CancerCare Manitoba
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CancerCare Manitoba Clinical Practice Guidelines

Provincial Consensus Recommendations for the Management and Surveillance of Stage I-III Melanoma

Version 1.0 – May 2024

CancerCare Manitoba Guideline
Disease Management – Melanoma
Developed by: Cutaneous DSG

1.0 Background

Aim and Purpose

Development of this clinical guide was undertaken for the purpose of knowledge translation of the current standards in practice for the management and surveillance of stage I-III melanoma in Manitoba. The overall aim is to improve the standard of care received by this patient population, through application of standardized evidence-based interventions and promotion of best practices.

Development Process

Local practices, clinical trials, and international consensus guidelines on the management and surveillance of melanoma were reviewed. Based on the evidence evaluated, a preliminary approach to management was devised and presented to the Cutaneous DSG for review. After an iterative process of revisions, the following consensus guideline for the management and surveillance of curative intent stage I-III melanoma in Manitoba was produced.

Patient Population and Healthcare Setting

The recommendations in this clinical guide are applicable to patients with curative-intent Stage I to III melanoma in Manitoba. This guideline is intended for outpatient use.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): CancerCare Manitoba physicians, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology and dieticians at CCMB, as well as health care providers at Community Cancer Program Network (CCPN) sites and Uniting Primary Care in Oncology Network (UPCON) clinics.

Disclaimer

This guideline document should be viewed as an evidence-informed practice tool, and as such, it does not represent an exhaustive text on the subject of management of curative-intent stage I-III melanoma or melanoma surveillance. Clinicians are advised to use it in their practice concomitantly with information from other evidence-informed sources. Literature is constantly changing and advances with the addition of systemic therapy in earlier stages of melanoma and de-escalation of surgery may occur.

Use of this guideline in the clinical setting should not preclude the use of the practitioner's independent clinical judgment. It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under her/his care, and ideally, this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

2.0 Methodology

Working Group

- Cutaneous Disease Site Group (DSG)
- Author: Dr. Rebekah Rittberg
- Reviewers: Cutaneous DSG members including Drs. Megan Delisle, Debjani Grenier, Sate Hamza, Pamela Hebbard, Scott Hurton, Marc Ranson, Justin Rivard, Ralph Wong. Additionally, the guideline was reviewed by Marc Geirnaert, Director of the Provincial Oncology Drug Program.
- Conflicts of Interest: None

Literature Search

A literature review was completed evaluating clinical trials, editorials, review papers and expert opinions on management and surveillance of melanoma. PubMed, Medline (Ovid) and grey literature were reviewed considering publications from 2010 to 2023. National and international guidelines were evaluated and local practices in Manitoba were considered. After several revisions, a consensus was reached among all physicians involved in the treatment of stage I-III melanoma at CancerCare Manitoba.

Maintenance

At CancerCare Manitoba clinical guidelines are considered 'living' documents which require ongoing evaluation, review and updating. Re-evaluation of this clinical guide is planned for 2026. The working group will revise and update the document as needed, with any critical new evidence brought forward before this scheduled review.

3.0 Definitions

Subtypes of Melanoma[1]

- Low-CSD melanoma (including superficial spreading melanoma)
- High-CSD melanoma/lentigo maligna melanoma
- Desmoplastic melanoma
- Spitz melanoma
- Acral melanoma
- Mucosal melanomas
- Melanoma arising in blue nevus

- Melanoma arising in giant congenital nevus
- Nodular melanoma
- Ocular melanoma
- Meningeal melanoma

Staging

Current melanoma staging is based on AJCC 8th addition.[2]

Molecular Evaluation

Prior to consideration of adjuvant or potentially neoadjuvant therapy melanoma specimens should be tested for *BRAF V600* mutations. All Stage 2B to Stage 4 melanoma should be tested for *BRAF V600E* IHC and if this is negative should then be sent for Q31 testing.
Frequently a more extensive molecular panel is completed, however currently non-*BRAF* mutations do not impact systemic therapy options in patients with curative intent melanoma.

