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Recurrence Patterns and Clinical Management after a Positive Sentinel Node Biopsy in Melanoma Patients

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ABSTRACT

Introduction melanoma patients who become stage III after a positive sentinel node biopsy (SNB) may have several patterns of recurrence patients and methods retrospective analysis of melanoma patients who have undergone SNB in a single institution from 2000 to 2015. Results There were 111 recurrences (45.1%) among 246 (20.3%) SNB positive patients and median DRFS was 77.7 months. After initial treatment, further recurrences occurred in 68 (77.3%) patients, regardless the site of initial recurrence conclusions multimodal strategies are recommended to achieve better results when managing stage III melanoma patients after a positive SNB

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Introduction

Managing stage III melanoma patients can be challenging, since it is a heterogeneous group of patients whose melanoma-specific survival (MSS) at 10 years ranges from 24% to 88% (1). Even focusing on patients who become stage III after a positive sentinel node biopsy (SNB) still leads to a complex subgroup of patients.

Current guidelines recommend nodal surveillance with ultra-sound as the ideal management of these patients, in addition by adjuvant treatments with either anti PD-1 immunotherapy (IO) or targeted therapy (TT) based on BRAF status (2). Immediate completion lymph node dissection (CLND) after SNB has become an alternative recommendation since two large prospective randomized trials had shown no benefit in outcomes such as distant recurrence free survival (DRFS), overall survival (OS) and MSS when comparing surgery versus observation (3–5).

However, recent reports have demonstrated that some patients in this specific subset – nodal surveillance after positive SNB – had recurred even after receiving adjuvant treatments and it is not clear how to manage them, especially when they do not harbor BRAF gene mutations (6–9). To date, the evidence to support the decision between salvage surgeries versus further lines of treatment is not strong enough and these decisions are based on clinical and pathological features and often carried in multidisciplinary boards (10–12).

Moreover, each patient belongs to a social and economic environment, impacting the access to follow-up exams and the possibility of undergoing adjuvant treatments (13, 14). Establishing a standard of care, which considers all these variables to manage such a heterogeneous group of patients, demands a huge effort.

We aim to describe a single-center cohort of melanoma patients with positive SNB, reporting how the patterns of recurrence and further treatments impacted in clinical outcomes.

Patients and methods

We performed a retrospective analysis of melanoma patients who have undergone SNB at A.C.Camargo Cancer Center (São Paulo/SP),

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which is a single Brazilian institution, from 2000 to 2015. This period was defined to assure that all patients would have at least five years of follow-up. Our local ethics committee approved this research.

Clinical and pathology data were collected from medical records, including primary tumor characteristics such as Breslow thickness (mm) and mitotic rate (figures/mm^2); SNB status, recurrences and current survival status. We have been performing SNB according to current guidelines since 1997 and our routine during this period, regarding nuclear medicine work-up, surgery and pathology report has already been previously reported (15, 16).

DRFS was calculated from the date of SNB to the date of the first recurrence, after radiologic and/or pathological confirmation. Recurrences were categorized as M1a (skin and lymph nodes), M1b (lungs only), M1c (visceral), and M1d (CNS). MSS was calculated from the date of SNB to the date of death caused by melanoma. The survival curves were estimated by the Kaplan-Meier method and the comparisons between the groups were performed by the log-rank test. The Cox semi parametric proportional hazards model was fitted to assess which variables would be associated with the endpoints (17).

Results

From 1,213 patients who underwent SNB, 246 (20.3%) presented at least one positive sentinel node and were considered for our analysis. Male patients were predominant (56.5%) and the mean age was 52.34 years (range 5 – 86, SD 16.86). Median follow-up was 79.13 months (95% CI 70.38 – 87.88, SE 4.46).

Superficial spreading was the most common subtype (56.5%) and the mean Breslow thickness was 3.8 mm (range 0,4 – 29, SD 3.7) (Supplementary Table 1). According to the 8th Edition of the American Joint Committee on Cancer (AJCC) (1), there were 77 stage IIIA patients (31.3%), 40 IIIB (16.3%), 124 IIIC (50.4%) and 5 IIID patients (2.0%). Clinical outcomes regarding staging are summarized in Figures 1, 2A and B.

