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PRACTICE GUIDELINE

Locoregional management of in-transit metastasis in melanoma: an Ontario Health (Cancer Care Ontario) clinical practice guideline

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ABSTRACT

Objective The purpose of this guideline is to provide guidance on appropriate management of satellite and in-transit metastasis (ITM) from melanoma.

Methods The guideline was developed by the Program in Evidence-Based Care (PEBC) of Ontario Health (Cancer Care Ontario) and the Melanoma Disease Site Group. Recommendations were drafted by a Working Group based on a systematic review of publications in the MEDLINE and EMBASE databases. The document underwent patient- and caregiver-specific consultation and was circulated to the Melanoma Disease Site Group and the PEBC Report Approval Panel for internal review; the revised document underwent external review.

Recommendations "Minimal ITM" is defined as lesions in a location with limited spread (generally 1–4 lesions); the lesions are generally superficial, often clustered together, and surgically resectable. "Moderate ITM" is defined as more than 5 lesions covering a wider area, or the rapid development (within weeks) of new in-transit lesions. "Maximal ITM" is defined as large-volume disease with multiple (>15–20) 2–3 cm nodules or subcutaneous or deeper lesions over a wide area.

- In patients presenting with minimal ITM, complete surgical excision with negative pathologic margins is recommended. In addition to complete surgical resection, adjuvant treatment may be considered.
- In patients presenting with moderate unresectable ITM, consider using this approach for localized treatment: intralesional interleukin 2 or talimogene laherparepvec as 1st choice, topical diphenylcyclopropenone as 2nd choice, or radiation therapy as 3rd choice. Evidence is insufficient to recommend intralesional bacille Calmette–Guérin or CO_2 laser ablation outside of a research setting.
- In patients presenting with maximal ITM confined to an extremity, isolated limb perfusion, isolated limb infusion, or systemic therapy may be considered. In extremely select cases, amputation could be considered as a final option in patients without systemic disease after discussion at a multidisciplinary case conference.
- In cases in which local, regional, or surgical treatments for ITM might be ineffective or unable to be performed, or if a patient has systemic metastases at the same time, systemic therapy may be considered.

Key Words In-transit metastasis, melanoma, ITM, practice guidelines

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INTRODUCTION

According to *Canadian Cancer Statistics*[1,2], the projected number of cases of melanoma in Canada in 2017 was 7200 (18.5 per 100,000 population), with 1250 deaths, making melanoma the 8th most common cancer and the 15th in mortality. In Ontario, 4129 cases of melanoma were predicted for 2018 (26.4 per 100,000 population), representing 4.6% of all cancers[3]. Actual data from 2013 indicated 3409 new cases of melanoma (24.7 per 100,000 population, 4.4% of all

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cancers) and 519 deaths (1.9% of all cancer deaths). For the period 2009–2013, 5-year survival was 86.6%[3].

In patients diagnosed with melanoma, approximately 4%–10% will develop in-transit metastasis (ITM) and satellite metastasis[4–6]. In-transit metastasis is a cutaneous or subcutaneous locoregional recurrence of disease that generally occurs in close proximity to the site of the primary lesion and travels toward the draining lymph node basin; satellite metastasis generally occurs within 2 cm of the primary lesion[4,5]. In the present guideline, the term "ITM" is considered to include satellite metastasis.

The presence of ITM can be an indicator of an increased risk of developing disseminated disease. The 5-year survival rate ranges widely and depends largely on associated metastases to the surrounding lymph nodes[4]. Patients with ITM can experience severe morbidity, including pain, bleeding, and infection, particularly in the presence of numerous large lesions, with ulceration of the tumours[4,5]. Resection of the ITM is the preferred treatment. If resection is not possible, little high-quality evidence is available to suggest which subsequent treatment is best. The Program in Evidence-Based Care (PEBC) of Ontario Health (Cancer Care Ontario) [OH(CCO)] developed the present guideline, which contains recommendations for the interventions that could have the greatest efficacy for ITMs of varying degrees.

