Surgical Management of Head and Neck Cutaneous Melanoma: Regional Staging and Multidisciplinary Treatment of Locally Advanced Cases

Péter Lázár MD, DMD

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Péter Lázár MD, DMD

Supervisors:
Erika Gabriella Kis, MD, PhD, Associate Professor
Prof. József Piffkó, MD, DMD, PhD, Full Professor

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2 List of publications forming the basis of the dissertation

1. **Lázár P**, Molnár E.T., Bende B., Vass G., Baltás E., Paczona R., Varga E., Piffkó J., Kemény L., Oláh J., Kis E.G.
   Challenges in the Complex Management of Neglected Cutaneous Melanomas in the H&N Area: A Single Center Experience.
   Journal of Clinical Medicine, 2023 Feb 28;12(5):1910.
   IF: 4.5 Q1
2. **Lázár P**, Boa K., Mezőlaki N., Varga Z., Besenyi Zs., Baltás E., Varga E., Oláh J., Kis E.G., Piffkó J., Paczona R.
   Sentinel Node Biopsy for Head and Neck Melanoma: A 12-Year Experience from a Medium-Volume Regional Center.
   Journal of Clinical Medicine, 2026 Jan 17;15(2):763.
   IF: 4.5 Q1

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1. Ágoston D., Baltás E., Ócsai H., Rátkai S., **Lázár P**., Korom I., Varga E., Németh I.B., Dósa-Rácz Viharosné É., Gehl J., Oláh J., Kemény L., Kis E.G.
   Evaluation of Calcium Electroporation for the Treatment of Cutaneous Metastases: A Double-Blinded Randomized Controlled Phase II Trial.
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2. Paria S., Lapides R., Saravi B., Rajagopal A., Müller A., Kölblinger P., Wang-Evers E., Manstein D., Navarini A., **Lázár P**., Kemény L., Adhikari K., Németh I., Roider E.
   Acyl-CoA Synthetase Long Chain Family Member 4 (ACSL4): A Novel Prognostic Marker in Cutaneous Melanoma.
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   Surgical Management of Progressive Hemifacial Atrophy With De-Epithelialized Profunda Artery Perforator Flap: A Case Report.
   Journal of Oral and Maxillofacial Surgery, 2017 Mar;75(3):596–602.
2. Vörös A., Csörgő E., Kővári B., **Lázár P**., Kelemen G., Rusz O., Nyári T., Cserni G.
   Different Methods of Pretreatment Ki-67 Labeling Index Evaluation in Core Biopsies of Breast Cancer Patients Treated with Neoadjuvant Chemotherapy and Their Relation to Response to Therapy.
   Pathology and Oncology Research, 2015 Jan;21(1):147–155.

3. Vörös A., Csörgő E., Kővári B., **Lázár P**., Kelemen G., Cserni G.
   The Use of Digital Images Improves Reproducibility of the Ki-67 Labeling Index as a Proliferation Marker in Breast Cancer.
   Pathology and Oncology Research, 2014 Apr;20(2):391–397.

3 List of abbreviations

AJCC – American Joint Committee on Cancer

BRAF – B-Raf proto-oncogene

CLND – Completion lymph node dissection

CP-GEP – Clinicopathologic and gene expression profiling

CT – Computed tomography

END – Elective neck dissection

FDG-PET – Fluorodeoxyglucose positron emission tomography

FN – False negative

FNR – False-negative rate

FOR – False-omission rate

H&E – Hematoxylin and eosin

H&N – Head and neck

IFN – Interferon

IHC – Immunohistochemistry

LMM – Lentigo maligna melanoma

MEDSOL – Medical documentation system

MEK – Mitogen-activated protein kinase

MM – Malignant melanoma

MMS – Mohs micrographic surgery

MRI – Magnetic resonance imaging

MSLT – Multicenter Selective Lymphadenectomy Trial

NCCN – National Comprehensive Cancer Network

NM – Nodular melanoma

NPV – Negative predictive value

OS – Overall survival

PD-1 – Programmed cell death protein 1

RCT – Randomized controlled trial

RFS – Recurrence-free survival

SLN – Sentinel lymph node

SLNB – Sentinel lymph node biopsy

SPECT/CT – Single-photon emission computed tomography/computed tomography

TNM – Tumor, node, metastasis classification

US – Ultrasonography

WLE – Wide local excision

4 Introduction

4.1 Epidemiology

Cutaneous melanoma is a malignant tumor that develops from melanocytes in the basal layer of the skin [1]. Melanocytes are also found in the uvea of the eye and in mucosal tissues, so melanoma can also occur in these locations. However, uveal and mucosal melanomas usually have a more aggressive biological behavior and they require different treatment strategies [2]. Therefore, they are considered separate oncological entities. For this reason, this PhD thesis focuses only on cutaneous melanoma.

Melanoma mainly affects older age groups, and its incidence increases significantly from the fifth decade of life. This pattern is especially typical for melanomas developing on body areas exposed to chronic sun damage, such as the head and neck (H&N) region [3]. However, melanoma also affects younger age groups as well and represents a significant proption of cancer-related mortality among them. Epidemiological data show that H&N melanomas represent approximately 20% of all melanoma cases [4]. Chronic sun exposure plays an important role in melanoma development, but it is also associated with specific histological subtypes that occur more frequently in the sun exposed areas, such as lentigo maligna and lentigo maligna melanoma [5].

The incidence of melanoma has been continuously increasing in recent decades. The highest incidence has been reported in Queensland, Australia, mainly due to the high UV radiation and the large proportion of fair-skinned residents [3, 6]. In Europe, Switzerland and the Scandinavian countries show the highest incidence rates. This may be explained by periodically intense UV exposure, lifestyle-related factors, and successful screening programs [7].

In Hungary, melanoma incidence is higher than in the Central European region, and significant regional differences can also be observed within the country[8]. The city of Szeged has the highest annual number of sunshine hours in Hungary, which may contribute to the high incidence measured in this region (30 per 100,000 inhabitants).

Compared to other cancers, such as colorectal or breast cancer, melanoma incidence may seem relatively low at first glance [9]. However, due to its high mortality rate, melanoma represents a major public health concern. In the past, the prognosis of advanced-stage

melanoma was particularly poor. In recent years, new treatment options - including immunotherapy and targeted therapies - have led to a significant improvement in survival [10, 11]. Therefore, melanoma-specific mortality has decreased during the past decade despite the increasing incidence.

A unique and clinically important feature of melanoma is that—unlike many internal malignancies—it is visible on the skin. This is especially true for lesions in the H&N region. In theory, this should result in early recognition and rapid diagnosis. However, late diagnosis is still relatively common, even in visible body areas. Several factors may explain this discrepancy, including limited patient awareness, atypical clinical presentation, advanced age, fear of seeking medical care, and possible diagnostic errors [12].

These epidemiological characteristics highlight melanoma as a clinically relevant tumor type. Within cutaneous melanomas, H&N melanomas represent a distinct subgroup due to their specific biological behavior and clinical features, which will be discussed in the following chapters.

4.2 Head and Neck Melanoma - A Distinct Clinical Entity

H&N melanoma represents a distinct subgroup of cutaneous melanoma and is often regarded as a separate clinical entity. This distinction is related not only to the anatomical location but also to the different biological behavior and the specific diagnostic and therapeutic challenges associated with this complex region [4]. Numerous studies have demonstrated that the prognosis of H&N melanoma is generally worse than that of the melanomas arising on the trunk or extremities [13]. Therefore, accurate staging and individualized treatment are particularly important in this patient population.

The poorer prognosis of H&N melanoma is multifactorial. Contributing factors include the predominance of melanoma subtypes that are more difficult to recognize, the advanced age of patients, diagnostic delays, and the technical difficulties of both surgical and oncological management [14]. From a surgical perspective, wide local excision remains the cornerstone of melanoma treatment. However, achieving guideline-recommended margins in the H&N region is often challenging due to the proximity of important anatomical structures. In many cases, optimal margins cannot be achieved without compromising function or aesthetics [15].

Reconstruction of surgical defects is therefore complex and requires careful preoperative planning to balance oncological safety with acceptable functional and cosmetic outcomes [16].

Management of H&N melanoma is further complicated by the region's highly complex and variable lymphatic anatomy. The H&N region contains more than 300 lymph nodes and the drainage pathways are often multidirectional and unpredictable. Primary tumors frequently drain to multiple nodal basins, and sentinel lymph nodes may be located in surgically challenging areas, such as the intraparotid, retroauricular, or deep cervical regions [17].

SLNB is the most accurate method for detecting occult micrometastases in melanoma patients with clinically node-negative disease and represents the strongest independent prognostic factor in early-stage melanoma [18]. However, SLNB in the H&N region is technically more challenging than in other anatomical locations. This is partly due to the frequent presence of multiple sentinel lymph nodes and the potential "shine-through" effect caused by the close proximity of the primary tumor to the draining lymphatic basins. In addition, the complex regional anatomy makes it more difficult to identify and remove the deeply located lymph nodes or nodes situated within the parotid gland.

These challenges resulted in higher false-negative rates during the early implementation of SLNB in H&N melanoma compared with other anatomical sites, which has contributed to the persistent underutilization of the technique in this region [19, 20]. Consequently, many patients may not undergo proper, guideline-recommended staging, particularly outside high-volume tertiary centers.

Despite these early concerns, evidence demonstrates that SLNB in H&N melanoma can be performed safely and effectively in experienced centers [21]. When essential prerequisites are met—including advanced nuclear medicine imaging, standardized histopathological processing, and surgical expertise in H&N anatomy—the diagnostic performance of SLNB is comparable to other anatomical regions. In the era of modern adjuvant systemic therapies, the prognostic importance of lymph node status has further increased, as it directly influences patient selection for contemporary, guideline-based treatment.

In summary, H&N melanoma differs substantially from melanoma at other anatomical sites due to its poorer prognosis, specific surgical and reconstructive challenges, and highly variable lymphatic drainage patterns. Standard melanoma guidelines are often difficult to apply

directly in this region and therefore require individualized clinical care. Nevertheless, it is essential that patients have access to appropriate, evidence-based treatment, including in smaller or regional centers when referral to high-volume tertiary institutions is not feasible.

4.3 Melanoma staging

Melanoma management is fundamentally based on staging. The TNM classification system describes the status of the primary tumor (T), regional lymph nodes (N), and distant metastasis (M). It has become a key tool for defining prognosis in cutaneous melanoma. For many years, TNM has been used as a standardized classification system for the evaluation of the disease extent, prediction of survival outcomes, and for the design of clinical trials.

Thanks to the increasing knowledge about clinical prognostic factors and histological markers that better predict melanoma outcomes and treatment response, the 8th edition of the American Joint Committee on Cancer (AJCC) cancer staging manual was published [22]. The AJCC staging classification uses a TNM-based approach, but it is more focused on clinical care of the individual patient to support more individualized treatment decisions.

