Journal of
Personalized Medicine

MDPI

Review

Surgical Management of Cutaneous Melanoma in the Era of Neoadjuvant Immunotherapy and Precision Oncology

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Abstract

Surgery remains central to melanoma care, but its indications and sequencing increasingly depend on disease stage, systemic treatment and individual risk. This narrative review examines established and emerging surgical strategies across stages I–IV, including the limitations of sentinel lymph node biopsy (SLNB) as a stand-alone prognostic measure and the potential contribution of artificial intelligence (AI) and digital pathology. Landmark trials, follow-up reports, clinical guidelines and selected prognostic and computational studies were assessed qualitatively. The original targeted bibliographic search was supplemented during revision through 5 November 2026. No meta-analysis or formal certainty assessment was performed. Stages I–II require thickness-adapted excision and individualized consideration of nodal staging; adjuvant anti-PD-1 therapy is an option for eligible stage IIB/IIC disease. Clinicopathological algorithms, including BAUSSS, address limitations of nodal status alone but do not establish the safety of replacing indicated SLNB. In stage III, surveillance has replaced routine completion lymph node dissection after a positive sentinel node, while neoadjuvant immunotherapy and pathological response increasingly guide treatment of macroscopic disease. Stage IV surgery is reserved for selected multidisciplinary indications. AI studies support diagnostic assistance, risk estimation and response prediction, but clinical utility for changing surgical extent remains unproven. Personalized melanoma surgery requires stage-specific integration of anatomical, pathological and molecular information. Prognostic discrimination, treatment-benefit prediction and the safety of surgical omission are distinct evidentiary questions.

Keywords: cutaneous melanoma; melanoma surgery; disease stage; sentinel lymph node biopsy; BAUSSS; neoadjuvant immunotherapy; pathological response; digital pathology; artificial intelligence

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Academic Editors: László Mangel and Mircea Tampa

Received: 17 October 2026
Revised: 5 November 2026
Accepted: 18 November 2026
Published: 22 November 2026

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1. Introduction

Cutaneous melanoma accounted for approximately 330,000 new cases and 59,000 deaths worldwide in 2022 [1]. Surgery remains the principal curative treatment for localized disease, but effective systemic therapies have changed when an operation is performed, what information is required beforehand and how postoperative treatment is selected. AJCC eighth-edition staging provides a common anatomical framework, while patient characteristics, actionable mutations and treatment response add information that stage alone cannot capture [2,3].

Randomized trials have replaced unnecessarily extensive primary excisions with thickness-adapted margins. Sentinel lymph node biopsy (SLNB) introduced pathological assessment of clinically occult nodal disease; subsequent trials showed that a positive sentinel node does not routinely require completion lymph node dissection (CLND) [4–12]. These developments should be distinguished from the current debate about the incremental prognostic and treatment-selection value of SLNB itself. Nodal status, the probability of nodal involvement and the probability of melanoma-related death are related but different outcomes.

Adjuvant checkpoint blockade and BRAF/MEK inhibition reduce recurrence in defined high-risk populations [13–16]. Neoadjuvant immunotherapy has subsequently improved event-free survival in resectable advanced melanoma, creating an opportunity to assess biological response before postoperative treatment is chosen [17,18]. Pathological response can inform adjuvant treatment within validated regimens; using that response to omit therapeutic nodal surgery is a separate question [19–22].

This review organizes the evidence by stages I–IV, addressing surgery, systemic therapy, molecular testing, response assessment and future directions within each stage. A dedicated section evaluates AI and digital pathology in diagnosis, prognosis and treatment response. The proposed concept of biology-guided melanoma surgery is used as an organizing framework, not as a validated predictive model or an additional indication for an operation.

2. Review Approach

This focused narrative review used targeted PubMed searches, supplemented by web-indexed PubMed/MEDLINE records, primary journal or publisher websites and reference checking of relevant studies and guidelines. The initial literature search of 17 October 2026 was supplemented by focused searches through 5 November 2026. Searches were limited to these sources and were not intended to constitute a systematic review.

Search concepts combined melanoma with surgical margins or wide local excision; sentinel lymph node biopsy, age, prognosis or BAUSSS; stage II and adjuvant immunotherapy; neoadjuvant therapy, pathological response or named trials; BRAF, molecular profiling or metastasectomy; and artificial intelligence, deep learning, digital pathology, whole-slide imaging, prognosis or immunotherapy response. Specific searches also used trial acronyms, article titles and DOI identifiers to verify key publications. These were iterative, topic-specific searches rather than a single exhaustive Boolean strategy.