METHODS

Guideline Developers

This guideline was developed by the Satellite and In-Transit Melanoma Guideline Development Group, which was convened at the request of the Melanoma Disease Site Group of OH(CCO). The project was led by a small Working Group, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in radiation oncology, surgical oncology, and health research methodology. Other members of the guideline development group served as the Expert Panel and were responsible for the review and approval of the draft document. Conflict of interest declarations were collected for all participants and were managed in accordance with the conflict-of-interest policy of the Program in Evidence-Based Care (PEBC).

Guideline Development

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[7,8]. The process includes a systematic review of the literature, interpretation of the evidence, and drafting of recommendations by the Working Group; internal review by content and methodology experts; and external review by clinicians. The PEBC's guideline development methods are described in more detail in the *Program in Evidence-Based Care Handbook* and the PEBC *Methods Handbook*. The present publication focuses on the guideline recommendations, with a brief summary of methods used; the full 5-part document, including the systematic review, can be found on the OH(CCO) Web site[9].

Guideline Objective

This guideline makes recommendations about the appropriate management of satellite metastasis and ITM from melanoma.

Research Questions

- What treatments are available for ITM, and what are the response, recurrence, survival, quality of life, and toxicity outcomes associated with each one?
- What are the recommended treatments for patients with ITM? What is the recommended sequence of treatments?

Target Population

These recommendations apply to adult patients diagnosed with ITM from melanoma with or without lymph node metastasis [stage IIIC according to the updated 8th edition of the American Joint Committee on Cancer (AJCC) staging manual[10]]. It should be noted that the 7th edition of the AJCC staging system for melanoma uses the term "intralymphatic metastases" (satellitosis and ITM) and includes patients with stage IIIB or IIIC disease[11]. The literature included in the evidence base overlapped the change in definition; patients defined under the 7th edition of the AJCC manual (stages IIIB and IIIC) were therefore included. Patients with regional lymph node or distant metastasis were not included.

Literature Search

The MEDLINE and EMBASE databases were searched for randomized controlled trials (RCTs) and non-RCTs with prospective and retrospective study designs that evaluated local and regional treatment modalities for patients with ITM, published from 1980 to 1 January 2019. The RCTs were assessed for quality using components of the Cochrane Risk of Bias tool (http://handbook.cochrane.org/, Part 2, Section 8.5).

Development of Recommendations

The Working Group drafted recommendations based on the systematic review. Where evidence was limited, recommendations were based on the professional experience of the authors, and that approach is noted in the Qualifying Statements or the Interpretation of the Evidence section following each recommendation.

Review Process

The draft guideline underwent internal review by a panel of content experts (the Expert Panel) and a methodology panel (the Report Approval Panel). The Melanoma Disease Site Group members served as the Expert Panel; that group consisted of surgical and medical oncologists, pathologists, dermatologists, and a patient representative. The Report Approval Panel consisted of the PEBC Scientific Director and two other members with expertise in clinical and methodology issues. The Working Group incorporated the feedback of both panels.

Patients, cancer survivors, or caregivers participated as Consultation Group members. They reviewed copies of draft document and provided feedback on its comprehensibility, appropriateness, and feasibility.

External review included a targeted peer review to obtain direct feedback on the draft guidelines from a small number of content experts, and a professional consultation intended to facilitate dissemination of the final guidelines to Ontario practitioners who are the intended users of the guideline. All clinicians with an interest in melanoma, skin cancer, dermatology, surgical oncology, or medical oncology in the PEBC database were contacted by e-mail as part of the professional consultation. Comments from the reviewers and responses by the Working Group are detailed in the full report on the OH(CCO) Web site[9].

RESULTS OF THE LITERATURE REVIEW

Two systematic reviews[4,12] were included based on their content, quality, and relevance to the research questions. One assessed the efficacy and toxicity associated with intralesional interleukin 2 (IL-2) for the treatment of in-transit melanoma[4]; the other evaluated the efficacy of isolated limb infusion (ILI) with melphalan and actinomycin D for melanoma[12].

