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Guidelines

# An Ontario Health (Cancer Care Ontario) Clinical Practice Guideline: Surveillance Strategies in Patients with Stage I, II, III or Resectable IV Melanoma Who Were Treated with Curative Intent

S. Rajagopal [*], X. Yao [†‡], W. Abadir [§], T.D. Baetz [¶], A.M. Easson [||], G. Knight [**], E. McWhirter [††], C. Nessim [‡‡], C.F. Rosen [§§], A. Sun [¶¶], F.C. Wright [||||], T.M. Petrella [***]

[*] *Trillium Health Partners, Credit Valley Hospital, Peel Regional Cancer Centre, Mississauga, Ontario, Canada*
[†] *Department of Oncology, Department of Health Research Methods Evidence and Impact, McMaster University, Hamilton, Ontario, Canada*
[‡] *Program in Evidence-Based Care, Ontario Health (Cancer Care Ontario), Hamilton, Ontario, Canada*
[§] *Odette Cancer Centre, Sunnybrook Health Sciences Centre, Ontario, Canada*
[¶] *Cancer Centre of Southeastern Ontario, Queen's Cancer Research Institute, Kingston, Ontario, Canada*
[||] *Department of Surgery, Marvelle Koffler Breast Centre, Mount Sinai Hospital, Toronto, Ontario, Canada*
[**] *Department of Oncology, Grand River Regional Cancer Centre, Grand River Hospital, Kitchener, Ontario, Canada*
[††] *Department of Medical Oncology, Juravinski Cancer Centre, Hamilton Health Sciences, Hamilton, Ontario, Canada*
[‡‡] *Department of Surgery, University of Ottawa, The Ottawa Hospital, Ottawa, Ontario, Canada*
[§§] *Division of Dermatology, Toronto Western Hospital, University Health Network, University of Toronto, Toronto, Ontario, Canada*
[¶¶] *Department of Radiation Oncology, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada*
[||||] *Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada*
[***] *Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada*

## Abstract

*Aims:* To make recommendations on managing the surveillance of patients with stage I, II, III or resectable IV melanoma who are clinically free of disease following treatment with curative intent.

*Materials and methods:* This guideline was developed by Ontario Health's (Cancer Care Ontario's) Program in Evidence-Based Care and the Melanoma Disease Site Group (including seven medical oncologists, four surgical oncologists, three dermatologists, one radiation oncologist and one patient representative). The MEDLINE, EMBASE, Cochrane Library, PROSPERO databases and the main relevant guideline websites were searched. Internal and external reviews were conducted, with final approval by the Program in Evidence-Based Care and the Melanoma Disease Site Group. The Grading of Recommendations, Assessment, Development and Evaluation approach was followed, and the Modified Delphi method was used.

*Results:* Based on the current evidence (eight eligible original study papers and four relevant guidelines) and the clinical opinions of the authors of this guideline, the initial recommendations were made. To reach 75% agreement for each recommendation, the Melanoma Disease Site Group (16 members) voted twice and one recommendation was voted on three times. After a comprehensive internal and external review process (including national and international reviewers), 12 recommendations, three weak recommendations and six qualified statements were ultimately made.

Authors for correspondence: X. Yao, Program in Evidence-Based Care, Cancer Care Ontario, Department of Oncology, McMaster University, Juravinski Site, 699 Concession Street, Hamilton, L8V 5C2, Ontario, Canada.

Authors for correspondence: S. Rajagopal, Trillium Health Partners, Credit Valley Hospital, Peel Regional Cancer Centre, 2200 Eglinton Avenue West, Mississauga, L5M 2N1, Ontario, Canada.

Authors for correspondence: T. Petrella, Odette Cancer Centre, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, M4N 3M5, Ontario, Canada.

*E-mail addresses:* Sudha.rajagopal@thp.ca (S. Rajagopal), yaoxia@mcmaster.ca, ccopgi@mcmaster.ca (X. Yao), Teresa.petrella@sunnybrook.ca (T.M. Petrella).

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*Conclusions:* After a systematic review, a comprehensive internal and external review process and a consensus process, the current guideline has been created. The guideline authors believe that this guideline will help clinicians, patients and policymakers make well-informed healthcare decisions that will guide them in clinical melanoma surveillance and ultimately assist in improving patient outcomes.


