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Guideline 8-9 IN REVIEW

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

The Use of Adjuvant Radiation Therapy for Curatively Resected Cutaneous Melanoma

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An assessment conducted in December 2025 placed Guideline 8-9 IN REVIEW. This means that it is undergoing a review for currency and relevance. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 8-9 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/31771

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The Use of Adjuvant Radiation Therapy for Curatively Resected Cutaneous Melanoma

Section 1: Recommendations

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

GUIDELINE OBJECTIVES

To determine when adjuvant radiation therapy (RT) should be considered for stage I-III melanoma patients following resected curative treatment.

TARGET POPULATION

Patients diagnosed with stage I-III cutaneous melanoma who have received curative resection of their melanoma comprise the target population for this guideline. The target population includes both patients diagnosed with primary melanoma and those with recurrence at the primary site or nodal recurrence.

INTENDED USERS

The intended users for this guidelines are all members of the multidisciplinary melanoma team, including radiation oncologists, medical oncologists, surgeons, and dermatologists.

RECOMMENDATIONS

Recommendation Preamble

There is minimal evidence to inform recommendations on the use of adjuvant RT for stage I-III melanoma patients. Based on the available evidence, the Adjuvant RT Guideline Development Group suggests the following recommendations. For ease of recommendation use, the target population has been broken down into four groups based on disease presentation and histology. Due to the lack of high-quality evidence to inform these recommendations, it is suggested that these cases be discussed in multidisciplinary case conferences. Additionally, special attention to ensure prospective adjuvant RT patients fully understand the benefits and risks of treatment is warranted so that informed decisions can be made.

Patients with Primary Melanoma and Recurrence at the Primary Site

Recommendation 1

- For patients at high risk for recurrence at the primary site following curative resection, adjuvant RT may be a reasonable option if adequate clear margins are unachievable.

Qualifying Statements for Recommendation 1

- Patients at high risk for recurrence include those with melanomas located on the head and neck, or when positive margins or satellitosis features are present.
- Adequate primary excision margins for melanoma are fully detailed in PEBC Guideline 8-2.

Recommendation 2

- No evidence-based recommendation for adjuvant RT can be made for patients following curative resection for primary melanoma with satellites, or for recurrence at the primary melanoma site; however, based on expert opinion of the Working Group, adjuvant RT may be a reasonable option for these patients if adequate clear margins are unachievable.

Qualifying Statements for Recommendation 2

- Further surgery is the preferred option for these patients, but if adequate clear margins cannot be achieved, adjuvant RT can be considered.
- Adequate primary excision margins for melanoma are fully detailed in PEBC Guideline 8-2.

Patients with Desmoplastic/Neurotropic Melanoma

Recommendation 3

- For patients diagnosed with desmoplastic melanoma, adjuvant RT following curative resection for the primary tumour is a reasonable option to improve local control.

Patients with In-Transit Primary and In-Transit Recurrent Melanomas

Recommendation 4

- No evidence-based recommendation can be made for patients following curative resection for in-transit primary melanoma or in-transit recurrences; however, based on the expert opinion of the Working Group, adjuvant RT may be considered on a case-by-case basis.

Stage III Melanoma Patients with High Risk for Lymph Node Relapse and All Patients with Nodal Recurrence

Recommendation 5

- Following lymphadenectomy either for stage III melanoma patients at high risk for lymph node relapse, or for all patients with nodal recurrence, adjuvant RT to the regional nodal basin is a reasonable option to improve local regional control.

Qualifying Statements for Recommendation 5

- Patients at high risk for lymph node relapse can include those with large lymph nodes (≥3 cm), multiple involved lymph nodes (≥1 parotid, or ≥2 cervical or axillary, or ≥3 inguinal or epitrochlear), extracapsular extension, or prior recurrent disease.
- Adjuvant RT is associated with improved local regional control, but has no impact on relapse-free survival or overall survival. The benefits of adjuvant RT must be weighed against the increased probability of long-term skin and regional toxicities including lymphedema for individual patients.

Adjuvant RT Fractionation Schedule

Recommendation 6

- A standard fractionation schedule may be considered when planning adjuvant RT.

Qualifying Statements for Recommendation 6

- Standard fractionation schedules are defined as those that deliver ≤2.5 Gy per fraction daily for at least 20 fractions.

FURTHER QUALIFYING STATEMENTS

- Caution should be used when directing adjuvant RT to the head and neck region due to a possibility of increased adverse events.

The Use of Adjuvant Radiation Therapy for Curatively Resected Cutaneous Melanoma

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To determine when adjuvant radiation therapy (RT) should be considered for stage I-III melanoma patients following resected curative treatment.

TARGET POPULATION

Patients diagnosed with stage I-III cutaneous melanoma who have received curative resection of their melanoma comprise the target population for this guideline. The target population includes both patients diagnosed with primary melanoma and those with recurrence at the primary site or nodal recurrence.

INTENDED USERS

The intended users for this guidelines are all members of the multidisciplinary melanoma team, including radiation oncologists, medical oncologists, surgeons, and dermatologists.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation Preamble

There is minimal evidence to inform recommendations on the use of adjuvant RT for stage I-III melanoma patients. Based on the available evidence, the Adjuvant RT Guideline Development Group suggests the following recommendations. For ease of recommendation use, the target population has been broken down into four groups based on disease presentation and histology. Due to the lack of high-quality evidence to inform these recommendations, it is suggested that these cases be discussed in multidisciplinary case conferences. Additionally, special attention to ensure prospective adjuvant RT patients fully understand the benefits and risks of treatment is warranted so that informed decisions can be made.

Patients with Primary Melanoma and Recurrence at the Primary Site

Recommendation 1
For patients at high risk for recurrence at the primary site following curative resection, adjuvant RT may be a reasonable option if adequate clear margins are unachievable.
Qualifying Statements for Recommendation 1
• Patients at high risk for recurrence include those with melanomas located on the head and neck, or when positive margins or satellitosis features are present. • Adequate primary excision margins for melanoma are fully detailed in PEBC Guideline 8-2.
Key Evidence for Recommendation 1
Three retrospective single-arm cohort studies were identified that inform this recommendation. Two of these cohort studies reviewed the medical records of both primary and recurrent disease populations [1,2], while the third only assessed patients with primary head and neck melanomas [3]. The cohort study that focused on primary head and neck melanomas determined that adjuvant RT led to a 94% five-year local control rate and a five-year survival of 58% [3]. This study also reported a five-year Grade 1 complication-free survival of 82%, 94% for Grade 2 complications, and 99% for Grade 3 complications [3]. Of

the two cohort studies that assessed both patients with primary melanoma and recurrent disease at the primary site, one found a 87% five-year local regional control rate and a five-year overall survival of 46% for all patients [1], while the other study found a five-year in-field recurrence rate of 11% for all patients [2].

Interpretation of Evidence for Recommendation 1

The studies that inform this recommendation are of low quality, with only one focused on primary melanoma patients exclusively. Additionally, the one study that did focus on primary melanoma only assessed patients with head and neck melanoma. Local recurrence after wide local excision with adequate clear margins is rare and occurs in fewer than 5% of cases [4]. Thus, surgical resection is considered to be the best option for all patients; however, based on this low-quality evidence, the Disease Site Group (DSG) believes that when adequate clear margins are unachievable, a weak recommendation for patients at high risk for primary site recurrence is warranted. Rates of local recurrence can rise up to 17% when melanomas are located on the head and neck and to 14% to 16% when satellitosis features are present [4]. The Working Group has considered these high-risk features, as well as positive margins, to define patients at high risk for recurrence.

Recommendation 2

No evidence-based recommendation for adjuvant RT can be made for patients following curative resection for primary melanoma with satellites, or for recurrence at the primary melanoma site; however, based on expert opinion of the Working Group, adjuvant RT may be a reasonable option for these patients if adequate clear margins are unachievable.

Qualifying Statements for Recommendation 2

- Further surgery is the preferred option for these patients, but if adequate clear margins cannot be achieved, adjuvant RT can be considered.
- Adequate primary excision margins for melanoma are fully detailed in PEBC Guideline 8-2.

Key Evidence for Recommendation 2

The literature search did not identify any studies that specifically assessed the role of adjuvant RT in patients with primary melanoma plus satellites, or any studies that assessed the role of adjuvant RT for melanoma that has recurred at the primary site. One of the cohort studies that reviewed the medical records of patients with multiple subtypes and stages of melanoma included 21 patients with recurrence limited to the primary tumour site, but this study did not separately analyze these patients [2]. The same retrospective cohort study included three patients with satellites [2], while another retrospective cohort study reported satellitosis as an RT indication without indicating how many individuals fit this criterion [1].

Interpretation of Evidence for Recommendation 2

There was no evidence to inform this recommendation, but the consensus of the Working Group was that adjuvant RT was a potentially beneficial option for these patients. The expected local recurrence rate in these patients following surgery alone would be approximately 15% [4] and the clinical expert opinion of the Working Group was that a lower probability of local recurrence could be achieved with adjuvant RT in at least some patients.