Eighty primary studies (eight RCTs and seventy-two nonrandomized observational studies) were identified that met the inclusion criteria. Of the RCTs, the OPTiM trial evaluating intralesional talimogene laherparepvec (T-VEC)[13–15] and a trial by Cornett *et al.*[16] evaluating isolated limb perfusion (ILP) with or without tumour necrosis factor α (TNF-α) were considered to have a low risk of bias. One trial by Olofsson Bagge and colleagues[17,18] evaluating ILP as adjuvant treatment to excision was also included; it was rated as having an unclear risk of bias. The remaining RCTs, plus the observational studies, were considered to have high risk of bias. For most agents studied, the evidence was limited and of low quality. The full systematic review provides details of the methodologic characteristics and clinical outcomes of the included studies[9].

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Based on the systematic review, and supplemented by professional experience where indicated, clinical recommendations and qualifying statements were developed.

Preamble

In the recommendations that follow, the terms "minimal ITM," "moderate ITM," and "maximal ITM" are used. The relevant 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 have to be considered. Although no precise categorization has been developed, for the purposes of the present guideline, "minimal ITM" is defined as lesions in a location with limited spread (generally 1–4 lesions); the lesions are generally superficial, often clustered together, and surgically resectable. "Moderate ITM" is considered to be more than 5 lesions covering a wider area, or the rapid development (within weeks) of new in-transit lesions. 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 ITM."

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

Recommendation 1

In patients presenting with minimal ITM, complete surgical excision with negative pathologic margins is recommended. In addition to complete surgical resection, adjuvant treatment may be considered.

Qualifying Statements

In the case of this recommendation, "minimal ITM" refers to lesions in a location with limited spread as determined by the clinician and as defined in the Preamble.

To rule out distant metastases (including brain metastases), any patient with new ITM should be staged using integrated positron-emission tomography–computed tomography (PET-CT) or computed tomography (CT) of the chest, abdomen, and pelvis; plus either brain magnetic resonance imaging (MRI) or head CT. Imaging of the affected area (CT or MRI) could be completed if it would inform clinical decision-making.

Surgical excision should be performed only in instances in which surgical morbidity is determined to be low. A review by a multidisciplinary team in a high-volume centre should be completed in such cases.

Wide local excision of the in-transit lesion is not required; however, excision to achieve a pathologically negative margin is required.

Adjuvant systemic therapy may be considered for ITM being surgically resected. For recommendations about adjuvant systemic therapy, consult the PEBC guideline on adjuvant systemic therapy[19].

Key Evidence

At the time of writing, no systematic reviews and only one primary study[20] captured in the systematic literature search had evaluated excision for minimal ITM. Excision is currently the standard of care for cases of ITM that are minimal in size and spread, and for which surgical excision would carry low surgical morbidity.

Interpretation of the Evidence

This recommendation was based on the expert opinion of the Working Group and is currently the standard of practice within cancer centres in Canada. If adjuvant therapy is being considered as an option for affected patients, the PEBC guideline on systemic adjuvant therapy outlines the appropriate systemic therapies based on the clinical evidence and should be consulted[19,21].

Recommendation 2

In patients presenting with moderate unresectable ITM, consider using this approach for localized treatment:

- 1st choice: intralesional IL-2 or T-VEC (Imlygic: Amgen Canada, Mississauga, ON)

- 2nd choice: topical diphenylcyclopropenone (DPCP)
- 3rd choice: radiation therapy

Evidence is insufficient to recommend intralesional bacille Calmette–Guérin (BCG) or CO_2 laser ablation outside a research setting.

Qualifying Statements

In the case of recommendation 2, "moderate ITM" is based on lesions whose number makes resection unreasonable or for which surgical resection would carry a high level of morbidity, or on the rapid appearance (within weeks) of new lesions.

