v. 4, n. 50, 2024

International Journal of Health Science

# DIAGNOSTIC ADVANCES IN CUTANEOUS MELANOMA: INTEGRATING TECHNIQUES AND MARKERS FOR ACCURATE DETECTION OF METASTASES

***Ana Leticia Rabelo***
Faculdade de Medicina de Jundiaí (FMJ)
Jundiaí - SP

***Marina Silva Prado***
Faculdade São Leopoldo Mandic (FSL Mandic)
Campinas - SP

***Lara Bardella Caldeira***
Universidade de Marília (UNIMAR)
Marília - SP

***Angélica Lupinacci de Araújo Santos***
Universidade de Marília (UNIMAR)
Marília - SP

***Natália Rufino***
Centro Universitário de Jaguariúna (UniFaJ)
Jaguariúna - SP

***Fernanda Dourado***
Faculdade de Medicina Nova Esperança (FAMENE)
João Pessoa - PB

***Júlia Tamiozzo Benini***
Universidade Paranaense (UNIPAR)
Umuarama - PR

***Julia Lopes Hemza***
Universidade Anhembi Morumbi (UAM)
São Paulo – SP

***Isa Glenda Oliveira da Rocha***
Escola Bahiana de Medicina e Saúde Pública (EBMSP) Salvador - BA

***Amanda Tollini de Moraes***
Faculdade de Medicina de Bauru da Universidade de São Paulo (USP)
Bauru - SP

***Lara de Almeida Peralta***
Faculdade de Medicina de Petrópolis (FMP)
Petrópolis - RJ

***Marianne Ritter Afonso***
Universidade de Marília (UNIMAR) Marília - SP

**Abstract:** This study presents an integrative review focused on diagnostic methods to detect metastases in cutaneous melanoma, emphasizing advanced imaging techniques, molecular markers and recent technological advances. A systematic search was conducted in the PubMed database, resulting in 79 relevant studies. After inclusion and exclusion criteria, five studies were selected for analysis. The review highlights the importance of histological features in predicting micrometastases in sentinel lymph nodes, emphasizing the significance of risk stratification in patients with stage IIIA melanoma with micrometastases, highlighting the role of advanced imaging techniques such as PET and MRI. Predictors of metastases in non-sentinel lymph nodes in cutaneous melanoma depend on the integration of molecular markers and imaging techniques in risk assessment.
**Keywords:** Cutaneous melanoma; Diagnostic methods; Metastases.

## INTRODUCTION

Cutaneous melanoma is the most lethal skin cancer, accounting for a high mortality rate among primary skin cancers. The accuracy of diagnosis at an early stage is crucial, as early stages of melanoma have a good prognosis and are potentially treatable with surgery alone. On the other hand, advanced stages exhibit a much worse prognosis, with high rates of recurrence and metastasis. Therefore, accurate and early diagnoses are essential to improve patients' chances of survival, significantly reducing the risks associated with incorrect diagnoses. In addition to histological examination, which remains the "gold standard" for diagnosing cutaneous melanoma, immunohistochemistry has proven to be a valuable tool, with an increasing number of markers being identified and incorporated into clinical practice (Ricci et al., 2022).

Micrometastasis plays a critical role in the progression of cutaneous melanoma, being generated earlier than previously thought. Recent studies highlight the importance of a more comprehensive approach to cancer staging that considers the burden of cancer cells in different tissue compartments. Early detection of micrometastases, through advanced imaging technologies and other diagnostic tools, can revolutionize the management of cutaneous melanoma, allowing for earlier and more personalized interventions. This perspective has significant implications for clinical practice, suggesting the need to update cancer staging systems and take a more holistic view in approaching high-risk cancers (Sinclair et al., 2024).

The development and progression of cutaneous melanoma involves malignant transformations of melanocytes, cells responsible for producing pigment in the skin. Understanding the etiology and pathogenesis of cutaneous melanoma is essential for developing more effective diagnostic strategies. Research continues to explore the factors that contribute to the emergence and progression of melanoma, providing a basis for improving diagnostic methods and therapeutic approaches (Strashilov & Yordanov, 2021; Laudicella et al., 2020).

This integrative review aims to analyze diagnostic methods for detecting cutaneous melanoma metastasis, focusing on imaging techniques, molecular markers and recent technological advances. By synthesizing existing literature and identifying gaps in current knowledge, this review aims to provide a basis for future research and improvements in clinical practice, with the aim of improving outcomes for patients with cutaneous melanoma.