4.0 Recommendations

Staging Investigations

1) Patients require a complete physical examination with specific attention to evidence of lymphadenopathy, suspicious skin lesions, tumor satellites, or signs of distance metastatic disease.[1]
2) All patients with Stage 2B or higher should undergo a CT of the chest, abdomen, and pelvis. Other parts of the body including neck or limbs may require a CT depending on location of the primary melanoma. If a PET scan is completed then a CT of the chest, abdomen, and pelvis is not necessary.[3]
3) All patients with Stage 2B or higher require intracranial imaging preferentially with an MRI brain.[4] A CT brain should only be used in patients who have a contraindication to undergo an MRI.
4) All Stage 2B or higher require testing for BRAF V600E IHC and if this is negative should then be sent for Q31 testing. These test results cab take multiple weeks to obtain so ordering as early as possible is highly recommended to be completed on original biopsy.
5) All stages 2B or higher should have staging investigations and BRAF V600E IHC requested at the time of initial consultation at CancerCare Manitoba. Staging investigations should be completed before curative-intent surgery. The results of BRAF V600E do not affect surgical planning and are not needed before curative-intent surgery. This test should be requested as soon as possible to avoid delays in adjuvant treatment.
6) If patients are to receive therapy (BRAF and MEK inhibitors) then evaluation of ejection fraction should be completed prior to starting therapy using a MUGA or echocardiogram.[5,6] EKG to evaluate QTc interval is also required prior to starting targeted therapy.

Treatment

Adjuvant immunotherapy and targeted therapy have been used in melanoma patients in Manitoba since January 2020. There is emerging data that neoadjuvant therapy may provide additional benefit over adjuvant therapy in some melanoma patients with measurable disease (palpable or radiographically identified).[7] Each patient requires an individual assessment and there may be multiple reasons that the below treatment options are not recommended or administered based on competing comorbidities, patient preferences, or contraindications to therapy. This is also assuming that patients are accepting of the most aggressive therapy offered. There may be a multitude of explanations as to why patients do not receive the below therapy. Benefit of systemic therapy in reducing the risk of melanoma recurrence differs based on stage as well as melanoma subtype.

Stage I to 2A

1) Surgery is the mainstay of treatment.
2) SLNB is recommended based on Breslow thickness of the melanoma.[3,8]
    a. Thin melanoma (≤1.0 mm): SLNB is generally not recommended if <0.8mm without ulceration however may still be considered in younger patients (<35 years of age) with higher rate of mitoses.
    SLNB can be considered if 0.8 to 1.0 mm or any lesion with ulceration.
    b. Intermediate thickness melanoma (>1.0 mm to 4.0 mm): SLNB is recommended in all patients with intermediate thickness melanoma.

