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RESEARCH ARTICLE

Indocyanine Green–Guided Sentinel Lymph Node Biopsy in Melanoma: Assessing Clinical Value in a Cohort Over 1000 Patients

Daniela Duarte-Bateman[1,2] | Alan Shen[3] | Yanwen Chen[2] | Jorge Arpi-Palacios[1,2] | Eduardo Williams[3] | Viren Patel[1] | Rebecca Knackstedt[1] | Brian R. Gastman[1,3]

[1]Department of Plastic Surgery, Cleveland Clinic, Cleveland, Ohio, USA | [2]Lerner Research Institute, Cleveland Clinic, Cleveland, Ohio, USA | [3]Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, Ohio, USA

Correspondence: Brian R. Gastman (gastmab@ccf.org)

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ABSTRACT

Background: The sentinel lymph node biopsy (SLNB) remains the standard for identifying micrometastasis in melanoma. In this study, we utilized our prospectively maintained database to assess whether adding indocyanine green (ICG) fluorescence imaging to radioisotope lymphoscintigraphy improved sentinel node detection and, consequently, clinical outcomes.

Methods: Consecutive patients with cutaneous melanoma who underwent dual technique SLNB by the senior author (B.R.G.) from 2012 to 2022 were enrolled. All patients with a negative SLNB result were subjected to a minimum follow-up period of 12 months. Positive and false-negative rates were calculated, and recurrence-free survival (RFS) was used as a measure of clinical outcomes.

Results: A total of 1267 patients were identified. The average age was 62 years, with 526 females (41.6%). The mean Breslow depth was 1.82 mm (range 0.2–24 mm). Among 3403 SLNs sampled, 358 were positive (91.1% identified by both modalities). The false-negative rate was 8.5% (25/293), and the median time to recurrence was 13.7 months (range: 2.8–60.4 months). The 12-month RFS for stages IA-IIC were 99%, 98%, 95%, 97%, and 84%, respectively ($p = 0.016$).

Conclusions: These findings support the use of an ICG-based dual technique in SLNB for melanoma, demonstrating diagnostic precision with excellent patient outcomes.

1 | Introduction

Surgery remains a cornerstone of melanoma management, with sentinel lymph node biopsy (SLNB) serving as the standard of care for regional staging [1]. Accurate detection of micrometastatic disease within sentinel nodes is critical, as it directly informs pathologic staging, guides decisions regarding adjuvant therapy, and shapes subsequent surveillance strategies, including nodal monitoring [2]. Historically, a positive SLNB frequently prompted completion lymph node dissection (CLND) to assess additional nodal involvement. However, contemporary practice has moved away from routine CLND following a positive SLNB, underscoring the diagnostic accuracy and prognostic value of SLNB alone [3, 4]. Consequently, optimizing the SLNB technique and performance is essential, as it has meaningful implications for prognosis, treatment selection, and overall clinical outcomes.

Leveraging our prospectively updated database [5, 6], herein, we investigated the clinical value of a SLNB dual technique of radioisotope lymphoscintigraphy with indocyanine green (ICG) fluorescence imaging on clinical outcomes now in a cohort exceeding 1000 patients with melanoma.

2 | Materials and Methods

After Institutional Review Board approval, primary cutaneous melanoma patients who underwent SLNB using radioisotope lymphoscintigraphy with technetium-99 sulfur colloid (TechneScan [Curium, London, United Kingdom]; TechneColl [Mallinckrodt, Staines-upon-Thames, United Kingdom]), and ICG-based fluorescence imaging (Quest Spectrum Quest Medical Imaging B.V., Middenmeer, The Netherlands), herein referred to as ICG-based dual technique, from January 2012 to December 2022, were prospectively enrolled and included for analysis. Patients were selected for SLNB based on the guidelines established by the National Comprehensive Cancer Network (NCCN). Patients with a Breslow depth of < 1 mm were offered an SLNB due to mitosis, ulceration, or a positive deep margin on biopsy. The surgical approach was as previously described by Knackstedt et al. [6].

