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

Surveillance of Patients with Stage I, II, III, or Resectable IV Melanoma Who Were Treated with Curative Intent

S. Rajagopal, X. Yao, W. Abadir, T. Baetz, A. Easson, G. Knight, E. McWhirter, C. Nessim, C.F. Rosen, A. Sun, F.C. Wright, T. Petrella, *the Melanoma Surveillance Guideline Development Group*

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For information about this document, please contact **S. Rajagopal and T. Petrella**, through the PEBC at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775 E-mail: ccopgi@mcmaster.ca

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

Guideline Report History

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Surveillance of Patients with Stage I, II, III, or Resectable IV Melanoma Who Were Treated with Curative Intent

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 update the 2015 guideline of the Program in Evidence-Based Care (PEBC) Ontario Health (Cancer Care Ontario) to provide guidance for managing surveillance of patients with stage I, II, III, or resectable IV melanoma who are clinically disease-free after treatment with curative intent (following the definition of American Joint Committee on Cancer [AJCC] Pathological Prognostic Stage Groups in the 2017 Cancer Staging Manual, the 8th edition).

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 8th edition AJCC staging system (Appendix 1) [1].

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 in the province of Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

The strength of recommendations for this guideline includes three categories: Recommendation, Weak Recommendation, and No Recommendation (definitions and corresponding verb wording are provided in Appendix 2).

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/or a surgeon, family physician, cancer nurse specialists should occur every six to 12 months for three years, then annually for two 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/.

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/or a

surgeon, medical oncologist, cancer nurse specialist should occur every three to six months in years 1 to 3, then every six months in years 4 to 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 six to 12 months should be considered to screen for asymptomatic recurrence or metastatic disease in years 1 to 3, then annually in years 4 to 5. **[Strength: Recommendation]**

2.4 Annual brain magnetic resonance imaging (MRI) can be considered for years 1 to 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/.

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/or a surgeon, medical oncologist, or cancer nurse specialist should occur every three to six months in years 1 to 3, then every six months in years 4 to 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 six to 12 months should be considered to screen for asymptomatic recurrence or metastatic disease in years 1 to 3, then annually in years 4 to 5. **[Strength: Recommendation]**

3.4 Annual brain MRI can be considered for years 1 to 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]**

3.5 For patients with a positive sentinel lymph node, ultrasound scans of the draining nodal basin should be done every four to six months for years 1 to 3, and then every six months for years 4 to 5, if no complete lymph node dissection is 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 CCO Guideline "8-6 Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities".

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.

Recommendation 4

4.1 Patients may be transitioned to a primary care physician who has had training in melanoma care for follow-up after five 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]**
Qualifying Statements for Recommendation 4
4.2 Patients should have access to return to the dermatology, surgery, or medical oncology clinic if clinically needed.

Surveillance of Patients with Stage I, II, III, or Resectable IV Melanoma Who Were Treated with Curative Intent

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To update the 2015 guideline of the Program in Evidence-Based Care (PEBC) Ontario Health (Cancer Care Ontario) to provide guidance for managing surveillance of patients with stage I, II, III, or resectable IV melanoma who are clinically disease-free after treatment with curative intent (following the definition of American Joint Committee on Cancer [AJCC] Pathological Prognostic Stage Groups in the 2017 Cancer Staging Manual, the 8th edition).

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 8th edition AJCC staging system (Appendix 1) [1].

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 in the province of Ontario.

RECOMMENDATIONS, KEY EVIDENCE, AND JUSTIFICATION

The strength of recommendations for this guideline includes three categories: Recommendation, Weak Recommendation, and No Recommendation (definitions and corresponding verb wording are provided in Appendix 2).

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/or a surgeon, family physician, cancer nurse specialists should occur every six to 12 months for three years, then annually for two 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

One randomized controlled trial (RCT) [2] and two comparative studies [3, 4] recruited stage IA, IB, and IIA patients as part of their target populations. Based on the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach (details in **Section 4**), the certainty of the evidence for each intervention comparison is "Low" in the RCT, and "Very Low" in the two comparative studies. The key evidence from these included studies is summarized in the following table. The Rueth 2014 study that involved imaging examination evaluations did not report the potential adverse effects of imaging examinations as follow-up evaluations.

Study, Design	Stage (N)	IA-IIA (N)	EG vs. CG	Outcomes

Moncrieff 2022[a], RCT	IA-IIC: 388	IA-IIA: 318	F/U strategies following 2015 NICE guideline or 2013 Netherland guideline: PH and PE, and structured SSE education reinforced at each visit. **EG:** Frequency of the above F/U strategies in years 1-5: IA-IB: 1, 1, 1, 1, 1; IIA: 2, 2, 1, 1, 1. **CG:** Frequency of the above F/U strategies in years 1-5: IB-IIA: 4, 3, 2, 2, 2.	At 5 years, •DSS: HR, 1.00; 95% CI, 0.49 to 2.07; p=0.99 •DFS: HR, 0.92; 95% CI, 0.56 to 1.53; p=0.76 •OS: HR, 0.90; 95% CI, 0.49 to 1.66; p=0.74 •DMFS: HR, 0.99; 95% CI, 0.54 to 1.82; p=0.98. •Recurrence or second primary melanoma rate: HR, 0.87; 95% CI, 0.54 to 1.39; p=0.57. •PRO: NS [5].
Rueth 2014, Retro	I-IIIC: 1600	I: 724, II: 72	**EG:** clinical PE + CT or PET/CT every 6 or 12 months vs. **CG:** clinical PE alone every 3 months for 5 years or until recurrence.	For stage I: •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. •PPV = 1% vs. 5% for CT vs. PET/CT yearly for stage I, and 5% vs. 13% for stage II. •DSS (CT vs. PET/CT yearly): stage I: 92% vs. 92% stage II: 76% vs. 76%.
Ribero 2017, Retro	IB-IIA: 1149	IB: 783 IIA: 366	**EG:** PH and PE and SSE 3 times/year for 3 years, then 2 times/year for 2 years; plus biomarker tests 2 times/year for 2 years vs. **CG:** PH and PE and SSE 2 times/year for 5 years; plus US of regional lymph node basins 2 times/year; plus abdomen US once/year for 5 years.	•DMFS: HR, 0.78; 95% CI, 0.51 to 1.16; p=0.22. •MSS: HR, 1.24; 95% CI, 0.81 to 1.90; p=0.32. •NMFS: HR, 0.88; 95% CI, 0.51 to 1.50; p=0.64.

Abbreviations: CG, control group; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; EG, experimental group; F/U, follow-up; HR, hazard ratio; MSS, melanoma-specific survival, NICE, National Institute for Health and Care Excellence Evidence Search; NMFS, nodal metastasis-free survival; NS, no statistically significant difference between two groups; OS, overall survival; PE, physical examinations; PET, positron emission tomography; PH, patient history; PPV, positive predictive value; PRO, patient-reported outcomes; RCT, randomized controlled trial; Retro, retrospective comparative study; SSE, skin self-examination, US; ultrasound; vs., versus.

[a] There is no subgroup analysis for IA-IIA patients. The results from 386 of 388 included patients. Based on the data provided, we presented patient stages according to the 8th edition American Joint Committee on Cancer staging system.

Justification for Recommendation 1

For Stage IA, IB and IIA, the surveillance of patients with physicians or nurse specialists trained in skin examinations is deemed to be important in the diagnosis of recurrent melanoma or new primary melanomas. The reviewed data and the expert opinion of the Working Group support the recommended frequency of the follow-up evaluations (i.e., every six to 12 months for three years, then annually for two years or as clinically indicated) which is also supported by the existing guidelines (National Comprehensive Cancer Network [NCCN] 2022 [6] and American Academy of Dermatology [AAD] 2019 [7]). The members of Patient Consultation Group believed that patients' quality of life was a critical outcome. The evidence indicated that the patient-reported outcomes were not statistically significant between the two groups in the RCT [2]. After they added that patients' caregivers who were involved in decision-making should be provided education regarding SSE and sun safety as well as patients, they supported these recommendations.

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/or a surgeon, medical oncologist, cancer nurse specialist should occur every three to six months in years 1 to 3, then every six months in years 4 to 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 six to 12 months should be considered to screen for asymptomatic recurrence or metastatic disease in years 1 to 3, then annually in years 4 to 5. **[Strength: Recommendation]**

2.4 Annual brain magnetic resonance imaging (MRI) can be considered for years 1 to 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 [2] and two comparative studies [3, 4] recruited stage IIB and IIC patients as part of their target populations. Based on the GRADE approach (details in **Section 4**), the certainty of the evidence for each intervention comparison is "Low" in the two RCTs, and "Very Low" in the two comparative studies. The key evidence from these included studies is summarized in the following table. For the studies that treated imaging examinations as follow-up evaluations, none of them reported the potential adverse effects or false positive results of imaging examinations. Three ongoing studies will provide relevant evidence for photo-surveillance and dermoscopy in target populations (details in **Section 4**).

Study, Design	Stage (N)	IA-IIA (N)	EG vs. CG	Outcomes
Moncrieff 2022[a], RCT	IA-IIC: 388	IIB-IIC: 70	F/U strategies following 2015 NICE guideline or 2013 Netherland guideline: PH and PE, and structured SSE education reinforced at each visit. **EG:** Frequency of the above F/U strategies in years 1-5: IIB-IIC: 3, 3, 2, 1, 1. **CG:** Frequency of the above F/U strategies in years 1-5: IIB-IIC: 4, 3, 2, 2, 2.	At 5 years, •DSS: HR, 1.00; 95% CI, 0.49 to 2.07; p=0.99 •DFS: HR, 0.92; 95% CI, 0.56 to 1.53; p=0.76 •OS: HR, 0.90; 95% CI, 0.49 to 1.66; p=0.74 •DMFS: HR, 0.99; 95% CI, 0.54 to 1.82; p=0.98. •Recurrence or second primary melanoma rate: HR, 0.87; 95% CI, 0.54 to 1.39; p=0.57. •PRO: NS
Rueth 2014, Retro	I-IIIC: 1600	II: 72	**EG:** clinical PE + CT or PET/CT every 6 or 12 months vs. **CG:** clinical PE alone every 3 months for 5 years or until recurrence.	Stage II: •Life-expectancy gains were ≤2 months for all stage groups with imaging F/U. •PPV = 5% vs. 13% for CT and PET/CT. •DSS (CT vs. PET/CT twice/year): 76% vs. 76%. •DSS (CT vs. PET/CT yearly): 76% vs. 76%.
Kurtz 2017, Retro	IIA-IIIC: 247	IIA-IIB: 125; IIC: 21	**EG:** IIA-IIB: Clinical PE and at least 2 serial chest x-rays; IIC: clinical PE plus at least two serial PET/CT or	Stage IIA-B: •RFS: p=0.75 at 5 years. •OS rate = 96%; 95% CI, 0.89 to 0.98 vs. 95%; 95% CI, 0.88 to 0.99; p=NS at 35 months. stage IIC and IIIA-C:

			whole-body CT and brain MRI. vs. **CG:** Clinical PE	•Routine whole-body imaging detected 50% of recurrences leading to additional surgery and/or treatment.

Abbreviations: CG, control group; CI, confidence interval; CT, computed tomography; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; EG, experimental group; F/U, follow-up; HR, hazard ratio; NICE, National Institute for Health and Care Excellence Evidence Search; NS, no statistical significantly difference between two groups; OS, overall survival; PE, physical examinations; PET, positron emission tomography; PH, patient history; PPV, positive predictive value; PRO, patient-reported outcomes; Retro, retrospective comparative study; RFS, recurrence-free survival; SSE, skin self-examination; vs., versus.

[a] There is no subgroup analysis for IIB-IIC patients. The results included patients with stages IA, IB, and IIA. The results from 386 of 388 included patients. Based on the data provided, we presented patient stages according to the 8th edition American Joint Committee on Cancer staging system.

Justification for Recommendation 2

Patients with stage IIB and IIC melanoma are at high risk of recurrence with survivals of 82% and 75%, respectively, at 10 years [8]. These are similar to what we see for stage IIIA and IIIB disease. Given their high recurrence risk and the fact that they are now being treated with adjuvant therapy, the Working Group feels that it is important to screen for early recurrence or metastatic disease. We also now have systemic treatment that has been shown to prolong overall survival (OS) in the metastatic setting and those treated with a lower burden of disease have longer survival outcomes [9]. The evidence in the literature available at this time is not up to date with this rapidly evolving treatment landscape and these four included papers started to recruit patients more than 10 years ago prior to the advent of our new adjuvant therapies.

Therefore, after balancing the benefits and harms, the expert opinion of the Working Group is that screening in this population should be considered in keeping with the screening employed in patients with stage III disease. The Rueth 2014 study showed that PET/CT has a higher positive predictive value (PPV) and a lower false positive rate than CT. Considering availability and resources, we did not make a recommendation to favour PET/CT compared with CT only. However, the potential false-positive results after imaging examinations and the unnecessary management of these false-positive patients afterward should be considered and discussed with the patients. Additionally, patients should be informed of the potential risk of secondary cancer from CT or PET/CT examinations (having more radiation than CT alone), although this risk is very low [10]. Patients' preferences should be respected.

The members of Patient Consultation Group believed that patients' quality of life was the critical outcome. The evidence indicated that the patient-reported outcomes were not statistically significant between two the groups in the Moncrieff 2020 trial [11]. After the Working Group added that patients' caregivers who were involved in decision-making should be provided education regarding SSE and sun safety as well as patients, they supported 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/or a surgeon, medical oncologist, or cancer nurse specialist should occur every three to six months in years 1 to 3, then every six months in years 4 to 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 six to 12 months should be considered to screen for asymptomatic recurrence or metastatic disease in years 1 to 3, then annually in years 4 to 5. **[Strength: Recommendation]**

3.4 Annual brain MRI can be considered for years 1 to 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]**

3.5 For patients with a positive sentinel lymph node, ultrasound scans of the draining nodal basin should be done every four to six months for years 1 to 3, and then every six months for years 4 to 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 CCO Guideline "8-6 Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities".