Any patient with new ITM should be staged to rule out distant metastases (including brain metastases) with PET-CT or CT of chest, abdomen, and pelvis; plus either brain MRI or head CT. Imaging of the affected area (CT or MRI) could be completed if it would inform 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 cases of moderate ITM.

Some small trials not meeting the review criteria[22–24], suggest that using tretinoin (Retin-A: Bausch Health Companies, Laval, QC) and imiquimod (Aldara: Bausch Health Companies) together with IL-2 might increase the rate of complete response (CR). That approach is now being used in some centres.

Adjuvant therapy trials included patients rendered disease-free after surgery and did not include patients with response to local treatment (topical or injected). Data about whether systemic treatment after local treatment would be of additional benefit are therefore lacking.

At the time of guideline publication, these treatments are *not* approved for use in Ontario:

- Electrochemotherapy
- Intralesional PV-10 (Rose bengal)
- Allovectin-7 (Vical Incorporated, San Diego, CA, U.S.A.)
- T-VEC

In Ontario, costs for DPCP, Retin-A, and imiquimod are not funded by the provincial health insurance plan.

Key Evidence

When considering a treatment strategy for patients with ITM, IL-2 was considered a suitable first-line therapy based on the literature review, the expert opinion of the Working Group, and the tolerability of IL-2 for patients.

The systematic review of IL-2 by Byers *et al.*[4] included six observational studies with 140 patients and 2182 lesions. A CR was reported for 77.9% of lesions and 49.6% of patients. An additional retrospective study of 31 patients by Hassan *et al.*[25] reported results only on a per-patient basis; 32.3% experienced a CR, and 54.8%, a partial response (PR). With respect to toxicity, the tolerability of IL-2 in the systematic review by Byers *et al.*[4] was good, with localized pain and swelling, and mild flu-like symptoms. Three grade 3 adverse events (AEs), namely rigors, headache, and fever with arthralgia, were reported. In Hassan *et al.*[25], toxic effects were minor; 1 patient developed cellulitis, and most patients experienced fatigue, fever, and chills for 24 hours.

Based on the results of the OPTiM phase III clinical trial[13–15], T-VEC was also considered a suitable first-line therapy for patients with ITM. That trial randomized 436 patients with unresected stage IIIB or IV melanoma 2:1 to receive T-VEC or subcutaneously administered granulocyte–macrophage colony–stimulating factor[15]. There were 2116 injected lesions, and 981 un-injected non-visceral lesions. Median overall survival (OS) was 23.3 months compared with 18.9 months (hazard ratio: 0.79; 95% confidence interval: 0.62 to 1.00; $p = 0.0494$), and 4-year OS was 34.5% compared with 23.9%. A CR occurred in 16.9% compared with 0.7% of patients, and a PR, in 14.6% compared with 5.7%. Grade 3 or greater AEs occurred in 11.3% compared with 4.7% of patients. The only grade 3 or 4 AE occurring in more than 2% of patients was cellulitis (T-VEC: $n = 6$, 2.1%). Of patients treated with T-VEC, those achieving a CR experienced an estimated 88.5% 5-year OS; for those not achieving a CR, it was 35%. In the T-VEC arm, achievement of CR on a per-lesion basis was 47% for injected lesions and 22% for un-injected lesions; per-lesion achievement of PR was 17% and 12%. The ability to cause a response in un-injected lesions has been called a "bystander effect"[26,27]. The efficacy of T-VEC was most pronounced in patients with stage IIIB, IIIC, or IVM1a disease and in those with treatment-naïve disease[15].

Evidence for DPCP consisted of two small retrospective studies[28,29]. A CR occurred in 22%–46% of patients, and a PR, in 38%–39%. Survival data were available from only one study, and the median OS was 20.9 months[28]. Response rates varied between the studies, and Damian *et al.*[29] reported a difference in the CR rate for patients with thin and with bulky disease (61% vs. 21%).

