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OPINION PAPER

NEW CLINICAL NEEDS IN MELANOMA STAGING: IS THERE STILL ROOM FOR SINGLE LYMPH NODE EXCISION?

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ABSTRACT: the presence of metastatic cells in the first draining lymph node is crucial for staging melanoma, traditionally treated by the removal of the regional nodal basin until few years ago. The results of some prospective studies of surgical strategy and the introduction of immunotherapy and targeted therapy has significantly changed clinical practice, reshaping the role of lymph node dissection. Single Lymph Node Biopsy (SLNB) is now used for accurate staging with less invasive surgery, aiding in identifying patients who may benefit from adjuvant therapy. The aim of this review is to enlighten the needs perceived during everyday clinical practice. Prognostication in melanoma is still a challenge, with serum lactate dehydrogenase (LDH) as the only biomarker. Elevated LDH levels correlate with worse outcomes in advanced melanoma.SLNB time and curative role are debated, with studies suggesting that the timing of SLNB may influence outcomes and that SLNB has limitations in predicting mortality, especially in different age groups. The use of precision medicine tools like circulating tumour DNA (ctDNA) tests and the emerging role of neoadjuvant immune checkpoint inhibitors (ICI) are improving outcomes.
While SLNB still remains fundamental, further research is needed to identify which patients' subgroups benefit the most from it.

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IMPACT STATEMENT: This article challenges conventional melanoma staging by reintroducing single lymph node excision as a selective tool in modern practice. It proposes refined clinical criteria for its use, aiming to guide oncologists toward more personalized and pragmatic staging decisions in the era of precision oncology.

Key words: *melanoma; SLNB; surgery; biomarkers; clinical needs.*

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INTRODUCTION

The presence of metastatic dissemination in the first draining lymph node of a melanoma is an essential element for correct staging according to international guidelines (1). For decades, the most common initial route for metastatic spread has been recognized as the lymphatic drainage of the primary lesion. Over the last few decades, studies on surgical strategy and the revolutionary therapeutic introductions of immunotherapy and targeted therapy have reshaped the role of lymph node dissection and transformed survival rates in both adjuvant and metastatic settings (1).
Results from the Multicenter Selective Lymphadenectomy Trial II (2) have clearly demonstrated that there is no survival advantage from complete lymph node dissection when compared to ultrasound surveillance of the locoregional district. The concept of the Single Lymph Node Biopsy (SLNB) was developed for

melanoma by D.L. Morton in the late 1980s, based on earlier lymphoscintigraphy studies.

The benefits of this procedure include more accurate staging of the regional node, combined with less invasive and morbid surgery. According to current guidelines, SLNB can help identify patients with at least pT1b melanoma who may benefit from adjuvant therapy. In histopathological procedures, SLNB positivity rates vary, with a reported false-negative rate as high as 10% (3).

Following the excellent results from the Checkmate 238, Keynote-054, and COMBI-AD trials in 2018, adjuvant treatment has become standard clinical practice for patients with stage III melanoma (4, 5). Furthermore, Pembrolizumab has demonstrated significant improvements in both Relapse-Free Survival (RFS) and Distant Metastasis-Free Survival (DMFS) in pivotal adjuvant trials for stage IIB/C disease, making these stages eligible for adjuvant therapy (6). New therapeutic options are emerging following the excellent results from the phase 3 NADINA trial (7) and the randomized phase 2 SWOG S1801 trial. These trials are clearing a path for the implementation of neoadjuvant (Nivolumab + Ipilimumab) or perioperative (Pembrolizumab) regimens for stage III melanoma patients with clinical evidence of lymph node dissemination or satellitosis.

This review aims to highlight the needs perceived in everyday clinical practice.

CLINICAL PATHOLOGICAL FEATURES, BIOMARKERS, AND GENE EXPRESSION PROFILING

Do we have reliable biomarkers for melanoma prognostication? Currently, lactate dehydrogenase (LDH) is the only biomarker consistently associated with prognosis in melanoma (8). Several studies have suggested that a baseline elevation of serum LDH (sLDH) is associated with poorer treatment outcomes in patients with stage IV metastatic melanoma (24). In a study by Fischer *et al.* (9), molecular and immunological characteristics were not significantly associated with sLDH status. It is possible that sLDH is associated with worse outcomes primarily as a surrogate for tumour burden, as a strong correlation was found with the number of metastatic sites (9). However, some multivariate analyses have provided evidence that sLDH is associated with poorer outcomes independent of tumour burden (9).