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

Four comparative studies [3, 12-14] recruited stage III patients. Based on the GRADE approach (details in **Section 4**), the certainty of the evidence for each intervention comparison is "Very Low" in these comparative studies. The key evidence from these included studies is summarized in the following table. No studies reported the potential adverse effects of imaging examinations. Three ongoing studies will provide relevant evidence for photo-surveillance and dermoscopy in target populations **(Appendix 7).**

Study, Design	Stage (N)	III, (N)	EG vs. CG	Outcomes
Rueth 2014, Retro	I-IIIC: 1600	IIIA: 136, IIIB: 368, IIIC: 304	**EG:** clinical PE + CT or PET/CT every 6 or 12 months vs. **CG:** clinical PE alone every 3 months for 5 years or until recurrence.	Stage III: •Life-expectancy gains were ≤2 months for all stage groups with imaging F/U. •The additional regional recurrence detection rate, 6%; distant recurrence, 8% for stage III using routine surveillance CT or PET/CT annually. •PPV = 4-13% vs. 12-32% for CT and PET/CT. •DSS (CT vs. PET/CT twice/year): IIIA: 76% vs. 76% IIIB: 53% vs. 53% IIIC: 37% vs. 38% •DSS (CT vs. PET/CT yearly): IIIA: 76% vs. 76% IIIB: 52% vs. 53% IIIC: 36% vs. 37%
Kurtz 2017, Retro	IIA-IIIC: 247	IIIA: 59, IIIB: 30, IIIC: 12	**EG**: clinical PE plus at least two serial PET/CT or whole-body CT and brain MRI. vs. **CG:** Clinical PE	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 2021, Retro	III-IIID: 177	IIIA: 53, IIIB: 42, IIIC: 78, IIID: 4	F/U: Low intensity or no surveillance; Moderate intensity; High intensity Patients (n=159): 70 (44%); 42 (26%); 47 (30%) Clinical PE: >every 6 months; Every 6 months; Every 3 months Nodal basin US: >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	•Recurrence among 3 groups (recurrence risk=1/3.7 vs. 1/4 vs. 1/3.3); p=0.33. •Recurrence by receipt of adjuvant systemic therapy; p=0.76. •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).

Dieng 2022, Retro	III-IIID: 473	IIIA: 89, IIIB: 146, IIIC: 231, IIID: 7	**EG:** CT or PET/CT every 3 to 4 months (n=141), or every 6 months (n=47) ≥ 5 years vs. **CG:** CT or PET/CT every 12 months (n=285) ≥ 5 years	•Distant recurrences (intensive vs. biannual vs. annual CT or PET/CT): 84% vs. 51% vs. 38%; p<0.0001. •Distant recurrences (IIIA vs. IIIB vs. IIIC vs. IIID): 27% vs. 57% vs. 60% vs. 86%; p<0.0001. •OS (biannual vs. annual): HR, 1.21; 95% CI 0.65 to 2.28; p=0.545. OS (intensive vs. annual): HR, 5.20; 95% CI, 3.53 to 7.66; p<0.001. •MSS (biannual vs. annual): multivariable HR, 1.25; 95% CI, 0.66 to 2.40; p=0.495. •MSS (intensive vs. annual): HR, 5.28; 95% CI, 3.55 to 7.87; p<0.001. •DDFS (biannual vs. annual): HR, 1.69; 1.02 to 2.78; p=0.040. •DDFS (intensive vs. annual): HR, 4.57; 3.23 to 6.45; p<0.001.

Abbreviations: CG, control group; CT, computed tomography; DDFS, distant disease-free survival; DFS, disease-free survival; DSS, disease-specific survival; EG, experimental group; F/U, follow-up; HR, hazard ratio; MRI, magnetic resonance imaging; MSS, melanoma-specific survival; NED, no evidence of disease; OS, overall survival; PE, physical examinations; PET, positron emission tomography; PPV, positive predictive value; Retro, retrospective comparative study; US, ultrasound; vs., versus.

Justification for Recommendation 3

It seems that the evidence from medical literature supports the active radiologic screening of patients with stage IIIA or higher with routine CT or PET/CT and MRI scans where available. However, there is no evidence to support that intensive CT or PET/CT evaluations such as every three to four months rather than lower frequency of CT or PET/CT evaluations lead to better patient-related outcomes. We now have systemic treatment that has been shown to prolong OS and melanoma-specific survival (MSS) for this stage group of patients [9]. It is also known that patients who begin treatment with a lower burden of disease have improved survival compared with those treated with a more advanced disease [9]. The Rueth 2014 study showed that PET/CT has a higher PPV than CT. Considering availability and resources, we did not make a recommendation to favour PET/CT compared with CT only. After balancing the benefits and harms, the expert opinion of the Working Group is the above recommendation. However, the potential false-positive results after imaging examinations and the unnecessary management of these false-positive patients afterward should be considered and discussed with the patients. Additionally, patients should be informed of the potential risk of secondary cancer from CT or PET/CT examinations (having more radiation than CT alone), although this risk is very low [10]. Patients' preferences should be respected.

The members of Patient Consultation Group thought that patients' quality of life was a critical outcome. There was no eligible evidence to report patient-reported outcomes. After they added that patients' caregivers who were involved in decision-making should be provided education regarding SSE and sun safety as well as patients, they supported 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 five 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]**

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

There is no eligible evidence from the medical literature at this moment.

Justification for Recommendation 4

The Working Group members believe that patients remaining in remission for five years are at a lower risk of recurrence or metastatic disease. They can therefore undergo ongoing follow-up with their family physician and dermatologist if clinically appropriate. These patients should, however, have

expedited access to return for specialized follow-up if the need arises as early detection and treatment will affect patient outcomes.

DISCUSSION

Because of limited evidence, the Working Group made the above recommendations mainly based on their clinical opinions and received an agreement rate of ≥ 75% for each recommendation among 16 melanoma Disease Site Group (DSG) members through a consensus process (see details in Section 5). This guideline went through internal review and external review processes (see details in Section 5), and every recommendation is generally consistent with other current guidelines from National Institute for Health and Care Excellence [NICE] 2022 [15], NCCN 2022v3 [6], AAD 2019 [7], and Australian Wiki 2019 guidelines [16].

Currently, Kashani-Sabet and his colleagues published consensus statements on optimal practice and the role of gene expression profile testing in early detection and prognostic assessment of cutaneous melanoma (2023) [17]. However, the paper does not include literature evidence. Their consensus statements do not result in changing our current recommendations. All PEBC documents are maintained and updated through an annual assessment and subsequent review process (see the details in Section 3: Guideline Methods Overview). When new evidence that can impact the recommendations is available, the recommendations should be updated as soon as possible.

FURTHER RESEARCH

Although we made recommendations regarding imaging evaluations with their frequencies during the surveillance of patients with stages IIB and above, they were mainly based on the Melanoma DSG members' clinical opinions. More high-quality relevant studies are needed to address these issues. Also, in this updated systematic review, there is no eligible evidence investigating the roles of photo-surveillance, dermoscopy, or biomarkers in the target population. More research is needed to explore these issues in the surveillance of target patients.

GUIDELINE LIMITATIONS

There are no family physicians in the Working Group, but Recommendations 1 and 4 are highly related to their daily practice. Although the external reviewers include family physicians, it would be more thoughtful to recruit a family physician to the Working Group in the next update process. The cost-effectiveness of surveillance interventions is beyond the scope of the PEBC guideline. The Working Group members leave resource consideration to other decision-makers in Ontario Health (Cancer Care Ontario).

Surveillance of Patients with Stage I, II, III, or Resectable IV Melanoma Who Were Treated with Curative Intent

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). 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) or Disease Site Group (DSG) 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.

BACKGROUND FOR GUIDELINE

In 2015, the Working Group of the Melanoma DSG developed a clinical practice guideline titled "Follow-up of Patients with Stage I, II, III, or Resectable IV Melanoma Who Were Treated with Curative Intent" [18]. The PEBC document assessment conducted in 2019 indicated that this guideline needed updating because clinical practice has changed since the previous guideline was developed, especially in terms of clinical follow-up of imaging examinations. For example, there may be some new evidence available since 2015 that may potentially change the original recommendations. Treatments for different stages of melanoma patients have been changed which may also contribute to the change in how patients are followed.

GUIDELINE DEVELOPERS

This guideline was developed by the Melanoma DSG (Appendix 3), which was convened at the request of the Skin Cancers Advisory Committee.

The project was led by a Working Group of the Melanoma DSG, 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 dermatology, medical oncology, surgical oncology, radiation oncology, and health research methodology. Other members (including a patient representative) of the Melanoma DSG, 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 3, 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 [19, 20]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft

recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II assessment tool (4) 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 and to improve the completeness and transparency of reporting in practice guidelines.

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 evidence of the magnitude of the desirable and undesirable effects of an intervention or accuracy of a test, and take into account the certainty of the evidence, the values of key stakeholders (e.g., patients, clinicians, policy makers, etc.), and the potential impact on equity, acceptability and feasibility of implementation. A list of any implementation considerations (e.g., costs, human resources, and unique requirements for special or disadvantaged populations, dissemination issues, etc.) is 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 Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether any guideline could be endorsed. Evidence-based guidelines with systematic reviews that addressed the research question (see Section 4) were included. Guidelines older than three years (published before 2019) were excluded. Guidelines based on consensus or expert opinion were excluded.

The following sources were searched for guidelines from January 2019 to July 28 2022 with the search term of melanoma: NICE, Canadian Medical Association Journal Infobase, Scottish Intercollegiate Guidelines Network, NCCN, American Society of Clinical Oncology, National Health and Medical Research Council – Australia Clinical Practice Guidelines Portal, Cancer Council Australia – Cancer Guidelines Wiki guideline websites, and ECRI Guideline Trust® Database.

Assessment of Guidelines

The quality of the relevant existing guidelines was assessed by using the AGREE II tool [21]. Only the guidelines with a score in the rigour of development domain, which assesses the methodological quality of the guideline, above 50% were included. The assessment results are shown in Appendix 4. Four guidelines from NICE 2022 [15], NCCN 2022v3 [6], AAD 2019 [7], and Australian Wiki 2019 guidelines [16] were included. Although the authors of each of these guidelines stated that they conducted a systematic review, the recommendations they made were based mainly on clinical opinion. The Working Group members decided to develop recommendations based on current evidence for the Ontario context.

GUIDELINE REVIEW AND APPROVAL

Internal Review

The guideline was evaluated by the Patient Consultation Group, the Melanoma DSG, and the PEBC Report Approval Panel (RAP).

Five patients/survivors/caregivers participated in the Consultation Group. They reviewed copies of the draft recommendations and provided feedback on its comprehensibility, appropriateness, and feasibility to the health research methodologist who relayed the feedback to the Working Group for consideration.

For the guideline document to be approved, 75% of the all the Melanoma DSG members (16 clinical experts) must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC RAP, a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are 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 are contacted and asked to provide feedback on the guideline recommendations through a brief online survey.

DISSEMINATION AND IMPLEMENTATION

The guideline will be published on the OH (CCO) website and may be submitted for publication to a peer-reviewed journal. The Professional Consultation of the External Review is 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, and the Guidelines International Network (GIN) Library, etc.

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Surveillance of Patients with Stage I, II, III, or Resectable IV Melanoma Who Were Treated with Curative Intent

Section 4: Systematic Review

INTRODUCTION

Melanoma skin cancer develops in the melanocyte cells of the skin. Although melanoma skin cancer can start in other parts of the body where melanocytes are found, these types of melanomas are rare [22]. As of January 1, 2018, melanoma of the skin accounted for 5.5% (93,890 cases) of all cancer diagnoses in the past 25 years in Canada. In 2022, it is estimated that in Canada, there will be 9000 new cases of melanoma and 1200 deaths from this disease[22].

Surgical resection is the current standard of care as curative treatment for melanoma. Adjuvant therapies have been approved for stage IIb to resected stage IV melanoma due to the resulting improvement in relapse free survival following curative intent surgery , [23, 24]. For patients who are clinically disease-free after receiving curative-intent treatment, a substantial risk of both locoregional recurrence and metastatic disease still exists. In order to improve patient outcomes, it is important to know what surveillance evaluations are optimal and how frequently they should be performed. As described in **Section 3**, the Melanoma DSG Working Group derived research question(s) outlined below based on the objective(s) of this guideline (**Section 2**) and conducted this systematic review to answer these questions.

This systematic review has been registered on the PROSPERO website (International prospective register of systematic reviews) with the following registration number CRD42021246482.

RESEARCH QUESTIONS

1. 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:
    a. 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 effect from imaging examinations, and patient-reported outcomes)?
    b. At what frequency should these evaluations be performed to improve patient outcomes?
    c. 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?
    d. At what frequency should these evaluations be performed to detect new primary melanomas and improve patient outcomes?

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

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 Systematic Reviews

The following databases were searched for existing systematic reviews and meta-analyses from January 2015 to June 5, 2022: MEDLINE, EMBASE, Cochrane Database of Systematic Reviews, and PROSPERO. The search strategies are reported in Appendix 5. Systematic reviews were included if they addressed at least one research question and included at least one original study that met our study selection criteria for original studies below, and the review had a moderate overall rating as assessed with the AMSTAR 2 tool [25]. If more than one systematic review met the inclusion criteria, then one systematic review for each outcome per comparison was selected based on its age, quality, and the best match with our study selection criteria.

No existing systematic review was found to meet the above selection criteria. Therefore, we conducted our own systematic review to answer these research questions.

Search for Primary Literature

Literature Search Strategy

The following databases were searched for relevant evidence from January 1, 2015, to June 5, 2022: MEDLINE, EMBASE, PubMed, and the Cochrane library. The full search strategies are reported in Appendix 5.

Study Selection Criteria and Process

Inclusion Criteria

An article was eligible for inclusion if it met all of the following pre-planned criteria:

1. The recruited patients were clinically disease-free after receiving curative-intent treatment.
2. It reported our interested outcomes, was an RCT or comparative study, and the analyzed sample size was ≥30 patients per group.
3. It compared any evaluations (e.g., clinical follow-up, laboratory tests, and imaging) with any frequency to be performed for surveillance.
4. If a study could answer Q2, it can be a single-arm study with a sample size of ≥100 patients.
5. For a conference/meeting abstract, it should be an RCT reporting any above outcomes.

Exclusion Criteria

An article or abstract was excluded if it met any of the following pre-planned criteria:

1. It was published in a language other than English due to limited access to translation services.
2. It was published in the form of a letter, animal study, editorial, or commentary.
3. Studies recruited >20% or an uncertain percentage of non-target patients but did not have a subgroup analysis for target patients.
4. There is no clear information on the frequency of surveillance examinations.
5. Patients had ocular melanoma.

A review of the titles and abstracts was conducted by one reviewer (XY). For studies that warranted full-text review, XY reviewed each article and discussed with the other Working Group members to confirm the final study selections. The reference lists of eligible papers were manually searched and the eligible papers that were published before 2018 were forward searched in PubMed for potentially included articles.

Ranking Importance of Outcomes

The survival outcomes (such as OS or disease-free survival [DFS]) and recurrence were ranked as "CRITICAL", and the outcomes of detection rate of a new primary melanoma, change in treatment, secondary cancer from different frequencies of CT or PET/CT examinations from surveillance, and patient-reported outcomes were ranked as "IMPORTANT" by the Working Group members. One patient representative from the Melanoma DSG ranked all the outcomes as "CRITICAL" (Appendix 6).

Data Extraction and Assessment of Risk of Bias

All included primary studies underwent data extraction by XY, and all extracted data and information were subsequently audited by an independent auditor. The Cochrane Collaboration Risk of Bias 2.0 tool was used to assess the risk of bias for each outcome for included RCTs [26]. The Risk of Bias in Non-randomised Studies of Interventions tool was used to assess the risk of bias for each outcome for included non-randomized studies [26].