According to current guidelines during the study's period, immediate CLND was offered to all patients and 242 (98.3%) underwent surgery. Adjuvant radiotherapy was performed in eight patients (3.3%) and 38 (15.4%) underwent interferon based adjuvant treatments, but only 21 (8.5%) were able to complete it to the end.

There were 111 recurrences (45.1%) and median DRFS was 77.7 months (95% CI 34.90 – 123.96, SE 22.72). Age at diagnosis, acral subtype, Breslow thickness, mitotic rate, vascular invasion, ulceration, number of positive sentinel nodes and non-sentinel positive nodes were associated to recurrence after single Cox regression. However, only mitotic rate (HR 1.090 [95% CI 1.053 – 1,129], $p < 0.0001$) and ulceration (HR 1.949 [95% CI 1.113 – 3.414], $p = 0.02$) were statistically significant after multiple Cox regression.

The most common site of recurrence was skin and lymph nodes (M1a – 48.4%), with a 1.6% recurrence rate in the same nodal basin of CLND. Visceral metastasis (no lungs, no CNS/M1c) happened in 24.2% of patients, followed by lungs (M1b – 19.8%) and CNS (M1d – 7.7%). The first recurrence occurred in multiple topographies in 21.6% of these patients. There were 45 patients (40.5%) who underwent surgery as the initial treatment after recurrence. Sixteen patients underwent chemotherapy (14.4%), and 6 (5.4%) patients received high dose interleukin-2 alone or in combination with chemotherapy (BioCT). Seven patients (6.3%) received IO and 3 patients (2.7%) received TT (Figure 1). The site of recurrence was statistically associated with the treatment received by these patients ($p < 0.001$).

Exclusive surgical treatment was performed to 63.6% of patients with cutaneous and nodal recurrences, whereas it was performed to 33.3% of patients with lung recurrence, 22.7% with visceral recurrences and 14.3% of patients with recurrences to CNS. Patients who were treated with surgery after first recurrence presented better melanoma specific survival (MSS) (HR 0.508 [95% CI 0.293 – 0.881], p 0.008 – Figure 2C).

On the other hand, a non-surgical approach was performed to half of the patients with visceral and/or lung recurrences, 42.9% of patients with CNS recurrences and 34.1% of patients with skin or nodal lesions. Patients who developed

