xie and Liu.[16] Risk tables indicate units at risk in the weighted pseudopopulation.

Figure 2. Inverse probability of treatment weighting (IPTW)-adjusted survival curves by sentinel lymph node biopsy (SLNB) performance in immunosuppressed patients.

Footnote Fig 2: Survival curves adjusted by age, sex, year of diagnosis, and American Joint Committee on Cancer 8th edition and Brigham and Women's Hospital tumor stages via stabilized IPTW average treatment effect weights. *P* value from the IPTW-adjusted log-rank test described by Xie and Liu.[16] Risk tables indicate units at risk in the weighted pseudopopulation.

Table I. Tumor data by patient immune status and SLNB performance

	Tumors, No. (%)							
	Immunocompetent host				Immunosuppressed host			
	Observation (N=596)	SNLB (N=42)	Total (N=638)	P-value*	Observation (N=145)	SNLB (N=28)	Total (N=173)	P-value*
Age at diagnosis, y Median (Q1-Q3)	81.5 (74.0, 88.0)	73.5 (67.2, 82.0)	81.0 (74.0, 87.0)	< .001	74.0 (67.0, 81.0)	70.5 (66.0, 76.0)	73.0 (67.0, 81.0)	.213
Sex				.251				.232
Men	370 (62.1)	30 (71.4)	400 (62.7)		107 (73.8)	24 (85.7)	131 (75.7)	
Women	226 (37.9)	12 (28.6)	238 (37.3)		38 (26.2)	4 (14.3)	42 (24.3)	
BWH Stage				< .001				.001
T1	230 (38.6)	4 (9.5)	234 (36.7)	< .001	46 (31.7)	4 (14.3)	50 (28.9)	.212
T2a	206 (34.6)	15 (35.7)	221 (34.6)	.87	59 (40.7)	7 (25.0)	66 (38.2)	.242
T2b	133 (22.3)	17 (40.5)	150 (23.5)	.039	35 (24.1)	14 (50.0)	49 (28.3)	.042
T3	27 (4.5)	6 (14.3)	33 (5.2)	.039	5 (3.4)	3 (10.7)	8 (4.6)	.242
AJCC8 Stage				.002				.402
T1	176 (29.5)	5 (11.9)	181 (28.4)	.051	38 (26.2)	6 (21.4)	44 (25.4)	
T2	53 (8.9)	2 (4.8)	55 (8.6)	.568	9 (6.2)	1 (3.6)	10 (5.8)	
T3	345 (57.9)	30 (71.4)	375 (58.8)	.208	93 (64.1)	19 (67.9)	112 (64.7)	
T4	22 (3.7)	5 (11.9)	27 (4.2)	.08	5 (3.4)	2 (7.1)	7 (4.0)	
Tumor anatomical location				.876				1.000
Hand/Foot	38 (6.4)	3 (7.1)	41 (6.4)		10 (6.9)	1 (3.6)	11 (6.4)	
Head & Neck	450 (75.6)	31 (73.8)	481 (75.5)		110 (75.9)	22 (78.6)	132 (76.3)	
Trunk & Extremities	107 (18.0)	8 (19.0)	115 (18.1)		25 (17.2)	5 (17.9)	30 (17.3)	
Tumor diameter, mm Median (Q1-Q3)	20.0 (12.0, 30.0)	30.0 (20.0, 40.0)	20.0 (13.0, 30.0)	.001	20.0 (12.0, 26.0)	20.5 (13.0, 33.2)	20.0 (12.0, 28.0)	.345
Tumor thickness, mm† Median (Q1-Q3)	7.0 (4.5, 10.5)	8.0 (6.0, 10.0)	7.0 (4.6, 10.2)	.256	7.0 (4.0, 10.0)	7.0 (5.0, 8.8)	7.0 (4.4, 10.0)	.649
Histologic differentiation				.621				.005
Well	159 (28.4)	11 (26.2)	170 (28.3)		39 (29.1)	1 (3.7)	40 (24.8)	.01
Moderate	310 (55.5)	23 (54.8)	333 (55.4)		70 (52.2)	17 (63.0)	87 (54.0)	.398
Poor	90 (16.1)	8 (19.0)	98 (16.3)		25 (18.7)	9 (33.3)	34 (21.1)	.238
Perineural invasion				.852				.142
Absent	418 (76.4)	33 (78.6)	451 (76.6)		111 (78.7)	18 (64.3)	129 (76.3)	
Present	129 (23.6)	9 (21.4)	138 (23.4)		30 (21.3)	10 (35.7)	40 (23.7)	
Bone invasion				.026				.316
Absent	574 (96.3)	37 (88.1)	611 (95.8)		140 (96.6)	26 (92.9)	166 (96.0)	
Present	22 (3.7)	5 (11.9)	27 (4.2)		5 (3.4)	2 (7.1)	7 (4.0)	
Adjuvant radiotherapy				.809				.423
No	521 (87.4)	36 (85.7)	557 (87.3)		119 (82.1)	20 (74.1)	139 (80.8)	
Yes	75 (12.6)	6 (14.3)	81 (12.7)		26 (17.9)	7 (25.9)	33 (19.2)	
Local recurrence				1.000				.627
No	513 (86.1)	36 (85.7)	549 (86.1)		114 (78.6)	21 (75.0)	135 (78.0)	
Yes	83 (13.9)	6 (14.3)	89 (13.9)		31 (21.4)	7 (25.0)	38 (22.0)	
Nodal recurrence				< .001				.803
No	448 (75.2)	41 (97.6)	489 (76.6)		116 (80.0)	22 (78.6)	138 (79.8)	
Yes	148 (24.8)	1 (2.4)	149 (23.4)		29 (20.0)	6 (21.4)	35 (20.2)	
Overall recurrence				0.015				0.284
No	404 (67.8)	36 (85.7)	440 (76.6)		95 (65.5)	15 (53.6)	110 (63.6)	
Yes	192 (32.2)	6(14.3)	198 (23.4)		50 (34.5)	13 (46.4)	63 (36.4)	
Distant metastasis				1.000				.467
No	535 (95.4)	39 (97.5)	574 (95.5)		103 (89.6)	23 (95.8)	126 (90.6)	
Yes	26 (4.6)	1 (2.5)	27 (4.5)		12 (10.4)	1 (4.2)	13 (9.4)	

