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Active Surveillance of Melanoma Patients with Sentinel Node Metastasis: An International Multi-Institution Evaluation of Post-MSLT-2 Adoption and Early Outcomes

Running Title: Post-MSLT2 adoption and outcomes

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Lay summary:

For patients with melanoma of the skin and microscopic spread to lymph nodes, monitoring with ultrasound is an alternative to surgically removing the remaining nodes. We studied adoption and real-world outcomes of ultrasound monitoring in over 1,000 patients treated at 21 centers worldwide, finding that most patients now have ultrasounds instead of surgery. While slightly more patients have cancer return in the lymph nodes with this strategy, this can typically be removed with delayed surgery. Compared to the up-front surgery strategy, ultrasound monitoring results in the same overall risk of melanoma coming back at any location or of dying from melanoma.

Precis:

In an international cohort of over 1,000 sentinel-node positive melanoma patients treated at 21 melanoma centers since the publication of landmark trials supporting active nodal basin surveillance as an alternative to completion lymph node dissection, there has been high adoption of active surveillance. Compared to completion lymph node dissection, active surveillance patients had more nodal recurrences but comparable recurrence-free and disease-specific survival at this early assessment, including among patients receiving adjuvant therapy without prior completion lymph node dissection.

Twitter:

Major melanoma centers worldwide have adopted active nodal basin surveillance in lieu of completion node dissection for sentinel node positive patients, yielding similar early outcomes to MSLT2 and DeCOG including in adjuvant therapy recipients.

Abstract

Background: For sentinel lymph node (SLN) positive cutaneous melanoma, the Second Multicenter Selective Lymphadenectomy Trial (MSLT-2) demonstrated equivalent disease-specific survival (DSS) with active surveillance using nodal

ultrasound versus completion lymph node dissection (CLND). Adoption and outcomes of active surveillance in clinical practice and in adjuvant therapy recipients are unknown.

Methods: In a retrospective cohort of SLN positive adults treated at 21 institutions in Australia, Europe, and the United States from 6/2017-11/2019, we evaluated the impact of active surveillance and adjuvant therapy on all-site recurrence-free survival (RFS), isolated nodal RFS, distant metastasis-free survival (DMFS), and DSS using Kaplan Meier curves and Cox proportional hazard models.

Results: Among 6347 SLN biopsies, 1,154 (18%) were positive with negative distant staging. 965 patients received active surveillance (84%), 189 (16%) underwent CLND. 439 patients received adjuvant therapy (surveillance 38%, CLND 39%), majority (83%) anti-PD1 immunotherapy. After 11 months median follow-up, 220 patients have recurred (surveillance 19%, CLND 22%) and 24 had melanoma-related death (surveillance 2%, CLND 4%). 68 had isolated nodal recurrence (surveillance 6%, CLND 4%). In adjuvantly-treated patients without prior CLND, all isolated nodal recurrences were resectable. On risk-adjusted multivariable analyses, CLND was associated with improved isolated nodal RFS (HR 0.36 (0.15-0.88)) but not all-site RFS (HR 0.68 (0.45-1.02)). Adjuvant therapy improved all-site RFS (HR 0.52 (0.47-0.57)). DSS and DMFS did not differ by nodal management or adjuvant treatment.

Conclusions: Active surveillance has been adopted for most SLN-positive patients. At initial assessment, real-world outcomes align with randomized trial findings including in adjuvant therapy recipients.

Keywords: Melanoma, cutaneous malignant; sentinel lymph node; lymph node excision; watchful waiting; immunotherapy; cohort studies; follow-up studies;

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Supplemental Tables

1. Participating institutions and regions
2. Multivariable analysis of factors associated with completion lymph node dissection
3. Method of recurrence detection by location of first recurrence
4. Characteristics of sentinel lymph node positive patients with reasons for exclusion from randomized trials of active surveillance versus completion lymph node dissection

Supplemental Figures

1. Reasons for early discontinuation of adjuvant therapy at a participating comprehensive cancer center
2. Disease-specific mortality by nodal management and receipt of adjuvant systemic therapy

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Introduction

Management of melanoma patients with positive sentinel lymph nodes (SLNs) has changed dramatically over the past decade. While completion lymph node

dissection (CLND) was previously recommended for patients with positive SLNs, two large multi-institutional randomized controlled trials have recently demonstrated equivalent oncologic outcomes with active nodal surveillance. In lieu of CLND, active surveillance entails serial clinical assessments and nodal basin ultrasounds, reserving therapeutic lymph node dissection for those patients who develop clinically evident nodal disease.[1-4] The second Multicenter Selective Lymphadenectomy Trial (MSLT-2), published in 2017, demonstrated no difference in melanoma-specific survival for SLN-positive patients on active surveillance compared to CLND.[3] Likewise, the German Dermatologic Cooperative Oncology Group study (DeCOG-SLT) demonstrated no differences in recurrence-free survival (RFS), distant metastasis-free survival (DMFS), or overall survival for patients managed with active surveillance versus CLND.[5,6]

Concurrently, landmark trials of immune checkpoint blockade and BRAF/MEK inhibitors have changed the standard of care regarding adjuvant therapy in resected stage III melanoma.[7-11] These trials mandated CLND prior to initiation of adjuvant therapy for SLN-positive patients so do not reflect the experience of patients receiving active nodal basin surveillance and adjuvant therapy. Conversely, the vast majority of participants in the aforementioned studies of active nodal basin surveillance versus CLND received no adjuvant therapy. As a result, there is no randomized evidence to support provision of modern adjuvant systemic therapy in patients who receive active nodal surveillance in lieu of CLND.

Our first objective was to describe adoption of active surveillance in SLN-positive patients since the publication of MSLT-2 in a large, diverse cohort of international high-volume melanoma centers, including factors associated with the decision to perform CLND versus active surveillance and fidelity to the ultrasound-based surveillance protocol used in the randomized trials. Second, we sought to compare early outcomes of active surveillance with specific attention to patients receiving adjuvant systemic therapy.

Methods

Study Design and Support

The study was approved by the Institutional Review Board (IRB) of Moffitt Cancer Center which served as the Coordinating Center. Participating institutions obtained

respective IRB/Ethics approval and performed independent data abstraction, providing data to the Coordinating Center in compliance with institutional requirements and negotiated Data Use Agreements. All study data had been collected during standard of care evaluation, treatment, and follow-up.

Data Sources and Study Cohort

Included patients were ≥18 years old, had clinically node-negative cutaneous melanoma without macroscopic satellite or in-transit disease, underwent SLN biopsy between June 1, 2017 and June 30, 2019, and had metastatic disease in at least one SLN. Patients were excluded if they had regional or distant metastasis on staging studies prior to or immediately following positive SLN biopsy. Staging studies were provider- and institution-dependent and consisted of any combination of computed tomography, positron emission tomography (PET) or PET/CT, and magnetic resonance imaging (MRI) of the brain. Staging studies that were performed after positive SLN biopsy were completed prior to a final determination regarding nodal management (surveillance versus CLND), and only those patients who were found to have no evidence of disease were included in the cohort. Additional exclusions were prior or concurrent (second primary) invasive melanoma and insufficient medical records. Participating institutions had pre-existing active surveillance protocols for SLN positive patients who did not undergo CLND. Patients were offered adjuvant therapy at the discretion of treating clinicians. Unlike recent adjuvant therapy trials, patients were not required to undergo CLND prior to adjuvant treatment.

