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Sentinel Lymph Node Biopsy in Primary Cutaneous Melanoma

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Cancer Care Alberta

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Background

In the latest available data from 2018, 906 adult patients were diagnosed in Alberta with cutaneous melanoma, and 75 adults died from cutaneous melanoma. The age-standardized incidence rates (ASIRs) increased significantly by 1.5% in females and 1.7% in males annually between 1998 and 2018.[1] Between 2016 and 2018, the estimated five-year survival rate for cutaneous melanoma was 89%. The incidence of cutaneous melanoma will continue to increase in Alberta with 1,020 new cases and approximately 100 deaths projected in 2023.

Some controversy exists regarding the surgical management of regional lymph nodes in melanoma. Historically, elective lymph node dissection (ELND) was recommended to control metastases. However, this procedure was not shown to provide any survival benefit in randomized trials and was associated with high morbidity.[2] Subsequently, intraoperative lymphatic mapping and sentinel lymph node biopsy (SNLB) were introduced as an alternative that would allow for excision of only the sentinel draining lymph nodes, limiting complete lymph node dissection (CLND) to patients with metastasis to the sentinel node (SN).[3] More recently, the MSLT-II trial found that CLND did not improve melanoma-specific survival compared to observation and nodal ultrasonography in patients with sentinel lymph node metastases, despite an increase in regional disease control with the more extensive surgery, which is why these patients are now offered ultrasound (US) surveillance instead. Therapeutic lymph node dissection (TLND) would be done for those patients on US surveillance who recurred in the nodal basin at risk.

This guideline aims to provide current recommendations on nodal management in melanoma.

Guideline Questions

1. What are the indications for SLNB?
2. What are the contraindications for SLNB?
3. How should the SN be examined pathologically?
4. What is the recommended approach for the management of patients with confirmed positive sentinel lymph nodes?
5. When is therapeutic lymph node dissection indicated (TLND)?

Search Strategy

For the 2024 guideline update, Medline was searched from Jan 1, 2014, through to Jan 10, 2024, for meta-analyses, systematic reviews, clinical trials, and observational studies involving human subjects, published in English using the following medical subject heading [MeSH] terms: “melanoma”, “sentinel lymph node biopsy”, and “lymph node excision”. In addition, keyword searches of titles and abstracts used the terms “melanoma”, “sentinel lymph node biopsy”, “complete lymph node dissection”, “therapeutic lymph node dissection”, “cutaneous”, “surveillance”, and “follow-up”. A

total of 135 studies were identified from the Medline search. An additional 22 studies were identified from other sources. From these studies, 39 were summarized into evidence tables and considered for inclusion in this guideline.

In addition to a Medline search, the ECRI Guidelines Trust database, and the websites of well-known cancer guideline developers were searched for relevant and current (i.e., published between 2019 to 2024) clinical practice guidelines. Recommendations from a total of 12 clinical practice guidelines were summarized in the evidence tables. Evidence tables are available upon request by e-mailing guru@ahs.ca.

Target Population

The recommendations outlined in this guideline apply to adults over the age of 18 years with biopsy-confirmed malignant melanoma. Different principles may apply to pediatric patients.

Recommendations

The 8th edition American Joint Committee on Cancer (AJCC) melanoma staging system is presented in the Appendix.

1. a) Clinicians should consider using a melanoma sentinel lymph node metastasis nomogram to predict the probability of nodal basin metastasis in patients with cutaneous melanoma, aiding in decision-making about the need for a SLNB.