AJCC8, American Joint Committee on Cancer 8th edition; *BWH*, Brigham and Women's Hospital ; *SLNB*, sentinel lymph node.

* P-values from Kruskal-Wallis rank sum test for numerical variables, Fisher's exact test for count data and Cochran-Armitage trend test for ordinal variables. When the omnibus test was statistically significant, post-hoc tests were carried out adjusting for multiple comparisons using Holm's method.

† Depth of invasion measured from granulose layer of non-tumoral skin to deepest tumoral nest.

Table II. IPTW-adjusted 5-year clinical outcomes by SLNB in immunocompetent and immunosuppressed patients

Outcomes[†]	Observation, % (95%CI)	SLNB, % (95%CI)	ARR, % (95%CI)	NNT (95%CI)[††]	*P* value	RMST difference, months, (95%CI)	*P* value
Immunocompetent patients							
Nodal recurrence–free survival	70.04 (66,75)	99.51 (99,100)	29.5 (25,34)	3.4 (3.3,5)	< .001	15 (12,18)	< .001
Recurrence-free survival	63.66 (59,69)	95.14 (90,100)	31.5 (24,39)	3.2 (2.5,5)	< .001	15 (9,21)	< .001
Disease-specific survival	80.67 (77,85)	98.08 (95,100)	17.4 (12,23)	5.7 (5,10)	< .001	6 (3,9)	< .001
Overall survival	50.00 (45,55)	81.72 (64,100)	31.7 (11,52)	3.2 (10,2)	.003	9 (2,16)	.010
Immunosuppressed patients							
Nodal recurrence–free survival	74.13 (66,83)	77.79 (59,100)	3.7 (-19,27)	-	.76	2 (-10,13)	.77
Recurrence-free survival	53.94 (44,67)	52.13 (31,88)	-1.8 (-31,28)	-	.90	-6 (-23,10)	.44
Disease-specific survival	80.39(71,91)	78.22 (58,100)	-2.2 (-27,23)	-	.86	-3 (-12,7)	.62
Overall survival	49.65 (40,61)	41.26 (21,81)	-8.4 (-38,21)	-	.58	-10 (-23,3)	.14

AJCC8, American Joint Committee on Cancer 8th edition; ARR, absolute risk reduction; *BWH*, Brigham and Women's Hospital; *IPTW*, inverse probability of treatment weighting; *NNT*, number needed to treat; *RMST*, restricted mean survival time; *SLNB*, sentinel lymph node biopsy.

[†] All outcomes and measures of effect adjusted by age, sex, year of diagnosis, and AJCC8 and BWH tumor stages via stabilized IPTW average treatment effect weights.

[††] NNT and 95% CI not displayed when differences are not significant, or value is negative.

Table III. HRs and 95% CI from Cox regression model showing the effects of SLNB on different clinical outcomes by immune status.

	Crude model		IPTW-adjusted†		IPTW-adjusted + SLNB status††	
Outcomes	**HR (95%CI)**	***P* value**	**HR (95% CI)**	***P* value**	**HR (95% CI)**	***P* value**
Immunocompetent patients						
Nodal recurrence	0.09 (0.01-0.62)	.015	0.05 (0.01-0.43)	.006	0.06 (0.01-0.48)	.008
Overall recurrence	0.44 (0.2-1)	.049	0.31 (0.12-0.77)	.013	0.34 (0.13-0.88)	.022
Disease-specific mortality	0.35 (0.09-1.43)	.14	0.17 (0.04-0.72)	.016	0.18 (0.04-0.77)	.020
Overall mortality	0.38 (0.18-0.8)	.011	0.33 (0.15-0.71)	.004	0.35 (0.16-0.75)	.007
Immunosuppressed patients						
Nodal recurrence	1.31 (0.54-3.18)	.55	1.04 (0.32-3.38)	.95	0.44 (0.09-2.1)	.30
Overall recurrence	2.04 (1.11-3.79)	.02	1.77 (0.74-4.28)	.20	1.63 (0.63-4.2)	.32
Disease-specific mortality	1.95 (0.64-5.91)	.24	1.63 (0.46-5.79)	.45	0.53 (0.06-4.64)	.57
Overall mortality	1.32 (0.65-2.68)	.45	2 (0.85-4.72)	.11	1.73 (0.63-4.78)	.29

AJCC8, American Joint Committee on Cancer 8th edition; ARR, absolute risk reduction; *ATT*, average treatment effect among the treatment population; *BWH*, Brigham and Women's Hospital; HRs, hazard ratios; NNT, number needed to treat; *RMST*, restricted mean survival time.
† Adjusted by age, sex, year of diagnosis, and AJCC8 and BWH tumor stages via stabilized IPTW-ATT weights.
†† Adjusted by age, sex, year of diagnosis, and AJCC8 and BWH tumor stages via stabilized IPTW-ATT weights and further adjusted by SLNB status (positive/negative) in regression model.