Outcomes

Descriptive endpoints included the proportion of patients who initiated active surveillance, received adjuvant systemic therapy, and adhered to surveillance. Adherence was defined having at least one ultrasound per six-month period of disease-free follow-up, a conservative metric based on the every four-month protocol in MSLT-2 to allow for delays related to scheduling. The primary comparative endpoint was all-site recurrence-free survival (RFS), which was evaluated for active surveillance versus CLND patients. RFS was defined as time from sentinel lymph node biopsy to recurrent melanoma at any site, diagnosed by clinical and/or radiographic findings, and biopsy

confirmed when feasible. While some patients with recurrent disease have gone on to have multiple recurrence events, only the first recurrence event for each patient was included in the primary analysis. Patients were censored for death or at last clinical follow-up. Secondary endpoints were isolated nodal basin recurrence, defined as initial recurrence in a sentinel node basin without local, in-transit, or distant disease, distant metastasis-free survival (DMFS) defined as distant metastasis identified during the follow-up period either as a site of first recurrence or subsequent recurrence, and disease-specific survival (DSS) which were considered exploratory given the short follow-up duration.

All-site and isolated nodal RFS was compared based on nodal management with active surveillance versus CLND and receipt of adjuvant systemic therapy. BRAF mutational analysis was not required prior to initiation of adjuvant systemic therapy, though it was ultimately performed in about two-thirds of the study cohort. Additionally, because a substantial proportion of the cohort had tumor or nodal characteristics that would have excluded them from MSLT-2 (microsatellitosis, extranodal extension (ENE), >3 three positive nodes in trunk or extremity tumors, >6 positive nodes in head/neck tumors), an exploratory analysis was performed in this subgroup.

Statistical Analysis

Descriptive statistics included chi-squared independence tests, two-sample t-tests, and Wilcoxon rank sum tests according to data distributions, with a two-tailed significance level of 5%. Kaplan-Meier survival curves were created for all-site RFS, isolated nodal basin RFS, and DMFS, compared by nodal management and adjuvant therapy using log-rank tests stratified by location of treating center (US, Europe, or Australia). Adjusted analyses were performed for all-site RFS and isolated nodal basin RFS using Cox proportional hazards models, with results reported as Hazard Ratios (HR) and 95% Confidence Intervals. Covariates for adjustment were selected a priori and included age, American Joint Committee on Cancer (AJCC) 8th Edition stage, tumor location, total number of positive SLNs, ENE, and largest nodal tumor deposit. Patients with missing values for included covariates or outcomes were excluded.

In the Cox models, proportionality of hazards was verified using Lin's Supremum test.[12] For variables not meeting the proportionality of hazards (PH) assumption but with a significant association with the outcome on univariate analysis, interaction between the variable and time was added to account for non-proportional hazards. Variables violating the PH assumption and with non-significant association with the outcome were removed. DSS was evaluated using a cumulative incidence function curve with comparisons using Gray's test and the Fine and Gray Method of competing risk assessment.[13,14] Statistical analyses were performed using SAS 9.4 and Stata 15.1.

Results

There were 6,347 SLN biopsies performed at the 21 participating institutions (Supplemental Table 1). Among these, 1,165 patients (18%) had at least one positive SLN, of which 11 patients were excluded yielding a final cohort of 1,154 patients. Reasons for exclusion included distant metastases on staging (N=4), multiple primaries (N=2), loss to follow-up before decision regarding CLND versus active surveillance (N=4), and diffuse benign lymphadenopathy precluding ultrasound surveillance (N=1). CLND was performed in 189 participants (16%) while the remaining 965 (84%) received active surveillance.

Factors Associated with Completion Lymph Node Dissection

CLND was performed more often for younger patients, those with head/neck primary sites, greater Breslow thickness, presence of microsatellites, and BRAF mutation, but not tumor ulceration (Table 1). Nodal features associated with performance of CLND included more positive SLNs, ENE, and larger nodal deposits. Patients treated in the US and Europe were more likely to undergo CLND than in Australia. On multivariable analysis, factors associated with performance of CLND included head and neck primary, higher number of positive sentinel nodes, larger nodal tumor, and location of treating center (Supplemental Table 2). Documented reasons for CLND were available in 103 of 189 cases with some having more than one rationale. These included patient preference (42 of 103, 41%), surgeon recommendation (19 of 103, 18%), burden of disease based on features of the primary tumor and/or involved SLNs (33 of 103, 32%), inability to participate in active surveillance due to travel constraints (25 of 103, 24%), and for additional prognostic information (14 of 103, 14%).

In patients undergoing CLND, 49 of 189 (26%) had at least one positive non-SLN in the completion specimen. CLND resulted in upstaging according to AJCC 8th edition in 14 of 189 cases (7%). Five patients with T2-3 lesions were upstaged from IIIB to IIIC, nine with T4 lesions were upstaged from IIIC to IIID.

Active Surveillance Strategies

For active nodal basin surveillance, 16 of 21 institutions used primarily ultrasound while five used cross-sectional imaging (CT or PET/CT). In patients having ultrasound surveillance, 58% underwent at least one nodal basin ultrasound per 6-month follow-up period (range by treating center 35% to 83%). Among sites reporting all types of imaging performed during follow-up, 89% of active surveillance patients had at least one image per 6-month interval. Adjuvant therapy patients were less likely to have adherent ultrasound surveillance (31% versus 69%, $p<0.01$), but had more cross-sectional imaging (47% versus 20%, $p<0.01$).

Disease Recurrence and Methods of Detection

Patients were followed for a median of 11 months (25th-75th percentile 6-17 months). During this time, 220 (19%) patients recurred at any site. Modalities by which first recurrences were detected are delineated in Supplemental Table 3. Among loco-regional only recurrences, 65% were detectable by patient symptoms and/or clinical exam. Fifty-three percent of distant-only initial recurrences were detected by CT and/or PET alone, while 24% were associated with clinical findings (12% based on clinical findings alone, 12% by clinical and imaging findings), 5% by brain MRI only and the remainder by multiple or unknown modalities. In the 68 patients with isolated nodal basin recurrences, 6% were detected solely on clinical assessment, 21% were detected only by nodal basin ultrasound, and 22% were detected on clinical assessment and/or ultrasound along with another modality. Thirty-four percent of isolated nodal basin recurrences were only detected on CT, PET, and/or PET/CT, while method of detection was not reported for the remaining 18% of isolated nodal recurrences.

The proportion of patients with recurrence at any site was comparable with active surveillance and CLND (179 of 965, 19% and median follow-up of 10.8 months, versus

41 of 189, 22% at median follow-up of 13.0 months, p=0.31) (Table 3). In unadjusted survival analyses, performance of CLND did not significantly impact all-site RFS (p=0.84) or isolated nodal basin RFS (p=0.11) (Figure 1). Recurrence limited to draining nodal basin(s) occurred in 6% of active surveillance patients (61 of 965) and 4% of CLND patients (7 of 189) (p=0.16).

