Ontario Health
Cancer Care Ontario

Guideline 8-10

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Ontario Health (Cancer Care Ontario)

Locoregional Management of In-Transit Metastasis in Melanoma

F.C. Wright, S. Kellett, A. Sun, T. Hanna, C. Nessim, N.J. Look Hong, C.A. Giacomantonio, C.F. Temple-Oberle, X. Song, T.M. Petrella, and the Melanoma Disease Site Group

An assessment conducted in November 2024 deferred the review of Guideline 8-10. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document. (PEBC Assessment & Review Protocol)

Guideline 8-10 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/63026

Section 1: Recommendations
Section 2: Guideline – Recommendations and Key Evidence
Section 3: Guideline Methods Overview
Section 4: Systematic Review
Section 5: Internal and External Review

Report Date: February 18, 2020

For information about this document, please contact Frances Wright, the lead author, through the PEBC via:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

For information about the PEBC and the most current version of all reports, please visit the OH (CCO) website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822 Fax: 905 526-6775 E-mail: ccopgi@mcmaster.ca

PEBC Report Citation (Vancouver Style): Wright FC, Kellett S, Sun A, Hanna T, Nessim C, Look Hong NJ, et al. Guidelines for the management of in-transit metastasis in melanoma. Toronto (ON): Ontario Health (Cancer Care Ontario); 2020 Feb 18. Program in Evidence-Based Care Guideline No.: 8-10.

PUBLICATIONS RELATED TO THIS REPORT

Wright FC, Kellett S, Look Hong NJ, Sun AY, Hanna TP, Nessim C, Giacomantonio CA, Temple-Oberle CF, Song X, Petrella TM (2020). Locoregional management of in-transit metastasis in melanoma: an Ontario Health (Cancer Care Ontario) clinical practice guideline. Current Oncology, 27(3):e318-325.

Locoregional Management of In-Transit Metastasis in Melanoma

Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, the systematic review, and the guideline development proocess, see the Full Report.

GUIDELINE OBJECTIVES

To provide guidance on appropriate management of satellite and in-transit metastases from melanoma.

TARGET POPULATION

These recommendations apply to adult patients diagnosed with satellite lesions or in-transit metastases (ITM) from melanoma with or without lymph node metastasis. Patients with regional lymph node or distant metastasis were not included.

INTENDED USERS

Intended users of this guideline are oncologists specializing in the treatment of patients with melanoma within the province of Ontario. Other intended users include dermatologists, plastic surgeons, otolaryngologists, nuclear medicine doctors, and pathologists.

RECOMMENDATIONS

Preamble

In the following recommendations the terms minimal, moderate, and maximal ITM are used. This determination is a clinical decision best made by experts in melanoma surgery. Size, location, number of lesions, rapidity of development of new lesions, and depth of lesions within the skin, subcutaneous fat, or muscle all need to be considered. While there is no precise categorization, for the purposes of this guideline, we defined minimal ITM as lesions in a location with limited spread (generally 1-4 lesions); lesions are generally superficial, often clustered together, and surgically resectable. Moderate disease is considered to be >5 lesions covering a wider area or when new in-transit lesions develop rapidly (over weeks). Late presentation large-volume disease with multiple (>15-20) 2-3 cm nodules or subcutaneous or deeper lesions over a wide area is considered maximal.

While treatment intent in the following recommendations is to improve survival, it is acknowledged that a large portion of patients will have incomplete response or subsequent relapse. Follow-up (surveillance) and retreatment is standard of care, but was not within the scope of this guideline. The following recommendations are based on the available evidence supplemented by expert opinion; however, the quality and extent of comparative evidence is poor for ITM and enrolment in a clinical trial should be considered if available.

Recommendation 1
• In patients presenting with minimal ITM, complete surgical excision with negative pathological margins is recommended. In addition to complete surgical resection, adjuvant treatment may be considered.
Qualifying Statements for Recommendation 1
• In the case of this recommendation, minimal in-transit disease refers to lesions in a location with limited spread as determined by the clinician and as defined in the preamble. • Any patient with new in-transit disease should be staged to rule out distant metastases (including brain metastases) with positron emission tomography-computed tomography (PET-CT) and either head CT, brain magnetic resonance imaging (MRI), or CT of the head, chest, and pelvis. Imaging of the affected area (CT or MRI) could be completed if it would inform the clinical decision making. • Surgical excision should only be performed in instances where surgical morbidity is determined to be low. A review by a multidisciplinary team in a high-volume centre should be completed in these cases. • A wide local excision of the in-transit lesion is not required; however, an excision to achieve a pathologically negative margin is required. • Adjuvant systemic therapy may be considered for ITM undergoing surgical resection. For recommendations regarding adjuvant systemic therapy treatments, please refer to *PEBC Guideline 8-1: Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma* [1].