Table 1. AJCC Staging System Summary

AJCC Stage	Primary tumor (T)	Regional lymph nodes (N)	Distant metastasis (M)	Clinical description
Stage 0	Tis	N0	M0	Melanoma in situ
Stage IA	T1a	N0	M0	Thin melanoma without ulceration
Stage IB	T1b or T2a	N0	M0	Thin or intermediate melanoma with increased risk
Stage IIA	T2b or T3a	N0	M0	Intermediate thickness melanoma
Stage IIB	T3b or T4a	N0	M0	Thick melanoma
Stage IIC	T4b	N0	M0	Very thick ulcerated melanoma
Stage III	Any T	N1–N3	M0	Regional nodal or in-transit metastasis
Stage IV	Any T	Any N	M1	Distant metastatic disease

Table 2. AJCC T-Category Classification of Cutaneous Melanoma Based on Breslow Thickness and Ulceration

T category	Breslow thickness	Ulceration	Definition
Tis	In situ	Not applicable	Melanoma confined to the epidermis
T1a	< 0.8 mm	Absent	Thin melanoma, lowest risk
T1b	< 0.8 mm with ulceration OR 0.8–1.0 mm	Present or absent	Thin melanoma with increased risk
T2a	1.01–2.0 mm	Absent	Intermediate thickness melanoma
T2b	1.01–2.0 mm	Present	Increased risk melanoma
T3a	2.01–4.0 mm	Absent	Thick melanoma
T3b	2.01–4.0 mm	Present	High-risk melanoma
T4a	> 4.0 mm	Absent	Very thick melanoma
T4b	> 4.0 mm	Present	Very high-risk melanoma

There are many challenges in daily clinical practice to assess staging accurately. Staging strongly depends on histopathological evaluation of the primary tumor and regional lymph node status. Accurate staging is essential because it can prevent incorrect clinical decisions and unnecessary discomfort and anxiety for the patient. It also has economic relevance, as it can help to avoid unnecessary, expensive treatments. Initial staging for correct decision making is mainly based on two major pillars: the histopathology of the primary tumor and imaging examinations, when they are indicated.

The T category is determined mainly by the histological characteristics of the primary tumor, especially Breslow thickness and ulceration. These parameters are the most important tumor-related risk factors for recurrence and development of metastasis. They support the initial treatment planning and the decision about further staging examinations.

The presence of regional lymph node metastasis represents a major biological and clinical turning point in melanoma progression [23]. Micrometastasis can be present even in cases where the neck status is clinically negative and imaging is normal. Therefore, accurate regional staging is very important for correct risk assessment. Regional lymph node status largely determines whether the patient will be managed with observation only or with adjuvant systemic therapy [24]. Stage I–II melanoma is limited to local disease, while stage III melanoma has metastasized to the regional lymph nodes [25]. The presence of distant metastasis classifies

the patient as stage IV. The most common sites of distant metastasis are the lung, brain, bone and liver. In these cases, systemic therapy is usually indicated.

Staging has become even more important in the modern era, because melanoma treatment already includes systemic therapies in earlier stages. Due to immunotherapy and molecularly targeted therapies, melanoma care has become more risk-based and multidisciplinary. In this setting, accurate staging largely determines the prognosis and the treatment strategy. This is especially important in patient groups with worse prognosis, such as H&N melanoma patients, and is only possible with precise regional staging [26].

4.4 Treatment algorithm of cutaneous melanoma

The National Comprehensive Cancer Network (NCCN) cutaneous melanoma guideline provides a standardized, stage-based therapeutic workflow for the management of cutaneous melanoma [27]. The guideline offers a clear and practical pathway for routine cases in everyday clinical practice. However, individual patient factors and specific clinical situations (eg. locally advanced disease or anatomically challenging tumor locations) may require tailored decision-making. These decisions are made through multidisciplinary collaboration. At our institution, melanoma management is discussed at regular skin tumor board meetings involving dermatologists, radiologists, H&N surgeons (including maxillofacial, otolaryngology, and plastic surgeons), medical oncologist, nuclear medicine specialists, and pathologists.

The first step in melanoma management is the identification of a clinically suspicious pigmented lesion, followed by histological confirmation. Whenever feasible, the NCCN guideline recommends excisional biopsy, as it allows accurate histopathological diagnosis and staging. Key pathological parameters, including Breslow thickness and the presence of ulceration, determine the T category.

Surgical treatment is still the cornerstone of therapy. Standard management consists of wide local excision (WLE) of the primary tumor. The recommended excision margins are based on the Breslow thickness: 1 cm for tumors thinner than 1 mm, 1–2 cm for tumors measuring 1–2 mm, and 2 cm for tumors thicker than 2 mm. In clinical practice, these margins may need to be modified to preserve function and achieve acceptable aesthetic outcomes, particularly in anatomically sensitive regions such as the H&N. In such cases, careful preoperative planning is essential to balance oncological safety with functional and cosmetic considerations [28].

Regional staging with SLNB is a key component of melanoma management in clinically node-negative patients. It is currently the only reliable method for detecting occult nodal micrometastases, which cannot be excluded by physical examination or conventional imaging alone. According to NCCN recommendations, SLNB should be performed for melanomas with a Breslow thickness greater than 0.8 mm or for thinner melanomas with high-risk pathological features, such as ulceration. Sentinel lymph node status provides critical prognostic information and strongly influences disease staging and subsequent treatment [29].

The result of SLNB has a major influence on further patient management. A negative SLNB confirms disease limited to the primary site. In these cases, regular follow-up becomes the mainstay of care. The frequency and intensity of follow-up are determined by the pathological stage of the primary tumor. In patients with thick primary melanoma, adjuvant systemic therapy may be considerd despite a negative SLNB. In contrast, a positive SLNB results in upstaging to stage III disease, which significantly defines the therapeutic approach. In the modern treatment era, such patients are considered for adjuvant systemic therapies, including molecularly targeted treatments and immune checkpoint inhibitors. As a result, the role of SLNB has become even more important, as it directly guides the selection of patients - particularly those with intermediate thickness melanoma- who may benefit from systemic therapy [30].

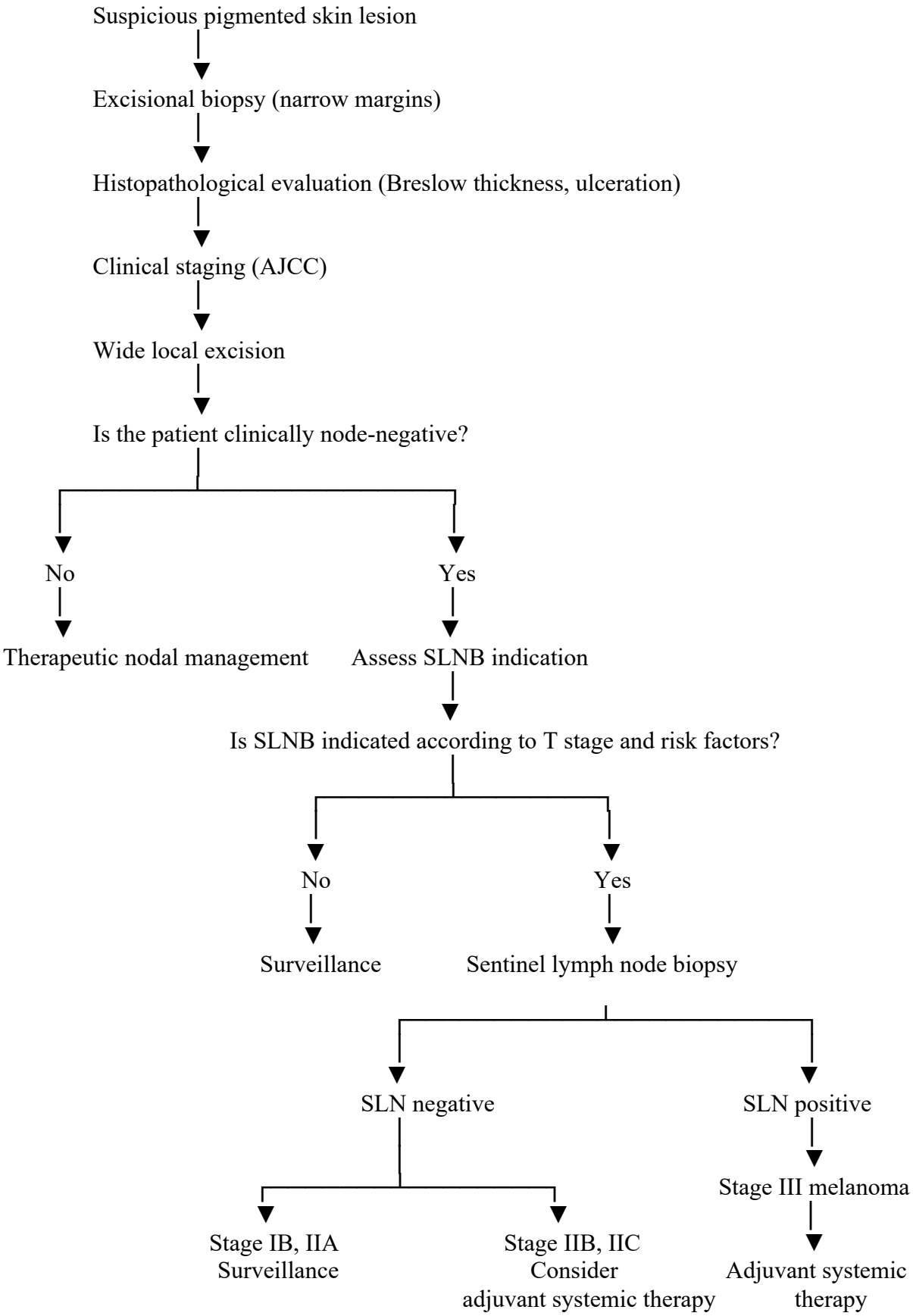
In cases where lymph node metastases are present at the time of diagnosis, management is significantly different. Surgical treatment may include therapeutic cervical lymph node dissection in addition to wide local excision. This is followed by multidisciplinary evaluation to determine the need for systemic therapy, due to the higher likelihood of disseminated disease.

In stage IV melanoma, systemic therapy is the primary treatment modality. However, palliative treatment options may play an important role in selected patients. Radiotherapy may be indicated for symptomatic brain, bone, or soft tissue metastases to achieve local disease control and symptom relief. In addition, electrochemotherapy, a local ablative therapy can be considered for cutaneous or subcutaneous metastatic lesions. This is particularly true in cases where surgical resection is not feasible and when local control is required to improve quality of life.

Follow-up strategies are also defined by the NCCN guideline. The primary goal is the early detection of local recurrence, regional nodal disease, or distant metastases. Patient

education is a fundamental part of follow-up care, particularly regarding self-examination and adherence to scheduled surveillance visits. Regular clinical assessments and imaging form an essential part of long-term melanoma management. The overall patient pathway according to the NCCN guideline is summarized in Figure 1.

Figure 1. NCCN guideline summary



4.5 Neglected melanoma – when guideline-based algorithms are not fully applicable

International guidelines provide a clear and standardized treatment algorithm for most patients with cutaneous melanoma. However, sometimes strict adherence to these standard protocols is not always feasible. One such scenario involves patients who present with advanced disease, characterized by locally extensive primary tumors that often require complex surgical management and reconstruction.