The synthesis prioritized peer-reviewed human studies relevant to cutaneous melanoma: randomized trials for treatment effects; prospective cohorts for response-directed strategies; observational studies for surgical selection and biomarkers; and development or validation studies for prognostic and AI models. Current professional guidelines provided clinical context. English-language reports were considered, without a fixed lower publication-date limit, so foundational surgical studies could be retained. Uveal and mucosal melanoma-specific management, animal- or laboratory-only studies, isolated case reports, retracted articles and reports without sufficient verifiable clinical information were outside the princi-

pal evidence base. Mechanistic statements were included only as context. Acral melanoma was included within cutaneous disease where represented in the source population.

Publications were checked for overlapping trial names, populations, treatment arms and follow-up periods. The primary report and later analyses of the same cohort were treated as a single evidence stream; later reports were retained when they added survival, toxicity, quality-of-life or biomarker information. Pooled analyses containing previously reported patients were not counted as independent confirmation. Discordant findings were considered according to study design, population, endpoint, follow-up, treatment era, external validation and confounding. Randomized comparisons informed causal treatment claims; model performance and observational associations were not treated as proof that changing an operation improves outcomes.

Selection and appraisal were qualitative. No prospectively registered protocol, duplicate independent screening, exhaustive screening counts, formal risk-of-bias score or pooled effect estimate is reported. The review therefore remains susceptible to selection and publication bias. Tables distinguish established treatment evidence from exploratory prediction and surgical de-escalation research.

3. Evidence Synthesis by Disease Stage

3.1. Stage I Melanoma

3.1.1. Primary Surgery and Selective Nodal Staging

Stage I disease is localized, without regional or distant metastases. Complete diagnostic excision establishes Breslow thickness, ulceration and other histopathological features before definitive wide local excision. A 1 cm clinical margin is recommended by ESMO for invasive primaries up to 2 mm thick; other guidance permits a range for selected intermediate-thickness lesions. The margin policy should therefore be identified explicitly and adapted to anatomical constraints without assuming that narrower margins are oncologically equivalent [2,4,23–25].

SLNB is generally not offered for pT1a melanoma, is discussed for pT1b disease and is recommended for clinically node-negative tumors thicker than 1 mm, subject to fitness and whether the result would influence management [23,26]. Technical mapping studies established the procedure, while MSLT-I demonstrated staging and disease-control value without a statistically significant melanoma-specific survival advantage in its overall intermediate-thickness population [7–9]. A positive sentinel node changes the pathological stage to stage III; it does not represent persistent stage I disease.

Counseling should distinguish the chance of a positive node from the risk of dying from melanoma. The Melanoma Institute Australia nomogram estimates nodal positivity using clinicopathological factors and has undergone external validation [27,28]. In contrast, BAUSSS combines Breslow thickness, age, ulceration, melanoma subtype, sex and anatomical site to estimate melanoma mortality without requiring SLNB [29]. It is a clinicopathological algorithm, rather than a molecular assay or a synonym for AI. These tools address different endpoints and should not be treated as interchangeable.

Dixon and colleagues compared age-specific predictions of nodal positivity and survival and examined Tübingen cohort data. They reported a mismatch between these outcomes at age extremes, with relatively frequent predicted nodal positivity despite low mortality in younger patients and substantial mortality despite lower nodal positivity in older patients [30]. Their proposed age-based restrictions on SLNB are controversial and do not establish the safety of omission. The analysis supports age-sensitive interpretation of prognosis; current indications still require integration of tumor features, comorbidity, patient preferences and the clinical consequences of knowing nodal status [23,26].

3.1.2. Systemic Therapy, Molecular Testing and Future Directions

Routine adjuvant or neoadjuvant systemic therapy is not established for completely resected stage I melanoma. Routine actionable-mutation testing is not recommended at this stage [23,31]. Consequently, pathological response after systemic treatment is not a routine stage I endpoint. Histological regression in an untreated primary should not be equated with treatment-induced pathological complete response.

Future work should determine whether well-calibrated risk tools can safely refine SLNB selection and surveillance, particularly at age extremes. Molecular gene-expression profiles should not currently replace standard SLNB selection: the Society of Surgical Oncology consensus identifies insufficient evidence for routine management changes based on these assays [32]. Computational pathology may improve risk estimation, but a reduction in unnecessary procedures must be demonstrated prospectively rather than inferred from discrimination statistics alone.

3.2. Stage II Melanoma

3.2.1. Excision Margins and the Changing Value of SLNB

Stage II encompasses node-negative primaries with higher-risk thickness and ulceration combinations. Under ESMO guidance, excision uses a 1-cm margin for tumors up to 2 mm and 2 cm for thicker tumors [23]. Randomized comparisons support avoiding 4 cm margins when 2 cm is adequate, but the UK thick-melanoma trial cautions against extending this logic to a 1 cm margin for all thick primaries [5,6,33,34]. MelMarT demonstrated feasibility and differences in reconstructive burden, not definitive long-term equivalence of 1 and 2 cm margins [35]. Table 1 summarizes the surgical evidence.