   Based on a large patient dataset, refined predictive variables, and robust external validation, the Sentinel Node Metastasis Risk Prediction Tool developed by the Melanoma Institute Australia (MIA) is the preferred nomogram. The MIA nomogram incorporates six important biological factors to predict a patient's risk: age, tumour thickness (mm), melanoma subtype, mitoses/mm^2, ulceration, and lymphovascular invasion. *(Level of Evidence: IV[4,5]; Strength of Recommendation: B)*

   b) In the context of staging, SLNB:
   - Is not recommended if the SN metastasis risk is less than 5%. *(Level of Evidence: I[6]; Strength of Recommendation: A)*
   - May be considered if the SN metastasis risk is between 5% to 10%. *(Level of Evidence: I[6] IV[7,8]; Strength of Recommendation: A)*
   - Should be offered if the SN metastasis risk is greater than 10%. *(Level of Evidence: I[9]; Strength of Recommendation: A)*

   Qualifying Statements: While melanoma sentinel lymph node metastasis calculators provide valuable data to inform clinical decision-making, they are not the only factor in determining whether a patient should undergo SLNB. Although a nomogram may indicate a high probability of SN metastasis, clinicians may choose not to proceed with SLNB due to other patient-specific

factors such as advanced age, poor performance status, dementia, and other comorbidities. In such cases, the decision should prioritize patient preference and quality of life.

If there are concerns about the accuracy of a partial biopsy of the primary tumour that might not accurately reflect the extent of the tumour due to significant regression or residual tissue, offering a SLNB for a more comprehensive assessment is reasonable.

2. a) SLNB is performed to assess for microscopic metastasis in a nodal basin and is not suitable for patients with pathologically positive lymphadenopathy confirmed by positive fine-needle aspiration cytology and/or core biopsy of palpable lymph nodes.

   b) Factors that may pose relative contraindications for SLNB include:
   - Prior wide excision of the primary tumour with flap closure or skin graft.[10]
   - Prior extensive surgery such as neck dissection.[11,12]
   - Rare allergy to blue dye and radiocolloid.[3,13,14] Indocyanine green and fluorescence imaging can be used as an alternative.[15]
   - Pregnancy. Due to concerns about potential effects on the fetus, radiocolloids should be used instead of blue dye if SLNB is performed.[16]

3. a) Examination of the hematoxylin and eosin (H&E)-stained slides from various levels across serially sliced sentinel lymph nodes is recommended to help detect microscopic melanoma metastasis. To further improve the sensitivity for detecting microscopic melanoma metastases, immunohistochemical (IHC) stains such as HMB45, MART1/MelanA, SOX10 or melanocytic cocktails should be incorporated. *(Level of Evidence V[17]; Strength of Recommendation: B)*

   b) Given the prognostic significance of the SN, the pathology report should include at minimum information about: *(Level of Evidence V[17]; Strength of Recommendation: B)*
   - Total number of lymph nodes with tumour
   - Number of SNs with tumour (if applicable).
   - Size of largest SN metastatic deposit (if applicable).
   - Size of largest non-SN metastatic deposit (if applicable).
   - Extranodal extension.
   - Matted nodes.
   - Total number of lymph nodes examined (sentinel and non-sentinel).
   - Number of SNs examined.

   a) Most patients with confirmed nodal metastasis based on a positive SLNB do not require a CLND. Instead, patients should undergo thorough clinical observation and ultrasound (US) surveillance of the nodal basin every 4 to 6 months for the first 2 years, followed by every 6

months during years 3 through 5. *(Level of Evidence: I[18,19] IV[20,21] V[22]: Strength of Recommendation: A)*

Qualifying Statement: Although the MLST II trial involved performing nodal US of the dissected nodal basin every 4 months for 2 years and then every 6 months for the next 3 years,[23] the working group chose to align with Ontario's recommended practice, which offers slightly more flexibility in the frequency of these procedures.[22]

b) For SN-positive patients undergoing routine whole body imaging with PET/CT, US surveillance may be unnecessary. However, it is important to note that changes in the lymph node hilum visible on US can be overlooked on CT. *(Level of Evidence: IV[24]; Strength of Recommendation: C)*

c) CLND may be offered in situations where frequent surveillance is impractical for patients and/or the radiologic expertise is unavailable. However, patients should be counselled appropriately about complications such as lymphedema. *(Level of Evidence: V[25]: Strength of Recommendation: B)*

CLND generally includes:[25]

