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

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An assessment conducted in December 2025 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

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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.

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Locoregional Management of In-Transit Metastasis in Melanoma

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

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 metastases. 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.

Locoregional Management of In-Transit Metastasis in Melanoma

Section 2: Guideline – Recommendations and Key Evidence

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 metastases (stage IIIc according to the updated American Joint Committee on Cancer [AJCC], 8th Edition [5]). This definition of ITM is based on the updated AJCC 8th edition, and 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 [6]. The literature included overlapped this change in definition; therefore, patients defined under the previous AJCC guidelines, stages IIIb and IIIc, were included. 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, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

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].
Key Evidence for Recommendation 1
• At the time of this Guideline there were no systematic reviews and only one primary study [7] that evaluated excision for minimal in-transit disease captured in this systematic literature search. This procedure is currently the standard of care for cases of ITM that are minimal in size and spread and where surgical excision would carry a low surgical morbidity.
Interpretation of Evidence for Recommendation 1
• 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 these patients, *PEBC Guideline 8-1: Systemic Adjuvant Therapy for Patients at High Risk for Recurrent Melanoma* should be consulted as this Guideline outlines the appropriate systemic therapies based on the clinical evidence.

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.

Key Evidence for Recommendation 2

- When considering a treatment strategy for patients with ITM, IL-2 was considered to be a suitable first-line therapy based on evidence in Table 4-9, the expert opinion of the Working Group, and tolerability of IL-2 for patients.
- The systematic review of IL-2 by Byers et al. [8] included six observational studies with 140 patients and 2182 lesions. CR was reported for 77.9% of lesions and 49.6% of patients. An additional retrospective study of 31 patients by Hassan et al. [9] reported results only on a per-patient basis; 32.3% had CR and 54.8% had partial response (PR). With respect to toxicity, the tolerability of IL-2 in the systematic review by Byers et al. was good, with localized pain and swelling, and mild flu-like symptoms. There were three grade 3 adverse events (AEs) reported, including rigors, headache, and fever with arthralgia [8]. In Hassan et al., toxic effects were minor; one patient developed cellulitis, and most patients experienced fatigue, fever, and chills for 24 hours [9].
- T-VEC was also considered to be a suitable first-line therapy for patients with ITM based on the results of the OPTiM phase III clinical trial [10-12]. Four hundred thirty-six patients with unresected stage IIIb/IV melanoma were randomized at a 2:1 ratio to receive T-VEC versus subcutaneously administered granulocyte macrophage colony-stimulating factor (GM-CSF) [11]. There were 2116 injected lesions and 981 uninjected non-visceral lesions. Median overall survival (OS) was 23.3 months versus 18.9 months (hazard ratio [HR]=0.79; 95% confidence interval [CI] 0.62 to 1.00, p=0.0494) and four-year OS was 34.5% versus 23.9%. Complete response occurred in 16.9% versus 0.7% of patients and PR occurred in 14.6% versus 5.7% of patients. Grade >3 AEs occurred in 11.3% versus 4.7% of patients. The only grade 3 or 4 AE occurring in >2% of patients was cellulitis (T−VEC, n=6 [2.1%]).Of patients treated with T−VEC, those with CR had estimated 88.5% five-year OS compared

with 35% for those without CR. Complete response rates (on a per lesion basis) in the T−VEC arm for injected and uninjected lesions were 47% and 22%, respectively, while PR was 17% versus 12%. This ability to cause response in non-injected lesions has been referred to as a bystander effect [13,14]. T−VEC efficacy was most pronounced in patients with stage IIIb, IIIc, or IVM1a disease and in patients with treatment-naive disease [11].

- Evidence for DPCP consisted of two small retrospective studies [15,16] (see Table 4-15). CR occurred in 22% to 46% of patients and PR in 38% to 39% of patients. Survival data were only available from one study and the median OS was 20.9 months [15]. While response rates varied among the studies, Damian et al. [16] found a difference in CR rates between patients with thin and bulky disease (61% vs. 21%).
- The selection of radiation therapy was based on the expert opinion of the Working Group and supported by one observational study that evaluated palliative radiation therapy in a subset of 24 patients with ITM [17]. 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). Union for International Cancer Control (UICC) stage III patients (ITM or lymph node metastases) had a median OS of 22 months (1-year OS 74±12%, 5-year OS 32±14%). Due to the diffuse spread of the lesions, the exact tumour volume was not available for patients with ITM [17].
- Three randomized controlled trials (RCTs) were available that evaluated intralesional BCG as adjuvant therapy to surgical excision [18-20]. The control groups for all studies were clinical observation. In each case there was no significant difference in response or survival rates 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) were recorded [18,19].
- CO_2 laser ablation was used in two observational studies [21,22]. OS ranged from 65-67%; however, response rates were not reported in either study. CO_2 laser treatment was well tolerated and the only observed AE was a grade 1 wound infection that did not require treatment in four patients [22].

Interpretation of Evidence for Recommendation 2

- This recommendation was based on the combined clinical experience of the Working Group members, availability of the interventions in Canada, and 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 as well as the availability, applicability, and feasibility of using the evaluated local interventions in Canada. The interventions listed above would be reasonable for patients with moderate ITM. In most cases the patient populations for these studies consisted of patients with non-resectable metastasis that would be amenable to topical or local therapies. There was a broad range of survival data, response rates, and heterogeneity in patient selection, outcome measures, and management strategies, which prohibited the interventions from being directly comparable to each other.
- IL-2 and T-VEC are considered to be the preferred therapies. IL-2 was considered to be suitable for first-line therapy based on the clinical experience of the Working Group members and because the CR rate per patient was higher (32% to 50% for IL-2 vs. 17% for T-VEC). IL-2 is readily available in Canada and is a non-invasive 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 may increase

the CR rate when used in combination [2-4]. T-VEC was also considered suitable for first-line therapy based on the results of the OPTiM trial [10-12]; however, at the time of this guideline, T-VEC has not been approved for use in Ontario outside of a clinical trial.
- Topical DPCP was determined to have a lower benefit to harms profile than 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 is a standard therapy before progressing onto more invasive options such a regional or systemic therapy.
- With each therapy, a multidisciplinary team should be consulted in a high-volume centre as only a subset of patients with ITM will potentially benefit from the local therapies listed above as there was significant selection bias associated with the patients chosen for these studies. Extent, previous therapy, as well as comorbidities should be taken into consideration when selecting the appropriate intervention.
- The remaining local interventions that were evaluated in this Guideline were not selected, based on their lack of clinical evidence (intralesional interferon-alpha [IFN-α] or Allovectin-7), availability in Canada (PV-10, Allovection-7, ECT) or their feasibility for use within Canadian cancer centres (ECT).

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.

Key Evidence for Recommendation 3

- ILI using melphalan plus actinomycin D was investigated in one systematic review which included seven studies [23]; ten other observational studies [24-33] evaluated ILI (see Table 4-16). The systematic review found CR in 33% of patients and PR in 40% of patients.

Across the studies that were not included in the systematic review, the CR rates ranged from 6% to 41% and PR ranged from 5.3% to 68%. Median OS for three primary studies that reported this outcome ranged from 30.9 months to 41 months. Due to the heterogeneity in the treatment patterns and included patients, the data could not be pooled.

- ILP was used in three RCTs [34-36] and 34 non-randomized studies of patients with ITM (see Tables 4-17 to 4-19). The rate of CR varied from 20% to 90%, with rates of 35% to 65% reported in most studies.
    - In the RCT by Cornett et al. [34], one arm received hyperthermic ILP with melphalan and the other hyperthermic ILP with melphalan plus tumour necrosis factor-alpha (TNF-α). Lienard et al. [35] randomized patients to either ILP with melphalan plus TNF or to subcutaneous IFN-γ for two days followed by IFN-γ plus ILP as in the first arm. Cornett et al. reported CR of 25% versus 26% at three months and 20% versus 42% at six months, while Lienard et al. [35]reported CR of 68.8% versus 78.1%; these 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 conducted by Hafstrom et al. [37] in 1991 and updated by Olofsson Bagge et al. [36] 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 up with more than 25 years of observation time after randomization; there was no statistically significant difference in OS over time between the wide excision and the wide excision plus ILP groups (p=0.24). It should be noted that this study had a small population, and therefore should be interpreted with caution [36].
- Six studies compared the regional therapies ILI and ILP [38-43] (see Table 4-20). CR for ILI was 17% to 30%, while CR for ILP was 32% to 60%. In each case ILP was superior to ILI in term of response rates; in three studies there was a statistically significant difference. In the study by Sharma et al. [43], OS was 54% versus 77%, p=0.10). In the study by Dosset et al, [40], one-year OS was 85% versus 78%, three-year OS was 55% versus 51%, and five-year OS was 18% versus 31%; these differences were not statistically significant. Toxicity data were scarce; however, high grade toxicities were found in the ILP cohorts versus the ILI cohorts [40,42].

Interpretation of Evidence for Recommendation 3

- 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 members could not recommend either ILI or ILP as being superior over the other. In the absence of a high-quality randomized trial comparing ILI and ILP in a controlled ITM patient population, it is suggested that a review by a multidisciplinary team in a high-volume centre should be completed in cases where maximal disease is suspected. While not widely utilized throughout Canada, ILI and ILP are typically utilized in patients with high burden, non-resectable ITM that is within a limb that can safely be isolated. ILP has better response rates but it is unclear whether this translates into better survival. ILP also carries a higher toxicity, including higher rates of rare side effects such as compartment syndrome and amputation. In cases where regional therapies are being considered, careful patient selection should be completed by a multidisciplinary team.

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.
Key Evidence for Recommendation 4
• This recommendation was based on the expert opinion of the Working Group members and is currently the standard of practice within cancer centres in Ontario. These cases should be discussed by a multidisciplinary team in a high-volume centre.

RELATED GUIDELINES

- 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 V5. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1161.

- Wright F, Souter LH, Easson A, Murray C, Toye J, McCready D, et al. Primary excision margins and sentinel lymph node biopsy in cutaneous melanoma. Toronto (ON): Cancer Care Ontario; 2017 November 13. Program in Evidence-Based Care Guideline No.: 8-2 V2. Available from https://www.cancercareontario.ca/en/content/primary-excision-margins-and-sentinel-lymph-node-biopsy-cutaneous-melanoma.

- Easson AM, Cosby R, McCready DR, Temple C, Petrella T, Wright F, et al. Surgical management of patients with lymph node metastases from cutaneous melanoma of the trunk or extremities. Easson A, Salerno J, reviewers. Toronto, ON: Cancer Care Ontario; 2012 Dec 4 [Endorsed with partial update 2018 Aug]. Program in Evidence-Based Care Evidence-Based Series No.: 8-6 V2 ENDORSED. Available from: https://www.cancercareontario.ca/en/content/surgical-management-patients-lymph-node-metastases-cutaneous-melanoma-trunk-or-extremities.

Locoregional Management of In-Transit Metastasis in Melanoma

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Ontario Health (Cancer Care Ontario) (OH (CCO)). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of OH (CCO) supported by the Ontario Ministry of Health (OMH). All work produced by the PEBC is editorially independent from the OMH.

JUSTIFICATION FOR GUIDELINE

Oncologists in the province of Ontario are being asked to treat patients with melanoma with satellite and ITM and there are currently no guidance documents providing advice on the most appropriate management for these patients.

GUIDELINE DEVELOPERS

This guideline was developed by the Satellite and In-Transit Melanoma GDG (Appendix 1), which was convened at the request of the Melanoma Disease Site Group.

The project was led by a small Working Group of the Satellite and In-Transit Melanoma GDG, 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 Satellite and In-Transit Melanoma GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [44,45]. This process includes a systematic review, interpretation of the evidence and draft recommendations by the Working Group, internal review by content and methodology experts and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [46] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original

evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of known implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations may be provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine if an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

The following criteria were used to select potentially relevant guidelines:

- Guidelines published after the year 2010.
- Guidelines that included a systematic review of the literature that covered at least one of the outcomes of interest.

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument.

- A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A search of the primary literature was required (see Section 4).
- Guidelines Developed by Alberta Health Services, the National Comprehensive Cancer Network, and the European Society for Medical Oncology all propose recommendations on the management of satellite and ITM in patients with melanoma, but none were considered appropriate for adaptation or endorsement due to the date of publication, methodology, or scope.

GUIDELINE REVIEW AND APPROVAL

Internal Review

Guideline approval required that 75% of the content experts who comprise the GDG Expert Panel cast a vote indicating whether or not they approved the document, or abstained from voting for a specified reason, and of those that voted, at least 75% approved the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, unanimously approved the document. The Expert Panel and RAP members could specify that approval was conditional, and that changes to the document were required.

Patient and Caregiver-Specific Consultation Group

Four patients/survivors/caregivers participated as Consultation Group members for the Management of In-transit Metastasis in Melanoma Working Group. They reviewed copies of the draft recommendations and provided feedback on its/their comprehensibility, appropriateness,

and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

External Review

Feedback on the approved draft guideline was obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise were identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline were contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline is published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review was intended to facilitate the dissemination of the guideline to Ontario practitioners. Section 1 of this guideline is a summary document to support the implementation of the guideline in practice. OH (CCO)-PEBC guidelines are routinely included in several international guideline databases including the CPAC Cancer Guidelines Database, the CMA/Joule CPG Infobase database, NICE Evidence Search (UK), and the Guidelines International Network (GIN) Library.

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Locoregional Management of In-Transit Metastasis in Melanoma

Section 4: Systematic Review

INTRODUCTION

According to the Canadian Cancer Statistics [47,48], the projected number of cases of melanoma in Canada in 2017 was 7200 (18.5 per 100,000) with 1250 deaths, making melanoma the eighth most common cancer and 15th in mortality. In Ontario, there were predicted to be 4129 cases of melanoma in 2018 (26.4 per 100,000 people), representing 4.6% of cancers [49]. Actual data from 2013 indicated 3409 new cases of melanoma (24.7 per 100,000; 4.4% of all cancers) and 519 deaths (1.9% of all cancer deaths). Five-year survival for the period 2009-2013 was 86.6% [49]. In patients diagnosed with melanoma, approximately 10% will develop ITM and satellite metastasis [8,50]. ITM 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 [8,50]. The presence of ITM may be a prognostic indicator of disseminated disease. Five-year survival rates range widely and are largely dependent on associated metastases to the surrounding lymph nodes [8]. Patients with ITM commonly experience severe morbidity including pain, bleeding, and infection, particularly if numerous large lesions exist with ulceration of the tumours [8,50]. Resection of the ITM is the preferred treatment. If resection is not possible there is little high-quality evidence to suggest which subsequent treatment is best. This guideline aims to evaluate the available evidence and provide recommendations on which intervention(s) may have the greatest efficacy for ITM of varying degrees.

The Working Group of the In-transit Melanoma GDG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group members derived the research questions outlined below.

RESEARCH QUESTION

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

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. MEDLINE, Embase and the Cochrane Database of Systematic reviews were systematically searched from the years 1980 to December 2018. Search terms included “melanoma”, “in adj transit”, “in-transit” and terms for interventions including “limb infusion”, “limb perfusion”, “BCG”, “IL-2”, etc. The full search strategy can be found in Appendix 2. In addition, websites/databases of specific

guideline developers that used systematic reviews as their evidentiary base, as well as systematic review producers, were also searched using the same keywords for the same period.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [51] tool to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

A search for existing primary studies was completed for interventions where there was not an existing systematic review. Alternatively, if there was an existing systematic review, a primary literature search was conducted to fill in any time-frames that were not covered by that systematic review. Below are methods for locating and evaluating primary studies. The quality of included RCTs were evaluated with the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [52].

Literature Search Strategy

OVID was used to systematically search the MEDLINE and Embase databases for studies that evaluated local and regional treatment modalities for patients with ITM, published from 1980 to January 1, 2019. The literature search strategy included keywords for ITM, and the interventions commonly used to treat these patients. The complete literature search strategy can be found in Appendix 2. In addition to the MEDLINE and Embase databases searches, referenced lists of included systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

Studies were included if they met the following criteria:

- Patients had ITM (stage IIIc) in any location. This staging was based on the AJCC 2018 staging guide [5]; however, since the literature review searched studies prior to this update, ITM was also defined as stage IIIb and IIIc, based on the AJCC 7th Edition [6].
- More than 20 patients enrolled (total; all trial arms combined)
- RCTs; non-randomized clinical trials with prospective, retrospective study design
- Data available for at least one of the following outcomes:
    - Survival
    - PR and CR rate
    - AEs/toxicity
- Evaluated one or more of the following interventions:
    - Local therapies
        - T-VEC
        - BCG
        - Intralesional IL-2
        - Intralesional PV-10 (Rose Bengal)
        - ECT
        - Laser (including pulsed dye laser, CO_2)
        - Surgery
        - Radiation therapy
        - Local topical therapies
            - DPCP
            - Imiquimod (Aldara®)
    - Regional therapies:

- ILI
- ILP

All hits from the OVID literature search were entered into a reference management software (EndNote X6), where duplicate citations were removed. A review of the titles and abstracts that resulted from the search was conducted by one reviewer (SK). For items that warranted full-text review, on reviewer (SK) reviewed each item in collaboration and confirmed by two reviewers (FW and TP). The list of proposed studies was verified by the Working Group. The literature search flow diagram can be found in Appendix 3.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data were extracted by one individual (SK) with assistance from FW and TP. Ratios, including HRs, were expressed with a ratio <1.0 indicating reduced risk for recurrence or death, unless otherwise indicated. All extracted data and information were audited by an independent auditor.

RCTs were evaluated with the Cochrane Risk of Bias tool for Randomized studies [52]. A quality assessment on the single-arm non-comparative studies was not conducted as the quality of these studies was very low.

Synthesizing the Evidence

Due to the anticipated variation in reported comparisons and outcomes measured, a meta-analysis was not planned.

RESULTS

Search for Existing Systematic Reviews

The search for systematic reviews identified 235 possible reviews on the treatment of in-transit or satellite melanoma metastasis. Two systematic reviews were chosen for inclusion in the evidence base based on their content, quality, and relevance to the research questions [8,23]. One [8] assessed the efficacy and toxicity associated with intralesional IL-2 for the treatment of ITM. Kroon et al. evaluated the efficacy of ILI with melphalan and actinomycin D for melanoma [23].

Search for Primary Literature

A primary search for literature was conducted to evaluate interventions that did not have a systematic review already published. In cases where there was already an existing systematic review, a search of the primary literature was conducted from the end date of the search in the reviews.

Literature Search Results

In total, 80 primary studies were identified that met the inclusion criteria (Appendix 3). Table 4-1 summarizes the number of studies per intervention.

