ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

REVIEW ARTICLE

Progress in the surgical treatment of early-stage malignant melanoma

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Abstract

Surgical treatment of early-stage malignant melanoma has shifted from traditional wide margins to precise, individualized approaches. This article systematically reviews the standards for surgical margin width and their impact on locoregional recurrence and survival outcomes, emphasizing how tumor thickness and anatomical location guide margin design. Sentinel lymph node biopsy, an important staging and prognostic tool, has greatly improved detection accuracy and safety through technological innovation and multimodal imaging, gradually replacing traditional lymphadenectomy and supporting more evidence-based treatment decisions. Mohs micrographic surgery, a minimally invasive, precise-margin technique, has shown significant advantages in functionally sensitive areas and specific tumor subtypes, achieving real-time comprehensive pathological assessment of margins and maximizing functional preservation, thereby reducing locoregional recurrence rates. Advances in systemic therapies, particularly immunotherapy and targeted therapy, are profoundly reshaping the timing and scope of surgeries through models such as neoadjuvant therapy, promoting a "response–adaptive" surgical approach. Individualized surgical strategies based on patient age, tumor thickness, molecular characteristics, and tumor location differences allow rational adjustment of surgical margins and adjuvant treatment planning, while integration with neoadjuvant and adjuvant systemic therapies may reduce operative extent, postoperative complications, and impairment in quality of life. Multidisciplinary cooperation and the integration of telemedicine technology also play key roles in surgical decision-making and follow-up. Looking ahead, the surgical treatment of early-stage malignant melanoma will further integrate molecular biology and advanced imaging technologies for precise staging and precise surgery, transform unresectable lesions through neoadjuvant therapy, and establish new models of minimally invasive and individualized treatment, ultimately improving patient survival rates and quality of life.

Keywords: Early-stage melanoma; Surgical margins; Sentinel lymph node biopsy; Lymphadenectomy; Mohs micrographic surgery; Neoadjuvant therapy

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Citation: Zhang J, Zhu Z, Han W. Progress in the surgical treatment of early-stage malignant melanoma. *Eurasian J Med Oncol*. doi: 10.36922/EJMO026050058

Received: January 31, 2026

Revised: March 2, 2026

Accepted: March 9, 2026

Published online: April 27, 2026

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1. Introduction

Malignant melanoma is an aggressive neoplasm derived from epidermal melanocytes. Its global prevalence has shown a persistent upward trend, making it the primary contributor to mortality associated with cutaneous cancers.[1] In recent years, the concept of surgical treatment for early-stage malignant melanoma has undergone a fundamental transformation, shifting from empiric wide excision toward precision, de-escalation, and functional preservation. Surgery has traditionally served as the primary and most effective treatment for resectable early-stage malignant melanoma, evolving from extensive radical excisions to more conservative, biologically guided methods. The main objectives of surgical intervention are the removal of the primary tumor and the evaluation of regional lymph nodes, both of which have been refined through clinical trial data and a better understanding of tumor biology. In recent years, the philosophy of surgical treatment has shifted dramatically: it has moved from emphasizing maximally tolerable resection to favoring a strategy based on minimally effective intervention,[2] emphasizing both cancer control and the preservation of functional and aesthetic outcomes. Meanwhile, the core principles of oncological surgery, such as complete resection, negative pathological margins, no-touch technique, and en bloc resection, remain fundamental principles of oncologic surgery that must be strictly adhered to in clinical practice.

With early intervention becoming mainstream, the core role of surgical treatment has been redefined: to maximize the preservation of organ function and morphological appearance while ensuring radical tumor resection, particularly in key aesthetic and functional areas such as the head and neck and limbs. The integration of reconstructive principles has further promoted individualized and rational surgical planning. This review provides a detailed examination of the development of surgical techniques, major technological advancements, combination with systemic therapies, and emerging trends in the management of early-stage malignant melanoma.

2. Basis and historical development of surgical treatment for early-stage malignant melanoma

The pathogenesis of melanoma arises from a complex interaction among environmental influences, genetic predisposition, and the host's immune status.[3] Mechanisms include genetic and epigenetic alterations, aberrant activation of critical signaling cascades such as mitogen-activated protein kinase and phosphoinositide 3-kinase/protein kinase B, disruptions of cell cycle control and apoptotic pathways, evasion of immune surveillance, and restructuring of the tumor microenvironment.[4]

Melanoma exhibits significant pathological heterogeneity: approximately 30% of cases occur in the head and neck region, 5–12% are hereditary, and lentigo maligna melanoma has a relatively high incidence in the head and neck, making surgical margin assessment particularly critical. In terms of pathological features, tumor thickness (Breslow thickness) and the presence of ulceration are important prognostic factors, with tumor depth being positively correlated with the risk of local recurrence. The Clark staging system categorizes tumors into five distinct grades according to the depth of pathological invasion. In contrast, the Breslow system employs tumor thickness, measured in millimeters, as an independent prognostic indicator.[5] Furthermore, early-stage malignant melanoma exhibits a high mutation frequency and can be categorized into distinct genetic subtypes, including *BRAF*-mutant, *RAS*-mutant, *NF1*-mutant, and triple-negative (wild-type) variants.[6] These molecular features also provide the basis for individualized selection of perioperative systemic therapy.

The gradual understanding of the biological and pathological characteristics of melanoma has driven the century-long evolution of surgical treatment concepts, which can be roughly divided into three core stages.

The traditional principles of surgical treatment for early-stage malignant melanoma date to Handley's observations in 1907, recommending a 5 cm margin from the edge of the primary tumor with fascial excision, a practice followed for nearly 50 years.[7] In fact, as early as the mid-nineteenth century, William Norris systematically described the characteristics of melanomas and proposed genetic predisposition, advocating extensive resection of primary melanomas, including surrounding normal tissue. Samuel Cooper emphasized the importance of early excision of the primary lesion. In 1892, Herbert Lumley Snow proposed removing regional lymph nodes, arguing that these nodes functioned as a "trap" to inhibit hematogenous spread. This concept gave rise to the surgical principle of complete resection of the primary tumor with regional lymph node dissection, which subsequently evolved into a key component of contemporary surgical strategies for melanoma.[8] Before the 1960s and 1970s, 3–5 cm margins were the surgical standard, and traditionally, extensive resection principles were followed for stage I–II patients, including extensive resection of early tumors and regional lymph node dissection after positive sentinel lymph node biopsy (SLNB). The surgical approach at this stage was centered on mechanical wide resection, overlooking the tumor's biological heterogeneity, leading to higher surgical complications and functional impairments without

survival benefits.