- In the axilla: levels I-III.
- In the parotid gland: superficial parotidectomy with facial nerve preservation, accompanied by a neck dissection of the draining nodal basins.
- In the groin: inguinofemoral dissection. A positive PET/CT scan should be considered the primary indication for conducting Iliac/obturator dissection.[26]

4. a) TLND is recommended alongside wide local excision of the primary tumour after core biopsy or FNA confirmation of clinically involved lymph nodes that are amenable to resection, and for nodal recurrence. *(Level of Evidence: V[25]; Strength of Recommendation: B)*

   b) Immediate lymphatic reconstruction could be considered after inguinal or axillary lymphadenectomy to mitigate the risk of extremity lymphedema. *(Level of Evidence: IV[27,28] V[29]; Strength of Recommendation: B)*

Discussion

Sentinel Lymph Node Biopsy (SLNB)

MSLT-I was a landmark trial that aimed to determine whether SLNB could accurately identify patients with clinically occult nodal metastases and whether immediate CLND *for positive SLNB* provided superior outcomes compared to *T*LND performed in response to nodal recurrence detected during observation.[9] In the trial, 2,001 patients with primary cutaneous melanomas were randomly assigned to either wide excision and nodal observation, with *T*LND for nodal relapse, or wide excision and SLNB, with immediate CLND for nodal metastases detected on biopsy. There was no significant

treatment-related difference in the 10-year melanoma-specific survival rate (MSS, the primary endpoint) seen in the overall study population (21% with and 79% without nodal metastases). However, among patients with intermediate-thickness melanomas (1.2 to 3.5 mm) and patients with thick melanomas (>3.5 mm), the mean 10-year disease-free survival (DFS) rates were significantly improved in the SLNB group compared with the observation group (71% vs. 65% intermediate thickness melanomas and 51% vs. 41% thick melanomas). Among patients with intermediate-thickness melanomas, the 10-year MSS rate was 62% among those with metastasis versus 85% for those without metastasis, and among patients with thick melanomas, the respective rates were 48% and 65%.

Risk Factors for Regional Nodal Metastasis

In addition to increased Breslow thickness (>1 mm), several other patient and pathological factors are associated with a higher risk of regional nodal metastasis in cutaneous melanoma, including younger age, mitotic rate (≥ 1 mm^2), ulceration, Clark level (IV/V), and lymphovascular invasion. These factors help to determine the role of SLNB.[6-8,30-41]

The role of SLNB in variants of melanoma and melanocytic lesions with uncertain biologic behavior is evolving. While mixed desmoplastic melanoma tends to metastasize to lymph nodes and should be offered a SLNB, pure desmoplastic melanoma has a low likelihood of nodal metastasis, making SLNB unnecessary.[42,43] For patients with atypical spitzoid tumour, pigmented epithelioid melanocytoma (PEM, also known as animal-type melanoma), and primary dermal melanoma, the use of SLNB has been debated. Atypical spitzoid tumour and PEM show a high rate of nodal metastasis rate, though this has little impact on prognosis.[44-47] In contrast, primary dermal melanoma has a lower probability of nodal metastasis, which questions the need for SLNB in these cases.[48,49]

The need for a SLNB in patients with microsatellitosis in the primary tumour or satellitosis/in-transit metastasis at presentation (at least Stage IIIB) has become less certain since these patients are now immediately eligible for systemic therapy. The decision to perform a SLNB should be individualized. It may be considered if there is potential to obtain additional prognostic information such as upstaging the patient to Stage IIIC or IIID or to achieve nodal control through the procedure.[50]

Despite promising results and growing interest in advanced molecular testing platforms, such as gene expression profiling (GEP), for predicting the prognosis of sentinel lymph nodes, their current clinical applicability is hindered by methodological concerns, a paucity of prospective validation, and limited correlation with recognized clinicopathological variables.[51]