Study Design and Quality

Systematic Reviews

The systematic reviews were assessed using AMSTAR (Table 4-2) [51]. The quality of the systematic reviews was considered to be low to moderate. This was mainly because the quality of the included studies was not assessed and, therefore, was not taken into consideration when the conclusions were formulated.

Table 4-1. Included studies and systematic reviews

Local Therapy	
Intralesional Allovectin-7	1 RCT [53]
Intralesional BCG	3 RCTs [18-20]
CO_2 Laser ablation	2 retrospective studies [21,22]
Electrochemotherapy	9 prospective studies [54-62]
Intralesional IFN-α	1 prospective study [63]
Intralesional T-VEC	1 RCT (including follow-up) [10,11]
Intralesional Interleukin-2 therapy	1 systematic review with 6 observational studies included [8] 1 retrospective study [9]
Intralesional PV-10	2 prospective studies [jiang64,65]
Surgical Excision	1 retrospective study [7]
Radiation Therapy	1 retrospective study [17]
Amputation	2 retrospective studies [66,67]
DPCP (Topical)	2 prospective studies and 1 retrospective study [15,16,68]
Imiquimod (Topical)	No evidence
Regional Therapy	
ILI	1 systematic review [23] 3 prospective studies and 7 retrospective studies [24-33]
ILP	2 RCTs evaluating ILP with or without TNF-α [34,35] 1 RCT evaluating ILP as adjuvant treatment to excision [36,37] 34 primary studies [69-101]; 11 prospective and 23 retrospective studies
ILI and ILP	6 retrospective studies [38-43]

Abbreviations: BCG, bacille Calmette-Guerin; CO_2, carbon dioxide; DPCP, diphenylcyclopropenone; IFN, interferon; ILI, isolated limb infusion; ILP, isolated limb perfusion; RCT, randomized controlled trial; TNF-α, tumour necrosis factor alpha; T-VEC, talimogene laherparepvec

RCTs

RCTs were assessed with the Cochrane Risk of Bias Tool [52] (Table 4-3). Given the lack of comparative RCTs, most of the studies included in these reviews were prospective or retrospective cohorts. As such, the inherent limitations of retrospective designs should be taken into consideration when reviewing evidence from these studies. The quality was varied.

Observational Studies

The quality of the observational studies included were assessed to be very low/poor as they were non-comparative studies with no patient randomization and were not able to control for potential confounders and were susceptible to selection bias. The risk of bias for these non-comparative, observational studies was assessed to be high. In some cases, the studies employed a comparative study design; however, these comparisons were frequently comparisons between the modes of delivery and were not relevant comparisons for this guideline (i.e., compared with another intervention or control group). In cases where comparisons were relevant (i.e., ILI vs. ILP), the studies were still considered to be low quality due to their retrospective design, and lack of control for confounders.

Table 4-2. AMSTAR checklist for included systematic reviews

AMSTAR Checklist Study	1. Was an *a priori* design provided?	2. Was there duplicate study selection and data extraction?	3. Was a comprehensive literature search performed?	4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	5. Was a list of studies (included and excluded) provided?	6. Were the characteristics of the included studies provided?	7. Was the scientific quality of the included studies assessed and documented?	8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	9. Were the methods used to combine the findings of studies appropriate?	10. Was the likelihood of publication bias assessed?	11. Was the conflict of interest included?
Byers, 2014[8]	Y	Y	Y	N	N	Y	Y	Y	Y	N	Y
Kroon, 2014 [23]	Y	N	Y	N	N	Y	Y	Y	Y	N	N

Abbreviations: N, no; Y, yes

Table 4-3. Cochrane Risk of Bias Tool for included RCTs

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall Risk of Bias Assessment
Andtbacka, 2015 [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	**Low Risk of Bias**
Bedikan, 2010 [53]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	**High Risk of Bias**
Cornett, 2016 [34]	Low risk	Low risk	Low risk	Unclear risk	Low risk	Low risk	**Low Risk of Bias**
Olofsson Bagge [36,37]	Low risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk	**Unclear Risk of Bias**
Lienard, 1999 [35]	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	**High Risk of Bias**
Brocker, 1986 [18]	Low risk	Unclear risk	High risk	High risk	Low risk	Low risk	**High Risk of Bias**
Paterson, 1984 [19]	Unclear risk	High risk	High risk	High risk	Low risk	Low risk	**High Risk of Bias**
Sterchi, 1985 [20]	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	**High Risk of Bias**

Interpretation: High Risk of Bias: Bias may alter results seriously; Unclear Risk of Bias: a risk of bias that raises some doubt about the results; Low risk of Bias: Bias, if present, is unlikely to alter the results seriously [52]

Outcomes by Intervention

Due to heterogeneity in patient selection, procedure methods, and outcome measures, the results could not be pooled. As a result, ranges only for survival and response are given.

Surgical excision remains the preferred therapy for ITM in cases where surgical morbidity if determined to be low. In cases where surgery cannot be performed, other therapeutic options may be considered for patients with ITM. The treatments are categorized into local or regional therapies. The following sections describe the various interventions for both local and regional therapies for patients with ITM.

Local Therapies (Intralesional and Topical)

Allovectin-7 (Single versus Multiple Injections)

Bedikian et al. [53] conducted a phase II study to determine the optimal dosage of Allovectin-7 and to determine the efficacy of Allovectin-7 if the optimal dose was administered intralesionally to a single injectable lesion or of the optimal dose as administered to multiple injectable lesions (see Table 4-4). While this study was considered to be a phase II study, the comparison was between the mode of delivery and not comparing one intervention to another or a control group. Study subjects were patients with stage III or IV metastatic melanoma whose disease was recurrent or unresponsive to standard therapy, or who refused alternative therapy, and where surgery was not considered a curative option. The optimal dose was found to be 2 mg. Patients with a single lesion were administered the 2 mg dose. Patients with two or more injectable lesions were randomized to either single or multiple lesions injected. For all patients the overall response rate (ORR) was 11.8% (95% CI 6.2% to 17.4%). The median duration of response was 13.8 months. In addition, 32 (25.2%) patients had stable disease while the remaining 80 patients (63.0%) had progressive disease. Patients presenting with a single injectable lesion were more likely to respond than those presenting with multiple lesions. Additionally, there was no statistically significant difference when the 2 mg of Allovectin-7 is divided and injected into multiple lesions or injected into one lesion.

Intralesional BCG versus Clinical Observation

Three RCTs [18-20] evaluated BCG as an adjuvant therapy to surgical excision in patients with ITM melanoma (see Table 4-5). Administration of BCG was intralesional in all trials and also oral in one [19]. The overall quality of these trials was poor, with each having a high risk of bias due to deficiencies in blinding. Sample sizes in the BCG arms ranged from 19-99 patients and control arms ranged from 19-100 patients. In each trial, patients underwent surgical excision and BCG was used as adjuvant therapy. Control arms were standard observation only. The mean follow-up periods in the trials ranged from 21 to 48 months. With the exception of Aranha et al. [102], three trials included data on the number of relapses as compared with the control arm [18-20]. OS was reported in two studies [19,20]. In all studies with reported outcomes, there was no statistical significance between the intervention and control arms in terms of number of relapses and OS. Toxicity data were reported in Paterson et al. [19], and intralesional and oral doses of BCG had minimal side effects and was well tolerated in most of the patients.

CO_2 Laser Ablation

Two observational studies [21,22] evaluated the efficacy of CO_2 laser ablation in patients with melanoma with cutaneous in-transit and satellite metastases (see Table 4-6). Only skin lesions with a diameter of not more than 5 mm were deemed amenable to CO_2 laser. The number of lesions treated per session ranged from three to 329, with the majority having <10 lesions treated per session. In terms of OS, van Jarwaarde et al. observed that after the first laser treatment, the median OS was 14 months (range 1-41 months) [22]. In nine of 22 patients,

one treatment was performed and led to a mean duration of regional control of 11 weeks. Ten patients needed an average of four treatments (range, 1-17) to achieve regional control. Two patients were not able to achieve regional control and underwent regional treatments. The treatment was well-tolerated with only one grade 1 AE observed [22]. Similarly, Hill et al. observed an OS of 67% at 12 months and 56% of patients were controlled with three or fewer laser treatments within the first year [21]. Patients were excluded from enrolment if the size of the lesions were >1.5 cm in diameter. The number of lesions per patient varied between 3 and 450. The treatment was also well tolerated with few AEs [21].

Electrochemotherapy

Eight observational studies [54-56,58-62] summarized in Table 4-7 evaluated the use effectiveness of ECT for in-transit and satellite melanoma metastasis. The majority of these studies used bleomycin and ECT; however, one study also used cisplatin [58]. In some studies, the design was comparative; however, the mode of delivery was not a relevant comparison and no studies evaluated ECT in comparison with another intervention or a control group. In the largest study, Caraco et al. [55] reported 89 patients (60 ITM, 2 local recurrence, 24 distant cutaneous) who underwent a total of 126 courses of ECT with bleomycin. The median size of lesions was 12 mm (range, 2-35 mm) and there was no information regarding the number of lesions treated per patient. Three months after the ECT treatments, 34 patients (38.2%) had a PR and 43 had a CR (48.3%). Twelve patients (13.5%) had no change or progressive disease. The ORR of all treated lesions was 67.5%. ECT was well tolerated throughout the patient population with 33 patients having only local pain, and locoregional myalgia in 12 patients. No significant AEs were observed. In a two-year longitudinal study conducted by the European Standard Operating Procedures of Electrochemotherapy [58], eligible patients were to have a life expectancy >3 months, measurable cutaneous or subcutaneous tumour nodules suitable for application of electric pulses but not bigger than 3 cm in diameter, a treatment-free interval of at least two weeks from previously applied therapy, Karnofsky performance status greater than 70% or World Health Organization <2, and adequate hematological and renal function. Patients must have been offered standard treatment according to the policies of the country of residence. ECT was considered either in the case of progression of the disease despite use of standard treatments or when patients did not wish to receive standard treatment. An overall response of 84.8% was achieved and there were no significant differences between the route of administration or drug used. At 150 days after the treatment (median follow-up was 133 days) local tumour control rate for ECT was 88% with bleomycin administered intravenously, 73% with bleomycin administered intratumourally, and 75% with cisplatin administered intratumourally. There were no major AEs observed [58]. In the remaining studies, the ORR was variable, ranging from 50% to 100%. The size of metastasis was a predictor of response in one study with lesions <3 cm having a better response rate than lesions >3cm; however, it should be noted that the majority of lesions in the study population were <3 cm (138 lesions vs. 24 lesions) and the median diameter was 12 mm [59].

Table 4-4. Summary of studies included for Allovectin-7

Study	Study Type	Patient population	Intervention	Response Rates	Survival	Toxicity
Bedikian et al, 2010 [53]	RCT	Regional stage III melanoma that was recurrent of unresponsive to standard therapy, or who refused alternative therapy, and where surgery was not considered a curative option.	Group 1: Single injectable lesion Group 2: 2+ injectable lesions randomized into: Group 2S: Single lesion injected and Group 2M: multiple lesions injected (up to 5 lesions)	Response=15 patients (11.8%) Non response: 112 (89.2) # of injectable lesions: 1: 14 responders; 58 non-responders >1: 1 responder; 54 responders p=0.0019 (only sig. subgroup difference in analysis) Group 1: Response: 14 patients Non-response: 58 Group 2S Response: 0 Non-response: 26 Group 2M Response: 1 Nonresponse: 25	In 15 responders the median duration of response was 13.8 months	Grade 1: 195 Grade 2: 71 Grade 3: 15 Grade 4: 15 Grade 5: 2

Abbreviations: RCT, randomized controlled trial

Table 4-5. Summary of studies included for intralesional BCG

Study	Study Type	Patient population	Intervention	Response Rate	Survival	Toxicity
Brocker. 1986 [18]	RCT	Arm 1: 44 Arm 2: 63	Arm 1: Intralesional BCG Arm 2: clinical observation	Number of relapses Arm 1: 13/44 (29.5%) Arm 2: 19/63 (30.1%)	NR	NR
Paterson, 1984 [19]	RCT	Arm 1: 99 Arm 2: 100	Arm 1: Intralesional and oral BCG Arm 2: clinical observation	Number of relapses: Arm 1: 24/99 (24.2%) Arm 2: 33/100 (33%)	Arm 1: 82/99 Arm 2: 76/100	Injected: erythematous pruritic reaction in most patients. Detectable regional lymph node enlargement in minority Oral: Mild diarrhea: 7 patients. 2 patients stopped oral dosage
Sterchi,1985 [20]	RCT	Arm 1: 19 Arm 2: 19	Arm 1: DTIC-BCG Arm 2: DTIC	Number of relapses Arm 1: 6/19 (31.5%) Arm 2: 7/19 (36.8%)	Arm 1: 14/19 Arm 2: 14/19	NR

Abbreviations: BCG, bacille Calmette-Guerin; DFS, disease-free survival; DTIC, dacarbazine; NR, not reported; RCT, randomized controlled trial

Table 4-6. Summary of studies included for CO_2 laser ablation

Study	Study Type	Patient population	Intervention	Response Rates	Survival	Toxicity
Van Jarwaarde et al, 2015 [22]	Retrospective review	22 patients with satellite or ITM	CO_2 laser treatments	median duration of regional control: 14 weeks 9/22 only 1 treatment was required for local control 10 patients needed an average of 4 treatments (1-17) In 3 patients CO_2 laser was not able to achieve local control and these patients underwent ILP	Median OS after 1st laser treatment: 14 (range, 1–41) months	NA
Hill et al, 1993 [21]	Retrospective review	60 patients with ITM	CO_2 laser treatments	NS	OS: 67% (at 12 months)	NS

Abbreviations: CO_2, carbon dioxide; ITM, in-transit metastasis; NA, not available; NS, not specified; OS, overall survival

Table 4-7.Summary of studies included for electrochemotherapy

Study	Study Type	Patient Population	Intervention	Response rate	Survival	Toxicity
Kunte et al, 2017 [57]	Prospective study	Histologically malignant melanoma with measurable cutaneous metastases, or mucosal lesions, suitable for application of electric pulses	Electrochemotherapy with intratumoural or intravenous injection of bleomycin	By lesion CR: 229/394 (58%) PR: 77/394 (20%) SD: 79/394 (20%) PD: 6/394 (2%) By patient CR: 55/114 (48%) PR: 29/114 (25%) SD: 26/114 (23%) DP: 3/114 (3%)	1-year OS: 67% 1-year MSS: 74%	Skin reaction: 63 patients (42%); grade 3 in 2 patients Nausea (grade 1-2):5 patients (3%); flu-like symptoms (grade 1–2):6 patients (4%); lymphedema (grade 1–2):4 patients (3%)
Mir-Bonafe et al, 2015 [60]	Retrospective and prospective data collection	31 patients nodular (8 cases), superficial spreading (7 cases), acral (4 cases), desmoplastic (3 cases), and lentigo maligna (1 case).	Electrochemotherapy with intravenous injection of bleomycin	CR 23% of patients PR 49% of patients At 1 yr, response was maintained in 17 patients Disease progression occurred after the ECT cycle in 15 (28%) of cases. In 5 of the 15 patients with PR, disease progression occurred 8 to 12 months after treatment	NA	NA
Caraco et al, 2015 [55]	Prospective study	60 patients with ITM; 5 local recurrence, 24 distant cutaneous	Electrochemotherapy with intravenous injection of bleomycin	3 months after the ECT treatments, PR: 34 (38.2%) CR: 43 (48.3%). NC or PD: 12 (13.5%) The ORR of all treated lesions was 67.5%	NA	NA
Solari et al, 2014 [62]	Prospective, study	39 patients (20 with patients)	Electrochemotherapy with intravenous injection of bleomycin • 22 patients received only 1 treatment; • 12 patients received 2 treatments; • 4 patients received 3treatments • 1 patient was treated 4 times.	CR: 2 (10%) PR: 9 (45%) CR/PR: 11 (55%) SD: 3 (15%) PD: 6 (30%) SD/PD: 9 (45%)	NA	No SAE or CTC grade 3 or 4 were observed.
Ricotti et al, 2014 [61]	Prospective study	30 patients (654 skin metastatic nodules)	Electrochemotherapy with Intravenous Bleomycin	ORR: 100% CR: 67.28% PR: 32.72% 214 metastatic lesions from 24 patients received a second ECT session- 141 showed	NA	NA

Study	Study Type	Patient Population	Intervention	Response rate	Survival	Toxicity
				a further complete response. 24 months later, the local tumour control rate was 72%.		
Caraco et al, 2013 [56]	Prospective, study	60 patients with relapsed and refractory melanoma (n=25) or in-transit metastases (n=35)	Electrochemotherapy with intravenous injection of bleomycin	3 months after the ECT session, PR: 23 patients (38.3%) CR: 29 patients (48.4%). NC/PD: 8 patients (13.3%) Objective response rate of all treated lesions was 86.6%. 13 patients (21.7% overall, 44.8% of those with a CR) experienced a long-lasting response to ECT after one session and were free of disease after a mean follow-up of 27.5 months	NA	NA
Campana et al, 2012 [54]	Prospective study	Patients with melanoma: IIIb – 32 (38%) IIIc – 25 (29%) IV – 28 (33%)	Electrochemotherapy with bleomycin Bleomycin was injected intravenously in patients with >7 skin lesions; intratumourally in patients with 1-6 lesions; and a combination of intravenous and then intratumoural injection in patients with multiple lesions.	NA	2-year LPFS: 87%	NA
Matthiessen et al, 2011 [59]	Prospective, study	52 patients with cutaneous metastasis; 21 patients with melanoma	Electrochemotherapy with bleomycin 21 patients treated intratumourally 30 patients treated by IV (no data outcome comparing mode of delivery)	<u>Cutaneous metastasis <3 cm</u> CR: 68% PR: 18% <u>Cutaneous metastasis >3 cm</u> CR: 8% PR: 23%	<u>NA</u>	Well tolerated; no SAE; no CTC grade III or IV toxicities
Marty et al, 2006[58]	Prospective study	Melanoma – 32 patients (190 nodules)	Electrochemotherapy Intratumoural administration of bleomycin or Cisplatin intravenously	CR: 73.7% PR: 11.1% NC: 10.5% PD: 4.7% Median follow-up was 133 days and range 60–380 days	NA	NA

Abbreviations: CR, complete response; CTC, Common Toxicity Criteria Version 3.0; ECT, electrochemotherapy; IV, intravenous; LPFS, local progression-free survival; MSS, melanoma-specific survival; NA, not available; NC, no change; ORR, overall response rate; OS, overall survival; PD, progressive disease; PR, partial response; SAE, severe adverse events; SD, stable disease