Synthesizing the Evidence

When clinically and methodologically homogeneous results from two or more studies were available, a meta-analysis was conducted using the RevMan software version 5.4.1 (as recommended by the Cochrane Library). When a meta-analysis was inappropriate, the results of each study were presented individually in a descriptive fashion. The hazard ratio (HR) or relative risk (RR), rather than the number of events at a specific time, was the preferred statistic for meta-analysis if provided. HR/RR was expressed with a ratio of <1.0 indicating that patients in the experimental group had a lower probability of experiencing an event; conversely, an HR >1.0 suggested that patients in the control arm had a lower probability of experiencing an event.

When a meta-analysis was conducted, the chi-squared (X^2) test was used to test the null hypothesis of homogeneity, and a probability level less than or equal to 10% ($p \leq 0.10$) was considered indicative of statistical heterogeneity. If heterogeneity was detected, the I^2 index was used to quantify the percentage of variability in the effect estimates due to heterogeneity. A two-sided significance level of $\alpha=0.05$ was assumed.

Assessment of the Certainty of the Evidence

The certainty of the evidence per outcome for each comparison, taking into account risk of bias, inconsistency, indirectness, imprecision, and publication bias was assessed using the GRADE approach [27].

RESULTS

Primary Literature Search Results

There were 17,978 publications from the medical databases search, and 13,966 citations needed to be screened after deduplication. After reviewing the titles and abstracts, 236 articles needed full-text screening and six full-text articles met the pre-planned study selection criteria [4, 5, 11-14]. Among them, two were RCTs from the same MELFO trial [5, 11] reporting interim results at three years and four were retrospective comparative studies [4, 12-14]. After checking the reference lists of these six papers and conducting a forward literature search for two of them that were published before 2018, there was one additional included paper—the Rueth 2014 study [3]. Thus, overall, seven studies were included in this systematic review. One paper reported quality of life (QoL) results of 275 patients from an ongoing trial (NCT03116412) at one-year follow-up time [28]. Since this paper did not report interim analyses for recurrence and survival outcomes at one year, the preplanned sample size was 1300, and the estimated completion date is December 2026, we did not include this paper in our analysis and listed it in the ongoing trials table (Appendix 7). On December 19, we found a new publication of the

MELFO trial reporting the final results at five years [2]. Eventually, there are six studies that met our pre-planned study selection criteria.

There are five RCTs focusing on SSE [29-33]. However, these trials did not indicate when the recruited patients were clinically disease-free after receiving curative-intent treatment and how to perform SSE with other follow-up strategies at one, two, or five years after patients were clinically disease-free to lead to better patient-centred outcomes, such as recurrence or survival outcomes. Hence, they did not meet our preplanned study selection criteria. But we summarized their data in Appendix 8 for readers' interests.

The six studies' and patients' characteristics are listed in Table 4-1. A PRISMA flow diagram [34] with reasons for study exclusion is presented in Appendix 9.

Risk of bias assessment for individual study

The results of risk of bias assessments for each comparison per outcome of six studies are shown in Appendix 10. For the MELFO trial, due to blinding issue, the risk of bias for most outcomes was "Some concerns" [2, 5, 11]. All the five retrospective comparative studies did not perform methods to control confounders [3, 4, 12-14]. Thus, the risk of bias was critical for the confounding domain, which resulted in the overall risk of bias for any outcome to be "Critical". Although the authors of the Dieng 2022 study stated that they performed multivariable analyses and "stratified by substage for melanoma-specific survival (MSS) and OS", there were no details regarding which variables selected and input in the multivariable models, and we were unable to find the detailed substage data for MSS and OS in the full text and supplementary materials. We contacted authors on discrepancy of outcomes' data between text and supplementary materials but received no response [14].

Certainty of the evidence

The aggregate evidence certainty for each comparison of interventions was moderate to low for the MELFO trial; very low for five non-randomized comparative studies after considering the other four factors (inconsistency, indirectness, imprecision, and publication bias) together from the GRADE approach. A meta-analysis or network meta-analysis was inappropriate to perform because of the large number of different interventions, patient populations, and outcomes among the included studies in this systematic review; for the same reason, the traditional GRADE summary tables for each outcome were not presented as well.

Research Questions 1.

The MELFO trial mixed recurrence and second primary melanoma outcomes together [2]. All the five non-randomized comparative studies did not report the detection of second primary melanoma as an outcome [3, 4, 12-14].

(1) Comparison: Different follow-up schedules for clinical follow-up without imaging evaluations (stages IA to IIC)

The MELFO trial [2] recruited patients with stage IA to IIC stage melanoma and was conducted in the Netherlands (n=181) [5] and United Kingdom (n=207) [11]. The AJCC seventh edition were used to evaluate patients' stage when they were recruited, but the authors provided sufficient data for us to present patients' stage data using the AJCC eighth edition. Patients in both experimental and control groups received the same follow-up strategies following 2015 NICE guideline or 2013 Netherland guideline including patient history and physical examination, and structured SSE education reinforced at each visit by surgical oncologists, dermatologists, or nurse practitioners performed in the hospital. The laboratory testing and diagnostic imaging were only offered to patients with suspicious recurrent disease. However, patients in the experimental group received a lower frequency of the follow-up

evaluations based on the different stages (i.e., at the 1st, 2nd, 3rd, 4th, and 5th year after surgery treatment, IA-IB stage patients received the follow-up times as 1,1,1,1,1; IIA patients received 2,2,1,1,1; and IIB-IIC patients received 3,3,2,1,1, respectively). The patients regardless of stages in the control group received the same frequency of the follow-up evaluations, i.e., 4,3,2,2,2 times of the follow-up at 1st, 2nd, 3rd, 4th, and 5th year, respectively. The trial reported that at five years, there were no statistically significant difference for recurrence or second primary melanoma rate (HR, 0.87; 95% confidence interval [CI], 0.54 to 1.39; p=0.57), disease-specific survival (DSS) (HR, 1.00; 95% CI, 0.49 to 2.07; p=0.99), DFS (HR, 0.92; 95% CI, 0.56 to 1.53; p=0.76), OS (HR, 0.90; 95% CI, 0.49 to 1.66; p=0.74), and distant metastasis-free survival (DMFS) (HR, 0.99; 95% CI, 0.54 to 1.82; p=0.98) between the experimental and control groups (Table 4-2). For patient-reported outcomes, 240 (62%) were assessed at five years. No statistically significant difference was found between the groups on Impact of Event Scale, State-Trait Anxiety Inventory, Cancer Worry Scale, and RAND-36 scores at five years (Table 4-2).

(2) Comparison: CT versus (vs.) PET/CT vs. clinical examination (stages I to III)

The Rueth 2014 study used stage-specific Markov models based on single-institution, patient-level data (n=1600) to simulate the natural history of patients with stage I–III melanoma [3]. It made several assumptions to perform the models, such as "80% of early imaging-detected regional recurrences and 20% of early imaging-detected distant recurrences could be surgically treated with curative intent". Patient age ranged from eight to 95 years with no subgroup analysis for adults. It compared the imaging follow-up strategy of CT or PET/CT on the chest, abdomen, and pelvis performed every six or 12 months for five years or until recurrence for each patient in the cohort, with clinical examinations performed every three months for different stage patients. Additionally, it compared outcomes of CT and PET/CT with six-month and 12-month intervals for different stage patients, respectively (Table 4-2). The additional regional recurrence detection rate for imaging examination was 2.6% to 5.2% and the distant recurrence rate was 1.8% to 3.6% for stage I patients regardless of imaging modality or imaging frequency, and was 6.4% and 8.4%, respectively, for stage III patients using routine surveillance CT or PET/CT performed every 12 months. For stage I patients, life expectancy was 52 months without surveillance imaging, and the increase in life expectancy with PET/CT imaging every six months was 0.4 months with a relative survival increase of 0.7%. For stage IIIC patients, life expectancy was 30 months without surveillance imaging, and the increase in life expectancy with PET/CT imaging every six months was two months with a relative survival increase of 6.8%. The PPV for CT and PET/CT with six-month or 12-month interval during the five years were low for any stage patients, such as 13% versus 32% for CT versus PET/CT with 12-month interval for stage IIIC patients. The false positive rate of CT was 20% and PET/CT was 9% overall. Life-expectancy gains were ≤2 months for all stage patients.

(3) Comparison: Clinical examinations + imaging vs. clinical examination only (Stages IIA to IIIC)

The Kurtz 2017 study included 125 patients from stage IIA to IIB patients and 122 patients from stage IIC to IIIC [13]. Seventy-six patients with stage IIA to IIB melanoma, and 105 patients with stage IIC to IIIC received at least two serial chest x-rays, and at least two serial PET/CT or whole-body CT and brain MRI except the regular clinical physical examinations, respectively. Comparing with patients receiving clinical physical examinations only, those with additional imaging examinations had little or no difference for OS rate (96%; 95% CI, 0.89 to 0.98 vs. 95%; 95% CI, 0.88 to 0.99), and no detailed information for recurrence-free survival (RFS) (p=0.753) in stage IIA to IIB patients at five years. There were no survival data reported between

intervention and control groups in stage IIC to IIIC patients. However, for patients at all stages, 25 of the 42 recurrences (60%) were detected by clinical physical examinations alone, and the remainder was detected using imaging. For stage IIC and IIIA-C patients, routine whole-body imaging detected 50% of recurrences that led to additional surgery and/or treatment. (Table 4-2).

(4) Comparison: Ultrasound-based + physical examination follow-up vs. clinically based follow-up (Stages IB to IIA)

The Ribero 2017 study compared data from two tertiary melanoma referral centres, including patients with stage IB or IIA [4]. Group 1 (n=554) with the clinical-based follow-up strategies including only physical examinations every four months for the first two years and then every six months for the remaining three years. Additionally, laboratory tests (including complete blood cell count, biochemical profile, lactate dehydrogenase, serum S100B protein, melanoma-inhibitory-activity protein, and beta-2 microglobulin) were performed every six months for five years. Group 2 (n=595) included an ultrasound-based follow-up strategies plus physical examination every six months for five years, the regional lymph node basins ultrasound every six months, and abdomen ultrasound every 12 months for five years. Patients in both groups received instructed SSE. The recurrence detection rate was the same in the two groups (12% vs. 12%; RR, 1.03; 95% CI, 0.76 to 1.40; p=no statistical significance). There is little to no difference in DMFS (HR, 0.78; 95% CI, 0.51 to 1.16; p=0.22;) and in nodal metastasis-free survival (HR, 0.88; 95% CI, 0.51 to 1.50; p=0.64) favouring clinical-based follow-up strategies; and in MSS (HR, 1.24; 95% CI, 0.81 to 1.90; p=0.32) favouring ultrasound-based follow-up strategies (Table 4-2) although all of them are not statistically significant.

(5) Comparison: Different follow-up schedules with imaging evaluations (stages IIIA to IIID)

The Broman 2021 study analyzed 159 of 177 patients with stage IIIA to IIID [12]. Surveillance regimens were determined by treating medical and surgical oncologists. Surveillance consisted of scheduled clinical assessments at approximately three- to six-month intervals with or without imaging (including nodal basin ultrasound, CT, PET/CT, and brain MRI). Levels were classified into low, moderate, and high (Table 4-2). Patients in the high-intensity surveillance group were more likely to have received adjuvant therapy. At a median of 24 months follow-up, 27% of patients experienced recurrence. The recurrence risk was 27% (1/3.7) vs. 25% (1/4) vs. 30% (1/3.3) (p=0.33); and 33%, 60%, and 40% in the low-, moderate-, and high-intensity surveillance group, respectively, achieved a disease-free interval after surgery or complete response to systemic therapy for patients without a statistical significance among the three groups (p=0.28) (Table 4-2).

The Dieng 2022 study compared intensive (every three or four months) (n=141) or biannual (n=47) with annual (n=285) CT or PET/CT in patients with stage IIIA, IIIB, IIIC, or IIID for a median follow-up time of 6.2 years [14]. The results showed that patients in the intensive CT or PET/CT surveillance groups had a higher distant recurrence detection rate for all stage III patients (intensive vs. biannual vs. annual: 84% vs. 51% vs. 38%; p<0.001) (Table 4-2). The results for OS, MSS, and distant disease-free survival (DDFS) favoured the annual CT or PET/CT follow-up strategy (Table 4-2). The OS results showed HR, 1.21; 95% CI, 0.65 to 2.28; p=0.545 when biannual versus annual imaging, and HR, 5.20; 95% CI, 3.53 to 7.66, p<0.001 when intensive versus annual imaging. For MSS, HR was 1.25; 95% CI, 0.66 to 2.40; p=0.495 when biannual versus annual imaging, and HR was 5.28; 95% CI, 3.55 to 7.87; p<0.001 when intensive versus annual imaging. For DDFS, HR was 1.69; 95% CI, 1.02 to 2.78; p=0.040 when biannual versus annual imaging, and HR was 4.57; 95% CI, 3.25 to 6.45; p<0.001 when intensive versus

annual imaging. However, patients who were selected into the intensive surveillance group had worse clinical characteristics than those in the other two groups and patients in the biannual group had worse clinical characteristics than those in the annual group such as age, ulceration rate). Thus, there are biological reasons for the intensive surveillance group to have more patients with distant recurrence detection rate and worse survival results, which led to a challenge to interpret the effects of the different follow-up strategies. We contacted the authors about discrepancy in results reported in supplementary and the Dieng 2022's full text but did not receive a response.

Research Questions 2

There is no evidence that met our study selection criteria to answer Research Question 2.

Ongoing, Unpublished, or Incomplete Studies

The National Cancer Institute Clinical Trials Database (http://www.clinicaltrials.gov/) was searched on May 10, 2022, for potential trials meeting the selection criteria for this systematic review. There are 25 ongoing, unpublished, or incomplete trials that should be checked for potential inclusion in a future update of this guideline (Appendix 6).

DISCUSSION

This systematic review included one RCT with low certainty of evidence, and five non-randomized comparative studies, also with very low certainty of evidence. The data in these trials addressed follow-up strategies and their frequencies in adult patients with stage I, II, III, or resectable IV melanoma who are clinically disease-free after receiving curative-intent treatment. The RCT indicated that a reduced follow-up schedule with clinical follow-up strategies was safe and cost-effective for patients with stage IA–IIC melanoma patients [2]. However, the percentage of stages IIB to IIC was 18% (n=70) without a subgroup analysis. Therefore, from this RCT it is uncertain whether these extra imaging follow-up strategies improve patient-related outcomes.

The results from the five comparative studies showed that PET/CT had a higher PPV and a lower false-positive rate than CT to detect recurrence in stages I to III patients [3]. They showed that surveillance strategies with imaging examinations could detect approximately 40% additional recurrences in stage IIA to IIIC patients and detected 50% of recurrences for stage IIC and IIIA-C patients, that led to additional management such as surgery [13]. There was no clear evidence to support that the addition of ultrasound to follow-up strategies would lead to better patient outcomes in stage IB to IIA patients[4]. Intensive or biannual imaging surveillance did not lead to better patient-related outcomes than annual imaging surveillance in stages IIIA to IIID patients [12, 14]. However, the certainty of the evidence from these five comparative studies is very low as methods to control potential confounding variables were not performed, such as a multivariable analysis or balancing the patients' characteristics at baseline between the comparative groups.