Table 1. Randomized surgical evidence informing contemporary melanoma care.

Study	Population and Comparison	Principal Finding	Clinical Interpretation
WHO trial [4]	Localized melanoma ≤2 mm; 1 versus 3 cm margins	No demonstrated survival disadvantage with 1 cm	Supports limited margins in the studied population
Intergroup trial [6]	Melanoma 1–4 mm; 2 versus 4 cm margins	No significant survival advantage for 4 cm	Avoid unnecessarily wide excision
Swedish/Danish trial [5]	Melanoma >2 mm; 2 versus 4 cm margins	No survival advantage for 4 cm	Supports 2 cm margins for thick primaries
UK trial [33,34]	Melanoma >2 mm; 1 versus 3 cm margins	More locoregional recurrence with 1 cm; later melanoma-specific mortality difference	Does not support routine 1 cm margins for thick tumors
MSLT-I [7]	Clinically node-negative disease; SLNB-based management versus observation	Better disease-free outcomes; no significant overall MSS benefit in the intermediate-thickness group	Staging and disease-control information; no universal survival claim
MSLT-II [10]	Positive SLNB; CLND versus ultrasound surveillance	No MSS benefit; better regional control but greater lymphedema with CLND	Routine CLND can be avoided in suitable patients
DeCOG-SLT [11,12]	Positive SLNB; CLND versus observation	No survival benefit from CLND, including final follow-up	Supports surveillance after microscopic nodal involvement

Original synthesis of the cited trials. Comparisons concern different populations and should not be pooled informally. CLND, completion lymph node dissection; MSS, melanoma-specific survival; SLNB, sentinel lymph node biopsy.

SLNB can identify occult stage III disease and inform prognosis, surveillance and systemic treatment options. However, its incremental clinical utility must be reconsidered when adjuvant therapy is already available for stage IIB/IIC disease. ESMO permits discussion of omission in selected T3b/T4a/T4b patients eligible for adjuvant treatment, while emphasizing the potential loss of staging information and implications for locoregional management [23]. This is a shared decision, not evidence that nodal status is irrelevant. Importantly, the pivotal stage IIB/IIC adjuvant trials enrolled pathologically node-negative patients; their results do not themselves validate an SLNB-omission pathway [36,37].

BAUSSS is relevant to this discussion because it estimates mortality from readily available clinical and primary-tumor features [29]. Nevertheless, a high predicted mortality risk is not proof of benefit from a particular adjuvant regimen, and a low estimate does not demonstrate that missing occult nodal disease is harmless. Comparative assessment should use calibrated absolute risks and the decision the model is intended to support. Models that incorporate nodal findings remain relevant: an international retrospective study developed and externally validated individualized recurrence and melanoma-specific survival estimates after SLNB [38].

3.2.2. Adjuvant Immunotherapy and Molecular Characterization

Completely resected stage IIA disease is generally managed with surgery and surveillance; adjuvant anti-PD-1 therapy is considered for eligible stage IIB/IIC patients [23,31,39]. In KEYNOTE-716, pembrolizumab improved recurrence-free and distant metastasis-free outcomes compared with placebo. At the final distant-metastasis analysis, the 36-month distant metastasis-free survival estimates were 84.4% and 74.7%, respectively, with a hazard ratio of 0.59 [36,40]. Subsequent follow-up extends the same randomized population [41]. CheckMate 76K independently demonstrated a recurrence-free survival benefit with nivolumab; its primary analysis reported a hazard ratio of 0.42 and grade 3/4 treatment-related adverse events in 10.3% versus 2.3% with placebo [37]. Different follow-up and populations preclude ranking these agents through cross-trial comparisons.

The discussion should address absolute recurrence risk, competing illness, persistent immune-related toxicity and the maturity of survival evidence. A recurrence endpoint should not be presented as a proven overall survival advantage. Actionable-mutation testing can be considered in stage IIB/IIC but is not routinely recommended in stage IIA; BRAF testing may inform subsequent treatment planning without establishing BRAF/MEK inhibition as a routine stage II adjuvant treatment [23,31].

3.2.3. Pathological Assessment and Anticipated Changes

Because routine treatment begins with surgery, standard pathology establishes risk rather than measuring neoadjuvant response. Pathological complete response is therefore not a routine treatment-selection endpoint in stage II. Prognostic ctDNA associations in resected high-risk disease provide a rationale for prospective studies, but undetectable ctDNA cannot exclude residual disease or justify omission of staging or recommended treatment [42].