Table 4-8. Summary of studies included for T-VEC

Study	Study Type	Patient Population	Intervention	Survival	Response Rate	Toxicity
Atabacka et al, 2019 [12]	Randomized trial (OPTiM), final results	436 pts	295 intralesional T-VEC and subcutaneous 141 GM-CSF	At median 49 months follow-up , median OS 23.3 months T-VEC, 18.9 months GCSF, HR=0.79; 95% CI 0.62 to 1.00, p=0.0494 In patients with CR: 5-y OS 88.5%	DRR 19.0% vs. 1.4%, odds ratio 16.6; 95% CI 4.0 to 69.2; p<0.0001 ORR 31.5% vs. 6.4%, CR by patient: 16.9% vs. 0.7% PR by patient: 14.6% vs. 5.7% Disease Control Rate: 76.3% vs. 56.7%	Most common AEs were fatigue, chills, pyrexia, nausea, influenza-like illness and highest during first 3 cycles Treatment-related grade 3-4 AEs 11.3% vs. 4.7%
Andtbacka, 2016 [10]	Randomized trial (OPTiM trial)	437 patients with previously treated and untreated, unresected, stage IIIb–IV melanoma	intralesional T-VEC or subcutaneous GM-CSF 295 were randomized to T-VEC and 141 to GM-CSF	Previously reported in Andtbacka et al, 2015 (below)	*By lesion:* T-VEC arm: CR: 47% (injected lesions); 22% (uninjected non-visceral lesions); 9% (visceral lesions)	NA
Andtbacka et al, 2015 [11]	Randomized trial (OPTiM trial)	436 patients with stage IIIb to IV unresected melanoma	Arm 1 assigned to receive T-VEC: 291 Arm 2 assigned to receive GM-CFS: 127 Median 10 lesions per T-VEC patient, of which median 5 lesions injected with T-VEC; 3274 assessable lesions (2116 injected) in 285 patients	Median OS: 23.3 months T-VEC vs. 18.9 months GM-CSF; p=0.051 Estimated 4-y OS 33% vs. 21% OS stage IIIb/IIIc: HR=0.48; 95% CI 0.29 to 0.80 Median potential follow-up (time from random assignment to analysis) was 44.4 months (range, 32.4 to 58.7 months) at the primary analysis of OS.	*By patient* T-VEC Arm: DRR: 16.3 (OR 8.9) ORR: 26.4% CR: 32 (10.8%) PR: 46 (15.6%) GM-CSFS arm: DRR: 3 (2.1%) ORR: 5.7% CR: 1 (<1%) PR: 7 (5%) DRR and ORR differences were statistically significant between the two arms. DRR for stage IIIb/IIIc: 33% vs. 0% (95% CI 19.1 to 43.9) ORR stage IIIb/IIIc 52.3% vs. 2.3%, 95% CI 34.2 to 60.8	NA

Abbreviations: AEs, adverse events; CI, confidence interval; CR, complete response; DRR, durable response rate; GM-CSF, granulocyte macrophage colony-stimulating factor; NA, not available; ORR, overall response rate; PR, partial response; T-VEC, talimogene laherparepvec

T-VEC versus GM-CSF

The OPTiM study (see Table 4-8) was a good-quality phase III study that randomized 436 patients with unresected stage IIIb/IV melanoma at a 2:1 ratio to receive T‑VEC versus subcutaneously administered GM-CSF [11]. Patients were included if they were at least 18 years of age with histologically confirmed, not surgically resectable, stage IIIb to IV melanoma suitable for direct or ultrasound-guided injection (at least one cutaneous, subcutaneous, or nodal lesion or aggregation of lesions >10 mm in diameter). Durable response rate (DRR) of the T-VEC arm was 16.3% and the ORR rate was 26.4%. The median OS was 23.3 months. Grade >3 AEs occurred in 36% of patients receiving T-VEC. The only grade 3 or 4 AE occurring in >2% of patients was cellulitis (T-VEC, n=6 [2.1%]). T-VEC efficacy was most pronounced in patients with stage IIIb, IIIc, or IVM1a disease and in patients with treatment-naive disease. In a follow-up of the same study, patterns of clinical response with T-VEC in patients with ITM were evaluated [10]. Responses were reported by lesion. CR rates in the T-VEC arm for injected and uninjected lesions were 47% and 22%, respectively. The ability to cause response in non-injected lesions has been referred to as a bystander effect [13,14]. Patients who experienced progression prior to response did not have a difference OS when compared with patients who did not have progression prior to response (p=0.35) [10]. Final results were reported subsequent to the literature search and have been included in the table [12].

Intralesional IL-2

One systematic review plus one observational study that were outside of the systematic review search dates evaluated the efficacy of intralesional IL-2 therapy in patients with ITM (see Table 4-9). In the systematic review [8], six observational studies were included. There was heterogeneity in both treatment dosages as well as treatment interval; therefore, a meta-analysis could not be performed, but the results were pooled based on subjects and lesions. After pooling the lesions (2182 lesions dispersed over 131 patients), CR was seen in 78%. After pooling subjects (140 patients), 50% achieved a CR. Treatment was generally well tolerated, with localized pain and swelling, and mild flu-like symptoms. There were three grade 3 AEs reported, including rigors, headache, and fever with arthralgia [8]. One observational study also evaluated IL-2 in patients with ITM and found similar results [9]. In 31 consecutive patients who presented to a tertiary care cancer centre for treatment of ITM with IL-2, 10 patients (32%) achieved a pathologic CR (pCR), 17 (55%) had a PR, and four (19%) had progressive disease on treatment. Kaplan-Meier survival curves and multivariable Cox regression analysis determined IL-2 therapy was associated with OS (log-rank p=0.004) and improved progression-free survival (adjusted HR=0.11; 95% CI 0.02 to 0.47, p=0.003) [9].

Intralesional Rose Bengal (PV-10)

Two multicentre phase II observational studies summarized in Table 4-10 [64,65] evaluated the efficacy and safety of intralesional Rose Bengal in patients with refractory cutaneous or subcutaneous metastatic melanoma. Eligible patients had biopsy-proven confirmation of melanoma and at least one cutaneous or subcutaneous lesion >0.2 cm in diameter. Fifty-five percent of patients had less than 10 lesions and 26% of patients had more than 10 lesions. In 9%, the lesions were too numerous to count. All patients had prior surgical excision, and other prior therapies included nodal biopsy, regional chemotherapy, and immunotherapy. For target lesions, the best ORR was 51%, and the CR rate was 26%. Median time to response was 1.9 months, and median duration of response was 4.0 months, with 8% of patients having no evidence of disease after 52 weeks. AEs were predominantly mild to moderate and locoregional to the treatment site, with no treatment-associated grade 4 or 5 AEs [65].

Table 4-9. Summary of studies included for IL-2

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
Hassan et al, 2015 [9]	Retrospective review	32 patients with melanoma with ITN treated with intralesional IL-2; median 16 lesions injected per patient; 18 pt received systemic therapy	IL-2 injected intralesionally for one cycle every 2 weeks. Biopsies of lesion(s) were performed 8 weeks after completion of treatment	pCR: 10/31 patients (32.3%) PR: 17/31 (54.8%) PD: 4/31 (12.9%)	Patients with CR: 100% OS Patients without CR: 43% OS pCR to IL-2 therapy was associated with OS (log-rank p=0.004), PFS, (log-rank p=0.004), and LPFS (logrank p=0.051)	NA
Byers et al, 2014 [8]	Systematic review (search dates 1980-2012)	6 studies	Intralesional IL-2 2182 lesions evaluated 140 patients	Response rates by lesions: Complete response rate: 78% (1700/2182) Partial response rate: 2.5% (54/2182) Progression or no response: 19.6% (428/2182) Response rates by patients: Complete response 0% - 69%, with average of 49.6% (68/137)	Not included in review, but reported in some included studies • Boyd, 2011 [103]: 5-y OS 80% for complete responders and 33% for partial responders • Weide, 2010 [104]: 2-y OS 77% stage IIIb/c and 53% stage IV • Ridolfi, 2003 [105]: 3-y DFS 37%, 3-y OS 45% • Radny 2003 [106]: for stage III 2-y OS 100% and 5-y OS 63%; for stage IV 2-y OS 33%	Majority were Grade 1 and 2; two Grade 3

Abbreviations: IL-2, interleukin-2; ILI, Isolated limb infusion; ILP, isolated limb perfusion; LPFS, local progression-free survival; NA, not available; pCR, pathologic complete response; PD, progressive disease; PFS, progression-free survival; PR, partial response; RC, regional chemotherapy

Table 4-10. Summary of studies included for Rose Bengal (PV-10)

Study	Study Type	Patient Population	Intervention	Survival	Response Rates	Toxicity
Read et al, 2018 [64]	Prospective study	45 patients accessible dermal and Subcutaneous ITM	Intralesional PV-10	Median DFS: 2.1 months (mean 5 months) OS (month): 12: 90.4% 24: 84.8% 36: 68.1% 48: 64.5%	CR: 19 (42.2%) PR: 20 (44.4%) SD: 3 (6.7%)	Grade 1: 67 Grade 2: 37 Grade 3: 3 Grade 4: 0 Grade 5: 0 Injection site edema (62.2%), transient pain (29.3%) blistering (18.3%)
Thompson et al, 2015 [65]	Prospective study	80 patients with refractory metastatic melanoma after a median of 6 previous interventions 62 stage III, 18 stage IV	Intralesional PV-10 into up to 20 cutaneous and subcutaneous lesions (additional new or non-target lesions could be included after the first cycle) up to four times over a 16-week period and were followed for 52 weeks	Stage III Mean OS 12 months (89% 1-year survival, median not reached) Stage IV Median OS: 6.5 months (39% 1-year survival)	51% BORR (best overall response rate): 26% CR + 25% PR	Pain (80%) Edema (41% Mild (4%) or moderate (4%) injection site photosensitivity Severe generalized photosensitivity (1%)

Abbreviations: CR, complete response; DFS, disease-free survival; ITM, in-transit metastasis; OS, overall survival; PR, partial response; SD, stable disease

Table 4-11. Summary of studies included for intralesional IFN-α

Study	Study Type	Patient Population	Intervention	Response Rate	Survival	Toxicity
Von Wussow et al, 1988 [63]	Prospective Study	51 metastatic melanoma with at least 1 cutaneous metastasis	26 patients: highly purified natural IFN-α $6x10^6$ IU three times per week. 25 patients: $10x10^6$ IU three times per week of a recombinant Intralesional IFN-α2b (rIFN-α2b). If more than one skin metastasis, only injected one of them	Systemic Response CR: 3 (6%) PR: 6 (12%) NC: 16 (31%) PD: 26 (51%) Local Response (injected lesion) CR: 16 (31%) PR: 7 (14%) NC: 26 (51%) PD: 2 (4%) Non-injected skin metastases 21% CR + PR	NA	Flu-like symptoms (95%) Pain at injection site (21%) Apathia and fatigue requiring dose reductions (26%) Granulocytopenia: 15 patients with WHO Grade 1 (<1500/µl); 3 patients with WHO Grade 2 granulocytopenia (<1000/µl)

Abbreviations: CR, complete response; IFN, interferon; NC, no change; PD, progressive disease; PR, partial response; WHO, World Health Organization

Intralesional Interferon-alpha

One observational study [63] evaluated the efficacy of intralesional INF-α on 58 patients with metastatic melanoma who had undergone one or more previous treatments (see Table 11). Previous treatments included wide excision (46 patients), lymphadenectomy (41 patients), radiation (11 patients), and chemotherapy (24 patients). Twenty-six patients were administered highly purified natural IFN-α $6x10^6$ IU three times per week. Twenty-five patients were administered $10x10^6$ IU three times per week of a recombinant IFN-a2b (rIFN-α2b). Twenty-three of 51 skin metastases injected with IFN-α were reduced in size by at least 50% (16 CR, 7 PR) Twenty-six metastases were stable under the injections, whereas two lesions progressed. Inflammatory reactions were not noticed during therapy in locally injected or any other observable tumour site. Treatment with IFN-α was well tolerated.

Radiation Therapy

One study [17] evaluated palliative radiation therapy in a subset of 24 patients with ITM (see Table 4-12). Most patients underwent previous therapy, although the types were not specified for the patients with ITM alone. Due to the diffuse spread of the lesions, the exact tumour volume was not available for patients with ITM; therefore, no median tumour volume was assessed for this group. 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). In patients with UICC stage III disease (ITM or lymph node metastases) OS was a median of 22 months (1-year OS 74%, 5-year OS 32%).

Surgery

An observational study [7] evaluated 33 patients with loco-regional relapse after removal of a primary tumour; of these, 21 had ITM (see Table 4-13). The patients had local surgical excision to remove the ITM and survival rates were calculated [7]. The number of tumours in the patients with recurring disease ranged from one to six, and the median was 1.7. The five-year survival for patients who had wide local excision (more than 2 cm, median 5 cm) was 58% and the five-year disease-free survival was 12% (Table 4-13).

Amputation

Two observational studies [66,67] evaluated amputation as a palliative treatment option for patients with melanoma with ITM (see Table 4-14). Read et al. [67] evaluated a total of 55 amputations in 51 patients. The most common reason for amputation was the resistance to regional therapy, pain management, as well as progression of ITM. Regional chemotherapy was used prior to amputation in 58% of patients. The overall five-year survival for stage III ITM was 34.1% and for stage III patients who underwent amputation with a curative intent was 38.4%. Similarly, in Jaques et al., major amputation with curative intent was undertaken in 43 patients; ITM was one of the indications in 33 patients. Five-year disease-free survival was 35% with a median follow-up of 160 days [66].

Table 4-12. Summary of studies included for radiation therapy

Study	Study Type	Patient Population	Intervention	Survival	Response Rate	Toxicity
Seegenschmiedt, 1999 [17]	Retrospective study	121 patients total; 24 ITM and 33 lymph node metastases (UICC III)	Palliative radiation therapy External beam RT using linac 6-10 MV photons or 4-18 MeV electrons, with 2D or 3D planning. Median total dose 48 Gy (range 12-66 Gy); median duration of RT was 21days (range 8-56 days) 77 pts received conventional RT with 4-5 weekly fractions of 2-3 Gy. 44 pts mostly with large soft tissue metastases received hypofractionated RT with 3.5-6.0 Gy dose per fractions (data from table; restated as 3.1-6 Gy in the text)	OS in UICC III patients: median 22 months, 1-y 74±12%, 5-y 32±14%	Data not reported separately for ITM; UICC stage III includes ITM or lymph node metastasis UICC III: 44% CR and 33% PR	Data not reported separately for ITM; results are for full study Mostly minor: 53% grade 1 and 17% grade 2 toxicity. 2 pts with grade 3-4 soft tissue ulceration

Abbreviations: ITM, in-transit metastasis; NA, not available

Table 4-13. Summary of studies included for surgery

Study	Study Type	Patient Population	Intervention	Survival	Response Rate	Toxicity
Fotopoulos et al, 1998 [7]	Retrospective review	33 patients with loco-regional recurrence in the lower extremities (21 with ITM); 1-6 tumours in the recurrence (median 1.7)	Surgical excision; 8 palliative due to distant metastases, 24 curative intent	5-year DSF: 12% Median DSF 16 months (Range 1-104 months) Total Survival: 58% Median OS: 31 months (range 5-264) <u>Curative intent surgery:</u> DFS: median 22 months (4-104) <u>Palliative intent surgery:</u> DFS: 5 months (1-24 months) Difference was statistically significant.	NA	NA

Abbreviations: DFS, disease-free survival; ITM, in-transit metastasis; NA, not available; OS, overall survival

Table 4-14. Summary of studies included for amputation

Study	Study Type	Patient Population	Intervention	Survival	Response Rates	Toxicity
Read et al, 2015 [67]	Retrospective review	51 patients, including 67% with advanced ITM Advanced melanoma for which limb-sparing strategies have been exhausted	Amputation	Survival from the time of Melanoma diagnosis MSS: 87.1 months 5-year survival: 62.4% Survival from the time of amputation MSS: 12.6 months 5-year survival: 22.8% MSS was significantly better (p=0.004) for patients undergoing potentially curative amputations than for patients undergoing palliative amputation Regional chemotherapy was used before amputation for 58% of the patients, and for those with ITM, it was associated with an increased interval between ITM diagnosis and amputation	NA	NA
Jaques et al, 1989 [66]	Retrospective review	58 patients with(stage IIIa: 35%; stage IIIb: 19%; 42% stage IIIab); 43 pt with curative intent Advanced or recurrent malignant melanoma; included 33 pt with ITM	Amputation	ITM was one of the indications for amputation in 33 patients, and local control of disease was achieved in 30 of 43 patients. 5-year DFS: 35% (median follow up, 160 months)	NA	NA

Abbreviations: DFS, disease-free survival; ITM, in-transit metastasis; MSS, melanoma-specific survival; NA, not available

Topical Therapies

Topical DPCP

Two observational studies [15,16] evaluated the use of DPCP on patients with ITM (see Table 4-15). Read et al. studied 58 patients who had satellite or ITM (see Table 4-15). All lesion morphology types were included and lesions were all >2 mm in diameter. DPCP was administered using 0.005% DPCP in an aqueous cream base applied topically to target lesions with a surrounding 1 cm margin that was left unoccluded [15]. The ORR was 61.1%, with CR rate of 22.2%, PR rate of 38.9%, stable disease rate of 24.1%, and progressive disease rate of 14.8%. Damian et al. [16] reported similar response rates in patients included in their study. CR, PR, and no response were seen in 23 patients (46%), 19 patients (38%), and 9 patients (18%), respectively. CR rates for thin disease and bulky disease were 61% and 21%, respectively [16].

Topical Imiquimod

No studies were found that met the inclusion criteria as all had sample sizes less than the predetermined size.

Regional Therapies

Isolated Limb Infusion

One systematic review [23] and 10 observational studies [24-33] evaluated the use of ILI in patients with ITM (see Table 4-16). The systematic review evaluated 576 patients in seven non-comparative, observational studies. The treatment was ILI using melphalan and actinomycin D. Response rates were variable: CR, 33% (range, 26% to 44%); PR 40% (range, 33% to 56%); stable disease, 14% (range: 0% to 29%); and progressive disease, 13% (range, 0% to 29%). Regional toxicity following ILI was low; no visible effect of the treatment or slight erythema or edema was observed in 79% of the patients, while considerable erythema and/or edema with blistering was experienced by 19%. In 2% there was a threatened or actual compartment syndrome. No procedure-related amputation was reported. The 10 observational studies also had variable results for survival and response rates. OS was variable among the studies; however, it was found to be longer in patients with lower burden of disease (38.4 months vs. 30.9 months [33]). Kroon et al. [24] evaluated age as an indicator for response; however, differences between the two groups (<75 years vs. >75 years) were not statistically significant. Response rates were similar to the systematic review and were variable through the studies. As with OS, age was not an indicator of response; however, patients with low burden of disease were 3.5 times more likely than patients with high burden of disease to have a response to treatment at three months [28,32].