Although most of these eligible papers were published in or after 2020, all of them started recruiting patients around 2010 (>10 years ago), prior to the advent of our new adjuvant therapies, which have been shown to prolong RFS. Therapies in the metastatic setting have shown improvements in OS and those treated with a lower burden of disease have longer survival outcomes [9]. The current evidence in the literature may not be up to date with this rapidly evolving treatment landscape. Thus, accurately identifying recurrence and metastases are crucial for patients to obtain timely optimal treatment in order to improve patient-related outcomes. Simultaneously, the potential false-positive results after imaging evaluations, and

the management of these false-positive events should be considered and discussed with each patient. For example, one single-arm study showed that 152 (46%) patients with stage IIIA–D melanoma under follow-up with CT or PET/CT every six or 12 months for five years had false positive findings, and 34 invasive procedures were undertaken for benign lesions, including biopsy, colonoscopy, and surgery (e.g., total hysterectomy) [35]. Additionally, patients should be informed of the potential risk of secondary cancer from CT or PET/CT examinations (having more radiation than CT alone), although this risk is very low [10].

This is an updated systematic review, and the literature search date was from January 2015 to June 2022. In our previous systematic review [18], the literature search date was from January 2000 to February 2015, and we included single-arm studies and comparative studies reporting diagnostic outcomes (such as sensitivity and specificity) of surveillance evaluations. After reviewing the papers included in the previous review, only one paper met our current study selection criteria—the Tarhini 2009 study [36]. The Tarhini 2009 study recruited patients with stages IIB to III melanoma and reported that a change of the S100B biomarker (from the baseline to any later time points: weeks 4 to 6, weeks 12 to 14, and weeks 48 to 52) in 162 patients seemed to be associated with a worse relapse-free survival and OS compared with 378 patients without a change in the S100B biomarker value. However, the changed value of the S100B biomarker was not included in the multivariable analysis to control for potential confounders. Further research is needed to ascertain which biomarkers will help clinicians differentiate those patients that are at the high risk and who will best respond to therapy.

There are five RCTs regarding SSE, but they did not meet our pre-planned study selection criteria mainly because the recruited patient population was not clinically disease-free after receiving curative-intent treatment, and patient-related outcomes were not reported at the 1st, 2nd, 3rd, 4th, and/or 5th year. However, SSE is an effective strategy to assist patients to find recurrences, new primary melanomas, and metastasis in the target population.

Our systematic review has some limitations. First, the literature search was limited to English-language publications, which can potentially lead to missing some relevant articles published in non-English languages. Second, we only searched four literature databases (MEDLINE, EMBASE, PubMed, and the Cochrane library) due to time limitations. Thus, it is possible that some relevant papers in other medical databases have been missed.

FUTURE RESEARCH

High-quality studies regarding imaging follow-up strategies with optimal frequencies should be conducted, especially in high-risk stage II, III, and resected stage IV patients. SSE follow-up strategies with different frequencies should be investigated and combined with clinical follow-up, and/or with imaging, biomarkers, and dermoscopy. Furthermore, subgroup analyses for different stage patients should be performed.

Table 4-1. Study and patient characteristics (study order is based on the publication year and alphabetical by first author's last name)

Study (Trial name); Country	Sample Size (n)	Stage; Received adjuvant treatment	Mean/ Median age (range/SD)	F/U strategy and frequency		Who performed F/U strategy
				Intervention (experimental group)	Control (conventional group)	
Randomized controlled trial for Question 1/Question 2.						
Moncrieff 2022[a] (MELFO); UK, The Netherlands	388	IA-IB[b]: 64% IIA[b]:18% IIB[b]:15% IIC[b]: 3%; NR	61 years (IQR, 50 to 69)	F/U strategies following 2015 NICE guideline or 2013 Netherland guideline: Patient history and PE, and structured SSE education reinforced at each visit.		Surgical oncologists, dermatologists, or nurse practitioners
				n=192. Frequency of F/U strategies at 1st, 2nd, 3rd, 4th, 5th year after surgery for primary melanoma: IA-IB: 1, 1, 1, 1, 1; IIA: 2, 2, 1, 1, 1; IIB-IIC: 3, 3, 2, 1, 1.	n=196. Frequency of F/U strategies at 1st, 2nd, 3rd, 4th, 5th year: IA-IIC: 4, 4, 4, 2, 2.	
Retrospective comparative studies for Question 1.						
Rueth 2014[c]; USA	1600	I: 45% II: 4.5% IIIA: 8.5% IIIB: 23% IIIC: 19%; NR	61 years (range, 8 to 95)	Imaging F/U strategy, n=NR. Frequency of F/U: CT or PET/CT imaging of the chest, abdomen, and pelvis performed every 6 or 12 months for 5 years or until recurrence for each patient in the cohort.	Clinical PE, n=NR. Frequency of F/U: every 3 months or until recurrence for each patient in the cohort.	NR
Kurtz 2017[d]; USA	247	IIA: 19% IIB: 31% IIC: 9% IIIA: 24% IIIB: 12% IIIC: 5%; 17% (6% in IIB, 10% in IIC,25% in IIIA, 43% in IIIB, 42% in IIIC)	NR	IIA-B: n=76, clinical PE plus at least 2 serial chest x-rays. IIC/IIIA-C: n=105, clinical PE plus at least two serial PET/CT or whole-body CT and brain MRI. At each increasing substage, a greater percentage of patients were followed with serial imaging.	IIA-B: n=49, clinical PE; IIC/IIIA-C: n=17 clinical PE.	NR

Ribero 2017[e]; Italy, Spain	1149	IB: 68% IIA: 32%; NR	54 years (IQR, 42 to 65)	Spanish cohort, n=554: patient history and PE plus SSE education. Complete laboratory testing[f] with serum biomarkers was also performed. Frequency of F/U: patient history and PE every 4 months for the first 2 years, then every 6 months for the remaining 3 years. Laboratory tests[g] every 6 months for 5 years.			Italian cohort, n=595: US-based F/U, patient history, PE plus SSE education. Frequency of F/U: patient history and PE every 6 months for 5 years. US of the regional lymph node basins every 6 months for 5 years. Abdomen US every 12 months for 5 years.	Trained dermatologists
Broman 2021[g]; USA	177	IIIA: 30% IIIB: 24% IIIC: 44% IIID: 2%; 37%	65 years (IQR, 53 to 75)	Surveillance[h]	Low intensity or no surveillance	Moderate intensity	High intensity	Medical and surgical oncologists
				Patients (n=159)	70 (44%)	42 (26%)	47 (30%)	
				Clinical PE	Less than every 6 months	Every 6 months	Every 3 months	
				Nodal basin ultrasound[i]	Less than every 6 months	Every 6 months	Every 6 months	
				CT or PET/CT	Less than every year	Every year	Every 6 months	
				Brain MRI	Not specified	Not specified	Every year	
Dieng 2022[g]; Australia	473	IIIA: 19% IIIB: 31% IIIC: 49% IIID: 1%; NR	56 years (range, 19 to 89)	Imaging F/U strategy: CT or PET/CT, no additional information on other procedures done during F/U by clinicians. Frequency of F/U: every 3 to 4 months (n=141), or every 6 months (n=47) over at least 5 years[j].			Imaging F/U strategy: CT or PET/CT, no additional info on other procedures done during F/U by clinicians. Frequency of F/U: every 12 months at least 5 years[j] (n=285).	Clinicians (not specified)

Abbreviations: AJCC, American Joint Committee on Cancer; CT, computed tomography; F/U, follow-up; IQR, interquartile range; MELFO, melanoma follow-up study; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; NR, not reported; PE, physical examination; PET, positron emission tomography; SD, standard deviation; SSE, skin self-examination; UK, The United Kingdom; US, ultrasound, USA, The United States of America

[a] We presented patient stages according to the 8th edition AJCC staging system based on the data provided .

[b] Patient stage information is from 110 patients at end of study of The Netherland trial [5] and 207 patients from the United Kingdom trial [11].

[c] The patient stages were determined according to the 6th edition AJCC staging system.

[d] No mention of the AJCC staging system edition that was used to determine patient stages.

[e] The patient stages were determined according to the 7th edition AJCC staging system.

[f] Laboratory includes complete blood cell count, biochemical profile, lactate dehydrogenase, serum S100B protein, melanoma-inhibitory-activity protein and beta-2 microglobulin.
[g] The patient stages were determined according to the 8th edition AJCC staging system.
[h] Surveillance regimens were determined by treating medical and surgical oncologists.
[i] Nodal recurrences detected clinically were identified by surgeons, radiation oncologists, and surgical oncologists.
[j] Clinicians may have ordered further imaging on the basis of patients' symptoms or findings of the routine tests; these were considered as 'extra investigations' and not part of the routine schedule.

Table 4-2. Outcomes (study order is based on the publication year and alphabetical by first author's last name)

Study (Trial name); Country	Mean/Median F/U time (range); F/U rate	Recurrence/new primary melanoma detection	Survival outcome	PRO
Randomized controlled trial for Question 1/Question 2.				
Moncrieff 2022 (MELFO); The Netherlands, UK	5 years; 99.5% for recurrence and survival outcomes, 62% for PRO	Recurrence or second primary melanoma rate: HR, 0.87; 95% CI, 0.54 to 1.39; p=0.57.	DSS: HR, 1.00; 95% CI, 0.49 to 2.07; p=0.99.DFS: HR, 0.92; 95% CI, 0.56 to 1.53; p=0.76. OS (univariable analysis): HR, 0.90; 95% CI, 0.49 to 1.66; p=0.74. DMFS (univariable analysis): HR, 0.99; 95% CI, 0.54 to 1.82; p=0.98.	240 (62%) were assessed at 5 years. No statistically significant difference was found between two groups on IES, STAI, CWS, and RAND-36 scores at 5 years.
Retrospective comparative studies for Question 1.				
Rueth 2014; USA	5 years; NA	Overall CT vs. PET/CT for 6-month interval: 4737 per 10,000 patients vs. 6305 per 10,000 patients. Overall CT vs. PET/CT for 12-mo interval: 2032 per 10,000 patients vs. 2707 per 10,000 patients. Compared to clinical examination alone, the additional regional recurrence detection rate, 3%–5%; distant recurrence, 2%–4% for stage I	DSS (CT vs. PET/CT for 6-months interval): I: 92% vs. 92% II: 77% vs. 77% IIIA: 76% vs. 76% IIIB: 53% vs. 53% IIIC: 37% vs. 38% DSS (CT vs. PET/CT for 12-months interval): I: 92% vs. 92%	NR

		regardless of imaging modality or imaging frequency; the additional regional recurrence detection rate, 6%; distant recurrence, 8% for stage III using routine surveillance CT or PET/CT performed every 12 months.	II: 76% vs. 76% IIIA: 76% vs. 76% IIIB: 52% vs. 53% IIIC: 36% vs. 37% For stage I: life expectancy was 52 months, the increase was 0.4 months with routine PET/CT surveillance every 6 months. For stage IIIC: life expectancy was 30 months, the increase was 2 months with routine PET/CT surveillance every 6 months.	
Kurtz 2017; USA	IIA-B: 35 months, IIC-IIIC: 32 months; 100%	For all stages combined, 25/42 recurrences (60%) were detected by clinical. PE alone, the rest (40%) were detected with imaging; for stage IIC-IIIC, 50% of recurrences were detected with imaging. No comparison between two intervention groups.	For stage IIA-B: RFS: p=0.75 at 5 years. OS rate at 35-month F/U=96%; 95% CI, 0.89 to 0.98 vs. 95%; 95% CI, 0.88 to 0.99; p=NS. For IIC-IIIC: NR.	NR
Ribero 2017; Italy, Spain	4.1 years (IQR, 1.2 to 7.6); 100%[a]	Recurrence (clinical-based F/U vs. US-based F/U): 69/554=12% vs. 72/595=12% RR=1.03; 0.76 to 1.40; p=NS.	DMFS: HR, 0.78; 95% CI, 0.51 to 1.16; p=0.22. MSS: HR, 1.24; 95% CI, 0.81 to 1.90; p=0.32. NMFS: HR, 0.88; 95% CI, 0.51 to 1.50; p=0.64.	NR
Broman 2021; USA	24 months (IQR, 17 to 33); 90%	48 (27%) recurred. No difference in recurrence among 3 groups (recurrence risk=1/3.7 vs. 1/4 vs. 1/3.3); p=0.33. No difference in recurrence by receipt of adjuvant systemic therapy; p=0.76.	33%, 60%, and 40% with low-, moderate-, and high-intensity surveillance achieved a disease-free interval after surgery or complete response to systemic therapy (p=0.28).	NR

Dieng 2022; Australia	6.2 years (95% CI; 6.0 to 6.4 years); 100%[d]	Distant recurrences (intensive vs. biannual vs. annual CT or PET/CT): 119/141=84% vs. 24/47=51% vs. 109/285=38%; p<0.0001. Distant recurrences (IIIA vs. IIIB vs. IIIC vs. IIID): 24/89=27% vs. 83/146=57% vs. 139/231=60% vs. 6/7=86%; p<0.0001.	OS (biannual vs. annual)[c]: multivariable HR, 1.21; 0.65 to 2.28; p=0.545. OS (intensive[b] vs. annual)[c,d]: multivariable HR, 5.20; 3.53 to 7.66; p<0.001. MSS (biannual vs. annual)[c]: multivariable HR, 1.25; 0.66 to 2.40; p=0.495. MSS (intensive[b] vs. annual)[c]: multivariable HR, 5.28; 3.55 to 7.87; p<0.001. DDFS (biannual vs. annual)[c]: multivariable HR, 1.69; 1.02 to 2.78; p=0.040. DDFS (intensive[b] vs. annual)[c,d]: multivariable HR, 4.57; 3.25 to 6.45; p<0.001.	NR

Abbreviations: CI, confidence interval; CT, computed tomography; CWS, Cancer Worry Scale; DDFS, distant-disease free survival; DFS; disease-free survival; DSS, disease-specific survival; DMFS, distant metastasis-free survival; F/U, follow-up; HR, hazard ratio; IES, Impact of Event Scale; IQR, interquartile range; MELFO, melanoma follow-up study; MSS, melanoma-specific survival; NA, not applicable; NMFS, nodal metastasis-free survival; NR, not reported; NS, no statistical significance; OS, overall survival; PET, positron emission tomography; PRO, patient-reported outcomes; RAND-36, Mental and Physical Component scales; RR, relative risk; RFS, recurrence-free survival; STAI-S, State-Trait Anxiety Inventory-State version; UK, The United Kingdom; US; ultrasound; USA, The United States of America.

[a] Since this was a retrospective study, we assume that the authors collected the data from all the patients.

[b] Intensive is defined as a follow-up every 3 to 4 months.

[c] The data were provided from supplemental materials of the Dieng 2022 study.