The principal research need is to identify who benefits enough from adjuvant therapy to justify its toxicity. Trials should separately evaluate improved risk estimation, prediction of treatment benefit and safe reduction of SLNB or surveillance burden. Evidence for treatment-related chronic toxicity and for computational prognostic models supports these questions without resolving them [43–45].

3.3. Stage III Melanoma

3.3.1. Microscopic Nodal Disease After a Positive Sentinel Node

Microscopic sentinel-node disease and clinically detectable nodal disease require different treatment pathways. MSLT-II and DeCOG-SLT found no survival advantage from routine CLND after a positive sentinel node; surveillance with high-quality nodal ultrasonography therefore replaces immediate dissection in most appropriately selected patients [10–12]. Contemporary observational evidence supports adoption of this approach [46]. The ability to attend surveillance and access expert ultrasonography remains important. These trials do not justify omitting therapeutic surgery for an initially bulky nodal metastasis.

After complete resection, adjuvant anti-PD-1 therapy is supported by KEYNOTE-054 and CheckMate 238, while COMBI-AD supports dabrafenib plus trametinib for eligible BRAF V600-mutant disease [13–16]. Trial populations and nodal tumor-burden requirements differ; the smallest-volume stage IIIA disease should not be assumed to have the same absolute benefit as high-risk macroscopic stage III disease. BRAF V600 testing is central to selecting a targeted option, while broad profiling does not automatically change management in every resectable patient [23,31]. Treatment effects cannot be transferred across settings: RELATIVITY-098 did not improve recurrence-free survival by adding relatlimab to adjuvant nivolumab after complete resection of stage III/IV disease [47].

3.3.2. Macroscopic Resectable Disease and Neoadjuvant Treatment

OpACIN, OpACIN-neo and other early studies established feasibility, explored dosing and associated pathological response with durable disease control [48–52]. SWOG S1801 then randomized patients with resectable stage IIIB–IV melanoma to perioperative or adjuvant-only pembrolizumab; estimated 2-year event-free survival was 72% versus 49% [17]. NADINA, in macroscopic resectable stage III disease, compared neoadjuvant nivolumab plus ipilimumab followed by surgery and response-directed adjuvant treatment with surgery followed by nivolumab. Estimated 12-month event-free survival was 83.7% versus 57.2%, and 59.0% of patients in the neoadjuvant group achieved major pathological response [18]. These are distinct regimens and populations, not a direct comparison of neoadjuvant combinations.

In NADINA, major pathological responders omitted adjuvant treatment, while planned surgery remained part of the strategy [18]. Current European guidance supports neoadjuvant immunotherapy for suitable patients with pathologically confirmed macroscopic regional disease [23,31]. Baseline staging, documented resectability, immune-related toxicity assessment and a planned surgical interval are required. Progression, toxicity or loss of operability before surgery must be incorporated into counseling and monitoring [53,54]. Neoadjuvant nivolumab plus relatlimab has encouraging phase II results, but does not carry the same evidentiary weight as a phase III comparison [55]. Table 2 summarizes the trial-specific surgical implications.

Resectable satellite or in-transit disease also falls within stage III, including presentations without nodal involvement. Limited deposits may be excised when morbidity is acceptable; extensive, rapidly recurring or unresectable disease requires multidisciplinary consideration of systemic or regional therapy. Findings from nodal index-lesion studies cannot automatically be transferred to every in-transit presentation [23,31].

Table 2. Neoadjuvant studies and their specific implications for surgery.

Study	Design and Treatment	Main Contribution	What It Does Not Establish
OpACIN and OpACIN-neo [48,49,51,52]	Early-phase stage III studies; ipilimumab plus nivolumab	Feasibility, dosing and association of pathological response with outcomes	Routine surgical omission or superiority over all alternative regimens
SWOG S1801 [17]	Randomized phase II; perioperative versus adjuvant-only pembrolizumab; stage IIIB–IV	2-year EFS 72% versus 49%	Safety of omitting planned resection
NADINA [18]	Randomized phase III; neoadjuvant nivolumab/ipilimumab versus surgery then nivolumab; macroscopic stage III	12-month EFS 83.7% versus 57.2%; response-directed adjuvant therapy	Routine omission of TLND after response
PRADO [19–21]	Nonrandomized phase II; index-node response directs surgery and adjuvant treatment	Omission of TLND in most major responders; durable follow-up	Randomized equivalence to standard TLND
Nivolumab and relatlimab [55]	Small phase II neoadjuvant study	Encouraging pathological responses	Phase III evidence for this regimen or its use to reduce surgery
INMC update 2026 [56]	Pooled trial and nontrial data; 1038 patients	Long-term response–outcome associations across regimens	Independent replication of component cohorts or randomized omission evidence

Original synthesis. Trial estimates retain their own endpoints and follow-up. EFS, event-free survival; INMC, International Neoadjuvant Melanoma Consortium; TLND, therapeutic lymph node dissection. MPR denotes ≤10% residual viable tumor.