Since the 1970s, the philosophy of surgical treatment has shifted from radical mechanical resection to strategies based on tumor biology and the body's anti-tumor capacity, emphasizing tumor biology over the mere extent of surgery. Breslow first proposed the concept of "tumor thickness" in 1970, using its measurement to predict prognosis. He found that melanomas with a thickness of less than 0.76 mm were linked to a minimal risk of recurrence or metastasis. This discovery prompted a shift in clinical practice, leading to the widespread adoption of minimally invasive surgical techniques and the establishment of precise surgical margins.[9] Subsequently, a number of prospective randomized trials (such as the World Health Organization [WHO] trial, the Swedish trial, and the United States [US] Intergroup trial) systematically compared the effects of different margin widths, confirming that narrow margins (1–2 cm) showed no significant differences from wider margins (3–5 cm) in terms of overall survival (OS) and disease-free survival (DFS), with both yielding a low local recurrence rate (<5%). For example, a radial margin of 1 cm is adequate for primary tumors less than 1 mm thick, while a 2 cm margin is effective for primary lesions ranging from 1 to 4 mm in thickness.[10] By the 1980s, these studies had driven a shift in clinical practice toward more conservative margin ranges.

In the early 1990s, Morton introduced and popularized SLNB, radically revolutionizing regional lymph node management for melanoma. The fundamental concept involves removal of the initial lymph node infiltrated by tumor cells, with therapeutic lymph node dissection performed exclusively when the sentinel lymph node (SLN) is positive. This approach markedly decreases the incidence of complications associated with conventional extensive lymph node dissection.[11] As the first international multicenter randomized phase III clinical trial, the Multicenter Selective Lymphadenectomy Trial I (MSLT-I) validated the accuracy and safety of SLNB: the overall identification rate of sentinel lymph nodes reached as high as 95.3%, and the complication rate was low (10.1%). Widespread use of SLNB has enabled precise regional lymph node staging and allowed for narrower safe resection margins for primary melanomas, ultimately establishing a standardized resection margin protocol stratified by Breslow thickness. This protocol recommends a 5-mm margin for *in situ* melanoma, 1 cm for tumors < 1 mm thick, 1–2 cm for 1–2 mm-thick lesions, and 2 cm for tumors > 2 mm in thickness.[12] At the same time, SLNB has fully replaced conventional elective lymph node dissection in mainstream clinical practice. This paradigm shift is primarily driven by two critical drawbacks of elective lymph node dissection: its notably high incidence of postoperative complications and the well-documented finding that approximately 20% of affected patients have pathologically confirmed lymph node positivity.[13] Meanwhile, completion lymph node dissection (CLND) has been increasingly abandoned in clinical practice for SLNB-positive patients, as it delivers no survival advantage while carrying a high risk of morbidity.[14,15]

With the development of precise resection techniques and breakthroughs in targeted and immunotherapies, the surgical treatment of early-stage melanoma has entered a new era of multidisciplinary integration. Mohs micrographic surgery (MMS) enables complete circumferential and deep evaluation of tumor resection margins through intraoperative immunohistochemistry (IHC) (e.g., melanoma antigen recognized by T cells 1 [MART-1] staining), achieving 100% histopathological assessment. This approach is especially well-suited for critical anatomical regions, including the head and neck, offering the potential for enhanced, long-term tumor control and improved overall survival outcomes.[16] Furthermore, with the rapid advancement of targeted therapy and immunotherapy, surgical intervention is no longer a standalone treatment modality but has become a core component of an integrated therapeutic system deeply integrated with systemic therapy, thereby promoting further downgrading and individualization of surgical approaches.[15] To date, the surgical treatment of early-stage malignant melanoma has evolved from traditional wide excision to individualized margin adjustment based on pathological characteristics. Through the synergy of SLNB for precise staging, precise resection techniques, and systemic therapy, a balance has been achieved between minimally invasive, individualized, and curative treatment. Key milestones in the surgical treatment of melanoma are summarized in Table 1.

3. Norms for surgical margin width and advances in its clinical practice

The rational selection of surgical margins is a critical component in the surgical treatment of early-stage malignant melanoma, with the objective of preserving normal tissues and organ functions to the greatest extent while ensuring radical tumor resection. In recent years, ongoing updates to clinical evidence on margin width have driven the ongoing optimization of margin strategies.

3.1. Research progress on the impacts of different margin widths on local recurrence and survival rates

The impact of different surgical margin widths on local recurrence and survival prognosis in patients with early-

Table 1. Timeline of the development of surgical treatments for early-stage melanoma

Timeline	Proposer	Theory
Mid-19th century	William Norris	First advocated extensive resection for primary melanoma
1892	Herbert Lumley Snow	Advocated the surgical principle of radical en bloc resection of the primary lesion plus regional lymph node dissection, laying an important foundation for modern surgical treatment of melanoma
1907	Handley	Recommended a 5 cm safety margin combined with fascial excision
1960s–1970s	–	Established a 3–5 cm surgical margin as the standard
1970	Breslow	First proposed the concept of tumor thickness, identifying it as a prognostic determinant and using it to guide stratified margin selection
1990	Morton	Introduced and popularized SLNB, with the core principle of resecting the first lymph node involved by tumor cells
2010s–present	–	Further refinement of surgical strategies, with the widespread application of Mohs micrographic surgery, enables real-time comprehensive circumferential pathological assessment of margins and maximal preservation of tissue function, thereby reducing the local recurrence rate
2023	Guidelines from NCCN, CSCO, ESMO, etc.	Confirmed that the risk of local recurrence in melanoma is positively correlated with Breslow thickness, and stratified resection strategies should be guided by tumor thickness

Abbreviations: CSCO: Chinese Society of Clinical Oncology; ESMO: European Society for Medical Oncology; NCCN: National Comprehensive Cancer Network; SLNB: Sentinel lymph node biopsy.

stage malignant melanoma is one of the core topics in clinical research. Existing studies have mainly focused on margin strategies for techniques such as traditional wide local excision (WLE) and MMS.[17]

A systematic review and meta-analysis involving 43 studies with a total of 9,098 patients provides high-level evidence-based evidence for the selection of margin width: when the initial surgical margin width is 5–10 mm, the local recurrence rate of patients is the lowest (0.3%, 95% confidence interval [CI]: 0.2–0.5%, $p < 0.001$), which is significantly lower than that of the 1–5 mm group (2.3%) and the 5 mm group (1.4%); and both melanoma *in situ* and invasive melanoma exhibited a trend of reduced local recurrence with a 5–10 mm margin.[18]

For the precise application of margin resection techniques, multiple studies have confirmed the significant

advantages of MMS in margin control. For melanoma *in situ* and lentigo maligna, the local recurrence rate of MMS was only 0.8%, significantly lower than the 8.7% rate with traditional WLE.[19] For periorbital melanoma managed with MMS guided by IHC, the mean initial surgical margin width was 7.4 mm, and the local recurrence rate was 2.4%. This recurrence rate is considerably lower than the 17%–35% range commonly reported for conventional WLE.[20] In patients diagnosed with non-invasive melanoma in the head and neck region, MMS demonstrated a minimal surgical margin of 7.3 mm, accompanied by an exceptionally low local recurrence rate of 0.81%. This finding underscores the efficacy of MMS in achieving precise margin delineation while optimizing tissue conservation.