[d] We contacted the authors about discrepancy in results reported in supplementary (Dieng 2022 [supplementary materials]) and the Dieng 2022's full text but did not receive a response.

Surveillance of Patients with Stage I, II, III, or Resectable IV Melanoma Who Were Treated with Curative Intent

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Melanoma DSG, the Patient Consultation Group, and the PEBC RAP (Appendix 2). The results of these evaluations and the Working Group's responses are described below.

Melanoma DSG Review and Approval

Of the 16 DSG members, all voted by November 8, 2022, for the first round. Among the drafted 15 recommendations and six qualifying statements, three recommendations did not reach the agreement rate of 75% (Appendix 11). On November 11, 2022, the Melanoma DSG held an online meeting to discuss all the comments raised by DSG members. The 15 revised recommendations and five revised qualifying statements were then sent to the Melanoma members to vote again. There was one recommendation did not reach the agreement rate of 75%, i.e., "Recommendation 4.1 Patients can be transitioned to a primary care physician for follow-up after five years. Annual follow-up with a dermatologist should continue." (Appendix 12). After discussing among SR, TP, and XY on December 2, 2022, this recommendation was changed to "Recommendation 4.1 Patients may be transitioned to a primary care physician for follow-up after five years depending on the stages of the disease and clinical risk factors. Annual follow-up with a dermatologist should continue as clinically indicated."

Patient Consultation Group

Five patients/survivors/caregivers representatives in the Patient Consultation Group reviewed the draft document and provided their comments at an online meeting on December 14, 2022. Their main comments were: (1) If MRI of the brain is not immediately available, patients would like to discuss with their clinicians what they should do: i.e., try to obtain an MRI at another location, or undergo head CT instead, etc. (2) They wanted to know whether their QoL would be impacted after these recommendations are in place. (3) They suggested that caregivers who were involved in decision-making should be provided education regarding SSE and sun safety as well as patients. (4) "Routine blood tests" for any stage patients with asymptomatic recurrence or metastatic disease, but what did the routine blood tests refer to. (5) They appreciated the tables to present the evidence under Key Evidence section for each recommendation. (6) The education to patients and caregivers can consider equity and be based on different cultures; thus, the clinicians may be provided this kind of training. (7) In Recommendation 4, when patients were transferred to primary care physicians, these clinicians are preferred to have specific training for melanoma. The Working Group incorporated the Patient Consultation Group comments into the Recommendations and the Justification for Recommendation section under in Section 2.

RAP Review and Approval

Three RAP members, including the PEBC's Scientific Director, reviewed and approved this document on December 14, 2022. The main comments from the RAP 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 RAP.

Comments	Responses
1. Is PET/CT for follow-up surveillance a currently funded indication in Ontario?	So far PET/CT for follow-up surveillance of asymptomatic patients is not a currently funded indication in Ontario. The Working Group members want Ontario to consider this point through these recommendations.
2. There is reference on page 14 to "synthesizing the evidence" which is boilerplate and not relevant to this guidance document and in my opinion could be removed	We performed a meta-analysis for recurrence or second primary melanoma for two RCTs and reported the pooled RR in Table 4-2. Thus, we have added RR under "synthesizing the evidence" part.
3. To the non-melanoma expert, there would be value of including the pathology stage groups from the 8th edition of the 2017 Cancer Staging Manual as an appendix.	We have added this information in Appendix 1.
4. The recommendations include history and skin examination by dermatologist and/or other specialists but do not mention physical examination. Given the observation in the Kurtz study that 25 of 42 recurrences were detected by physical examination, shouldn't physical examination be a standard part of surveillance?	We have revised the first bulletin under Recommendations 1-3 as "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/or a surgeon, family physician, cancer nurse specialists…".
5. I generally agree with the recommendations but do feel that more could be said about access and cost to the surveillance procedures and particularly to PET/CT. Although I do not expect to see a cost-effectiveness analysis, it might be helpful to provide an estimate of the cost of a PET/CT as cost and access challenges should be part of an informed discussion with a patient.	It is not in the scope of this guideline to address cost or access.
6. For Recommendation 4.1 "Patients may be transitioned to a primary care physician who has had training in melanoma care for follow-up after five years depending on the stages of the disease and clinical risk factors. Annual follow-up with a dermatologist should continue as clinically indicated.", the authors should describe more details regarding what kind of follow-up evaluations should be done like Recommendations 1-3, and what are the clinical indicators for annual follow-up with a dermatologist.	After five years, patients are considered to be at a lower risk but their risk never goes to zero and hence the expert opinion of the Working Group was that patients be followed annually. However, there is no eligible evidence investigating the details of annual follow-up after five years. When the relevant evidence is available, we will update this recommendation as soon as possible.

EXTERNAL REVIEW

Targeted Peer Review

Twelve targeted peer reviewers (nation-wide and international) who are considered to be clinical experts on the topic with broad expertise (medical oncologists, surgical oncologists, plastic surgeons, family doctors, and dermatologists) were identified by the Working Group.

Five agreed to be the reviewers (Appendix 1). Results of the feedback survey are summarized in Table 5-3. The main comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=5)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.			1	3	1
2. Rate the guideline presentation.				2	3
3. Rate the guideline recommendations.				3	2
4. Rate the completeness of reporting.			1		4
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				1	4
6. Rate the overall quality of the guideline report.			1	1	3
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				2	3
8. I would recommend this guideline for use in practice.				2	3
9. What are the barriers or enablers to the implementation of this guideline report?	• Educating people in the field, who are not involved with the guideline development, who are not the key opinion leaders, who might work in more rural areas and who might not have melanoma as their focus, but part of their practice: they need to know the updates made in order for them to look them up, the next time they have a patient that falls within these guidelines. • Potential barriers include access to adequate dermatological follow up and access to primary care for Stage 1A-2A and transition after five years for other melanoma patients to primary care. • There are several barriers to the implementation of this guideline: proximity to skin cancer health care practitioner, availability of primary care physician to make the initial referral, lack of possible referral to appropriate skin cancer health care practitioner from the family doctor (based on family doctor's knowledge of the guideline), availability of PET/CT, CT, MRI. Publication in journals and dissemination of information through family medicine colleges, communities and journals would be enablers. Oncologists				

	and dermatologists or other skin cancer specialists will be up to date based on guideline publication. • At this time, there are many patients in Ontario who do not have a primary care provider.

Table 5-4. Summary of the Working Group's responses to comments from targeted peer reviewers.

Comments	Responses
1. There is no evidence on dermoscopy use for surveillance and skin examination and the value of dermoscopy in detecting a secondary melanoma or recurrence was not mentioned, nor was it used in the study selection criteria and process.	In Appendix 5. Literature Search Strategy, we used dermoscopy or photo with their alternative terms to search medical databases. There is no eligible evidence that met our pre-planned study selection criteria at present. We have added "dermoscopy or photo-surveillance" into the research question. Since dermoscopy is current standard of care for skin lesion assessment (diagnostic accuracy is improved when clinicians have been adequately trained in the use of dermoscopy, thus it has become standard of care for many dermatologists in the evaluation of lesions suspicious for melanoma from the clinical perspective), in Recommendations 1-3, we recommended that "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),…" for the target patient populations based on the consensus. Three ongoing studies will provide relevant evidence in the next two to three years (Appendix 7 on page 45). When new evidence can impact any of the current recommendations, we will update this guideline as soon as possible.
2. One concern I have is that although the PET/CT has been proven to have a higher positive predictive value and lower false positive rate, the guideline still offers CT as an alternative screening tool. I think that this is a substandard recommendation and will lead to increased heathcare costs (due to higher false positive rate) and higher patient anxiety and possible later stage detection and disease in some patients.	Due to the limited resource of PET/CT, CT is still an option during surveillance in Ontario.
3. In Recommendation 3, should a line be added that "While there are no studies specifically addressing resected stage IV melanoma patients, this subgroup of patients are included with the stage III group of patients because similar to the stage III patients, resected stage IV patients are considered potentially cured yet high risk for recurrence within 5 years of treatment and the risk of recurrence falls significantly beyond five years."	We accepted reviewer's comment, and have added this sentence under "Qualifying statement": 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.

4. There is no discussion or information given to the Working Group/patient group on dermoscopy usage and the value it has in surveillance.	We have added one sentence: "in this updated systematic review, there is no eligible evidence investigating the roles of photo-surveillance, dermoscopy, or biomarkers in the target population. More research is needed to explore these issues in the surveillance of target patients." under FUTURE RESEARCH on page 8. Also, please have a look at the relevant response to Comment 1. in this table.
5. Consider using the MELFO schedule here; it would reduce a lot of visits for the healthcare providers, as there are many stage I patient.	The frequencies of the follow-up strategies in the MELFO trial in years one to five are: once a year for IA-IB; twice a year for the first two years and then once a year for IIA. In Recommendation 1, we suggested "every six to 12 months for three years or as clinically indicated, then annually for two years or as clinically indicated." for stages IA to IIA. Thus, both clinicians and patients can make their decisions based on individual patients' situation.
6. For Recommendations 2 and 3, is this regardless of the fact if patients are or are not using adjuvant therapy? I would argue that shortening the imaging intervals DURING adjuvant therapy from six to three months might help prevent unnecessarily continuing with ineffective adjuvant therapy for another three months, thereby saving them from potential toxicity and costs.	Yes the surveillance schedules are regardless of whether or not they are on adjuvant therapy.
7. Please see "Stahlie EHA, et al. The use of FDG-PET/CT to detect early recurrence after resection of high-risk stage III melanoma. J Surg Oncol. 2020 Dec;122(7):1328-1336." It shows that most recurrences are already found very early (first scan at three months). Recent publication shows that the value of ultrasound is low, since it is rarely a solitary recurrence to the nodal basin, but can more frequently be a recurrence outside the nodal basin or a combination of distant and nodal recurrence: Montgomery, K.B., T.A. Correya, and K.K. Broman, Real-World Adherence to Nodal Surveillance for Sentinel Lymph Node-Positive Melanoma. Ann Surg Oncol, 2022. 29(9): p. 5961-5968. (MIA (unpublished data) confirms this).	We thank the reviewer very much for providing two relevant articles. Neither article meets our pre-planned study selection criteria. The Stahlie 2020 paper is a single-arm study with a small sample size (<50 patients for each cohort). Without comparison, we are uncertain whether the result of the recurrence detection was only due to PET/CT alone or not. Although Montgomery et al listed the comparison (ultrasound vs. non-ultrasound) in their Table 2, they did not report the outcome results in the two groups separately. Also, except for ultrasound, they didn't report whether patients accepted any other follow-up strategies, such as clinical examinations, CT, etc. in each group.
8. As there are no up-to-date Ontario guidelines for melanoma follow up, these recommendations provide a backbone for clinicians to utilize. However, we need to ensure that we update them as soon as literature is available based on current treatment guidelines.	All the PEBC's guidelines that are older than one year will be assessed annually to make them current and clinically relevant.

9. On page 17, paragraph 1 regarding the Ribero paper—please clarify last line of paragraph. The data seem to show no difference in MSS and thus favours clinical surveillance (not US).	As we described under **Synthesizing the Evidence,** "HR/RR was expressed with a ratio of <1.0 indicating that patients in the experimental group had a lower probability of experiencing an event; conversely, an HR >1.0 suggested that patients in the control arm had a lower probability of experiencing an event.". To make it clearer, we have added "although all of them are not statistically significant." on page 17.
10. in the Dieng study, the HRs for OS, MSS, DFSS are comparable for annual versus biannual, which supports the conclusion "favouring annual imaging." Upon reviewing the full paper, patients selected for intensive surveillance had worse clinical characteristics in this non-randomized study that impacted the survival of the intensive imaging group.	We agree with the reviewer's comments, and that is why the certainty of evidence is very low for all the comparative study after assessment.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All the oncologists, dermatologists, and family doctors in the PEBC database who showed interest in melanoma, and the clinical experts whom the Working Group members recommended were contacted by email to inform them of the survey. Seventy-six professionals in Ontario were contacted. Thirteen (17%) responses were received and five indicated no interest in this guideline. Thus, the voting results from eight clinicians are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

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

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1 (13%)	2 (25%)	5 (62%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	1 (13%)			2 (25%)	5 (62%)
3. I would recommend this guideline for use in practice.	1 (13%)			1 (12%)	6 (75%)
4. What are the barriers or enablers to the implementation of this guideline report?	1) Wait times and timely referrals. Access to diagnostics and treatment in a timely manner. 2) Access to imaging for advanced stages. 3) Need to act in the best interests of the patients to improve outcomes.				

Table 5-6. Summary of the Working Group's responses to comments from professional consultants.

Comments	**Responses**
1. It needs a summarized version - I think even some practitioners will get lost in all of the	After the external review, we will provide a summary of all the recommendations in Section 1.

data and so a nicely worded/simple 'public summary' would help with implementation.	
2. In Section 2, it indicates that there were three levels for 'strength of recommendations', but it looks like only Recommendation 2 has a 'strength' listed for it?	Under each recommendation, we presented several sub-recommendations. Some of them are "Recommendations" and others are "Weak Recommendations". Thus, we have added the recommendation strength after every sub-recommendation.
3. As a surgeon, I need time in my practice to see new patients that need surgery. I will not be able to follow postoperative patients for this regular monitoring although I believe it is necessary. I cannot get a dermatologist to follow patients for surveillance at the present time. This leaves the responsibility on mostly family doctors practices in settings outside of academic hospitals. What about patients without a family doctor?	How to solve this resource question is beyond the scope of this guideline. We leave resource consideration to other decision-makers in Ontario Health (Cancer Care Ontario). But we hope that this guideline can guide their resource management.

Final vote

After External review, the current Recommendation 4.1 "Patients may be transitioned to a primary care physician for follow-up after five years depending on the stages of the disease and clinical risk factors. Annual follow-up with a dermatologist should continue as clinically indicated." was circulated to the 16 DSG members to vote again, and the agreement rate was 88%, which reaches our consensus threshold of 75% (Note in Appendix 12). One DSG member disagreed and provided the following comments, "I think it is unrealistic to follow patient for up to five years and then identify a trained family doctor in melanoma to follow. they are few and far between. At best it is OK to return to primary care.". Another DSG member voted "Abstain".

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 Working Group and approved by the Melamona DSG and the PEBC RAP.

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Appendix 1. Melanoma pathological stages (the 8th edition American Joint Committee on Cancer staging system)[a]

Pathological stage group	Tumor (T)	Nodes (N)	Metastasis (M)
0	Tis	N0	M0
IA	T1a	N0	M0
IA	T1b	N0	M0
IB	T2a	N0	M0
IIA	T2b	N0	M0
IIA	T3a	N0	M0
IIB	T3b	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIB	T0	N1b, N1c	M0
IIIC	T0	N2b, N2c, N3b or N3c	M0
IIIA	T1a/b-T2a	N1a or N2a	M0
IIIB	T1a/b-T2a	N1b/c or N2b	M0
IIIB	T2b/T3a	N1a-N2b	M0
IIIC	T1a-T3a	N2c or N3a/b/c	M0
IIIC	T3b/T4a	Any N≥N1	M0
IIIC	T4b	N1a-N2c	M0
IIID	T4b	N3a/b/c	M0
IV	Any T, Tis	Any N	M1

[a]Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma of the skin. In: Amin MB, Edge SB, Greene FL, et al, eds. AJCC Cancer Staging Manual. 8th ed. New York: Springer International Publishing; 2017:563-585.