Predictive variables included age, sex, tumor location, Breslow thickness, mitotic index, regression, ulceration, and histologic subtype. Cutaneous melanoma staging was retrospectively assigned based on the eighth edition of the American Joint Committee on Cancer (AJCC) staging system [7]. Given our institution's role as a tertiary referral center, initial biopsy reports were unavailable for a small subset of patients. However, outside medical records confirmed a stage I/II disease diagnosis. Intraoperative results included SLN localization, means of SLN identification, and the number of SLNs harvested. When applicable, the ex vivo radioactivity reading of each SLN was recorded. Nodes were considered positive if there were any tumor cells noted within the node on pathological analysis. Postoperatively, patients were followed up by the melanoma multidisciplinary team and examined for evidence of recurrence.

2.1 | Outcome Measurements

We first calculated the false-negative rate (FNR) and adjusted false-negative rate (AFNR) to confirm the accuracy of the technique. The FNR was defined as the proportion of patients with false-negative SLNB (regional nodal recurrence with or without local or in-transit recurrence in previously sampled negative sentinel lymph node basin) to patients with true-positive (correctly diagnosed lymph node metastasis) and false-negative SLNB (i.e., false-negative/true-positive + false-negative). The AFNR was defined as the proportion of patients with false-negative SLNB (regional nodal recurrence without local or in-transit recurrence in previously sampled negative sentinel lymph node basin) to patients with true-positive (patients correctly diagnosed with lymph node metastasis) and false-negative SLNB (i.e., false-negative/true-positive + false-negative).

We assessed the recurrence-free survival (RFS) among patients who underwent ICG-based dual technique SLNB. RFS was operationally defined as the duration spanning from the initial SLNB procedure to either the occurrence of melanoma recurrence or mortality from any cause. Follow-up duration was meticulously computed from the surgical date to the final follow-up appointment or the date of demise. Importantly, all patients with a negative SLNB result were subjected to a minimum follow-up period of 12 months to be included in this study, ensuring a comprehensive evaluation of their outcomes over time.

2.2 | Statistical Analysis

Categorical variables were summarized using frequencies and percentages, while continuous variables were summarized using mean and standard deviation. FNR and AFNR were calculated as described above. To evaluate the impact of the SLNB alone on survival outcomes, we focused on patients treated before the approval of adjuvant therapy for stage II melanoma, thus avoiding adjuvant therapy bias. Given that RFS is an established endpoint for assessing systemic therapies in the context of regulatory approval and thus provides a rigorous benchmark, we used it to evaluate the impact of these technological advances on survival outcomes. RFS was estimated using the Kaplan-Meier method and compared using a log-rank test between patient groups. RFS was calculated at 12 and 18 months post-SLNB.

As a means of evaluating our results against available literature, we focused on patients with stage IIB/IIC melanoma and compared our RFS data to that of the landmark trials KEYNOTE 716 [8] and CheckMate76K [9], which examined the same subgroup using non-ICG-based SLNB and whose 12-month analyses supported approval of anti-PD-1 adjuvant therapy in this population.

3 | Results

3.1 | Cohort Characteristics

During the study period, 1267 consecutive patients with a new primary cutaneous melanoma diagnosis without clinical evidence of regional metastasis underwent ICG-based dual technique SLNB. Patients ranged from 18 to 98 years old, with an average age of 62 years. There were 741 (58.4%) men and 526 (41.6%) women. At initial biopsy, the mean Breslow thickness at the time of diagnosis was 1.82 mm (range, 0.2–24 mm). Ulceration was present in 311 patients (24.5%), 59.3% of patients had a mitotic rate between 1 and 10 mm^2 and 8.7% had a rate greater than 10 $mm.^2$ 39.6% and 32% of patients had T stage 1 and 2, respectively. The majority of patients (49.4%) had superficial spreading melanoma, followed by the nodular subtype (22.1%). Melanomas were found on the trunk (29.7%), upper extremities (24.2%), head and neck (25.7%), and lower extremities (20.2%), as illustrated in Figure 1. The median follow-up duration stood at 26.1 months, spanning from 0 to 136.9 months. Among SLNB-negative patients specifically, the average follow-up period was 25.9 months, ranging from 0 to 136.9 months. Patient and melanoma characteristics are listed in Table 1.