Table 4-15. Summary of studies included for DPCP

Study	Study Type	Patient Population	Intervention	Survival	Response Rate	Toxicity
Read et al, 2017 [15]	Prospective single-arm study	54 patients with satellite or ITM	Diphencyprone (DPCP) 2% DPCP solution in acetone applied to the medial aspect of the upper arm with a Finn Chamber. 0.005% DPCP in an aqueous cream base applied topically to target lesions with a surrounding 1 cm margin that was left unoccluded. Eventually, concentrations between 0.005% and 1% were used once to twice per week for up to 24–48 h of total duration.	Median follow-up: 21.8 months. OS: 59.3% Median OS time of 20.9 months from DPCP treatment commencement and 28.8 months from the time of ITM diagnosis. In this patient group, the 12-, 24- and 36-month overall survival rates were 76.2%, 67.2% and 51.3%, respectively, using a Kaplan–Meier survival estimate	On per patient basis CR 22% PR 39% SD 24% RD 15%	NA
Damian et al, 2014 [16]	Prospective study	50 patients biopsy-proven recurrent disease unable to be treated surgically; in transit or cutaneously metastatic Unsuitable or refractory to conventional therapy (surgery, radiotherapy, regional or systemic chemotherapy)	Concentration ranged from 0.00001% to 10%, with most patients needing concentrations of 0.001% to 0.1%. DPCP. Due to slow response, imiquimod was added for 2 patients	NA	CR: 23 patients (46%) PR: 19 patients (38%) NR: 9 patients (18%) Thin disease: 61% CR, 7% no response Bulky disease: 21% CR, 37% no response	NA

Abbreviations: CHS, contact hypersensitivity; CR, complete response; DPCP, diphenylcyclopropenone; ITM, in-transit metastasis; NA, not available; NR, no response; OS, overall survival; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease

Table 4-16. Summary of studies included for ILI using melphalan ± actinomycin D

Study	Study Type	Patient Population	Intervention	Response Rate	Survival	Toxicity
Kroon et al, 2014 [23]	Systematic Review	7 studies with a total of 576 patients	ILI using melphalan and actinomycin D	Response rates following ILI: CR: 33%; PR: 40%; OR (CR + PR): 73%, SD: 14%; PD: 13%	NS	Wieberdink toxicity Grade I: 33% Grade II: 46% Grade III: 19% Grade IV: 2% Grade V: 0%
Li et al, 2018 [25]	Prospective study	150 patients with ITM (59% had high BOD)	ILI with melphalan and actinomycin D	ORR: 41% CR: 6% PR: 35% SD: 53% PD: 7%	Median follow-up time: 47 months (3-99) Median PFS: 6 (range 4.9-7.1) Median OS: 15.2 months (12.5-17.9)	Grade I, II, III and IV limb toxicities after ILI occurred in 6 (4%), 77 (51%), 66 (44%) and 1 (1%) patients, respectively, but no grade V toxicity was observed
Kroon et al, 2017 [24]	Prospective study (age)	unresectable in-transit metastases of the limb, with or w/o involvement of lymph nodes >75: 148 patients <75: 168 patients	ILI with melphalan and actinomycin D	<u><75 years:</u> CR: 63 (38%) SD: 25 (15%) PD: 13 (8%) <u>>75 years:</u> CR: 41 (27%) SD: 32 (22%) PD: 9 (6%)	<u>Median follow-up:</u> 22 months No stat sig difference was seen in OS	Grade III/IV toxicity was seen in 32 elderly patients (22%) and 62 younger patients (37%; p=0.003).
Chin-Lenn et al, 2015 [28]	Retrospective review	54 ILIs on 52 patients	ILI with using melphalan with or without actinomycin D	<u>Initial response:</u> @ 3 months CR: 14 patients (30%) PR: 13 patients (26%) PD: 13 patients (28%) BOD was a significant (p=0.01) predictor of response.	<u>MSS:</u> 12 months was 77% 24 months 57%; 60 months 43%	NS
Muilenburg et al, 2015 [32]	Retrospective review	160 pts with AJCC stage IIIb or IIIc melanoma	ILI using melphalan and actinomycin D (80% of ILIs were performed in the lower extremities)	Low burden of disease vs. high burden of disease OR: 3.51 (p<0.001) low BOD patients were 3.5 times more likely than high BOD patients to have a response to treatment at 3 months	OS: low BOD: 38.4 months; high BOD: 30.9 months (p=0.146)	NS

Study	Study Type	Patient Population	Intervention	Response Rate	Survival	Toxicity
Beasley et al, 2015 [27]	Prospective review	28 patients with ITM who had previously failed RC with LPAM	TMZ via ILI	MTD patients @ 3 months CR: 2/19 patients (10.5%) PR: 1/19 patients (5.3%) SD: 3/19 patients (15.8%) PD: 13/19 patients (68.4%) Maximum administered dose 1ptn PR 4 patients SD	NS	Toxicity data were not divided by indication subgroups
Wong et al, 2014[107]	Retrospective Review	176 patients with AJCC stage IIIb and IIIc melanoma	ILI using melphalan and actinomycin D (n=154), ILI+RES (n=22)	Initial response: @ 3 months ILI+RES group had PR: 15 (68%) SD: 2 (9%) PD: 5 (23%) ILI alone: CR: 52 (34%) PR: 30 (19%) SD: 15 (10%) PD: 46 (30%)	Median OS was 30.9 months for ILI alone, OS not reached for ILI+RES group. No sig difference in OS between the ILI-alone and ILI+RES groups, p=0.304 DFS: ILI+RES=12.4 v ILI=9.6, p=0.978 Within the ILI+RES group, those with an initial PR after ILI had improved DFS versus those with SD or PD after ILI, p<0.0001.	NS
Beasley et al, 2012 [26]	Retrospective review	36 Patients with UE melanoma and 173 patients with LE melanoma	ILI with melphalan and actinomycin D (normothermic)	UE: CR: 10 (28%) PR: 9 (22%) SD: 5 (14%) PD: 10 (28%) 2 lost to follow-up LE: CR: 53 (32%) PR: 35 (21%) SD: 18 (11%) PD: 51 (5%) 2 patients lost to follow-up	NS	NS
McClaine et al, 2012	Retrospective review	32 ILIs (27 patients with ITM)	ILI Melphalan and actinomycin D	1 year CR: 41% PR: 6% PD: 53%	NS	The most common post procedure symptoms were edema (88%), numbness (59%), and

Study	Study Type	Patient Population	Intervention	Response Rate	Survival	Toxicity
				Last follow-up (592 ±294 days) CR: 41% PR: 6% PD:53%		pain (59%). By 3 months and at the time of last follow-up, the most common symptoms were edema (82%), numbness (65%), and stiffness (35%). No patients reported impaired limb function at the time of last follow-up compared with baseline.
Kroon et al, 2009 [29]	Retrospective review	185 patients who underwent ILI 99patients <age 75 86patients >age 75	ILI with melphalan and actinomycin D	<age 75 (median follow-up time 20 months) CR 41/58 (41%) OR: 86/16 (84%) Limb recurrence-free interval 20 months follow-up time 21 months) CR: 29/57 (34%) OR: 72/14 (84%) Limb recurrence-free interval 27 months Differences not statistically significant	<age 75 (Median follow-up time 20 months) Median OS: 41 months >age 75 (median follow-up time 21 months) Median OS: 34 months Differences not statistically significant	Of the patients <75 years, 51% experienced limb toxicity grade III/IV whereas this occurred in 31% of the patients >75 years. This difference in toxicity was statistically significant (p=0.009) while systemic toxicity, complications, and long-term morbidity were similar Pooled: Grade I (no reaction) occurred in 3 patients, grade II (slight erythema and edema) in 105 patients, grade III (considerable erythema and edema ± blistering) in 72 patients, and grade IV (threatened or actual compartment syndrome) in 5 patients. No patient developed grade V

Study	Study Type	Patient Population	Intervention	Response Rate	Survival	Toxicity
						toxicity (requiring amputation)
Lidner et al, 2004 [30]	Retrospective review	44 patients with planned double ILI 78 patients with single ILI	ILI with melphalan and actinomycin D	Double ILI CR: 41% PR: 47% SD: 12% PD: 0% Median duration of response: 18 (6-60) Single ILI CR: 41% PR: 41% SD: 12% PD: 6% Median duration of response: 17 (7-44) Differences not stat sig (p=0.08).	NS	After double ILI more patients experienced Wieberdink Grade III or IV limb toxicity

Abbreviations: AJCC, American Joint Committee on Cancer; BOD, burden of disease; CR, complete response; ILI, isolated limb infusion; LE, lower extremity; LPAM, L-phenylalanine mustard; MSS, melanoma-specific survival; MTD, maximum tolerated dose; NS, not significant; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RC, regional chemotherapy; RES, resection; SD, stable disease; TMZ, temozolomide; UE, upper extremity; w/o, without

Isolated Limb Perfusion

Details of studies are reported in Table 4-17 for studies evaluating ILP with or without TNF-α, Table 4-18 for the RCT evaluating wide local excision with or without ILP, and Table 4-19 for studies that evaluated ILP with melphalan only. One good-quality RCT was included that evaluated the efficacy of ILP in treating ITM with or without the use of TNF-α [34] and an additional poor-quality RCT was identified that evaluated the efficacy of ILP and TNF-α with or without IFN-γ in addition to a historical control population of patients who received ILP with melphalan alone [35]. One poor-quality RCT was included evaluating ILP as adjuvant treatment to excision [36,37]. Thirty-four observational studies were included that evaluated the efficacy of ILP with or without TNF-α or melphalan only in ITM populations [69-101]. While some of the observational studies are comparative, the comparisons are between the mode of delivery and not between ILP and another intervention or control group; and therefore not a relevant comparison for this Guideline. In the RCTs that evaluated the efficacy of ILP with or without TNF-α, Cornett et al. [34] and Lienard et al. [35] found no statistically significant difference between the two treatment arms. 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 [34]. In the study conducted by Lienard et al. [35], patients were randomized into two arms; one arm was ILP with TNF-α and IFN-γ, and the other was ILP with TNF-α without IFN-γ. These arms were also compared with a historical control population of patients who received ILP with melphalan alone and no TNF-α or IFN-γ. The RCT originally conducted by Hafstrom et al. [37] in 1991, and updated by Olofsson Bagge et al. [36] 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 up with more than 25 years of observation time after randomization, and there was no statistically significant difference in OS over time. It should be noted that this study had a small population, and therefore should be interpreted with caution [36]. The remainder of the studies included was observational studies that evaluated ILP with melphalan and TNF-α or with melphalan alone. In the observational studies that evaluated ILP with melphalan and TNF-α, the response results varied. The responses to treatment ranged widely across all studies.

ILI Compared with ILP

There were six studies comparing ILI to ILP [38-43] (see Table 4-20). In each case ILP tended to be superior to ILI in term of response rates; in one study this was a statistically significant difference ($p<0.001$) [40]. In terms of OS, ILP tended to be superior in two studies [40,43]. In Dosset et al., survival was improved for the ILI group at one year and three years (85% vs. 78% and 55% vs. 51%, respectively) but was surpassed by ILP in year 5 (31 vs. 18%); however, the difference in OS between the ILI and ILP groups did not reach statistical significance [40]. Toxicity data were scarce; however, more high-grade toxicities (Wieberdink Scale >3) were found in the ILP cohorts versus the ILI cohorts when reported in the studies. This did not reach statistical significance in Dosset et al. ($p=0.14$) [40,42].

Ongoing, Unpublished, or Incomplete Studies

Ongoing studies in patients with ITM are currently underway for systemic therapies (nivolumab, ipilimumab) adjuvant to ILP (NCT02094391, NCT03685890).

Table 4-17. Summary of studies using melphalan ILP with or without TNF-α

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
ILP with +/- TNF-α RCTs						
Cornett et al, 2006 [34]	RCT	124 patients with ITM 58 Arm 1 58 Arm 2	Arm 1: Hyperthermic ILP with melphalan Arm 2: Hyperthermic ILP with melphalan and TNF-a	Response to treatment @3 months Arm 1(n=58) CR 25% PR:39% SD: 28% LP: 11% OR: 62% Arm 2 (n=58) CR: 26% PR: 43% SD: 22% LP: 9% OR: 69% Response to treatment @ 6 months Arm 1 (n=44) CR: 20% PR: 27% SD: 18% LP: 34% OR: 48% Arm 2 (n=45) CR: 42% PR: 13% SD: 20% LP: 24% OR: 56%	NS	Total Toxicity: Any grade III or higher: Arm 1: 38% Arm 2: 48% Limb loss: Arm 1:0% Arm 2: 3%
Lienard et al, 1999 [35]	RCT	Arm 1: 32 patients Arm 2: 32 patients Historical control (not randomized) Arm 3: 103 patients	Arm 1 (TM-ILP): ILP using TNF-α and melphalan Arm 2 (TIM-ILP): IFN-γ (sc for 2 d) then IFN-γ (sc) plus ILP using melphalan + TNF-α	Arm 1: CR:68.8% PR: 21.9% NC: 6.3% PD: 3.1% Arm 2: CR: 78.1% PR: 21.9% NC: -	Median survival time (Kaplan-Meier) Arm 1: 819 days Arm 2: >705 days Combined: 873 days	NS

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
			Arm 3:ILP with melphalan only M-ILP (historical control data)	PD: - <u>Arm 3:</u> CR: 52.4% PR: 25.2% NC: 16.5% PD: 5.8%		
Non-RCTs						
Smith et al. 2018 [93]	Prospective study	179 patients	Hyperthermic ILP with melphalan and TNF-α	< age 75 CR: 26 (38.2%) PR: 27 (39.7%) >age 75: CR: 21 (52.5%) PR: 15 (37.5%)	LPFS: median 11 months	Grade 1: 6 patients Grade 2: 0 patients Grade 3: 1 patient Grade 4: 2 patients Grade 5: 1 patient
Madu et al, 2017 [83]	Retrospective cohort study	96 patients >age 70	ILP with melphalan ± TNF-α	ORR: 81% CR: 47%	Median follow-up: 16 months LPFS: 6 months Patients with a CR: 16 months MSS: 38 months 3-year MSS: 52% 5-year MSS: 38%	Wieberdink IV: 2.2% (2)
Bagge et al, 2016 [71]	Prospective study	68 patients with ITM	Hyperthermic ILP (melphalan and melphalan + TNF-α)	NS	NS	HRQoL was negatively affected by tumour burden (<10 tumour): p=0.02)
Smith et al. 2015 [92]	Prospective study	129 patients with ITM	TM-ILP	ORR: 81.8%	2-year PFS: 27.8%; median PFS: 11 months MSS @ 2 years: 42.7% Median OS: 21 months.	NS
Deroose et al, 2015 [74]	Prospective study	32 patients with repeat ILPs (5 patients had more than 3 ILPs)	TM-ILP	CR: recorded after 24 TM-ILPs (65%). LRR; 59%	3-year survival: 56% 5-year survival: 35%; OS: 45 months	mild (70%Wieberdink I–II)

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
Hoekstra et al, 2014 [81]	Prospective study	60 patients with in-transit metastasis	Upper and lower limb ILPs; M-ILP: 19 patients TM-ILP: 41 patients	OR rate after 57 ILPs: 90% (84% M-ILPs; 93% TM-ILPs) CR: 27 patients (45%) PRs: 27 patients (45%), NR: 3 patients (age was a sig. factor p=0.003) <u>Local Control</u> Positive lymph node status was associated with local progression and was the only significant prognostic factor for local progression in multivariable analysis (p=0.036) <u>Systemic Disease</u> Absence of CR and Stage IIIc disease were independent prognostic factors for progression to systemic disease.	NS	NS
Deroose et al, 2012 [73]	Retrospective Review	173 patients with in transit metastasis	TM-ILP (axillary (n=7, 4%), iliac (n=85, 51%), and femoral (n=75, 45%) approach.)	<u>Response Rate:</u> CR was more often observed in stage IIIb patients: 77% IIIb vs. 49% IIIc vs. 38% IV; IIIb vs. IIIc, p=0.002; IIIb vs. IV, p=0.003; IIIc vs. IV, p=0.45). <u>Local progression</u> LP: 56% (n=93) median time was 13 months	3-year survival: 40% (±4%) 5-year survival: 26% (±4%) 10-year survival: 13% (±3%) Median OS was 24 months. OS did correlate with stage of disease (p=0.001), size of the lesions (p=0.001), and a CR (p=0.001)	NS
Deroose et al, 2011 [75]	Retrospective review	124 TM-ILPs were performed in 111 patients	TM-ILP via an axillary, iliac, femoral or popliteal approach	<u>Clinical Response:</u> ORR: 93.2%. Stage of disease was the only stat sig predictor of CR in multivariate analysis. <u>Local Progression:</u> Progression was less rapid in patients with a complete response to TM-ILP than in those with PR or no change: 19 *versus* 6 months (p<0.001).	5-year MSS: 27.3% 10 year MSS: 16.4% MSS was influenced by: sex (p<0.001), age (p=0.019), Breslow thickness	I=0 II=71.2% III=25.4% IV=2.5% V=0.8%

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
				Systemic progression: Patients with stage IIIa disease had a significant longer time to systemic progression than those with stage IIIb disease: 55 *versus* 11 months (p<0.001) IIIa disease had a significant longer time to systemic progression than those with stage IIIb disease: 55 *versus* 11 months (p<0.001) The median time to systemic progression after a complete response to TM-ILP was 32 months, compared with 7 months in patients who had PR or no change (p<0.001). In multivariable regression analysis, sex (*p*=0.006) and stage of disease (p=0.002) remained significant, whereas age became a significant prognostic variable (p=0.007)	(p=0.052), size of the largest lesion (p<0.001), disease stage (IIIa versus IIIab, p<0.001; IIIa versus IIIab, p<0.001), and complete response after TM-ILP (p<0.001)	
Alexander et al, 2010 [69]	Prospective study	91 stage IIIb or IIIc patients (90 patients assessable)	TM-ILP: 43 patients M-ILP: 47 patients	NS	***Results combined*** PFS: 12.5 months OS: 47.4 months 5 – year actuarial OS: 43% 10-year actuarial OS: 34% Low tumour burden (≤20 lesions) was associated with prolonged PFS, p<0.011	NS
Rossi et al, 2010 [91]	Retrospective review	112 patients with ITM	Arm 1: TM-ILP 58 patients Arm 2: M-ILP 53 patients	Arm 1: CR: 61% PR 29% OR 90%		Arm 1: 2 patients (grade IV: 1; Grade V: 1 Arm 2: 2 patients (Grade III: 2)