Appendix 2. Strength definition of Recommendations for this Guideline (modified based on GRADE approach[a])

Strength	Definition	Verb wording
Recommendation to use the intervention	The guideline Working Group[b] believes the benefits of the surveillance strategies in patients with stage I, II, III, or resectable IV melanoma **who are clinically disease-free** after treatment with curative intent clearly outweigh the harms for nearly all patients and the group is confident to support the recommended action.	Be recommended to go for …; Should be done
Weak Recommendation to use the intervention	The guideline Working Group[b] believes the benefits and harms of the surveillance strategies in the target population are closely balanced or are more uncertain but still adequate to support the recommended action.	Be suggested to go for …; May/can be done; Consider doing …
No Recommendation for the intervention	The guideline Working Group[b] is uncertain whether the benefits and harms of the surveillance strategies in the target population are balanced and does not recommend a specific action.	There is no recommendation for or against …
Weak Recommendation NOT to use the intervention	The guideline Working Group[b] believes the benefits and harms of the surveillance strategies in the target population are closely balanced or are more uncertain but still adequate to support the recommended action.	Be suggested against …; May/cannot be done; Do not consider doing …
Recommendation NOT to use the intervention	The guideline Working Group[b] believes the harms of the surveillance strategies in the target population clearly outweigh the benefits for nearly all patients and the group is confident to support the recommended action.	Be recommended to against …; Should not be done
	The factors considered in the above judgments include desirable and undesirable effects of the maintenance therapy, the certainty of evidence, patient preference, health equity, acceptability, feasibility, and generalizability in Ontario.	

[a] Schünemann H, Brozek J, Guyatt G, Oxman, AD (editors). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. [updated October 2013].

[b] The guideline Working Group includes five medical oncologists, three surgical oncologists, two dermatologists, one radiation oncologist, and one guideline methodologist.

Appendix 3. Affiliations and conflict of interest declarations

(1). Members of the Working Group

Name	Affiliation	Declarations of interest
Sudha Rajagopal, Medical Oncologist	Credit Valley Hospital Peel Regional Cancer Centre Mississauga	Received $500 or more in a single year in a consulting capacity from BMS, Merck, Novartis, and Pfizer.
Xiaomei Yao, Health Research Methodologist	Program in Evidence-Based Care, Ontario Health (Cancer Care Ontario), McMaster University, Hamilton	None
Wadid Abadir, Dermatologist	Odette Cancer Centre, Toronto	None
Tara Baetz, Medical Oncologist	Cancer Centre of Southeastern Ontario Kingston, Kingston	Received $500 or more in a single year to act in a consulting capacity from Bristol Myers Squibb, Merck, Servier, Gilead, Novartis, AstraZeneca, AbbVie, Roche, Sanofi, and Sun Pharma. Received an honorarium from Pfizer of $500 or more in a single year. Received grants or other research support from Seattle Genetics, either as principal or co-investigator, in any amount.
Alexandra Easson, Surgical Oncologist	Princess Margaret Hospital Toronto, Toronto	None
Gregory Knight, Medical Oncologist	Grand River Regional Cancer Centre, Kitchener	Received $500 or more in a single year to act in a consulting capacity- participated in multiple advisory boards for multiple companies.
Elaine McWhirter, Medical Oncologist	Juravinski Cancer Centre Hamilton, Hamilton	Received $500 or more in a single year to act in a consulting capacity from Merck, BMS, Novartis, EMD Serrono, Sanofi-Genzyme, Roche, Medison.
Carolyn Nessim, Surgical Oncologist	The Ottawa Hospital, Ottawa	Received $500 or more in a single year to act in a consulting capacity for Novartis Sanofi advisory board, one time meeting.
Cheryl F. Rosen, Dermatologist	Toronto Western Hospital, Toronto	Received $500 or more in a single year to act in a consulting capacity from BMS, Novartis, AbbVie, Amgen and UCB.
Alexander Sun, Radiation Oncologist	Princess Margaret Cancer Centre, Toronto	None
Frances Wright, Surgical Oncologist	Sunnybrook Cancer Centre, Toronto	Received $500 or more in a single year to act in a consulting capacity. Funds from Merck (talk), BMS (talk), and Novartis (talk) were all donated to the University of Toronto. Received unrestricted research grant from Roche.

Teresa Petrella, Medical Oncologist	Odette Cancer Centre, Toronto	None

(2). Patient representative

Name	Declarations of interest
Randall Conrod	None
Lise Craig	None
Patricia Sevean	None
Bob Tuck	None
Sharon Tan	None

(3). Melanoma Surveillance Guideline Development Group

Name, Expertise	Affiliation	Declarations of interest
David McCready, Surgical Oncologist	Princess Margaret Hospital, Toronto	Stocks, bonds, or stock options valued at $500 or more in Johnson & Johnson
Annette Cyr, Patient Representative	Not available	None
Christian Murray, Dermatologist	Skin Surgery Centre, University of Toronto, Toronto	None
Caroline Hamm, Medical Oncologist	Windsor Regional Cancer Centre, Windsor	
Xinni Song, Medical Oncologist	The Ottawa Hospital Cancer Center, Ottawa	Received $500 or more in a single year in a consulting capacity from BMS, Merck, Novartis, Pfizer, also received clinical trial supports by Seattle Genetics, Roche, BMS, Merck, AstraZeneca, Gilead, Pfizer.

(4). Members of the Report Approval Panel

Name, Expertise	Affiliation	Declarations of interest
William K. Evans, Medical Oncologist	Oncosynthesis Consulting Inc.	None
Donna E. Maziak, Surgical Oncologist	Ottawa Hospital, Ottawa, Ontario, Canada	None
Jonathan Sussman, Radiation Oncologist	Juravinski Cancer Centre, Hamilton, Ontario, Canada	None

(5). Targeted Peer Reviewers

Name, Expertise	Affiliation	Declarations of interest
Alexander Van Akkooi, Surgical Oncologist	Melanoma Institute Australia,	Received $500 or more in a single year to act in a consulting capacity from Amgen, BMS,

	Sydney, Australia	Novartis, MSD, Merck-Pfizer, Pierre Fabre, Provectus, Sanofi, Sirius Medical, 4SC. Received grants or other research support, either as principal or co-investigator, in any amount, from Amgen and Merck-Pfizer. Been a principal investigator for a clinical trial involving any of the objects of study, regardless of the source of funding: EORTC 2139 – Columbus AD trial (NCT05270044).
Monica Bertolo, General Practitioner	Dr. B. Skin Disorders Clinic, St. Catherines	Currently owns a relevant business entity, in whole or in partnership: Dr. Monica Bertolo Medicine Professional Corporation.
Linda Lee, Medical Oncologist	Niagara Health, St. Catherines	None
Jessica Singh, Medical Oncologist	Simcoe Muskoka Regional Cancer Centre, Barrie	None
Claire Temple-Oberle, Plastic Surgeon	The University of Calgary, Calgary	None

Appendix 4. Quality assessment results for four existing relevant guidelines

Guideline	Domain 1: Scope and Purpose	Domain 2: Stakeholder Involvement	**Domain 3: Rigor of Development**	Domain 4: Clarity of Presentation	Domain 5: Applicability	Domain 6: Editorial Independence
AAD 2019	92%	89%	**83%**	89%	23%	96%
Australian CPG 2018 and 2019	44%	50%	**60%**	92%	35%	75%
ESMO 2019	6%	25%	**42%**	69%	33%	79%
NCCN 2022v3[a]	28%	56%	**50%**	67%	40%	75%
NICE 2022	94%	97%	**89%**	89%	71%	88%

Abbreviations: AAD, American Academy of Dermatology; CPG, Clinical Practice Guidelines; ESMO, European Society for Medical Oncology; NCCN, National Comprehensive Cancer Network; NICE, National Institute for Health and Care Excellence.

[a] The results come from our assessment of the NCCN 2021v2 for "Melanoma: Cutaneous". Since the methods used to conduct the 2022v3 should be the same as those to conduct the NCCN 2021v2, we did not re-assess the quality of 2022v3.

Appendix 5. Literature Search Strategy

(1) Search Strategies for Medline and Embase databases

	#	Searches
Section A: Disease and/or population	1	exp melanoma/ or melanoma$.mp. or exp Hutchinson's Melanotic Freckle/ or (melanotic adj2 freckle$).mp.
	2	exp malignant lentigo/ or (malignan$ adj2 lentigo).mp.
	3	1 or 2
Section B: Intervention or diagnostic test	4	bone scan$.tw,kw.
	5	(magnetic resonance imag$ or magnetic resonance spectroscop$).tw,kw. or magnetic resonance imaging/
	6	(dynamic adj4 (MRI or magnet$)).tw,kw.
	7	(diffusion weight$ adj3 (MRI or magnet$)).tw,kw.
	8	(MPMRI or MP-MRI or MR$2 or DWI$ or DW-MRI or DCE$ or NMR$ or fmri).tw,kw.
	9	((T1-weighted or T2-weighted) adj3 imag$).tw,kw.
	10	(MR$1 adj (imag$ or spectroscop$ or scan$ or tomograph$)).tw,kw.
	11	(magnet$ adj (imag$ or spectroscop$ or scan$ or resonance)).tw,kw.
	12	exp Magnetic Resonance Imaging/ or exp Magnetic Resonance Spectroscopy/
	13	(Dermoscop$ or electrical impedance spectroscopy or Raman spectroscopy).tw,kw.
	14	monitor$.ti. or (asymptomatic and (recurrence or recurrent or high-risk)).tw.
	15	(follow-up or follow up or followup or following up or followed up).ti,kw.
	16	Surveillanc$.mp.
	17	((transfer or transit$ or model$ or multidisciplinary) adj5 (care or team$)).tw,kw.
	18	(exp ultrasonography/ or ultrasound$.tw,kw. or ultrasonic$.tw,kw. or ultrasonog$.tw,kw.) and nodal basin.tw,kw.
	19	single photon emission computer tomography/ or single photon emission computed tomography/ or (spect or spect?ct).tw,kw.
	20	Tomography, emission-computed/ or (emission and tomograph$).tw. or exp positron emission tomography/ or pet.tw,kw.
	21	exp Positron Emission Tomography Computed Tomography/ or PET-CT.tw,kw. or PET?CT.tw,kw.
	22	PET-FDG.tw. or fluorodeoxyglucose f 18/ or fluorodeoxyglucose/ or fluorodeoxyglucose.tw,kw.
	23	(LDH or lactate dehydrogenase or S100* or TSH or thyroid-stimulating hormone or ACTH or adrenocorticotropic hormone cortisol or CBC or complete blood count or FBC or full blood count or Circulating DNA or Melanoma Dx or blood test* or blood work* or (lab adj2 test*) or (lab* adj2 exam*) or Electrolyte* or blood cell count or (liver adj function*) or LFTs or LFs or hepatic function*).ti,kw.
	24	Photo*.tw,kw.
	25	Physicians, Primary Care/ or General Practitioners/ or Physicians, Family/
	26	(family doctor* or physician* or practitioner*).tw,kw. or primary care.ti,kw.
	27	or/4-26
Section C: Exclusion strategies	28	(comment or letter or editorial or note or erratum or letter erratum or abstract or short survey or news or newspaper article or patient education handout or case report or historical article).pt. or abstract report/ or letter/ or case study/
	29	exp animal/ not (exp human/ or humans/)
	30	28or 29
	31	(3 and 27) not 30
	32	limit 31 to yr="2015 -Current"

(2) Search Strategies for the Cochrane Library

#	Searches
1	melanoma.tw.
2	surveillance.tw.
3	surveillance.tw. or follow-up.ti.
4	1 and 3
5	limit 4 to yr="2015 -Current"

(3) Search Strategies for PubMed

(family doctor*[Title/Abstract] OR physician*[Title/Abstract] OR practitioner*[Title/Abstract] OR primary care OR GP*[Title/Abstract] OR FP*[Title/Abstract]) AND (monitor*[Title/Abstract] OR follow-up[Title/Abstract] OR follow up[Title/Abstract] OR followup[Title/Abstract] OR following up[Title/Abstract] OR followed up[Title/Abstract] OR surveillanc*[Title/Abstract] OR (asymptomatic[Title/Abstract] AND (recurrence[Title/Abstract] OR recurrent[Title/Abstract] OR high-risk[Title/Abstract]))) AND melanoma[Title]

((LDH[Title/Abstract] OR lactate dehydrogenase[Title/Abstract] OR S100*[Title/Abstract] OR TSH[Title/Abstract] OR thyroid-stimulating hormone[Title/Abstract] OR ACTH cortisol[Title/Abstract] OR adrenocorticotropic hormone cortisol[Title/Abstract] OR CBC[Title/Abstract] OR complete blood count[Title/Abstract] OR FBC[Title/Abstract] OR full blood count[Title/Abstract] OR Circulating DNA[Title/Abstract] OR Melanoma Dx[Title/Abstract] OR blood test*[Title/Abstract] OR blood work*[Title/Abstract] OR laboratory test*[Title/Abstract] OR Electrolyte*[Title/Abstract] OR blood cell count[Title/Abstract] OR (liver adj function*[Title/Abstract]) OR LFTs[Title/Abstract] OR LFs[Title/Abstract] OR (hepatic function*[Title/Abstract]))) AND (melanoma[Title])

Appendix 6. Ranking results of importance for outcomes in the Working Group

Outcomes	**Of limited importance**	**Important but not critical**	**Critical**
Rating Scale:	1 (1-3 scores) (least importance)	2 (4-6 score)	3 (7-9 scores) (most importance)
Overall survival			3
Disease-free survival/disease-specific survival			3
Recurrence detection			3
Detection rate of a new primary melanoma		2	
Change in treatment (surrogate outcome to indirectly improve survival rate if there is no survival outcome reported)		2	
Secondary cancer from different frequencies of imaging examinations from surveillance (such as x-ray and PET/CT)		2	
Patient-reported outcomes (e.g., Quality of life, satisfaction, and anxiety)		2	

Abbreviations: CT, computed tomography; PET, positron emission tomography

Appendix 7. Ongoing trials (Searching https://clinicaltrials.gov/ on May 10, 2022)