3.2 | SLNB Results

A total of 3403 sentinel lymph nodes were sampled in 1267 patients. Of the sentinel nodes, 3162 (92.9%) were identified by both radioactivity and ICG, 182 (5.4%) by radioactivity alone, and 59 (1.7%) by ICG alone (Table 2). There were 268 patients (21.2%) with at least one positive sentinel node (i.e., true-positive patients). A total of 358 positive sentinel nodes were

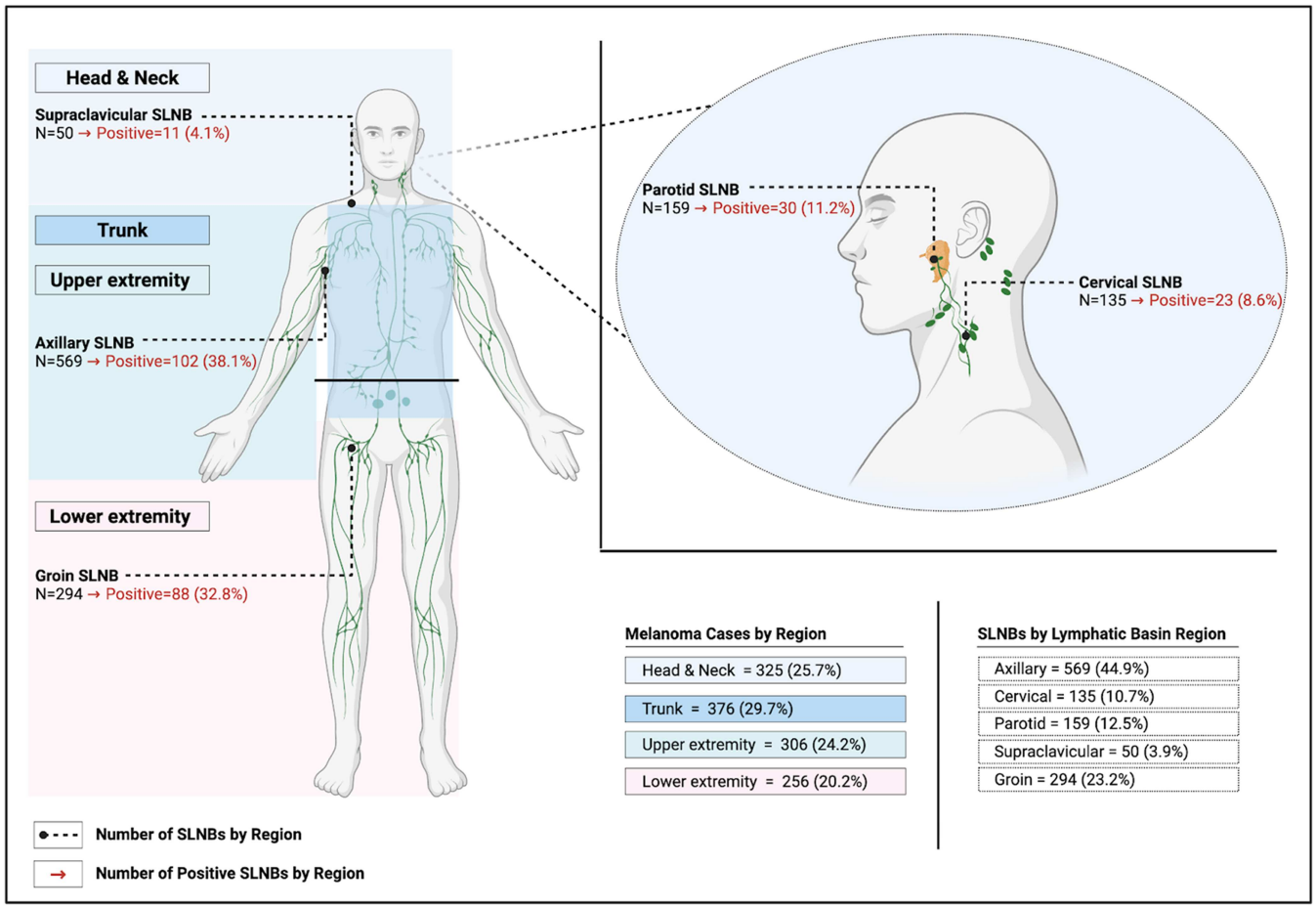

FIGURE 1 | Distribution of melanoma and sentinel lymph node biopsy (SLNB) by anatomical region. This figure illustrates the anatomical distribution of melanoma in the head and neck, upper extremity, trunk, and lower extremity. It illustrates specific lymph node basins where SLNB was performed and depicts the lymph node status (positivity) across anatomical locations. SLNB, sentinel lymph node biopsy. Created in BioRender. Arpi, J. (2025) https://BioRender.com/c42m766.

identified. Of these, 326 (91.1%) were identified by radioactivity and ICG, 29 (8.1%) by radioactivity alone, and 3 (0.8%) by ICG alone (Table 2). The most common SLNB location was the axilla (38.1%), followed by the groin (32.8%), cervical (8.6%), and parotid (11.2%) (Figure 1). When analyzed by T stage, the distribution of positive SLNB results was as follows: 16 patients with T1a, 27 with T1b, 57 with T2a, 30 with T2b, 36 with T3a, 43 with T3b, 14 with T4a, and 37 with T4b (Table 1).

3.3 | Patients With a Negative SLNB and Nodal Recurrence (i.e., FNR)