Multiple randomized controlled trials have delivered key evidence for thickness-stratified melanoma margin guidelines.[21] The 1980 WHO multicenter trial demonstrated that for melanomas with a thickness of <2 mm, 1 cm, and 3 cm margins yielded no differences in OS and DFS, yet patients with tumors > 1 mm in thickness in the 1 cm margin group had a higher rate of local recurrence. The US Intergroup trial compared 2 cm and 4 cm margins for melanomas measuring 1–4 mm in thickness and found comparable 10-year survival rates (70% versus 77%) and extremely low local recurrence rates (0.4% versus 0.9%), establishing 2 cm as the safe standard margin. The United Kingdom trial compared 1 cm and 3 cm margins for melanomas > 2 mm in thickness, showing a slightly higher local recurrence rate (3.3% vs. 2.9%) and a significantly shorter melanoma-specific survival in the 1 cm margin group ($p = 0.041$), whereas the Swedish trial found no survival differences when comparing 2 cm and 4 cm margins. Current clinical guidelines recommend margin widths stratified by tumor thickness: 1 cm for pT1 (≤1.0 mm), 1–2 cm for pT2 (1.01–2.0 mm), and 2 cm for pT3/pT4 (≥2.01 mm).[22]

However, the direct correlation between surgical margin width and survival outcomes remains controversial.[23] None of the six large randomized controlled trials validated a survival benefit of wide margins for OS or recurrence-free survival, with multiple retrospective studies showing no significant survival difference between MMS and WLE.[24] A study on invasive eyelid and periorbital melanoma indicated that no local recurrence was observed in cases with negative margins confirmed by IHC-assisted MMS, suggesting that precise margin control may be more important than margin width alone. Regarding residual tumors, 3.1% of WLE specimens exhibited residual melanoma, primarily linked to lentigo maligna/lentigo maligna melanoma, nodular subtypes, elevated mitotic rates, and larger tumor diameters. However, this finding did not significantly affect long-term survival outcomes. Furthermore, cumulative evidence from relevant clinical studies supports the implementation of a uniform 1-cm resection margin irrespective of primary tumor thickness. This strategy yields local recurrence rates equivalent to those achieved with wider excision margins, while concurrently reducing the incidence of surgical complications.[25] In parallel, the Mikroskopisch kontrollierte Chirurgie (microscopically controlled surgery) technique, which enables high-precision histologic margin evaluation, permits the use of a reduced 1-cm resection margin for neoplasms such as dermatofibrosarcoma protuberans—as opposed to the traditional 2-cm margin mandate—without elevating the risk of postoperative recurrence.[25]

In summary, the totality of available clinical evidence to date supports that a 5–10 mm surgical resection margin is the optimal strategy, most notably in cases treated with MMS. This margin regimen can effectively minimize the risk of local tumor recurrence, under the premise that the clinicopathological characteristics of the tumor and regional anatomical factors are compatible with the implementation of this approach,[26] yet the survival benefit of wide margins has not been clearly established.

3.2. The impact of functional and anatomical factors on margin selection

In selecting surgical margins for early-stage malignant melanoma, the anatomical site-specificity and the need for functional preservation are important considerations for adjusting margin width.

In 2021, Bund *et al.*[27] pointed out that although the current European Society for Medical Oncology guidelines recommend standard margins of 0.5 cm, 1 cm, and 2 cm for *in situ* melanoma, tumors with a thickness of ≤2 mm, and thicker tumors, respectively, a reduced safe margin is acceptable for acral and facial melanoma to preserve function, which reflects the necessity of adjusting margin guidelines based on anatomical sites.

In 2022, Kofler *et al.*[28] further defined the concept of "problematic sites," which include the eyelid, nose, lip, ear, genitalia, and acral regions. When resecting tumors in the aforementioned special areas, strictly adhering to the standard margin width often leads to disfigurement or loss of organ function in patients. Therefore, the clinical community has proposed the "function-first" principle to guide surgical margin adjustment: on the core premise of ensuring R0 resection (pathologically negative margins), minimize resection in an individualized manner based on local anatomical structures and functional boundaries. This strategy relies on precise preoperative evaluation and intraoperative pathological monitoring, with the core goal

of maximizing the preservation of the patient's appearance and function while eradicating the tumor. Moreover, precise tissue-preserving resection techniques such as MMS, when applied in these areas, can effectively reduce the local recurrence rate, further supporting the feasibility of individually adjusting the margin width based on tumor location, and highlighting the importance of preserving function and aesthetics in margin decision-making.

Clinical practice at specific anatomical sites further validates the impact of functional factors on margin selection. Kato *et al.*[29] reported that the selection of surgical margins for plantar melanoma requires a thorough balance between tumor resection and preservation of foot weight-bearing function. Large tissue defects are prone to complications such as chronic non-healing and walking impairment. In addition, Thacoor *et al.*[24] proposed that to reduce the risk of allergic reactions to SLN tracers, extensive local resection should be prioritized before the tracer injection. This operational strategy also reflects the coordination and unity of the principles of functional preservation and margin radical cure, further confirming the significant impact of functional factors on margin decision-making and surgical process design.

4. Technological innovation and clinical application of sentinel lymph node biopsy

The advent of SLNB technology has revolutionized regional lymph node management in early-stage malignant melanoma, marking a pivotal milestone in the transition of melanoma surgical treatment from extensive radical resection to precise stratification. Currently, SLNB is the gold standard for assessing regional lymph node status in early-stage melanoma, with its technical framework continuously refined and clinical indications progressively standardized.

4.1. Core value of sentinel lymph node biopsy in staging and prognosis of early-stage melanoma

Sentinel lymph node biopsy is the most accurate method for pathological staging (pN staging) of clinically localized melanoma. Currently, guidelines in multiple countries recommend its use for early-stage melanoma patients with a tumor thickness ≥ 1 mm, or ≥0.8 mm when accompanied by other high-risk factors.[30] Its core value lies in identifying patients without clinical lymph node metastasis through precise staging. As a representative clinical example, among patients with primary melanoma, the SLNB positive rate shows a significant stepwise increase with rising tumor thickness, particularly in patients with lesions measuring 1–4 mm or greater than 4 mm.[31] International multicenter randomized clinical trials, including MSLT-I, DeCOG-SLT, and MSLT-II, have established the significant value of SLN biopsy for staging, prognosis, and guiding selective treatment in patients with clinically localized melanoma. These studies have demonstrated that a positive SLN status is a critical predictor of both recurrence risk and OS.[32]

The SLN biopsy-positive rate is significantly positively correlated with tumor thickness. In melanoma patients with tumor thickness of 1–4 mm or >4 mm, the SLNB positive rate progressively increases with increasing tumor thickness.[26] Multiple international multicenter randomized clinical trials (including MSLT-I, DeCOG-SLT, and MSLT-II) have confirmed that SLN positivity is a key predictor of recurrence and survival in patients with clinically localized melanoma, and it holds irreplaceable value for patient staging, prognosis assessment, and individualized treatment planning.