Among active surveillance patients with isolated nodal basin recurrence, 51 of 61 (84%) had undergone nodal resection by the time of data collection. Three patients underwent selective lymph node dissection (i.e. removal of only clinically involved nodes rather than clearance of the nodal basin) due to high comorbid disease burden or as part of a trial while the majority underwent formal therapeutic lymph node dissection. Management of the remaining nodal recurrences is unknown or not yet determined, but to our knowledge there have been no instances of unresectable recurrence in a sentinel node basin. Patients with concurrent nodal and other site recurrence were treated with systemic therapy and none required nodal surgery for SLN basin-associated symptoms.

Adjuvant Treatment

Thirty-nine percent of CLND patients (74 of 189) and 38% of active surveillance patients (365 of 965) received adjuvant systemic therapy. Adjuvant therapy patients more often had ulcerated primary tumors, greater Breslow thickness, more positive SLNs, larger nodal tumor deposits, ENE, and higher pathologic stage (Table 2). Patients receiving adjuvant therapy were younger and more likely to be treated in the US and Australia than Europe.

Single-agent anti-PD 1 immunotherapy was the most common adjuvant regimen (364 of 439, 83%) with nivolumab being most frequently used (332, 76% versus pembrolizumab 32, 7%). Twenty-one patients (5%) received anti-CTLA4 or combination immunotherapy, 40 (9%) received BRAF/MEK inhibitor therapy including 27% of patients who were ultimately found to have BRAF mutated tumors, and 14 (3%) received other treatments. Patients remained on adjuvant systemic therapy for a median of 6 months (25^{th}-75^{th} percentile 3-10 months), with some still on treatment at the time of data collection, and others discontinuing due to toxicity or relapse (Supplemental Figure 1).

Comparing patients who received adjuvant therapy to those who did not (in whom median follow-up times were 10.0 and 11.8 months, respectively), unadjusted analyses demonstrated no differences in all-site RFS (p=0.80) or isolated nodal basin RFS (p=0.96) (Figure 1). The patterns of recurrence were comparable among patients who received adjuvant therapy versus those who did not (Table 3). Specifically in patients receiving adjuvant therapy, active surveillance patients had more isolated nodal basin recurrences (6% versus 1% after CLND, p=0.09) but fewer distant recurrences (6% versus 15%, p=0.01). There was no difference in all-site RFS for patients with BRAF mutated versus wildtype tumors (p=0.69).

Multivariable Analysis of All-Site and Isolated Nodal Basin Recurrence Free Survival

On risk-adjusted multivariable analysis, performance of CLND was associated with a 64% reduction in isolated nodal basin recurrence (HR 0.36 (95% CI 0.15-0.88)) while increasing nodal tumor deposit size was associated with worse isolated nodal basin RFS (Table 4). Factors associated with worse all-site RFS included higher stage relative to IIIA, head/neck tumor location relative to lower extremity, and larger nodal tumor deposit (Table 4). The Cox model confirmed that patients treated with adjuvant therapy had high baseline high risk of recurrence. However, for each month of follow-up receipt of adjuvant therapy was associated with a 48% reduction in all-site recurrence (0.52 (0.47-0.57)).

Distant Metastasis-Free and Disease-Specific Survival

One-hundred seven patients (9%) developed distant metastasis as part of a first or subsequent recurrence during follow-up, including 82 (9%) of active surveillance patients and 25 (13%) of CLND patients (p=0.040). The proportions of patients with distant metastasis were comparable based on receipt of adjuvant therapy in unadjusted analyses (40 of 439, 9% with adjuvant therapy versus 67 of 712, 9% without adjuvant therapy, p=0.87). At the median follow-up of 11 months there were no statistically significant differences in distant metastasis-free survival based on nodal management (p=0.17) or adjuvant therapy (p=0.94).

At the end of follow-up, 1,116 participants were alive. Twenty-four of the 38 deaths were due to melanoma, including 7 after CLND (4%) and 17 in active surveillance patients (2%) (p=0.26). Among patients who received adjuvant systemic

therapy, there were 9 melanoma-specific deaths (2%), while 15 patients (2%) who did not receive adjuvant systemic therapy had died due to melanoma by study end (p=0.45) (Supplemental Figure 2).

Patients Having MSLT-2 Exclusion Criteria

Fifteen percent of patients (N=171) had at least one reason that they would have been excluded from MSLT-2 (Supplemental Table 4). Though these patients were more likely to undergo CLND (52 of 171, 30%) than patients without exclusion criteria (137 of 983, 14%) (p<0.01), the majority (70%) received active surveillance. In this group, isolated nodal basin recurrence occurred in 12 of 119 (10%) active surveillance patients and 3 of 52 (6%) CLND patients (p=0.08). Distant recurrence as the first site of recurrence occurred in 13 of 119 (11%) active surveillance patients and 14 of 52 (27%) CLND patients (p=0.01). By comparison, for patients without exclusion criteria rates of isolated nodal recurrence were 6% (49 of 846) with active surveillance and 3% (4 of 137) after CLND (p=0.17), while rates of distant recurrence were 11% (50 of 846) with active surveillance and 7% (10 of 137) with CLND (p=0.53).

Discussion

In this post-MSLT-2 era international, multi-institutional cohort study of cutaneous melanoma patients with positive sentinel lymph nodes, only 16% of patients underwent CLND, demonstrating widespread uptake of active nodal basin surveillance at participating centers. This represents a dramatic change in surgical practice over a period of less than three years.[15] At this initial assessment, findings align with those of the MSLT-2 and DeCOG-SLT trials. While there were higher rates of isolated nodal recurrence with active surveillance, these were salvageable with therapeutic lymph node dissection and there was no significant difference in all-site RFS, DMFS, or DSS. A considerably larger proportion of active surveillance patients in modern clinical practice received adjuvant systemic therapy than in the MSLT-2 or DeCOG-SLT trials. Adjuvant therapy patients had similar patterns of recurrence and the rate of isolated nodal basin recurrence remained low, even in those without prior CLND.

Recurrence rates in this study were commensurate with those of MSLT-2 and DeCOG-SLT at comparable points in follow-up. In both randomized trials, approximately

one-fifth of patients recurred in the first year of follow-up, compared to 19% at 11 months in this cohort.[3,5] Patterns of recurrence were also similar. As found in MSLT-2 and DeCOG-SLT, there were higher rates of isolated nodal basin recurrence among patients who did not undergo CLND.

Patients who were selected to undergo CLND in clinical practice had thicker primary tumors and more extensive nodal involvement including number of positive nodes, size of nodal metastasis, and higher incidence of extranodal extension, so it is not surprising that the rate of positive non-sentinel nodes (26%) was higher than previously published rates.[16] Still, this means that the majority of patients who underwent CLND had no additional positive nodes. Further, there were no instances of unresectable sentinel node basin recurrence in active surveillance patients. Considering the high risk of disease outside the nodal basin in SLN-positive patients, the ability to salvage isolated nodal recurrences using therapeutic node dissection, and the potential morbidity of lymphadenectomy, this study re-affirms the value of active nodal basin surveillance to limit subsequent lymph node dissection to the minority of patients with recurrence limited to the nodal basin.[17]

Almost 40% of patients treated at participating centers received adjuvant systemic therapy. In clinical practice, patients with higher risk primary and nodal features were more likely to receive adjuvant treatment. The finding of no difference in recurrence rates for patients based on receipt of adjuvant therapy on unadjusted analyses but improvement in recurrence free survival in multivariable analyses adjusted for these risk factors supports the benefit of adjuvant treatment in the higher risk patients in which it was used. Granted, longer follow-up is needed to confirm these findings, as the median recurrence free survival in adjuvant immunotherapy trials was approximately two years.[7-11]

In the rapidly changing landscape of advanced melanoma management, this real-world cohort of patients treated from 2017-2019 still may not reflect current adjuvant management. As approvals of anti-PD-1 immunotherapy and BRAF/MEK inhibitors by international regulatory bodies occurred after the initial eligibility period of this study, the finding of adjuvant therapy use in 39% of patients may under-represent

what is now happening in practice.[18,19] Further, relapse rates reported in this study may be higher than what is now being achieved in SLN-positive melanoma.