A total of 999 patients had a negative SLNB and were therefore classified as stage I/II. Among these, 236 were T1a, 222 T1b, 249 T2a, 69 T2b, 79 T3a, 60 T3b, 26 T4a, and 27 T4b. It is important to note that, according to NCCN guidelines, T1a patients typically do not warrant SLNB; thus, this cohort consists of cases with additional features that placed them in the "consider SLNB" category. Our cohort included 409 patients with stage IA, 227 with stage IB, 138 with stage IIA, 92 with stage IIB, and 39 with stage IIC melanoma.

A total of 25 patients experienced recurrence in the initially deemed negative nodal basin. Among these patients, 20 exhibited no evidence of local or in-transit recurrence, while five had simultaneous local or in-transit recurrence. This resulted in an FNR of 8.5% (25/293) and an AFNR of 6.8% (20/293). The median follow-up time for patients that presented recurrence was 38.7 months (range: 4.4–103.5 months). The median time to recurrence was 13.7 months (range: 2.8–60.4 months).

3.4 | RFS Outcomes in Stage I/II Melanoma Patients

Considering that the 12-month benchmark was pivotal for the FDA approval of pembrolizumab and nivolumab in landmark trials, we analyzed our data at this specific timepoint. The 12-month RFS rates in our cohort for stages IA, IB, IIA, IIB, and IIC were 99%, 98%, 95%, 97%, and 84%, respectively ($p = 0.016$) (Figure 2).

In light of the relative paucity of survival outcome data, particularly RFS, in studies evaluating surgery alone, and given that recent trials in stage IIB/C disease [8, 9] have reported such outcomes, we conducted a subgroup analysis within this population. We compared our findings with the placebo arms of these trials, which represent patients managed with surgical treatment alone. While landmark trials provide useful benchmarks for contextualization, we acknowledge that direct

TABLE 1 | Baseline patient characteristics.