3.3.3. Molecular Testing and Pathological Response

BRAF V600 status should be established in stage III because it affects available systemic options. Neoadjuvant BRAF/MEK inhibition can produce substantial pathological regression, but long-term NeoCombi and NeoTrio data show why response after targeted therapy should not be assigned the same prognostic meaning as response after checkpoint blockade [57,58]. Tumor profiling may facilitate trial participation; routine molecular findings do not independently determine the extent of nodal resection.

Standardized pathological assessment quantifies residual viable melanoma within the treated tumor bed, together with regression-related fibrosis, necrosis and inflammatory changes. Pathological complete response indicates no residual viable tumor; major pathological response includes complete response and up to 10% viable tumor. Partial response comprises more than 10% and up to 50%, and non-response more than 50%, under commonly used INMC categories [22]. Reporting should specify the sampled lesion, specimen handling, tumor-bed assessment and response definition. A radiological response is not a substitute for this examination.

The original INMC pooled analysis associated pathological response with favorable survival [59]. Its 2026 update included 1038 patients from 26 centers, encompassing trials and nontrial cohorts, and reinforced the long-term prognostic value of major response after immune checkpoint blockade [56]. However, regimen selection and postoperative

treatment were not uniformly randomized; overlapping cohorts and confounding limit causal inferences about adjuvant or surgical omission.

PRADO specifically tested response-directed management after neoadjuvant ipilimumab plus nivolumab. The resected index node determined subsequent treatment, and therapeutic lymph node dissection (TLND) was omitted in most major responders [19]. Five-year follow-up supports durable outcomes, while comparisons with OpACIN-neo remain nonrandomized [20,21]. Concordance between index-node and basin response supports the approach but cannot guarantee that every unexamined node is free of viable tumor [60]. NADINA validates a neoadjuvant and response-directed adjuvant strategy; it does not establish routine omission of TLND.

3.3.4. Future Directions Within Stage III

The next step is prospective testing of less extensive nodal surgery with standardized sampling, regional-recurrence endpoints, rescue pathways and patient-reported outcomes. ctDNA dynamics and COMBI-AD biomarker analyses support further risk stratification, but demonstrate prognostic association rather than the clinical benefit of a ctDNA-directed operation [61–63]. Biomarker negativity should not independently trigger surgical omission.

Intralesional talimogene laherparepvec and daromun studies investigate additional preoperative approaches, while individualized neoantigen therapy with pembrolizumab in KEYNOTE-942 explores postoperative personalization [64–66]. These strategies require regimen-specific evaluation; their results should not be generalized into permission to omit otherwise indicated surgery. AI-assisted immune profiling is another candidate for treatment selection, discussed in Section 4.

3.4. Stage IV Melanoma

3.4.1. Systemic Treatment and Molecular Profiling

Systemic therapy is the treatment backbone for most stage IV disease. Long-term CheckMate 067 follow-up demonstrates durable benefit from checkpoint blockade [67]. Anti-PD-1 therapy, combinations with CTLA-4 or LAG-3 blockade, and BRAF/MEK inhibition in molecularly eligible patients provide different efficacy–toxicity balances. Five-year RELATIVITY-047 results published in October 2026 further support sustained benefit from nivolumab plus relatlimab over nivolumab in advanced disease [68]. BRAF V600 testing is required to identify a targeted-treatment option; broader profiling may identify additional actionable alterations or clinical trials, particularly in unresectable disease [23].

DREAMseq and SECOMBIT support immunotherapy-first sequencing for many eligible patients with BRAF V600-mutant melanoma, while symptoms, disease tempo, contraindications and the need for rapid control influence individual decisions [69,70]. The presence of an actionable mutation does not itself justify metastasectomy. Surgery can also provide tissue for adoptive tumor-infiltrating lymphocyte treatment; randomized evidence for this therapy creates a distinct tissue-procurement role that should be separated from an attempt at complete oncological resection [71].

3.4.2. Selection for Surgery and Interpretation of Response

Potential indications include complete resection of selected oligometastatic disease, local treatment of isolated progression during otherwise effective systemic therapy, diagnostic clarification, tissue procurement and symptom palliation. Decision-making considers overall disease control, performance status, morbidity and whether surgery can achieve a clinically meaningful goal. Retrospective metastasectomy and oligoprogression series report favorable outcomes in selected patients, but selection and disease biology prevent attributing survival differences to surgery alone [72–74].