Patients with Desmoplastic/Neurotropic Melanoma

Recommendation 3
For patients diagnosed with desmoplastic melanoma, adjuvant RT following curative resection for the primary tumour is a reasonable option to improve local control.
Key Evidence for Recommendation 3
Two retrospective cohort studies compared the medical records of patients diagnosed with desmoplastic melanoma who were either treated with resection or resection plus adjuvant RT. One cohort study focused on patients with primary melanoma [5], while the other reviewed the records of patients with primary melanoma and recurrent disease [6]. For the study that focused on patients with primary melanoma, univariate regression analysis determined that patients with adverse prognostic features were more often offered RT; however, a multivariate regression analysis was used to control for these confounders [5]. The second cohort study did not conduct any statistical testing to compare patient characteristics before treatment [6]. Both studies found that local control rates were significantly improved following adjuvant RT (five-year: 76% versus 95%; p=0.015 [5], 10-year: 74% versus 91%; p=0.009 [6]). Only one cohort study reported on survival and found no difference in 10-year disease specific survival when comparing patients who did and did not receive adjuvant RT [6]. This cohort also reported on adverse events and found that 9.9% and 8.5% of patients experienced a moderate or severe adverse event, respectively, after adjuvant RT with a hypofractionated schedule [6]. These events included hypothyroidism, delayed wound healing, edema, xerostomia, keratoconjunctivitis sicca, osteoradionecrosis (severe), nonhealing scalp wound (severe), and skin graft failure (severe).
Interpretation of Evidence for Recommendation 3
There are limited low-level data to inform this recommendation. However, given that recurrence rates of 23% to 48% have been reported for desmoplastic melanomas [4] and the significant improvement in local control rates following adjuvant RT reported in the identified studies, the DSG feels confident in recommending adjuvant RT for these patients. The high rate of adverse events in these two studies is concerning. The cohort study that reported on adverse events did not specify the primary location for those patients who experienced an adverse event, but examination of the reported events indicates that moderate and severe adverse events occurred in the head and neck regions. A qualifying statement has been included asking for caution in the use of adjuvant RT in these areas due to the possibility of seeing more adverse events.

Patients with In-Transit Primary and In-Transit Recurrent Melanomas

Recommendation 4
No evidence-based recommendation can be made for patients following curative resection for in-transit primary melanoma or in-transit recurrences; however, based on the expert opinion of the Working Group, adjuvant RT may be considered on a case-by-case basis.
Key Evidence for Recommendation 4
The literature search did not identify any studies that assessed the use of adjuvant RT in this population.
Interpretation of Evidence for Recommendation 4
There was no evidence to inform this recommendation, but the consensus of the Working Group was that adjuvant RT was a potentially beneficial option for these patients. In –transit recurrence rates are high [7] and a retrospective review of patients who were diagnosed with in-transit recurrence as a first site of recurrence has indicated that 21.5% of these patients progress to regional node metastasis and 42.5% progress to distant metastasis [8]. The clinical expert opinion of the Working Group was that a lower probability of local recurrence

may be achieved with adjuvant RT in at least some patients diagnosed with in-transit melanoma.

Stage III Melanoma Patients with High Risk for Lymph Node Relapse and All Patients with Nodal Recurrence

Recommendation 5

Following lymphadenectomy either for stage III melanoma patients at high risk for lymph node relapse, or for all patients with nodal recurrence, adjuvant RT to the regional nodal basin is a reasonable option to improve local regional control.

Qualifying Statements for Recommendation 5

- Patients at high risk for lymph node relapse can include those with large lymph nodes (≥3 cm), multiple involved lymph nodes (≥1 parotid, or ≥2 cervical or axillary, or ≥3 inguinal or epitrochlear), extracapsular extension, or prior recurrent disease.
- Adjuvant RT is associated with improved local regional control, but has no impact on relapse-free survival or overall survival. The benefits of adjuvant RT must be weighed against the increased probability of long-term skin and regional toxicities including lymphedema for individual patients.

Key Evidence for Recommendation 5

A randomized controlled trial (RCT) conducted by the Trans-Tasman Radiation Oncology Group (TROG) enrolled patients at high risk for lymph node field relapse and those with a first relapse within the regional nodal basin. Patients were randomized to either adjuvant RT with 48Gy in 20 fractions or an observational arm [9,10]. The RCT reported a 52% to 56% relative reduction in lymph node field relapse as a first relapse for patients who received adjuvant RT (hazard ratio [HR], 0.52; 95% confidence interval [CI], 0.31-0.88; p=0.023 [10]; HR, 0.56; 95%CI, 0.32-0.98; p=0.041 [9]). In absolute terms, after six years of follow-up, lymph node field relapse as a first relapse occurred in 23 of 109 patients (21%) in the RT group, versus 39 of 108 patients (36%) in the observation group [10]. Both the original 40 month follow-up publication [9] and the recent 73-month extended patient follow-up publication [10] found no difference in overall or relapse-free survival. The RCT builds on older retrospective studies that reported improved five-year regional control rates for cervical (43% versus 93%; p<0.0001) and axillary lymph nodes (48% versus 91%; p<0.0001) following adjuvant RT [11], as well as improved two year regional control rates following adjuvant RT to neck and parotid lymph nodes (56% versus 78%; p=0.015) [12]. Five additional retrospective studies found no difference in control rates when comparing patients who did and did not receive adjuvant RT [13-17]; however, all studies also found that patients with worse prognostic features were offered adjuvant RT and no adjustment was made to compensate for these confounding factors. None of the identified studies reported a difference in overall survival when comparing those who did and did not receive adjuvant RT, but according to multivariate analysis, one retrospective study found that both five-year disease specific survival and distant metastasis-free survival were improved following adjuvant RT [11].

Publication of a 73-month follow-up from the TROG RCT indicated that patients in the RT arm experienced worse regional symptoms, increased limb volumes, and common Grade 2-4 long-term RT toxicity [10]. However, a validated quality of life (QoL) tool (FACT-G; Functional Assessment of Cancer Therapy - General) indicated no differences in QoL between the RT and observation groups [10]. Retrospective studies that compared patients who did and did not receive adjuvant RT found either that the five-year rate of lymphedema was higher following adjuvant RT compared with surgery alone [11], or that the rate of lower

extremity lymphedema following adjuvant RT to the inguinal lymph nodes was insignificantly increased compared with patients who only received dissection [14]. A single-arm retrospective cohort study reported a five-year Grade 2 and Grade 3 complication rate that is dependent upon the lymph node disease site, with higher rates in lymphedema and all complications highest after RT to the groin, followed by axillary lymph nodes, then cervical nodes, and finally, epitrochlear nodes [18]. Other single-arm cohort studies reported a five-year Grade 2 complication rate of 10% following adjuvant RT to cervical lymph nodes [19] and 18% following adjuvant RT to axillary lymph nodes [20].

Interpretation of Evidence for Recommendation 5

Although the TROG RCT was of much higher quality than the retrospective cohort studies, the cohort studies were still considered for this recommendation. Since long-term adverse events for the TROG RCT were limited, the cohort studies were used to inform the rate of long-term toxicities. The rate of reported adverse events is substantial; however, after wide excision and complete lymph node dissection for all stage III melanoma, the risk of local relapse for these patients is 15% [21]. Additionally, the presence of any of the high-risk features included in the Qualifying Statement for this recommendation results in a 30% to 50% rate of subsequent nodal recurrence after surgery alone [4]. The Working Group believes that adjuvant RT is a reasonable option for patients at high risk for recurrence, but cautions clinicians to weigh the increased probability of long-term toxicities for each patient.

Adjuvant RT Fractionation Schedule

Recommendation 6

A standard fractionation schedule may be considered when planning adjuvant RT.

Qualifying Statements for Recommendation 6

- Standard fractionation schedules are defined as those that deliver ≤2.5 Gy per fraction daily for at least 20 fractions.

Key Evidence for Recommendation 6

The literature search did not identify any studies that directly evaluated control rates or rate of adverse events for a standard fractionated schedule compared with a hypofractionated schedule. When comparing studies that reported use of a standard fractionated schedule [5,9,17,22] with studies that reported use of a hypofractionated schedule [2,3,6,11-13,16,18-20,23,24], local and regional control rates appear to be similar (local control rate: 78% to 95% versus 87% to 94%; regional control rate: 85% to 90% versus 74% to 94%). One retrospective cohort study reported on adverse events after standard fractionation and noted a Grade 2 adverse event rate of 22% and a Grade 3 rate of 0% [17]. Six retrospective cohort studies reported on adverse events after hypofractionated schedules and noted a Grade 2 rate of 9% to 25% and a Grade 3 rate of 0% to 5% [11,12,18-20,24].

Interpretation of Evidence for Recommendation 6

Hypofractionated RT regimens, which deliver a higher dose per fraction, were developed to compensate for the historical belief that melanoma was relatively radio-resistant compared with other types of cancers. However, more recent radiobiological and clinical studies [25], as well as earlier *in vitro* studies [21], have confirmed that melanoma cells are radiation responsive. Even though the limited data identified could not be used to directly compare control rate and rates of adverse events for the two schedules, the available evidence supports equivalent disease control using a standard fractionated schedule. Additionally, a historical RCT conducted by the Radiation Therapy Oncology Group that compared four fractions of 8 Gy (32 Gy total dose) delivered weekly with 20 fractions of 2.5 Gy (50 Gy total dose) delivered daily found nearly identical control rates with the two RT regimens [26]. Due

to the relatively high rates of adverse events reported with hypofractionated schedules, newer studies have adapted a conventional standard fractionated schedule. The clinical expert opinion of the Working Group is that a lower probability of adverse events may be possible with a lower radiation dose per fraction schedule (standard fractionation).

FURTHER QUALIFYING STATEMENTS

- Caution should be used when directing adjuvant RT to the head and neck region due to a possibility of increased adverse events.

RELATED GUIDELINES

- Members of the Melanoma Disease Site Group. Systemic adjuvant therapy for patients at high risk for recurrent melanoma. Toronto (ON): Cancer Care Ontario: 2013 Nov. Program in Evidence-Based Series No.: 8-1 Version 4. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/1161
- Wright F, Spithoff K, Easson A, Murray C, Toye J, McCready D, et al. Primary excision margins and sentinel lymph node biopsy in clinically node-negative cutaneous melanoma of the trunk or extremities. Toronto (ON): Cancer Care Ontario; 2010 May. Program in Evidence-based Care Evidence-Based Series No.: 8-2. Available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/51116

The Use of Adjuvant Radiation Therapy for Curatively Resected Cutaneous Melanoma

Section 3: Guideline Methods Overview

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

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) [27]. The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

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

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

Radiation oncologists in the province are being asked to treat melanoma patients with adjuvant radiation therapy (RT) and there are currently no guidance documents on when this treatment is appropriate.