## METHOD

PubMed databases were searched using relevant search terms such as "cutaneous melanoma", "diagnosis of metastasis", "imaging techniques" and "molecular markers". The search was restricted to studies published in English and without date restrictions. After the initial search, 79 relevant studies were identified. These studies were then evaluated based on predefined inclusion and exclusion criteria. Inclusion criteria may have included studies that specifically address diagnostic methods for cutaneous melanoma and studies that investigate imaging techniques, molecular markers, and related technological advances. Exclusion criteria may have included studies that did not fit the research question or studies that were not available in full text.

After selecting the studies, relevant data were extracted and synthesized. This may include information about the characteristics of the studies, methods used, results and conclusions reached. Study synthesis involves organizing and integrating data to identify patterns, trends, and gaps in the literature. Of the 79 studies initially identified, five final studies were selected based on their relevance, methodological quality and contribution to answering the research question (Figure 1.0). These five studies represent a representative sample of the available literature on the topic and were used to inform the final conclusions of the integrative review.

## RESULTS

The integrative review includes six studies that addressed different aspects of the detection of micrometastases in sentinel lymph nodes, prognostic factors and survival outcomes in patients with cutaneous melanoma (**Table 1.0**).

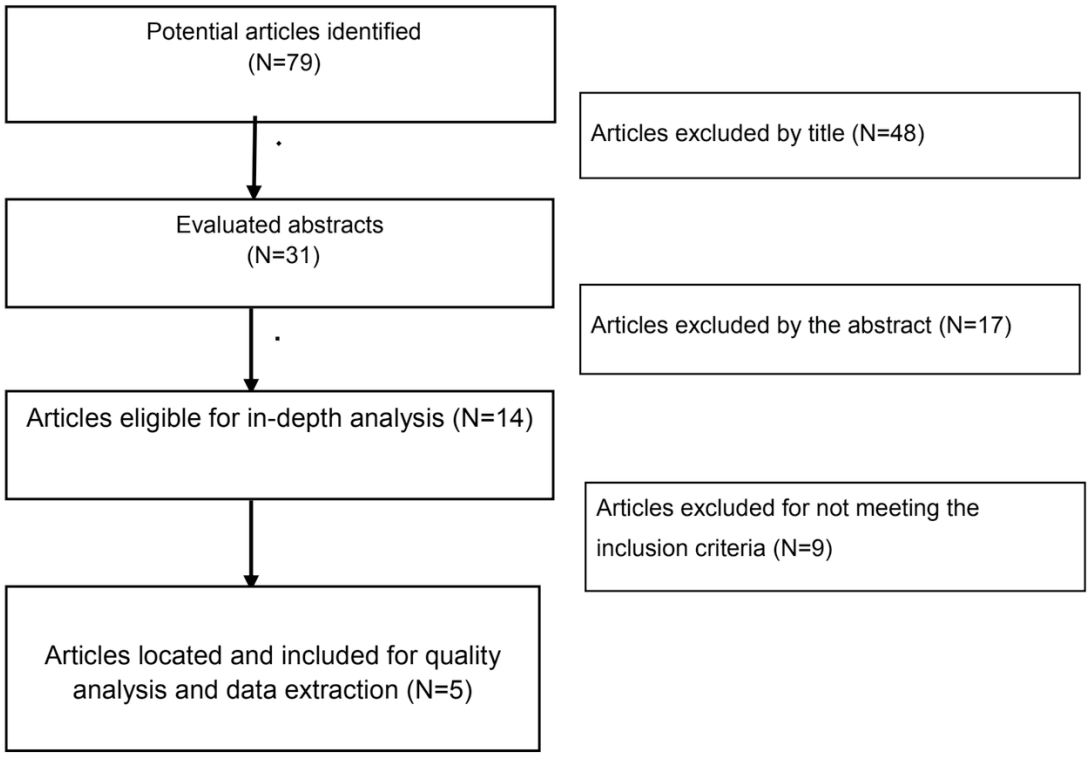


Figure 1.0: Flowchart of the distribution of articles found and selected.