*Key words:* Clinical practice guideline; follow-up; frequency; imaging; melanoma; surveillance

## Introduction

In 2022, about 9000 new cases of melanoma were diagnosed, resulting in over 1200 estimated deaths in Canada [1]. The initial treatment for melanoma involves surgical removal; further treatment is determined based on the stage of the tumour [2].

In 2015, the Melanoma Disease Site Group in Ontario collaborated with the Program in Evidence-Based Care (PEBC) of Ontario Health (Cancer Care Ontario) to develop a clinical practice guideline entitled 'Follow-up of patients with stage I–III, or resectable IV melanoma who were treated with curative intent'. Since the development of the previous guideline, there have been notable changes in clinical practice that have led to changes in surveillance patterns. Thus, the Working Group guideline authors, which included five medical oncologists, three surgical oncologists, two dermatologists and one radiation oncologist from the Melanoma Disease Site Group and one methodologist from PEBC have updated the 2015 clinical practice guideline. The aim is to provide guidance for managing the surveillance of patients with stage I, II, III or resectable IV melanoma who are clinically free of disease following treatment with curative intent.

### *Research Questions*

For adult patients (≥18 years old) with stage I, II, III or resectable IV melanoma who are clinically disease free after receiving curative-intent treatment:

- Which follow-up evaluations (i.e. clinical follow-up, laboratory tests, photo-surveillance, dermoscopy and imaging) are optimal to improve patient outcomes (e.g. survival, recurrence, side-effects from imaging examinations and patient-reported outcomes)?
- At what frequency should these evaluations be performed to improve patient outcomes?
- Which follow-up evaluations (i.e. clinical follow-up, photo-surveillance and dermoscopy) are optimal to detect a new primary melanoma and improve patient outcomes?
- At what frequency should these evaluations be performed to detect new primary melanomas and improve patient outcomes?

When can these patients be transitioned to primary care for follow-up?

### *Target Population*

These recommendations apply to patients with stage I, II, III or resectable IV melanoma who are clinically disease free after treatment with curative intent. Pathological staging is according to the eighth edition of the American Joint Committee on Cancer (AJCC) staging system (Appendix A) [3].

### *Intended Users*

Intended users of this guideline are medical oncologists, dermatologists, surgical oncologists, radiation oncologists, family doctors and other clinicians who are involved in the follow-up care of patients with melanoma.

### *Materials and Methods*

The methods of the Practice Guidelines Development Cycle were used to conduct this guideline [4,5]. As part of this process, a systematic review was conducted. The Working Group interpreted evidence and drafted recommendations; content and methodology experts carried out an internal review and then completed an external review; Ontario clinicians and other stakeholders completed an external review. On the Ontario Health (Cancer Care Ontario) website, the methods are described in further detail [6]. The systematic review will be published separately. Briefly, the databases for EMBASE, PROSPERO, MEDLINE and the Cochrane Library were screened for existing systematic reviews, original studies, abstracts and systematic review-based guidelines that were relevant from 1 January 2015 to 5 June 2022. The main relevant guideline websites (American Society of Clinical Oncology, Canadian Medical Association Journal Infobase, Cancer Council Australia – Cancer Guidelines Wiki guideline websites, ECRI Guideline Trust® Database, National Comprehensive Cancer Network (NCCN), National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network) were similarly searched from 1 January 2019 to 28 July 2022. On 12 July 2022, the National Cancer Institute Clinical Trials Database was searched for ongoing and unpublished trials. The Appraisal of Guidelines for Research and Evaluation (AGREE) Instrument version II, (AGREE II) tool was used to assess the quality of the relevant existing guidelines [7]. Only the guidelines that received a score above 50% in the rigour of development domain, which evaluates the

guideline's methodological quality, were included. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach was followed [8] and the Modified Delphi method was used [9].

*Internal Review*

Three groups reviewed and approved the report: the Melanoma Disease Site Group in Ontario (comprising seven medical oncologists, four surgical oncologists, three dermatologists, one radiation oncologist and one patient representative), the Patient Consultation Group and the PEBC Report Approval Panel.

*External Review*

*Targeted Peer Review*

Five of the 12 international and national peer reviewers who were dominated by the Working Group members during the guideline development process agreed to participate in the review. Conflict of interest forms were signed by all internal reviewers and targeted peer reviewers (Appendix B.1–B.5).

*Professional Consultation*

All the clinicians in the PEBC database (spanning across Canada, but primarily concentrated in Ontario) with potential interest in this guideline were sent a brief online survey.