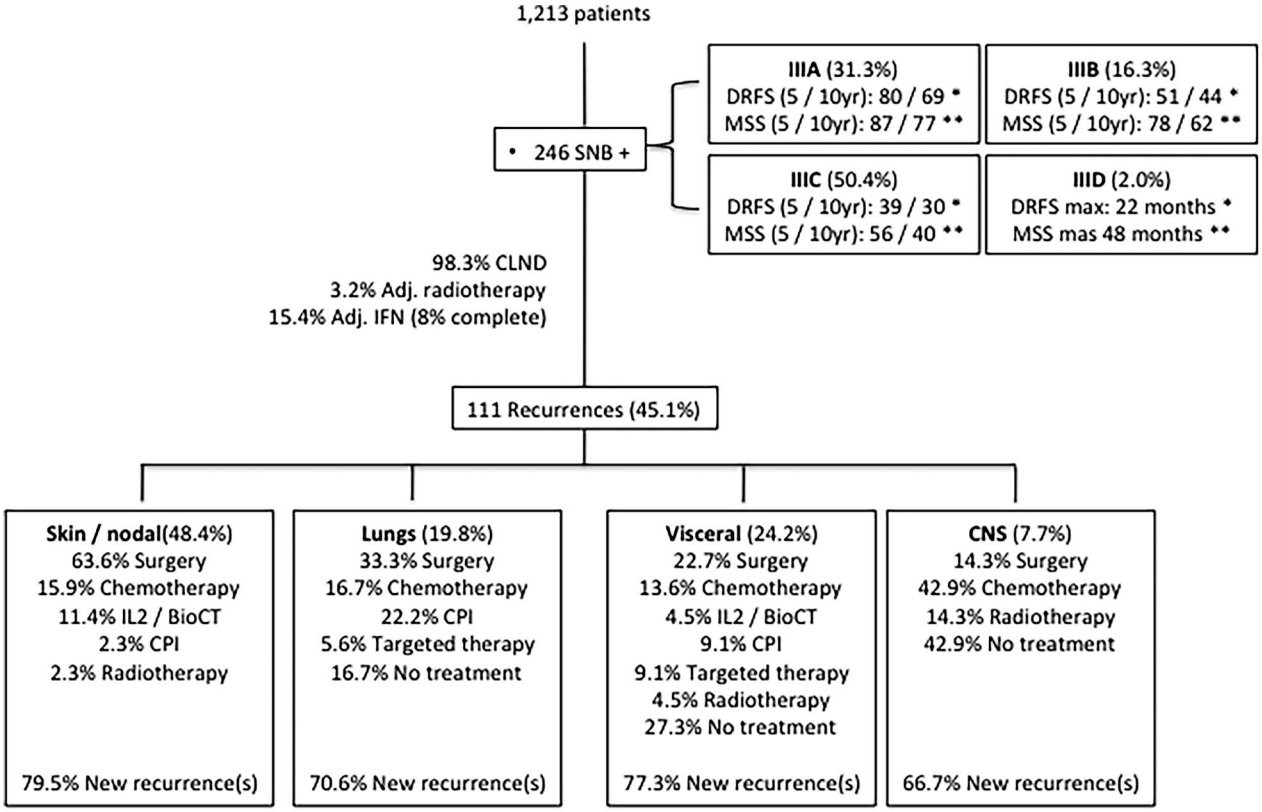

Figure 1. Summary of clinical outcomes of melanoma patients after a positive sentinel node biopsy considering staging (upper right part) and site of recurrence (lower central part). (SNB: sentinel node biopsy, DRFS: Distant recurrence free survival, MSS: Melanoma specific survival, IFN: interferon, IL2: interleukin 2, BioCT: biochemotherapy, CPI: check point inhibitors, * see Figure 2A, ** see Figure 2B)

recurrences to CNS were also considered for best supportive care (BSC) in 42.9% of the cases.

Further recurrences occurred in 68 (77.3%) patients after initial treatment. Considering the site of first recurrence, 79.5% of patients who presented initially with cutaneous recurrences developed new recurrences, followed by 77.3% in the group of visceral recurrences, 70.6% in the group of lung recurrences and 66.7% in the group with CNS recurrences as the first site (p 0.768).

Discussion

This study comprises a large cohort of stage III melanoma patients after SNB from Latin America with a long follow-up. Most risk factors that were statistically significant in our single Cox analysis can be found in literature such as Breslow thickness, ulceration and the number of harvested nodes (3, 4, 18, 19). However, mitotic rate as a continuous variable was statistically significant after multiple Cox analysis and thus should also be considered in risk assessment, as mentioned in the current AJCC staging system paper (1).

Regarding outcomes, MSS at 5 years was 87% in stage IIIA, 78% IIIB, 56% IIIC and no IIID patient was alive after four years in our cohort (Figure 2). Our rates are comparable to the AJCC ones, as well as the Central Malignant Melanoma Registry (CMMR) and the European Organization for research and Treatment of Cancer (EORTC) (20).

Our recurrence rate (45.1%) can be compared to the Memorial Sloan Kettering Cancer Center (MSKCC) data (42.7%)(21), although our median follow-up is longer. Recent data from the MD Anderson Cancer Center (MDACC) has shown 27% of recurrence in a cohort that also comprised patients who have undergone modern adjuvant treatments (8). It is important to reinforce that most of our patients had not undergone adjuvant treatments due to the period of the study since both current options have become available in Brazil for the adjuvant scenario after 2018.