GUIDELINE DEVELOPERS

This guideline was developed by the Adjuvant RT GDG (Appendix 1), which was organized at the request of the Melanoma Disease Site Group.

The project was led by a small Working Group of the Adjuvant RT GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group had expertise in medical oncology, radiation oncology, surgical oncology, and health research methodology. Other members of the Adjuvant RT GDG served as the Expert Panel. Expert Panel members are content experts and are responsible for reviewing the guideline during Internal Review. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [27,28]. This process includes a systematic review, interpretation of the evidence by the Working Group, resulting recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [29] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*.

PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as cost, human resources, and unique requirements for special or disadvantaged populations 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 Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE) and Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse.
- Guideline developer websites: Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), European Society of Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN), and British Association of Dermatologists (BAD).

The following criteria were used to select potentially relevant guidelines:

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

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

- A search for existing guidelines for adaptation or endorsement did not yield an appropriate source document. A search of the primary literature was required (see section 4).
- Guidelines developed by Alberta Health Services [30], Australian Cancer Network [31], BAD [32], the Dutch Working Group on Melanoma [33], and NCCN [34] all propose recommendations on the use of adjuvant RT for melanoma patients, but none were considered appropriate for adaption or endorsement.

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether 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 Report Approval Panel (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

The PEBC external review process includes a Targeted Peer Review that is intended to obtain feedback on the draft report from several content experts, and a Professional Consultation, in the form of a brief online survey, that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

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Section 4: Systematic Review

INTRODUCTION

Although cutaneous melanoma is an uncommon disease compared with non-melanoma skin cancers, melanoma is still the seventh most common malignancy in Canada for both men and women [35]. Incidence rates for melanoma have increased over the past several decades with men showing a 2.3% increase between 2001 and 2010, and women experiencing a 2.9% increase over the same time period [35]. It is estimated in Canada that 3,700 men and 3,100 women will develop a new case of melanoma in 2015 [35]. For patients with stage I and II melanoma, local recurrence after wide local excision with adequate clear margins is rare and occurs in fewer than 5% of cases [4]. However for stage III melanoma patients, even after wide excision and complete lymph node dissection, the risk of local relapse is 15% [21]. For patients with high-risk features, the risk for relapse increases to 30% to 50% [21]. The features associated with high risk for primary tumour recurrence include desmoplastic subtype, positive margins, location on the head or neck, recurrent disease, and thick primary lesions with ulceration and satellitosis [4]. The features associated with high risk of nodal relapse include extracapsular lymph node extension, multiple involved lymph nodes, lymph node size, or recurrent disease, [4].

Melanoma was originally believed to be a radio-resistant tumour; however, melanoma cell line studies verified that melanoma cells are in fact radiation responsive [21]. Further historical clinical studies demonstrated a role for radiation therapy (RT) in the treatment of gross disease [26,36]. Although early diagnosis and surgical resection remain the first-line treatment for melanoma, for high-risk patients, adjuvant RT may play a role in reducing recurrence by targeting micrometastatic disease.

The Working Group of the Adjuvant RT Guideline Development Group developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of the guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. Is adjuvant RT to the primary site appropriate after resected curative treatment for primary melanoma?
    a. In patients with melanoma?
    b. In patients with desmoplastic/neurotropic melanoma?
    c. In patients with primary melanoma with satellites?
2. Is adjuvant RT to the regional nodal basin appropriate after resected curative treatment in patients at high risk for regional recurrence of melanoma?
3. Is adjuvant RT appropriate after resected curative treatment for in-transit primary melanomas?
4. Is adjuvant RT appropriate after curatively resected treatment for recurrent melanoma?
    a. For recurrence at the primary site?
    b. For in-transit recurrence?
    c. For recurrence within the lymph node basin?
5. Does a standard RT fractionation schedule provide equivalent disease control compared with a hypofractionated schedule?

Primary outcomes of interest for each question were control rate, survival rate, and adverse event rates.

METHODS

This evidence review was developed using a planned two-stage method, summarized here and described in more detail below.

1. Search and evaluation of existing systematic reviews: If one or more existing systematic reviews are identified that address the research questions and are of reasonable quality, then those systematic reviews would form the core of the evidence review.
2. Systematic review of the primary literature: This review would focus on those areas not covered by existing reviews if any are located and accepted.

Search for Systematic Reviews

A search was conducted for existing systematic reviews. Systematic reviews published as a component of practice guidelines were also considered eligible for inclusion. An electronic search employing OVID was used to systematically search the MEDLINE and EMBASE databases for systematic reviews on the follow-up care of curatively treated melanoma patients. OVID was searched from 2000 to week 30 of 2015 using the following keywords: "melanoma", "malignant melanoma", "adjuvant radiotherapy", and "adjuvant radiation therapy". In addition, websites/databases of specific guideline developers that used systematic review as their evidentiary base, as well as systematic review producers, were also searched, using the same keywords and for the same time period. These websites/databases included: Australian Cancer Network (ACN), British Association of Dermatologists (BAD), Cochrane Database of Systematic Reviews, Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and European Society of Medical Oncology (ESMO). Only the most recent systematic review when multiple reviews were found with overlapping outcomes, were chosen for further evaluation.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) tool [37] to determine whether existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

Below are methods for locating and evaluating primary literature if no existing systematic review were identified, or if identified reviews were incomplete in some fashion. If the identified systematic reviews are incomplete, then the primary literature review might be reduced in scope (e.g., subject areas covered, time frames covered).

Literature Search Strategy

OVID was used to systematically search the MEDLINE and EMBASE databases for articles related to adjuvant radiation following curative resection of cutaneous melanoma, published between 2000 and week 30 of 2015. Studies that enrolled patients with non-cutaneous melanoma were not included in this review. The complete literature search strategy can be found in Appendix 2. In addition to the MEDLINE and EMBASE databases searches, reference lists of included systematic reviews and primary literature were scanned for potentially useful studies.

Study Selection Criteria and Process

All hits from the OVID literature search were input into reference management software (EndNote X6), where duplicate citations were removed. Due to the limited amount of prospective data that was expected to be found, the Working Group searched for randomized controlled trials (RCTs), as well as non-randomized studies. However, cohort studies that enrolled less than 30 patients, as well as case series, letters, editorials, and studies not published in English were excluded from the evidentiary base. Since the Working Group knew *a priori* that the evidence base would be comprised of predominantly retrospective cohort studies with patients treated in the 1980s through the early 2000s, only studies published after the year 2000 were included in an effort to exclude older treatment regimens that would not inform current recommendations.

A review of the titles and abstracts that resulted from the search was performed by one reviewer (LS) and verified by a second (AS). For those items that warranted full-text review, one reviewer (LS) determined whether the inclusion and exclusion criteria were met. The list of proposed studies was verified by a second reviewer (AS).

Data Extraction and Assessment of Study Quality and Potential for Bias

Data were extracted from all studies that passed full-text review by one reviewer (LS). All extracted data and information were audited by an independent auditor.

Important quality features, such as study design, comparison type, group allocation method, recruitment method, sources of bias, and sources of funding, for each study were extracted. To evaluate the risk of bias within the identified studies, the Cochrane Risk of Bias Tool (Cochrane Handbook, Chapter 8) was used for randomized studies, while A Cochrane Risk of Bias Assessment Tool: for Non-Randomized Studies of Interventions (ACROBAT-NRSI; [38]) was used for cohort studies.

Synthesizing the Evidence

Due to the anticipated large variation in study quality and outcomes measured, a meta-analysis was not planned.

RESULTS

Search for Existing Systematic Reviews

The search for existing systematic reviews identified 13 possible reviews on the use of adjuvant RT for curatively resected melanoma. After a review of the methodology employed in these review, only one could be considered systematic and of adequate quality [39]. Full-text review of the 2001 Fife and Thompson systematic review [39] determined that of the eight studies included, only one was a complete study published after our inclusion start date of 2000 [2]. As such, the systematic review was not assessed by AMSTAR and will not be further discussed within this systematic review.

Search for Primary Literature

Literature Search Results

Twenty studies were identified that met inclusion criteria (Figure 4-1). Table 4-1 summarizes the number and types of studies included per research question and for each specific melanoma patient subgroup when appropriate. Since many of the identified studies enrolled a mixed melanoma patient population, many studies are included for multiple research questions (Table 4-1).