## Results

Eight articles with low to very low quality matched our pre-planned study selection criteria [10–17]. Five relevant guidelines were found and the quality assessment results are displayed in Appendix C. Four guidelines from NICE 2022 [18], NCCN 2022v3 [19], American Academy of Dermatology (AAD) 2019 [20] and Australian Wiki 2019 guidelines [21] were included based on our criteria. The evidence available to answer the two research questions is limited. Thus, the initial recommendations made by the Working Group were based on their clinical experience, existing guidelines and the current evidence.

*Internal Review*

*Melanoma Disease Site Group Review and Approval*

All 16 members of the Melanoma Disease Site Group voted for the first round by 8 November 2022. Among the 15 recommendations and six qualifying statements that were drafted, three of the recommendations did not reach the 75% agreement rate (Appendix D). An online discussion meeting was held on 11 November 2022. The revised version of the 15 commendations and six qualifying statements was then sent to the Melanoma Disease Site Group members to vote again. There was one recommendation that did not reach the agreement rate of 75% (Recommendation 4.1) (Appendix E).

*Patient Consultation Group*

Five patient/survivor/caregiver representatives in the Patient Consultation Group reviewed the draft document and provided their comments at an online meeting on 14 December 2022.

*PEBC Report Approval Panel Review and Approval*

Three PEBC Report Approval Panel members reviewed and approved this document on 14 December 2022.

*External Review*

*Targeted Peer Review*

Responses were received from five reviewers by 21 February 2023. Key results of the feedback survey are summarised in Appendix F.

*Professional Consultation*

Seventy-six Ontario professionals were contacted by 24 February 2023. Among those contacted, 17% (13/76) responded, five of whom did not express interest in the guideline. Eight clinicians were ultimately consulted, and their voting results are summarised in Appendix G.

After external review, among the 16 Disease Site Group members, the agreement rate was 88% for the revised Recommendation 4.1.

## Recommendations, Key Evidence and Justification

There are three categories for the strength of recommendations for this guideline: recommendation, weak recommendation and no recommendation (see Appendix H for definitions and corresponding verb wording). There are 12 recommendations, three weak recommendations and six qualifying statements in the guideline.

*Recommendation 1*

For patients with stage IA, IB or IIA melanoma who are clinically disease free after receiving curative-intent treatment:

1.1 Clinical follow-up with history and physical examination with full skin and lymph node examination by a dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a family physician/cancer nurse specialist should occur every 6–12 months for 3 years, then annually for 2 years or as clinically indicated [strength: recommendation].

1.2 Routine biomarker or blood tests and imaging evaluations to screen for asymptomatic recurrence or metastatic disease are not recommended [strength: recommendation].

1.3 In conjunction with routine follow-up, healthcare providers should provide education to patients and patients' caregivers who are involved in decision-making regarding skin self-examination (SSE) and sun safety [strength: recommendation].

*Qualifying Statements for Recommendation 1*

1.4 For details of SSE, refer to Skin Cancer Self-exam on the Canadian Dermatology Association website (https://dermatology.ca/public-patients/skin/melanoma/).

*Key Evidence for Recommendation 1*

Target populations included stage IA, IB and IIA patients in one randomised controlled trial (RCT) [14] and two comparative studies [16,17]. According to the GRADE approach, the level of certainty regarding the evidence for each comparison of interventions is classified as 'low' and 'very low'. Table 1 provides a summary of the key evidence extracted from these studies.

*Justification for Recommendation 1*

Surveillance of patients by physicians or nurse specialists trained in skin examinations is considered crucial for the diagnosis of new primary melanomas or recurrent melanoma or in stage IA, IB and IIA. The recommended frequency of follow-up evaluations, which suggests scheduling them every 6–12 months for the first 3 years, followed by annual evaluations for the next 2 years or as clinically indicated, is supported by the reviewed data and expert opinion of the Working Group. These recommendations are supported by existing guidelines, such as NCCN 2022 [19] and AAD 2019 [20]. The Patient Consultation Group emphasised the importance of patients' quality of life as a critical outcome. The evidence from the RCT did not demonstrate statistically significant differences in patient-reported outcomes between the two groups [14]. Upon including that education on SSE and sun safety should be extended to the caregivers of patients who are involved in decision-making in addition to patients, these recommendations were supported.