	All cases ($n = 1267$)	SLNB positive ($n = 268$)	SLNB negative ($n = 999$)	p value
Gender (n, %)				0.055
Male	741 (58.5)	171 (63.8)	570 (57.1)	
Female	526 (41.5)	97 (36.2)	429 (42.9)	
Age, years (mean, SD)	62.52 ± 16.08	61.96 ± 16.65	62.67 ± 15.93	0.521
Tumor size, cm^2 (mean, SD)	1.36 ± 1.04	1.84 ± 1.29	1.19 ± 0.88	< 0.001
Tumor thickness, mm (mean, SD)	1.82 ± 1.91	2.87 ± 2.66	1.54 ± 1.53	< 0.001
Mitosis, mm^2 (n, %)				
None	365 (28.8)	35 (13.1)	330 (33.0)	< 0.001
1−10	751 (59.3)	184 (68.7)	567 (56.8)	
> 10	110 (8.7)	42 (15.7)	68 (6.8)	
Unknown	41 (3.2)	7 (2.6)	34 (3.4)	
Ulceration (n, %)				< 0.001
Yes	311 (24.5)	118 (44.0)	193 (19.3)	
No	925 (73.0)	146 (54.5)	779 (78.0)	
Unknown	31 (2.4)	4 (1.5)	27 (2.7)	
T stage (n, %)				< 0.001
T1a	252 (19.9)	16 (6.0)	236 (23.6)	
T1b	249 (19.7)	27 (10.1)	222 (22.2)	
T2a	306 (24.2)	57 (21.3)	249 (24.9)	
T2b	99 (7.8)	30 (11.2)	69 (6.9)	
T3a	115 (9.1)	36 (13.4)	79 (7.9)	
T3b	103 (8.1)	43 (16.0)	60 (6.0)	
T4a	40 (3.2)	14 (5.2)	26 (2.6)	
T4b	64 (5.1)	37 (13.8)	27 (2.7)	
Unknown	39 (3.1)	8 (3.0)	31 (3.1)	
Melanoma location (n, %)				0.004
Head and neck	325 (25.7)	66 (24.6)	259 (25.9)	
Trunk	376 (29.7)	77 (28.7)	299 (25.9)	
Lower extremities	256 (20.2)	76 (28.4)	180 (18.0)	
Upper extremities	306 (24.2)	46 (18.3)	257 (25.7)	
Other	2 (0.2)	0 (0)	2 (0.2)	
Melanoma subtype (n, %)				< 0.001
Superficial	621 (49.0)	88 (33.0)	533 (53.9)	
Nodular	277 (21.8)	109 (40.8)	168 (17.0)	
Lentigo	68 (53.6)	6 (2.2)	62 (6.3)	
Nevoid	59 (4.7)	7 (2.6)	52 (5.3)	
Other	162 (12.8)	44 (10.1)	118 (11.8)	
Unknown	80 (6.3)	14 (5.2)	66 (6.6)	
Follow-up time, months (median, range)	26.1 (0−136.9)	27.4 (0.69−113.1)	25.9 (0−136.9)	0.331

comparisons are inherently limited by differences in study design and patient populations.

Our cohort included 111 stage IIB/C patients with a median follow-up time of 26.9 months (range: 0.2–101.4 months). The combined RFS for stage IIB/IIC patients in our cohort was 92.9% at 12 months and 90.4% at 18 months (Figure 3). In comparison, the placebo arm of KEYNOTE-716 [8] reported RFS rates of 83.1% at 12 months and 77.0% at 18 months, while the placebo arm of CheckMate-76K [9] demonstrated a 12-month RFS rate of 79.4%.

TABLE 2 | Sentinel lymph node biopsy (SLNB) results.

	All cases ($n = 1267$)	SLNB positive ($n = 268$)	SLNB negative ($n = 999$)	p value
Location (n, %)				0.009
Cervical	135 (10.7)	23 (8.6)	112 (11.2)	
Parotid	159 (12.5)	30 (11.2)	129 (12.9)	
Supraclavicular	50 (3.9)	11 (4.1)	39 (3.9)	
Axilla	569 (44.9)	102 (38.1)	467 (46.7)	
Groin	294 (23.2)	88 (32.8)	206 (20.6)	
Other	60 (4.7)	14 (5.2)	46 (4.6)	
Total sentinel nodes sampled	3403	358	3045	
Sentinel nodes sampled per patient (mean, SD)	2.69 ± 1.65	2.72 ± 1.66	2.68 ± 1.64	0.739
Sentinel nodes identified by (n, %)				0.022
ICG and radioactivity	3162 (92.9)	326 (91.1)	2836 (93.1)	
Radioactivity only	182 (5.4)	29 (8.1)	153 (5.0)	
ICG only	59 (1.7)	3 (0.8)	56 (1.8)	