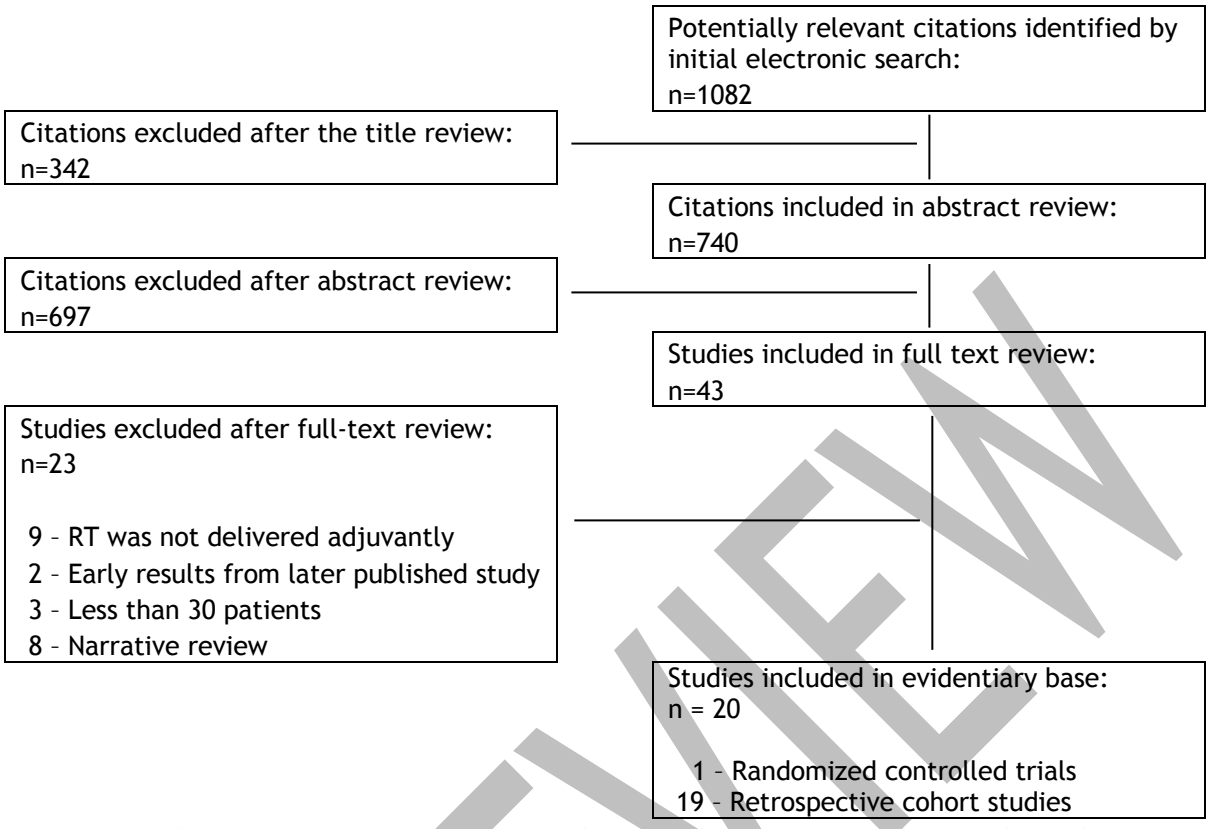

Figure 4-1. Selection of systematic reviews and primary literature from the search results of MEDLINE and EMBASE.

Note: There was only one randomized controlled trial identified by the literature search, but two publications.

Abbreviation: RT, radiation therapy.

Table 4-1. Studies selected for inclusion.

Research Question	Population	Studies [ref]
Q1. Is adjuvant RT to the primary site appropriate after resected curative treatment for primary melanoma?	Stage I-III melanoma patients	3 retrospective cohort studies [1-3]
	Stage I-III desmoplastic/neurotropic melanoma patients	3 retrospective cohort studies [2,5,6]
	Stage I-III primary melanoma patients with satellites	1 retrospective cohort study [2]
Q2. Is adjuvant RT to the regional nodal basin appropriate after resected curative treatment in patients at high risk for regional recurrence of melanoma?	Stage III melanoma patients at high risk for local regional recurrence following lymphadenectomy	1 RCT (2 publications) [9,10] 10 retrospective cohort studies [12,15-20,22,23,40]
Q3. Is adjuvant RT appropriate after resected curative treatment for in-transit primary melanomas?	Stage III melanoma patients who have undergone resection for in-transit melanoma	No studies identified
Q4. Is adjuvant RT appropriate after curatively resected treatment for recurrent melanoma?	Stage I-III melanoma patients who have undergone resection for recurrence at the primary site	1 retrospective cohort study [2]
	Stage I-III melanoma patients who have undergone resection for in-transit recurrence	No studies identified

Research Question	Population	Studies [ref]
	Stage I-III melanoma patients who have undergone resection for recurrence within the lymph node basin	13 retrospective cohort studies [1,2,11-14,18-20,22-24,40]
Q5. Does a standard RT fractionation schedule provide equivalent disease control compared with a hypofractionated schedule?	Stage I-III melanoma patients	No studies identified

Abbreviations: RCT, randomized controlled trial; ref, reference number; RT, radiation therapy.

Study Design and Quality

The primary literature returned 21 publications, from 20 studies that met the study selection criteria. A description of the study design and quality of the studies can be found in Appendix 3. The evidentiary base was comprised of one RCT with two resulting publications [9,10] and 19 retrospective cohort studies [1-3,5,6,11-20,22-24,40] (Figure 4-1, Table 4-1). The Trans-Tasman Radiation Oncology Group (TROG) RCT [9,10] was of moderate quality (Appendix 3) and, as the only RCT identified, was the highest quality study included in this review. The 19 retrospective cohort studies were of low to very low quality based on their retrospective design, which often introduced selection and performance bias (Appendix 3). Of particular note, many of the retrospective cohort studies that compared patients who did and did not receive adjuvant RT offered RT to patients with worse prognostic features without adjusting for this confounder. Additionally, these studies were limited by small population sizes, mixed primary and recurrent disease melanoma populations, and variable RT doses and schedules within studies (Appendix 3).

Outcomes

The results are organized by research question and subdivided into specific melanoma patient populations where appropriate. All included studies are summarized in the text with more complete details found in tables. The three main outcomes of interest were control rate, survival rate, and rate of adverse events. In terms of control rate, the included studies reported on relapse rate, local control rate (LCR), regional control rate (RCR), and local regional control rate (LRCR). Survival within the studies was reported infrequently as overall survival (OS); as such, disease-specific survival (DSS), relapse-free survival (RFS), disease-free survival (DFS), and distant metastasis-free survival (DMFS) data were extracted as a surrogate for OS when necessary. In order to compare the included studies, information related to the RT schedule and total RT dose, as well as the RT site/field were extracted. Additionally, if enrolled patients were offered adjuvant systemic therapy, the number of patients who received each type of therapy was extracted. When studies inform multiple research questions, only details appropriate for the specific research question are included for that question.

Research Question 1: Is adjuvant RT to the primary site appropriate after resected curative treatment for primary melanoma?

Patients with Melanoma

Three retrospective studies assessed the use of adjuvant RT to the primary site after resected curative treatment [1-3]. In one study, an undefined number of patients also received adjuvant interferon therapy [1], while in the other two studies, adjuvant systemic therapy was not offered or not reported. The cohort study by Stevens et al [2] enrolled a mixed population of primary and recurrent disease patients, with 32 patients having disease limited to the

primary tumour site, but only 11 of these enrolled patients were treated for the primary tumour, while 21 were diagnosed with recurrent disease at the primary site. Identified studies indicated that adjuvant RT to the primary site following resected curative treatment for primary melanoma resulted in five-year local control rates of 87% to 97% [1-3] (Table 4-2). Five-year OS for these patients was reported at 46% to 58% [1,3] (Table 4-2). Only one identified study reported on adverse events [3] and indicated a five-year complication-free survival of 82% for Grade 1 adverse events, 94% for Grade 2, and 99% for Grade 3 adverse events (Table 4-2).

Patients with Desmoplastic/Neurotropic Melanoma

Two retrospective studies assessed the use of adjuvant RT to the primary site following curative resection in patients diagnosed with desmoplastic melanoma [5,6]. An additional single-arm retrospective study included a mixed melanoma subtype population, of which 10 patients of a total 174 enrolled had been diagnosed with desmoplastic melanoma [2]. Patients diagnosed with desmoplastic melanoma were pooled and analyzed alongside a total of 32 patients with disease limited to the primary tumour site [2] (Table 4-2). None of the three included studies reported on the use of adjuvant systemic therapy in enrolled patients. The cohort study with a mixed melanoma subtype population of which only 10 were diagnosed with desmoplastic melanoma did not analyze the desmoplastic patients separately [2]. The study reported a five-year recurrence rate of 11% for all patients [2] (Table 4-2).

The other two cohort studies, which focused on desmoplastic melanoma patients, compared patients who did and did not receive adjuvant RT [5,6]. One of the cohort studies compared the patients at baseline and univariate regression analysis indicated that compared with patients receiving surgery alone, adjuvant RT was used significantly more frequently for patients with Clark level V tumours, head and neck locations, greater than 4mm Breslow thickness, pure desmoplastic melanoma, perineural invasion, and positive surgical margin [5]. This study used multivariate analysis to account for these baseline differences in patient characteristics. The other cohort study did not compare baseline characteristics of the included patients [6]. Both studies found that adjuvant RT to the primary site significantly improved five-year local control rates compared with surgery alone [5,6] (Table 4-2). However, the one study [6] that reported on survival did not find any difference in OS, DSS, or DMFS when comparing patients who were treated with RT compared with those who received only surgery (Table 4-2). In terms of adverse events, one cohort study utilizing a hypofractionated regimen [6] reported a five-year rate of 18% for moderate and severe RT-related complications (Table 4-2). The second cohort study [5] did not provide a rate for adverse events, but instead listed skin erythema, pain, and fatigue as common acute side effects, and skin fibrosis, skin pigment changes, and telangiectasias as long-term side effects of adjuvant RT (Table 4-2).

Patients with Primary Melanoma with Satellites

One retrospective study, which enrolled a mixed melanoma population, included three patients with tumour satellites of the total 174 enrolled melanoma patients [2]. These patients were pooled and analyzed with 29 other patients with disease limited to the primary tumour site (Table 4-2). As discussed above, the Stevens et al cohort study [2] reported a 11% five-year in-field recurrence rate for all 174 enrolled patients (Table 4-2).

Table 4-2. Studies assessing the use of adjuvant RT to the primary site following resected curative treatment for primary melanoma.