Source: Rabelo AL et al. (2024)

| Study | Kind of study | Patients | Results |
|---|---|---|---|
| **Moncrieff et al., 2022** | Multicenter analytical study. | 3,607 patients with primary cutaneous melanomas | SLN tumor deposit of 0.3 mm as an ideal cutoff for survival stratification. Five-year disease-specific survival rates were 80.3% (≥ 0.3 mm) and 94.1% (< 0.3 mm). |
| **Hellmich et al., 2021** | Comparative analytical study. | 132 SLNs from 104 patients diagnosed with melanoma. | Flow cytometry exhibited a sensitivity of 50% and specificity of 85%. 8-fold flow cytometric DCCD in SLNs with high tumor burden. |
| **Rajaee et al., 2021** | Systematic review and meta-analysis. | 50 studies analyzed. | Risk factors: age >50, stage T 3 or 4, Clark level IV/V, ulceration, microsatellite, lymphovascular invasion, nodular histology, location of the primary tumor. |
| **Pallara et al., 2023** | Retrospective study. | 1,200 melanoma patients underwent SLN biopsy. | 38 cases (3.2%) with negative lymphoscintigraphic scan. Older NV group with more frequent head and neck melanomas. |
| **Woeste et al., 2021** | Retrospective cohort study. | 2,305 patients with stage IIIA melanoma. | N2a was an independent risk factor for worse OS. Significant difference in OS for patients undergoing SLN biopsy plus CLND |

**Source:** Rabelo AL et al. (2024)

## DISCUSSION

The studies by Hellmich et al. (2021) and Rajaee et al. (2021) address the detection of metastases in melanoma, but focusing on different methods and predictors. Hellmich et al. explore the application of flow cytometry in the rapid quantification of melanoma cells in SLN, showing a significant positive correlation with immunocytology, especially in cases of high tumor burden. Although the sensitivity of flow cytometry still needs to be improved for early detection of micrometastases, its findings are promising. In contrast, Rajaee et al. identify predictors of non-sentinel lymph node metastases (NSNM) through a systematic review and meta-analysis, highlighting clinical and tumor factors such as age, tumor stage and specific characteristics of the SLN. Both studies highlight the importance of advanced imaging techniques, such as PET and MRI, in the early detection of metastases.

Moncrieff et al. (2022) emphasizes the importance of risk stratification in patients with SLN micrometastases from stage IIIA melanoma, highlighting the need to identify those who would benefit most from adjuvant systemic therapy. This international multicenter study, involving 3,607 patients, demonstrated that the maximum dimension of SLN tumor deposits of 0.3 mm is a critical cutoff for survival, with specific survival rates of 80.3% for deposits ≥ 0.3 mm compared to 94.1% for deposits < 0.3 mm. This finding underlines the effectiveness of advanced imaging techniques, such as PET and MRI, which are essential for detecting minute tumor deposits with greater precision.

Hellmich et al. (2021) highlights the potential application of flow cytometry in the rapid quantification of melanoma cells in SLN. In a group of 104 patients with melanoma, flow cytometry was used to detect the melanoma-associated chondroitin sulfate proteoglycan, demonstrating a sensitivity of 50% and specificity of 85% compared to traditional histopathology and immunocytology methods.

Although flow cytometry is not yet sensitive enough for early detection of micrometastases, it showed a significant positive correlation in disseminated cancer cell density (DCCD) with immunocytology (Spearman's $\rho = 0.7$, $P < 0.0001$), especially in cases of high tumor burden, where DCCD was significantly higher. This advancement is complemented by advanced imaging techniques, such as MRI and PET, which continue to be fundamental for visualizing early-stage metastases.

According to Rajaee et al. (2021), who carried out a systematic review and meta-analysis, it was possible to identify predictors of metastases in non-sentinel lymph nodes (NSNM) in patients with cutaneous melanoma. The results showed that clinical and tumor factors, such as age over 50 years, stage T3 or T4, Clark level IV/V, ulceration, microsatellites, lymphovascular invasion, nodular histology and location of the tumor in the extremities compared to the trunk, are consistent predictors of NSNM. Furthermore, specific features of the SLN, such as the presence of more than one positive SLN, micrometastatic tumor burden, diameter greater than 2 mm, extracapsular extension, and non-subcapsular location, have also been identified as significant risk factors. These findings underscore the need for advanced imaging techniques such as MRI and PET, which are crucial for detecting metastases at early stages.

Pallara et al. (2023) examined the effectiveness of preoperative lymphoscintigraphy in detecting SLN in patients with cutaneous melanoma, identifying that failure to visualize the SLN is more common in older patients and with head and neck melanomas. This technical limitation did not significantly influence

overall survival (OS) or disease-free survival (DFS), suggesting that the absence of SLN visualization must not be immediately interpreted as a poor prognosis. However, this finding underscores the need for close surveillance, potentially using ultrasound to monitor all possible lymphatic drainage basins.