In this dissertation, we refer to this patient population as having “neglected melanoma.” This term describes the delayed clinical presentation of the disease and does not refer to a specific histological subtype. The causes of late diagnosis are multifactorial and may include initial clinical misdiagnosis, delayed referral, fear of medical interventions, limited acces to medical care and patient-related neglect. Regardless of the underlying cause, the consequence is the same: the primary tumor may reach a large size. At this point, standard treatment algorithms developed mainly for early-stage melanoma are no longer directly applicable.

The selection of neglected melanomas in our study was based on the extent of the primary tumor from a surgical perspective, rather than histological characteristics. Melanomas with a diameter greater than 3 cm were included, reflecting the increased surgical and reconstructive complexity associated with these large lesions. Within this group, an extreme subtype can be identified, referred as giant melanoma. Giant melanomas are defined as melanomas with a diameter exceeding 10 cm and represent the most advanced type of neglected melanomas [31].

In patients with neglected or giant melanoma, standard excisional biopsy is often not feasible, which result in incomplete initial staging. The proximity of critical anatomical structures in the H&N region does not allow the use of guideline-recommended wide local excision margins. Most guidelines recommend delayed reconstruction when primary wound closure is not possible, however this approach is often impractical in patients with extensive defects [32, 33]. In addition, advanced patient age and comorbidities commonly encountered in this population that further emphasize the need to minimize surgical complexity and operative time.

Regional staging with SLNB is also challenging in patients with large, locally extensive melanomas, and the reliability of the results may be limited. The indication for SLNB in these cases should therefore be individualized and is primarily justified when the patient is considered a potential candidate for future systemic therapy.

Appropriate follow-up is of particular importance in patients with neglected melanoma, as the primary tumor has remained undetected and untreated for a prolonged period. In these cases, a closer surveillance may be needed to allow earlier detection of recurrence or metastasis.

The management of neglected melanomas requires close multidisciplinary collaboration. Effective treatment planning depends on individualized decision-making among dermatologists, oncologists, radiologists, and surgeons. These cases clearly highlight that early diagnosis and timely access to appropriate treatment are fundamental pillars of effective melanoma care.

In summary, neglected melanomas represent a clinically challenging subgroup of cutaneous melanoma in which treatment frequently differs from guideline-based algorithms and needs individualized, multidisciplinary management. For this reason, the first part of this dissertation focuses specifically on the treatment and outcomes of this patient population.

4.6 Sentinel Lymph Node Biopsy in Melanoma: Rationale and Special Considerations in the Head and Neck

SLNB is the standard procedure for regional staging in patients with clinically node-negative cutaneous melanoma. Sentinel lymph node status represents the most important independent prognostic factor in early-stage melanoma and plays an important role in risk stratification. As a result, SLNB has become a cornerstone of contemporary, risk-adapted melanoma management [34].

International guidelines define the indication for SLNB based on the estimated probability of regional lymph node metastasis. Over time, these recommendations have evolved in parallel with growing clinical experience. While SLNB was previously recommended mainly for melanomas with a Breslow thickness greater than 1.0 mm, the current threshold has been lowered to 0.8 mm. In addition, SLNB may also be considered in thinner melanomas when high-risk histopathological features, such as ulceration, are present [35].

The clinical purpose of SLNB has changed over the past decade. Initially, SLNB was introduced with the aim of improving regional disease control, and a positive sentinel lymph node finding was routinely followed by completion lymph node dissection (CLND). However, the results of large randomized clinical trials demonstrated that although CLND reduces the risk of regional nodal recurrence, it does not improve melanoma-specific or overall survival. Consequently, routine CLND is no longer recommended in patients with a positive SLNB [34, 36].

In the modern treatment era, SLNB is therefore primarily a staging procedure rather than a therapeutic intervention. Its principal value lies in providing accurate prognostic information and identifying patients who may benefit from adjuvant systemic therapy. It should be noted that many of the landmark SLNB trials were conducted before the widespread use of immune checkpoint inhibitors and targeted therapies, which further limits the potential therapeutic relevance of CLND in current clinical practice[37].

Accurate regional staging is particularly important in H&N melanoma, a subgroup associated with poorer prognosis and higher rates of regional and distant recurrence. Historically, SLNB in the H&N region was considered technically challenging. One major reason is the highly variable lymphatic drainage of this anatomical area, where sentinel lymph nodes are frequently multiple and may be located in different nodal basins[38]. In addition, surgical access to deeply located or intraparotid lymph nodes is technically challenging and may be associated with increased morbidity. The close proximity of the primary tumor site to the draining lymph nodes may also complicate intraoperative detection due to the so-called shine-through effect [39].

Because of these factors, early studies reported lower sentinel lymph node identification rates and higher false-negative rates for H&N melanoma compared with melanomas arising on the trunk or extremities [19]. This perception persisted for many years and led to hesitation among clinicians. This may partly explain the lower utilization of SLNB in patients with H&N melanoma [40, 41]. Omission of SLNB can result in incomplete staging and incomplete risk assessment, potentially preventing eligible patients from receiving timely adjuvant systemic therapy.

During the past two decades, several technical and methodological advances have significantly improved the reliability of SLNB in H&N melanoma. Preoperative

lymphoscintigraphy combined with SPECT/CT imaging has enhanced anatomical localization of sentinel lymph nodes, particularly in complex drainage areas [42, 43]. Intraoperative dual-tracer techniques using radiocolloid and blue dye further increase detection rates and help overcome the shine-through phenomenon. In parallel, advances in histopathological processing, including serial sectioning and immunohistochemical staining with markers such as HMB-45 and Melan-A, have improved the detection of micrometastatic disease [44].

As a result of these developments, growing evidence from experienced centers demonstrates that SLNB can be performed safely and with acceptable diagnostic accuracy in H&N melanoma. Nevertheless, access to SLNB remains limited in many healthcare systems, and the procedure is routinely available only in a small number of institutions. This situation is also characteristic of Hungary, where H&N SLNB is performed in relatively few specialized centers.

Therefore, an important clinical question is whether SLNB can be implemented with comparable safety and diagnostic reliability in medium-volume centers. This issue is particularly relevant in H&N melanoma, where accurate staging is essential for appropriate patient selection for systemic therapy. The second part of this dissertation addresses this question by evaluating the feasibility and diagnostic performance of SLNB in a medium-volume university center with established nuclear medicine, surgical, and histopathological expertise.

4.7 Rationale of the Present Thesis

The management of melanoma has changed considerably over recent decades. Although international guidelines provide evidence-based frameworks for diagnosis and treatment, everyday clinical practice often involves complex situations. In these cases, strict adherence to standardized algorithms is not possible and individualized decision-making is required.

This dissertation addresses two clinically relevant challenges in contemporary melanoma care. The first focuses on neglected, late-presenting melanomas, which illustrate the limitations of guideline-based pathways and frequently require individualized, multidisciplinary management.

The second relates to the feasibility and diagnostic performance of sentinel lymph node biopsy in H&N melanoma, with particular attention to its implementation in medium-volume regional centers.

Together, these topics reflect a common clinical challenge: how to provide guideline-based yet patient-centered melanoma care under non-ideal conditions. Therefore, the aim of this thesis is to examine key aspects of melanoma management in a regional academic setting, with emphasis on accurate staging, surgical decision-making, and multidisciplinary collaboration.

5 Aims and Objectives

5.1 Aim of the Dissertation

The aim of this doctoral dissertation is to investigate selected challenges in the surgical management of cutaneous melanoma of the H&N region, with particular emphasis on accurate staging and individualized treatment strategies in real-world clinical practice.

By analyzing institutional experience from a medium-volume regional center, this thesis evaluates the applicability and limitations of current guideline-based recommendations in both early-stage and advanced H&N melanoma

5.2 Specific Objectives

1. To analyze the management of neglected and locally advanced H&N melanomas
    - To describe clinical characteristics and surgical treatment strategies in late-presenting cases
    - To evaluate oncologic, functional, and aesthetic outcomes
2. To evaluate the role of sentinel lymph node biopsy in H&N melanoma
    - To assess the feasibility, safety, and prognostic relevance of SLNB in a medium-volume regional center
    - To analyze sentinel lymph node identification rates, false-negative outcomes, and long-term oncologic results
3. To evaluate the applicability of current melanoma guidelines in complex clinical scenarios within a regional academic center.
    - To demonstrate that guideline-based melanoma care can be safely implemented in regional centers with appropriate expertise

6 Patients and Methods

6.1 Study Design and Setting

This dissertation is based on two retrospective, single-center clinical studies conducted at the University of Szeged, Hungary. Both studies investigated patients with primary cutaneous melanoma of the H&N region treated within the institutional melanoma care pathway. Clinical decision-making was coordinated through a multidisciplinary skin tumor board involving specialists in dermatology, maxillofacial surgery, otorhinolaryngology, nuclear medicine, oncology, radiology, and pathology.

All patients were managed according to contemporary international guidelines, adapted to individual clinical circumstances and anatomical considerations specific to the H&N region. Demographic, clinical, surgical, histopathological, and follow-up data were retrieved retrospectively from the institutional electronic medical record system (MEDSOL). The studies were conducted in accordance with the Declaration of Helsinki and were approved by the institutional ethics committee of the University of Szeged (protocol code: MEL-RETRO 001, SZTE-40/2015; the approval date was 5 February 2015, and the last extension date was 19 March 2025). Due to the retrospective design, informed consent requirements were waived or obtained in accordance with local ethical regulations.

Although the two study cohorts differ in their clinical characteristics and specific methodological approaches, both analyses were conducted within the same institutional melanoma care framework and reflect real-world multidisciplinary decision-making in the management of H&N melanoma.

6.2 Neglected and Locally Advanced H&N Melanoma Study

6.2.1 Study Design and Patient Selection

This retrospective study included patients with neglected or late-presenting primary cutaneous melanoma of the H&N region treated surgically between January 2008 and December 2019. Inclusion criteria were a maximum tumor diameter greater than 3 cm and primary surgical treatment performed at the University of Szeged.

6.2.2 Preoperative Evaluation

All patients underwent histological confirmation of melanoma prior to definitive surgery. Preoperative radiological staging was performed to exclude clinically evident nodal or distant metastatic disease. Treatment strategies were defined by the multidisciplinary tumor board, taking into account tumor characteristics, patient-related factors, and expected therapeutic benefit.

6.2.3 Surgical Treatment and Reconstruction

Wide local excision of the primary tumor was performed in all cases, with resection margins adapted to anatomical and patient-specific considerations. Immediate reconstruction was performed in every patient. The surgical plan was individualized according to defect size, anatomical location, involvement of aesthetic subunits, patient age, and comorbidities.

Reconstructive techniques included local and regional flaps, cervicofacial flaps, rotation and transposition flaps, split-thickness skin grafts, full-thickness skin grafts, and combined approaches when necessary.

6.2.4 Nodal Management

Sentinel lymph node biopsy was not performed in this cohort based on multidisciplinary tumor board decisions. Reasons for omission included the large size of the primary tumor, which limited the reliability of lymphatic mapping; advanced patient age or comorbidities precluding further oncologic treatment; patient refusal; or the lack of therapeutic consequence of nodal staging.