*Recommendation 2*

For patients with stage IIB or IIC melanoma:

2.1. Clinical follow-up with history and physical examination with full skin and lymph node examination by a dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist should occur every 3–6 months in years 1–3, then every 6 months in years 4–5, or as clinically indicated [strength: recommendation].
2.2. Routine biomarker or blood tests to screen for asymptomatic recurrence or metastatic disease are not recommended [strength: recommendation].
2.3. Computed tomography (CT) or positron emission tomography (PET)/CT scans every 6–12 months should be considered to screen for asymptomatic recurrence or metastatic disease in years 1–3, then annually in years 4–5 [strength: recommendation].
2.4. Annual brain magnetic resonance imaging (MRI) can be considered for years 1–5. MRI (no radiation) of the brain is preferred for routine screening where available; otherwise, head CT may be considered after discussing with patients [strength: weak recommendation].
2.5. In conjunction with routine follow-up, healthcare providers should provide education to patients and patients' caregivers who were involved in decision-making regarding SSE and sun safety [strength: recommendation].

*Qualifying Statements for Recommendation 2*

2.6. For the details of SSE, refer to Skin Cancer Self-exam on the Canadian Dermatology Association website (https://dermatology.ca/public-patients/skin/melanoma/).

*Key Evidence for Recommendation 2*

One RCT [14] and two comparative studies [13,17] included patients with stage IIB and IIC melanoma. The level of certainty regarding the evidence for each intervention comparison was classified as 'low' and 'very low'. The key findings are summarised in Table 2. There are three ongoing studies that are expected to provide relevant evidence regarding dermoscopy and photo-surveillance in the target populations.

*Justification for Recommendation 2*

Individuals diagnosed with stage IIB and IIC melanoma face a high risk of recurrence, with 10-year survival rates of 82% and 75%, respectively [22]. These survival rates are comparable with those observed in stage IIIA and IIIB cases. Considering the elevated risk of recurrence and the utilisation of adjuvant therapy in their treatment, the Working Group emphasises the importance of early screening for recurrence or metastatic disease. In addition, we currently have systemic treatments that have shown the ability to extend overall survival in the metastatic setting, with patients who have a lower disease burden experiencing longer survival outcomes [23]. However, it is important to note that the existing literature lacks up-to-date information on this rapidly evolving treatment landscape. The three papers included in the analysis started patient recruitment over a decade ago, prior to the introduction of our new adjuvant therapies. After careful evaluation of the advantages and disadvantages, the Working Group's expert opinion suggests that screening should be considered in this population, aligning with the screening protocols applied to patients with stage III disease. The study conducted by Rueth *et al.* in 2014 [17] showed that PET/CT presents a higher positive predictive value and a lower false-positive

**Table 1**
Key evidence for Recommendation 1

| Study, design | Stage (*n*) | IA–IIA (*n*) | Experimental group versus control group | Outcomes |
|---|---|---|---|---|
| Moncrieff [14], randomised controlled trial | IA–IIC: 388 | IA–IIA: 318 | Follow-up strategies following 2015 NICE guideline or 2013 Netherlands guideline: Patient history and a physical examination, with structured SSE education reinforced at each visit.<br>Experimental group: frequency of the above follow-up strategies in years 1–5:<br>IA–IB: 1, 1, 1, 1, 1; IIA: 2, 2, 1, 1, 1.<br>Control group: frequency of the above follow-up strategies in years 1–5:<br>IB–IIA: 4, 3, 2, 2, 2. | At 5 years<br>• DSS: HR 1.00; 95% CI 0.49–2.07; $P = 0.99$<br>• DFS: HR 0.92; 95% CI 0.56–1.53; $P = 0.76$<br>• OS: HR 0.90; 95% CI 0.49–1.66; $P = 0.74$<br>• DMFS: HR 0.99; 95% CI 0.54–1.82; $P = 0.98$<br>• Recurrence or second primary melanoma rate:<br>HR 0.87; 95% CI 0.54–1.39; $P = 0.57$<br>• PRO: NS. |
| Rueth [17], retrospective comparative study | I–IIIC: 1600 | I: 724, II: 72 | Experimental group: clinical physical examination + CT or PET/CT every 6 or 12 months versus Control group: clinical physical examination alone every 3 months for 5 years or until recurrence. | For stage I:<br>• Life expectancy increase was 0.4 months (0.7%) and the additional regional recurrence detection rate was 3–5% and distant recurrence was 2–4% by using PET/CT every 6 months for 5 years.<br>• PPV = 1% versus 5% for CT versus PET/CT yearly for stage I and 5% versus 13% for stage II.<br>• DSS (CT versus PET/CT yearly): stage I: 92% versus 92% stage II: 76% versus 76% |
| Ribero [16], retrospective comparative study | IB–IIA: 1149 | IB: 783<br>IIA: 366 | Experimental group: patient history and physical examination, with SSE three times/year for 3 years, then two times/year for 2 years; plus biomarker tests two times/year for 2 years versus Control group: patient history and physical examination, with SSE two times/year for 5 years; plus ultrasound of regional lymph node basins two times/year; plus abdomen ultrasound once/year for 5 years. | • DMFS: HR 0.78; 95% CI 0.51–1.16; $P = 0.22$<br>• MSS: HR 1.24; 95% CI 0.81–1.90; $P = 0.32$<br>• NMFS: HR 0.88; 95% CI 0.51–1.50; $P = 0.64$ |