Selection of radiation therapy was based on the expert opinion of the Working Group, supported by one observational study that evaluated palliative radiation therapy in a subset of 24 patients with ITM[30]. The median total radiation dose for all patients was 48 Gy (mean: 45 Gy; range: 12–66 Gy), and the median duration of the radiation therapy series was 21 days (mean: 25 days; range: 8–56 days). Patients with Union for International Cancer Control stage III disease (ITM or lymph node metastases) experienced a median OS of 22 months (1-year OS rate: 74% ± 12%; 5-year OS rate: 32% ± 14%). Because of diffuse spread of the lesions, the exact tumour volume for patients with ITM was not available[30].

Three RCTs that evaluated intralesional BCG as adjuvant therapy to surgical excision were available[31–33]. The control groups for all studies were clinical observation. In each case, no significant differences in response or survival rates were observed when the intervention and control arms were compared. When toxicity was evaluated, intralesional BCG was considered to be tolerable, and no serious AEs (grade 3 or greater) were recorded[31,32].

Ablation by CO_2 laser was used in two observational studies[34,35] that reported OS rates in the range 65%–67%; however, response rates were not reported in either study. Treatment by CO_2 laser was well-tolerated; the only observed AE was grade 1 wound infection (4 patients) that did not require treatment[35].

Interpretation of the Evidence

This recommendation was based on the combined clinical experience of the Working Group members and the availability of the interventions in Canada, and was informed by the available evidence. The demographics and subtypes of patients with ITM vary widely, and therefore the literature that evaluated the efficacy of the interventions was unable to be compared in a way that would be meaningful for recommendation development. However, the Working Group was able to infer some comparative value from the toxicity data and from the availability, applicability, and feasibility of using the evaluated local interventions in Canada.

The interventions listed in the recommendation would be reasonable for patients with moderate ITM. In most cases, the populations for the relevant studies consisted of patients with nonresectable metastasis that would be amenable to topical or local therapies. A broad range of reported survival data and response rates, and heterogeneity in patient selection, outcome measures, and management strategies prohibited direct comparison of the interventions one with another.

The preferred therapies are IL-2 and T-VEC. Based on the clinical experience of the Working Group members and because the CR rate per patient was higher (32%–50% for IL-2 vs. 17% for T-VEC), IL-2 was considered to be suitable for first-line therapy. In Canada, IL-2 is readily available and is delivered in a noninvasive procedure that carries minimal risk for serious AEs. The Working Group members weighed the potential response benefits of IL-2 against the harms outlined in the evidence and determined that IL-2 would be a suitable first-line intervention for patients with moderate ITM. Imiquimod and tretinoin cream can be added to the IL-2 at the clinician's discretion and might increase the CR rate when used in combination[22–24]. Based on the results of the OPTiM trial, T-VEC was also considered suitable for first-line therapy[13–15]; however, at the time of writing, T-VEC has not been approved for use in Ontario outside a clinical trial.

Topical DPCP was determined to have a lower benefit-to-harms profile than either IL-2 or T-VEC based on the expert opinion of the Working Group and the available clinical evidence.

Radiation therapy was identified as a third choice based on the clinical experience of the Working Group members, and it is a standard therapy before progressing to more invasive options such a regional or systemic therapy.

With each therapy, a multidisciplinary team in a high-volume centre should be consulted, because only a subset of patients with ITM will potentially benefit from these local therapies, given the significant selection bias associated with the patients chosen for the relevant studies. Extent, prior therapy, and comorbidities should be taken into consideration when selecting the appropriate intervention.

The remaining local interventions that were evaluated for the guideline were not selected as options based on a lack of clinical evidence (intralesional interferon alfa, Allovectin-7), unavailability in Canada (PV-10, Allovection-7, electrochemotherapy), or infeasibility for use in Canadian cancer centres (electrochemotherapy).