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Cohort studies that assessed patients diagnosed with primary melanoma				
Bonnen et al, 2004 [3] Sample size: n=157 Treatment: wide local excision plus RT Primary site: Head and neck Median F/U: 68 months (range, 7-185 months)	RT indication: Clinically LN negative head and neck melanomas ≥1.5mm thick or Clark level ≥IV RT field: Primary site plus ipsilateral LNs where appropriate Hypofractionated regimen (all patients) • Total dose: 30Gy (median) • Schedule: 6Gy fractions twice weekly for 2.5 weeks	• 5y LCR*: 94% • 5y RCR*: 89% • 5y LRCR*: 86%	• 5y OS*: 58% • 5y DFS*: 58% • 5y DMFS*: 63%	• 5y complication-free survival*: ○ Gr1: 82% ○ Gr2: 94% ○ Gr3: 99%
Strom et al, 2014 [5] Sample size: n=277 total with desmoplastic melanoma • 96 pure, 82 mixed histology, 99 unknown Treatment: • Surgery only: n=164 • Surgery plus RT: n=113 (patients with multiple adverse prognostic features) Primary site: Head and neck • 44% of surgery group, 71% of RT group Other location • 56% of surgery only group, 29% of RT group	RT indication: Diagnosis of desmoplastic melanoma RT field: Scar plus 2-4cm Hypofractionated regimen (n=unknown) • Total dose: 30Gy • Schedule: 6Gy fraction twice weekly over 2.5 weeks Conventional regimen (n=unknown) • Total dose: 59.4-68Gy • Schedule: once-daily fraction of 1.8-2Gy	• Multivariate regression analysis used to control for difference in baseline for RT and non-RT patients • 5y LCR* improved following RT (p=0.015) ○ Surgery: 76% ○ RT: 95% • HR: 0.15 (95%CI, 0.06-0.39; p<0.001) by Cox multivariate analysis		• Common acute side effects: skin erythema, pain, fatigue • Common long-term side effects: skin fibrosis, skin pigment changes, telangiectasias

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Median F/U: 43.1 months				
Cohort studies that assessed patients diagnosed with primary melanoma or recurrent melanoma				
Chang et al, 2006 [1] Sample size: n=56 • 27 with primary disease and 29 with recurrence Treatment: wide local excision plus RT Primary site: head and neck (87%), axilla (5%), upper torso (4%), groin (2%), upper extremity (2%) Median F/U: 4.4 years (range, 7.2-173 months)	RT indication: Close or positive margins, gross disease, satellitosis, disease recurrence, ≥3 positive LNs, >3cm diameter LN, ECE, cervical LN involvement RT field: Primary site and regional LNs where appropriate Hypofractionated regimen (n=41/56, 73.2%) • Total dose: 30Gy • Schedule: 5 fractions of 6Gy twice weekly for 2.5 weeks Conventional regimen (n=14/56, 25.0%) • Total dose: 60Gy (median) • Schedule: once-daily fraction of 2Gy (median)	• 5y in-field LRCR: 97%	• 5y OS: 46%	
Guadagnolo et al, 2014 [6] Sample size: n=130 total with desmoplastic melanoma • 100 pure, 30 mixed histology • 110 diagnosed with primary disease, 20 with recurrent disease Treatment: • Surgery only: n=59 • Surgery plus RT: n=71	RT Indication: Histologic diagnosis of desmoplastic melanoma RT field: Primary site (n=71) plus draining LN region where appropriate (n=18/71, 25.4%) Hypofractionated regimen • Total dose: 30Gy (n=68/71, 95.8%), 36Gy (n=2/71, 2.8%), 60Gy (n=1/71, 1.4%) • Schedule: 5 fractions of 6Gy twice weekly over 2.5 weeks (n=68/71, 95.8%), 6Gy twice weekly over 3	• 5y LCR improved following RT (p=0.009) ○ Surgery only: 74% ○ RT: 91%	• 5y OS*: 69% (all patients) • 10y DSS ○ Surgery: 84% ○ RT: 77% (p=0.83) • 10y DMFS: pure desmoplastic ○ Surgery: 73% ○ RT: 72% (p=0.83) • 10y DMFS: mixed histology ○ Surgery: 100% ○ RT: 76% (p=0.07)	• 2.8% developed mild adverse events: skin fibrosis and delayed wound healing • 9.9% developed moderate adverse events: hypothyroidism (n=2), delayed wound healing (n=2), edema (n=1), xerostomia (n=1), keratoconjunctivitis sicca/ blepharitis (n=1) • 8.5% developed severe adverse events: osteoradionecrosis (n=3),

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Primary site: face (34%), scalp (22%), upper extremity (20%), trunk (15%), neck (5%), lower extremity (4%) Median F/U: 6.6 years (range, 11-288 months)	weeks (n=2/71, 2.8%), 30 fractions of 2Gy (n=1/71, 1.4%)			nonhealing scalp wound requiring surgical revision (n=2), skin graft failure (n=1)
Stevens et al, 2000 [2] Sample size: n=174 total • n=11 with primary melanoma (10 desmoplastic, 3 with tumour satellites) Treatment: excision plus RT Primary site: all 174 patients - head and neck (45%), trunk (27%), limbs (14%), occult (14%) Median F/U: 30 months (range, 6-116 months)	RT indication: Patients with disease limited to primary tumour site – Positive surgical margins, neurotropic desmoplastic histopathology, close excision margins, recurrence with perineural spread, tumour satellites, early or multiple recurrences RT field: Primary site (n=32/174; 11 primary melanoma, 21 recurrence at primary site) • Head and neck 81.2%, trunk 18.8% Hypofractionated regimen (all patients) • Total dose: 30-36Gy • Schedule: 5-7 fractions twice weekly over 2.5 weeks	• 5y in-field recurrence rate (all patients): 11%	• 3y DMFS for patients with primary melanoma: 60%	

Abbreviations: CI, confidence interval; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; ECE, extracapsular extension; F/U, follow-up; Gy, Gray; HR, hazard ratio; LCR, local control rate; LN, lymph node; LRCR, local regional control rate; OS, overall survival; RCR, regional control rate; RT, radiation therapy; y, year.
Note: * indicates that the rate was calculated using an actuarial method.

Research Question 2: Is adjuvant RT to the regional nodal basin appropriate after resected curative treatment in patients at high risk for regional recurrence of melanoma?

One RCT [9,10] and 10 retrospective cohort studies [12,15-20,22,23,40] assessed the role of adjuvant RT in stage III melanoma patients who are at high risk for local regional recurrence following lymphadenectomy. The included RCT conducted by TROG enrolled patients from 16 hospitals in Australia, New Zealand, the Netherlands, and Brazil [9,10]. Enrolled patients were at high risk for lymph node field relapse and were randomized to an adjuvant RT group (n=122) or an observation group (n=126). Patients who had a previous local or in-transit relapse and those who had previous nodal surgery were excluded from the study, but it is unclear whether patients with a first relapse to lymph nodes were eligible for inclusion [9,10]. Additionally, cytotoxic chemotherapy was not permitted during or close to when RT was performed, but 3% to 5% of patients were receiving adjuvant interferon [9]. Two publications were identified for this RCT. The first article was published after patients had been followed for 40 months (interquartile range [IQR], 27-55 months) and focused on disease control, survival, and early toxic events [9]. The RCT reported a 56% relative reduction in relapse for patients who received adjuvant RT compared with the observation group (hazard ratio [HR], 0.56; 95% confidence interval [CI], 0.32-0.98; p=0.041), but no difference in overall survival (HR, 1.37; 95%CI, 0.94-2.01; p=0.12) (Table 4-3) [9]. The second article included 73 months (IQR, 21-116 months) of follow-up and reported that adjuvant RT reduced the relative risk of lymph node field recurrence by 52% (HR, 0.52; 95%CI, 0.31-0.88; p=0.023), but there was still no survival difference between groups (HR, 1.27; 95%CI, 0.89-1.79; p=0.21) (Table 4-3) [10]. Longer patient follow-up enabled for the investigation of long-term toxic events. Late surgical and RT toxic events, limb volumes, quality of life (QoL), and a regional symptoms were recorded from randomization through diagnosis of distant relapse or end of study. Grades 2 to 4 late RT-related adverse events were common (74% of patients) and were mainly associated with skin (42%) and subcutaneous tissue (50%) [10]. The study reported two Grade 4 toxic events, both of which occurred after RT to the head and neck and affected a major nerve and the inner ear [10]. At baseline, there were no differences in mean limb volumes between treatment arms; however, over the period of zero to 60 months, patients receiving RT experienced a significant increase in lower limb volume (15.0% versus [vs.] 7.7%; difference, 7.3%; 95%CI, 1.2-13.1; p=0.014). The difference in upper limbs were small and there was no significant difference between groups (10.5% vs. 7.0%; p=0.25). There was also no difference in Grade 3 lymphedema between the treatment groups for any lymph node field location [10]. When assessing QoL, a validated QoL tool (Functional Assessment of Cancer Therapy – General [FACT-G]) indicated no differences in QoL between the RT and observation groups, while according to the regional symptomatology questionnaire total score, patients receiving RT experienced worse symptoms than patients who only received surgery at three, six, and 12 months [41].