Dutriaux *et al.* (10) found a similar correlation between higher levels of sLDH and decreased Progression-Free Survival (PFS) and Overall Survival (OS) in patients with advanced BRAFV600-mutant melanoma and brain metastases who were treated with targeted therapy. Additionally, sLDH levels may differ among patients with stage IV metastatic melanoma due to variations in the extent of organ damage and the influence of comorbidities (8, 9).

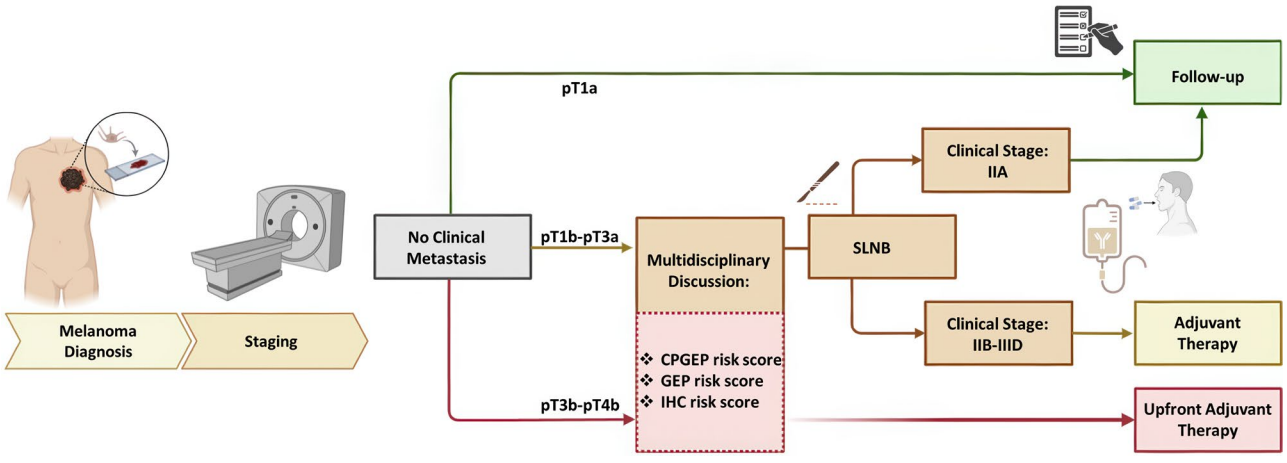

Figure 1. *Melanoma staging and treatment according to anatomopathological T stage features.*
The absence of clinical metastasis determines a pivotal juncture in the therapeutic management of the patients, to date pT1a patients are candidate to periodic follow-up, on the other hand pT1b-pT3a and pT3b-pT4b patients are multidisciplinary discussed to receive sentinel lymph node biopsy to define a clinical IIA, resulting in clinical follow-up, or IIB-IIID stage, leading to adjuvant therapy. In the recent future, it is hypothesized a different management for pT3b-pT4b patients based on the CPGEP, GEP and IHC risk scores (dashed square), which could allow to avoid SNLB and to an upfront adjuvant therapy. Immunohistochemistry (IHC), clinicopathological and gene expression profile (CPGEP) gene expression profile (GEP), sentinel lymph node biopsy (SNLB).

Some studies have also revealed that an Interferon-gamma (IFN-γ) signature can be useful in distinguishing patients at high risk of recurrence from those at low risk (11). Immunotherapies engage the immune system to target and eliminate cancer cells and can stabilize malignancies until immune escape mechanisms lead to progression. A long-term follow-up of the KEYNOTE-001 trial revealed that 12% of the 105 melanoma patients who were initially classified as having a complete response after anti-PD-1 treatment eventually had detectable disease in their serum, suggesting their tumours were held in a state of clinically undetectable equilibrium (11).

IFN-γ signalling is critical for the early response to checkpoint blockade, and inactivating IFN-γ sensing in tumour cells promotes resistance to immunotherapy (11). It is hypothesized that IFN-γ inhibits tumour growth and promotes CD8+ T cell-directed responses through improved antigen presentation. However, the long-term role of IFN-γ remains unknown because biopsies cannot be obtained when patients have clinically undetectable disease (11). Moreover, IFN-γ has negative feedback mechanisms that can, in some cases, promote tumour growth (11).