6.2.5 Outcome Assessment

Patients were followed according to institutional surveillance protocols. Functional and aesthetic outcomes were assessed clinically during follow-up using a subjective four-grade scale (poor, acceptable, good, excellent), based on surgeon evaluation and patient-reported satisfaction.

6.3 Sentinel Lymph Node Biopsy Study

6.3.1 Patient Selection and Eligibility

All consecutive patients with primary cutaneous H&N melanoma who underwent SLNB at the Department of Oral and Maxillofacial Surgery between 2010 and 2022 were retrospectively identified. SLNB was performed in a selected subgroup of patients based on contemporary guideline recommendations, multidisciplinary tumor board decision-making, tumor-related risk factors, and the anticipated impact of SLNB findings on subsequent management.

Indications for SLNB evolved over the 12-year study period. During the earlier years of the study, SLNB was generally recommended for patients with clinically node-negative disease and a Breslow thickness ≥1.0 mm, in accordance with prevailing international guidelines at that time. Following subsequent guideline updates, the threshold was lowered to ≥0.8 mm, and additional high-risk histopathological features were considered. For the purposes of analysis, all tumors were reclassified according to current AJCC criteria to ensure consistency across the cohort. No pT1a melanomas underwent SLNB in the present study.

Reasons for non-performance of SLNB included melanoma thickness below guideline thresholds, advanced patient age or relevant comorbidities, limited eligibility for subsequent systemic therapy, patient preference or refusal after informed discussion, prior excision at an external institution, or a multidisciplinary decision that SLNB was unlikely to influence clinical management. In such cases, patients were managed according to guideline-based surveillance strategies.

6.3.2 Sentinel Lymph Node Biopsy Procedure

Following histological verification of the primary melanoma, wide local excision was performed with margins determined according to contemporaneous NCCN guidelines. Preoperative lymphoscintigraphy was performed in all patients to identify sentinel lymphatic drainage basins.

Sentinel lymph node biopsy was performed using a combined radiotracer and blue dye technique according to standard protocols. Preoperative dynamic lymphoscintigraphy was carried out on the day before surgery following peritumoral injection of technetium-99m–labelled human albumin colloid. As part of the dual-mapping approach, 0.5–2.0 mL of vital blue dye was injected intradermally 15–20 minutes prior to skin incision.

Intraoperatively, sentinel lymph nodes were identified using a handheld gamma probe in conjunction with visual identification of blue-stained lymphatic channels and nodes. Lymph

nodes demonstrating significant radiotracer uptake and/or blue dye staining were considered sentinel lymph nodes and were excised. Ex vivo radioactivity counts were measured and compared with background activity in the surgical bed. Sentinel lymph node excision was continued until residual background counts were less than 10% of the activity of the hottest node removed.

6.3.3 Histopathological Examination

All excised skin specimens and sentinel lymph nodes were fixed in 4% buffered formaldehyde for 24 hours at room temperature using a 1:10 tissue-to-fixative volume ratio. Representative sections of the primary tumor were submitted for routine histological evaluation, while sentinel lymph nodes were entirely embedded in paraffin blocks.

Serial 4-µm sections were cut and stained with hematoxylin–eosin. To increase diagnostic sensitivity, additional immunohistochemical analyses were performed using Melan-A and/or HMB-45 antibodies to detect isolated tumor cells and micrometastases. Automated immunohistochemical staining was performed using a Leica BOND-MAX autostainer with a polymer-based horseradish peroxidase detection system, and all slides were counterstained with hematoxylin.

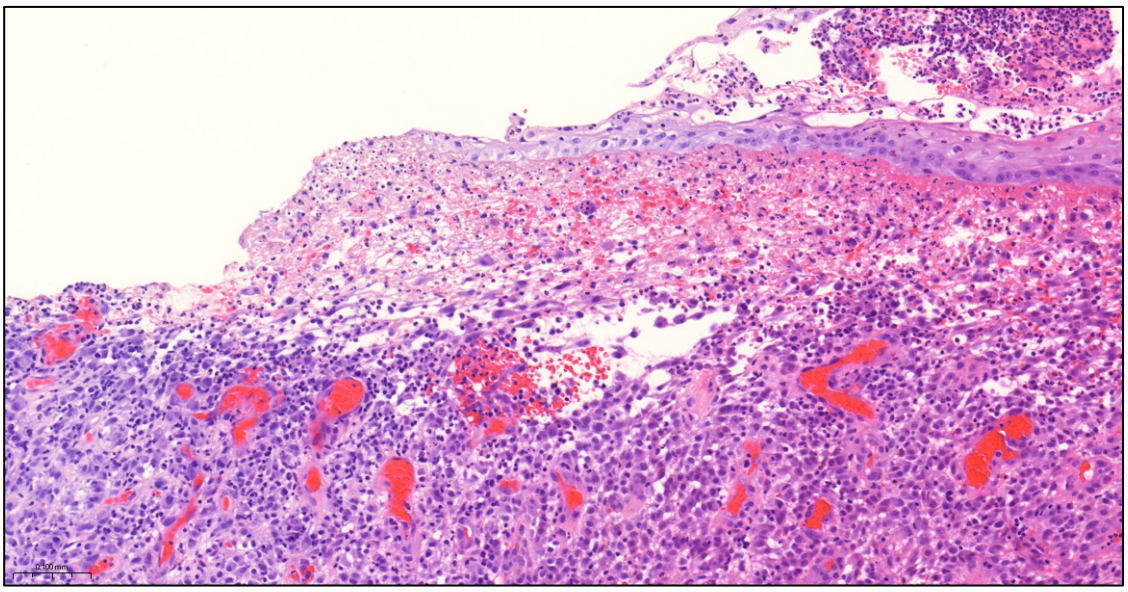


Figure 2. Histopathological Image of an Ulcerated Primary Cutaneous Melanoma. *Image courtesy of the Department of Dermatology and Allergology, University of Szeged.*

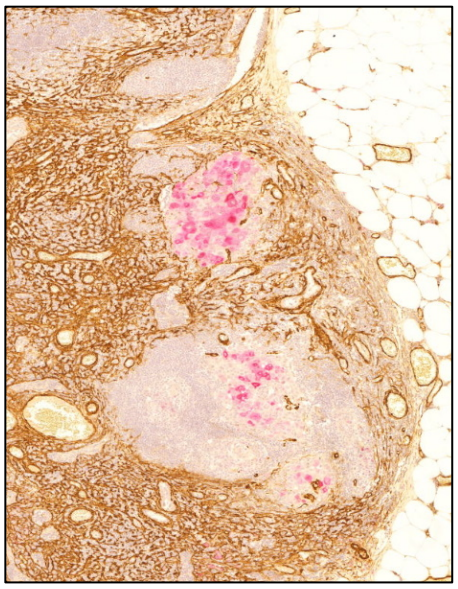


Figure 3. Histopathological Image of a Positive Sentinel Lymph Node Biopsy Showing Metastatic Melanoma. *Image courtesy of the Department of Dermatology and Allergology, University of Szeged.*

6.3.4 Postoperative Management

Patients with histopathologically positive SLNB findings underwent completion lymph node dissection and received intermediate-dose adjuvant interferon therapy (3 × 5–10 MIU IFN-2b subcutaneously). Patients with negative SLNB results and a Breslow thickness >1.5 mm received low-dose interferon therapy (3 × 3 MIU IFN-2a weekly for one year), in accordance with international guidelines in effect during the study period.

6.3.5 Endpoints and Outcome Definitions

The primary endpoints of the study were sentinel lymph node identification rate, false-omission rate (FOR), recurrence-free survival (RFS), and overall survival (OS).

For all time-to-event analyses, the date of primary tumor excision was used as the uniform index date (time zero), as this date was consistently available for all patients and represents a clinically relevant starting point for follow-up.

Overall survival was defined as the time from the date of primary tumor excision to death from any cause. Patients who were alive at last contact were censored at the date of last follow-up. Recurrence-free survival was defined as the time from the date of primary tumor excision to the first documented recurrence (local, satellite/in-transit, regional nodal, or distant metastasis). Patients without recurrence were censored at the date of last follow-up.

Regional nodal recurrence was defined as the occurrence of metastatic disease within the previously mapped and biopsied lymphatic basin following a negative SLNB, without preceding or simultaneous local or in-transit recurrence. Such events were classified as false-negative (FN) outcomes, consistent with definitions used in large H&N melanoma SLNB series [45]. The false-omission rate was calculated as FN / (FN + TN). Patients without documented recurrence or death were censored at the date of last clinical follow-up.

6.3.6 Statistical Analysis

Survival outcomes were estimated using the Kaplan–Meier method. Associations between SLNB status and overall survival were evaluated using univariate Cox proportional hazards regression models, with negative SLNB serving as the reference category. Given the modest cohort size and limited number of events, multivariable analyses were not performed to avoid model overfitting.

Statistical analyses were conducted using SPSS software (version 26; IBM, Armonk, NY, USA). A p-value < 0.05 was considered statistically significant.

6.3.7 Literature Comparison

To contextualize the present findings, a structured review of previously published SLNB series in cutaneous H&N melanoma was performed. Literature searches were conducted using PubMed and additional biomedical databases, applying combinations of the following keywords: *"H&N," "melanoma," "sentinel lymph node biopsy,"* and *"SLNB."* Titles and abstracts were screened to identify potentially relevant studies.

Full texts of potentially eligible articles were reviewed, and studies were included if they met the following predefined criteria: (1) inclusion of patients with primary cutaneous H&N melanoma; (2) performance of sentinel lymph node biopsy; (3) inclusion of at least 75 patients undergoing SLNB; (4) reporting of follow-up duration; and (5) availability of nodal outcome metrics, including false-negative outcomes, false-omission rates, or sufficient data to derive these measures. Studies focusing solely on technical feasibility or mixed anatomical sites without H&N–specific outcome data were excluded.

From the eligible studies, data on sentinel lymph node identification rate, reported nodal outcome metrics, and follow-up duration were extracted and summarized descriptively (Table 3). Given heterogeneity in reporting standards across published series, the false-omission rate was selected as the primary comparative metric. No formal meta-analysis was performed.

7 Results

7.1 Neglected Melanoma Study

7.1.1 Patient Characteristics and Tumor Presentation

Between 2008 and 2019, five patients with large primary cutaneous melanomas of the H&N region (>3 cm in maximum diameter) were identified. The cohort included four female and one male patient, with a median age of 76 years (range: 63–92 years). Tumor size ranged from 3 cm to 29 cm, including one giant melanoma measuring 29 × 15 cm located on the scalp.

Primary tumor locations included the scalp and forehead (n = 1) and the cheek with or without lower eyelid involvement (n = 4). Average tumor thickness was 9.6 mm, and ulceration was present in the majority of cases. Delayed presentation was attributed to fear of medical care, low disease awareness, or prior misdiagnosis.