The 10 additional retrospective cohort studies were all published before publication of the TROG RCT [9,10]. Four of these cohort studies [18,20,23,40] included patients who may have been concurrently receiving immunotherapy, cytotoxic chemotherapy, and/or adjuvant interferon. The majority of these cohort studies included both patients with primary stage III melanoma with nodal involvement as well as patients with recurrent nodal disease [12,18-20,22,23,40] (Table 4-3), without separately analyzing the effects of adjuvant RT on the groups. Only four of the studies [12,15-17] retrospectively compared patients who received adjuvant RT with those that received only surgery (Table 4-3). All four of these studies suffered from selection bias, as all four did not account for patient characteristic differences at baseline and, in all studies, patients with poorer prognostic factors were offered adjuvant RT. In one study, the adjuvant RT group consisted of more patients with head and neck melanoma and thicker tumours [15]; in another, more patients with cervical lymph node involvement were offered

adjuvant RT [17]; in the third, all patients at high risk for local or regional recurrence were treated with adjuvant RT [16]; and in the final study, RT patients had more extensive surgery (p=0.003), higher median number of involved nodes (p=0.01), more patients had extracapsular extension (p=0.026), and more patients were advanced stage (p=0.10) [12]. Even though these confounders were not accounted for, one study found that adjuvant RT improved RCR compared with surgery alone [12], while three studies found no difference in LCR [15], RCR [17], or regional recurrence rate [16] (Table 4-3). All four studies found no difference between groups for OS [12,16,17] or DSS [15].

The six retrospective cohort studies that only assessed patients who had received adjuvant RT reported 10-year local control rates of 94% [19], five-year RCRs of 87% to 89% [18,20,23], five-year LRCRs of 90% [40], and a local recurrence rate of 22.4% [22] (Table 4-3). Studies that reported OS reported a 10-year OS of 39% [19], a five-year OS of 50% to 51% [20,23], and a median OS range of 26 months [40] to 38.3 months [22] (Table 4-3). One study [18] did not report on overall survival and instead reported a five-year DSS of 49% (Table 4-3). In terms of adverse events, studies reported a five-year Grade 1 complication rate of 12% to 14% [19,20] and a five-year Grade 2 or 3 complication rate of 17% to 18% [18,20], as well as 27.8% of patients reporting Grade 1 or 2 toxic events [12], and 22% of patients experiencing a Grade 2 toxicity [17] (Table 4-3). Lymphedema was the most common adverse event reported by many studies, with 9% to 21% of patients having experienced lymphedema [18,20,22] (Table 4-3).

Table 4-3. Studies assessing the use of adjuvant RT to the regional nodal basin following lymphadenectomy.

Study, Population	RT Details	Control Rate	Survival	Adverse Events
RCT that assessed patients at high risk for local regional recurrence				
TROG RCT Burmeister et al, 2012 [9] and Henderson et al, 2015 [10] Sample size: n=248 total Treatment: • RT arm (intention-to-treat): n=122 • Observation control arm (intention-to-treat): n=126 Primary site • Trunk: 30% RT, 21% obs • Leg: 24% RT, 24% obs • Head and neck: 16% RT, 17% obs • Arm: 14% RT, 17% obs • Unknown: 16% RT, 20% obs Median F/U: 40 months (range, 27-55 months)	RT indication: High risk of lymph node field relapse, defined by ≥1 involved parotid LNs, ≥2 involved cervical or axillary LNs, ≥3 involved inguinal LNs, or presence of extranodal tumour spread, or a maximum diameter of the largest metastatic LN of ≥3cm for cervical LNs or ≥4cm for an axillary or inguinal LNs RT field: Dissected LN field (43% axilla, 32% groin, 25% head and neck) and lymphadenectomy scar Standard fraction regimen • Total dose: 48Gy (n=109/115, 94.8%), <48Gy (n=5/115, 4.3%), >48Gy (n=1/115, 0.9%) • Schedule: 20 fractions over 4 weeks (30 day max)	• Fewer patients in RT group had LN field relapse as a first relapse (HR, 0.56; 95%CI, 0.32-0.98; p=0.041 [9]; HR, 0.52; 95%CI, 0.31-0.88; p=0.23 [10])	• OS was not significantly different between groups (HR, 1.37; 95%CI, 0.94-2.01; p=0.12 [9]; HR, 1.27; 95%CI, 0.87-1.79; p=0.21 [10])	• 2 weeks after RT the most common early reported toxic effects (Grade 3 and 4) were: ○ Radiation dermatitis – 3 events after RT to head and neck, 10 events after RT to axilla, 6 events after RT to ilio-inguinal ○ Pain – 2 events after RT to axilla • 20% (n=18/90) patients developed Grade 3 toxic events ○ 10% (n=9/90) affecting skin ○ 7% (n=6/90) affecting subcutaneous tissue • 2 Grade 4 toxic events after RT to head and neck • Lower limb volume significantly higher in patients receiving adjuvant RT (15.0% vs. 7.7%; difference, 7.3%; 95%CI, 1.5-13.1; p=0.014) • There was no difference in QoL by FACT-G • RSQ total score indicated significantly worse scores for patients who received RT at 3 (p<0.0001), 6 (p=0.00095), and 12 (p=0.0082) months post-randomization •

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Cohort studies that assessed patients diagnosed with stage III melanoma with nodal involvement				
Fuhrmann et al, 2001 [15] Sample size: n=116 Treatment: • Lymphadenectomy only: n=58 • Lymphadenectomy plus RT: n=58 Primary site • Trunk: 39.7% surgery, 37.9% RT • Lower extremity: 37.9% surgery, 31.0% RT • Upper extremity: 17.2% surgery, 12.1% RT • Head and neck: 3.4% surgery, 19.0% RT Median F/U: not reported Approximate F/U: 6-14 years	RT indication: ≥2 positive LNs, or LN with a diameter of >1cm, or ECE RT field: Involved LN regions Mixed RT regimen • Total dose: 50–65Gy (n=51/58, 87.9%), 70Gy (n=1/58, 1.7%), <50Gy (n=4/58, 6.9%), unknown (n=2/58, 3.4%) • Schedule: 2.0-3.8Gy/fraction ○ Details limited	• LCR not significantly different between groups (p>0.05) ○ Surgery: 21% ○ RT: 16%	• DSS not significantly different between groups (p>0.05) ○ Surgery: 74% ○ RT: 83%	
Bibault et al, 2011 [17] Sample size: n=86 total Treatment: • Lymphadenectomy only: n=26 • Lymphadenectomy plus RT: n=60 Primary site: not reported	RT indication: ≥4 positive LNs, ECE, or LN with >3cm diameter RT field: Involved LN basins (cervical 28%, axillary 37%, inguinal 35%) Conventional regimen • Total dose: ≤50Gy (range, 30-70Gy; n=30/60, 50%) or >50Gy (n=30/60, 50%)	• No RCR different between surgery only and RT groups (p=0.17) • 5y RCR better for patients who received a higher RT dose than lower ○ 80% for ≥50Gy dose vs. 35% for <50Gy dose (p=0.004)	• No difference in OS for surgery compared with RT group (p=0.18)	• Grade 2 toxicity reported by 15 patients (22%) treated with RT • No Grade 3 toxicity reported

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Median F/U: 73 months (range, 2-158 months)	• Schedule: 5 fractions of 2Gy (range, 1.8-3Gy) per week to a total of 25 fractions (range, 10-44)			
Moncrieff et al, 2008 [16] Sample size: n=716 total Treatment: • Neck dissection: n=587 • Neck dissection plus RT: n=129 Primary site: not reported Median F/U: 34.7 months	RT indication: ECE, or parotid involvement, or ≥2 positive LNs, or LN with >3cm diameter RT field: Involved cervical LN fields and primary disease site if pathologically identified high risk factors Hypofractionated regimen (all RT patients) • Total dose: 33Gy (range, 30-60Gy) • Schedule: 5.5Gy fractions twice weekly for 3 weeks	• No difference in 6y regional recurrence rate (p=0.20) ○ Surgery: 6.1% ○ RT:10.1%	• No difference in OS between neck dissection and neck dissection plus RT groups (p=0.394)	
Cohort studies that assessed patients diagnosed with stage III melanoma with nodal involvement or lymph node recurrence				
Ballo et al, 2003 [19] Sample size: n=160 (71 with positive LNs at primary diagnosis, 89 with LN recurrence) Treatment: cervical LN dissection plus RT Primary site: head and neck (78.8%), unknown (21.2%) Median F/U: 78 months	RT indication: cervical LN metastases at initial diagnosis, or cervical LN recurrence RT field: Cervical LNs Hypofractionated regimen (all patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks	• 10y LCR*: 94% • 10y RCR*: 94%	• 10y OS: 39% • 10y DSS: 48% • 10y DMFS: 43% • 10y DFS: 42%	• 5y Grade 1 complication rate*: 12% ○ Skin reactions • 5y Grade 2 complication rate*: 10% ○ Ipsilateral decreased hearing (n=3), clinical hypothyroidism (n=2), wound breakdown (n=2), bone exposure (n=1), mild ear pain (n=1) • No Grade 3 complications
Ballo et al, 2006 [18] Sample size: n=466 (410 with LN disease at	RT indication: ECE, or a LN with ≥3cm diameter, or ≥4 positive LNs, or recurrent disease after previous LN dissection	• 5y RCR*: 89%	• 5y DSS*: 49% • 5y DFS*: 42% • 5y DMFS*: 44%	• 5y Grade 2 or Grade 3 complication rate*: 19% ○ n = 70 (15.0%) developed Grade 2