In addition to imaging techniques, specific molecular markers, such as melanoma-related messenger RNA expression, and advances such as flow cytometry for quantifying tumor cells, as well as liquid biopsy for detecting circulating tumor cells, offer less invasive and more sensitive to monitor disease progression.

The study by Woeste et al. (2021) reveals that the presence of multiple positive lymph nodes (N2a) in patients with stage IIIA melanoma is associated with worse overall survival (OS) compared to the presence of just one positive lymph node (N1a). This distinction is crucial for personalizing adjuvant therapy recommendations, suggesting that the extent of micrometastatic lymph node disease must be carefully considered. Advanced imaging techniques, such as MRI and PET, are critical for early and accurate detection of metastases. Technological advances, including flow cytometry for quantifying tumor cells and liquid biopsy for detecting circulating tumor cells, offer less invasive and more sensitive methods for monitoring melanoma progression.

These methods complement traditional approaches and allow for more rigorous monitoring, especially in cases where preoperative lymphoscintigraphy does not visualize lymph nodes, as observed by Pallara et al. (2023). The integration of these advanced techniques allows for a more detailed and earlier assessment of metastatic spread, facilitating more precise therapeutic interventions and potentially improving the clinical outcomes of patients with cutaneous melanoma.

## FINAL CONSIDERATIONS

Considering the results of the studies analyzed, it becomes clear that the detection of metastases in cutaneous melanoma requires a comprehensive approach that integrates several diagnostic techniques.

The research highlights the importance of histological features, risk stratification and the use of advanced imaging techniques, such as high-resolution ultrasound, PET MRI, for accurate detection of micrometastases and appropriate therapeutic intervention. Furthermore, the application of molecular markers and technological advances, such as flow cytometry and liquid biopsy, promises to improve diagnostic sensitivity and enable less invasive monitoring of disease progression. Taken together, these advanced approaches provide a more detailed and earlier assessment of metastatic spread, which may result in more precise therapeutic interventions and, potentially, better clinical outcomes for patients with cutaneous melanoma.

## REFERENCES

1. Hellmich L, Witte KE, Ebinger M, Ulmer A. Flow Cytometry for Detection and Quantification of Micrometastases in Sentinel Lymph Nodes from Patients with Primary Melanoma. J Surg Res. 2021; 257:477-485.

2. Laudicella R, Baratto L, Minutoli F, Baldari S, Iagaru A. Malignant Cutaneous Melanoma: Updates in PET Imaging. Curr Radiopharm. 2020;13(1):14-23.

3. Moncrieff MD, Lo SN, Scolyer RA, et al. Clinical Outcomes and Risk Stratification of Early-Stage Melanoma Micrometastases From an International Multicenter Study: Implications for the Management of American Joint Committee on Cancer IIIA Disease. J Clin Oncol. 2022;40(34):3940-3951.

4. Mraz-Gernhard S, Sagebiel RW, Kashani-Sabet M, Miller JR 3rd, Leong SP. Prediction of sentinel lymph node micrometastasis by histological features in primary cutaneous malignant melanoma. Arch Dermatol. 1998;134(8):983-987.

5. Pallara T, Annovazzi A, Cristiani R, et al. Nonvisualized sentinel node on preoperative lymphoscintigraphy in primary cutaneous melanoma: an 11-year retrospective survey. Nucl Med Commun. 2023;44(5):345-350.

6. Rajaee A, Sadr-Eshkevari P, McMasters KM, Egger ME. Predictors of Nonsentinel Lymph Node Metastasis in Cutaneous Melanoma: A Systematic Review and Meta-Analysis. J Surg Res. 2021;260:506-515.

7. Ricci C, Dika E, Ambrosi F, Lambertini M, Veronesi G, Barbara C. Cutaneous Melanomas: A Single Center Experience on the Usage of Immunohistochemistry Applied for the Diagnosis. Int J Mol Sci. 2022;23(11):5911.

8. Sinclair R, Wong XL, Shumack S, Baker C, MacMahon B. The role of micrometastasis in high-risk skin cancers. Australas J Dermatol. 2024;65(2):143-152.

9. Strashilov S, Yordanov A. Aetiology and Pathogenesis of Cutaneous Melanoma: Current Concepts and Advances. Int J Mol Sci. 2021;22(12):6395.

10. Woeste MR, McMasters KM, Egger ME. Stage IIIa Melanoma and Impact of Multiple Positive Lymph Nodes on Survival. J Am Coll Surg. 2021;232(4):517-524.e1.