Recommendation 3

In patients presenting with maximal ITM (late presentation, large-volume disease, multiple 2–3 cm nodules) confined to an extremity, these interventions may be considered:

- ILP
- ILI
- 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

In the case of recommendation 3, maximal ITM, because of late presentation, large-volume disease, and multiple 2–3 cm nodules, would likely not benefit from injection therapies.

Any patient with new ITM should be staged to rule out distant metastases (including brain metastases) with PET-CT or CT of chest, abdomen, pelvis; plus either brain MRI or head CT. Imaging of the affected area (CT or MRI) could be completed if it would inform the clinical decision-making.

The regional therapies listed in this recommendation are limited to use in patients with ITM confined to a limb (arm or leg) in which 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 is not reviewed in this guideline, it may be considered in patients with maximal ITM. Immunotherapy and targeted therapy have been found to be of benefit in the metastatic setting and for adjuvant use in completely resected melanoma[19].

A review by a multidisciplinary team in a high-volume centre should be completed for patients in whom maximal disease is suspected.

Key Evidence

One systematic review[12] (which encompassed seven studies) and ten other observational studies[36–45] evaluated ILI using melphalan and actinomycin D. The systematic review reported a CR in 33% of patients and a PR in 40%. In the studies not included in the systematic review, CR rates ranged from 6% to 41%, and PR rates, from 5.3% to 68%. Median OS in the three primary studies that reported that outcome ranged from 30.9 months to 41 months. Given the heterogeneity in the treatment patterns and patients included, the data could not be pooled.

Use of ILP was reported in three RCTs[16,17,46] and thirty-four nonrandomized studies of patients with ITM. The CR rate varied from 20% to 90%, with rates of 35%–65% reported in most studies.

In the RCT by Cornett *et al.*[16], patients in one study arm received hyperthermic ILP with melphalan; those in the other arm received hyperthermic ILP with melphalan plus TNF-α. Lienard *et al.*[46] randomized patients to either ILP with melphalan plus TNF-α or to subcutaneous interferon γ for 2 days, followed by interferon γ plus ILP as in the first arm. Cornett *et al.*[16] reported CR rates of 25% and 26% at 3 months and 20% and 42% at 6 months; Lienard *et al.*[46] reported CR

rates of 68.8% and 78.1%. The differences were not statistically significant. Toxicity was higher in the TNF-α arm in Cornett *et al.*, although more grade 4 AEs occurred in the melphalan plus TNF-α arm. No single category of AE was statistically more frequent.

The RCT originally reported by Hafstrom *et al.*[18] in 1991 and updated by Olofsson Bagge *et al.*[17] in 2014 compared patients randomly allocated to wide excision (n = 36) or wide excision plus ILP (n = 33), with stratification for upper or lower extremity localization. Patients were followed for more than 25 years of observation time after randomization, and no statistically significant difference in OS over time was evident between the wide excision and the wide excision plus ILP groups (p = 0.24). It should be noted that the population in the study was small, and therefore the results should be interpreted with caution[17].

Six studies compared the regional therapies ILI and ILP[47–52]. The CR rate for ILI was 17%–30%, and the CR rate for ILP was 32%–60%. In each case, ILP was superior to ILI in terms of the response rate; in three studies, the difference was statistically significant. In the study by Sharma *et al.*[52], OS was 54% compared with 77%, p = 0.10. In the study by Dossett *et al.*[49], the 1-year OS rate was 85% compared with 78%, the 3-year OS rate was 55% compared with 51%, and the 5-year OS rate was 18% compared with 31% (differences that were not statistically significant). Toxicity data were scarce; however, high grade toxicities were found in the ILP cohorts compared with the ILI cohorts[49,51].