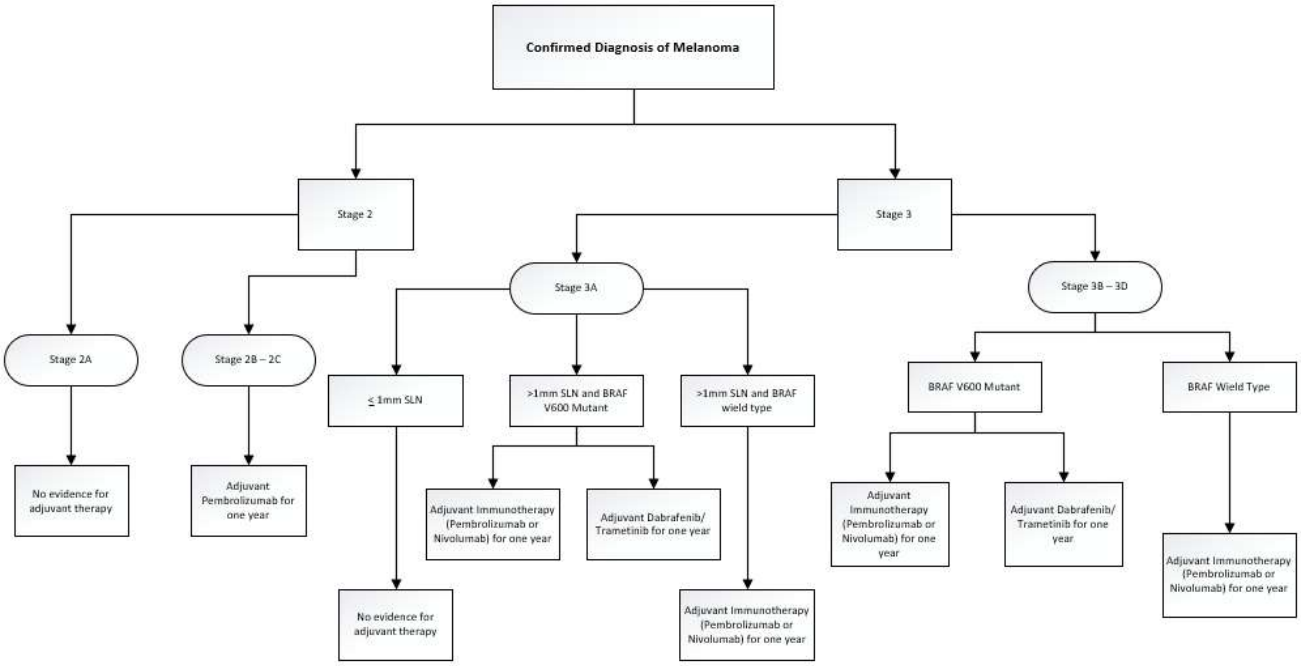
Stage 2B to 2C

1) Surgical resection should be completed with SLNB.[8]
2) Adjuvant pembrolizumab may be administered for a total of 1 year in patients with resected Stage 2B and 2C (T3b or T4a/b with a negative SLNB) to reduce risk of disease recurrence.[9] Adjuvant therapy should be initiated within 12 weeks of surgery.

Stage 3

1) Low risk resected node positive disease includes patients with Stage 3A with a SLN with ≤1 mm of lymph node metastasis. In these patients' surveillance alone is recommended without adjuvant therapy.[10]
2) Stage 3 melanoma patients with positive SLNB should be reviewed by a surgical oncologist or at Cutaneous Disease Site Group Case Conference if completion dissection is recommended over ultrasound surveillance.
3) Adjuvant therapy should be considered for resected Stage 3A (with >1mm with lymph node metastasis), 3B, 3C and 3D melanoma with options based on *BRAF V600* mutation status.[5,6,11,

4) Patients with stage 3A disease with >1mm lymph node metastasis without a *BRAF V600* mutation are eligible for adjuvant pembrolizumab, and patients with stage 3B-D without a *BRAF V600* mutation disease are eligible for nivolumab or pembrolizumab.[6,11,12]
5) Patients with Stage 3B, 3C and 3D melanoma and harbouring *BRAF V600* mutation, are eligible for 1 year of adjuvant dabrafenib/trametinib, or adjuvant immunotherapy.[5,6,11,12]
6) Neoadjuvant pembrolizumab could be considered in patients with clinically or radiographically detectable Stage 3B to 3D disease. Once resection is completed then pembrolizumab is continued to complete 1 year of therapy.[7]
7) Adjuvant radiotherapy is not standard and may be considered based on individual patient characteristics. This could include cases when adequate resection margins are not possible or when contraindications to adjuvant systemic therapy exist.



Follow-Up

1) Frequency of follow up is based on stage of melanoma. High level evidence based guidelines for optimal surveillance is lacking.[13] Patients with Stage 2B melanoma or higher should undergo 2 years of more intense surveillance followed by another 3 years of less intense surveillance.[4]
2) History and physical examination[4]:
    a. Stage 1A, 1B or 2A every 6-12 months for year 1-3 then yearly for year 4 and 5.

   b. Stage 2B, 2C and stage 3 every 3-6 months for year 1-3, then every 6 months for year 4 and 5.