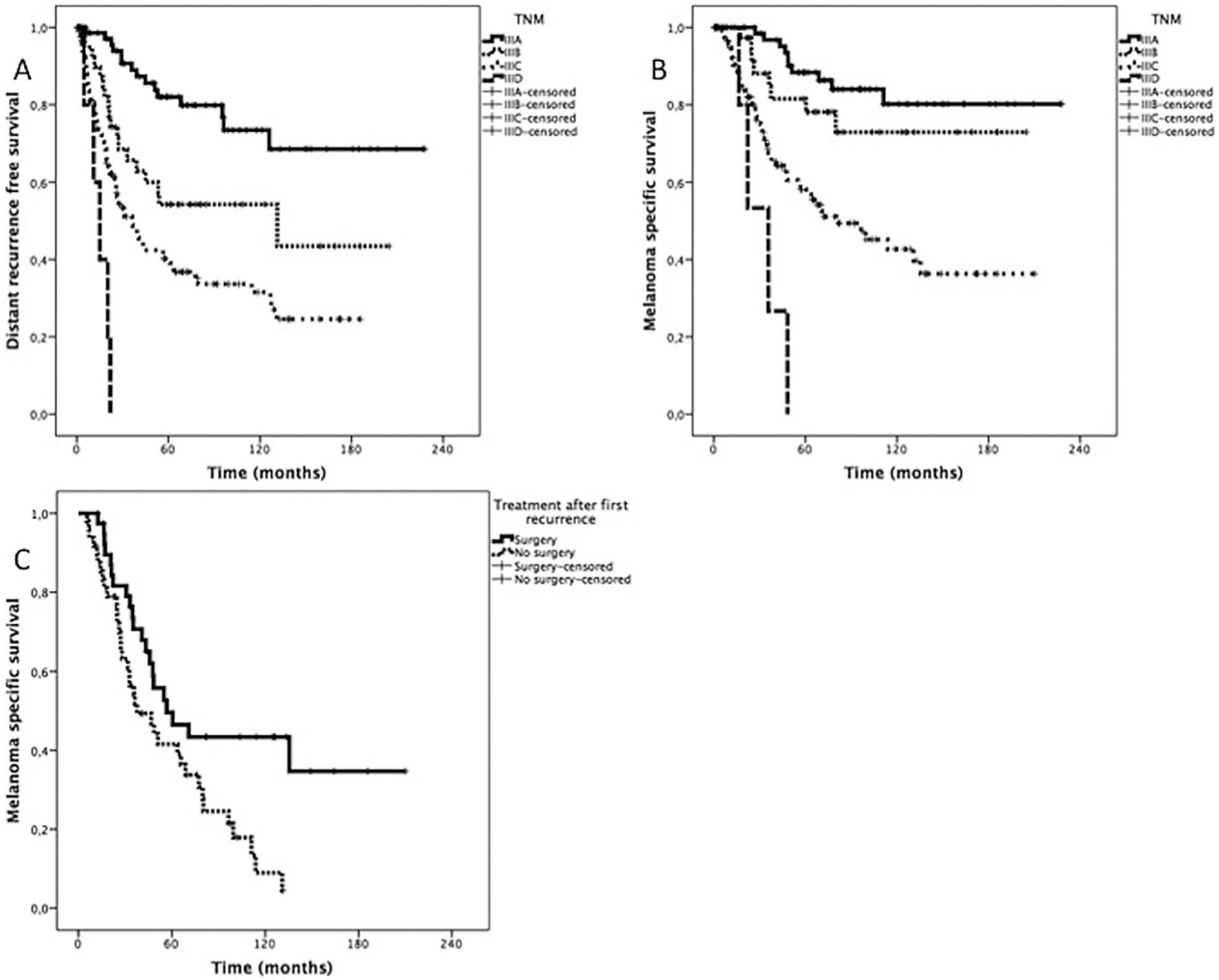

Figure 2. Kaplan Meier curves for A) Distant recurrence free survival according to TNM staging (log rank < 0.0001); B) Melanoma specific survival according to TNM staging (log rank < 0.0001) and C) Melanoma specific survival according to treatment after first recurrence (log rank 0.008).