Because the aforementioned adjuvant therapy trials mandated CLND, loss of regional nodal basin control in active surveillance patients on adjuvant therapy has been a concern for many providers.[20-22] In our patients receiving adjuvant therapy without prior CLND, 5% have had isolated nodal recurrence, which is comparable to the rate of isolated nodal recurrence for active surveillance patients not receiving adjuvant therapy. Findings from the multivariable analysis demonstrate no impact of CLND on recurrence-free survival after adjusting for treatment with adjuvant therapy which would mean that CLND neither helps nor impedes the activity of adjuvant treatment, though longer follow-up is needed to confirm this.

Study findings do highlight a current dilemma in managing active surveillance patients who develop isolated nodal recurrence during the adjuvant treatment period. Whether these recurrences represent regional failure due to incomplete clearance of the nodal basin or treatment-resistant disease is an area of active controversy. This has implications for whether the patient resumes the same adjuvant treatment after the nodal recurrence is addressed.

A subset of patients in this study who received active surveillance would have been excluded from the MSLT-2 and DeCOG trials based on extranodal extension, microsatellitosis, and/or number of positive nodes. In these patients with at least one exclusion criteria, there was a trend toward fewer isolated nodal recurrences after CLND compared to active surveillance, but the rate of distant recurrence was significantly higher in the CLND than the active surveillance group. This finding may indicate that patients with exclusion criteria have heightened risk of distant disease when CLND is performed. Alternatively, in this non-randomized cohort these findings may represent selection bias toward performance of CLND in high-risk patients, whose true risk cannot be adequately characterized by the presence of any one exclusion criterion. Given the ongoing controversy regarding nodal management for SLN-positive patients who were not represented in prior randomized trials, this merits further study.

At the participating centers there was significant variation in adherence to the MSLT-2 and DeCOG-SLT surveillance protocols. Some centers did not have access to

high quality nodal basin ultrasound or preferred cross-sectional imaging.[23,24] At sites with ultrasound access, just under 60% of patients had a minimum of 6-monthly ultrasounds performed. Though ultrasound has greater sensitivity and specificity for detection of nodal basin recurrence when studied in a research context, findings may be more variable in clinical practice based on who performs the ultrasound and the anatomic site that is being visualized. In this cohort, patients receiving adjuvant therapy often had cross-sectional imaging in lieu of nodal basin ultrasound. The added value of nodal basin ultrasound in adjuvant therapy patients who have cross-sectional imaging has not been established and would be best studied in a prospective fashion with all patients receiving both ultrasound and cross sectional imaging at designated intervals.[23] In addition, there is limited evidence that early detection of recurrence impacts long-term oncologic outcomes so the optimal surveillance strategy for sentinel node positive remains unknown.[4,24-26]

The short follow-up duration provides early insight into real-world outcomes of active surveillance in SLN-positive patients but limits the ability to draw firm conclusions. Recognizing that the majority of melanoma recurrences occur within two years of diagnosis, subsequent assessments of this cohort are planned. Further, unlike a randomized trial design which balances groups with respect to both measured and unmeasured variables, in this cohort study we were unable to account for potentially unmeasured variables which could have impacted patient selection for CLND versus active surveillance and receipt of adjuvant therapy. CLND patients had more complete nodal staging, which could have influenced adjusted analyses. However, few patients were upstaged by CLND findings and in many prognostic models the status of non-sentinel nodes is less relevant that other features of the primary tumor and SLNs.[27]

While we have provided some information regarding reasons for performance of CLND, this is limited by the retrospective study design. We were also unable to determine the specific reasons for patients' receipt of adjuvant therapy or the rationale for the selected treatment. Also, while the inclusion of multiple international institutions increases study generalizability, central review of pathology and imaging was not carried out and post-relapse treatment was not standardized.

Although the institutions included in this study were diverse in their geographic distribution, all are major melanoma treatment centers. The adoption of active nodal basin surveillance and fidelity to an active surveillance protocol outside these referral centers has not been explored. Further, it is unknown whether similar oncologic outcomes will be achieved in other settings that may be more reflective of melanoma management in non-specialist centers worldwide.

Conclusion

This real-world cohort study demonstrates a high level of adoption of active surveillance at many of the major melanoma-treatment centers throughout the world. Early findings reinforce the conclusions of MSLT-2 and DeCOG-SLT that active surveillance is an effective strategy for sentinel lymph node-positive patients that limits unnecessary lymph node dissections and their attendant morbidities, though long-term survival data are needed. Use of adjuvant therapy in patients who have or have not undergone CLND yields a similarly low rate of isolated nodal basin recurrences, which are largely salvageable with therapeutic lymph node dissection. Future studies should seek to refine our understanding of which active surveillance patients benefit most from adjuvant therapy and when, if ever, to perform CLND.

Table 1. Characteristics of patients undergoing completion lymph node dissection versus active surveillance

	Surveillance N=965	**Dissection N=189**	**P-Value**
Location of Treating Center			
Australia	174 (18)	8 (4)	<0.01
Europe	129 (13)	29 (15)	
United States	662 (69)	152 (80)	
Age (years), mean±SD	59±16	57±16	0.11
Male Sex, N (%)	590 (61)	122 (65)	0.38

Tumor Location, N (%)[a]			
Head/Neck	118 (12)	39 (21)	<0.01
Trunk	366 (38)	75 (40)	
Upper Extremity	181 (19)	41 (22)	
Lower Extremity	299 (31)	34 (18)	
Breslow Thickness (mm)			
<=1.0	103 (11)	22 (12)	0.04
>1.0-2.0	295 (30)	45 (24)	
>2.0-4.0	325 (34)	57 (30)	
>4.0	242 (25)	65 (34)	
Tumor Ulceration, N (%)[a]	377 (40)	80 (43)	0.37
Presence of Microsatellites, N (%)[a]	75 (9)	25 (13)	0.05
Number of Positive Nodes, N (%)			
1	755 (78)	120 (64)	<0.01
2-3	200 (21)	57 (30)	
4+	10 (1)	12 (6)	
Size of SLN metastasis, millimeters, median (25^{th}-75^{th} percentile)[a,b]	0.5 (0.0-2.0)	1.7 (0.1-6.0)	<0.01
Extranodal Extension, N (%)[a]	52 (6)	25 (13)	<0.01
AJCC 8^{th} Edition Stage			
IIIA	279 (39)	89 (20)	<0.01
IIIB	221 (23)	25 (13)	
IIIC	413 (43)	102 (54)	
IIID	11 (1)	12 (6)	
BRAF Mutation Status, N (%)			
Mutant	280 (46)	65 (57)	0.04
Wildtype	329 (54)	50 (43)	
Adjuvant Systemic Therapy, N (%)	365 (38)	74 (39)	0.75