Nomograms. Several institutions, including Memorial Sloan Kettering Cancer Center (MSKCC) and the Melanoma Institute of Australia (MIA), have developed and validated nomograms that use a combination of the risk factors to estimate the risk of SN positivity. The MSKCC tool collects patient age, melanoma thickness, Clark level, tumour location, and ulceration to calculate a patient's probability of SN metastasis. This nomogram was externally validated using data from a multi-institutional clinical trial (n=979),[52] and has been further evaluated and validated by three different

institutions.[53-55] MIA sought to develop an improved online risk calculator using an updated and refined set of clinicopathologic parameters to more accurately predict SLN positivity.[4] Its model replaced body site and Clark level of the primary melanoma in the MSKCC model with mitotic rate, melanoma subtype, and lymphovascular invasion. The MIA model has been shown to more accurately estimate the risk of SLN positivity in patients than the MSKCC model,[4] and has been validated using a European national patient cohort (n=3,049).[5]

Indications. The selection of patients for lymphatic mapping and SLNB primarily depends on the risk of nodal basin metastases, along with the patient's suitability for surgery, and overall treatment goals. Patients should be assessed for lymphatic mapping and SLNB based on their estimated risk of nodal metastases using the MIA prediction tool. Generally, SLNB is not recommended for patients with a nodal metastasis risk less than 5%, may be considered if the nodal metastasis risk is 5 to 10%, and should be offered if the risk of nodal metastasis is greater than 10%. If there are concerns about the accuracy of a partial biopsy that might not accurately reflect the extent of the tumour due to significant regression or residual tissue, offering a SLNB for a more comprehensive assessment is reasonable.

Absolute contraindication. SLNB is contraindicated in patients with pathologically positive (N1) lymphadenopathy based on a positive fine-needle aspiration cytology (FNAC) and/or core biopsy of palpable lymph nodes.[56] The presence of pathologically positive lymphadenopathy based on positive FNAC and/or core biopsy of palpable lymph nodes indicates a more advanced stage of disease, making SLNB less suitable due to altered lymphatic drainage patterns, increased risk of false negative results, limited clinical utility, and the availability of alternative management strategies.

Relative contraindications. Several factors make SLNB challenging. Prior wide excision of the primary tumour with a flap closure or skin graft is especially challenging if the primary was on the trunk, an area with multiple drainage sites. Prior extensive surgery such as neck dissection may pose relative contraindications for SLNB due to the disruption of the lymphatic pathways from the primary tumour.[10-12] These factors may increase the technical difficulty of the procedure and decrease its accuracy in correctly staging the disease. Additional relative contraindications to SLNB include patients with known allergies to blue dye and radiocolloid[3,13,14], as well as pregnant patients. For patients with rare allergies to blue dye and radiocolloids, indocyanine green and fluorescence imaging can be used as a safe alternative.[15] In pregnant patients, while SLNB itself is not contraindicated, the blue dye used to identify the SN should be avoided due to concerns about its potential effects on the fetus.[16] Thus, if SLNB is pursued, radiocolloids should be used as a safer alternative.

Pathology

Intraoperative frozen-section evaluation has been shown to reduce accuracy of pathologic assessment of SNs in melanoma patients and is associated with practical drawbacks, including extended operation time.[57] Thus, the College of American Pathologists (CAP) recommend examination of the hematoxylin and eosin- (H&E) stained slides from various levels across serially sliced SNs to increase the sensitivity of detecting microscopic melanoma metastasis.[17] To further improve the sensitivity for detecting microscopic melanoma metastases, CAP recommends also

incorporating immunohistochemical (IHC) stains such as HMB45, MART1/MelanA, or SOX10.[17] Although CAP does not specifically address the use of PRAME for distinguishing between nodal nevi and melanoma metastasis, the National Comprehensive Cancer Network (NCCN) recommends that in cases of equivocal histologic findings in the SLN, additional IHC staging for PRAME, and/or consultation with an experienced dermatopathologist should be considered.[25]