In terms of indications, SLNB has been incorporated into clinical guidelines in multiple countries worldwide and is routinely recommended for patients with T1b stage (thickness > 0.8 mm or with ulceration) or higher-stage melanoma.[24] Although SLNB is not routinely recommended for the T1a stage patients, this population still exhibits a 4.4% SLN positivity rate. Factors such as younger age, primary tumor in the head and neck, vascular invasion, and mitotic rate ≥ 2/mm^2 are significantly associated with an increased risk of SLN positivity.[33]

Survival analysis data further confirmed the prognostic stratification value of SLNB: the 5-year melanoma-specific survival rate was significantly lower in SLN-positive patients compared to SLN-negative patients. Among T1a-stage patients, the 5-year survival rate was 90.7% in SLN-positive cases and 99.5% in SLN-negative cases.[34] Additionally, in patients with clinical stage IIB/C melanoma, prognostic models incorporating SLN status offer a greater net benefit in predicting the risk of five-year melanoma-specific death compared with models relying solely on clinicopathological factors. This clinical benefit is particularly pronounced in the younger patient population, where roughly 11 out of every 100 study subjects are able to forgo the administration of unwarranted adjuvant therapy that would otherwise be clinically indicated.[35]

Although SLNB itself has not been shown to improve OS, its prognostic information is crucial for decision-making regarding adjuvant therapy, and SLN-positive patients are more likely to receive adjuvant immunotherapy or targeted therapy. Traditional CLND is gradually being deemphasized because it does not provide a significant survival advantage. Multiple multicenter randomized trials support the use of close ultrasound monitoring rather than routine CLND for patients with positive SLN. Evidence

indicates that early removal of lymph node metastases through SLN excision significantly improves survival rates. In light of the aforementioned clinical evidence, the WHO has formally designated SLN excision as a standardized surgical procedure, recommended for the routine clinical management of patients with primary tumors exceeding 1 mm in thickness.[36]

Regarding surgical timing, studies have shown that performing SLNB either ≤ 7 days or >7 days after primary tumor resection has no significant impact on DFS or melanoma-specific survival. Nevertheless, for patients with pathologically confirmed positive SLNs, performing SLNB within a 30-day clinical window has been shown to correlate with a decreased risk of mortality.[37]

4.2. Improvement of sentinel lymph node biopsy accuracy by preoperative imaging and novel adjunctive technologies

The development of preoperative imaging and novel adjunctive technologies has provided crucial support for improving the accuracy of SLNB, including ultrasound, contrast-enhanced ultrasound (CEUS), radionuclide imaging, fluorescence imaging, and carbon nanoparticles. Meanwhile, the optimization of pathological detection methods and multidisciplinary collaboration have also played a pivotal role.

In the preoperative evaluation of regional lymphatic basins in patients with primary melanoma, conventional ultrasound has been shown to have only limited diagnostic reliability in routine clinical practice.[38] Large multicenter studies have demonstrated that a negative preoperative ultrasound result cannot completely rule out the possibility of lymph node metastasis. However, CEUS has demonstrated advantages in SLN localization and in differentiating benign from malignant lesions. A study by Deng *et al.*[39] involving 47 patients with malignant melanoma showed that the average number of SLNs detected by CEUS was 1.72 ± 0.10, with no statistically significant difference compared with the carbon nanoparticle injection method (1.79 ± 1.07, $p = 0.371$). Regarding the identification of micrometastases, CEUS demonstrated good diagnostic performance, with a sensitivity of 70.0%, a specificity of 97.3%, and an overall diagnostic accuracy of 91.5%. There was a high degree of concordance between the CEUS enhancement patterns and the corresponding pathological findings ($\kappa = 0.726$, $p < 0.001$). Additionally, it features a short acquisition time (approximately one minute) and can track lymphatic vessels to SLNs via subcutaneous injection of a contrast agent, providing functional imaging to assist in detecting micrometastases. The combination of preoperative ultrasound and radionuclide technology can further enhance localization efficacy. For example, Beger *et al.*[40] utilized a multimodal approach involving preoperative ultrasound and ^{99}Tc–albumin nanocolloid lymphoscintigraphy, complemented by intraoperative blue dye staining and hand-held gamma-probe detection. For the clinical detection of SLNs, this combined diagnostic strategy achieved robust performance, with an SLNB detection rate of 94.4% and a corresponding false-negative rate of 8.9%.

In radionuclide imaging technology, tracers such as sulfur colloid labeled with ^{99m}Tc rely on the phagocytic function of macrophages and have a long retention time in SLNs.[40] Dynamic or static imaging acquisition is required to be completed 15 to 30 min following injection, while the time interval between the scanning procedure and subsequent surgical intervention must be controlled to no more than 12 h. The timing of preoperative lymphoscintigraphy has a significant impact on localization accuracy. A meta-analysis by Wong *et al.*[41] showed that the same-day lymphoscintigraphy protocol had a lower false-negative rate than the day-before-surgery protocol, as it maintains high tracer activity and reduces errors caused by isotope decay and tracer migration. As a novel imaging technology, single-photon emission computed tomography/computed tomography (SPECT/CT) provides precise spatial localization of SLNs, which is particularly suitable for complex lymphatic drainage regions such as the head and neck. It helps identify additional SLNs and avoid tracer accumulation in non-lymph node sites, thereby improving the accuracy of SLNB. For example, Wollina *et al.*[42] used intradermal injection of ^{99m}Tc nanocolloid combined with patent blue V and preoperative SPECT-assisted localization, which significantly enhanced the precision of SLN resection.

The optimization of novel tracers and pathological detection techniques also supports improving the efficacy of SLNB. As an emerging technical modality in the field of surgical oncology, carbon nanoparticle tracers have been subjected to exploratory research and clinical testing for lymph node localization in a wide range of other solid malignancies.[43] A study by Deng *et al.*[39] indicated that carbon nanoparticle injection can stain lymphatic vessels and SLNs intraoperatively, but cannot distinguish benign from malignant lymph nodes; combining this method with CEUS can further improve the accuracy of intraoperative SLN localization in terms of pathological testing.[44]

Furthermore, the application of SLNB has been expanded to include pediatric populations. Numerous studies have indicated that the incidence of SLN involvement in children is substantially greater than in adults, ranging from 25% to 60%. This elevated rate

underscores a heightened need for accurate localization methods in this patient group.[45]

4.3. Controversies and the latest clinical evidence on completion lymph node dissection and active surveillance

With the widespread application of SLNB technology, whether SLN-positive patients require CLND has become a central point of contention in the management of regional lymph nodes for early-stage melanoma. In recent years, the results of several large-scale multicenter randomized clinical trials have fundamentally transformed clinical practice in this field, and CLND is no longer considered a mandatory standard treatment for SLN-positive patients.