AJCC8 = American Joint Committee on Cancer

[a] Unknown values for tumor location (N=1), tumor ulceration (N=19), presence of microsatellites (N=111), size of SLN metastasis (N=148), extra-nodal extension (N=42), AJCC8 stage (N=2), BRAF mutation (N=430), adjuvant systemic therapy (N=3); [b] includes patients with isolated tumor cells for which the size of SLN metastasis was reported as 0.0 millimeters

Table 2. Characteristics of patients based on receipt of adjuvant systemic therapy

	No Adjuvant N=712	Adjuvant N=439	P-Value
Location of Treating Center			
Australia	88 (12)	91 (21)	<0.01
Europe	125 (18)	33 (8)	
United States	499 (70)	315 (72)	
Age (years), mean±SD	59±16	57±15	0.02
Male Sex, N (%)	432 (61)	278 (63)	0.37
Tumor Location, N (%)[a]			
Head/Neck	97 (14)	59 (14)	0.86
Trunk	266 (37)	174 (40)	
Upper Extremity	141 (20)	80 (18)	
Lower Extremity	208 (29)	125 (29)	
Breslow Thickness (mm)			
<=1.0	97 (14)	28 (6)	<0.01
>1.0-2.0	230 (32)	110 (25)	
>2.0-4.0	225 (32)	155 (35)	
>4.0	160 (22)	146 (33)	
Tumor Ulceration, N (%)[a]	242 (34)	213 (50)	<0.01
Presence of Microsatellites, N (%)[a]	59 (10)	41 (10)	0.86
Number of Positive Nodes, N (%)			
1	560 (79)	314 (72)	0.02
2-3	142 (20)	113 (26)	
4+	10 (1)	12 (3)	

≥1.0mm	347 (49)	282 (64)	
Size of SLN metastasis, millimeters, median (25th-75th percentile)[a,b]	0.4 (0.0[b]-2.0)	1.2 (0.2-4.0)	<0.01
Extranodal Extension, N (%)[a]	33 (5)	44 (10)	<0.01
AJCC 8th Edition Stage, N (%)[a]			
IIIA	279 (39)	89 (20)	<0.01
IIIB	147 (21)	98 (22)	
IIIC	271 (38)	242 (55)	
IIID	13 (2)	10 (2)	
BRAF Mutation Status, N (%)			
Mutant	200 (48)	143 (47)	0.75
Wildtype	216 (52)	162 (53)	
Completion Lymph Node Dissection, N (%)	115 (16)	74 (17)	0.75

AJCC8 = American Joint Committee on Cancer, 8th edition; [a] Unknown values for receipt of adjuvant therapy (N=3), tumor location (N=1), tumor ulceration (N=19), presence of microsatellites (N=111), extra-nodal extension (N=42), AJCC8 stage (N=2), BRAF mutation (N=430); [b] includes patients with isolated tumor cells for which the size of SLN metastasis was reported as 0.0 millimeters

Table 3. Patterns of initial recurrence based on nodal management and receipt of adjuvant systemic therapy

Site of Recurrence	Nodal Management		Adjuvant Systemic Therapy[b]	
	Dissection N=189, N (%)	Surveillance N=965, N (%)	Yes N=439 (%)	No N=712 (%)
No Recurrence	148 (78)	786 (81)	358 (82)	573 (80)
Recurrence	41 (22)	179 (19)	81 (18)	139 (20)
Local-Regional[a] Only	11 (6)	40 (4)	19 (4)	32 (5)
SLN Basin Only	7 (4)	61 (6)	24 (5)	44 (6)
Distant Only	16 (8)	41 (4)	21 (5)	36 (5)

Multiple Sites	7 (4)	37 (4)	17 (4)	27 (4)
Including nodal	4 (2)	35 (4)	14 (3)	24 (3)
Not including nodal	3 (2)	2 (<1)	3 (1)	3 (1)

[a]Local-regional includes primary site and in-transit disease

[b]Data regarding adjuvant therapy not available for 3 participants

Table 4. Multivariable analysis of patient, tumor, and treatment factors associated with isolated nodal basin recurrence free survival (RFS) and all-site recurrence-free survival (RFS) in adult patients with cutaneous melanoma and positive sentinel lymph nodes

	Isolated Nodal Basin RFS HR (95% CI)	**P-value**	**All-Site RFS** HR (95% CI)	**P-value**
Number of Recurrence Events (% of total cohort)	*68 (6%)*		*220 (19%)*	
Age (per 1-year increase)	1.01 (0.99-1.03)	0.41	1.00 (0.99-1.01)	0.69
AJCC 8th Edition Stage		N/A		**<0.01**
IIIA	N/A[a]		Ref	
IIIB			**1.82 (1.08-3.06)**	
IIIC			**3.38 (2.19-5.23)**	
IIID			**4.88 (2.07-11.49)**	
Tumor Location		0.64		**0.03**
Lower Extremity	Ref		Ref	
Upper Extremity	1.21 (0.54-2.73)		1.32 (0.84-2.09)	
Trunk	1.43 (0.73-2.82)		1.16 (0.79-1.70)	
Head/Neck	0.90 (0.34-2.36)		**1.88 (1.21-2.93)**	
Number of Positive Nodes		0.67		0.60
1	Ref		Ref	
2-3	1.01 (0.53-1.95)		1.20 (0.85-1.69)	
4+	1.96 (0.44-8.66)		1.14 (0.53-2.46)	
Extranodal extension		0.26		0.52
Absent	Ref		Ref	
Present	1.67 (0.69-4.07)		1.17 (0.70-1.94)	
Size of SLN Metastasis (per 1mm increase)	**1.07 (1.02-1.12)**	**<0.01**	**1.11 (1.06-1.17)**	**<0.01**
Interaction between size of SLN Metastasis and Follow-Up Time	N/A[b]	N/A	0.99 (0.98-1.00)	**0.03**

Completion Lymph Node Dissection				
No	Ref	**0.02**	Ref	0.07
Yes	**0.36 (0.15-0.88)**		0.68 (0.45-1.02)	
Adjuvant Systemic Therapy				
Receipt at any Time	0.77 (0.43-1.37)	0.38	N/A[c]	N/A
Risk per month of follow-up (Interaction between Adjuvant Systemic Therapy and Time)	N/A[c]	N/A	**0.52 (0.47-0.57)**	**<0.01**

Cox proportional hazard models performed for outcomes of Isolated Nodal Basin Recurrence Free Survival (RFS) and All-Site RFS, adjusted for the above variables; HR = Hazard Ratio; CI = Confidence Interval, AJCC = American Joint Committee on Cancer; **Bold** denotes statistically significant findings; values <1 associated with decreased recurrence; values >1 associated with increased recurrence; [a]AJCC 8th edition stage not included in Isolated Nodal Basin RFS model due to lack of univariate association with the outcome and failure to meet proportionality of hazards assumptions; [b]interaction term for size of SLN metastasis and time required for All-site RFS outcome due to non-proportionality of hazards; [c]association of adjuvant systemic therapy with All-site RFS reported with interaction term for time-dependence due to non-proportionality of hazards