CI, confidence interval; CT, computed tomography; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HR, hazard ratio; MSS, melanoma-specific survival, NICE, National Institute for Health and Care Excellence; NMFS, nodal metastasis-free survival; NS, no statistically significant difference between two groups; OS, overall survival; PET, positron emission tomography; PPV, positive predictive value; PRO, patient-reported outcomes; SSE, skin self-examination.

rate compared with CT. However, considering factors such as availability and resources, we refrained from making a recommendation to favour PET/CT over CT alone. Nevertheless, the possibility of false-positive results arising from imaging examinations and the subsequent unnecessary management of false-positive patients should be taken into consideration and thoroughly discussed with patients. It is also essential to educate patients about the potential risk of developing secondary cancer from CT or PET/CT examinations, as these imaging modalities involve higher radiation exposure compared with CT alone, although this risk is minimal [24]. The preference of the patient should be respected.

The Patient Consultation Group members emphasised the significance of patients' quality of life as the critical outcome. The evidence from the Moncrieff *et al.*, 2020 trial

**Table 2**
Key evidence for recommendation 2

| Study, design | Stage ($n$) | IA–IIA ($n$) | Experimental group versus control group | Outcomes |
|---|---|---|---|---|
| Moncrieff [14], randomised controlled trial | IA–IIC: 388 | IIB–IIC: 70 | Follow-up strategies following 2015 NICE guideline or 2013 Netherlands guideline: patient history and physical examination, with structured SSE education reinforced at each visit. Experimental group: frequency of the above follow-up strategies in years 1–5: IIB–IIC: 3, 3, 2, 1, 1. Control group: frequency of the above follow-up strategies in years 1–5: IIB–IIC: 4, 3, 2, 2, 2. | At 5 years • DSS: HR 1.00; 95% CI 0.49–2.07; $P = 0.99$ • DFS: HR 0.92; 95% CI 0.56–1.53; $P = 0.76$ • OS: HR 0.90; 95% CI 0.49–1.66; $P = 0.74$ • DMFS: HR 0.99; 95% CI 0.54–1.82; $P = 0.98$. • Recurrence or second primary melanoma rate: HR 0.87; 95% CI 0.54–1.39; $P = 0.57$. • PRO: NS |
| Rueth [17], retrospective comparative study | I–IIIC: 1600 | II: 72 | Experimental group: clinical physical examination + CT or PET/CT every 6 or 12 months versus Control group: clinical physical examination alone every 3 months for 5 years or until recurrence. | Stage II: • Life-expectancy gains were ≤2 months for all stage groups with imaging follow-up. • PPV = 5% versus 13% for CT and PET/CT • DSS (CT versus PET/CT twice/year): 76% versus 76% • DSS (CT versus PET/CT yearly): 76% versus 76% |
| Kurtz [13], retrospective comparative study | IIA–IIIC: 247 | IIA–IIB: 125; IIC: 21 | Experimental group: IIA–IIB: clinical physical examination and at least two serial chest X-rays; IIC: clinical physical examination plus at least two serial PET/CT or whole-body CT and brain MRI versus Control group: clinical physical examination | Stage IIA–B: • RFS: $P = 0.75$ at 5 years. • OS rate = 96%; 95% CI 0.89–0.98 versus 95%; 95% CI 0.88–0.99; $P =$ NS at 35 months. stage IIC and IIIA–C: • Routine whole-body imaging detected 50% of recurrences leading to additional surgery and/or treatment. |

CI, confidence interval; CT, computed tomography; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; HR, hazard ratio; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; NS, no statistically significant difference between two groups; OS, overall survival; PET, positron emission tomography; PPV, positive predictive value; PRO, patient-reported outcomes; RFS, recurrence-free survival; SSE, skin self-examination.