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
				Arm 2: CR: 42% PR: 49% OR: 91%		
Di Filippo et al. 2009 [76]	Prospective study	113 (MD Anderson stage IIIa and IIIab)	TM-ILP	CR: 63% PR: 24.5% OR: 87.5% Bulky disease was an independent factor for tumour response (p=0.02)	5 year DFS: 24.53% 5 year OS: 49% Responders with CR did better with a 5-year OS of 66.9% as compared with non-CR whose 5-year overall survival was 27.1% (p=0.0001). stages IIIa and IIIab, the 5-year OS rates were 68.6% and 28.0%, respectively, the difference being statistically significant (p=0.03).	NS
Da Ponte et al, 2009 [96]	Retrospective review	102 ILPs in 87 patients	85 M-ILPs 17 TM-ILPs	ORR: 92.2% CR: 63.7% PR: 28.4% NR: 7.8% Complete response rate was significantly higher with M-ILP than with TM-ILP (69.4% vs. 35.3%, p=0.008)	5-year OS: 31.8%	NS
Hayes et al, 2007 [80]	Retrospective review	25 patients with ITM	TM-ILP	CR: 44% PR: 37% SD: 15% Median time to progression (months): 6 (range 1-8) At a median follow-up of 14 months, 66% of patients with melanoma who	NS	NS

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
				responded had not experienced local progression		
Noorda et al, 2006 [85]	Retrospective review	21 patients with ITM who had a failed previous perfusion	***Repeat*** TM-ILP for patients with a previous failed perfusion	CR: 13 (61%) PR: 2 (10%) NC: 1 (5%) PD: 5 (24%) Median limb recurrence-free survival was 13 months Overall median survival was 62 months after CR compared with 13 months for those without CR (p=0.05)	Median limb recurrence-free survival was 13 months Overall median survival was 62 months after CR compared with 13 months for those without CR (p=0.05)	Fourteen patients had mild acute regional toxicity after repeat ILP compared with 18 after the first ILP. 1 patient underwent amputation for critical limb ischemia 10 months following repeat ILP. The limb salvage rate was 95%.
Di Filippo et al, 2006 [77]	Retrospective review	113 patients with ITM	TM-ILP	CR: 63% PR: 24.5% SD: 12.5	NS	Grade 1 and 2 limb toxicity was recorded in 52.9% and 30.1% of the patients, respectively; 5.5% of patients exhibited a grade 3 and 4, whereas grade 5 limb toxicity was not recorded.
Grunhagen et al, 2005 [98]	Retrospective review	100 ILPs in 87 patients with ITM (25 ILPs in 21 patients were repeat ILPs because of failure of previous ILP treatment for extensive IT melanoma metastases)	***Repeat*** TM-ILPs for a failed previous perfusion	<u>Overall Response Rate (n=100):</u> CR: 69/100 (69%) PR: 26/100 (26%) NC: 5/100 (5%) Overall: 94% <u>Repeat ILPs (n=25)</u> CR: 19/25 (76%) PR: 5/25 (20%) NC: 1/25 (4%) Overall: 96% <u>Prior M-ILP (n=12)</u> CR: 10.12 (83%) PR: 2/12 (17%)	NS	<u>Standard dose:</u> OR: 96% CR:69% PR:27% NR:5% <u>Low-Dose:</u> OR: 94% CR:75% PR:19% NR:6% Systemic and local toxicity did not differ statistically

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
				NC: - Overall: 100% TM-ILP Repeats CR: 9/13 (69%) PR: 3/13 (23%) NC: 1/13 (8%) Overall: 92%		between reduced- and standard dose
Grunhagen et al, 2005 [79]	Retrospective Review	***Reduced Dosage study*** 82 TM-ILPs (standard dose) 16 TM-ILPs (low dose <3 mg in arm perfusions, <4 mg in leg perfusions	82 TM-ILPs (standard dose) 16 TM-ILPs (low dose)	Standard dose: OR: 96% CR:69% PR:27% NR:5% Low-Dose: OR: 94% CR:75% PR:19% NR:6% p=0.770 for complete response	NS	Systemic and local toxicity did not differ statistically between reduced- and standard dose
Rossi et al, 2004 [90]	Retrospective review	20 patients with ITM	Low-dose TM-ILP	CR: 70% PR: 25% NR: 5% OR: 95%	NS	Locoregional toxicity was mild (grade 1 or 2) in 95%
Noorda et al, 2004 [86]	Retrospective review	110 patients with unresectable melanoma of the extremities	Arm 1: 90 TM-ILP Arm 2: 40 M-ILP	CR Arm 1: 59% Arm 2: 45% Time to CR (months) Arm 1: 2 (1-3) Arm 2: 3 (2-6) Recurrence Rate Arm 1: 48% Arm 2: 56% Limb recurrence-free survival (months) Arm 1: 16 Arm 2: 30	Limb recurrence- free survival (months) Arm 1: 16 Arm 2: 30	NS

Study	Study Type	Patient Population	Intervention	Response Rates	Survival	Toxicity
Noorda et al, 2002 [84]	Retrospective study of TM-ILP or M-ILP in ***elderly*** patients	215 patients 149 patients <75 years old 53 patients >75 years old	ILP with or without TNF	>75 years old: CR:56% >75 years old CR:58%	NS	NS
Fraker et al, 1996 [78]	Retrospective review	38 patients with ITM	TM-IMP: 26 TM-ILP: 12	TM-ILP (4mg) OR:92% CR:76% PR:16% NR: TM-ILP (6mg): OR:100% CR:36% PR:64% Subgroup analyses showed that the lower complete response rate in the 6-mg TNF group was not explained by differences in disease burden or prior regional therapy.	NS	Regional toxicity, particularly painful myopathy and neuropathy, was greater with the 6-mg dose level and was considered dose-limiting.
Vaglini et al, 1994 [94]	Retrospective review	22 patients with ITM	Arm 1: 12 patients had TM-ILP total dosage TNF-, melphalan and IFN-gamma Arm 2: 10 patients received an escalating dosage of TNF-α, melphalan, and no IFN-gamma before or during surgery	Arm 1: CR 7 patients SD: 4 patients 50% of patients developed regional relapse 3-4 months after TM-ILP Median follow-up 10 months – 5 patients are still in CR, 4 are alive with disease, 2 died from melanoma and 1 died from treatment related complications (multi-organ failure) Arm 2: CR: 7 patients Partial remission: 3 patients Median follow-up 3 months: 2 patients developed regional relapse	NS	NS
Lejeune et al, 1993 [108]	Prospective study	44 patients with ITM	TM-ILP	CR: 39/44 patients (90.5%) PR: 5/44 patients follow-up: 13 months Recurrence 7/44 (16%) (2-13 months) Distant metastases: 17/44 Limb salvage 40/44	NS	NS

Abbreviations: CR, complete response; DFS, disease-free survival; HRQoL, health-related quality of life; IFN-γ, interferon-gamma; ILP, isolated limb perfusion; ITM, in-transit metastasis; LP, local progression; M-ILP, ILP using melphalan; MSS, melanoma-specific survival; OR, overall response; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RCT, randomized controlled trial; SD, stable disease; TIM-ILP, ILP using TNF-α + melphalan + subcutaneous IFN-γ; TM-ILP, ILP with TNF-α + melphalan; TNF, tumour necrosis factor; WE, wide excision

Table 4-18. Summary of studies using ILP adjuvant to wide local excision

Study	Study Type	Patient Population	Intervention	Overall Survival	Response Rate	Toxicity
Olofsson Bagge et al, 2014; Hafstrom, 1991 [36,37]	RCT	69 patients with ITM	Patients randomized to receive WE (n=36) or WE+ILP (n=33)	NS	WE+ILP group there were 20 deaths (61%) due to melanoma compared with 26 deaths (72%) in the WE group (p=0.31). Median MSS: 95 months for WE+ILP compared with 38 months for the WE group, an almost 5-year benefit without statistical significance (p=0.24).	NS

Abbreviations: ILP, isolated limb perfusion; ITM, in-transit metastasis; NS, not significant; RCT, randomized controlled trial; WE, wide excision

Table 4-19. Summary of studies for ILP with melphalan only

Study	Study Type	Patient Population	Intervention Details	Response Rate	Survival	Toxicity
Bagge et al. 2016 [71]	Retrospective study	52 patients with ITM	M-ILP - (12%), external iliacal (8%), and femoral (81%) Approaches); 2 patients had TM-ILP			Patients with increased tumour burden had decreased HRQoL scores (FACT-M) After ILP: HRQoL score 3, 6, and 12 months after ILP did not differ significantly from the baseline scores (paired analysis). At 12 months, a significant difference in overall HRQoL was observed, with higher scores for FACT-G (+1.0 vs. -13.0 points; p=0.04) and TOI (+1.9 vs. -14.0 points; p=0.04) as well as a trend shown in FACT-M (+1.7 vs. -14.6 points; p=0.08) for patients with a CR compared with no CR
Paulsen et al, 2014 [88]	Prospective study	84 patients with stage IIIa-c melanoma	M-ILP	Positive Response Rate after 4 weeks was 85%; CR: 42%, PR: 43%; 12% NC: 12% Progression: 3%	2 year survival: 57% 5 year survival 31%.	(Wieberdink Scale) I: 44% II: 43% III 11% IV 3%
Olofsson et al, 2013 [87]	Prospective study	163 patients with ITM; 155 evaluable	ILP axillary (n=9), brachial (n=3), subclavian (n=2), iliac (n=92), or femoral (n=57) approach. 148 received M-ILPs (91%)	65% CR (per patient basis) and 20% PR Sig. predictive factors for CR: - lymph node status and <10 in-transit metastases. With multivariate analysis, the only independent factor was the presence	Median OS :27 months, 2-year: 53% 5-year: 26% 10-year: 8%	(Wieberdink Scale): Grade I=0 (0%), grade II in 103 patients (63%), grade III in 53 patients (33%), grade IV in 5 patients (3%), grade V 0 (0%)

Study	Study Type	Patient Population	Intervention Details	Response Rate	Survival	Toxicity
			15 received melphalan +TNF-α (9%) [some of the patients after 2020 with bulky disease] Bulky disease subset: 14 patients M-ILP, 13 patients TM-ILP	of <10 in-transit metastases <u>Bulky disease:</u> CR 64% with M-ILP vs. 36% with TM-ILP (p=0.26); ORR 79% vs. 77%		
Reintgen et al, 2010 [89]	Prospective study	229 patients with extremity local/regional recurrence (all patients had clinical N0 disease at time of HILP)	HILP with melphalan	CR: 66% PR: 20%. SD: 10% PD: 4% of. Mean follow-up of 7 years, 27% of the patient that experienced a CR with the HILP recurred with an average disease free interval from the time of HILP of 12 months.	NS	NS
Boesch et al, 2010 [72]	Retrospectiv e review	152 patients with locoregionally metastasized malignant melanoma of the extremities (upper extremity n=10, lower extremity n=142) 51 patients were in stage IIIa according to M.D. Anderson's classification (ITM), 43 patients in stage IIIab (in-transit metastasis and regional lymph node metastases) and 58 patients in	Hyperthermic ILP	<u>Recurrence</u> The length of the interval until diagnosis of distant metastasis in patients with stage IIIa/IIIab correlated significantly (p=0.001) with local tumour response The length of the interval until distant metastasis occurred in patients with partial vs. complete remission correlated significantly (p=0.009)	<u>Recurrence-free interval</u> The length of the interval until diagnosis of distant metastasis in patients with stage IIIa/IIIab correlated significantly (p=0.001) with local tumour response The length of the interval until distant metastasis occurred in patients with partial vs. complete remission correlated significantly (p=0.009) <u>Survival rate</u> Median OS: 39 months (average 67 months).	(Wieberdink Scale) Grade V: 2 Grade IV: 6

Study	Study Type	Patient Population	Intervention Details	Response Rate	Survival	Toxicity
		stage IV (distant metastases).			5 year OS: 34%. Survival rate was dependant on the stage of disease (p>0.001) local tumour response rate had a significant influence on the survival rate (p=0.001)	
Knorr et al, 2006 [82]	Retrospective review	100 patients with ITM	HILP with melphalan and actinomycin D	IIIa CR: 65% PR:15% NR:2% IIIabc CR:55% PR:25% NR:8% IV CR: 45% PR:22% NR:33%	OS: 42 months; OS differed significantly upon stage	Severe toxicity (Wieberdink IV/V) was observed in 5 patients necessitating fasciotomy in four of them and above knee amputation in one patient. All further cases presented with grade II-III toxicity
Aloia et al, 2005 [70]	Retrospective review	58 patients with ITM	HILP with melphalan	CR: 57% PR: 31% NR: 12% OR: 88%	NS	NS
Noorda et al, 2003 [100]	Retrospective review	246 patients with stage II or III melanoma	M-ILP	CRR for patients who died within 1 year 47% (n=23; 95% CI 33% to 61%) compared with 64% (n=138; 95% CI 57% to 70%) in the surviving group (p=0:03) Prognostic factors for death within 1-year Stage of disease at the time of ILP IIIab OR=3.6 IIIb OR=4.6 IV OR=22	Median OS: 46 months (38-54 months) Overall 5-year survival: 42% (n=156)	NS

Study	Study Type	Patient Population	Intervention Details	Response Rate	Survival	Toxicity
Vrouenraets et al, 2001[95]	Retrospective review	415 patients with ITM	Normothermic M-ILP: 294 Mild hyperthermic M-ILP: 71 Mild hyperthermic TM-ILP: 50	NS	NS	Wieberdink Scale Grade I: 14 (3.4%) Grade II: 325 (78.3%) Grade III: 71(17.1%) Grade IV: 3 (0.7%) Grade V: 2 (0.5%) 'Mild' hyperthermic TM-ILP plus significantly increased the incidence of more severe acute regional toxicity compared with normothermic and 'mild' hyperthermic M-ILP (36% vs. 16% and 17%; p=0.0038). This may have been due to differences in hyperthermia scheduling
Thompson et al, 1997 [101]	Retrospective review	111 patients with ITM	M-ILP	CR: 73% PR: 13% OR: 86%	NS	NS
Meyer et al, 1998 [99]	Retrospective review	Group 1: n=163 (Hyperthermic M-ILP (in combination with actinomycin D) Group 2: n=20 (modified perfusion technique (90 min, drug continuously infused over 20 min into the arterial line)	Hyperthermic M-ILP (in combination with actinomycin D)	NS	10 year OS: 37%	NS
Edwards et al, 1990	Prospective study	84 patients WLE and M-ILP 84 patients WLE alone	84 patients M-ILP and WLE 84 patients WLE alone	Significant statistical increases in both DFS and OS rates for the subset of patients with lesions >2.0 mm in thickness who were perfused with	Significant statistical increases in both DFS and OS rates for the subset of patients with lesions >2.0 mm in thickness who were perfused with	

Study	Study Type	Patient Population	Intervention Details	Response Rate	Survival	Toxicity
				melphalan (25 patients in each group)	melphalan (25 patients in each group)	

Abbreviations: CI, confidence interval; CR, complete response; CRR, complete response rate; FACT-G, Functional Assessment of Cancer Therapy - General; FACT-M, Functional Assessment of Cancer Therapy - Melanoma; IFN, interferon; HILP, hyperthermic ILP; HRQoL, health-related quality of life; ILP, isolated limb perfusion; ITM, in-transit metastasis; M-ILP, ILP+melphalan; ORR, overall response rate; OS, overall survival; PR, partial response; TIM-ILP, ILP with TNF-α + melphalan + IFN gamma; TM-ILP, ILP+TNF-α and melphalan; WLE, wide local excision

Table 4-20. Summary of studies comparing ILI with ILP

Study	Study Type	Patient Population	Intervention	Response	Survival	Toxicity

Dossett et al, 2016 [40]	Retrospective review	203 Stage IIIb and IIIc melanoma	ILP (n=109) versus ILI (n=94)	Clinical Response:
				ORR: ILI: 53% vs. ILP: 80% (p<0.001)
				CR: ILI 29% vs. ILP 60% (p<0.001)
					1-year survival: ILI 85% and ILP 78%
					3-year survival: ILI 55% and ILP 51%
					5-year survival: ILI 18% and ILP 31%
						ILP:
						grade 1=9;
						grade II=62;
						grade III=26;
						grade IV=3;
						grade V=0
						ILI:
						grade I=14;
						grade II=67;
						grade III=16;
						grade IV=1;
						grade V=0

Lidsky et al, 2013 [41]	Retrospective review	258 patients with stage IIIb and stage IIIc melanoma	134 patients had ILI 81 patients had HILP	ILI cohort: PD: 32.1% n=43; CR: 29.9% (n=40) HILP cohort: PD: 11% (n=9); CR 44.4% (n=36) In the ILI cohort the only variable differing between patients with progressive disease and patients who experienced a complete response was age, with the patients who experienced progressive disease being younger 60 vs. 70, p<0.001)	NS	NS
Sharma et al, 2012 [43]	Retrospective review	214 patients with AJCC stage IIIb, C or IV	133 ILIs 81 Hyperthermic ILPs	ILI cohort: CR: 37 (28%) PR: 17 (13%) SD: 15 (11%) PD: 39 (29%) NE: 25 (19%) HILP cohort: CR: 36 (44%) PR: 7 (9%) NE: 8 (10%) • HILP was associated with a higher CR rate (44% vs. 28%, p=0.01) than ILI • Median time to first recurrence was longer for HILP-CR than ILI-CR (23 vs. 8 months, p=0.02).	3-y OS in patients with complete response: 54% ILI-CR and 77% HILP-CR, p=0.10	NS

Study	Study Type	Patient Population	Intervention	Response	Survival	Toxicity
Chai et al, 2012 [39]	Retrospective review	44 patients with in-transit melanoma	(28 HILPs and 70 ILIs); 37 patients (84%) had 2 procedures, 4 patients (9%) had 3 procedures, and 3 patients (6.8%) had 4 procedures. Sequences were divided into 4 groups: group A (ILI→ ILI), group B (ILI → HILP), group C (HILP→ ILI) group D (HILP→ HILP)	ILI: ORR: 33% (17% CR and 16% PR) HILP: ORR: 49.9% (32% CR and 18% PR) With comparing the CR and ORR no stat sig. difference was noted for CR or ORR (p=0.17 and p=0.12, respectively) Subgroup Analysis No statistically significant differences in subgroup analysis (lack of power to compare groups C and D)	NS	NS
Raymond et al, 2011 [42]	Retrospective Review	125 first time and 18 second time ILIs 62 first time; 10 second time HILPs	ILI: melphalan and actinomycin D HILP: melphalan alone	ILI: ORR:43% CR: 30% Median duration 24 months HILP: ORR: 81% CR: 55% Median duration of 32 months Toxicities similar but limb loss was great in the HILP cohort (2 patients vs. 0)	NS	Toxicities similar but limb loss was great in the HILP cohort (2 patients vs. 0)
Beasley et al, 2008 [38]	Retrospective review		58 ILI with melphalan 54 HILP with melphalan	ILI CR: 30% PR: 14% Median duration of CR 12 months HILP CR 57% PR 31%, Differences in response rates between ILI and HILP were statistically significant p<0.001)	NS	Grade 3+ adverse events 18% ILI vs. 32% HILP

Abbreviations: AJCC, American Joint Committee on Cancer; CR, complete response; HILP, hyperthermic ILP; ILI, isolated limb infusion; ILP, isolated limb perfusion; NE, not evaluable; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease

DISCUSSION

Surgical excision of ITM with a pathologically clear margin currently represents the standard of care where feasible. For the groups of patients where surgical excision has been deemed to be inappropriate, there is variability in which treatments will provide the best outcomes when balanced with toxicity.