To date, a series of landmark international multicenter randomized controlled trials have generated robust, high-level clinical evidence that underpins the clinical utility and application value of CLND in surgical oncology practice. The MSLT-II trial revealed that CLND enhances regional disease control rates, but it does not confer a significant improvement in OS. Similarly, the DeCOG-SLT study found that CLND does not provide a meaningful survival advantage and is associated with adverse effects, including lymphedema.[46] In the DeCOG trial, 483 patients were randomly assigned to receive CLND or observation, with three-year OS rates of 81.2% and 81.7%, respectively, showing no significant difference. MSLT-II enrolled 1,939 patients, and the three-year melanoma-specific survival rate was 86% for both the CLND and observation groups. The observation group had a higher local recurrence rate (15%), whereas the CLND group had an 18% higher incidence of lymphedema. Recent results from the DeCOG-SLT and MSLT-II trials further indicate that CLND did not lead to a significant improvement in melanoma-specific survival or distant metastasis-free survival among patients with positive SLNB. Furthermore, the occurrence of postoperative lymphedema was substantially more frequent in patients receiving CLND. Specifically, the MSLT-II study reported a lymphedema incidence of 24% in the CLND cohort, which was markedly higher than the 6% incidence observed in the non-CLND control group.[15]

Based on the above evidence, the current consensus in the academic community is as follows: for melanoma patients with positive SLNB, compared with active observation and monitoring, immediate CLND does not significantly improve overall survival and melanoma-specific survival; although meta-analyses show that immediate CLND can lead to better DFS and regional lymph node control rates, it is accompanied by a significant risk of surgical complications, especially lymphedema (with an incidence rate of approximately 24%), which can seriously affect patients' quality of life. Therefore, CLND is no longer a mandatory standard treatment for patients with positive SLN, and clinical decisions need to be fully individualized, weighing its potential benefits in local control against the risks of surgery-related complications.

The implementation of active surveillance approaches is strongly justified. An analysis of data from the National Cancer Database spanning 2012 to 2020 revealed that patients with clinically node-negative melanoma have a low risk of metastasis, with cerebral metastasis in particular being extremely rare (<0.1%).[44]

Therefore, it is advisable to develop targeted imaging screening strategies based on individual tumor characteristics (such as T stage, ulceration, and lymphovascular invasion [LVI]) to guide the choice between CLND and active surveillance. However, a population-based study by the Bay of Plenty District Health Board in New Zealand showed that the average size of SLN metastases in its cohort (3.53 mm) was larger than that in the MSLT-II cohort (1.07/1.11 mm), and the positivity rate of non-sentinel lymph nodes in CLND (23.8%) was higher than that in MSLT-II (11.5%). These clinical results demonstrate that, for high-risk patient groups characterized by bulky metastatic foci and restricted non-surgical therapeutic alternatives, the implementation of CLND may deliver more favorable clinical benefits compared with a watchful waiting observation strategy.[47] In addition, with the rapid development of adjuvant immunotherapy and targeted therapy, the clinical necessity of CLND has further decreased. After standardizing adjuvant therapy, the recurrence rate in the patient's lymph node area is expected to be lower than the 23% reported in the MSLT-II observation group. However, an early study by Fong *et al.*[48] reported that among 1,269 patients with intermediate-thickness melanoma in the MSLT-I trial, the SLNB plus immediate CLND group had a higher 5-year DFS rate.[49] This benefit was mainly attributed to a reduction in regional lymph node recurrence rate, suggesting that CLND still has clinical value for patients who cannot receive adjuvant systemic therapy.

5. Application and evaluation of minimally invasive surgical techniques in early-stage melanoma

Under the premise of ensuring radical tumor resection, maximal preservation of normal tissues and minimization of surgical trauma represent a critical direction for the surgical treatment of early-stage melanoma. Precision minimally invasive resection techniques, represented by MMS, have become an essential approach for treating melanoma in functionally and aesthetically critical areas,

owing to their core advantage of 100% assessment of resection margins. The clinical application scope and evidence system of these techniques are also continuously being refined.

5.1. Principles and advantages of Mohs micrographic surgery technology

The core surgical tenet of MMS lies in the layer-by-layer resection of tumor tissue, coupled with synchronous real-time histopathological evaluation implemented through intraoperative frozen section analysis.[50] During the surgery, the marginal tissues around and at the base of the tumor are stained and mapped to ensure complete tumor eradication with negative margins and to avoid unnecessary tissue resection. A key advantage of this technique is its excellent tissuesparing capacity. Resection is extended solely in regions where tumor involvement is detected, which effectively eliminates the excessive sacrifice of normal tissue inherent to traditional WLE.[51] In 90% of cases, the marginal length resected in the second stage does not exceed 50% of that resected in the first stage, reflecting the precision of the surgery. The principle and core advantages are illustrated in Figure 1.

5.2. Comparison of efficacy between Mohs surgery and traditional wide local excision

Compared with traditional WLE, MMS demonstrates a significant advantage in controlling the local recurrence rate (LRR). Data from multiple studies indicate that the risk of local recurrence with WLE is markedly higher than with MMS. For example, an analysis encompassing 12 comparative studies showed that the pooled LRRs for