3) Patients with a history of any stage of melanoma should be known to a dermatologist indefinitely.
4) Imaging surveillance (CT chest/abdomen/pelvis or PET)[3,4,13] :
   a. Stage 1A, 1B or 2A do not require imaging surveillance.
   b. Stage 2B, 2C and stage 3 require imaging every 3-6 months for year 1-3, then annually for year 4 and 5.
5) Regional nodal basin ultrasounds should be performed in patients with pathologically positive sentinel node who did not have complete lymph node dissection. This should occur every 4-6 months for year 1-2, every 6-12 months during year 3 and then annually for year 4 and 5.[14] Ultrasounds are in addition to CT/PET imaging.
6) Annual MRI brain should be completed for patients with Stage 2B to 3D melanoma for the years 1, 2 and 3, and may be considered for year 4 and 5.[4,13]
7) Blood work and tumor markers are not recommended as part of melanoma surveillance.[3,4]

Education

1) All patients should be educated on the importance of lifelong sun safety, avoidance of sunburns as well as extended UV exposure.[3]
2) Patients require education on lifelong regular self-skin examination.[3]
3) First degree relatives of a patient with a melanoma history are at increased risk of melanoma.[3]

References

1. Elder DE, Bastian BC, Cree IA, Massi D, Scolyer RA. The 2018 World Health Organization classification of cutaneous, mucosal, and uveal melanoma detailed analysis of 9 distinct subtypes defined by their evolutionary pathway. *Arch Pathol Lab Med*. 2020;144(4):500-522. doi:10.5858/arpa.2019-0561-RA
2. Edge S, Greene F, Schilsky R, et al. AJCC Cancer Staging Manual Eighth Edition. 2018:865-877.
3. Michielin O, Van Akkooi ACJ, Ascierto PA, Dummer R, Keilholz U. Cutaneous melanoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2019;30(12):1884-1901. doi:10.1093/annonc/mdz411
4. Lee CW, McKinnon JG, Davis N. Canadian melanoma conference recommendations on high-risk melanoma surveillance: A report from the 14th annual Canadian melanoma conference; Banff, Alberta; 20–22 February 2020. *Curr Oncol*. 2021;28(3):2040-2051. doi:10.3390/curroncol28030189
5. Dummer R, Hauschild A, Santinami M, et al. Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. *NEJM*. 2020;383(12):1139-1148. doi:10.1056/nejmoa2005493
6. Seth R, Messersmith H, Kaur V, et al. Systemic therapy for melanoma: ASCO guideline. *J Clin Oncol*. 2020;38(33):3947-3970. doi:10.1200/JCO.20.00198
7. Lieskovan SH, Lao CD, Fecher LA, et al. Neoadjuvant–Adjuvant or Adjuvant-Only Pembrolizumab

in Advanced Melanoma. *NEJM*. 2023:813-823. doi:10.1056/NEJMoa2211437

8. Wong SL, Faries MB, Kennedy EB, et al. Sentinel Lymph Node Biopsy and Management of Regional Lymph Nodes in Melanoma: American Society of Clinical Oncology and Society of Surgical Oncology Clinical Practice Guideline Update. *Ann Surg Oncol*. 2018;25(2):356-377. doi:10.1245/s10434-017-6267-7
9. Luke JJ, Rutkowski P, Queirolo P, et al. Pembrolizumab versus placebo as adjuvant therapy in completely resected stage IIB or IIC melanoma (KEYNOTE-716): a randomised, double-blind, phase 3 trial. *Lancet*. 2022;399(10336):1718-1729. doi:10.1016/S0140-6736(22)00562-1
10. Yushak M, Mehnert J, Luke J, Poklepovic A. Approaches to High-Risk Resected Stage II and III Melanoma. *Am Soc Clin Oncol Educ B*. 2019;(39):e207-e211. doi:10.1200/edbk_239283
11. Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant Pembrolizumab versus Placebo in Resected Stage III Melanoma. *NEJM*. 2018;378(19):1789-1801. doi:10.1056/nejmoa1802357
12. Ascierto PA, Del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB–C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. *Lancet Oncol*. 2020;21(11):1465-1477. doi:10.1016/S1470-2045(20)30494-0
13. Swetter S, Johnson D, Thompson JA, et al. Melanoma: Cutaneous. *NCCN Clin Pract Guidel Oncol*. 2023.
14. Faries MB, Thompson JF, Cochran AJ, et al. Completion Dissection or Observation for Sentinel-Node Metastasis in Melanoma. *N Engl J Med*. 2017;376(23):2211-2222. doi:10.1056/nejmoa1613210

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