Interpretation of the Evidence

This recommendation was based on the clinical experience of the Working Group. The clinical evidence for this recommendation was considered to be weak, and the Working Group could not recommend either ILI or ILP as being superior. In the absence of a high-quality randomized trial comparing ILI and ILP in a controlled ITM population, it is suggested that a review by a multidisciplinary team in a high-volume centre be completed in cases in which maximal disease is suspected. Although not widely used in Canada, ILI and ILP are typically applied in patients with high-burden nonresectable ITM that is within a limb that can safely be isolated. Response rates are better with ILP, but it is unclear whether those rates translate into better survival. Toxicity is also higher with ILP, including higher rates of rare side effects such as compartment syndrome and amputation. In cases in which regional therapies are being considered, a multidisciplinary team should perform careful patient selection.

Recommendation 4

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

Qualifying Statements

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 with locoregional treatments for any level—minimal, moderate, or maximal—of ITM. Therefore, while balancing adverse effects, local availability, and patient preference, systemic therapy should always be an option.

Key Evidence

This recommendation is based on the expert opinion of the Working Group members and is currently the standard of practice within cancer centres in Ontario. Such cases should be discussed by a multidisciplinary team in a high-volume centre.

DISCUSSION

In-transit disease is thought to reflect either intralymphatic or angiotrophic tumour spread of melanoma metastases between the primary site and the nearest lymph node basin, and to generally portend a poor prognosis for the patient[53]. However, ITM has a wide variety of presentations. The 8th edition of the AJCC staging manual for melanoma has updated the effect of ITM on staging and subcategorizes it into N1c, N2c, or N3c depending on the extent of regional lymph node involvement[53]. What is not currently defined by AJCC staging is the extent of in-transit disease and whether varying presentations or volumes of disease affect outcome. The present guideline is a first step in defining both the presentations of in-transit disease (because no internationally accepted definitions exist) and appropriate treatment options based on the patient's extent of ITM.

The treatment options for ITM from melanoma are vast, ranging from injectables such as PV-10, T-VEC, and IL-2 to more complex options such as ILP or ILI, and systemic therapy. This wide range of treatment modalities reflects the lack of clarity about both the optimal treatment of ITM and treatment sequencing if the first line of therapy fails. The Working Group for this guideline systematically reviewed the literature about ITM, developed definitions for the presentation of ITM, and based on the defined presentations, suggests appropriate treatment options and how to sequence those treatments—work that is especially timely in the context of new, efficacious systemic therapies. The Working Group also determined that a few clinical trials are either directly comparing local therapies or assessing combinations of local and systemic treatments (see NCT02557321 at https://ClinicalTrials.gov/).

In its recommendations, the Working Group used the available literature, attempting to balance potential morbidity with the efficacy associated with each treatment modality. For minimal disease, surgical resection is the suggested treatment. For moderate disease, injectables (IL-2 or T-VEC) are suggested as a first line of treatment. Generally, the latter treatments have minimal morbidity, mild skin reactions being the most common AEs[5,13,25]. For patients who present with maximal disease, ILI, ILP, or systemic therapy are suggested as treatment options. On review of the current literature, the Working Group believed that injectables would not be effective in dealing with a maximal volume of disease, although no trials have directly compared injectables with ILI, ILP, or systemic therapy.

In summary, the Working Group identified gaps in the literature:

- Standardized definitions for the common presentations of in-transit disease
- Clinical trials comparing treatment options, including the combination of systemic and local treatments
- Data about outcomes in patients with minimal, moderate, and maximal in-transit disease

The Working Group would strongly support international collaboration in those key areas.

REVIEW AND UPDATE

The currency of each PEBC document is ensured by periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. That process is described in the *Program in Evidence-Based Care Document Assessment and Review Protocol.*

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The complete version of this guideline and accompanying systematic review can be found on the OH(CCO) Web site at https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/63026.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: TMP reports grants from Roche, Novartis, Merck, and Bristol–Myers Squibb and has served on advisory boards for Novartis, Merck, Bristol–Myers Squibb, EMD Serono, and Sanofi outside the submitted work. FCW, SK, NJLH, AYS, TPH, CN, CAG, CFRO, and XS have no conflicts to disclose.

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