Study, Population	RT Details	Control Rate	Survival	Adverse Events
primary diagnosis, 56 with LN recurrence) Treatment: lymphadenectomy plus RT Primary site: head and neck (43.3%), trunk (18.2%), upper extremity (8.2%), lower extremity (5.8%), unknown (24.5%) Median F/U: 4.2 years (range, 2.5-243 months)	RT field: Involved LN basins (cervical 57%, axilla 33%, groin 9%, epitrochlear 1%) Hypofractionated regimen (94.8% of RT patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks			○ n = 7 (1.5%) developed Grade 3 • 5y Grade 2 or Grade 3 complication rate varied by LN disease site (p<0.0001) ○ Groin: 39% ○ Axillary: 30% ○ Cervical: 11% ○ Epitrochlear: 0% • 5y rate of symptomatic lymphedema*: 9% • 5y rate of symptomatic lymphedema varied by LN disease site (p<0.0001) ○ Groin: 27% ○ Axillary: 20% ○ Cervical: 1% ○ Epitrochlear: 0%
Ballo et al, 2002 [23] Sample size: n=89 (66 with first axillary disease, 23 with recurrent disease) Treatment: axillary node dissection plus RT Primary site: trunk (50.6%), upper extremity (18.0%), head and neck (3.4%), unknown (28.0%) Median F/U: 4.8 years (range, 6.7-159 months)	RT indication: ECE, LN with ≥3cm diameter, ≥4 positive LNs, or axillary recurrence after prior surgery RT field: Axillary LNs Hypofractionated regimen (96.6% of RT patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks	• 5y axillary control rate*: 87%	• 5y OS*: 50% • 5y DFS*: 46% • 5y DMFS*: 49%	
Beadle et al, 2009 [20]	RT indication: LN or axillary mass ≥3cm, ≥4 positive LNs, ECE, or	• 5y axillary control rate*: 88%	• 5y OS*: 51% • 5y DFS*: 43% • 5y DMFS*: 46%	• Arm edema was the most common complication (21%;

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Sample size: n=200 (163 with first axillary disease, 37 with recurrent disease) Treatment: axillary LN dissection plus RT Primary site: trunk (44.5%), upper extremity (23%), head and neck (1.5%), unknown (31%) Median F/U: 59 months (range, 5.9-283 months)	recurrent disease after initial surgical resection RT field: Axilla only (n=95) or axilla plus supraclavicular fossa (n=105) Hypofractionated regimen (98.5% of RT patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks			n=42/200; Grade not reported) • 5y treatment related complication rate ○ Grade 1: 14% ○ Grade 2: 18% ○ Grade 3: 0% • Grade 1 adverse events: fibrosis (n=2), rib fracture (n=1) • Grade 2 adverse events: brachial plexopathy (n=1, resolved completely), radiation pneumonitis in adjacent lung (n=1, resolved completely)
Conill et al, 2009 [40] Sample size: n=77 (50 with primary LN disease, 27 with recurrent disease) Treatment: lymphadenectomy surgery plus RT Primary site: not reported Median F/U: not reported	RT indication: ECE, ≥3 positive LNs, a LN with ≥3cm diameter, or LN recurrence RT field: Involved LN basins (cervical 15.6%, axillar 57.1%, groin 27.3%) Hypofractionated regimen (n=65/77, 84.4%) • Total dose: 30-36Gy • Schedule: 6Gy fractions twice weekly Conventional regimen (n=12/77, 15.6%) • Total dose: 44-50Gy • Schedule: 2Gy fractions five times a week	• 5y in-field LRCR*: 90%	• Median OS: 26 months (95%CI, 18-34 months) • Median DMFS: 16 months (95%CI, 13-18 months)	
Sherriff et al, 2012 [22]	RT indication: size and number of involved LN, close or involved margins, or ECE	• Patients followed 35 months (range, 3-140 months)	• Median OS: 38.3 months	• 6 (12.2%) patients developed lymphedema

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Sample size: n=49 (11 with no history of melanoma, 38 with LN recurrence) Treatment: nodal dissection plus RT Primary site: not reported Median F/U: 35 months (range, 3-140 months)	RT field: Involved LN basins (axilla 38.8%, head and neck 32.7%, ilio-inguinal 28.5%) Conventional regimen (all patients) • Total dose: 50 or 48Gy • Schedule: 20 fractions over 4 weeks	• Local recurrence rate: 22.4% • Distant recurrence rate: 53.1%		• 1 patient required a skin graft following wound breakdown • 1 patient developed hearing loss following RT to the left neck
Strojan et al, 2010 [12] Sample size: n=83 (76 with primary LN disease, 7 with regional recurrence after previous surgery) Treatment: • Nodal dissection: n=40 • Dissection plus RT: n=43 (higher risk factor patients) Primary site: not reported Median F/U: 2.1 years (range, 0.1-8.5 years)	RT indication: Results of the histopathologic examination of resected specimen RT field: Involved neck and parotid LNs Hypofractionated regimen (all patients) • Total dose: 60Gy (range, 47.8-78.8Gy) • Schedule: 5Gy fractions (range, 2-6Gy) over 20 days (range, 11-43)	• 2y RCR improved following RT (p=0.015) ○ Surgery: 56% (95%CI, 40-72%) ○ RT: 78% (95%CI, 63-92%)	• No difference in 2y OS ○ Surgery: 58% (95%CI, 42-73%) ○ RT: 51% (95%CI, 36-66%)	• Long-term complications assessed in patients who survived >6 months • No difference in rate of late toxic events between groups (p>0.05) ○ 27.8% (95%CI, 14.2-45.2%) patients who received RT reported 1 or more toxic events ○ Grade 1: 6 events ○ Grade 2: 4 events ○ Grade 3: 0 events

Abbreviations: CI, confidence interval; DFS, disease-free survival; DMFS, distant metastasis-free survival; DSS, disease-specific survival; ECE, extracapsular extension; FACT-G, Functional Assessment of Cancer Therapy – General; F/U, follow-up; Gy, Gray; HR, hazard ratio; LCR, local control rate; LN, lymph node; LRCR, local regional control rate; max, maximum; obs, observation control; OS, overall survival; QoL, quality of life; RCR, regional control rate; RCT, randomized controlled trial; RSQ, regional symptomatology questionnaire; RT, radiation therapy; TROG, Trans-Tasman Radiation Oncology Group; vs., versus; y, year.
Note: * indicates that the rate was calculated using an actuarial method.

Research Question 3: Is adjuvant RT appropriate after resected curative treatment for in-transit primary melanomas?

The literature search did not identify any systematic reviews or primary studies that assessed the role of adjuvant RT in stage III melanoma populations after undergoing resection for in-transit melanomas.

Research Question 4: Is adjuvant RT appropriate after curatively resected treatment for recurrent melanoma?

Recurrence at the Primary Site

The Stevens et al retrospective cohort study [2] that has been discussed previously included 21 patients with recurrent melanoma that was limited to the primary tumour site. Unfortunately, patient populations were not analyzed separately in this study. For all enrolled patients, adjuvant RT results in a five-year in-field recurrence rate of 13% [2].

In-transit Recurrences

The literature search did not identify any systematic reviews or primary studies that assessed the role of adjuvant RT for in-transit recurrences.

Recurrence within the Lymph Node Basin

There were 13 retrospective cohort studies identified that assessed the use of adjuvant RT to the regional nodal basins following curatively resected treatment for recurrence. Seven of these cohort studies [1,11,18-20,23,40] included patients who may have been concurrently receiving immunotherapy, cytotoxic chemotherapy, and/or adjuvant interferon. It again needs to be noted that of the 13 studies identified to inform this research question, nine of them enrolled both patients with primary melanoma with involved lymph nodes and those with recurrence within the lymph nodes following prior resection [1,2,12,18-20,22,23,40] and none of these studies assessed the control rates, survival, or rate of adverse effects separately for the different population types. It could be argued that due to the TROG RCT [9,10] inclusion criteria being somewhat unclear in whether patients with a first relapse to lymph nodes were eligible for inclusion, the TROG RCT should also be included here; however, for the sake of brevity, since the RCT was described previously, it will not be further discussed in this section.

Of the 13 included retrospective cohort studies, only four [11-14] compared the records of patients treated with adjuvant RT following lymphadenectomy with patients treated with lymphadenectomy alone (Table 4-4). Three of these studies compared baseline characteristics of the patients and found that patients with poorer prognosis were treated with adjuvant RT [12-14]. More specifically, the adjuvant RT arm consisted of more patients with extracapsular tumour extension [12,14], more extensive surgery [12], higher median number of involved nodes [12], more advanced stage tumours [12], and higher study-specific risk factor scores [12-14]. The fourth cohort study did not officially compare patients at baseline, but current reviewers note that more patients with cervical lymph node involvement were treated with adjuvant RT compared with those treated with surgery alone [11]. When assessing control rates, one study [11] reported an improved five-year RCR when adjuvant RT was delivered to cervical lymph nodes and axilla lymph nodes, but no difference in control when adjuvant RT was delivered to epitrochlear lymph nodes (Table 4-4). Another study [12] also reported an improved two-year RCR when adjuvant RT was delivered to neck and parotid nodes, while the final two comparative retrospective studies found no difference in two-year RCRs [14], or two-year ipsilateral regional recurrence rates [13] (Table 4-4). When reporting on OS, three of these comparative retrospective studies [12-14] found no difference in two-year OS when comparing patients who received adjuvant RT with those who only received surgery (Table 4-

4). However, according to multivariate analysis in the Agrawal et al retrospective study [11], five-year DSS and DMFS were improved following adjuvant RT (Table 4-4).

The nine retrospective cohort studies that only reviewed records of patients who had received adjuvant RT following resection for recurrent lymph node disease reported 10-year LCRs of 94% [19], five-year LCRs of 87% to 88% [20,23], three-year RCRs of 74% [24], five-year RCR of 89% [18], five-year LRCRs of 87% to 90% [1,40], and three-year local recurrence rates of 22.4% [22], as well as a five-year in-field recurrence rate of 11% [2] (Table 4-4). Seven of these studies reported on OS and indicated a 10-year OS rate of 39% [19], a five-year OS rate of 46% to 51% [1,20,23], a three-year OS rate of 38% [24], and a median OS rate of 26 to 38.3 months [22,40] (Table 4-4). The two studies that did not report on OS instead reported a three-year metastasis-free survival of 39% [2] and five-year DSS of 49% [18].