Figure Legend

Figure 1. All-site recurrence-free survival and isolated nodal basin recurrence-free survival by performance of completion lymph node dissection versus active surveillance and by receipt of adjuvant systemic therapy

A. All-site recurrence-free survival by completion lymph node dissection; B. Nodal basin recurrence-free survival by completion lymph node dissection; C. All-site recurrence-free survival by receipt of adjuvant systemic therapy; D. Nodal basin recurrence-free survival by receipt of adjuvant systemic therapy; HR=Hazard Ratio; 95% CI=95% Confidence Interval; Log-rank tests stratified by location of treating center (Australia, Europe, United States); Surv=Active surveillance; CLND=Completion lymph node dissection

References

1. Wong SL, Morton DL, Thompson JF, et al. Melanoma patients with positive sentinel nodes who did not undergo completion lymphadenectomy: a multi-institutional study. *Ann Surg Oncol.* 2006;13(6):809-816.
2. Klemen ND, Han G, Leong SP, et al. Completion lymphadenectomy for a positive sentinel node biopsy in melanoma patients is not associated with a survival benefit. *J Surg Oncol.* 2019;119(8):1053-1059.
3. Faries MB, Thompson JF, Cochran AJ, et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. *N Engl J Med.* 2017;376(23):2211-2222.
4. Leiter U, Buettner PG, Eigentler TK, Forschner A, Meier F, Garbe C. Is detection of melanoma metastasis during surveillance in an early phase of development associated with a survival benefit? *Melanoma Res.* 2010;20(3):240-246.
5. Leiter U, Stadler R, Mauch C, et al. Complete lymph node dissection versus no dissection in patients with sentinel lymph node biopsy positive melanoma (DeCOG-SLT): a multicentre, randomised, phase 3 trial. *Lancet Oncol.* 2016;17(6):757-767.
6. Leiter U, Stadler R, Mauch C, et al. Final Analysis of DeCOG-SLT Trial: No Survival Benefit for Complete Lymph Node Dissection in Patients With Melanoma With Positive Sentinel Node. *J Clin Oncol.* 2019;37(32):3000-3008.
7. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol.* 2015;16(5):522-530.
8. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy. *N Engl J Med.* 2016;375(19):1845-1855.
9. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *N Engl J Med.* 2018;378(19):1789-1801.
10. Weber J, Mandala M, Del Vecchio M, et al. Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma. *N Engl J Med.* 2017;377(19):1824-1835.

11. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. *N Engl J Med.* 2017;377(19):1813-1823.
12. Lin DY. MULCOX2: a general computer program for the Cox regression analysis of multivariate failure time data. *Comput Methods Programs Biomed.* 1993;40(4):279-293.
13. RJ G. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *Ann Stat.* 1988;16:1141-1154.
14. Fine JP GR. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc.* 1999;94:496-509.
15. Herb JN, Dunham LN, Ollila DW, Stitzenberg KB, Meyers MO. Use of Completion Lymph Node Dissection for Sentinel Lymph Node-Positive Melanoma. *J Am Coll Surg.* 2020;230(4):515-524.
16. McMasters KM, Wong SL, Edwards MJ, et al. Frequency of nonsentinel lymph node metastasis in melanoma. *Ann Surg Oncol.* 2002;9(2):137-141.
17. Coit D. The Enigma of Regional Lymph Nodes in Melanoma. *N Engl J Med.* 2017;376(23):2280-2281.
18. Kwak M, Farrow NE, Salama AKS, et al. Updates in adjuvant systemic therapy for melanoma. *J Surg Oncol.* 2019;119(2):222-231.
19. Moyers JT CE, Mitchell J, Patel A, Jeong ISD, Nagaraj G. Immunotherapy in resected stage III melanoma: An analysis of the National Cancer Database. American Association for Cancer Research; June 22, 2020, 2020; Virtual Meeting II.
20. Wong SL, Faries MB, Kennedy EB, et al. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. *J Clin Oncol.* 2018;36(4):399-413.
21. Hieken TJ, Kane JM, 3rd, Wong SL. The Role of Completion Lymph Node Dissection for Sentinel Lymph Node-Positive Melanoma. *Ann Surg Oncol.* 2019;26(4):1028-1034.
22. Eroglu Z BN, Grossman K, Markowitz J, Brohl A, Cisneros J, Cruse W, Harrington M, Gonzalez R, Sarnaik A, Zager J, Sondak V, Khushalani N. Retrospective analysis of patients with sentinel lymph node positive melanoma who received adjuvant nivolumab

without completion lymph node dissection. American Society of Clinical Oncology; 2019; Chicago, Illinois.

23. Xing Y, Bronstein Y, Ross MI, et al. Contemporary diagnostic imaging modalities for the staging and surveillance of melanoma patients: a meta-analysis. *J Natl Cancer Inst.* 2011;103(2):129-142.

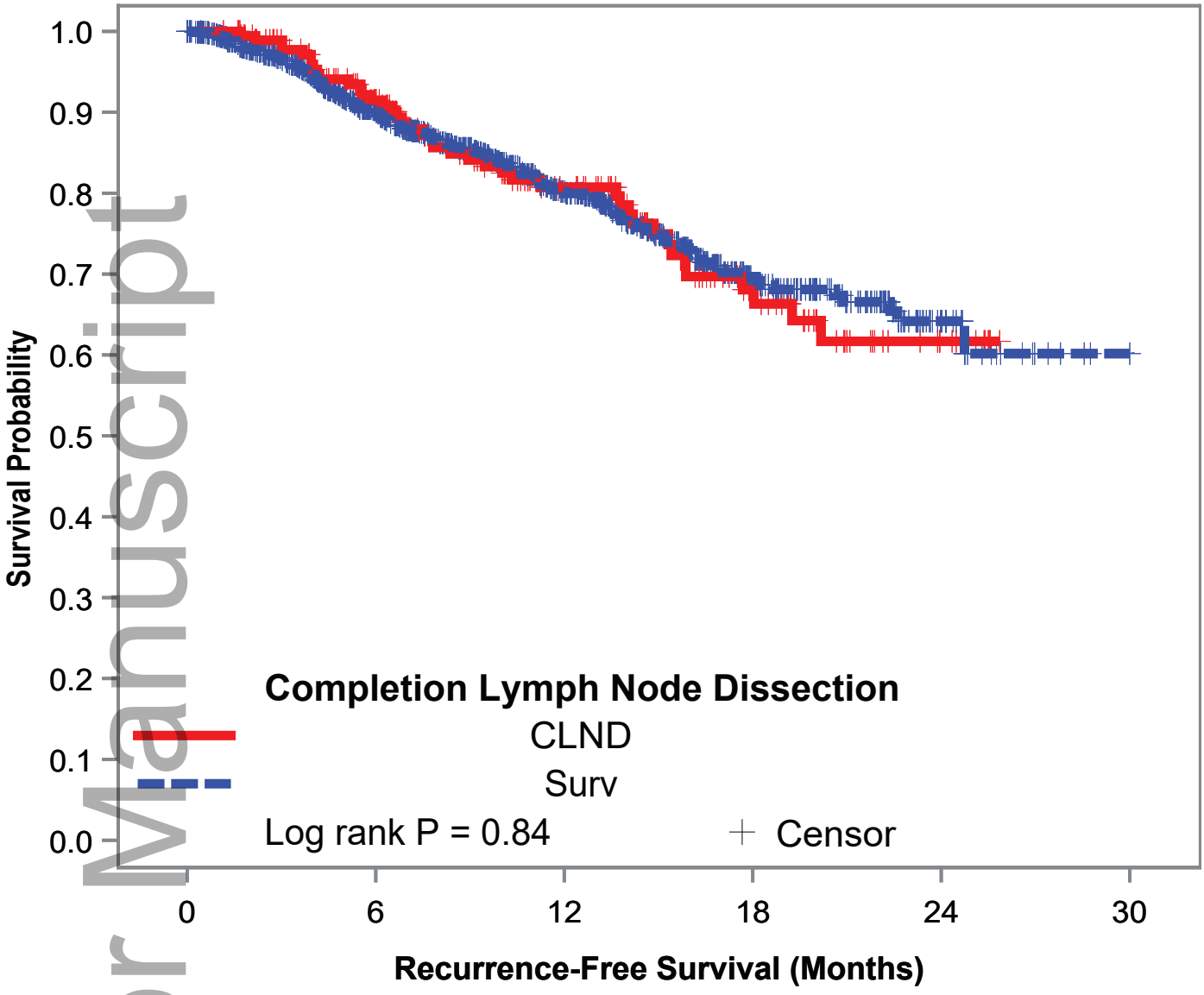
24. Dinnes J, Ferrante di Ruffano L, Takwoingi Y, et al. Ultrasound, CT, MRI, or PET-CT for staging and re-staging of adults with cutaneous melanoma. *Cochrane Database Syst Rev.* 2019;7:CD012806.