[15] revealed that between the two groups, differences in patient-reported outcomes were not statistically significant. Upon the Working Group's addition that education on SSE and sun safety be provided to the caregivers of patients who are involved in decision-making in addition to patients themselves, they expressed their support for these recommendations.

*Recommendation 3*

For patients with stage IIIA, IIIB, IIIC, IIID or resected IV melanoma:

3.1 Clinical follow-up with history and physical examination with full skin and lymph node examination by

a dermatologist (with photo-surveillance and dermoscopy if indicated) and a surgeon or a medical oncologist/cancer nurse specialist should occur every 3–6 months in years 1–3, then every 6 months in years 4–5, or as clinically indicated [strength: recommendation].

3.2 Routine biomarker or blood tests to screen for asymptomatic recurrence or metastatic disease are not recommended [strength: recommendation].

3.3 CT or PET/CT scans every 6–12 months should be considered to screen for asymptomatic recurrence or metastatic disease in years 1–3, then annually in years 4–5 [strength: recommendation].

3.4 Annual brain MRI can be considered for years 1–5. MRI (no radiation) of the brain is preferred for routine screening where available, otherwise a head CT may be considered after discussing with patients [strength: weak recommendation].

3.5 For patients with a positive sentinel lymph node, ultrasound scans of the draining nodal basin should be carried out every 4–6 months for years 1–3, and then every 6 months for years 4–5 if no complete lymph node dissection performed [strength: recommendation].

3.6 In conjunction with routine follow-up, healthcare providers should provide education to patients and patients' caregivers who were involved in decision-making regarding SSE and sun safety [strength: recommendation].

*Qualifying Statements for Recommendation 3*

3.7 In patients with positive sentinel lymph nodes, ultrasound screening should take place following recommendations in the Cancer Care Ontario Guideline '8-6 surgical management of patients with lymph node metastases from cutaneous melanoma of the trunk or extremities' [25].

3.8 For the details of SSE, refer to Skin Cancer Self-exam on the Canadian Dermatology Association website (https://dermatology.ca/public-patients/skin/melanoma/).

3.9 There are no studies specifically addressing patients with resected stage IV melanoma; this subgroup of patients is included with the stage III group of patients because of their similar clinical characteristics.

*Key Evidence for Recommendation 3*

Stage III patients were recruited in four comparative studies [10,12,13,17]. The level of certainty of the evidence for each intervention comparison in these comparative studies was classified as 'very low'. The key findings are summarised in Table 3. There are three ongoing studies (detailed in Appendix I) that will contribute relevant evidence for demoscopy and photo-surveillance in the target populations.

*Justification for Recommendation 3*

The available evidence from the medical literature suggests active radiological screening, including routine CT or PET/CT scans and MRI scans where available, for patients with stage IIIA or higher. However, there is a lack of evidence to support that conducting intensive CT or PET/CT evaluations at intervals as frequent as every 3–4 months, as opposed to lower frequencies of CT or PET/CT evaluations, results in improved patient-related outcomes. Currently, we have systemic treatments that have demonstrated the ability to extend overall survival and melanoma-specific survival among patients in this particular stage group [23]. Additionally, it is well-established that patients who initiate treatment with a lower disease burden experience enhanced survival outcomes in comparison with those who are treated at a more advanced stage of disease [23]. The Rueth *et al.*, 2014 study [17] demonstrated that PET/CT presents a higher positive predictive value compared with CT. Due to considerations of availability and resources, we refrained from making a recommendation that favours PET/CT over CT alone. Taking into account the advantages and disadvantages, the expert opinion of the Working Group is the aforementioned recommendation. However, it is important to consider and discuss with patients the potential occurrence of false-positive results following imaging examinations and the subsequent unnecessary management of patients who receive such false-positive diagnoses. Moreover, it is crucial to provide patients with information about the potential risk of developing secondary cancer from CT or PET/CT examinations, as these procedures involve higher radiation exposure compared with CT alone, although the risk is minimal [24]. The preference of the patient should be respected. The members of the Patient Consultation Group highlighted the importance of patients' quality of life as a primary outcome. The evidence from the Moncrieff *et al.*, 2020 trial [15] indicated that there were no statistically significant differences in patient-reported outcomes between the two groups. Following the Working Group's inclusion of the recommendation to educate not only patients but also the caregivers involved in decision-making about SSE and sun safety, support was expressed for these recommendations.