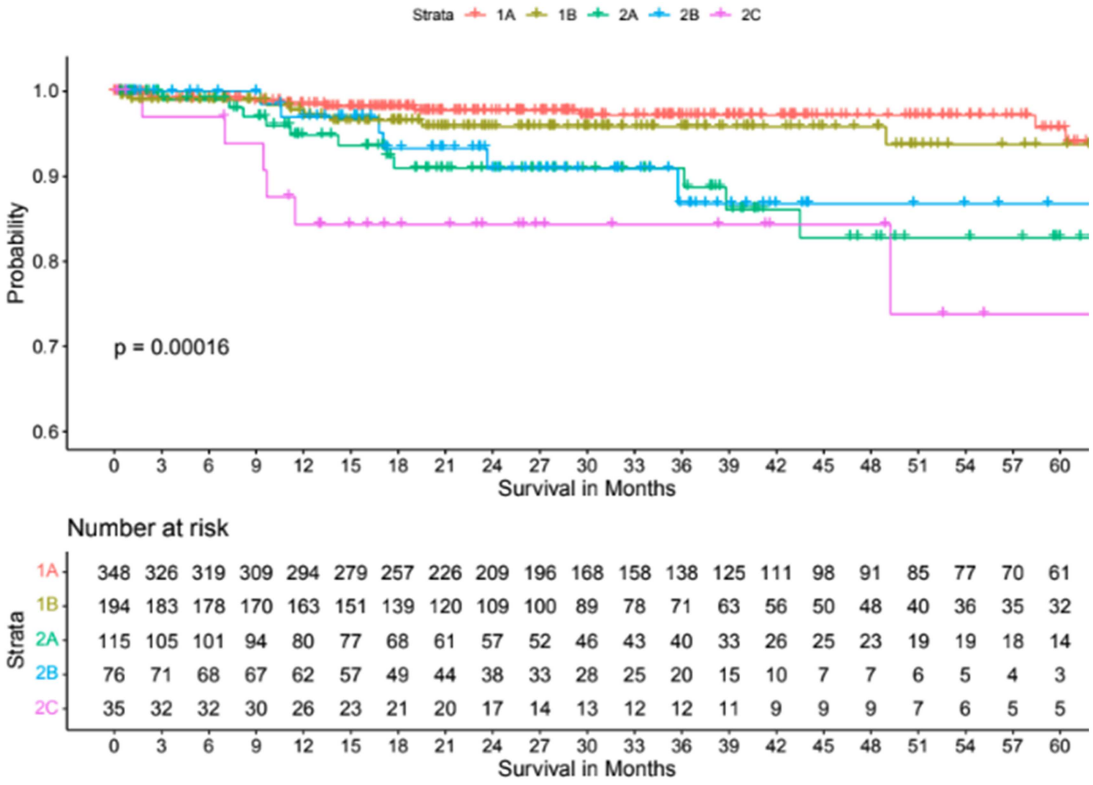

FIGURE 2 | Recurrence-free survival in melanoma stages IA–IIC. Kaplan–Meier curve illustrating recurrence-free survival in the study cohort for melanoma stages IA, IB, IIA, IIB, and IIC, with a minimum follow-up duration of 12 months. Statistical analysis revealed a significant difference in recurrence-free survival across stages ($p = 0.016$).