In July 2009, the Canadian Partnership Against Cancer and the Canadian Association of Pathologists, endorsed CAPs cancer protocols as the standard for cancer-pathology reporting in Canada.[58] According to CAPs protocol for the examination of excision specimens from patients with invasive melanoma of the skin, pathology reporting on the regional lymph nodes should include the total number of lymph nodes with tumour, the number of SNs with tumour (if applicable), the sizes of both the largest SN metastatic deposit and non-SN metastatic deposit (if applicable), whether extranodal extension and matted nodes are present, the total number of lymph nodes examined (sentinel and non-sentinel), and finally the number of SNs examined.[17]

Sentinel Node Positivity

CLND versus observation. Two practice changing trials, MSLT-II and DeCOG, randomized SN-positive patients to either complete lymph node dissection (CLND) or nodal basin observation enhanced with ultrasonography (US). In the MSLT-II trial, immediate CLND was not associated with increased MSS among nearly 2,000 patients. At a median follow-up of 43 months, in the per-protocol analysis the mean 3-year rate of MSS was similar in the CLND and observation group (86% and 86%, respectively; p=0.42 by log-rank test). The rate of DFS was a little higher in the CLND than in the observation group (68% and 63%, respectively; p=0.05 by log-rank test) at 3 years, based on an increased rate of disease control in the regional nodes at 3 years (92% vs. 77%; P<0.001 by log-rank test). However, non-SN metastases, found in 11.5% of patients in the CLND group were a strong, independent prognostic factor for recurrence (HR, 1.78; p=0.005). Importantly, lymphedema was noted in 24% of the patients in the CLND group and in only 6% of those in the observation group.[19] In the final analysis of the DeCOG trial (n=483), with a median follow-up of 72 months, no significant treatment-related difference was seen in the 5-year distant metastasis-free survival (DMFS) between the observation and CLND arms (68% vs. 65%, respectively; HR, 1.08; p=0.87). The 5-year recurrence-free survival (RFS) and overall survival (OS) also showed no difference (HR, 1.01 and 0.99, respectively).[18] As a result of these two trials, and reports on real-world outcomes,[20] most patients with confirmed SN metastases should undergo thorough clinical observation and US surveillance of the nodal basin rather than CLND. Even patients with microsatellites, extranodal extension in the SN, or greater than 3 positive SNs who were largely excluded from these randomized trials have been shown to benefit from nodal surveillance rather than CLND.[21]

Surveillance modality and frequency. In the MSLT-II study protocol, nodal surveillance consisted of examination and US every 4 months after a positive SNLB during years 1 to 2, then every 6 months during years 3 to 5, and then annually.[20] A slightly more pragmatic approach, recommended by Cancer Care Ontario that the Provincial Cutaneous Tumour Team endorses a clinical examination

and US every 4 to 6 months for years 1 to 2, and then every 6 months for years 3 to 5.[22] CLND may still be offered in situations where frequent surveillance is impractical for patients (e.g., travel or age) and/or the radiologic expertise is unavailable. However, patients should be counselled appropriately about complications such as lymphedema.[25]

A 2024 retrospective study has called into question the role of US nodal surveillance in SN positive patients in the era of adjuvant systemic therapy and cross-sectional imaging (CT or PET/CT).[24] The study included 225 SN positive patients, 53% of whom received adjuvant systemic therapy, with a median follow-up of 23 months. Of these patients, 36% developed a recurrence at any site; 11% recurred first in the SN positive field. The nodal recurrences were first detected by US in 3%, CT in 3%, and PET/CT in 3% of patients. All nodal recurrences on US were also evident on PET/CT vice versa. Given these results, for SN positive patient undergoing routine PET/CT imaging, US surveillance of the SN-positive field may be unnecessary. However, it is important to note that changes in the lymph node hilum visible on US can be overlooked on CT.

Lymph Node Dissection

CLND is now rarely offered and is reserved where frequent surveillance is impractical for patients and/or the radiologic expertise is unavailable.