*Recommendation 4*

4.1 Patients may be transitioned to a primary care physician who has had training in melanoma care for follow-up after 5 years depending on the stages of the disease and clinical risk factors. Annual follow-up with a dermatologist should continue as clinically indicated [strength: weak recommendation].

**Table 3**
Key evidence for Recommendation 3

| Study, design | Stage ($n$) | IA–IIA ($n$) | Experimental group versus control group | | | | Outcomes |
|---|---|---|---|---|---|---|---|
| Rueth [17], retrospective comparative study | I–IIIC: 1600 | IIIA: 136, IIIB: 368, IIIC: 304 | Experimental group: clinical physical examination + CT or PET/CT every 6 or 12 months versus Control group: clinical physical examination alone every 3 months for 5 years or until recurrence. | | | | Stage III:<br>• Life-expectancy gains were ≤2 months for all stage groups with imaging follow-up.<br>• The additional regional recurrence detection rate, 6%; distant recurrence, 8% for stage III using routine surveillance CT or PET/CT annually.<br>• PPV = 4–13% versus 12–32% for CT and PET/CT.<br>• DSS (CT versus PET/CT twice/year):<br><br>IIIA: 76% versus 76%<br>IIIB: 53% versus 53%<br>IIIC: 37% versus 38%<br>• DSS (CT versus PET/CT yearly):<br><br>IIIA: 76% versus 76%<br>IIIB: 52% versus 53%<br>IIIC: 36% versus 37% |
| Kurtz [13], retrospective comparative study | IIA–IIIC: 247 | IIIA: 59, IIIB: 30, IIIC: 12 | Experimental group: clinical physical examination plus at least two serial PET/CT or whole-body CT and brain MRI versus Control group: clinical physical examination | | | | For stage IIC and IIIA–C patients, routine whole-body imaging detected 50% of recurrences leading to additional surgery and/or treatment. For all stages combined, 25 of the 42 recurrences (60%) were detected by clinical examination alone, whereas the other (40%) were detected with imaging. |
| Broman [10], retrospective comparative study | III–IIID: 177 | IIIA: 53, IIIB: 42, IIIC: 78, IIID: 4 | Follow-up | Low intensity or no surveillance | Moderate intensity | High intensity | • Recurrence among three groups (recurrence risk=1/3.7 versus 1/4 versus 1/3.3); $P = 0.33$.<br>• Recurrence by receipt of adjuvant systemic therapy; $P = 0.76$.<br>• 33%, 60% and 40% in the low-, moderate- and high-intensity surveillance groups achieved a disease-free interval after surgery or complete systemic therapy ($P = 0.28$). |
| | | | Patients ($n = 159$) | 70 (44%) | 42 (26%) | 47 (30%) | |
| | | | Clinical physical examination | >every 6 months | Every 6 months | Every 3 months | |
| | | | Nodal basin ultrasound | >every 6 months | Every 6 months | Every 6 months | |
| | | | CT or PET/CT | >every year | Every year | Every 6 months | |
| | | | Brain MRI | Not specified | Not specified | Every year | |
| Dieng [12], retrospective comparative study | III–IIID: 473 | IIIA: 89, IIIB: 146, IIIC: 231, IIID: 7 | Experimental group: CT or PET/CT every 3–4 months ($n = 141$) or every 6 months ($n = 47$) ≥ 5 years versus Control group: CT or PET/CT every 12 months ($n = 285$) ≥ 5 years | | | | • Distant recurrences (intensive versus biannual versus annual CT or PET/CT): 84% versus 51% versus 38%; $P < 0.001$.<br>• Distant recurrences (IIIA versus IIIB versus IIIC versus IIID): 27% versus 57% versus 60% versus 86%; $P < 0.001$.<br>• OS (biannual versus annual): HR 1.21; 95% CI 0.65–2.28; $P = 0.545$.<br>• OS (intensive versus annual): HR 5.20; 95% CI 3.53–7.66; $P < 0.001$.<br>• MSS (biannual versus annual): multivariable HR 1.25; 95% CI 0.66–2.40; $P = 0.495$.<br>• MSS (intensive versus annual): HR 5.28; 95% CI 3.55–7.87; $P < 0.001$.<br>• DDFS (biannual versus annual): HR 1.69; 95% CI 1.02–2.78; $P = 0.040$.<br>• DDFS (intensive versus annual): HR 4.57; 95% CI 3.23–6.45; $P < 0.001$. |

CI, confidence interval; CT, computed tomography; DDFS, distant disease-free survival; DSS, disease-specific survival; HR, hazard ratio; MRI, magnetic resonance imaging; MSS, melanoma-specific survival; OS, overall survival; PET, positron emission tomography; PPV, positive predictive value.