Residual radiological masses may contain viable melanoma, fibrosis or treatment-related inflammation. Pathological assessment of a resected or biopsied lesion can clarify local response, but cannot establish eradication of disease elsewhere. The response thresholds developed in stage III neoadjuvant cohorts should not automatically determine the extent of stage IV surgery [22,53]. For patients rendered free of detectable disease, IMMUNED provides randomized evidence on adjuvant immunotherapy, including substantial toxicity; it does not establish which patients should first undergo metastasectomy [75].

3.4.3. Future Directions Within Stage IV

Prospective comparisons should define when local intervention adds benefit to effective systemic therapy and how best to select patients with oligoprogression. Candidate tools include longitudinal imaging, ctDNA and tissue-based response prediction, but none independently validates an operation. Studies should distinguish surgery intended for durable disease control from palliation or cell-therapy procurement, and should measure treatment-free time, symptoms and functional outcomes as well as survival. Table 3 integrates the stage-specific clinical questions.

Table 3. Stage-specific integration of surgery, systemic treatment and response.

Stage or Presentation	Surgery and Nodal Assessment	Systemic Therapy and Testing	Response Assessment and Research Priority
I	Thickness-adapted excision; selective SLNB discussion or recommendation according to risk	No routine perioperative systemic treatment; no routine mutation testing	No routine post-systemic response endpoint; validate safer nodal selection [23,26,29,30]
IIA	Wide excision and guideline-based nodal assessment	Surveillance after resection; no routine mutation testing	Pathology defines baseline risk; refine prognostic models [23,31]
IIB and IIC	Wide excision; individualized discussion of SLNB and its impact	Consider adjuvant anti-PD-1; actionable testing may be considered	No standard neoadjuvant response endpoint; identify net adjuvant benefit [23,36,37,40,41]
III with microscopic sentinel-node disease	Usually nodal ultrasound surveillance rather than routine CLND	Consider adjuvant treatment by risk; establish BRAF V600 status	Nodal burden informs risk; avoid assuming all IIIA disease has equal benefit [10–16,23]
III with macroscopic resectable disease	Neoadjuvant therapy followed by planned surgery in eligible patients	Immunotherapy integrated before surgery; BRAF testing	Standardized pCR/MPR assessment; validate response-directed TLND omission [17–22,56]
IV	Selected metastasectomy, oligoprogression treatment, palliation or tissue procurement	Systemic therapy is the backbone; BRAF and selected broader profiling	Local pathology does not prove systemic clearance; define added benefit of local treatment [23,68–75]

Original synthesis; guidance and eligibility depend on clinical context and local access. Molecular testing refers to actionable tumor alterations, not routine gene-expression prognostic assays. pCR, pathological complete response; MPR, major pathological response.

4. Artificial Intelligence and Digital Pathology

4.1. Diagnostic Assistance and Tissue Characterization

AI applied to clinical or dermoscopic photographs addresses a different task from AI applied to histological whole-slide images. Esteva and colleagues demonstrated image-based skin-lesion classification in a controlled retrospective setting [76]. Such work supports diagnostic assistance, but does not replace histological confirmation of a suspicious lesion or demonstrate safe modification of excision margins. In tissue sections, Hekler and colleagues showed that deep learning could classify selected melanoma and nevus images at a level comparable with the reference pathological assessment [77]. Performance on selected images should not be assumed to generalize to complete diagnostic workflows, rare variants or difficult borderline lesions.

Digital pathology enables slide review across centers, tumor-region annotation and quantitative analysis of immune-cell distribution. Sobottka and colleagues evaluated standardized immune phenotyping in metastatic melanoma, providing a basis for more reproducible tissue characterization [78]. The relevant surgical benefit would be better-informed diagnosis and multidisciplinary assessment. Autonomous diagnosis, reliable measurement across all histological variants and automatic selection of surgical margins require separate validation.

4.2. Prognostication in Localized Disease

Computational models can combine tissue features with clinicopathological variables rather than relying on images alone. MelanoMAP analyzed more than 3500 slides from international cohorts and integrated tumor-microenvironment features with patient and tumor characteristics [45]. In its external test cohort, the reported C-index was 0.82, compared with 0.66 for AJCC-derived features; improvement over a richer clinicopathological comparator was smaller and was not statistically established by the reported paired analysis. This illustrates why comparison with stage alone can exaggerate the apparent incremental value of a new digital marker.

For stage I–II management, a model must be calibrated at clinically meaningful risk thresholds and tested in the population in which it will be used. Prediction of recurrence, nodal positivity and melanoma mortality should remain separate endpoints. A prognostic model can identify risk without predicting benefit from immunotherapy. BAUSSS and conventional nomograms are therefore useful comparators for AI models, not evidence that AI has already replaced nodal staging [27–29,38].