Based on the evidence available and the current approvals for use within Canadian Cancer Centres, the Working Group members were able to stratify the treatments for patients with moderate ITM into first-choice, second-choice, and third-choice therapies. IL-2 was considered a first-choice therapy based on the expert opinion of the Working Group in addition to its current availability and approval for use within Canada as well as the evidence available. In the systematic review conducted by Byers et al. [8], CR was reported for 77.9% of lesions and 49.6% of patients. Hassan et al. [9] reported results only on a per-patient basis; 32.3% had CR and 54.8% had PR. In small studies combination therapy of IL-2 plus imiquimod have found pCR of 58% to 100% [2-4]. With respect to toxicity, the tolerability of IL-2 in the systematic review by Byers et al. [8] was good, with localized pain and swelling, and mild flu-like symptoms. There were three grade 3 AEs reported out of the 95 patients analyzed (3%), including rigors, headache, and fever with arthralgia. In Hassan et al. [9], toxic effects were minor; one patient developed cellulitis, and most patients experienced fatigue, fever, and chills for 24 hours. T-VEC was also considered to have high-quality evidence from the OPTiM RCT [11][8]. Complete response occurred in 16.9% versus 0.7% of patients and in 47% versus 22% of lesions. Median OS was 23.3 months versus 18.9 months (HR=0.79; 95% CI 0.62 to 1.00, p=0.0494) and four-year OS was 34.5% versus 23.9%. T-VEC is approved in the United States and Europe; however, at the time of this guideline is in not approved for use in Canada except in a clinical trial.

In patients with moderate ITM, second-choice therapy is topical DPCP. While evidence for DPCP consists of small, non-comparative observational studies, it has the potential to improve response and survival outcomes in patients with ITM with minimal toxicity. In addition to the studies in Table 4-15, we are aware of other studies that did not meet the inclusion criteria but that also suggest possible benefit. A study by Moncrieff et al. [109] reported 28.6% CR and 31.4% for topical DPCP in 35 patients with locoregional intralymphatic melanoma with low-volume disease. A study of 15 patients with unresectable ITM by Yeung et al. [68] reported 13% CR, 27% PR, 40% stable disease, and 20% progressive disease. Common AEs were blistering, development of dry skin, and intermittent pain. Gibbons et al. [110] treated 16 patients with topical DPCP and reported 37.5% CR and 25% PR; treatment was well tolerated and local toxicity easily controlled.

Third-choice therapy consists of radiation therapy, which was decided on by consensus of the Working Group and a last line of therapy prior to either regional or systemic treatments for patients with moderate ITM.

In patients presenting with maximal ITM (late presentation, large volume, multiple 2-3 cm nodules) confined to an extremity, ILI and ILP may be considered. While not widely utilized throughout Canada, ILI and ILP are typically utilized in patients with high burden, non-resectable ITM that is within a limb that can safely be isolated. This regional treatment for ITM allows tumours in extremities to be exposed to concentrations of chemotherapy up to 25 times higher than can be achieved with systemic administration, therefore avoiding systemic toxicity. Perfusion agents vary, but the majority of studies utilize melphalan as the primary chemotherapeutic drug. In recent years, addition of TNF-α to melphalan, as part of the hyperthermic ILP treatment to improve the durability and frequency of CRs, has been explored. ILP has better response rates but it is unclear if this translates into better survival. ILP also carries a higher toxicity, including rare side effects such as compartment syndrome and

amputation. In cases where regional therapies are being considered, careful patient selection should be completed by a multidisciplinary team.

Comparative studies with a controlled patient selection methodology will be needed to effectively compare the different treatments. Any future studies should incorporate high-quality trial-based design.

CONCLUSIONS

The management of patients with melanoma with satellite or ITM is an area where further research is warranted to evaluate the optimal treatment strategies for patients. Due to the complex nature of the disease and the various interventions available to clinicians, treatment should be dynamic and tailored based on the extent of the ITM. Further investigations should be trial-based study designs that control for confounders such a previous treatment and extent of ITM. Studies should focus on combinations of local therapies with or without the addition of systemic treatment or immunotherapy.

Locoregional Management of In-Transit Metastasis in Melanoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel, the PEBC RAP, as well as the Patient Consultation Group (Appendix A). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 12 members of the GDG Expert Panel, nine members voted and zero abstained, for a 75% response rate in August, 2019. Of those who voted, nine approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel

Comments	Responses
1. The dosing of the treatments listed is either not available in the document or very difficult to find. I suggest clarifying in a table or cite a reference so that for practical purposes the recommended dosing is clear.	The dosing of the treatments is now listed in Appendix 4.
2. I did not see (although I may have missed it) that we should indicate that staging of visceral sites of disease should occur for patients with new/progressing ITM as this would change the staging and treatment options.	The Working Group has added the following Qualifying Statement to Recommendations 1, 2 and 3, "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.

RAP Review and Approval

Three RAP members reviewed this document in July 2019. The RAP members conditionally approved the document in August 2019. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP

Comments	Responses
1. In Recommendation 2, the team has identified options that seem reasonable but are not currently available in Canada. So, can I confirm T-VEC is expected to get approval and that is why it is on the list compared with the ones listed in Qualifying Statement? I	Currently, there is no application to Health Canada regarding T-VEC.

would be more clear about that and to signal how one knows (or not) of its probable approval.	
2. I am unclear as to why BCG is recommended for second-line therapy when there is no evidence of effectiveness from the three – albeit poor quality - RCTs. I would take a second look and ensure the threshold of evidence being applied is consistent across the options that have been investigated.	Thank you for your comment. We have modified Recommendation 2 for BCG to the following, "There is insufficient evidence to recommend intralesional bacille Calmette-Guerin (BCG) outside of a research setting for second-line therapy."
3. I would be sure that within the recommendations you have a response to all the interventions that have been included in the systematic review, even if to say there are no recommendations for those interventions (e.g., amputation).	Thank you for pointing this out. The Working Group has ensured all interventions included in the systematic review are included within the recommendations. Recommendation 3 has been modified to include the following statement, "In selected cases, amputation could be considered as a final option if no systemic disease and discussed at a multidisciplinary case conference."

Patient and Caregiver-Specific Consultation Group

Five patients/survivors/caregivers participated as Consultation Group members for the Working Group. They reviewed the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the Working Group's Health Research Methodologist. The main comments from the Consultation Group are summarized in Table 5-3.

Table 5-3. Summary of the Working Group's responses to comments from the Consultation Group

Comments	Responses
1. Guideline was very complex with a lot of information. The recommendations are clearer when broken into the levels of in-transits. The qualifying statements and interpretation of the evidence helped clarify the recommendations.	Thank you for your comment.
2. There was weak evidence for most of the recommendations; however, the Working Group explained how they arrived at the recommendations in the interpretation section. The summary table was helpful.	Thank you for your comment.
3. The Working Group discussed morbidity and toxicity throughout and provided a good explanation of which treatments are and are not currently available in Canada. I wish	Thank you for your comment. The lack of discussion around quality of life is result of studies not routinely collecting and/or publishing quality of life data.

there was more of a discussion around quality of life.	
4. The recommendations do not have much flexibility in terms of patient preference but each case is recommended to be evaluated by a multidisciplinary team; you need to trust their clinical judgment/expertise and have confidence in the team assessing your case.	Thank you for your comment.

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Three targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. All three agreed to be the reviewers (Appendix 1). Results of the feedback survey are summarized in Table 5-4. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-5.

Table 5-4. Responses to nine items on the Targeted Peer Reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	2	1
2. Rate the guideline presentation.	0	0	1	1	1
3. Rate the guideline recommendations.	0	0	0	3	0
4. Rate the completeness of reporting.	0	0	1	1	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	0	0	3	0
6. Rate the overall quality of the guideline report.	0	0	0	3	0
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	0	0	1	1	1
8. I would recommend this guideline for use in practice.	0	0	0	2	1

9. What are the barriers or enablers to the implementation of this guideline report?	• It may be worthwhile adding a statement that complex cases such as these would benefit from consultation and co-management with centres of excellence. • It seems as if the authors are recommending ITM in any patient (minimal, moderate or high volume) be reviewed at a skin multidisciplinary case conference. I am unsure of the knowledge translation strategies in place to make sure that plastic surgeons, general surgeons, etc. are aware of this recommendation. • Practice variation by physicians (from simple excisions, morbid excisions with skin grafts/flaps, systemic therapy, etc.) is a real problem. Could this be remedied by knowledge translation strategies?

Table 5-5. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
1. Guideline Development • Cost of the various therapies and health economic assessment was not stated. • Key experts were included, except oncology pharmacists; their perspective on organizational impact may be interesting	PEBC guidelines do not analyze cost-effectiveness. Organization factors are not generally addressed in PEBC guidelines unless this is the specific topic requested.
2. Guideline Presentation • It may be useful to highlight that low/moderate/high volume disease is a clinical decision best made by experts in melanoma surgery. The category "moderate disease" is not well defined; it is noted that this means several ITMs but the thickness or thinness of the metastases is not mentioned. DCPC may be better for a broad field of thin lesions while IL-2 may be more appropriate for thicker lesions.	While categories are defined in the qualifying statements, a preamble has been added to the recommendations to make this clearer. The evidence review suggests the response rate for DPCP is low and therefore IL-2 or T-VEC are considered more appropriate even for thin lesions.
• Table 4-4 is extremely dense and very difficult to consult. Have you considered simplifying it and putting hyperlinks to more detailed info, so that those who really want can consult them? I would have preferred a smaller similar table for each therapeutic option, right before the discussion of each treatment modality, to avoid going back and forth.	There is a table for each treatment and we recognize that having the summary table before the others may be confusing. The summary table has been moved to a separate appendix.
• Would it be possible to have a flow diagram at the beginning for therapeutic	The authors considered these and decided the decision process is too complicated and

options? Hyperlinks could take the reader to the corresponding section (based on their specific interest). Users do not typically consult guidelines in linear fashion; rather they look for the specific clinical scenarios that interest them. • Please harmonize the ILP section. All other therapeutic modalities start directly with the studies. For ILP, you start with a brief description of the concept.	evidence too weak to make a flow diagram. A list of tables has been added that will allow the reader to go directly to a specific section of the literature review The description has been moved to the Discussion.
3. Guideline Recommendations • I have completed both ILP and ILI for patients with unresectable ITM without systemic metastases. Although the evidence provided is sound and indicates no preference for ILP versus ILI based on superiority of effectiveness/durability of response, the decision is generally clinical and is related to the need for nodal dissection. The qualifying statement for Recommendation 3 "For ILI, a nodal dissection is not completed unless gross nodal disease is present" is not in keeping with isolated limb therapy practice, at least at the large centre I worked at and across the United States. If gross nodal disease is present, ILP is selected as the procedure of choice (accepting the increased morbidity) as the response rates are higher (stated in Interpretation of Evidence for Recommendation 3). ILI is usually done for patients where a nodal dissection has already been completed at a previous procedure and the vessels cannot be isolated due to scarring. Catheter-based ILI is thus chosen, accepting the lower response rate but safer procedure in this setting. • CO_2 laser ablation: I do not feel comfortable seeing it as a recommendation as second-line therapy when there are little data. It has to be mentioned as an option, but not necessarily as a recommendation. • What are the recommendations for adjuvant topical therapies provided with IL-2 (Retin-A and imiquimod)? Should	We have considered the comment and modified the qualifying statement. We decline to provide further details of either procedure as this may vary among centres and is beyond the scope of the document. We have removed laser therapy as a second choice and indicated there is insufficient evidence for its use at this time. There are limited data to support use of Retin-A and imiquimod administered in

they be routinely added? Case by case? Higher volume cases or particular anatomic areas? • In recommendation 3, systemic therapy needs to be mentioned before consideration of amputation	conjunction with IL-2, and this has been added to the qualifying statements. System therapy was recommended, along with ILI and IPI; this may have been missed by the reader. We have revised the qualifying statements to indicate systemic therapy was not part of the literature review
4. Completeness • One of three DPCP studies with more than 20 patients was not included (Moncrieff, BJD 2016; describes response rates and survival in 35 prospective patients with ITM • The Canadian DPCP paper by Yeung (2017) with 15 patients is included, but not the Gibbons paper (An Bras Dermatol 2018) with 16 patients (35% CR, 25% PR). Given the very limited DPCP literature, might be worth mentioning the Gibbons paper (plus the Veverka 2018 Mayo Clinic report with n=13) as well as the three studies with more than 20 patients to give a more complete view of the DPCP literature. Given that we then have series from Canada, Australia, United Kingdom, United States, and Brazil it highlights that DPCP is now used in a range of centres. • The development process was very well documented. Its rigorousness despite the lack of clear-cut definitions and abundance of poor-quality studies is impressive.	This was a research letter [109] and thus did not meet the inclusion criteria; it has been added to the discussion. We have removed the paper by Yeung et al. from the results, and mention it in the discussion along with the studies by Moncrieff et al. [109] and Gibbons et al. [110] as additional studies of interest but not meeting the inclusion criteria. Veverka et al. [111] only reported on only nine patients, of which some had visceral or other metastases and is therefore not mentioned.
5. Is there sufficient information for decisions? • Some discussion should be had regarding systemic therapy and expected effect on ITM (in absence of distant metastatic disease). In the present guideline, it is only mentioned for unresectable, large volume disease. Does this recommendation change based on time from initial diagnosis to ITM presentation? Rapidity of lesions evolving? Patient characteristics? • In the patient case of low volume/isolated ITM, there is a statement that systemic therapy can be considered after surgical excision (in	We have added a qualifying statement to Recommendation 2 to indicate there is no evidence for or against use of systemic therapy following good response to local therapy.

Recommendation 1). Should this be the case for the moderate and high volume ITM as well (if IL-2 successful, etc.)? Even if ITM are managed the majority of these patients will relapse in a systemic fashion and if not receiving systemic therapy following treatment for their ITM, close surveillance should be mentioned (at a high-volume centre). • Some mention of the influence of the thickness/bulkiness of ITMs on treatment choice would make the Guidelines clearer • It allowed me to validate treatment decisions in my practice and question the relevance of maintaining a few treatment lines that have no relevance.	
Additional comments • Page 3 penultimate point: "Sentinel lymph node biopsy may be considered for patients with ITM by a multidisciplinary team"- this implies that sentinel lymph node biopsy might be done some time after initial melanoma treatment (i.e., some time after wide excision), at the time of in transit recurrence. Is this usual practice?	This is not usual practice, but may be appropriate in some cases. We have removed the reference to Guideline 8-2.
• Recommendation 2: Could clarify by adding: "In patients presenting with moderate, unresectable ITM, consider using the following approach for localized treatment, ***depending on the extent and thickness of ITMs***". Very thin, superficial lesions may be much better suited to topical treatment as first line, whereas thicker lesions may be better served by intralesional therapies. Alternatively, this could instead be included or clarified in the "Qualifying statements for recommendation 2" (i.e., "based on the number and thickness of lesions…")	Extent and thickness may influence the category minimal, moderate, or maximal (see added preamble as well), but within the moderate category we do not believe it is a separate factor. The evidence review suggests the response rate for DPCP is low and therefore IL-2 or T-VEC are considered more appropriate even for thin lesions.
• Page 8 "Interpretation of evidence for recommendation 3:" "ILP also carries a higher toxicity, including rare side effects such as compartment syndrome and amputation." This implies that ILI is not	The wording has been modified to indicate these may also occur in ILI though to a lesser extent

also sometimes associated with these side effects. • Page 73 Discussion: "In the case of patients with moderate ITM, second-line therapies to be considered are topical DPCP, intralesional BCG…" As no evidence for efficacy of BCG, this should be deleted. • Page 49, Table 4-16: Add Moncrieff et al; (0.000001% - 0.05% DPCP); add DPCP concentration range used in Damian et al. (0.00001 – 10%). • Rigorously developed methodological approach. • Thorough coverage of all treatment options for this disease. • Provides all key data to drive discussions with patients and treatment decisions. • To simplify reading and drive up use of the document, please consider formatting changes suggested above. • Do the guidelines also provide treatment specifics (e.g. administration protocols for IL2) or is that outside of their scope?	This has been revised As indicated above, Moncrieff et al. did not meet the inclusion criteria, but has been noted in the discussion. DPCP concentration in Damian et al. has been corrected. Treatment protocols were outside scope and the user may refer to the cited papers or the OH (CCO) website https://www.cancercareontario.ca/en/node/44511

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. Clinicians with an interest in melanoma, skin cancer, and surgical or medical oncology in the PEBC database were contacted by email to inform them of the survey. One hundred fifty professionals were contacted, all of which practice in Ontario. Eighteen (12.0%) responses were received. Thirteen stated that they did not have interest in this area or were unavailable to review this guideline at the time and one stated they were now retired. The results of the feedback survey from four people are summarized in Table 5-6. The main comments from the consultation and the Working Group's responses are summarized in Table 5-7.

Table 5-6. Responses to four items on the professional consultation survey.

	N=4 (2.7%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	3	1
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)

2. I would make use of this guideline in my professional decisions.	0	0	0	2	2
3. I would recommend this guideline for use in practice.	0	0	0	1	3
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers • Availability of IL-2 Enablers • Provides specific recommendations in an area where the quality of evidence is limited				

Table 5-7. Summary of the Working Group's responses to comments from professional consultants.