*Qualifying Statements for Recommendation 4*

4.2 Patients should have access to return to the dermatology, surgery or medical oncology clinic if clinically needed.

*Key Evidence for Recommendation 4*

Currently, there is a lack of eligible evidence available in the medical literature on this matter.

*Justification for Recommendation 4*

According to the Working Group members, patients who maintain remission for a period of 5 years face a lower risk of recurrence or metastatic disease. As a result, patients who meet this criterion can continue to receive regular follow-up care from their family physician and dermatologist, as deemed clinically appropriate. Should the need arise, these patients should have expedited access to specialised follow-up upon returning, as early detection and treatment will impact patient outcomes.

## Discussion

Due to the limited availability of evidence, the recommendations made above were based mainly on the clinical opinions of the Working Group. Among the 16 members of the Melanoma Disease Site Group, an agreement rate of ≥75% was received for each recommendation via the modified-Delphi consensus process (details are provided in Appendices D and E). An internal and external review process was undertaken for this guideline. The recommendations are consistent overall with the recommendations set out by other current guidelines, such as by the NICE 2022 [18], NCCN 2022v3 [19], AAD 2019 [20] and the Australian Wiki 2019 guidelines [21]. A recent publication that reviewed existing surveillance guidelines from 19 different organisations around the world was consistent in recommending patient education on SSE and sun safety, a stage-specific approach and follow-up and imaging for stage II–III every 3–12 months in first 3 years then yearly to 5 years [26].

Consensus statements have been published by Kashani-Sabet and colleagues [27] on optimal practice and the role of gene expression profile testing in early detection and prognostic assessment of cutaneous melanoma. However, literature evidence was not included in the paper. Thus, our current recommendations remain unaffacted by the consensus statements.

*Further Research*

We made recommendations for the frequency of imaging evaluations during the surveillance of stage IIB patients and above. However, these recommendations were based mainly on the clinical opinions of the Melanoma Disease Site Group members. To address this issue, more studies that are relevant and high quality are needed. Additionally, there is no eligible evidence in this updated systematic review that investigates the roles of photo-surveillance, dermoscopy or biomarkers in the target population. Further research that examines surveillance issues in target patients is necessary.

*Guideline Limitations*

Although Recommendations 1 and 4 are highly related to the daily practice of family physicians, no family physicians are in the Working Group. Although family physicians were included as external reviewers, the next update process would benefit from the Working Group recruiting a family physician. Examining the cost-effectiveness of surveillance interventions falls outside the scope of this PEBC guideline. Resource considerations are left to other Ontario Health (Cancer Care Ontario) decision makers according to the Working Group members.

*Updates*

All PEBC documents are maintained and updated through an annual assessment and subsequent review process.

## Author Contributions

SR, XY and TP drafted the first report. All authors contributed to study design, data collection, data interpretation and manuscript revision.

## Conflicts of Interest

S. Rajagopal reports a relationship with BMS, Merck, Novartis and Pfizer that includes: consulting or advisory. T.D. Baetz reports a relationship with Bristol-Myers Squibb, Seattle Genetics, Merck, Pfizer, Servier, Gilead, Novartis, AstraZeneca, AbbVie, Roche, Sanofi and Sun Pharma that includes: consulting or advisory and funding grants. G. Knight reports a relationship with multiple companies that includes: board membership and consulting or advisory. F.C. Wright reports a relationship with Merck, BMS, Roche and Novartis that includes: consulting or advisory, funding grants and speaking and lecture fees. C. Nessim reports a relationship with Novartis and Sanofi that includes: board membership and consulting or advisory. E. McWhirter reports a relationship with Merck, BMS, Novartis, EMD Serrono, Sanofi-Genzyme, Roche and Medison that includes: consulting or advisory. C.F. Rosen reports a relationship with BMS, Novartis, AbbVie, Amgen and UCB that includes: consulting or advisory.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clon.2024.01.012.

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