The benefit of adjuvant treatment is unequivocal. However, observing the relapse-free survival (RFS) curves from the pivotal trials of adjuvant treatments (22–24) may provide valuable information. On one hand, around 25% of patients will relapse during the first twelve months of IO regimen, which means recurrence during treatment. On the other hand, relapses happen in less than 10% of patients while receiving adjuvant TT.

Recent data shows benefit in changing treatments after initial failure, which is especially useful in BRAF mutated patients (6, 7). However, the ideal approach for BRAF wild type patients that relapse while or after receiving anti – PD1 is still controversial. Moreover, managing patients that are not amenable to receive adjuvant treatments can be even more difficult.

Several studies have focused on the surgical approach for melanoma recurrences, but most of them have the weakness of patient selection bias (25), which has probably also happened in our cohort, since salvage surgery was performed more commonly in patients with cutaneous and nodal metastasis (63.6%), who are often patients with low disease burden (Figure 2C). Nonetheless, recurrences after salvage surgery were observed in our patients regardless of the site where it was performed. It is also reported in other studies, which suggests that this approach is not enough in several cases (7).

The association of surgical and systemic therapies after relapse seems adequate according to recent reports and it can be found in current guidelines (2, 12, 26). The next step would be

how to better define the order of this multimodal approach (2).

For BRAF mutated patients after a positive SNB, nodal surveillance associated to adjuvant treatment with TT should be strongly considered, since it is expected low recurrence rates during the treatment itself (24). Besides that, recurrences could be managed changing treatment to IO, which has shown response rate over 60% (6). Surgery may be also considered just after recurrence, followed by adjuvant IO as observed in some patients of the Checkmate 238 trial (23).

For BRAF wild type patients it would be necessary a better risk stratification before deciding on the management. For low-risk patients, such as stage IIIA with metastatic deposits <1 mm after SNB, exclusive surveillance could be a reasonable option (27). It would minimize the toxicity of adjuvant treatment and, in case of nodal relapse, surgery could be offered without prejudice regarding outcomes (21). An unexpected systemic recurrence could be treated with anti PD-1 alone or associated with anti-CTLA4 as first line therapy (28).

For high-risk BRAF wild type patients, especially regarding nodal recurrence, CLND is still an option performed by some surgeons according to recent reports in literature (29) and should be considered to these patients, even though a lot has already been discussed regarding immediate CLND after a positive SNB (3–5). This proposal should not be seen as a curative approach, but as a strategy to avoid or to postpone recurrences during adjuvant treatments. Nodal exclusive recurrence was observed in 12.7% of the MDACC cohort of patients (receiving adjuvant treatment without CLND) (8) versus 1,6% in our data (after CLND), which suggests that some patients might benefit from a nodal clearance either before starting adjuvant immunotherapy or undergoing follow-up. Statistical tools for better identifying these patients might be valuable (19, 30).

The rationale for lymphadenectomy also applies for salvage metastasectomy, when feasible (12, 25, 26). Surgery should be considered for patients with no access to adjuvant treatments – such as the patients in our study, after treatment failure or patients who are not suitable for the expected toxicities of treatments.

We have demonstrated that stage III melanoma patients after a positive SNB are at risk for recurrence and, when it happens, multimodal management is recommended. A single center observation can be considered a weakness of this study. However, it was possible to evaluate patients with aggressive melanomas during a period of time that some treatment options were not available. Unfortunately, this limitation of resources is still observed in many places nowadays, which should strengthen our findings (14). Further studies evaluating patients that have undergone these new therapeutic strategies may allow us to perform more robust analysis and deliver stronger and practice changing conclusions.

Until better risk stratification tools are available (31, 32) the management of stage III melanoma patients after a positive SNB remains very challenging. The outcomes presented in this study, following what is currently reported in the literature, support the use of multimodal strategies discussed in multidisciplinary boards as a way to achieve better results for those patients.

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