4.3. Predicting and Assessing Treatment Response

In advanced melanoma, Johannet and colleagues integrated histological image analysis with clinical information to predict checkpoint-inhibitor response [79]. A larger 2026 multicenter study assessed pretreatment metastatic specimens from 1177 patients, using samples from 30 pathology laboratories and leave-one-hospital-out validation. Histology-based prediction achieved an AUROC of 0.63, increasing to 0.66 with clinical variables [80]. These modest values support continued investigation while cautioning against using a prediction to withhold effective treatment or select an operation.

In the neoadjuvant setting, Leek and colleagues evaluated a pathologist-supervised workflow for quantifying intratumoral lymphocytes in nodal melanoma biopsies. Validation on 159 whole-slide images from three early neoadjuvant trials linked the AI-derived score with major pathological response and event-free survival [81]. This is a pretreatment biomarker association, not an automated demonstration that viable tumor has disappeared after treatment.

Post-treatment assessment presents a different challenge: delineating the tumor bed and distinguishing residual viable melanoma from melanophages, fibrosis, necrosis and immune infiltrates. Digital annotation and quantitative segmentation could support response scoring, but the clinical reference remains expert assessment using standardized pathological criteria [22]. The cited AI studies do not validate autonomous assignment of pathological complete response or omission of TLND. Future paired pre- and post-treatment datasets should test agreement near the 10% major-response threshold, reproducibility across laboratories and the consequences of misclassifying small viable deposits. Table 4 separates diagnostic, prognostic and response-related applications.

Table 4. AI and digital pathology applications and limits in melanoma.

Clinical Task	Representative Evidence	Potential Application	Limitation for Current Surgical Decisions
Lesion diagnosis	Esteva et al. [76]; Hekler et al. [77]	Image classification to support clinical or pathological review	Selected image performance does not replace complete histology or determine margins
Immune phenotyping	Sobottka et al. [78]	Quantify immune-cell patterns on digitized tissue	Standardization is not proof of treatment or surgical benefit
Localized-disease prognosis	MelanoMAP [45]	Integrate tissue and clinicopathological features to estimate recurrence risk	Increment beyond strong clinical models and management utility require validation
ICI response prediction	Johannet et al. [79]; Schuiveling et al. [80]	Combine pretreatment histology with clinical data	Association and moderate discrimination do not justify withholding therapy or changing an operation
Neoadjuvant response prediction	Leek et al. [81]	AI-assisted intratumoral lymphocyte scoring in nodal biopsies	Pretreatment prediction is not post-treatment confirmation of pCR
Post-treatment response assessment	INMC pathological criteria [22]; digital segmentation as a proposed extension	Assist tumor-bed annotation and viable-tumor quantification	Autonomous response assignment and AI-directed TLND omission are not validated by the cited studies

Original synthesis. AI, artificial intelligence; ICI, immune checkpoint inhibitor; pCR, pathological complete response. Rows distinguish demonstrated research associations from proposed clinical applications.

4.4. Requirements for Clinical Implementation

Clinical adoption requires patient-level separation of training and testing data, geographically and temporally independent validation, and assessment across staining protocols, scanners, anatomical sites, age groups and melanoma subtypes. Multiple slides from one patient must not create information leakage. Missing tissue, biopsy-versus-resection differences and treatment selection can bias apparent performance, as illustrated by the heterogeneous specimens and clinical covariates in response-prediction studies [79–81].

Interpretability and discrimination are insufficient without calibration and demonstrated clinical benefit. A prospective workflow should specify the intended decision, human oversight, failure handling and monitoring for performance drift. For a surgical application, the relevant outcome is whether AI-assisted care improves safety, morbidity or oncological control compared with standard multidisciplinary care. The cited evidence does not yet establish this benefit.

5. Discussion

5.1. Reassessing the Role of Sentinel Lymph Node Biopsy

The evidence supports a more qualified description of SLNB than an unreserved claim that it is universally indispensable. It detects occult nodal disease, contributes to pathological staging and may change treatment or surveillance. Its value for an individual patient nevertheless depends on the incremental information obtained and what clinicians and patients would do with it. Stage IIB/IIC adjuvant options and age-related discordance between nodal positivity and mortality make that assessment more consequential [23,30,36,37].

BAUSSS offers an accessible approach to mortality estimation using information already available after primary excision [29]. The associated age-based critique deserves consideration, but a model-based or observational comparison is not a trial demonstrating the safety of withholding SLNB. Conversely, adherence to staging conventions should not prevent testing less invasive strategies. The appropriate comparison is between complete management pathways, with regional control, systemic treatment allocation, morbidity and survival measured prospectively. Contemporary models incorporating nodal findings also support individualized prediction, indicating that better prognostication and nodal assessment need not be mutually exclusive [38].