Comments	Responses
1. Is Recommendation 1 based on evidence (Table 4-4)? Consider reordering.	This is the first recommendation going in order from minimal to maximal disease, and not on strength of evidence.
2. Recommendation 2, page 4. For patients with moderate unresectable ITM, is the objective to improve survival or to palliate? It is unclear whether the expectation that surgical excision provides a possibility of cure, or only local control. This is worth stating.	For Recommendation 1 (surgery) the only paper (see Table 4-13) stated five-year disease-free survival of 12%, OS of 58%, and disease-free survival in the subgroup with curative intent of 22 months (4 to 104 months). For Recommendation 2 (moderate ITM), additional survival information has been added to Table 4-8 and Table 4-9. Treatment intent is curative, and this has been added to the preamble to the recommendations.
3. The recommendations are all based on expert opinion which is unusual for a guideline. It is worth stating in the Discussion, that there are limited data suggesting any treatment improves survival, and therefore, the recommendations were based on the best interpretation of response rates, balanced against toxicity	Recommendations are based on the limited data supplemented by expert opinion, and this is stated in the Interpretation of Evidence sections following each recommendation.
4. How is Table 4-4 organized? A reference to the relevant table for each intervention detailing the data is helpful.	This is a table and has been moved to Appendix 4. It summarizes the information in Tables 4-4 to 4-20. A list of tables has been added to help navigation in the document.
5. For the local therapies, I would have found it easier to follow if the table is presented according to the order the evidence is presented in the recommendations, i.e. on the different lines of	See above. Recommendations are in order of disease severity, while within a recommendation

therapy you are proposing. It is a little difficult to follow the evidence tables as it is laid out currently. For example, the first local therapy discussed is Allovectin-7, but it is neither recommended nor available in Ontario.	treatments are grouped according to evidence of benefit.
6. When providing recommendations for first-, second-, and third-line therapies, from a methodological point of view, you would expect the evidence to be based on studies conducted as in the patients as the respective lines. This is not the case here. If I understand correctly, this is presented based on the relative strength of the evidence and expert opinions. This should be stated in the methods.	The terminology used was unclear, and these do not refer to lines of therapy, but degree of benefit. The recommendation has been reworded so that "line" is replaced with "choice".
7. Radiation therapy was stated as third-line therapy in the interpretation of the evidence. For consistency, the evidence should be listed under its own bullet on page 5, and has its own subheading of third-line therapy.	This has been done.
8. Table 4-11, intralesional IFN-α, one primary study: for consistency study design should be provided in column 2.	It is indicated as a prospective study
9. The description of only the median total dose and number of treatment days for radiation treatment reduces the value of the description of this modality. More detailed information may not be available in the source document (preamble to Table 4-12, citing Seegenschmidt who is well known for describing radiation parameters in this way))	Some additional details have been added to the table.
10. The recommendations are primarily based on expert opinion given the quality of evidence available which is unusual for an evidence -based guideline. The recommendations for first-, second-, and third-line therapies are again based on expert opinion rather than evidence of the intervention being evaluated as for first-, second-, and third-line therapies. I suggest that a more explicit statement in the discussion section of the palliative nature of the intervention, the methodological considerations in formulating first-, second-, and third- line recommendations would help the reader to follow the methods in handling the evidence to arrive at the recommendations.	See 6 above and preamble added to recommendations.
11. Overall, a complex document, but efforts have clearly been made to organize logically. The biggest short-coming I found was the failure to elaborate on what constitutes "minimal" (p3), "moderate" (p4), and "maximal" ITM (p5 - does have some detail).	A preamble has been added to the recommendations, to supplement the definitions in the qualifying statements.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table A1-1. Members of the In-Transit Metastasis Management Working Group

Name	Affiliation	Declarations of interest
Frances C. Wright Working Group Chair Surgeon	Professor of Surgery, University of Toronto Temerty Chair of Breast and Melanoma Surgery, Louise Temerty Breast Cancer Centre, Sunnybrook Health Sciences Centre Program Director of General Surgery Oncology Fellowship, University of Toronto Quality and Knowledge Transfer Lead, OH (CCO) Skin Cancer Lead, OH (CCO)	Principal investigator for trial on IL-2 and in-transit metastasis outcomes. Included study: Yeung C, Petrella TM, Wright FC, Abadir W, Look Hong NJ. Topical immunotherapy with diphencyprone (DPCP) for in-transit and unresectable cutaneous melanoma lesions: an inaugural Canadian series. Expert Rev Clin Immunol. 2017;13(4):383-8. Unrestricted research grant from Roche PCODR application for IL-2 that was approved
Alex Sun Radiation Oncologist	Princess Margret Hospital Toronto, Ontario	No conflicts declared
Tim Hanna Radiation Oncologist	Cancer Research Institute at Queens University Kingston, Ontario	No conflicts declared
Carolyn Nessim Surgical Oncologist	The Ottawa Hospital Ottawa, Ontario	No conflicts declared
Nicole J. Look Hong Scientist	Sunnybrook Health Sciences Centre Toronto, Ontario	Published case series (NOT randomized trial): Yeung C, Petrella T, Wright F, Abadir W, Look Hong N. Topical Immunotherapy with Diphencyprone (DPCP) for In-Transit and Other Melanoma Cutaneous Lesions: An Inaugural Canadian Series. Expert Review of Clinical Immunology. 2017. 13(4):383-388. Published article: DPCP an option for treating melanoma lesions in Canadian patients. John Evans, Associate Editor. The

		Chronicle of Skin & Allergy. Online. December 2017.
Carman A. Giacomantonio Surgeon	Dalhousie University, Department of General Surgery Halifax, Nova Scotia	No conflicts declared
Claire F. Temple-Oberle Surgeon	Professor of Oncology Surgery University of Calgary Calgary, Alberta	Unrestricted educational grants from two breast implant companies (Allergan, $10K; Acelity, $5K annually ×3 years) for breast reconstruction awareness day Invited article: Temple-Oberle et al. Intra-lesional IL-2 therapy for in-transit melanoma. J Surg Oncol 2014 109 (4): 327-334
Xinni Song Medical Oncologist	Integrated Cancer Program The Ottawa Hospital Ottawa, Ontario	Consulting (BMS, Merck, Amgen, Novartis Advisory Boards) PI for trials funded by BMS and MERCK study
Teresa M. Petrella Medical Oncologist	Odette Regional Cancer Centre Toronto, ON	Grants from Roche, Merck, Novartis, BMS
Sarah Kellett Health Research Methodologist	Program in Evidence-Based Care Hamilton, Ontario	No conflicts declared

Table A1-2. COI declarations for the Expert Panel

Name	Affiliation	Conflict of Interest
Annette Cyr, Patient Representative	Melanoma Network of Canada Toronto, ON	No conflicts declared
Tara Baetz, Medical Oncologist	Cancer Centre of Southeastern Ontario Kingston, ON	$500 or more in a single year to act in a consulting capacity (BMS, Roche, Merck, Novartis Advisory Boards) PI for clinical trials involving Combi-D and Master Key
Gregory Knight, Medical Oncologist	Grand River Regional Cancer Centre Kitchener, ON	$500 or more in a single year to act in a consulting capacity (BMS, Amgen, Novartis Advisory Boards)

Name	Affiliation	Conflict of Interest
Caroline Hamm, Medical Oncologist	Windsor Regional Cancer Centre (WRH) Windsor, ON	No conflicts declared
Pablo Cano, Medical Oncologist	Sudbury Regional Hospital Sudbury, ON	No conflicts declared
Sudha Rajgopal, Medical Oncologist	Trillium Health Partners - Credit Valley Hospital Site Toronto, ON	No conflicts declared
Danny Ghazarian, Pathologist	Toronto General Hospital Toronto, ON	No conflicts declared
Alexandra Easson, Surgical Oncologist	Princess Margaret Hospital Toronto, ON	No conflicts declared
Elaine McWhirter, Medical Oncologist	Juravinski Cancer Centre Hamilton, ON	$500 or more in a single year to act in a consulting capacity (BMS, Roche, Merck, Novartis Advisory Boards)
Christian Murray, Dermatologist	Skin Surgery Centre, University of Toronto Toronto, ON	$500 or more in a single year to act in a consulting capacity (Advisory Board)
David McCready, Surgical Oncologist	Princess Margaret Hospital Toronto, ON	No conflicts declared
Jadranka Jambrosic, Dermatologist/Pathologist	Etobicoke, ON	No conflicts declared

Table A1-3. COI Declarations for the Report Approval Panel

Name	Affiliation	Declarations of interest
Laurie Elit	Associate Professor, McMaster University Department of Oncology Professor, McMaster University Department of Obstetrics and Gynecology. Hamilton ON	No conflicts declared
Jonathan Sussman	Director, Program in Evidence-Based Care, Hamilton ON	No conflicts declared
Melissa Brouwers	Director of the School of Epidemiology and Public Health, University of Ottawa. Ottawa ON	No conflicts declared

Table A1-4. COI Declarations for the Patient Consultation Panel

Name	Declarations of interest
Ms. Laurel Warr	No conflicts declared
Ms. Lise Craig	No conflicts declared
Mr. Bob Tuck	No conflicts declared
Ms. Patricia Sevean	No conflicts declared

Ms. Marissa Myers	No conflicts declared

Table A1-5. COI Declarations for the Targeted Peer Reviewers

Name	Affiliation	Declarations of interest
Diona Damian		No conflicts declared
Valerie Francescutti		Provides treatment for in-transit melanoma but guideline is unlikely to result in a substantial change in income
Ari Meguerditchian		No conflicts declared

Appendix 2: Literature Search Strategy

Systematic Review Literature Search Strategies

MEDLINE – Systematic Reviews

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy Run: Dec 1 2018

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1 exp melanoma/

2 melanoma$.mp.

3 (maligna$ adj5 melanoma$).mp.

4 or/1-3

5 "in-transit".mp.

6 (in adj transit).mp.

7 (transit adj metastas$).mp.

8 (local recurrence or locoregional recurrence or locoregional metas$ or locoregional spread).mp.

9 (satellite adj metas$).mp.

10 metastasis/ or lymphatic metastasis/

11 or/5-10

12 (limb adj infusion).mp.

13 (limb adj perfusion).mp.

14 (TVEC or " T-VEC" or (talimogene adj laherpareovec)).mp.

15 exp radiotherapy/

16 (BCG or bovis or bacille calmette-guerin or bacille calmette guerin).mp.

17 (DPCP or diphencyprone).mp.

18 (tumo?r necrosis factor or TNF or Rosenberg).mp.

19 (PV-10 or (Rose adj Bengal)).mp.

20 surgery/

21 (imiquimod or aldara).mp.

22 electrochemo$.mp.

23 laser therapy/

24 (PDL or pulsed dye laser).mp

25 (DNCB or dinitrochlorobenzene).mp.

26 (systemic adj3 (therapy$ or treatment$)).mp.

27 immunotherapy/

28 (PDL or PD-1 or PD-L1 or programmed cell death).mp.

29 (interleukin-2 or IL-2).mp.

30 (interferon$).mp.

31 or/12-30

32 4 and 11 and 31

33 exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.

34 32 and 33

35 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.

36 34 not 35

37 animal/ not (exp human/ or humans/)

38 36 not 37

39 limit 38 to english

40 limit 39 to yr="1980-2018"

****

EMBASE – Systematic Reviews

Database: Embase

Search Strategy Run: Dec 1 2018

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1 exp melanoma/

2 melanoma$.mp.

3 (maligna$ adj5 melanoma$).mp.

4 or/1-3

5 "in-transit".mp.

6 (in adj transit).mp.

7 (transit adj metastas$).mp.

8 metastasis/ or lymphatic metastasis/

9 or/5-8

10 (limb adj infusion).mp.

11 (limb adj perfusion).mp.

12 (TVEC or " T-VEC" or (talimogene adj laherpareovec)).mp.

13 exp radiotherapy/

14 (BCG or bovis or bacille calmette-guerin or bacille calmette guerin).mp.

15 (DPCP or diphencyprone).mp.

16 (tumo?r necrosis factor or TNF or Rosenberg).mp.

17 (PV-10 or (Rose adj Bengal)).mp.

18 surgery/

19 (imiquimod or aldara).mp.

20 electrochemo$.mp.

21 laser therapy/

22 (PDL or pulsed dye laser).mp

23 (DNCB or dinitrochlorobenzene).mp.

24 (systemic adj3 (therapy$ or treatment$)).mp.

25 immunotherapy/

26 (PDL or PD-1 or PD-L1 or programmed cell death).mp.

27 (interleukin-2 or IL-2).mp.

28 (interferon$).mp.

29 or/10-28

30 4 and 9 and 29

31 exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or

metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.

32 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.

33 or/28-33

34 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic: quality).ab.

35 (stud: adj1 select:).ab.

36 (35 or 36) and review.pt.

37 33 or 37

38 30 and 37

39 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.

40 38 not 39

41 animal/ not (exp human/ or humans/)

42 40 not 39

43 limit 42 to english

44 limit 43 to yr="1980-2018"

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Cochrane Library
Search Strategy Run: Dec 1 2018

(melanoma and ("in-transit metastas$ or "satellite metas$ or local recurrence or locoregional recurrence or locoregional metas$ or locoregional spread)).ti.ab. (36)

Primary Literature Search Strategies

MEDLINE: Primary Literature

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy Run: Jan 1 2019

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41 exp melanoma/

42 melanoma$.mp.

43 (maligna$ adj5 melanoma$).mp.

44 or/1-3

45 "in-transit".mp.

46 (in adj transit).mp.

47 (transit adj metastas$).mp.

48 (local recurrence or locoregional recurrence or locoregional metas$ or locoregional spread).mp.

49 (satellite adj metas$).mp.

50 metastasis/ or lymphatic metastasis/

51 or/5-10

52 (limb adj infusion).mp.

53 (limb adj perfusion).mp.

54 (TVEC or " T-VEC" or (talimogene adj laherpareovec)).mp.

55 exp radiotherapy/

56 (BCG or bovis or bacille calmette-guerin or bacille calmette guerin).mp.

57 (DPCP or diphencyprone).mp.

58 (tumo?r necrosis factor or TNF or Rosenberg).mp.

59 (PV-10 or (Rose adj Bengal)).mp.

60 surgery/

61 (imiquimod or aldara).mp.

62 electrochemo$.mp.

63 laser therapy/

64 (PDL or pulsed dye laser).mp

65 (DNCB or dinitrochlorobenzene).mp.

66 (systemic adj3 (therapy$ or treatment$)).mp.

67 immunotherapy/

68 (PDL or PD-1 or PD-L1 or programmed cell death).mp.

69 (interleukin-2 or IL-2).mp.

70 (interferon$).mp.

71 or/12-30

72 4 and 11 and 31

73 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.

74 32 not 33

75 exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.

76 34 not 35

77 animal/ not (exp human/ or humans/)

78 36 not 37

79 limit 38 to english

80 limit 39 to yr="1980-2019"

****

EMBASE – Primary Literature

Database: Embase

Search Strategy Run: Jan 1 2019

---

1 exp melanoma/

2 melanoma$.mp.

3 (maligna$ adj5 melanoma$).mp.

4 or/1-3

5 "in-transit".mp.

6 (in adj transit).mp.

7 (transit adj metastas$).mp.

8 (local recurrence or locoregional recurrence or locoregional metas$ or locoregional spread).mp.

9 (satellite adj metas$).mp.

10 metastasis/ or lymphatic metastasis/

11 or/5-10

12 (limb adj infusion).mp.

13 (limb adj perfusion).mp.

14 (TVEC or " T-VEC" or (talimogene adj laherpareovec)).mp.

15 exp radiotherapy/

16 (BCG or bovis or bacille calmette-guerin or bacille calmette guerin).mp.

17 (DPCP or diphencyprone).mp.

18 (tumo?r necrosis factor or TNF or Rosenberg).mp.

19 (PV-10 or (Rose adj Bengal)).mp.

20 surgery/

21 (imiquimod or aldara).mp.

22 electrochemo$.mp.

23 laser therapy/

24 (PDL or pulsed dye laser).mp

25 (DNCB or dinitrochlorobenzene).mp.

26 (systemic adj3 (therapy$ or treatment$)).mp.

27 immunotherapy/

28 (PDL or PD-1 or PD-L1 or programmed cell death).mp.

29 (interleukin-2 or IL-2).mp.

30 (interferon$).mp.

31 or/12-30

32 4 and 11 and 31

33 (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/

34 32 not 33

35 exp meta analysis/ or exp "meta analysis (topic)"/ or exp meta-analysis as topic/ or exp "systematic review"/ or exp "systematic review (topic)"/ or ((exp "review"/ or exp "review literature as topic"/ or review.pt.) and ((systematic or selection criteria or data extraction or quality assessment or jaded scale or methodologic$ quality or study) adj selection).tw.) or meta-analysis.mp. or (meta-analy: or metaanaly: or meta analy:).tw. or (systematic review or systematic overview).mp. or ((cochrane or medline or embase or cancerlit or hand search$ or hand-search$ or manual search$ or reference list$ or bibliograph$ or relevant journal$ or pooled analys$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes?s or quantitative overview$ or systematic) adj2 (review$ or overview$)).tw.