25. Freeman M, Laks S. Surveillance imaging for metastasis in high-risk melanoma: importance in individualized patient care and survivorship. *Melanoma Manag.* 2019;6(1):MMT12.

26. Leon-Ferre RA, Kottschade LA, Block MS, et al. Association between the use of surveillance PET/CT and the detection of potentially salvageable occult recurrences among patients with resected high-risk melanoma. *Melanoma Res.* 2017;27(4):335-341.

27. Verver D, van Klaveren D, van Akkooi ACJ, et al. Risk stratification of sentinel node-positive melanoma patients defines surgical management and adjuvant therapy treatment considerations. *Eur J Cancer.* 2018;96:25-33.

A



Patients-at-Risk

CLND	189	135	85	39	9	0
Surv	965	629	364	134	28	1

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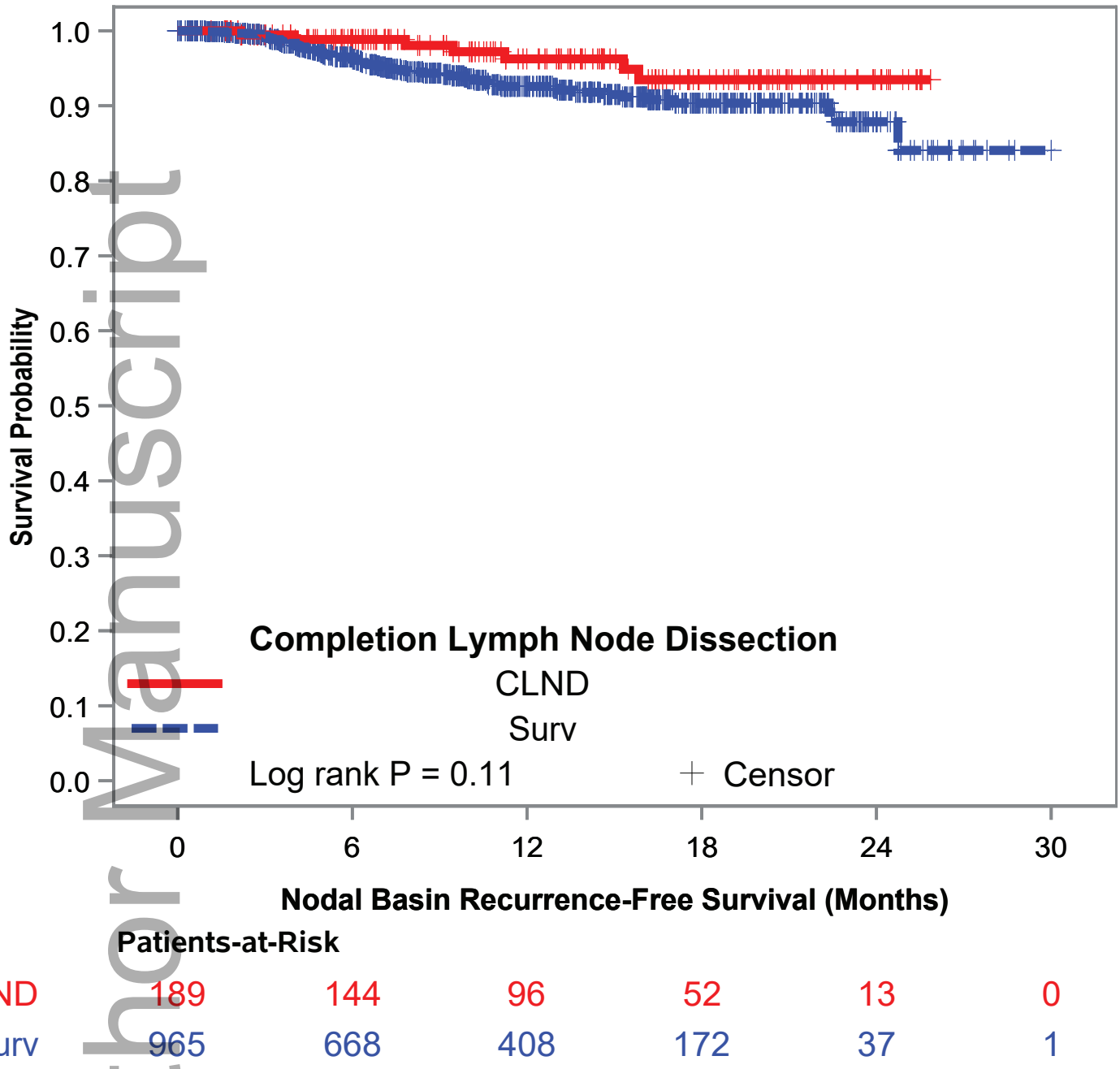