In a preclinical study, the viral expression of IL-12, a cytokine able to stimulate IFN-γ production and enhance the growth and cytotoxicity of natural killer (NK), CD8, and CD4 T cells, was found to "freeze" melanoma-bearing mice, with mice lasting over 120 days, neither clearing nor succumbing to their tumours (11). Consistent with the importance of IFN-γ in that model of equilibrium, transcriptomic data from The Cancer Genome Atlas (TCGA) were analysed, and a positive association was found between IL-12, IFN-γ -stimulated gene expression, and increased survival in melanoma patients. It was observed that, indeed, melanoma patients with higher expression of IFN-γ response genes fared better than patients with lower expression (11). In a study from Versluis *et al.* the role of IFN- γ signature was compared between an observation cohort and an adjuvant intention cohort. In both arms, better RFS were achieved in patients with high IFN-γ score (12). Another study from Long *et al.* (13) evaluated molecular and biochemical characteristics of patients who underwent adjuvant treatment with Nivolumab *vs* placebo in IIB/IIC stage melanoma, finding that better RFS was linked to higher IFN-γ signature, tumour mutational burden (TMB), and percentage of CD8+ T cells, and lower C reactive protein (CRP) levels. Despite what had been found in other cited studies, in this work, molecular biomarkers were not associated with RFS in patients who underwent a placebo treatment. In a study in which a biomarker-based signature was retrospectively analysed in patient treated with dabrafenib plus trametinib versus placebo in the COMBI-AD trial (14), a correlation between higher IFN-γ gene expression signature and prolonged RFS was found in both groups. Patients with low TMB had a substantial long-term RFS benefit from targeted therapy. Conversely, patients with high TMB seem to have a less pronounced benefit, especially if they had an IFN-γ signature lower than the median (14).

SURGICAL TIMING OF SLNB AND ITS CURATIVE ROLE

Given that there are no consensus guidelines on the optimal timing for performing SLNB in high-risk melanoma patients (**Figure 1**), a study involving 53,355 patients who underwent the procedure found that surgery was performed a median of 5-7 weeks after diagnosis (15). The study also revealed that for each week of delay, the probability of finding a positive node increased by 2.4%. Furthermore, patients with a higher Breslow depth index showed a significant increase in nodal positivity with increased time to surgery, although no significant trend was observed in T4 patients (15).

A study by Dixon *et al.* sought to evaluate the efficacy of SLNB in predicting mortality in melanoma patients at different ages, using data from the Tubingen University Database for patients who underwent SLNB between January 2000 and December 2014. The results showed that predicted SLNB-positive rates were significantly higher than mortality rates for 20-year-old patients, while the opposite was true for 80-year-old patients. This study highlights the limitations of SLNB in predicting mortality, suggesting it may lead to the overtreatment of younger patients and undertreatment of older patients (15).

In a multicentre international study by Moncrieff *et al.* (16), patients with pT1b-pT2a melanoma were analysed. This group has a reportedly low risk of a positive SLNB (10%), and even when a positive node is found, the 5-year survival rate for stage IIIA melanoma is 90% (16). The study, which included 3,610 patients with early primary cutaneous melanomas, found that only 11.4% had a positive SLNB, and the only clinical and histopathological characteristic associated with SLNB positivity was a mitotic rate greater than 1/mm^2. The authors concluded by sug-

gesting a re-evaluation of the indication for SLNB in early T-stage melanoma (16).

Another study from Kakish *et al.* tried to investigate the association of SLNB and survival in the elderly. What emerged from this retrospective study is that SLNB still adds prognostic information for elderly patients with melanoma and should not be eliminated in this population unless justified by poor performance status or patient preference. In the analysed cohort the decreasing in SLNB performance could correlate with a lack in the therapeutic offer for elderly melanoma patients (17). By quantifying the prognostic role of SLNB (18), Varey and colleagues found that the risk of regional node field relapse with SLNB plus adjuvant IO for T3b and T4 is around 9 *vs* 27% in all cases in which patients did not undergo surgery. Similarly, the node field recurrence rate with SLNB alone is around 14% compared to around 40% in patients in which both IO and surgery were not performed. Thus, in this setting of patients, SLNB should always be performed, improving the locoregional control of disease.

In Keynote 716 there was the possibility to undergo adjuvant therapy in stage IIB-IIC patients. This meant that even without nodal involvement, patients with melanomas characterized by a bad pathological T stage had the chance to lower the possibilities of recurrence (19).