TLND is reserved for patients who show evidence of missed clinically detectable lymphadenopathy after SLNB, including an early recurrence with clinically detectable lymphadenopathy appearing soon after a negative SLNB, or patients presenting at the outset with gross nodal disease. The procedure targets the nodal site where recurrence is found, typically the basin where SLNB was positive.[25] In the axilla, TLND involves removing nodes from levels I to III.[25] In the head and neck, TLND is modified according to the site of the primary and the location of the involved nodes. In the groin area, TLND involves an inguinofemoral dissection.[25] Whether the pelvic (iliac/obturator) nodes require removal is controversial. A retrospective review published in 2024 sought to establish the usefulness of PET/CT scans in confirming the indication pelvic dissection among 26 patients with malignant melanoma.[26] PET/CT was found to be 100% sensitive for pelvic nodal disease and 75% specific, with a positive predictive value for nodal involvement of 92%. As a result of this study, a positive PET/CT scan should be considered the primary indication for conducting Iliac/obturator dissection. In the future, CLND may be routinely preceded by neoadjuvant therapy, based on results of the SWOG 1801 trial.[59] This phase II randomized trial showed that among patients with stage III or IV melanoma undergoing surgical resection, event-free survival at 2 years was 72% in the neoadjuvant plus adjuvant pembrolizumab therapy group (n=154) and only 49% in the adjuvant pembrolizumab alone group (n=159).

Mitigating the Risk of Lymphedema when TLND is Required

Secondary lymphedema, stemming from lymph node dissection leads to considerable morbidity in melanoma patients undergoing inguinal or axillary lymphadenectomy (incidence ranges from 39% to 64%). Immediate lymphatic reconstruction, which has been well studied in breast cancer patients, has

also been shown to be safe and effective in reducing lymphedema in melanoma patients.[27-29,60,61] In a retrospective 2019 case-control study, 143 patients with positive-SLNB underwent CLND, 23 of whom also received immediate lymphatic reconstruction.[28] Frequency of lymphedema was compared among subjects undergoing and not-undergoing immediate reconstruction during CLND. With a minimum follow-up of 3 years, the frequency of lymphedema was significantly lower in the immediate reconstruction group than in the control group (4% vs. 24%, p=0.03). Based on this study, and others referenced here, immediate lymphatic reconstruction could be considered after inguinal or axillary lymphadenectomy to mitigate the risk of extremity lymphedema, while awaiting results of randomized controlled trial data on immediate lymphatic reconstruction (ClinicalTrials.gov Identifier: NCT 05136079).

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Appendix

AJCC 2017 (8th Edition) Anatomic Stage Groupings for Cutaneous Melanoma

	Clinical Staging [a]				Pathologic Staging [b]			
	T	N	M		T	N	M	5-year Survival (%)
0	Tis	N0	M0	0	Tis	N0	M0	100%
IA	T1a	N0	M0	IA	T1a T1b	N0	M0	99%
IB	T1b T2a	N0	M0	IB	T2a	N0	M0	97%
IIA	T2b T3a	N0	M0	IIA	T2b T3a	N0	M0	94%
IIB	T3b T4a	N0	M0	IIB	T3b T4a	N0	M0	87%
IIC	T4b	N0	M0	IIC	T4b	N0	M0	82%
III	Any T, Tis	≥N1	M0	IIIA IIIB IIIC IIID	T1a/b-T2a T0 T1a/b-T2a T2b/T3a T1a-T3a T3b/T4a T4b T4b	N1a or N2a N1b, N1c N1b/c or N2b N1a-N2b N2c or N3a/b/c Any N ≥N1 N1a-N2c N3a/b/c	M0	93% 77% 60% 24%
IV	Any T	Any N	M1	IV	Any T, Tis	Any N	M1	<10%

[a] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases.

[b] Pathologic staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumour surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.