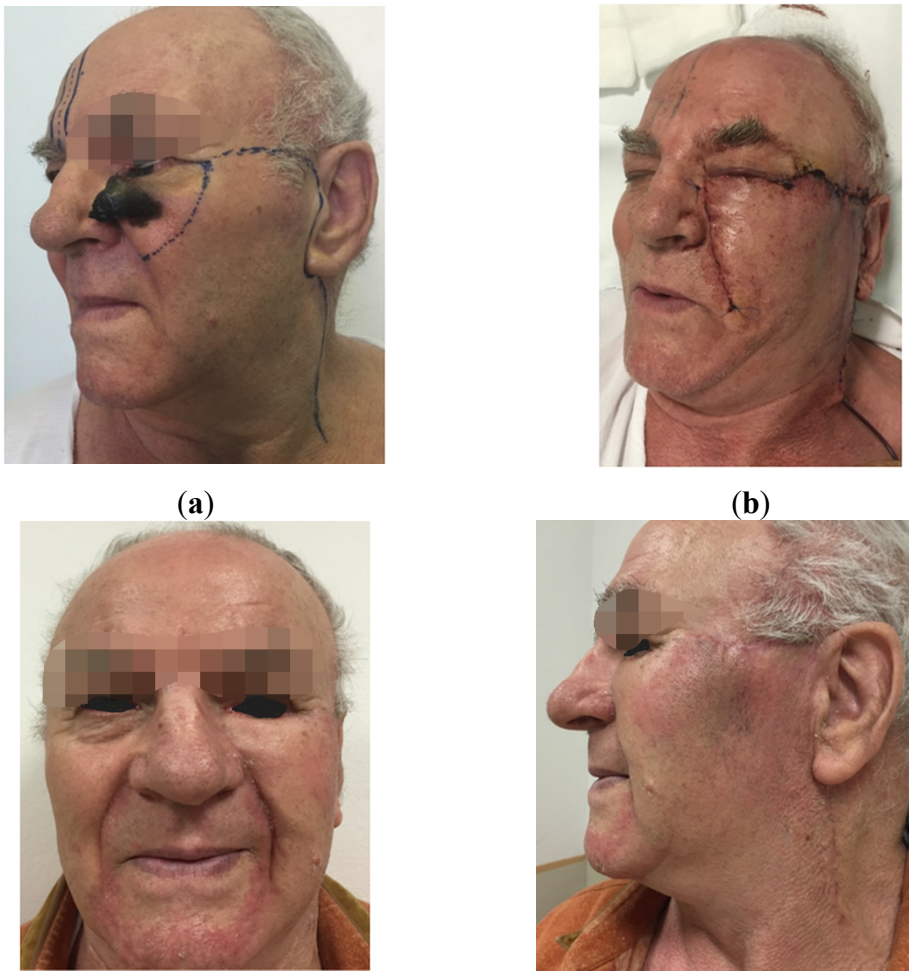
Table 3. Clinical, Surgical, and Outcome Characteristics of Patients with Neglected Cutaneous Melanoma

Patients	Gender	Age	Tumor size	Location/ Cosmetic units involved	Histopathology Ulceration (U)	AJCC stage	Reconstruction/ defect size	Resection margins and clearance	Other interventions/ treatments	Follow-up	Esthetic result
1	F	68	29x15cm	Scalp + Forehead 1b;9	NM Cl V. B:10.336mm pT4b U+	IIID	Split skin graft/ 33x19cm – 627cm^2	2cm – negative	Radical neck dissection BRAF-MEK inhibitor +PD1 inhibitor	52 mo. stable disease	Acceptable
2	F	92	9x7.6 cm	Cheek 4a,b;5b	LMM + NM Cl V. B: 17.860mm PT4b U+	IIc	Transpo-sitional flap, Cervico-facial flap/11x9.6cm – 105cm^2	1cm – negative	—	50 mo. tumor free	Good
3	F	92	2x3 cm	Cheek 4a,b,c	LMM Cl III. B: 2.736 mm pT3a U-	IIa	Cervico-facial flap/ 4x5cm – 20cm^2	1cm – negative	—	29 mo. tumor free	Good
4	M	76	3x1.5 cm	Cheek + Lower eyelid 4a, 3b	LMM + NM Cl V. B: 17.024mm pT4b U+	IIc	Extended Mus-tardé flap + amnion membrane graft/7x5.5cm – 38.5cm^2	2cm – negative	—	52 mo. tumor free	Good
5	F	63	3x1.3cm	Cheek + lower eyelid 3b,4a,b	LMM + NBCC Cl II. B: 0.152mm PT1a U-	Ia	Rotation flap + full thickness skin graft/ 5x3.3 cm – 165cm^2	1cm – negative	—	80 mo. tumor free	Excellent

7.1.2 Surgical Management and Reconstruction

All patients underwent wide local excision with 1–2 cm surgical margins, based on tumor thickness and multidisciplinary tumor board decision-making. Sentinel lymph node biopsy was not performed in any case, due to advanced patient age, limited eligibility for systemic therapy, technical limitations, or patient preference.

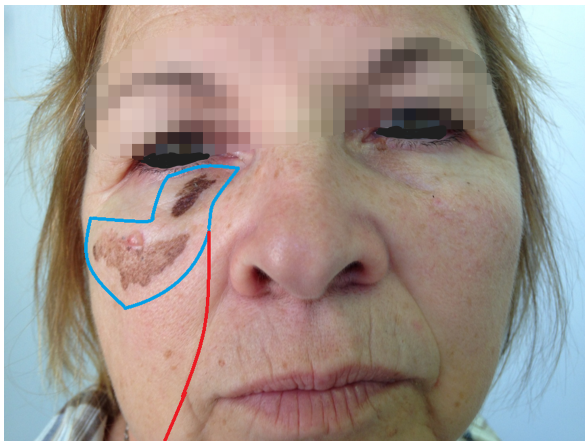
In all the cases, immediate reconstructive procedures were chosen on an individual basis as regards the localization, the size of the defects, and patient age and preferences as well. During reconstruction, the units and subunits of the face were respected for a better esthetic outcome. In two cases, in addition to the tumor removal from the cheek, the lower eyelid had to be removed either completely or partially. Therefore, in Patient 4, a modification of the Mustardé flap was used with amniotic membrane grafting in the upper part to substitute the conjunctiva (see Figure 4), and a rotation flap was performed in combination with full thickness skin grafting to the orbicularis oculi muscle in Patient 5 (see Figure 5).



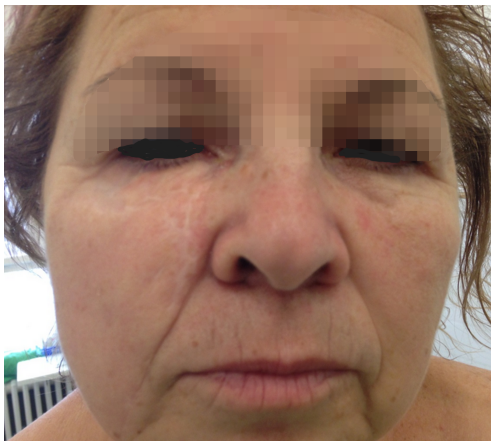
(**a**) (**b**)

(c1) (c2)

Figure 4. (a) Locally advanced NMM of the cheek preoperatively; (b) Two-week follow-up; (c) Six-month follow-up.



(**a**)



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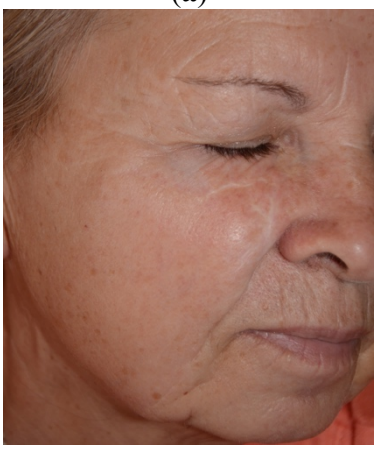
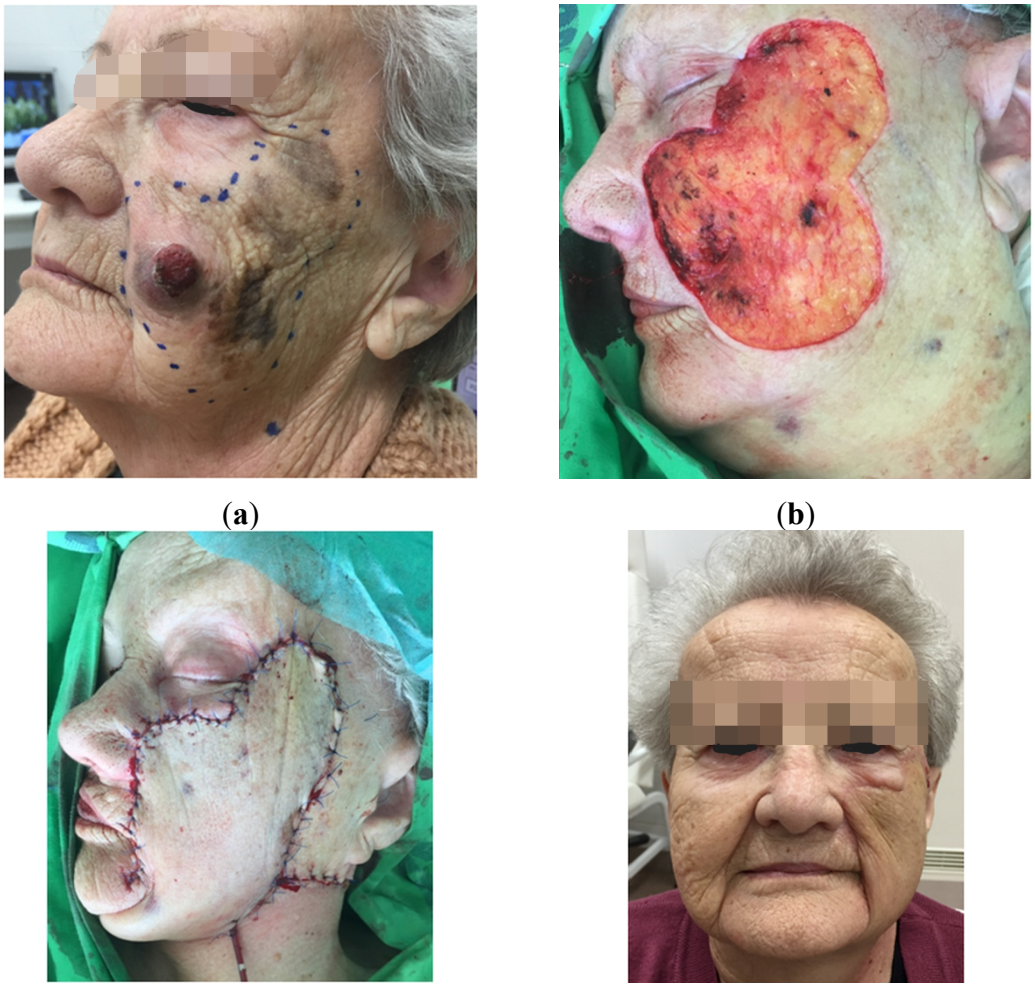


(**c**)

Figure 5. (**a**) Locally advanced LMM of the cheek preoperatively; (**b**) Six-month follow-up; (**c**) Five-year follow-up.