Protocol ID (Q1/2, or Q3); Country	Title	Study design, sample size (age)	Intervention	Control group	Outcomes	Estimated study completion date
NCT03116412 (Q1/2); Sweden	A Prospective Randomized Multicenter Trial to Assess the Role of Imaging During F/U After Radical Surgery of Stage IIb-c and III Cutaneous malignant Melanoma	RCT (phase: NA), 1300 (≥18 years)	Routine F/U according to national guidelines plus CT or PET scans and blood tests are scheduled at baseline, months 6, 12, 24 and 36	Routine F/U according to national guidelines	Primary outcome at 5 years: 1. OS Secondary outcomes at 3 years: 1. QOL/QLQ30 2. QOL/HADS	December 2026
NCT04385732 (Q1/2); Australia)	Melanoma Surveillance Photography to Improve Early Detection of Melanoma in Ultra-high and High Risk Patients	RCT (phase: NA), 580 (≥18 years)	Total body imaging using 2D or 3D Melanoma Surveillance Photography plus digital dermoscopy.	Clinical surveillance standard of care without Melanoma Surveillance Photography	Primary outcome at 2 years: 1. Diagnostic performance of melanoma surveillance Secondary outcomes at 2 years: 1. Cost-effectiveness of MSP 2. Diagnostic performance for melanoma 3. Diagnostic performance for keratinocyte lesions 4. Health-related QOL 5. Patient anxiety 6. Etc.	July 2024
NCT05253872 (Q1/2); Denmark	The MELAcare Study: A New Method for Surveillance of Melanoma Patients	RCT (phase: NA), 378 (≥18 years)	The MelaCare intervention: Meta-cognitive strategies and normalization of emotions, SSE and knowledge on when to seek clinical examination; 4 components and 3-5 sessions with an experienced and specially trained melanoma nurse.	Clinical follow-up according to the current standard of care for patients' clinical stage.	Primary outcome at 6-8 months, 12 months, and 24 months: 1. FCR Secondary outcomes at 6-8 months, 12 months, and 24 months: 1. Evaluation of change from baseline in depression score by the validated PHQ-9 2. Evaluation of change from baseline in anxiety score by the validated GAD-7	March 2028

					3. Evaluation of change from baseline in distress score by the validated distress thermometer 4. Evaluation of change from baseline in activation score by the validated patient activation measure 5. Evaluation of change from baseline in health status by the validated EQ-5D-3L 6. Etc.	
NCT04605822 (Q1/2); Switzerland	Clinical Performance of the New Artificial-intelligence Powered 3D Total Body Photography System VECTRA® in Early Melanoma Detection and Its Impact on Patients' Burden of Disease: A Prospective Cohort Study in a Real-world Setting	Cohort (phase: NA), 720 (≥18 years)	3D imaging Total Body Photography Vectra® WB360, 2D imaging FotoFinder ATBM® Master imaging system, Smartphone application (SkinVision®)	Standard-of-care clinical assessment of the skin	Primary outcomes at up to 24 months: 1. Analyses of histopathology reports of all excised suspectable lesions 2. Analyses of dermatologists' assessment of each pigmented skin lesion as benign (melanocytic nevi / dysplastic nevi) or malignant (melanoma) before and after (without and with knowledge of) computer-guided risk assessment scores 3. Analyses of 2D FotoFinder® Mole Analyzer scoring of pigmented skin lesions (0.0 - 1.0) 4. Analyses of 3D Vectra® WB360 imaging scoring of pigmented skin lesions (0- 10) 5. Analyses of Smartphone app Skin Vision® scoring of pigmented skin lesions (low, medium or high risk)	December 2023

					Secondary outcomes at up to 24 months: 1. Change in Distress thermometer (Patient-reported outcome) 2. Change in FACIT G7 Functional Assessment of Cancer Therapy - General - (7 item version) 3. Change in HADS 4. Change in MWS 5. Change in support need and uptake 6. Etc.	
ANZCTR12618000267257; Australia	Evaluation of the efficacy of 3D total body photography with sequential digital dermoscopy in a high-risk melanoma cohort: protocol for a randomised controlled trial	RCT (phase: NA), 330 (age not mentioned)	Clinical skin examinations every 6 months for 2 years, supported by 3D TBP imaging system.	Continue attending regular skin examination appointments (may include 2D TBP) and complete 6 monthly questionnaires.	Primary outcomes: 1. Compare clinical outcomes of the 3D TBP–SDDI approach with routine clinical care, including numbers of excisions or biopsies and histopathological findings 2. Compare health economic outcomes of the 3D TBP–SDDI approach with routine clinical care 3. Evaluate consumer acceptance of the intervention, psychological well-being, health behaviour and beliefs regarding sun protection and melanoma Secondary outcomes: 1. Assess feasibility of telehealth to deliver remotely captured 3D TBP–SDDI for teledermatologist review 2. Evaluate the degree of concordance between teledermatologist and in-person examination in terms of	August 2021 (We have contacted the primary investigator and this study has completed but the manuscript is under review by March 16 2023.)

					clinical assessment and management decisions 3. Identify rare and deleterious gene variants associated with melanoma risk 4. Refine a risk stratification model that combines medical history, family history, phenotypic risk factors and genetic results to produce a melanoma-risk score	
ACTRN12621000145808; Australia	Implementing a Stepped Care Model to Address Fear of Cancer Recurrence in Early Stage (0-II) Melanoma Patients - A Pilot Study	Cohort? (phase: NA), 108 (≥18 years)	Provision of a psycho-educational booklet, "Melanoma: Questions and Answers" and 3 psychotherapeutic telehealth sessions. Intervention is anticipated to be implemented for 18 months.	NA. Control group data from the original Melanoma Care Program will be used to estimate the likely fear of cancer recurrence patterns when no intervention is implemented.	Primary outcome: 1. Change in patient FCR severity, assessed using the FCR Inventory- 9 item severity subscale Secondary outcomes: 1. Change in patient melanoma-related knowledge assessed using the purpose-designed melanoma-related knowledge survey 2. Change in patient QOL assessed using the Assessment of QOL 8-Dimensions questionnaire 3. Patient acceptability assessed using qualitative themes derived from semi-structured interviews, process data and the Acceptability of Intervention Measure survey 4. Appropriateness of the intervention as viewed by patients, assessed through qualitative themes derived from semi-structured interviews, process data and the Intervention	November 2023

					Appropriateness Measure survey 5. Implementation stakeholder acceptability assessed using qualitative themes derived from expert groups and the Acceptability of Intervention Measure survey 6. Etc.	

Abbreviations: 2D, two-dimensional; 3D, three-dimensional; CT, computed tomography; EQ-5D-3L, Euroqol 5 dimensions, 3 levels questionnaire; FACIT G7, Functional Assessment of Chronic Illness Therapy- General 7 item version; FCR, Fear of Cancer Recurrence; F/U , follow-up; GAD-7, General Anxiety Disorder-7 questionnaire; HADS, Hospital, Anxiety and Depression Scale; MSP, Melanoma Surveillance Photography; MWS, Melanoma Worry Scale; NA, not applicable; OS, overall survival; PET, Positron Emission Tomography; PhQ-9, Patient Health Questionnaire-9; Q1, research question 1; Q2, research question 2; Q3, research question 3; QLQ30, Question of Life Questionnaire 30; QOL, Quality of Life; RCT, randomized controlled trial; SSE, skin self examination; TBP, Total Body Photography; TBP-SDDI, total-body photography in combination with sequential digital dermoscopy imaging.

Appendix 8. Summary of excluded RCTs for SSE (study order is based on the publication year and alphabetical by first author's last name)

Study (trial name); Country	Patient population Sample Size (n); Stage	Mean/Median age (range/SD)	Intervention	Control	Mean/Median F/U time (range); F/U rate	Recurrence and survival outcomes	PRO
Research question 1.							
Robinson 2020	341	21 to 80 years	n=197 (workbook) In phase 1, patients and partners read a 34-page colour work-book during an office visit, and received scorecards to record monthly scores of concerning moles for 24 months (a diary), a booklet of body diagrams to locate concerning moles, a lighted magnifying lens and a millimetre (mm) ruler. In Phase 2, online assessments self-reported performing SSE in the preceding 9 months for 18 months. In Phase 2, pairs completed online baseline (prior to randomization),	n=144 Standard of care (not specified)	Phase 1: 93% vs. 92% Phase 2: 84% vs. 90%	Phase 1 recurrence: 0:28/159=18% vs. 0% I:6/159=4% vs. 4/159=4% II:0% vs. 0% Phase 2 recurrence: 0: 15/194=8% vs. 0% I: 4/194=2% vs. 6/151=4% II: 0% vs. 2/151=1% Survival outcomes: NR	There was no significant SSE-induced anxiety among workbook training intervention participants in both phases over the time of active participation as assessed by responses to the following items: I feel in control of my health ($F(1,151) = 1.34$, $p>0.05$), I experience upsetting memories of having a melanoma ($F(1,151) = 0.07$, $p>0.05$), and I feel

			9, and 18-month surveys reporting their SSE practices in the preceding 9 months.				comfortable discussing my feelings with my skin check partner ($F(1,151) = 1.42$, $p>0.05$).
Manne 2021	116	51.1 ± 15.2 years	n=56 (mySmartCheck, which consisted of three modules[a] and a body mole map activity). F/U frequency: NR	n=60 (usual care, received no additional intervention aside from their usual non-study clinical care)[b]. F/U frequency: NR	Completed 13-week F/U survey: 43/56=77% vs. 56/60=93%	NR	There were no significant condition effects on perceptions of controllability or worry about recurrence. Participants who completed all three cores of mySmartCheck were more worried about recurrence (mean=3.42, SD=87) than those who did not (mean=2.82, SD=0.86).
Reilly 2021	240	18+ years	n=121 (ASICA intervention. Participants received training on how to use the app and how to conduct a TSSE[c]. All participants	n=119 (usual melanoma F/U) F/U frequency: every 3 months for 12 months.	Returned 12-month questionnaire: 82/121=68% vs. 86/119=72%	NR	NR

			continued with standard care and attended their usual structured melanoma follow up as per local guidelines.) F/U frequency: every 3 months for 12 months.				
Ackermann 2022	100	58.7 ± 12.0 years	n=49 (usual care plus patient-led surveillance, which composed of instructional videos on how to perform SSE, reminders to undertake SSE, a mobile dermatoscope attached to their smartphone, an application that facilitated store-and-forward teledermatology, and fast-tracked unscheduled clinic visits). F/U frequency: SSE every 2 months over a period of 6 months. Further F/U by telephone and email if tasks were overdue.	n=51 (usual care, an educational booklet 'Your Guide to early melanoma'[d]). F/U frequency: scheduled and unscheduled visits as needed and determined by treating physician(s) and educational booklet. n=51 (usual care, an educational booklet 'Your Guide to early melanoma'[d]). F/U frequency: scheduled and unscheduled visits as needed and determined by treating physician(s) and	6 months; 61% in intervention group and 71% in control group completed the 6-month questionnaire.	New primary melanoma or recurrence: 8/49=16% vs. 3/51=6%; OR=2.6 (95% CI, 0.6 to 10.7)[e]. Between-group difference in diagnosis with a subsequent new primary melanoma or recurrence: 10% (95% CI, -2% to 23%). Survival outcomes: NR	Between-group mean score difference for change in Fear of Cancer Recurrence Inventory severity subscale: -1.3 (95% CI, -3.1 to 0.5). Change in total Depression Anxiety and Stress Scales: -1.4 (95% CI, -5.8 to 2.0). Between-group difference for change in anxiety subscale: -0.1 (95% CI, -1.3 to 1.1).

				educational booklet.			Depression subscale score: -1.4 (95% CI, -3.2 to 0.4). Stress subscale score: 0.2 (95% CI, -2.2 to 2.6).
Research question 2.							
Robinson 2016, Turrisi 2015	494	Patient and partner population: 55 ± 10 years	n=159 (SSE workbook read in the office for 45 minutes and taken home). n=165 (in-person SSE training in the office for 30 minutes). n=71 (tablet SSE training in the office for 30 minutes). Patients with their partners had SSE reinforcement every 4 months by the study dermatologist, and monthly SSE was recommended. Patients were encouraged to continue with regularly scheduled	n=99. No SSE training. Patients were encouraged to continue with regularly scheduled follow-up visits with their customary dermatologist F/U frequency: every 4 months for 2 years.	24 months; 58% of patients were retained in the study.	New primary melanoma detection[f]: 53/395=13% vs. 16/99=16% Survival outcomes: NR	NR

			follow-up visits with their customary dermatologist. F/U frequency: every 4 months for 2 years.				

Abbreviations: CI, confidence interval; F/U, follow-up; MSKCC, Memorial Sloan Kettering Cancer Center; NR, not reported; OR, odds ratio; PRO, patient-reported outcomes; RCTs, randomized controlled trial; SD, standard deviation; SSE, skin self-examination; TSSE, thorough skin self-examination.

[a] Module 1, "Introduction," outlined the goals of the intervention, provided information about melanoma and risks of recurrence, skin cancer risk factors, reasons to engage in regular SSE, and strategies to prioritize SSE. Module 2, "Getting Ready to do a Skin Self-Check," assessed SSE experience and confidence performing SSE, how to recognize suspicious growths, the importance of getting help to examine hard to see areas, selecting strategies for completing monthly skin self-checks, and setting up an SSE action plan. Module 3, "Learn more about skin spots," contained more detailed information about non-cancerous skin growths to assist in differentiating between cancerous and non-cancerous growths. An online monthly self-check activity allowed participants to add new spots, move a spot, and/or delete a spot and characterize the spot. Participants could also set an automated reminder to schedule an appointment with their doctor to discuss a new spot.

[b] Patients seen at MSKCC received two handouts/brochures about SSE and verbal instructions from the nurse and dermatologist about the importance/rationale for secondary prevention of melanoma and general instructions on how to perform an SSE. Handouts included: (a) the AAD Skin Cancer brochure, which discusses the ABCDEs of melanoma (i.e., which stands for key features of melanoma, including **A**symmetry, **B**order irregularity, **C**olour variation (both inside the lesion as well as a colour different than other nevi on the body), **D**iameter greater than 6 mm, and **E**volving (a new or changing lesion) including graphic illustrations on how to conduct a SSE, and (b) an MSKCC brochure detailing how to do a SSE and what to look for (i.e., Do-U-C), and a link to a SSE instructional video. Patients who received TBP were recommended to use their photographs as part of their SSE. At all visits, the patient intake form included questions related to their current performance of SSEs (yes/no) and if no, the providers reminded them about their importance and addressed any potential barriers to SSE implementation.