AJCC 2017 (8th Edition) TNM Staging Categories for Cutaneous Melanoma

T	Thickness (mm)	Ulceration Status
Tx: Primary tumour thickness cannot be assessed (e.g., diagnosis by curettage)	NA	NA
T0: No evidence of primary tumour (e.g., unknown primary or completely regressed melanoma)	NA	NA
Tis (melanoma *in situ*)	NA	NA
T1	≤ 1.0	Unknown or unspecified
T1a	< 0.8	Without ulceration
T1b	< 0.8	With ulceration
	0.8 to 1.0	With or without ulceration
T2	>1.0 to 2.0	Unknown or unspecified
T2a	>1.0 to 2.0	Without ulceration
T2b	>1.0 to 2.0	With ulceration
T3	>2.0 to 4.0	Unknown or unspecified
T3a	>2.0 to 4.0	Without ulceration
T3b	>2.0 to 4.0	With ulceration
T4	> 4.0	Unknown or unspecified
T4a	> 4.0	Without ulceration
T4b	> 4.0	With ulceration
N	**Number of Tumour-Involved Regional Lymph Nodes**	**Presence of In-Transit, Satellite, and/ore Microsatellite Metastases**
NX	Regional nodes not assessed (e.g., SLNB not performed, regional nodes previously removed for another reason) Exception: Pathological N category is not required for T1 melanomas, use cN	No
N0	No regional metastases detected	NA
N1	1 tumour-involved node or in-transit, satellite, and/or microsatellite metastases with no tumour-involved nodes	
N1a	1 clinically occult (i.e., detected by SLN biopsy)	No
N1b	1 clinically detected	No
N1c	No regional lymph node disease	Yes
N2	2 or 3	
N2A	2 or 3 tumour-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumour-involved node	No

N2B	2 or 3 clinically occult (i.e., detected by SLN biopsy)	No
N2C	1 clinically occult or clinically detected	Yes
N3	≥4 tumour-involved nodes or in-transit, satellite, and/or microsatellite metastases with ≥2 tumour-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3A	≥4 clinically occult (i.e., detected by SLNB biopsy)	No
N3B	≥4, at least 1 of which was clinically detected, or presence of any number of matted nodes	No
N3C	≥2 clinically occult or clinically detected and/or presence of any number of matted nodes	Yes
M	Site	LDH (lactate dehydrogenase) Level
M0	No evidence of distant metastases	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1b(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Not elevated
M1d(1)		Elevated

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members of the Alberta Cutaneous Tumour Team include surgical oncologists, radiation oncologists, medical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Cutaneous Tumour Team and a methodologist from the Guideline Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in February 2011. This guideline was revised in March 2012, February 2013, February 2014, April 2016, and May 2024.

Levels of Evidence

I	Evidence from at least one large randomized, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomized trials without heterogeneity
II	Small, randomized trials or large randomized trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case-control studies
V	Studies without control group, case reports, expert opinion

Strength of Recommendations

A	Strong evidence for efficacy with a substantial clinical benefit; strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit; generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, etc.); optional
D	Moderate evidence against efficacy or for adverse outcome; generally not recommended
E	Strong evidence against efficacy or for adverse outcome; never recommended

Maintenance

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2027. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

Abbreviations

AJCC, American Joint Committee on Cancer; ASIR, age-standardized incidence rate; CAP, College of American Pathologists; CLND, complete lymph node dissection; CT, computed tomography; DFS, disease-free survival; DM, distant metastasis; ELND, elective lymph node dissection; FNA, fine needle aspiration; FNAC, fine need aspiration cytology; GEP, gene expression profiling; H&E, hematoxylin and eosin; HR, hazard ratio; IHC, immunohistochemistry; MIA, Melanoma Institute of Australia; MSKCC, Memorial Sloan Kettering Cancer Centre; MSS, melanoma-specific survival; NCCN, National Comprehensive Cancer Network; PET, positron emission tomography; PEM, pigmented epithelioid melanocytoma; SLNB, sentinel node biopsy; SN, sentinel node; TLND, therapeutic lymph node dissection; US, ultrasound.

Disclaimer

The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

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