In Patients 2 and 3, large cervicofacial flaps were transposed to the defect with extensive undermining on the neck and secured to the zygomatic bone by periosteal anchoring (see Figure 6).

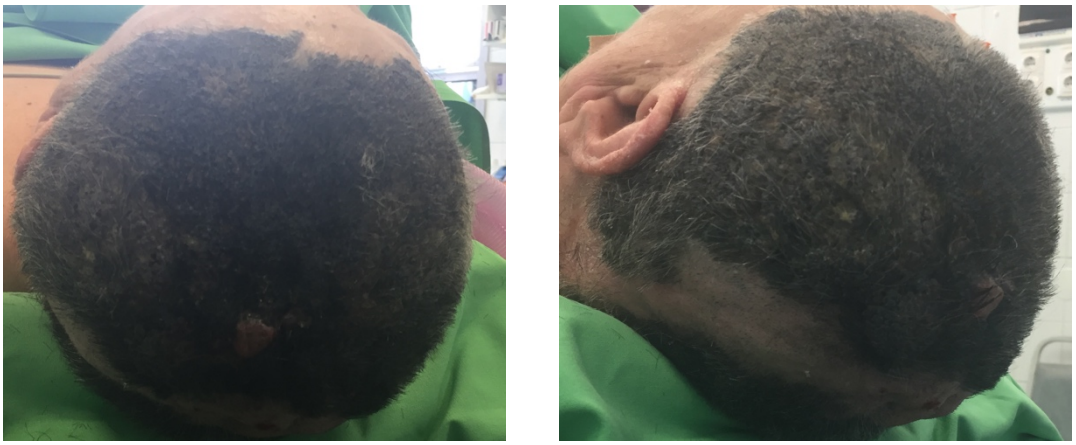


(**a**) (**b**)

(c) (d)

Figure 6. (a) Locally advanced LMM and NMM of the cheek preoperatively; (b) Defect after primary tumor excision; (c) Immediate postoperative picture; (d) Six-month follow-up.

In Patient 1, after the removal of the giant melanoma from the scalp, the 627cm^2 defect was covered with a split-thickness skin graft harvested from the left thigh. The skin graft healed well with complete graft take (see Figure 7).



(a1) (a2)

Figure 7. (**a**) Giant melanoma of the scalp preoperatively; (**b**) Two-week follow-up, healed mesh skin graft; (**c**) Six-month follow-up.

7.1.3 Oncological and Functional Outcomes

Early postoperative complications were limited to minor wound dehiscence in two cases and mild flap edema in one case. After a median follow-up of 52 months (range: 29–80 months), four of five patients remained free of local recurrence, regional lymph node metastasis, or distant disease.

One patient developed cervical lymph node metastases eight months after primary tumor excision and subsequently underwent radical neck dissection followed by systemic immunotherapy, achieving stable disease. Functional outcomes were rated as good or excellent in all patients, with preserved mimetic function. Esthetic outcomes were assessed as acceptable to excellent, with satisfactory scar quality and facial symmetry.

7.2 SLNB study

7.2.1 Patient and Tumor Characteristics

Thirty-eight patients with cutaneous melanoma of the H&N underwent SLNB at the Department of Oral and Maxillofacial Surgery, University of Szeged. The median patient age was 52 years (range 21.3–77.9), with a median follow-up time of 6.8 years. Median Breslow thickness was 3.12 mm (range 0.5–18.0).

Twenty-three patients (60.5%) were male and 15 (39.5%) were female. Tumors were most frequently located on the scalp (47.4%), followed by the face (31.6%), ear (15.8%), and neck (5.2%). Pathological staging revealed that 25 patients (65.8%) had tumors classified as pT3a or lower, while 12 patients (31.6%) had pT3b or higher tumors. Detailed demographic and clinicopathological characteristics are summarized in Table 4.

Table 4. Summary of Demographic and Tumor Characteristics of the Study Population

Characteristics		**No. of patients (%)**
Mean age, years (range)		52.17 (21.3-77.9)
Median Follow-up, years		6.8
Gender	Male	23 (60.5)
	Female	15 (39.5)
SLNB	Negative	30 (78.9)
	Positive	8 (21.1)
Pathological stage	pT3a or lower	25 (65.8)
	pT3b or higher	12 (31.6)
	NA	1 (2.6)
Anatomical distribution	Scalp	18 (47.4)
	Face	12 (31.6)
	Ear	6 (15.8)
	Neck	2 (5.2)
Mean Breslow, mm (range)		3.12 (0.5-18.0)

7.2.2 SLNB Performance, Nodal Outcomes, and Survival

At least one sentinel lymph node (range 1–2) was successfully identified in all patients, yielding a sentinel lymph node identification rate of 100%. No major perioperative complications were observed. Minor wound infection occurred in two patients and resolved with conservative management.

Histopathological examination identified positive sentinel lymph nodes in eight patients (21.1%), while 30 patients (78.9%) had negative SLNB results. During follow-up, regional nodal recurrence occurred in two of the 30 patients with negative SLNB findings (6.6%). These

events were classified as false-negative outcomes. Based on these findings, the false-omission rate was 6.7%, and the negative predictive value was 93.3%.

Kaplan–Meier survival analysis demonstrated longer RFS and OS among patients with negative SLNB findings compared with those with positive SLNB findings; however, these differences did not reach statistical significance (Figures 8 and 9). In univariate Cox regression analyses, SLN positivity was associated with numerically higher hazards for recurrence and death; however, these associations were not statistically significant, and confidence intervals were wide, reflecting the limited number of events.

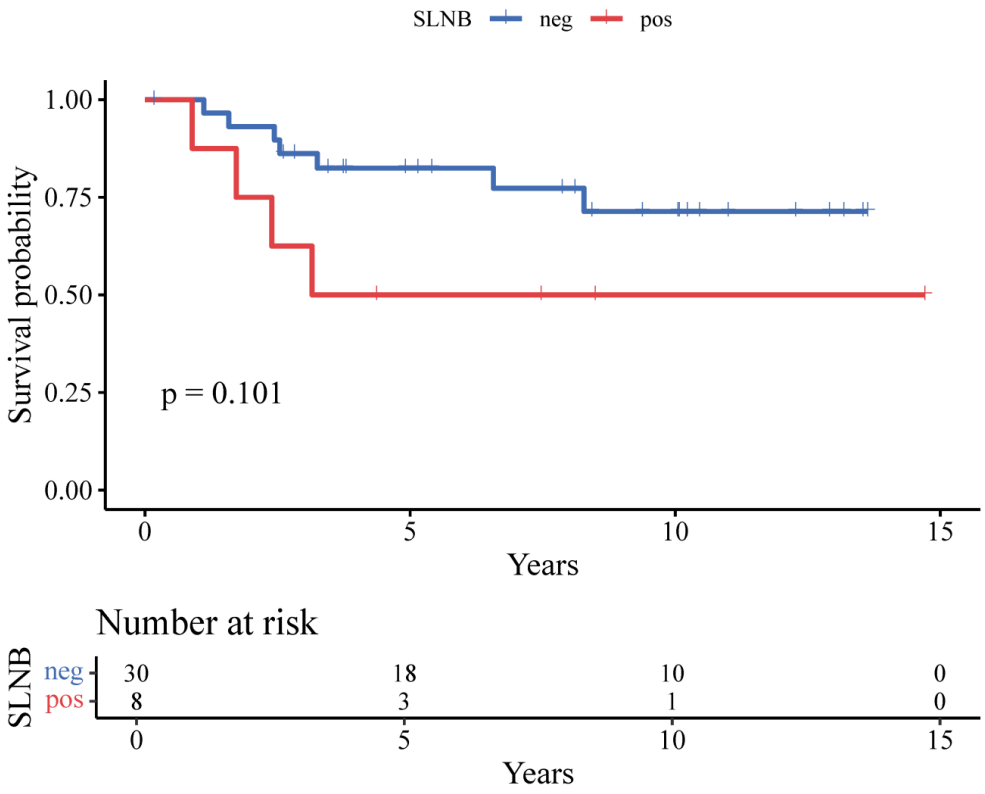


Figure 8. Kaplan–Meier overall survival (OS) curves for SLN-negative vs SLN-positive patients.

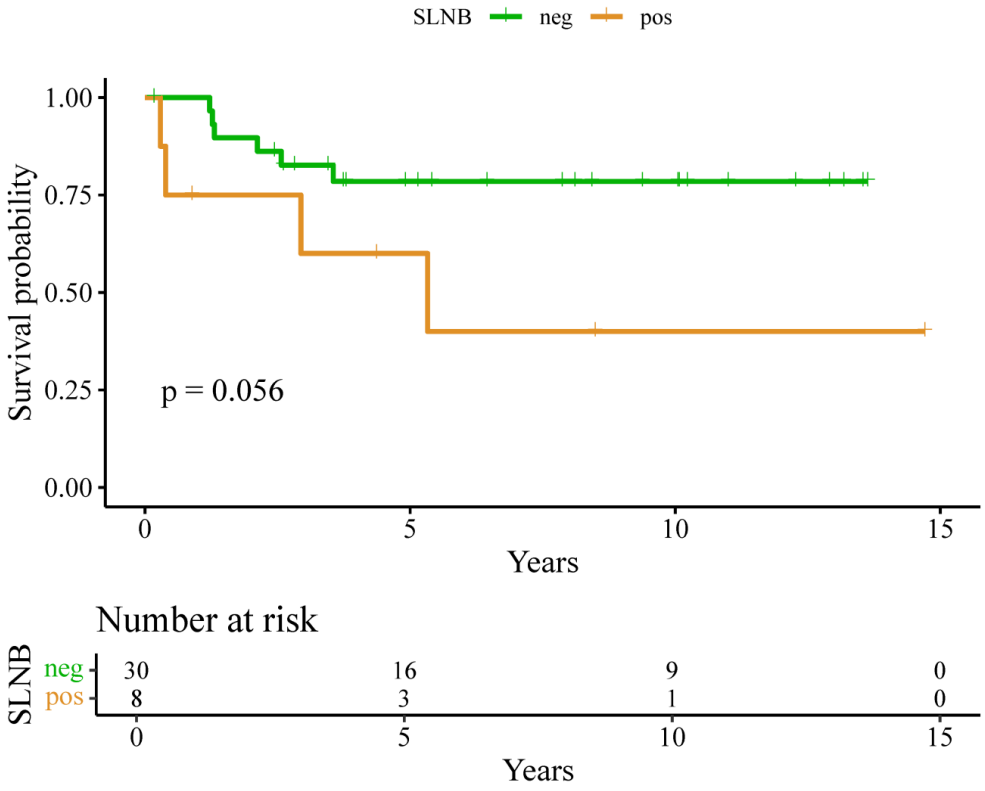


Figure 9. Kaplan–Meier recurrence-free survival (RFS) curves for SLN-negative vs SLN-positive patients.