This can lead to arguing the role of SLNB if all patients with a T stage between pT3b and pT4b, independently if with or without lymph nodal dissemination, will be recommended to undergo adjuvant treatment.

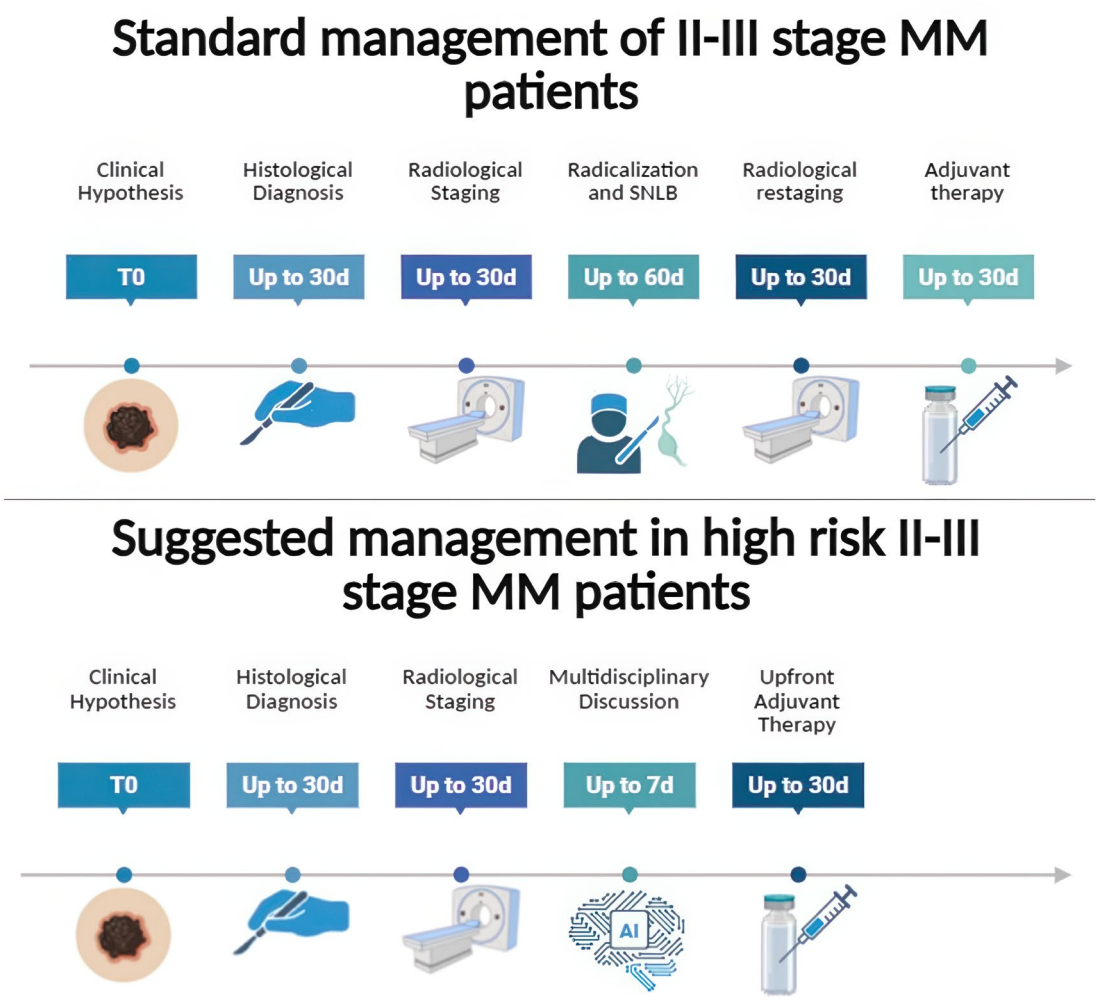

Figure 2. *Timeline of Events in clinical practice and in our proposed schedule.*
In high risk II-III stage MM patients, assessed via multidisciplinary discussion according to CP-GEP characteristics of primary excised lesion, we propose a different schedule of events compared to the Standard of Care. These patients should cut all the time and costs linked to radicalization, SLNB and radiological restaging, harbouring to an upfront adjuvant treatment.