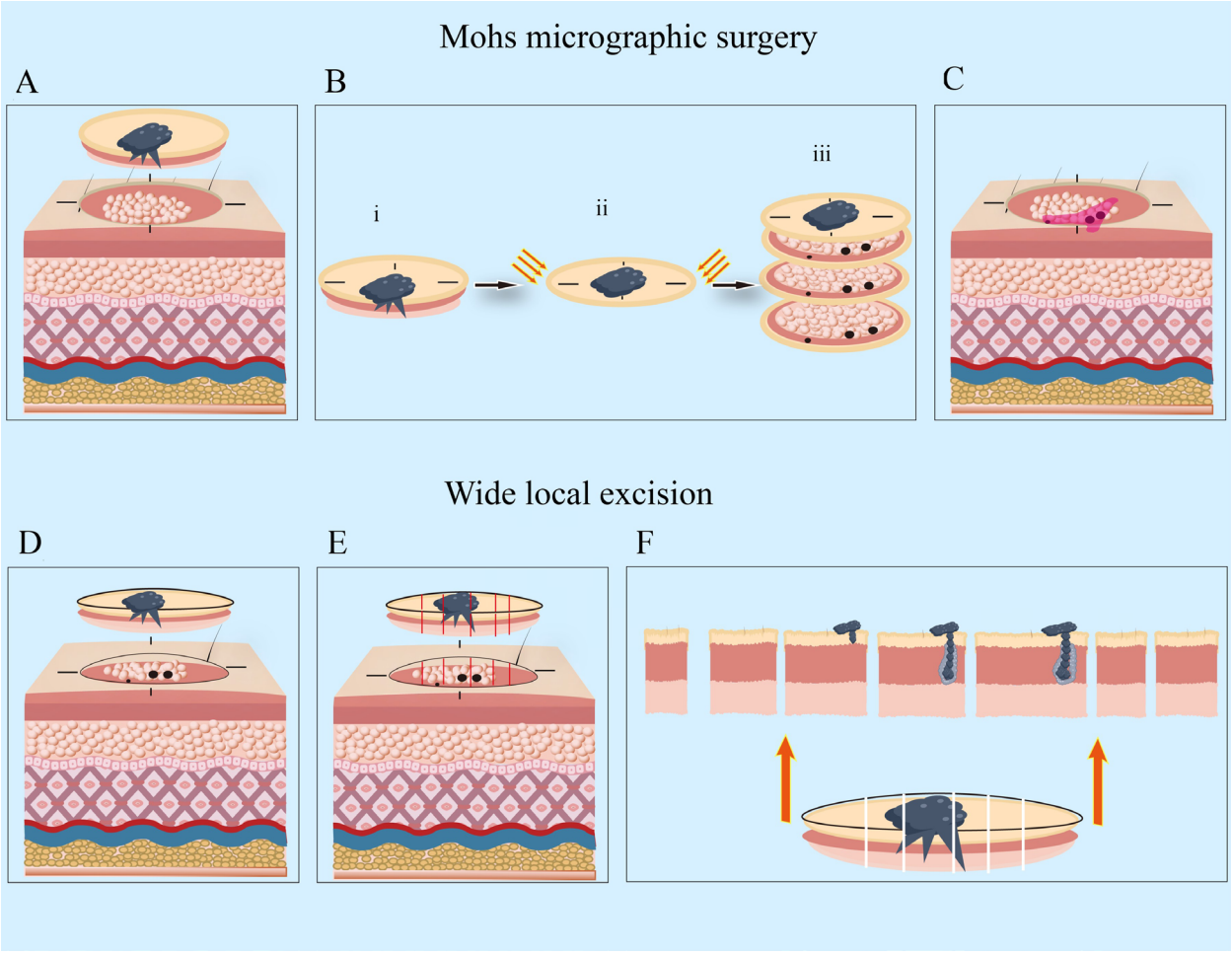


Figure 1. Comparison of Mohs micrographic surgery (MMS) and wide local excision (WLE) as two surgical approaches for melanoma. (A) MMS excision of melanoma. (B) Layered excision with examination of the basal margin for residual tumor. (C) Directed resection is performed only in the areas with residual tumor, and the cycle of "resection - marking - examination" is repeated until no tumor cells are detected in all sections. (D) WLE excision of melanoma. (E) "Bread slice" method used to assess for residual tumor. (F) Residual tumor cells remaining after excision. Figure created by authors.

WLE and MMS were approximately 7% and less than 1%, respectively, with the risk of local recurrence with WLE being 3.3 times that of MMS (95% CI: 1.81–5.89).[52] This advantage stems from MMS's microscopic examination of frozen sections of all peripheral and deep margins, combined with immunohistochemical staining (e.g., MART-1).[53]

Regarding the impact of different initial margin widths on the LRR of MMS, a systematic review and meta-analysis conducted in 2022, which included 43 studies and 9,098 cases, demonstrated that the group with an initial surgical margin of 5–10 mm exhibited the lowest local recurrence rate at 0.3% (95% CI: 0.2–0.5, $p < 0.001$). This rate was significantly lower than that of the 1–5 mm margin group (2.3%) and the ≤ 5 mm margin group (1.4%). A large-sample prospective cohort study on invasive melanoma of the trunk and proximal extremities (1,416 cases with a mean follow-up of 75 months) further confirmed that the actual LRR with MMS treatment was only 0.14% (two cases), significantly lower than the approximately 3% recurrence rate reported with traditional WLE. Long-term follow-up data also support the low-recurrence advantage of MMS; for instance, a 32-year follow-up showed that the LRR of early-stage and invasive melanoma treated with MMS was <0.15%. Even in the setting of head and neck melanoma, MMS has been associated with a decreased incidence of local recurrence compared with conventional WLE.[54]

In terms of survival outcomes, existing studies have shown that MMS and WLE yield comparable OS rates and melanoma-specific survival rates. Database and retrospective studies indicate no significant difference in OS between the two approaches, and some retrospective studies even suggest that MMS confers superior DFS in specific Breslow-thickness strata. Research on invasive melanoma of the trunk and proximal extremities has also confirmed that the MMS treatment group demonstrates favorable outcomes in terms of satellite/in-transit recurrence rate (1.1%) and DFS. For invasive melanoma of the head and neck region, multiple studies have demonstrated that MMS yields superior survival outcomes compared with WLE.

5.3. Current application and controversies of Mohs surgery in special sites and tumor subtypes

MMS has attracted increasing attention in the treatment of melanoma in functionally and cosmetically sensitive areas. By applying immunohistochemical staining to refine surgical margin assessment, this method offers an innovative therapeutic strategy for managing melanoma across specific anatomical regions and histological subtypes.[55] In the head and neck region, MMS is particularly indicated for early invasive melanoma (T1a-T2a) and poorly demarcated tumors (e.g., lentigo maligna melanoma), as it enables comprehensive intraoperative margin evaluation, thereby reducing the need to resect healthy tissue. A study involving 4,062 T1a-T2a patients treated with MMS showed that nearly 40% of the tumors were located in the head and neck. Furthermore, patients with these lesions who underwent MMS at academic and high-volume centers (defined as those handling eight or more cases annually) demonstrated significantly improved long-term survival rates compared to those treated at non-academic and low-volume facilities. This observed disparity may be explained by more thorough lymph node staging and the use of IHC-assisted enhanced pathological assessments at the aforementioned institutions.[56]

Melanoma of the hand, especially subungual melanoma, poses unique challenges in diagnosis and treatment. Traditional treatment mostly involves interphalangeal amputation, while the application of Mohs surgery in this site is still in the exploratory stage. Recent studies have demonstrated that for patients diagnosed with superficial subungual melanoma—whether *in situ* or with a Breslow thickness less than 0.5 mm—digit-preserving surgical approaches can yield substantial functional restoration. These procedures involve excision of the nail apparatus, with intraoperative dissection of margins down to the periosteum or coronal osteotomy of the distal phalanx, combined with local or free-flap reconstruction techniques such as ultra-thin superficial inguinal perforator flaps and extracellular matrix grafts. Importantly, this approach achieves survival outcomes comparable to those of traditional amputation, without significant differences in long-term prognosis.[57] However, controversy remains regarding the potential impact of complex reconstruction on postoperative local surveillance, with no conclusive evidence to support this concern.