36 34 not 35

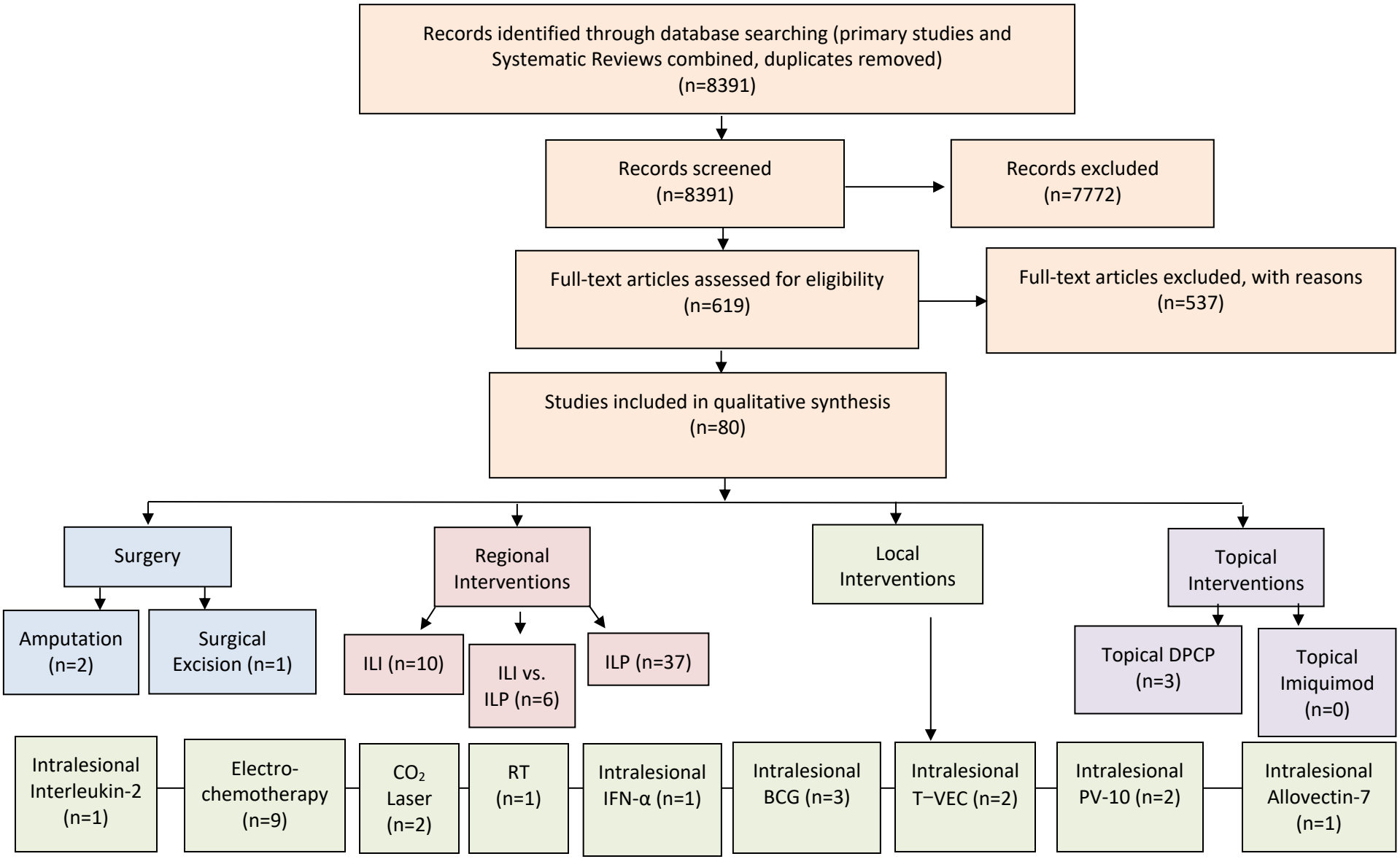
37 animal/ not (exp human/ or humans/)

38 36 not 37

39 limit 38 to english

40 limit 30 to yr="1980-2019"

Appendix 3: Systematic Literature Review Flow Diagram



Appendix 4: Summary of Intervention Results

Table A4-1. Summary of results by intervention

Intervention	Studies	Dosing of treatments	Subtype of patients with ITM	Survival	Response rate	Toxicity
Local Therapy						
Allovectin-7	1 RCT [53]	Bedikian et al. [80] - The first 9 patients were enrolled in a standard dose escalation scheme using three cohorts in which 3 patients in each cohort received an injection of one of the following doses: 0.5, 1.0, or 2 mg of Allovectin-7, once a week for 6 consecutive weeks	Patients who were unresponsive to standard therapy or who refused alternative therapy, and where surgery was not considered a curative option	In 15 responders the median duration of response was 13.8 months	Response=15 patients (11.8%) Non response: 112 (89.2) # of injectable lesions: 1: 14 responders; 58 non-responders >1: 1 responder; 54 responders p=0.0019 (only sig subgroup difference in analysis)	Grade 1: 195 Grade 2: 71 Grade 3: 15 Grade 4: 15 Grade 5: 2
Intralesional BCG	3 RCTs [18-20]	Brocker et al. [18] – No dosing information provided Paterson et al. [19] - Single intradermal 40 mg BCG injection, 40 mg oral BCG 5 days/month for one year, 40 mg intradermal injection again one year after initial injection, then 40 mg oral BCG for one more year Sterchi et al. [20] - DTIC: 300 mg/m^2 daily for 5 days every 35 days over a 2-year period DTIC + BCG: 300 mg/m^2 daily for 5 days every 35 days over a 2-year period + 100 pg intradermally at each of four sites adjacent to different groups of lymph nodes every 35 days for 1 year	No detail on the subtype of patients with ITM	No significant differences between BCG and clinical observation groups	*Number of relapses* Range BCG Arms: 21.4% to 31.5% Control Arms: 30.1% to 36.8%	NS
CO_2 Laser ablation	2 primary studies [21,22]	Van Jarwaarde et al. [22] - CO_2 laser was used with a wavelength of 10.6 mm, infrared and continuous power in the range of 7 to 10 Watts Hill et al. [21]– 10-20W of continuous wave laser power	lesions <5 mm in diameter were included [22] <1.5 cm in diameter were included [21]	OS @ 12 months range: 65% to 67%[21,22]	NS	NS
Electrochemotherapy	9 primary studies [54-62]	Campana et al, Caraco et al, Kunte et al, Marty et al, Mathiesson et al, Mir Bonafe et al, Ricotti et al, Solari et al. [54-62] - All treatments were performed using the Cliniporator™ device with with bleomycin intravenously administered 15,000 units/m^2.	Most studies were not specific in the sub-type of patients with ITM included Marty et al: measurable	2 year LPFS: 87% [54]	Range from Included Studies with data [55-62] CR: 10% to 73.7% PR: 11.1% to 45% PD: 4.7% to 30%	No grade III or IV SAEs were observed in the 2 studies [57,62] that evaluated adverse events

Intervention	Studies	Dosing of treatments	Subtype of patients with ITM	Survival	Response rate	Toxicity
			cutaneous or subcutaneous tumour nodules suitable for application of electric pulses but not bigger than 3 cm in diameter		Matthiessen et al, 2011: <u>Cutaneous metastasis <3cms</u> CR: 68% PR: 18% <u>Cutaneous metastasis >3cms</u> CR: 8% PR: 23%	
IL-IFN alpha	1 primary study [63]	Von Wussow et al. [63] - IFN-α preparation was injected intralesionally or perilesionally three times a week at a dose of 6 Mio. IU. In addition, 25 evaluable patients received rIFN-α2b, administered intralesionally at a dose of 10 Mio. IU three times a week.	Intralesional IFN-α was administered to patients who had undergone 1 or more previous treatments	NS	CR: 31% PR: 14% PD: 4%	NS
T-VEC	1 RCT; 1 follow-up of RCT [10,11]	Andtbacka et al. [11] - T-VEC was administered at 106 pfu/mL. Subsequent T-VEC doses of108 pfu/mL were administered 3 weeks after the first dose and then once every 2 weeks. Total T-VEC volume was up to 4.0 mL per treatment session. Injected volume per lesion ranged from 0.1 mL for lesions 0.5 cm to 4.0 mL for lesions 5 cm in longest diameter.	Unresectable ITM	Median OS: 23.3 months	CR: 10.8% PR: 15.6%	NS
Intralesional Interleukin-2 therapy	1 systematic review [8] 1 primary study [9]	Hassan et al. [9] - The maximum dose was B20 million IU per cycle. All in-transit lesions were injected intralesionally for one cycle every 2 weeks.	No detail on the subtype of ITM patients	NS	Byers, 2014(pooled): <u>Response rates by lesions:</u> mean CR: 78% mean PR: 2.5% PD: 19.6% <u>Response rates by patients:</u> CR 49.6% pCR: 10/31 (32%) [9]	Byers 2014: 2 grade III SAE
Intralesional PV-10	1 primary study [65]	Thompson et al. [65] - A single intralesional injection of PV-10 to uniformly infiltrate each lesion using 0.5 mL PV-10 per cm^3 of lesion volume.	Patients had to have at least 1 cutaneous or subcutaneous lesion >0.2cm in diameter	Mean OS @ 12 months: 89% (median not reaches @ 12 months)	CR: 26% PR: 25%	NS
Radiation Therapy	1 primary study [17]	Seegenschmiedt et al. [17] - External beam radiation therapy was applied using linac 6–10 MV photons or 4–18 MeV electrons.	No detail on the subtype of ITM patients; data for UICC stage III includes patients	OS in UICC III patients: median 22 months, 1-y	UICC III: 44% CR and 33% PR	NS

Intervention	Studies	Dosing of treatments	Subtype of patients with ITM	Survival	Response rate	Toxicity
			with either ITM or lymph node metastases	74±12%, 5-y 32±14%		
Surgical Excision	1 primary study [7]	Not applicable	The number of tumours in the recurring patients ranged from 1-6 and the median was 1.7.	Total Survival: 58% Median OS: 31 months (range 5-264)	NS	NS
Amputation	2 primary studies [66,67]	Not applicable	Most common reason for amputation was resistance to regional therapy, pain management and progression of ITM	5-year survival (range, months): 20-22.8	NS	NS
DPCP (Topical)	3 primary studies [15,16,68]	Damian et al. [16] – 0.01% to 0.1% DPCP, applied unoccluded for 24 hr. The concentration and duration were titrated over the course of subsequent applications to elicit moderate but tolerable contact dermatitis and was then reapplied once weekly for 2–24 hr Read et al. [15] - 0.005% DPCP applied topically to target lesions with a surrounding 1 cm margin. Eventually, concentrations between 0.005% and 1% were used once to twice per week for up to 24–48 h of total duration.	Patients with unresectable ITM	Survival data from Read et al. only Median OS: 20.9 12 month: 76.2% 24 month: 67.2% 36 month: 51.3%	Range [15,16,68] CR: 13% - 46% PR:27% - 38% PD: 18% - 20% pCR: 3/4 biopsies on 2 patients indicating a CR showed a pCR [68]	Tolerable treatment related adverse events without a significant reduction in QoL [68]
Regional Therapy						
ILI	1 systematic review [23] 10 primary studies [24-33]	Li et al. [25], Chin-Lenn et al. [28], Kroon et al. [29] - Melphalan (7.5 mg/L) plus dactinomycin (75 µg/L) Muilenberg et al. [32], Wong et al. [33] - Actinomycin-D (100 µg/L) and melphalan (7.5 mg/L for LE and 10 mg/L for UE) McClaine et al. [31] - Melphalan (7.5 mg/L for LE and 10 mg/L for UE) and actinomycin D (50 µg/L). Lindner et al. [30] - Melphalan (5–10 mg/L of tissue, with a lower limit of 20 mg and an upper limit of 100 mg) and actinomycin D (50–100 mg/L of tissue, with a lower limit of 200 µg and an upper limit of 500 µg) Beasley et al. [27] - starting dose of TMZ was 200 mg/m^2 × 0.09 body surface area (BSA) for the UE and 200 mg/m^2 x 0.18 BSA for the LE	Patients with unresectable ITM	All studies [25,29,32] (n=3): Median OS (range): 30.9 months – 41 months By Age [24,29]: <75: 41 months >75: 34 months	Systematic review [23] CR: 33% (range 26% to 44%) PR: 40% (range 33-56%) PD: 13% (range 0-29%). Range from Included studies with data:[23-31,33] CR: 10.5% to 41% PR: 5.3% to 47% PD: 0% to 68%	Varied between studies. Age was a significant factor for more serious adverse events [24,29]

Intervention	Studies	Dosing of treatments	Subtype of patients with ITM	Survival	Response rate	Toxicity
		Beasley et al. [26] - Melphalan (10 mg/L for the UE and 7.5 mg/L for the LE) and dactinomycin (100 µg/L for the UE and 75-100 µg/L for the LE) Kroon et al. [24] – dosing details not provided				
ILP	2 RCTs evaluating ILP with or without TNF-a [34,35] 1 RCT evaluating ILP as adjuvant treatment to excision [36] 34 primary studies [69-101]	Alexander et al. [69] - Melphalan dose of 10 mg/L for LE and 13 mg/L for UE. Thirty-seven patients received 0.2mg of IFN-α, 4 mg of TNFα, and melphalan. Six patients received 6mg of TNFα in addition to melphalan. Aloia et al. [70], Grun hagen et al. [79] – Melphalan dose of 10 mg/L for LE and 13 mg/L for UE. Bagge et al. [71] - 10 mBq was injected into the systemic circulation and 100 mBq into the perfusion system at a dose of 13 mg/L for UE or 10 mg/L for LE. Two patients TNFα injected as a 1-mg bolus dose 30 min before the melphalan infusion. Boesch et al. [72] - Melphalan (1.3 mg/kg body weight for LE and 0.7 mg/kg body weight for the UE) and dactinomycin (1 mg bolus for the LE and 0.5mg bolus for the UE). Cornett et al. [34] – Melphalan dose of 10 mg/L for LE and 13 mg/L for UE. Melphalan-alone arm - 25-minute sham-period of heated perfusion before melphalan perfusion to simulate the period of TNFα perfusion. Melphalan-plus-TNFα arm - 4 mg TNFα dose for femoral artery infusion and a 3 mg dose for popliteal, brachial, or axillary artery infusion. Deroose et al. [75] - Recombinant TNFα (1–3 mg bolus for UE or 1–4 mg bolus for LE) followed by melphalan dose of 10 mg/L for LE and 13 mg/L for UE Deroose et al. [73] – High dose: TNF (3–4 mg for LE and 3 mg for UE) and melphalan (10 mg/L for LE and 13 mg/L for UE). Low dose - TNFα (2mg for LE perfusion and 1 mg for UE). Deroose et al. [74] - ILP was performed as described by Eggermont et al. No further dosing information available.		Survival varied widely between studies. Results could not be combined due to variability in patient selection. Please see Table 4-17 for individual study results.	Response varied widely between studies. Results could not be combined due to variability in patient selection. Please see Table 4-17 for individual study results.	Toxicity varied widely between studies. Results could not be combined due to variability in patient selection. Please see Table 4-17 for individual study results.

Intervention	Studies	Dosing of treatments	Subtype of patients with ITM	Survival	Response rate	Toxicity
		Di Filippo et al. [76,77] - TNFα was injected when tumour temperature reached 41-41.5C, followed by melphalan (10 mg/L for LE and 13 mg/L for UE). Fraker et al. [78] - IFN (0.2mg), TNFα (4mg for LE and 3mg for UE) were administered sequentially and melphalan (10 mg/L for LE and 13 mg/L for UE). Hayes et al. [80] - Melphalan (0.5 mg/kg body weight for UE and 1.0 mg/kg body weight for LE) and TNFα (1 mg for UE and 2 mg for LE). Hoekstra et al. [81] - Melphalan (10 mg/L for LE and 13 mg/L for UE) and TNFα (1–2mg for LE and 1mg for the UE). Knorr et al. [82] - Melphalan (0.6-0.8 mg/kg body weight for UE and 1.2-1.4 mg/kg body weight for LE) and dactinomycin (1 mg for LE and 0.5 mg for UE). Lienard et al. [35] – IFN treatment arm: IFN (0.2mg) with TNFα (4mg for LE and 3mg for UE) and melphalan (10 mg/L for LE and 13 mg/L for UE). Other treatment arm: TNFα (4mg for LE and 3mg for UE) and melphalan (10 mg/L for LE and 13 mg/L for UE). Madu et al. [83] - Melphalan (10 mg /L) and TNFα (1 mg for the UE and 2 mg for the LE). Noorda et al. [84-86] – Melphalan (10 mg/L for LE and 13 mg/L for UE) and TNFα (4mg for the LE and 3mg for the UE). Eleven patients also received a daily injection of 0.2mg of IFN-γ for 2 days prior to surgery [86]. Seven patients also received a daily injection of 0.2mg of IFN for 2 days prior to repeat ILP [85]. Olofsson et al. [36,87] - Melphalan (0.45 mg/kg body weight for UE and 0.9 mg/kg body weight for LE). Half of the dose was administered initially, and the remaining half after 60 min of perfusion. Paulsen et al. [88] - Dosing of melphalan was 1 mg/kg body weight (until January 2002), and from 2002 as 10 mg/L perfusate. Melphalan alone was used in patients with multiple melanoma metastases, but administered in combination with TNFα (3 mg for UE or 4 mg LE) in re-perfusions and to patients with bulky tumours.				

Intervention	Studies	Dosing of treatments	Subtype of patients with ITM	Survival	Response rate	Toxicity
		Da Ponte et al. [96] – Melphalan only: 10mg/L for LE and 13mg/L UE. Melphalan plus TNFα: 10mg/L for LE and 13mg/L UE with 1 or 2mg of TNFα. Reintgen et al. [89] - Melphalan (1.2 mg/kg for LE lesions and 0.8 mg/kg for UE Rossi et al. [90] - 1 mg of TNFα and 10mg/L of melphalan were bolus-injected Rossi et al. [91] – dosing information not provided Smith et al. 2015, 2018 [92,93] - Melphalan (1mg/kg for LE and 0.4 mg/kg for UE) and TNFα (2 mg for LE and 1 mg for UE). Thompson et al. [101] - ILP was performed as described previously by Thompson et al. Vaglini et al. [94] – TNFα (2-4mg) and IFN-y (1.5x106 U), followed by melphalan (10mg/L) Second series: Escalating dosage of TNFα (starting at 1.5 or 1.0 or 0.5mg), and melphalan (10mg/L) Vrouenraets et al. [95] –For ILP,10 mg Melphalan 10mg/L for LE and and 13 mg/L for UE. TNF (4mg) was included in the perfusatefor iliac and femoral ILPs and 3 mg for axillary and brachial ILPs. IFN (0.2mg) was also administered during ILP.				

ILI vs. ILP	6 primary studies [38-43]	Not applicable	Patients with unresectable ITM	5-year OS [40]:
				ILI: 18%
				ILP: 31%
				
				OS [43]:
				ILI: 54%
				ILP:77%
					Range from studies with reported data: [38-43]
					ILI
					CR (range): 17% to 30%
					
					ILP
					CR (range): 44% to 60%
						Toxicity [40]
						ILP:
						grade 1=9;
						grade II=62;
						grade III=26;
						grade IV=3;
						grade V=0
						ILI:
						grade I=14;
						grade II=67;
						grade III=16;
						grade IV=1;
						grade V=0
						
						Limb loss greater in ILP (Raymond et al)

Abbreviations: BCG, bacille Calmette-Guerin; CR, complete response; DPCP, diphenylcyclopropenone; DTIC, dacarbazine; IL, intralesional; ILI, Isolated limb infusion; ILP, isolated limb perfusion; ITM, in-transit metastasis; LE, lower extremity; LPFS, local progression-free survival; NS, not stated or not evaluated; OS, overall survival; pCR, pathologic complete response; PD, progressive disease; PR, partial response; QoL, quality of life; RCT, randomized controlled trial; SAE, serious adverse event; TNF, tumour necrosis factor; T-VEC, talimogene laherparepvec; UE, upper extremity