Moreover, there is the necessity of underlining the role of lymphatic drainage pattern that can vary between patients, leading us to a possible false negative SLNB, as enlightened in a study from Cirocchi *et al.* (20), in which there was an important heterogeneity in the localization of the SLNB, in particular in the regions of posterior torso.

REAL-WORLD CLINICAL CHALLENGES

Therefore, the central question remains: to biopsy or not to biopsy? As the studies cited above demonstrate, the exact characteristics of the population that requires this locoregional treatment are not yet fully known. In the future, we will not blindly select all patients based on the characteristics mentioned in the guidelines. Instead, the focus should be on the characteristics appropriate for the individual patient, which will provide clearer information about the likelihood of locoregional or distant metastasis during active oncologic surveillance over 5 to 10 years.

The emerging role of precision medicine has led to studies investigating the use of personalized tests such as Signatera (21). This involves whole-exome sequencing of both tissue and peripheral blood to target patient-specific single nucleotide variants (SNVs), which can then be used to track circulating tumour DNA (ctDNA) in plasma (21). This tool shows promise in identifying high-risk primary melanoma patients under surveillance after resection to detect disease recurrence (21). Of course, other important data, such as the patient's working conditions, medical history, and clinicopathologic features like the Breslow index, must not be overlooked. All of these features are incorporated into predictive algorithms, such as the CP-GEP test Merlin or the GEP test MelaGenix, which will soon help us better identify the high-risk population for recurrence that should be selected for surgical intervention (21).

Another issue to consider is the integration of neoadjuvant or perioperative immune checkpoint inhibitors ICI treatments, as seen in the NADINA trial (7). Neoadjuvant ICIs have been shown to provide superior outcomes compared to approved adjuvant treatments, with a 2-year RFS of around 70-80% after two cycles of neoadjuvant Ipilimumab plus Nivolumab followed by surgery. In these trials, only patients who were non-responders or had a partial response received adjuvant treatment (7). When upfront systemic therapy leads to resectability, trials for advanced unresectable melanoma demonstrate better survival compared to ultimate systemic treatment (1). Therefore, ICIs for preoperative melanoma treatment have the potential to enhance patient outcomes and are likely to reshape the principles of treatment for both advanced and localized melanoma.

CONCLUSIONS

Currently, SLNB remains a crucial procedure for identifying individuals who can benefit from adjuvant therapy by providing precise staging with less invasive surgery. In this work, we have shed light on the clinical needs encountered in everyday practice. With LDH as the only established biomarker, melanoma prognosis remains difficult to assess. The curative role of SLNB must be re-evaluated. Even with potentially perfect timing, the inconsistency in predicting the usefulness of single lymph node excision is becoming evident, and it can also be seen as a hurdle between the patient and the start of adjuvant therapy. The application of precision medicine technologies, such as ctDNA assays, CP-GEP assessment, and the emerging role of neoadjuvant ICIs) is poised to redefine clinical node management.

What emerges from this work is the urgent need to find a new role for node sampling. Patients who would undergo adjuvant treatment with or without SLNB should be assessed with the aforementioned precision medicine tools in multidisciplinary discussions at high-volume centres, ensuring the best clinical practice for every single patient. In this way (**Figure 2**), we could reduce costs and time for national healthcare systems, avoiding surgical overtreatment for patients who would be treated regardless, and in other cases, avoiding unnecessary medications for patients with a low risk of recurrence for whom SLNB alone might be sufficient.

COMPLIANCE WITH ETHICAL STANDARDS

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Conflict of interest

TT has been advisor for Amgen and Novartis, BMS for Roche, Servier, Pierre Fabre, M.S.D.

Availability of data and materials

The data supporting the findings of this study are available upon reasonable request to the corresponding author.

Authors' contributions

Conception and design: FC, TT. Administrative support: AC, MF. Provision of study materials or patients: AE, MCG. Collection and assembly of data: VDF, FC, AC. Data analysis and interpretation: VDF, FC, AC, TT. All authors have contributed to the writing and the final approval of the manuscript.

Ethical approval

N/A.

Human studies and subjects

N/A.

Animal studies

N/A.

Publications ethics

The publication ethics followed by this study align with those outlined by the International Committee of Medical Journal Editors (ICMJE), regarding publishing and editorial issues in medical journals.

Plagiarism

The article provides a comprehensive review of the latest studies in the field, with accurate citations.

Data falsification and fabrication

The writing and contents of the article are entirely original and were developed entirely by the authors.

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