7.2.3 Intermediate-Risk Subgroup Analysis

Given that SLN histology remains a decisive factor in determining eligibility for adjuvant therapy, we conducted a separate analysis of patients with pT1b–pT3a melanoma—a subgroup for whom adjuvant treatment is not indicated under current guidelines without SLNB findings. This intermediate-risk subgroup included 27 patients, of whom five (18.5%) had positive SLNs, highlighting the clinical importance of SLNB in detecting patients who may benefit from closer surveillance or adjuvant therapy.

7.2.4 Comparison with Published Series

To contextualize our findings, sentinel lymph node identification rates, false-omission rates, and follow-up durations were compared with those reported in previously published large H&N melanoma series (Table 5). In the present cohort, the 100% identification rate and the false-omission rate of 6.7% were within the ranges reported in these studies.

Table 5. Comparative sentinel SLNB outcomes in previously published large H&N melanoma series and the present study, including sentinel lymph node identification rates, false-omission rates (FOR), and reported follow-up durations.

Study / Center (Year)	No. of H&N Melanoma Cases (SLNB)	SLN Identification Rate (%)	FN-Related Metric Reported	FOR (%)	Median/ Mean Follow-Up
Carlson et al. (2005) [46]	125	98–100	FN, FOR	6.8	Mean 34.7 months
Miller et al. (2011) [19]	153	~99	FN, FNR, FOR	6.7	Median 28.8 months
Erman et al. (2012) [21]	353	99.7	FOR	4.2	~35 months (~2.9 yrs)
Hanks et al. (2020/2021) [45]	356	~99	FOR	6.4	Median 4.9 yrs
Evrard et al. (2018) [29]	124	97.6	FOR	7.1	Mean 46.6 months
Passmore-Webb et al. (2019) [18]	143	100	FN, FOR	2.6	Median ~33 months
Present study (Szeged, Hungary)	**38**	**100**	**FN, FOR**	**6.7**	**Median 6.8 yrs**

8 Discussion

8.1 Principal Findings of the Dissertation

The present dissertation addresses two interrelated challenges in the management of H&N cutaneous melanoma: the treatment of neglected, locally advanced primary tumors and the implementation of SLNB in a medium-volume regional center.

The first main finding of this work is that surgical treatment continues to play a central role in melanoma care, even in the era of modern systemic therapies. In patients with neglected or locally advanced H&N melanoma, strict guideline-based algorithms are often difficult to apply. In these cases, wide local excision combined with immediate reconstruction resulted in satisfactory oncologic control and acceptable functional and aesthetic outcomes. Our results suggest that, in selected patients, immediate reconstruction does not compromise oncologic safety and may represent a reasonable and patient-oriented approach, especially in elderly patients or those with significant comorbidities.

The second principal finding is that SLNB can be performed safely and with reliable diagnostic accuracy in a medium-volume academic center, provided that adequate multidisciplinary institutional background is available. In our cohort, the sentinel lymph node identification rate and the false-omission rate were comparable to those reported by large international series, despite the long follow-up period. These findings indicate that institutional case volume alone is not the most important factor determining SLNB performance. Standardized surgical technique, appropriate nuclear medicine imaging, and careful histopathological evaluation appear to be equally important.

Furthermore, sentinel lymph node status provided clinically relevant prognostic information, particularly in intermediate-risk patients. In this patient population primary tumor characteristics alone are not sufficient for precise risk stratification. A considerable proportion of these patients had occult nodal metastases, highlighting the importance of SLNB in accurate staging and in selecting patients who may benefit from adjuvant systemic therapy.

Overall, the results of this dissertation support a balanced approach to H&N melanoma management, combining guideline-based recommendations with individualized decision-

making in a real-world clinical setting. The findings demonstrate that high-quality melanoma care can be provided outside high-volume tertiary centers when appropriate expertise and institutional infrastructure are present.

8.2 Management of Clinically Node-negative Neck

The management of the clinically node-negative neck was a controversial issue in the treatment of H&N melanoma. Regional lymph node status is one of the strongest prognostic factors in melanoma; however, at the time of primary diagnosis, only a minority of patients present with clinically detectable lymph node metastases. Historically, three main strategies have been used for the management of the clinically node-negative neck: watchful waiting, elective neck dissection, and SLNB [47].

Watchful waiting represents the least invasive approach. Using high-resolution ultrasonography, cervical lymph nodes can be continuously monitored in a noninvasive manner, with minimal patient burden and no radiation exposure. Ultrasound is well-suited for detecting macroscopic nodal metastases but cannot reliably identify micrometastatic disease. This strategy is therefore most appropriate for patients with thin melanomas and for patients who are not candidates for systemic therapy because of advanced age, significant comorbidities, or limited life expectancy. However, because this approach detects only macroscopic disease, regional metastases identified during surveillance may already be at a more advanced stage than those detected by SLNB [48].

In cases of neglected melanoma, ultrasound-based surveillance was selected in our cohort for several reasons, including patient preference, limited compliance, situations in which sentinel lymph node status would not influence subsequent treatment decisions, short life expectancy, and technical considerations. In large or locally advanced tumors, SLNB is often compromised by the so-called "shine-through" phenomenon, in which the close proximity of the primary tumor to the sentinel lymph node interferes with accurate intraoperative localization [49]. This limitation is particularly relevant in H&N melanoma with extensive primary tumors, where appropriate radiocolloid injection and reliable sentinel node identification become technically challenging, especially in lesions measuring 3 cm or more in diameter.

At the opposite end of the treatment spectrum is elective neck dissection (END). Historically, this approach was influenced by treatment principles derived from H&N

squamous cell carcinoma, where END is routinely performed in clinically node-negative necks because of the high risk of occult metastases and its demonstrated survival benefit [50]. This surgical philosophy was subsequently applied to melanoma management; however, melanoma differs substantially from squamous cell carcinoma in terms of biological behavior, lymphatic spread, and response to therapy. Prospective randomized clinical trials have failed to demonstrate a survival advantage for END in melanoma patients [51]. Moreover, END is associated with significant morbidity, including cranial nerve injuries. Consequently, elective neck dissection has been abandoned in the modern surgical management of melanoma.

Positioned between these two strategies, sentinel lymph node biopsy has emerged as the optimal approach for managing the clinically node-negative neck in melanoma. SLNB provides valuable prognostic information while it is minimally invasive. By selectively removing the first draining lymph node, SLNB enables the detection of micrometastatic disease with low surgical morbidity, a particularly important consideration in the anatomically complex and functionally sensitive H&N region.

8.3 SLNB

8.3.1 Feasibility and Diagnostic Accuracy in a Medium-volume Center

SLNB is currently considered the standard of care for regional staging in H&N melanoma. Historically, however, SLNB in this anatomical region was regarded as technically challenging. This was mainly attributed to the complex and highly variable lymphatic drainage of the H&N, the frequent occurrence of bilateral lymphatic drainage, and the common presence of the shine-through phenomenon. As a result, early studies reported lower sentinel lymph node identification rates and higher false-negative rates in H&N melanoma compared with melanomas arising at other anatomical sites[19, 20].

At the same time, an important objective of this dissertation was to evaluate whether SLNB can be performed safely and reliably in a medium-volume center. Although centralization of melanoma care is an important principle for ensuring high-quality treatment, its implementation may be difficult in certain healthcare systems, particularly in countries or regions with lower population density. If SLNB is restricted exclusively to high-volume tertiary centers, a considerable proportion of patients may lose access to guideline-recommended staging and appropriate subsequent therapy.

Early publications suggested a learning curve of approximately 30–40 cases for SLNB, reinforcing the perception that adequate performance could only be achieved in large tertiary oncology centers[52, 53]. However, accumulating evidence indicates that institutional case volume alone is not the decisive factor. When appropriate infrastructure is available—including high-quality nuclear medicine imaging, standardized histopathological evaluation, and surgeons experienced in H&N oncologic procedures—SLNB can be performed with diagnostic accuracy comparable to that reported by large referral centers. In this context, multidisciplinary collaboration plays a key role in achieving reliable outcomes.

In the second study of this dissertation, SLNB proved to be technically feasible in H&N melanoma, with a 100% sentinel lymph node identification rate. The observed false-omission rate was comparable to those reported by high-volume tertiary centers in the literature. These findings demonstrate that SLNB can be performed reliably outside major referral institutions when a standardized workflow and appropriate institutional background are present.

Several factors contributed to these favorable results. Preoperative lymphoscintigraphy combined with SPECT/CT imaging enabled precise localization of sentinel lymph nodes in this anatomically complex region. The application of standardized surgical techniques by a team experienced in H&N oncologic surgery was essential for achieving high identification accuracy. In addition, advances in histopathological processing—particularly standardized serial sectioning and immunohistochemical staining—significantly improved the detection of micrometastases and enhanced diagnostic reliability.

Taken together, these developments have established SLNB as a minimally invasive procedure with excellent identification rates and reliable diagnostic performance in H&N melanoma. The results of this dissertation support the notion that, with appropriate expertise and infrastructure, SLNB can be successfully implemented in medium-volume centers, thereby improving access to high-quality, guideline-based melanoma care.

8.3.2 Prongostic Value of SLN Status in the Modern Treatment Era

SLN status is one of the most important prognostic factors in melanoma, together with Breslow thickness. In our study, a clear trend was observed: patients with a negative SLN demonstrated more favorable recurrence-free survival and overall survival compared with

SLN-positive patients. Although these differences did not reach statistical significance, this was most likely due to the limited number of cases and events in the cohort.

The clinical importance of SLNB has further increased in the era of modern systemic therapies. Large randomized clinical trials have demonstrated no survival benefit for routine CLND compared with observation following a positive SLNB [36, 54, 55]. As a consequence, the role of SLNB has evolved over time. Rather than serving primarily as a tool for regional disease control, its main purpose is now accurate pathological staging and treatment planning. Identification of SLN-positive patients allows timely initiation of individualized adjuvant systemic therapy. It is also important that results from the MSLT-II trial suggest that SLNB may provide a degree of regional disease control in selected patients, as those undergoing SLNB showed a lower risk of regional nodal recurrence [37].

The prognostic value of SLNB is particularly pronounced in the intermediate-risk melanoma population. In these patients, prognosis cannot be reliably determined based on the histopathological characteristics of the primary tumor alone. In our study, nearly 20% of patients in the intermediate-risk group had a positive SLN. This finding underscores that omission of SLNB in this subgroup is not acceptable, as it would lead to incomplete staging and potentially deprive patients of appropriate, guideline-based systemic therapy.

8.4 Excision Margins, Timing and Choice of Reconstruction

8.4.1 Excision Margins

Current excision margin recommendations for cutaneous melanoma are primarily based on Breslow thickness and supported by randomized trials comparing narrower (1–2 cm) with wider (3–5 cm) margins [56-58]. Overall, these studies did not show consistent differences in local recurrence or overall survival across margin widths. However, one trial reported higher regional recurrence in melanomas >2 mm treated with 1 cm versus 3 cm margins [59]. Meta-analyses have provided heterogeneous results regarding the oncologic adequacy of 1 cm margins [60], and the absence of a direct randomized comparison of 1 cm versus 2 cm excision remains a key evidence gap currently investigated in the ongoing MelMarT trial [61].