In specific melanoma subtypes, lentigo maligna and recurrent melanoma represent key areas for MMS application. Studies on melanoma of the trunk and extremities have shown that 9.5% of cases—mainly recurrent melanoma and the lentigo maligna subtype—require a wider surgical margin than that recommended by the National Comprehensive Cancer Network (NCCN). By achieving resection with truly histologically negative margins, MMS significantly reduces the LRR (the predicted recurrence rate with traditional wide excision is approximately 2%, compared with 0.1% with MMS).[58] Clinical and pathological characteristics (such as patient age, tumor size, recurrence status, and the lentigo maligna subtype) are significantly associated with margin-positive

tumors, yet their combined predictive value is limited (with an information gain of only 11.6%).[59] This indicates that it is difficult to accurately predict which tumors require a wider margin based solely on preoperative assessment, further supporting the advantages of MMS for individualized and precise margin resection.

Despite the demonstrated advantages of MMS in the aforementioned scenarios, its application remains controversial. Technically, MMS has high requirements for operator training and equipment costs, and its operation is complex and time-consuming, which limits its popularization at the primary level. Due to the lack of unified standards across centers, there are significant differences in margin determination, repair methods, and other factors that affect comparisons and promotion of curative effects. There is no standardized process for the combined application of MMS and SLNB, and the timing coordination and operation connection are not unified, which increases the complexity of the operation. For this reason, authoritative guidelines from bodies such as the American Academy of Dermatology and the NCCN provide no clear endorsement of MMS in the management of melanoma of the trunk, extremities, and hands, resulting in a divergence between actual clinical practice and official guideline recommendations.[60]

6. Clinical practice and future directions of individualized surgical treatment strategies

With the deepening understanding of the biological characteristics of melanoma and the rapid advancement of precision surgical techniques and systemic therapies, the surgical treatment of early-stage malignant melanoma has entered a new era of personalized precision medicine. Clinical decision-making is no longer limited to tumor thickness stratification alone; it now involves careful consideration of multiple multidimensional factors, including patient-specific characteristics, tumor pathology and molecular features, and anatomical location to formulate the optimal individualized treatment plan.

6.1. Selection of surgical margins and adjuvant therapy based on patient and tumor characteristics

Patient-specific characteristics are the primary consideration in individualized treatment decisions, particularly in the selection of SLNB indications and the evaluation of the benefits of adjuvant therapy. Studies have indicated that age ≤ 42 years, primary tumor of the head and neck, LVI, and a high mitotic rate (≥2/mm^2) are high-risk factors for sentinel lymph node positivity. In contrast, for older patients (especially those aged over 75 years), the clinical benefits of adjuvant therapy are limited. Due to competing risks of non-tumor-related death, the number needed to treat (NNT) to prevent one melanoma-related death increases significantly (>25), which is much higher than that in the younger group (the NNT is approximately 14.7 for patients aged 40–44 years). Furthermore, treatment expenses increase substantially with age, and the NNT and corresponding costs are notably higher among patients harboring *BRAF* mutations.[61] Therefore, for elderly patients, the clinical benefits of SLNB and adjuvant therapy should be evaluated more carefully to avoid unnecessary overtreatment.

Tumor thickness, also known as Breslow thickness, is the most significant prognostic indicator for primary malignant melanoma. Clinically, this factor plays a vital role in determining optimal surgical margin sizes and in guiding decisions regarding SLNB implementation.[62] Based on tumor thickness and additional pathological indices, the NCCN guidelines recommend individualized adjustments to surgical margin width and SLNB strategies.[63] In clinical practice, a 2 cm surgical margin is recommended for melanoma of the trunk, extremities, and head and neck with a thickness exceeding 2 mm, and a thickness over 0.8 mm is an indication for axillary and regional lymph node SLNB. Multicenter research has demonstrated that the rate of SLN positivity is 7.6% in the pT1b category (tumor thickness 1.0–2.0 mm) and 12.8% in the pT2a category (tumor thickness 2.01–4.0 mm). These findings support a direct association between increasing tumor thickness and the likelihood of lymph node metastasis. For specific anatomical locations such as subungual melanoma of the fingers and toes, digit-preserving surgery with a 5 to 10 mm margin can effectively manage invasive cases. This strategy correlates with a low incidence of local recurrence and satisfactory survival results, which emphasizes that site-specific factors play a key role in the tailored design of surgical margins.[2]

Anatomical location further refines surgical strategies by influencing prognosis, surgical trauma, and the technical difficulty of SLNB. For melanoma of the head and neck, the success rate of SLN identification (approximately 85%) is significantly lower than that for the trunk and extremities (approximately 98%) due to the complex lymphatic drainage. Such cases require the use of dual tracers (the radionuclide ^{99}Tc and blue dye) and assistance with SPECT/CT imaging at high-volume centers to reduce the false-negative rate. Meanwhile, head and neck surgeries carry a high risk of procedure-related complications; for instance, in the management of melanoma located on the right lower lip, the application of neoadjuvant immunotherapy (specifically pembrolizumab) to reduce tumor size prior to MMS effectively minimizes surgical trauma. Furthermore,

distinct anatomical locations are associated with substantial prognostic heterogeneity. Tumors arising in the extremities (excluding the hands and feet) carry a favorable prognosis, whereas those located in the trunk and headneck region confer a worse prognosis; lesions involving the scalp, hands, and feet are linked to the most dismal prognosis of all subgroups.[64] This also provides an important reference for individualized surgery and adjuvant therapy decisions.

The molecular and pathological characteristics of the tumor (e.g., *BRAF* mutation status, programmed cell death ligand 1 (*PDL1*) expression, mitotic rate, and ulceration) form the basis for individualized strategies. The *BRAF* mutation status significantly influences the benefit of adjuvant therapy. Melanoma with high *PDL1* expression displays marked responsiveness to immunotherapy, and pathological complete remission can be achieved after neoadjuvant immunotherapy, thereby laying the foundation for reducing the extent of surgical resection.[65] Among pathological indicators, a mitotic rate > 1/mm^2 is the only independent factor for predicting SLN metastasis (especially high-risk metastasis in tumors with a maximum diameter > 1 mm; odds ratio = 1.95, $p = 0.008$).[66] A mitotic rate ≤ 1/mm^2 can significantly reduce the risk of sentinel lymph node positivity in the pT1b and pT2a subgroups (with likelihood ratios of 0.37 and 0.46, respectively). Combined with the detection of micrometastases via tumor ulceration (an adverse prognostic indicator independent of thickness) and multiplex IHC S−100, HMB−45, etc., these indicators form a comprehensive pathological decision-making framework that is used to determine the indications for SLNB and adjust the width of surgical margins.[67] Achieving the paradigm shift from "one-size-fits-all" to "tailor-made" treatment approaches.