5.2. Integrating Treatment Benefit and Morbidity

Biology-guided melanoma surgery describes the integration of disease distribution, actionable tumor features, response and patient priorities. It does not imply that every prognostic association should alter an operation. Randomized evidence supports surveillance after microscopic sentinel-node involvement; response-directed omission of therapeutic dissection is a different intervention with a different evidence base [10–12,19,20]. Likewise, a major response may support postoperative treatment decisions within a studied regimen without proving that surgery is unnecessary.

Reduced surgical burden must be considered alongside systemic toxicity. Persistent immune-related adverse events can remain after adjuvant anti-PD-1 therapy [43,44]. Long-term KEYNOTE-054 quality-of-life results did not show a significant average detriment, but group means do not exclude substantial morbidity in individual patients [82]. Multidisciplinary selection should account for these trade-offs, competing illness and access to surveillance or specialist pathological review [54,83].

5.3. Limitations of the Evidence and This Review

This targeted narrative synthesis cannot ensure comprehensive retrieval and does not formally grade certainty. Surgical cohorts are vulnerable to selection and immortal-time biases; trial populations, stage definitions and response endpoints differ. Long-term PRADO and pooled INMC findings improve follow-up but do not remove confounding or cohort overlap [20,56]. AI studies vary in specimen selection, validation design and intended outcome, and few test whether their use improves clinical decisions. These limitations preclude pooled cross-trial rankings, universal age thresholds for SLNB omission or transfer of pathological-response rules between systemic regimens.

6. Future Perspectives

The stage-specific priorities are complementary: more selective nodal staging in stage I; clearer identification of net adjuvant benefit in stage II; validated response-directed surgery in stage III; and definition of the added value of local treatment in stage IV. Across these settings, prospective studies should specify the action triggered by a biomarker before evaluating that biomarker as clinically useful.

Future protocols should link standardized pathology, imaging, molecular data and patient-reported outcomes while preserving independent external validation. For surgical de-escalation, monitoring, rescue treatment and regional control should be prespecified. For AI, comparison with strong clinicopathological models and assessment of the complete clinician-assisted workflow are essential. ctDNA, immune profiling and digital pathology are promising components of this research, but clinical benefit must be established before they routinely determine surgical extent [42,45,56,59,61–63,80,81].

7. Conclusions

Melanoma surgery should be considered within a stage-specific treatment pathway. Thickness-adapted excision remains fundamental in stages I–II, with individualized SLNB decisions and adjuvant treatment discussion for eligible stage IIB/IIC disease. Stage III management distinguishes microscopic sentinel-node involvement from macroscopic disease suitable for neoadjuvant therapy and standardized response assessment. Stage IV operations require a defined multidisciplinary purpose. BAUSSS, age-sensitive prognostic models and AI challenge overly simple risk estimates, but better prediction does not itself prove the safety of surgical omission. Prospective validation of management changes is necessary to translate biological information into operations with measurable patient benefit.

Author Contributions: Conceptualization, M.R. and M.F.; methodology, M.R. and M.F.; software, M.R. and A.G.; validation, A.G., D.S. and E.D.B.; formal analysis, M.R. and D.P.; investigation, M.R., M.F. and A.L.D.P.; resources, G.Z. and M.R.; data curation, M.R. and E.D.B.; writing—original draft preparation, M.R. and M.F.; writing—review and editing; visualization, M.S., D.S. and D.P.; supervision, M.R., E.D.L. and A.L.D.P.; project administration, M.R., M.F. and E.D.L.; funding acquisition, G.Z., A.G. and M.R. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable. This narrative review does not report original research involving human participants or animals.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Acknowledgments: During preparation and revision of this manuscript, ChatGPT (OpenAI, version: 4.0), accessed through the Pro 100 plan, was used to assist with literature identification, evidence synthesis, drafting, manuscript organization and reference formatting. AI output was not treated as primary scientific evidence. Responsibility for the content, verification and final approval of the manuscript rests with the authors.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

AI, artificial intelligence; AJCC, American Joint Committee on Cancer; AUROC, area under the receiver operating characteristic curve; BAUSSS, Breslow thickness, age, ulceration, subtype, sex and site; CLND, completion lymph node dissection; ctDNA, circulating tumor DNA; EFS, event-free survival; INMC, International Neoadjuvant Melanoma Consortium; MPR, major pathological response; MSS, melanoma-specific survival; pCR, pathological complete response; SLNB, sentinel lymph node biopsy; TLND, therapeutic lymph node dissection.

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