Accordingly, NCCN guidelines recommend 1 cm margins for melanomas <2 mm and 2 cm margins for melanomas >2 mm. In the H&N region, strict adherence may be limited by proximity to critical structures and reconstructive challenges, particularly in locally advanced

or neglected tumors. When margin reduction is unavoidable, available data suggest that margins <1 cm may be associated with increased local recurrence even in thin melanomas, supporting individualized, multidisciplinary decision-making to balance oncologic safety with functional and aesthetic preservation [62].

8.4.2 Immediate versus Delayed Reconstruction

The timing of reconstruction after melanoma excision requires balancing oncologic safety against treatment burden. Traditionally, reconstruction has been delayed until final histopathology confirms negative margins, because frozen sections or Mohs surgery are not standard approaches for invasive melanoma[63]. Delayed reconstruction facilitates straightforward re-excision if margins are positive, but prolongs treatment time, increases wound-care demands, and may reduce patient compliance.

In H&N melanoma, reported rates of positive final margins are approximately 5–12%. Margin positivity has been associated with desmoplastic subtype, advanced T stage, ulceration, and locally recurrent disease, although predictive factors are inconsistent, and some series identify age as the only reliable correlate [64,65]. For this reason, some authors advocate delaying local flap reconstruction even for early-stage lesions.

Immediate reconstruction can reduce the number of procedures, shorten overall treatment time, lower costs, and improve patient satisfaction, at the expense of potentially more complex re-excision if margins are positive. Re-excision is typically feasible after primary closure or skin grafting because tumor orientation is preserved; immediate local flap repair is more controversial but may be reasonable when the likelihood of clear margins is high and patient factors favor a single-stage strategy [66,67]. In our series, reconstruction was performed immediately in all cases (loco-regional flaps or skin grafts), reflecting the practical need to minimize staged care in neglected tumors, where advanced age, patient comorbidity and limited compliance often make prolonged treatment unrealistic.

8.4.3 Choice of Reconstruction in Large and Complex Defects

Reconstructive strategy following excision of H&N melanoma is primarily determined by defect size and anatomical location, local tissue characteristics, and patient-related factors; therefore, rigid reconstructive algorithms are generally not applicable. Primary closure may be feasible for small defects, particularly in regions with greater skin laxity such as the cheek.

However, primary closure in the perioral, perinasal, or periorbital regions carries a significant risk of functional or aesthetic distortion. Skin grafts represent a reliable reconstructive option for larger defects, although they may be associated with suboptimal contour, color, and texture match.

Local and locoregional flap techniques frequently provide superior aesthetic integration by replacing defects with tissue of similar characteristics. For moderate-sized defects of the cheek and zygomatic region, rotation or advancement flaps—including Mustardé-type techniques—allow stable coverage while respecting relaxed skin tension lines. Smaller defects may be reconstructed using transposition flaps, such as rhomboid or Esser flaps; however, these approaches may result in more noticeable scarring [68], [69]. In cases of extensive superficial defects, cervicofacial flaps represent a reliable reconstructive solution, providing adequate tissue volume and favorable color and texture match through wide undermining. Flap perfusion is supported by multiple cervical and clavicular perforators, and inclusion of the platysma muscle may further improve distal vascularity. In elderly patients, increased tissue laxity often permits reconstruction of large defects using these lower-morbidity regional techniques, avoiding the need for more complex reconstructive procedures.

In summary, optimal outcomes in H&N melanoma surgery depend on the integrated consideration of excision margins, reconstruction timing, and reconstructive modality. In selected patients—particularly those with neglected or locally advanced disease—single-stage tumor excision combined with immediate reconstruction using appropriately chosen grafts or local and regional flaps can provide acceptable oncologic, functional, and aesthetic outcomes while minimizing overall treatment burden.

8.5 Why Are H&N Melanomas Neglected?

Presentation with advanced primary melanoma in the H&N region is uncommon, as these tumors are generally visible to patients and often interfere with daily activities and social interaction. When neglect does occur, the underlying reasons are multifactorial and not always clearly identifiable. Contributing factors may include limited awareness of skin tumors, pursuit of alternative medical approaches, socioeconomic constraints, underlying medical or psychiatric conditions, fear of diagnosis or medical care, and diagnostic failure as well [70].

Fear of medical intervention appears to be a particularly important factor, especially in elderly patients, and may lead to prolonged delay until distressing symptoms such as bleeding, visual impairment, or malodor force medical attention. In such cases, it is essential to respect patient preferences and limitations and to tailor treatment strategies accordingly [71].

In this context, surgical treatment plays a pivotal role, as it offers rapid, effective, and potentially curative local disease control. The immediate and visible result of surgery may help restore patient trust in medical care and facilitate acceptance of further oncologic treatment that might otherwise be refused. This is particularly relevant in H&N melanomas, where tumors are frequently of lentigo maligna melanoma subtype and often lack BRAF mutations, limiting systemic treatment options [72]. In addition, advanced age, comorbidities, or limited compliance may further restrict eligibility for systemic therapies. Under these circumstances, the importance of surgery as the primary therapeutic modality is further emphasized. Although radiotherapy may represent a palliative or adjuvant alternative, it is often declined by patients due to the prolonged treatment course [73].

8.6 Future directions

The findings of the present dissertation, together with the author's related research activities, highlight several promising directions for future investigation in the management of H&N melanoma.

8.6.1 Refinement of risk stratification beyond sentinel lymph node biopsy

Sentinel lymph node biopsy remains the most important staging tool for clinically node-negative melanoma; however, it is an invasive procedure with recognized technical limitations in the H&N region. An important future challenge is the development of biology-driven risk stratification models that may refine or complement surgical staging.

In this context, the author's work on novel prognostic markers derived from primary tumor biology, including the investigation of ACSL4 as a prognostic factor in cutaneous melanoma, supports the concept that relevant recurrence risk information may be obtained directly from the primary tumor [74]. Recent data further reinforce this approach: a recent study demonstrated that a combined clinicopathologic and gene expression profiling model (CP-GEP, Merlin Assay) can accurately identify patients with H&N melanoma at high risk of recurrence even in the absence of sentinel lymph node biopsy [75]. Together, these findings suggest

that primary tumor–based molecular profiling may, in selected patients, complement surgical nodal staging, particularly in anatomically complex regions or in elderly and comorbid populations.

Prospective validation and integration of such markers into clinical decision algorithms will be essential before routine implementation. Nevertheless, continued refinement of prognostic models represents a key step toward more individualized melanoma management.

8.6.2 Novel locoregional therapies with immunomodulatory potential

Another important future direction concerns the treatment of advanced, recurrent, or palliative melanoma, particularly in patients who are not ideal candidates for extensive surgery or systemic therapy. Electrochemotherapy has become an established locoregional treatment modality for cutaneous melanoma metastases, providing effective local tumor control with acceptable morbidity [76].

Building on the established role of electrochemotherapy, which has demonstrated synergistic effects with immunotherapy through enhanced tumor antigen release [77], calcium electroporation has emerged as a novel locoregional treatment modality in which intracellular calcium overload induces tumor cell death via metabolic collapse. Early clinical evidence indicates that calcium electroporation is safe and effective in achieving local tumor control [78].

Future studies should focus on patient selection and optimal treatment sequencing, as well as on defining the potential role of calcium electroporation in multimodal treatment strategies, particularly in the head and neck region where functional preservation and quality of life are critical considerations.

8.6.3 Toward integrated, personalized melanoma care

Taken together, advances in molecular risk stratification and innovative locoregional therapies reflect a broader paradigm shift toward personalized, multidisciplinary melanoma management. In the future, treatment decisions in H&N melanoma are likely to rely on an integrated assessment of primary tumor biology, selective surgical staging, and tailored systemic and locoregional therapies.

The findings of the present dissertation support the feasibility of implementing such advanced, guideline-based melanoma care in medium-volume regional centers. Continued research in these directions may further reduce treatment-related morbidity, expand therapeutic options for vulnerable patient populations, and improve long-term oncologic and functional outcomes.

9 Summary

Cutaneous melanoma of the H&N region represents a distinct clinical subgroup of melanoma. It is characterized by complex regional anatomy, variable lymphatic drainage, and generally less favorable oncologic outcomes compared with melanomas arising at other anatomical sites. Although international guidelines provide standardized, evidence-based recommendations for diagnosis and treatment, real-world clinical practice is often more complex. In many cases, strict adherence to guidelines is limited by anatomical constraints, tumor- and patient-related factors.

The present doctoral dissertation examines selected challenges in the surgical management of H&N melanoma, with particular focus on accurate staging, individualized treatment strategies, and multidisciplinary clinical decision-making in a regional academic setting.

The first part of the dissertation focused on neglected and locally advanced H&N melanomas. These tumors are characterized by delayed presentation and large primary tumor size. In this retrospective study we analyzed surgical strategies, reconstructive approaches, and long term oncologic, functional and aesthetic outcomes. In all cases, wide local excision and immediate reconstruction were performed without sentinel lymph node biopsy, based on individualized multidisciplinary tumor board decisions. Despite advanced disease stage and significant reconstructive challenges, satisfactory local tumor control and acceptable functional and aesthetic outcomes were achieved during long-term follow-up. These results underline that surgical treatment continues to play a central role in melanoma management, even in the era of effective systemic therapies. This is particularly true for patients in whom staging procedures or adjuvant treatments are limited by technical feasibility, comorbidities, or patient preference.

The second study focused on clinically node-negative H&N cutaneous melanoma patients who underwent sentinel lymph node biopsy over a 12-year period. The aim was to evaluate the feasibility of SLNB, its diagnostic reability, and long-term oncologic outcomes, including sentinel lymph node identification rate, false-omission rate, recurrence-free survival, and overall survival. Sentinel lymph node biopsy was successfully performed in all included patients, resulting in a 100% identification rate without major perioperative complications. The observed false-omission rate was comparable to values reported by large international reference centers, despite long follow-up. Sentinel lymph node status provided important prognostic information, particularly in intermediate-risk patients, for whom treatment decisions cannot be

reliably based on primary tumor characteristics alone. These findings demonstrate that SLNB can be performed safely and with acceptable diagnostic accuracy in H&N melanoma outside high-volume tertiary centers, provided that appropriate surgical expertise, nuclear medicine support, and standardized histopathological processing are available.

In summary, the dissertation highlights that optimal management of H&N melanoma requires a balance between guideline-based recommendations and individualized, patient-centered decision-making. Accurate regional staging with SLNB remains essential for proper risk stratification in eligible patients. At the samte time, tailored surgical management remains the cornerstone of treatment in locally advanced or neglected cases.

Importantly, the results shows that high-quality melanoma care can be delivered in regional academic centers through multidisciplinary collaboration and appropriate institutional infrastructure.

Overall, this work contributes to the growing evidence supporting the safe implementation of sentinel lymph node biopsy in medium-volume centers, It also reinforces the continuing importance of surgery in the management of complex H&N melanoma cases. The findings support an approach that integrates evidence-based principles with real-world clinical considerations in orted to to achieve optimal oncologic and patient-centered outcomes.

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