4 | Discussion

The present study builds on our previous research [6], with more than double the number of patients, confirming the reliability of a SLNB dual technique of technetium-99m-labeled radiocolloid and ICG-fluorescence imaging for detecting occult metastatic disease in melanoma. For the first time, we explore the clinical impact, in terms of RFS, of this ICG-based dual technique. In this paper, we showcase how surgical innovations can lead to excellent melanoma outcomes.

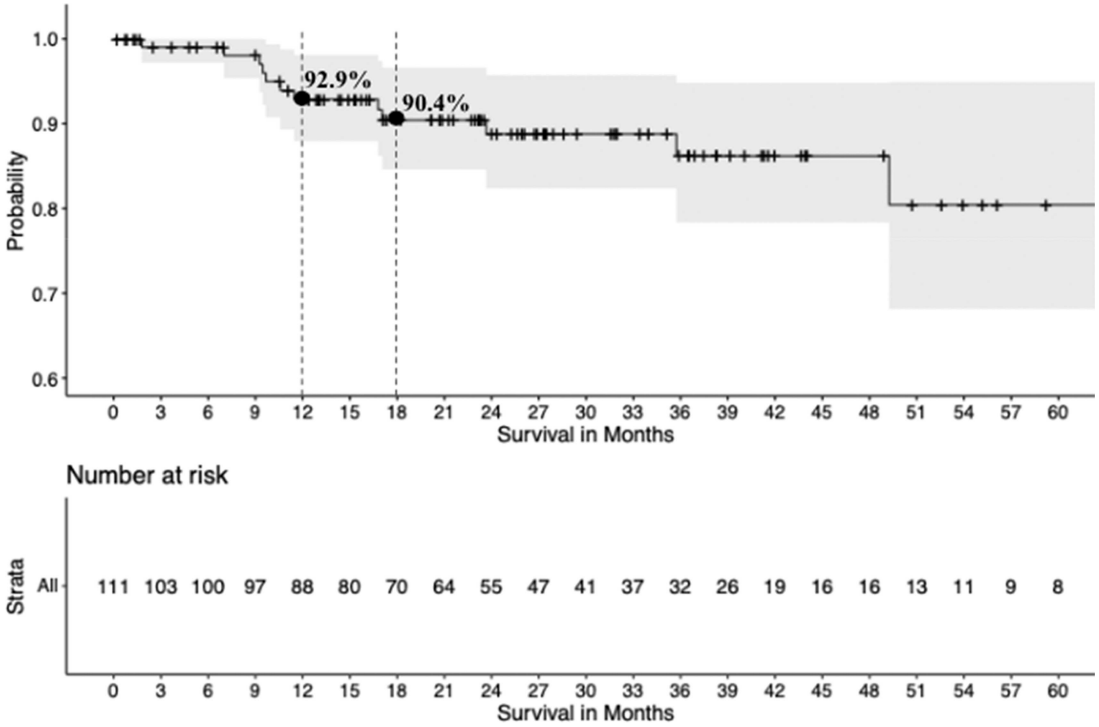

FIGURE 3 | Kaplan–Meier curves illustrate recurrence-free survival (RFS) in patients with melanoma stages IIB and IIC within the study cohort.

Over the last several years, adjuvant systemic therapies, particularly for stage III melanoma, have gained wide use based on the high rate of recurrences after surgery [3, 7–18]. With their implementation, survival outcomes have significantly improved in the past decade [7]. This improvement has been seen in both stage III patients (who commonly received adjuvant therapy) and in stage IIB/C patients (immunotherapy-naive patients, until recently) [19, 20]. A key reason for this improvement was the increased use of SLNB in both groups [2, 3]. This situation reflects the Will Rogers effect, where the greater use of a diagnostic tool (i.e., SLNB) leads to improved outcomes in two separate populations (i.e., stage II and III patients) [21]. This phenomenon underscores the efficacy of the SLNB in patient staging and highlights the potential for its enhancement, given that therapy decision-making largely depends on the SLNB results.