Recommendation 2

• In patients presenting with moderate, unresectable ITM consider using the following approach for localized treatment:
  ○ First choice: Intralesional interleukin (IL)-2 or talimogene laherparepvec (T‑VEC; Imlygic®)
  ○ Second choice: Topical diphenylcyclopropenone (DPCP)
  ○ Third choice: Radiation therapy
• There is insufficient evidence to recommend intralesional bacille Calmette-Guerin (BCG) or carbon dioxide (CO_2) laser ablation outside of a research setting.

Qualifying Statements for Recommendation 2
• In the case of Recommendation 2, moderate ITM is based on the number of lesions that makes resection unreasonable or where surgical resection would carry a high level of morbidity or when new lesions are appearing at a rapid rate (over weeks). • Any patient with new in-transit disease should be staged to rule out distant metastases (including brain metastases) with PET-CT and either head CT, brain MRI, or CT of the head, chest, and pelvis. Imaging of the affected area (CT or MRI) could be completed if it would inform the clinical decision making. • Clinical trials may be considered where appropriate and available. • A review by a multidisciplinary team in a high-volume centre should be completed for moderate ITM cases. • Some small trials, not meeting the review criteria [2-4], suggest that using tretinoin (Retin-A®)) and imiquimod (Aldara®) together with IL-2 may increase the rate of complete response (CR) and this is now being used in some centres. Imiquimod is not funded in Ontario. • Adjuvant therapy trials included patients rendered disease-free following surgery, and did not include patients with response to local treatment (topical or injections). There are therefore

no data on whether or not systemic treatment following local treatment would be of additional benefit.
- At the time of this Guideline publication, the following treatments are not approved for use in Ontario:
  - Electrochemotherapy (ECT)
  - Intralesional PV-10 (Rose Bengal)
  - Allovectin-7®
  - T-VEC
- In Ontario, costs for DPCP are not funded by the provincial health insurance plan.

Recommendation 3

- In patients presenting with maximal ITM (late presentation, large-volume disease, multiple 2-3 cm nodules) confined to an extremity, the following interventions may be considered:
  - Isolated limb perfusion (ILP)
  - Isolated limb infusion, (ILI) or
  - Systemic therapy
  - In extremely select cases, amputation could be considered as a final option in patients without systemic disease after discussion at a multidisciplinary case conference.

Qualifying Statements for Recommendation 3

- In the case of Recommendation 3, maximal ITM, based on late presentation, large-volume disease, and multiple 2-3 cm nodules, would likely not benefit from injections.
- Any patient with new in-transit disease should be staged to rule out distant metastases (including brain metastases) with PET-CT and either head CT, brain MRI, or CT of the head, chest, and pelvis. Imaging of the affected area (CT or MRI) could be completed if it would inform the clinical decision making.
- The regional therapies listed above are limited to use in patients with ITM confined to a limb (arm or leg) where a tourniquet can be placed above the highest in-transit lesion. For ILP, a nodal dissection is completed at the same time.
- Although systemic therapy was not reviewed in this guideline, it may be considered in patients with maximal ITM. Immunotherapy and targeted therapy have been found of benefit in the metastatic setting and for adjuvant use in completely resected melanoma [1].
- A review by a multidisciplinary team in a high-volume centre should be completed in cases where maximal disease is suspected.

Recommendation 4

- In cases where local, regional, or surgical treatments for ITM may be ineffective, unable to be performed, or if a patient has systemic metastases at the same time, systemic therapy may be considered.

Qualifying Statements for Recommendation 4

- A review by a multidisciplinary team in a high-volume centre should be completed for complex cases, including those for which systemic therapy is being considered.
- No studies were found that directly compared contemporary systemic therapy to locoregional treatments for any level (minimal/moderate/maximal) of ITM. As such, while balancing adverse effects, local availability, and patient preference, systemic therapy should always be an option.

References

1. Petrella TM, Baetz TD, Fletcher GG, Knight G, McWhirter E, Rajagopal S, et al. Systemic adjuvant therapy for adult patients at high risk for recurrent melanoma [Internet]. Toronto (ON): Cancer Care Ontario; 2019 Aug [cited Dec 9 2019]. Program in Evidence-Based Care Evidence-Based Series No.: 8-1 version 5. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1161.

2. Shi VY, Tran K, Patel F, Leventhal J, Konia T, Fung MA, et al. 100% complete response rate in patients with cutaneous metastatic melanoma treated with intralesional interleukin (IL)-2, imiquimod, and topical retinoid combination therapy: results of a case series. J Am Acad Dermatol. 2015;73(4):645-54.

3. Leventhal JS, Odell ID, Imaeda S, Maverakis E, King BA. Treatment of melanoma in-transit metastases with combination intralesional interleukin-2, topical imiquimod, and tretinoin 0.1% cream. JAAD Case Rep. 2016;2(2):114-6.

4. Garcia MS, Ono Y, Martinez SR, Chen SL, Goodarzi H, Phan T, et al. Complete regression of subcutaneous and cutaneous metastatic melanoma with high-dose intralesional interleukin 2 in combination with topical imiquimod and retinoid cream. Melanoma Res. 2011;21(3):235-43.