6.2. The impact of neoadjuvant and adjuvant systemic therapy on surgical planning

The rapid advancement of targeted therapy and immunotherapy has fundamentally transformed the treatment landscape of melanoma, profoundly influencing the surgical planning for early-stage and locally advanced melanoma. Surgical intervention is no longer an isolated therapeutic approach but has become a core component of an integrated treatment system deeply integrated with systemic therapy.

The application of neoadjuvant systemic therapy offers new possibilities for downgrading and optimizing surgical regimens. BRAF/MEK inhibitor combination therapy demonstrates high objective response rates and rapid therapeutic onset, thereby increasing flexibility in determining the optimal timing of surgery.[68] Emergency surgical resection should be prioritized only for critically ill patients with unstable vital signs. For high-risk stage III melanoma patients, existing evidence confirms that preoperative neoadjuvant immune checkpoint inhibitor therapy is safe and feasible, without significantly increasing the overall risk of complications or surgical complexity associated with lymph node dissection. Moreover, the high pathological response rate induced by this therapy can further simplify surgical procedures, reduce the extent of resection, and decrease surgery-related complications. For tumors in functionally critical areas such as the head and neck, neoadjuvant therapy-induced tumor regression enables patients who would otherwise require extensive resection to undergo more conservative functional-sparing surgery. This approach ensures radical treatment while significantly improving postoperative quality of life.

The application of adjuvant systemic therapy has also transformed traditional surgical approaches. Standardized adjuvant immunotherapy or targeted therapy can significantly reduce the risk of regional lymph node recurrence in SLN-positive patients, further diminishing the clinical necessity of CLND and making active surveillance one of the mainstream options for SLN-positive patients. Furthermore, the combined application of systemic therapy and surgery has also changed the clinical practice of metastasectomy. Data show that the utilization rate of melanoma metastasis resection increased significantly between 2016 and 2021, a trend closely associated with the widespread adoption of new systemic therapies. These findings imply that metastasectomy may be indicated in an expanded group of patients who achieve a positive response to systemic treatment, which further facilitates the personalized design of surgical interventions.[69]

6.3. Multidisciplinary collaboration in surgical treatment and consideration of patients' quality of life

The individualized treatment of early-stage malignant melanoma cannot be separated from support from a multidisciplinary team system, and the patient's quality of life and psychosocial needs have also become core aspects that cannot be ignored in surgical decision-making and full-course management.

Multidisciplinary team collaboration is of great significance for optimizing surgical decision-making and improving the prognosis and quality of life of patients undergoing surgical treatment for early-stage malignant melanoma. In 2023, a study by Na *et al.*[70] in the Waikato region of New Zealand showed that multidisciplinary cooperation among dermatology, general practitioners and plastic surgery, especially the use of teledermatology to realize contactless first specialist appointments, not only

achieved a 100% response rate but also significantly reduced the waiting time for patients to undergo their first specialist evaluation, thereby securing a critical window for early intervention. In addition, multidisciplinary collaboration is key to ensuring standardized patient management throughout the process. The Swedish TRIM prospective multicenter randomized trial evaluated patients' health-related quality of life using a standardized scale system, with a focus on psychological issues such as anxiety that may arise from imaging follow-up examinations.[71] The study suggested that multidisciplinary teams should ensure diagnostic and therapeutic efficacy while fully addressing patients' psychosocial support and optimizing individualized follow-up protocols. It also highlighted that insufficient multidisciplinary discussions in some regions have led to ineffective standardized referral and follow-up for stage II melanoma patients, further underscoring the necessity of multidisciplinary consultation in the comprehensive postoperative management of patients.

7. Conclusion

In summary, surgical treatment for early-stage malignant melanoma has undergone a profound paradigm shift. It has evolved from the past art of "wide excision" based on anatomical experience to today's science of "precision integrated surgery" grounded in tumor biology, evidence-based medicine, and multidisciplinary integration.

Regarding the width of surgical margins, multiple prospective randomized controlled trials and systematic meta-analyses have confirmed that formulating rational margin widths stratified by tumor thickness (e.g., 0.5 cm to 2 cm) can both ensure local tumor control and reduce functional and cosmetic impairments caused by overtreatment. Refined margin strategies, combined with MMS and IHC-assisted microscopic margin assessment, achieve complete pathological margin clearance and maximal tissue preservation. This approach is particularly suitable for the head and neck as well as other special anatomical sites, significantly reducing the risk of local recurrence without compromising overall survival.

Sentinel lymph node biopsy is the gold standard for staging and prognostic assessment in the management of regional lymph nodes in early-stage melanoma. Continuous advancements in preoperative imaging, novel tracer agents, and pathological detection techniques have further improved the detection rate and localization accuracy of SLN micrometastases. As one of the most important independent prognostic indicators, SLN status provides a core basis for decision-making regarding adjuvant systemic therapy. In recent years, CLND has been replaced in clinical practice by close surveillance and adjuvant therapy, as it has not been shown to improve survival and is associated with a significant increase in complications; individualized dynamic surveillance has gradually become the standard strategy.

Personalized treatment is the core direction of development in the surgical management of early-stage melanoma. The formulation of surgical plans requires careful consideration of patient age, tumor thickness, anatomical location, molecular mutation characteristics, and pathological risk indicators to achieve precise risk stratification and optimized treatment decision-making. The development of neoadjuvant and adjuvant systemic therapies has not only significantly improved long-term patient outcomes but also profoundly transformed the timing of surgery, extent of resection, and regional lymph node management strategies. This shift has propelled surgical interventions from a standalone treatment modality to a core component of an integrated therapeutic system deeply embedded within systemic therapy. Furthermore, the establishment of multidisciplinary collaboration frameworks enables further optimization of diagnostic and therapeutic processes, achieving a balance between radical tumor eradication and patients' quality-of-life requirements.

The future development of surgical treatment for early-stage malignant melanoma will revolve around the in-depth integration of precision medicine, minimally invasive technologies, and systemic therapy. The optimization of surgical margin strategies, the refinement of SLNB techniques, the standardization and widespread adoption of MMS, and the clinical validation of novel perioperative treatment strategies will remain the core research directions in this field.

Overall, surgical treatment for early-stage malignant melanoma is trending toward precision, minimally invasive, and comprehensive management based on individual patient characteristics, laying a solid foundation for improving prognosis and enhancing quality of life.

Acknowledgments

The authors acknowledge the support from the Affiliated Hospital of Jining Medical University and Shandong Provincial Hospital for providing research resources and technical assistance.

Funding

None.

Conflict of interest

The authors declare no conflicts of interest related to this

study.

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Ethics approval and consent to participate

Not applicable.

Availability of data

Not applicable.

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