While systemic therapies for melanoma are rapidly advancing, the surgical management of melanoma has seen little change [22, 23]. In our study using a novel dual technique, sentinel nodes were most commonly identified by both radioactivity and ICG. Our FNR of 8.5% and AFNR of 6.8%, observed with a median follow-up exceeding the median time to recurrence, are among the lowest reported in the literature [24–38], as previously published by our group [5]. These findings further support the added value of incorporating ICG into SLNB to enhance staging accuracy. The objective of this approach is not to require simultaneous positivity from both modalities. Rather, its value lies in the complementary ability of either modality to assist in sentinel node identification at different stages of the procedure.

During back-table confirmation, both modalities frequently demonstrate signals. However, intraoperatively, their utility may differ. Radiotracer guidance provides oncologic localization, whereas ICG offers real-time visual anatomical guidance that can assist the surgeon in re-centering the dissection toward the appropriate nodal basin. Depending on the anatomic region and operative circumstances, one modality may be more informative than the other. The strength of the approach lies in complementary functionality, not redundancy.

Notably, there were no cases in which both modalities failed to provide usable guidance. In rare instances, one modality identified a positive node when the other did not; however, this was not statistically significant. Among the 29 positive nodes identified exclusively by radioactivity. This can be attributed to limited dye penetration in certain anatomical regions. Notably, ICG alone identified three sentinel nodes that radioactivity did not and would have otherwise been missed. These corresponded to three different patients, two of whom had only that node identified, making ICG solely responsible for their positive SLNB result. In these cases, ICG enabled accurate diagnosis and helped reduce the overall FNR of the procedure. The third patient had six nodes identified by both radioactivity and ICG, and one node identified by ICG alone. Although ICG did not change the staging in this instance, it facilitated the removal of a cancerous node that would have otherwise remained in situ, potentially leading to a recurrence. While this finding may not be statistically significant, it highlights the complementary strengths of the two techniques and supports their combined use to enhance nodal detection, thereby improving the accuracy of staging and treatment.

We then made some exploratory comparisons of clinical outcomes to assess whether surgery alone, when paired with advanced techniques, might offer additional benefit. Compared to the KEYNOTE 716 [8] placebo group, our cohort demonstrated RFS rates of 92.9% versus 83.1% at 12 months, and 90.4% versus 77% at 18 months. Likewise, our cohort demonstrated a

12-month RFS rate of 92.9% versus 79.4% in the CheckMate 76K placebo group [9]. Although this observation should be interpreted with caution given inherent differences in patient populations and study design, it underscores the potential impact of advanced surgical techniques in optimizing SLNB outcomes. Moreover, it raises an important question as to whether adjuvant therapies, such as those used in these trials, primarily targeted nodal micrometastases that were too small to be detected by SLNB, or conversely, were missed due to less comprehensive SLNB techniques.

Raising such questions and advancing our surgical management is important, particularly in the era of limited CLND use and evolving adjuvant therapy strategies. By more accurately identifying patients with stage III disease through improved assessment of micrometastatic involvement, we reduce the likelihood of misclassifying higher-risk individuals as stage I/II. This, in turn, helps define a truly lower-risk cohort. Such surgical advances can thus refine patient selection for adjuvant therapy, ensuring that treatment is directed toward those most likely to benefit.

4.1 | Limitations and Future Directions

While our study provides robust evidence supporting the enhanced accuracy and clinical efficacy of SLNB, there are some limitations to consider. The retrospective nature of the study, despite prospective data collection, may introduce inherent biases. Additionally, the single-institution experience may limit the wide applicability of such findings. Future research should focus on further validating these findings in prospective, multicenter studies to confirm the reproducibility of our results across diverse patient populations.

5 | Conclusion

Our study demonstrates that technological advancements in SLNB, particularly the use of dual-modality imaging with technetium-99m and ICG can improve the accuracy of SLN identification. These advancements not only enhance staging accuracy but also lead to excellent clinical outcomes, measured by RFS, in patients with cutaneous melanoma.

Our findings highlight the utility of advanced SLNB techniques in SLN identification and RFS outcomes, likely by providing more accurate staging, thereby aiding in better therapy decision-making.

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Disclosure

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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