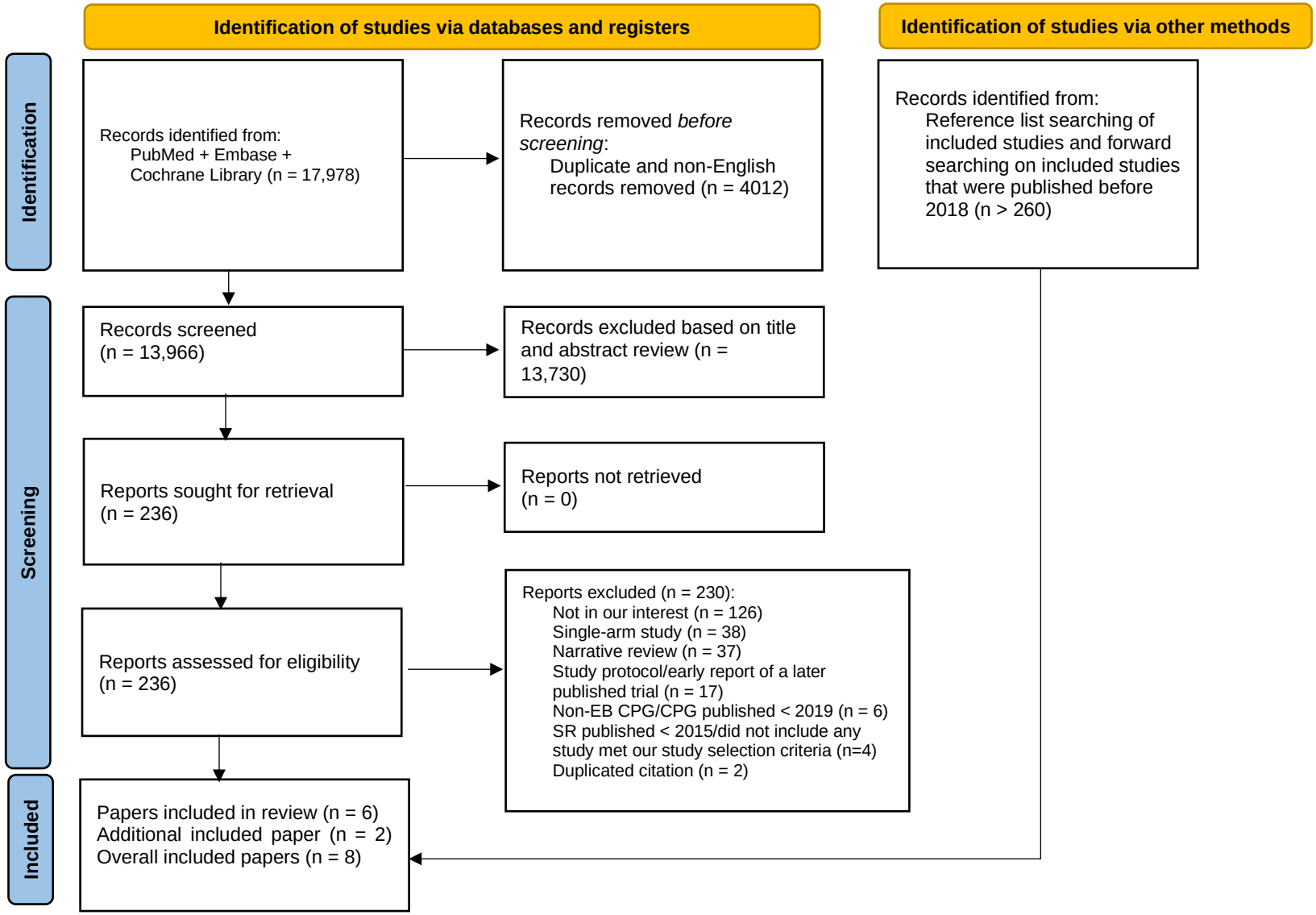
[c] Individuals could also use their Samsung Galaxy 7″ tablet to view their own individual digital skin map at any time. The device also included a digital camera, and the app included a video that instructed participants how to take photographs of skin lesions or other concerns that they had. Finally, the app had a structured electronic TSSE report form which was used to send a report, including attached photographs, of each individual TSSE direct to the Dermatology Nurse Practitioner for assessment and action as appropriate. Since participants all had experience of receiving melanoma follow-up examination no specific directions were given or restrictions made on the nature of skin concerns that they should report.

[d] This information came from the trial's protocol.

[e] Among the 11 participants diagnosed with new melanomas, there were a total of 13 melanoma diagnosed because one participant in the intervention group and one in the control had two melanoma diagnoses each. At the patient level, the unadjusted OR for a new melanoma diagnosis (intervention vs. control) was 3.1 (95% CI, 0.8 to 12.5). After accounting for the number of prior melanomas (<2 vs ≥2 prior melanomas), the adjusted OR (intervention vs. control) was 2.6 (95% CI, 0.6 to 10.7).

[f] Among 69 melanomas identified, three patients developed in-transit metastasis, and 66 developed new melanomas.

Appendix 9. PRISMA Flow Diagram



Appendix 10. Results of risk of bias assessment for six included studies

(1) One randomized controlled trial

Study		Domain 1: Randomization Process	Domain 2: Deviation from Intervention	Domain 3: Missing Outcome Data	Domain 4: Measurement of Outcome	Domain 5: Reported Results	Overall Risk of Bias Per outcome
Moncrieff 2022	Recurrence or second primary rate	Low	Some concern	Low	Some concern	Low	Some concern
	PFS/DSS	Low	Some concern	Low	Some concern	Low	Some concern
	PRO	Low	Some concern	High	Low	Low	High

Abbreviations: DSS, disease-specific survival; PFS, progression-free survival; PRO, patient-reported outcomes

(2) Five non-randomized comparative studies

Study		Domain 1: Bias due to confounding	Domain 2: Bias in selection of participants into the study	Domain 3: Bias in classification of interventions	Domain 4: Bias due to Deviation from Intended Intervention	Domain 5: Bias due to Missing Data	Domain 6: Bias in Measurement of Outcome	Domain 7: Bias in selection of the Reported Results	Overall Risk of Bias (per outcome)
Rueth 2014; USA	Recurrence rate	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical
	DSS	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical
Kurtz 2017; USA	RFS	Critical	Serious	Moderate	Serious	Low	Low	Low	Critical
	OS	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical
Ribero 2017; Italy, Spain	Recurrence rate	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical
	DMFS	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical
	MSS	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical
	NMFS	Critical	Serious	Moderate	NI	NI	Moderate	Low	Critical
Broman 2021; USA	Recurrence rate	Critical	Serious	Moderate	NI	NI	Moderate	Low	Critical
Dieng 2022	Recurrence rate	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical
	OS	Critical	Serious	Moderate	Serious	Low	Low	Low	Critical
	MSS	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical
	DDFS	Critical	Serious	Moderate	Serious	Low	Moderate	Low	Critical

Abbreviations: DDFS, distant disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; MSS, melanoma-specific survival; NI, no information; NMFS, nodal metastases-free survival; OS, overall survival; RFS, recurrence-free survival.

Appendix 11. The first-round vote results

Recommendation 1. For Stages IA, IB, and IIA

				Qualifying Statement
Decision	1.1 Clinical follow-up with history and full skin examination by a dermatologist (with or without photo-surveillance and dermoscopy), surgeon, family physician, or cancer nurse specialists should occur every six to 12 months for 3 years, then annually for 2 years or as clinically indicated.	1.2 Routine blood tests and imaging evaluations to screen for asymptomatic recurrence or metastatic disease are not recommended.	1.3 In conjunction with routine follow-up, healthcare providers should provide patient education regarding SSE (skin self examination) and sun safety.	We refer the details of SSE to Skin Cancer Self-exam on the Canadian Dermatology Association website https://dermatology.ca/public-patients/skin/melanoma/.
Agree	13	15	15	15
Disagree	3	1	1	1
Abstain	0	0	0	0
Agreement rate	13/16=81%	94%	94%	94%

Recommendation 2. For Stages IIB and IIC

						Qualifying Statement
Decision	2.1 Clinical follow-up, with a history and full skin examination by a dermatologist (with or without photo-surveillance and dermoscopy), surgical oncologist , medical oncologist, or cancer nurse specialist should occur every four to six months in years 1 and 2, every six months in year 3, then annually in years 4 to 5 or as clinically indicated.	2.2 Routine blood tests to screen for asymptomatic recurrence or metastatic disease are not recommended.	2.3 Routine CT, PET/CT scans every six to 12 months can be considered to screen for asymptomatic recurrence or metastatic disease in years 1 to 3, then annually in years 4 to 5.	2.4 Annual brain MRI can be considered for years 1 to 5.	2.5 In conjunction with routine follow-up, healthcare providers should provide patient education regarding SSE and sun safety.	We refer the details of SSE to Skin Cancer Self-exam on the Canadian Dermatology Association website https://dermatology.ca/public-patients/skin/melanoma/.
Agree	13	15	9	12	15	15
Disagree	3	1	5	3	1	1
Abstain	0	0	2	1	0	0
Agreement rate	81%	94%	56%	75%	94%	94%

Recommendation 3. For Stages III and IV with no evidence of disease

							Qualifying Statement		
Decision	3.1 Clinical follow-up with history and full skin examination by a dermatologist (with or without photo-surveillance and dermoscopy), surgical oncologist, medical oncologist, or a trained clinical nurse practitioner should occur every three to four months in years 1 through 3, then every six months in years 4 to 5, or as clinically indicated.	3.2 Routine blood tests to screen for asymptomatic recurrence or metastatic disease are not recommended.	3.3 Routine CT, PET/CT scans every six to 12 months can be considered to screen for asymptomatic recurrence or metastatic disease in years 1 to 3, then annually in years 4 to 5.	3.4 Annual brain MRI can be considered for years 1 to 5.	3.5 For patients with a positive sentinel lymph node, ultrasound scans of the draining nodal basin should be done every 4 to 6 months.	3.6 In conjunction with routine follow-up, healthcare providers should provide patient education regarding SSE and sun safety.	3.7 MRI of the brain may be used for routine screening where available, otherwise routine CT head may be considered.	3.8 In patients with positive sentinel lymph nodes, ultrasound screening should take place following recommendations in the CCO Guideline "8-6 Surgical Management of Patients with Lymph Node Metastases from	3.9 We refer the details of SSE to Skin Cancer Self-exam on the Canadian Dermatology Association website https://dermatology.ca/publ
Agree	11	15	10	12	15	15	13	15	15
Disagree	5	1	4	3	1	1	2	1	1
Abstain	0		2	1	0	0	1		
Agreement rate	69%	94%	63%	75%	94%	94%	81%	94%	94%

Recommendation 4. Transitioned to primary care for follow-up

		Qualifying Statement
Decision	Patients with stage IIB and above can be transitioned to a primary care physician for follow-up after 5 years. Yearly follow-ups with a dermatologist may continue.	Patients should have easy access to return to the dermatology, surgery or medical oncology clinic if clinically needed.
Agree	15	15
Disagree	1	1
Abstain	0	0
Agreement rate	94%	94%

Appendix 12. The second-round vote results

Recommendation 1. For Stages IA, IB, and IIA				Qualifying Statement
Decision	1.1 Clinical follow-up with history and full skin examination by a dermatologist (with photo-surveillance and dermoscopy if indicated), and/or a surgeon, family physician, cancer nurse specialist should occur every six to 12 months for 3 years, then annually for 2 years or as clinically indicated.	1.2 Routine blood tests and imaging evaluations to screen for asymptomatic recurrence or metastatic disease are not recommended.	1.3 In conjunction with routine follow-up, healthcare providers should provide patient education regarding SSE (skin self examination) and sun safety.	1.4 We refer the details of SSE to Skin Cancer Self-exam on the Canadian Dermatology Association website https://dermatology.ca/public-patients/skin/melanoma/.
Agree	13	16	16	16
Disagree	2	0	0	0
Abstain	1	0	0	0
Agreement rate	81%	100%	100%	100%

Recommendation 2. For Stages IIB and IIC						Qualifying Statement
Decision	2.1 Clinical follow-up with a history and full skin examination by a dermatologist (with photo-surveillance and dermoscopy if indicated), and/or a surgeon, medical oncologist, cancer nurse specialist should occur every six months in years 1 to 3, then annually in years 4 to 5 or as clinically indicated.	2.2 Routine blood tests to screen for asymptomatic recurrence or metastatic disease are not recommended.	2.3 CT or PET/CT scans every six to 12 months should be considered to screen for asymptomatic recurrence or metastatic disease in years 1 to 3, then annually in years 4 to 5.	2.4 Annual brain MRI can be considered for years 1 to 5. MRI of the brain is preferred for routine screening where available, otherwise, head CT may be considered.	2.5 In conjunction with routine follow-up, healthcare providers should provide patient education regarding SSE and sun safety.	We refer the details of SSE to Skin Cancer Self-exam on the Canadian Dermatology Association website https://dermatology.ca/public-patients/skin/melanoma/.
Agree	12	16	12	15	16	16
Disagree	4	0	2	1	0	0
Abstain	0	0	2	0	0	0
Agreement rate	75%	100%	75%	94%	100%	100%

Recommendation 3. For Stages III and IV with no evidence of disease							Qualifying Statement	
Decision	3.1 Clinical follow-up with history and full skin examination by a dermatologist (with photo-surveillance and dermoscopy if indicated), and/or a surgeon, medical oncologist, cancer nurse specialist should occur every three to six months in years 1 to 3, then every six months in years 4 to 5, or as clinically indicated.	3.2 Routine blood tests to screen for asymptomatic recurrence or metastatic disease are not recommended.	3.3 CT or PET/CT scans every six to 12 months should be considered to screen for asymptomatic recurrence or metastatic disease in years 1 to 3, then annually in years 4 to 5.	3.4 Annual brain MRI can be considered for years 1 to 5. MRI of the brain is preferred for routine screening where available, otherwise, head CT may be considered.	3.5 For patients with a positive sentinel lymph node, ultrasound scans of the draining nodal basin should be done every 4 to 6 months for years 1 to 3, and then every 6 months for years 4 to 5, if no CLND performed.	3.6 In conjunction with routine follow-up, healthcare providers should provide patient education regarding SSE and sun safety.	3.7 In patients with positive sentinel lymph nodes, ultrasound screening should take place following recommendations in the CCO Guideline "8-6 Surgical Management of Patients with Lymph Node Metastases from Cutaneous Melanoma of the Trunk or Extremities".	3.8 We refer the details of SSE to Skin Cancer Self-exam on the Canadian Dermatology Association website https://dermatology.ca/public-patients/skin/melanoma/.
Agree	13	16	13	16	15	16	16	16
Disagree	3	0	1	0	1	0	0	0
Abstain	0		2		0	0		
Agreement rate	81%	100%	81%	100%	94%	100%	100%	100%

Recommendation 4. Transitioned to primary care for follow-up		Qualifying Statement
Decision	4.1 Patients can be transitioned to a primary care physician for follow-up after 5 years. Annual follow-ups with a dermatologist should continue.	4.2 Patients should have easy access to return to the dermatology, surgery, or medical oncology clinic if clinically needed.
Agree	11	15
Disagree	4	1
Abstain	1	0
Agreement rate	69%	94%

NOTE: After External review, the revised Recommendation 4.1 "Patients may be transitioned to a primary care physician for follow-up after five years depending on the stages of the disease and clinical risk factors. Annual follow-up with a dermatologist should continue as clinically indicated." was voted by the 16 DSG members again. The agreement rate was 88%, which reaches our consensus threshold of 75%. One DSG member disagreed and

provided the following comments, “I think it is unrealistic to follow patient for up to five years and then identify a trained family doctor in melanoma to follow. they are few and far between. At best it is OK to return to primary care.” And another DSG member abstained.