Patients-at-Risk

CLND	189	144	96	52	13	0
Surv	965	668	408	172	37	1

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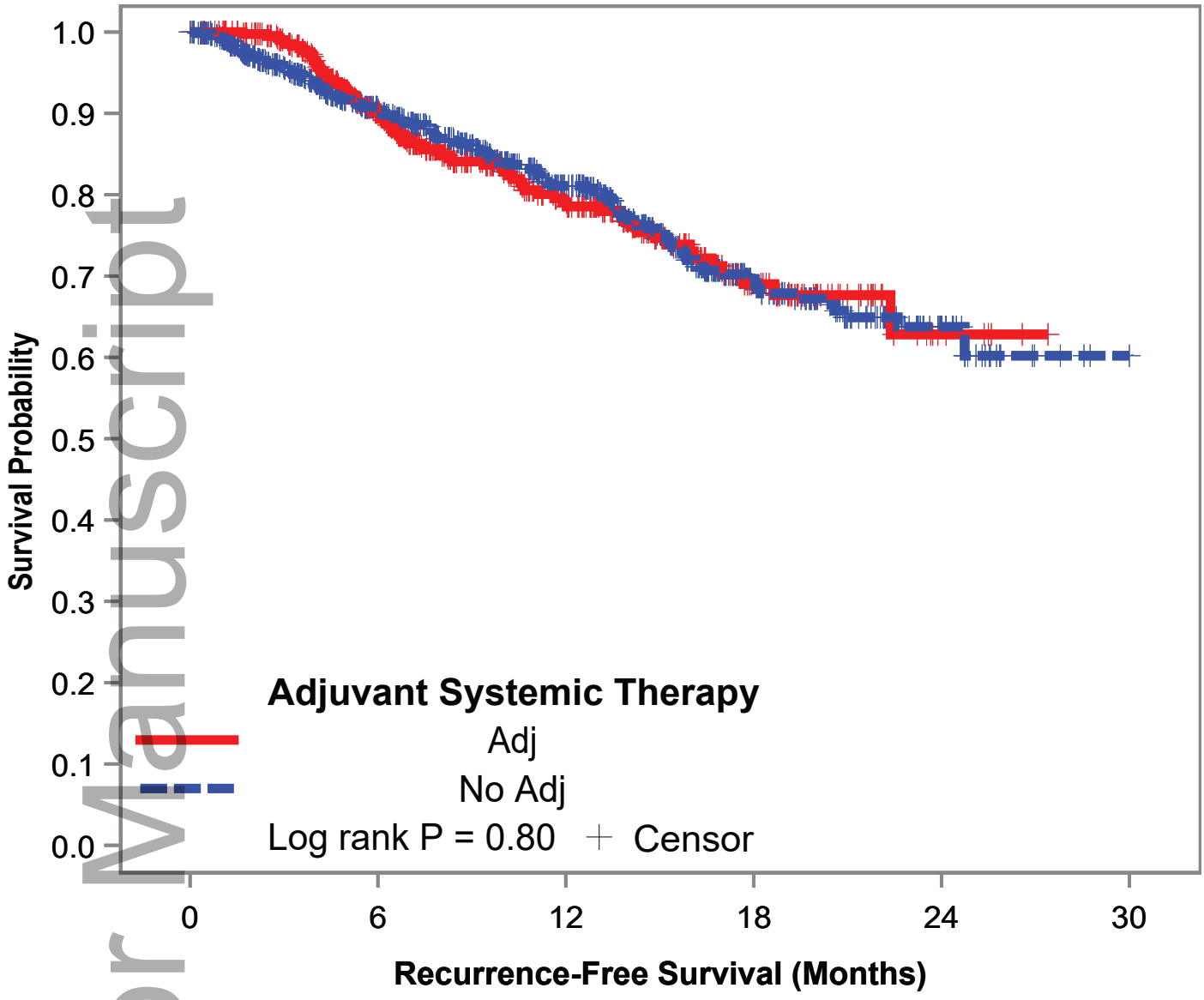

Patients-at-Risk

Adj	439	296	157	55	7	0
No Adj	712	468	292	118	30	1

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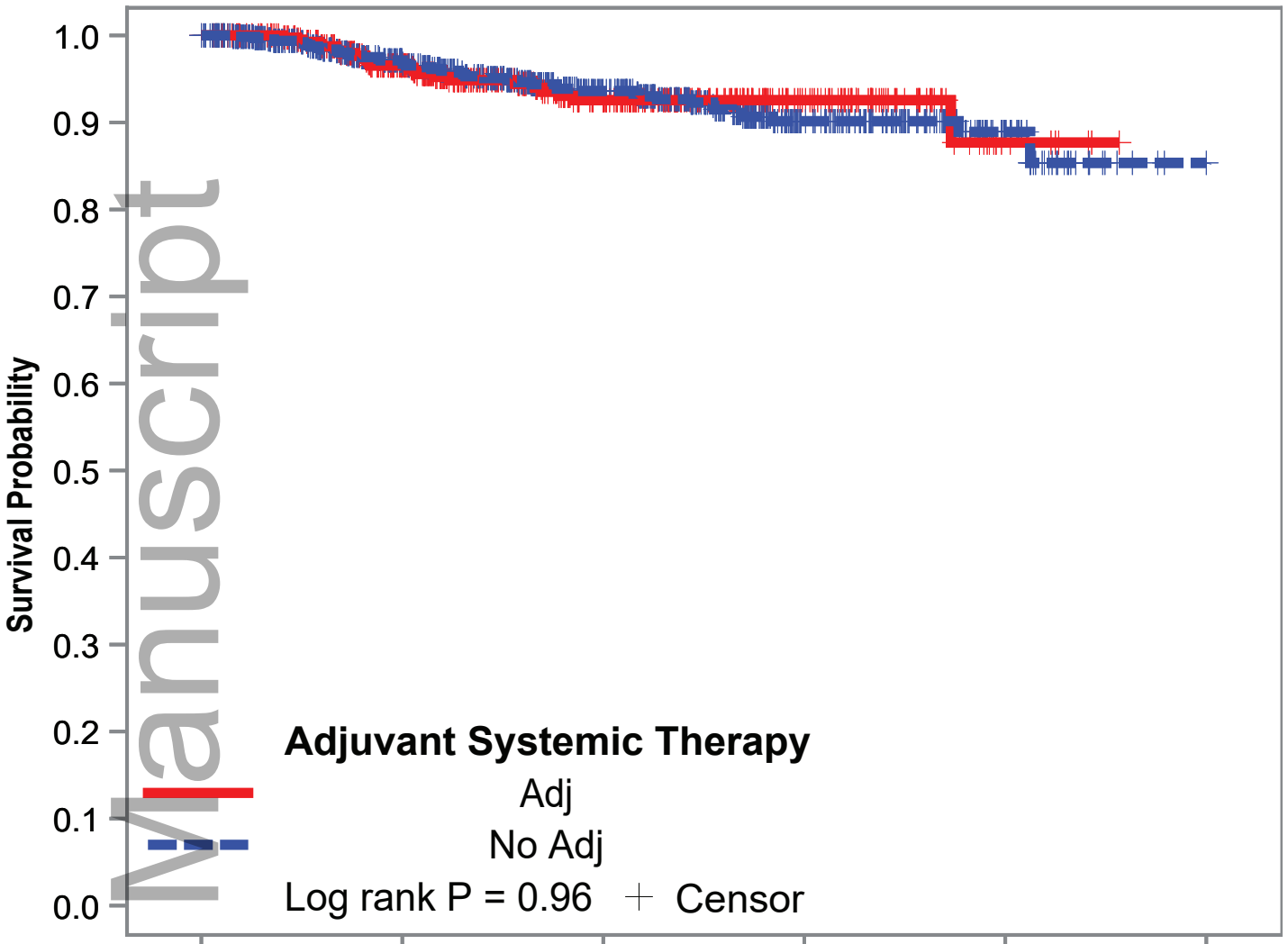

Patients-at-Risk

Adj	439	311	175	72	8	0
No Adj	712	501	329	152	42	1

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