Eight of the included retrospective cohort studies reported on adverse events following therapy with adjuvant RT. Multivariate analysis determined that the five-year rate of lymphedema was higher following adjuvant RT compared with surgery alone in one study [11], while another study that compared patients who did and did not receive adjuvant RT found no difference in rates of lymphedema between groups [14] (Table 4-4). Other studies reported a 9% rate of symptomatic lymphedema by five years [18], a 12% to 39% rate of lymphedema at three years [22,24], and a 21% rate of lymphedema over five years following adjuvant RT [20] (Table 4-4).

Table 4-4. Studies assessing the use of adjuvant RT to the regional nodal basin following curatively resected treatment for recurrence.

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Cohort studies that assessed patients diagnosed with lymph node recurrence				
Agrawal et al, 2009 [11] Sample size: 615 total Treatment: • Lymphadenectomy: n=106 • Lymphadenectomy plus RT: n=509 Primary site: head and neck (33%), trunk (25%), lower extremity (9%), upper extremity (10%), unknown (23%) Median F/U: 5 years (range, 5.3-284 months)	RT indication: Cervical LN basins: ≥2cm LN diameter, or ≥2 positive LNs, or ECE Axilla LN basins: ≥3cm LN diameter, or ≥4 positive LNs, or ECE Inguinal LN basins: ≥3cm LN diameter and ECE, or ≥3cm LN diameter and ≥4 positive LNs, or ≥4 positive LNs and ECE Epitrochlear LN basins: ≥3cm LN diameter, or ≥4 positive LNs, or ECE RT field: Involved LN basins (cervical 52.7%, axilla 38.1%, inguinal 8.6%, epitrochlear 0.6%) Hypofractionated regimen (99.0% of RT patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks	• 5y RCR* improved following RT to cervical LNs (p<0.0001) ○ Surgery: 43% ○ RT: 93% • 5y RCR* improved following RT to axilla LNs (p<0.0001) ○ Surgery: 48% ○ RT: 91% • 5y RCR* no different following RT to epitrochlear LNs (p=0.13)	• By multivariate analysis, 5y DSS was improved following RT (p<0.0001) ○ Surgery: 30% ○ RT: 51% • By multivariate analysis, 5y DMFS was improved following RT (p=0.0006) ○ Surgery: 28% ○ RT: 43%	• By multivariate analysis 5y rate of lymphedema higher following RT compared to surgery alone (p=0.001) ○ Grade 2 lymphedema noted in 9% (n=45/509) RT patients vs. 7.5% (n=8/106) surgery only patients
Ballo et al, 2004 [24] Sample size: n=40 Treatment: nodal resection plus RT Primary site: lower extremity (62.5%), trunk (30.0%), unknown (7.5%)	RT indication: ECE, ≥3cm LN diameter, ≥4 positive LNs, or LN recurrence after prior LN surgery RT field: Involved inguinal and/or pelvic LN basins Hypofractionated regimen (all patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly	• 3y RCR*: 74%	• 3y OS*: 38% • 3y DFS*: 27% • 3y DMFS*: 35%	• 3y complication rate* (any): 52% • 3y lymphedema rate: 39% • Most common complication was lower extremity lymphedema ○ Grade 1: 12.5% (n=5) ○ Grade 2: 25.0% (n=10) • Delayed wound healing also reported ○ Grade 2: 10.0% (n=4) ○ Grade 3: 5.0% (n=2)

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Median F/U: 22.5 months (range, 3.6-107 months)				
Gojkovic-Horvat et al, 2012 [14] Sample size: n=101 Treatment: • Nodal dissection: n=64 • Nodal dissection plus RT: n=37 (higher risk factor patients) Primary site: not reported Mean F/U: 5.3 years (range, 2.6-9.8 years)	RT indication: ≥3 positive LNs, ≥4cm LN diameter, ECE, disease recurrence, or satellitosis RT field: Groin LN basins Conventional regimen (n=36/37, 97.3%) • Median total dose: 50.6Gy (range, 50-72Gy) • Schedule: 5 fractions of 2-3Gy per week Hypofractionated regimen (n=1/37, 2.7%) • Median total dose: 50.6Gy (range, 50-72Gy) • Schedule: 6Gy fractions twice weekly	• 2y RCR not different between groups (p=0.395) ○ Surgery: 86% (95%CI, 76-95%) ○ RT: 91% (95%CI, 81-100%)	• 2y OS not different between groups (p=0.813) ○ Surgery: 56% (95%CI, 44-68%) ○ RT: 56% (95%CI, 39-72%)	• Rate of lower extremity lymphedema not different between groups (p=0.321) ○ Surgery: 29.2% (95%CI, 16.9-44.1%; Grade 1: n=4, Grade 2: n=10) ○ RT: 40.7% (95%CI, 22.4-61.2%; Grade 1: n=2, Grade 2: n=9)
Hamming-Vrieze et al, 2009 [13] Sample size: n=64 Treatment: • Nodal dissection only: n=24 • Nodal dissection plus RT: n = 40 (patients with poorer prognosis) Primary site: • Frontal/ temporal/ cheek: 58% RT, 51% surgery	RT indication: ECE, ≥3cm LN diameter, ≥2 or ≥3 positive LNs (based on year patient enrolled) RT field: Entire ipsilateral neck Hypofractionated regimen (all RT patients) • Total dose: 24-36Gy • Schedule: 6Gy fractions once a week for 4-6 weeks	• 2y ipsilateral regional recurrence rate not significantly different between groups (p=0.16) ○ Surgery: 46% ○ RT: 18%	• 2y OS not different between groups (p=0.07) ○ Surgery: 58% ○ RT: 26% • 2y DFS not different between groups (p=0.30) ○ Surgery: 29% ○ RT: 18%	

Study, Population	RT Details	Control Rate	Survival	Adverse Events
• Occipital: 28% RT, 33% surgery • Neck: 2% RT, 4% surgery • Midline: 12% RT, 13% surgery Median F/U: 2.5 years				
Cohort studies that assessed patients diagnosed with lymph node recurrence or with lymph node involvement at primary diagnosis				
Ballo et al, 2003 [19] Sample size: n=160 (71 with positive LNs at primary diagnosis, 89 with LN recurrence) Treatment: cervical LN dissection plus RT Primary Site: head and neck (78.8%), unknown (21.2%) Median F/U: 78 months	RT indication: cervical LN metastases at initial diagnosis, or cervical LN recurrence RT field: Cervical LNs Hypofractionated regimen (all patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks	• 10y LCR*: 94% • 10y RCR*: 94%	• 10y OS: 39% • 10y DSS: 48% • 10y DMFS: 43% • 10y DFS: 42%	• 5y Grade 1 complication rate*: 12% ○ Skin reactions • 5y Grade 2 complication rate*: 10% ○ Ipsilateral decreased hearing (n=3), clinical hypothyroidism (n=2), wound breakdown (n=2), bone exposure (n=1), mild ear pain (n=1) • No Grade 3 complications
Ballo et al, 2006 [18] Sample size: n=466 (410 with LN disease at primary diagnosis, 56 with LN recurrence) Treatment: lymphadenectomy plus RT Primary site: head and neck (43.3%), trunk (18.2%), upper extremity	RT indication: ECE, or ≥3cm LN diameter, or ≥4 positive LNs, or recurrent disease after previous LN dissection RT field: Involved LN basins (cervical 57%, axilla 33%, groin 9%, epitrochlear 1%) Hypofractionated regimen (94.8% of patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks	• 5y RCR*: 89%	• 5y DSS*: 49% • 5y DFS*: 42% • 5y DMFS*: 44%	• 5y Grade 2 or Grade 3 complication rate*: 19% ○ n = 70 (15.0%) developed Grade 2 ○ n = 7 (1.5%) developed Grade 3 • 5y Grade 2 or Grade 3 complication rate varied by LN disease site (p<0.0001) ○ Groin: 39% ○ Axillary: 30% ○ Cervical: 11% ○ Epitrochlear: 0% • 5y rate of symptomatic lymphedema*: 9%

Study, Population	RT Details	Control Rate	Survival	Adverse Events
(8.2%), lower extremity (5.8%), unknown (24.5%) Median F/U: 4.2 years (range, 2.5-243 months)				• 5y rate of symptomatic lymphedema varied by LN disease site (p<0.0001) ○ Groin: 27% ○ Axillary: 20% ○ Cervical: 1% ○ Epitrochlear: 0%
Ballo et al, 2002 [23] Sample size: n=89 (66 with first axillary disease, 23 with recurrent disease) Treatment: axillary node dissection plus RT Primary site: trunk (50.6%), upper extremity (18.0%), head and neck (3.4%), unknown (28.0%) Median F/U: 4.8 years (range, 6.7-159 months)	RT indication: ECE, ≥3cm LN diameter, ≥4 positive LNs, or axillary recurrence after prior surgery RT field: Axillary LNs Hypofractionated regimen (96.6% of patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks	• 5y axillary control rate*: 87%	• 5y OS*: 50% • 5y DFS*: 46% • 5y DMFS*: 49%	
Beadle et al, 2009 [20] Sample size: n=200 (163 with first axillary disease, 37 with recurrent disease) Treatment: axillary LN dissection plus RT Primary site: trunk (44.5%), upper extremity (23%), head and neck (1.5%), unknown (31%)	RT indication: LN or axillary mass ≥3cm, ≥4 positive LNs, ECE, or recurrent disease after initial surgical resection RT field: Axilla only (n=95) or axilla plus supraclavicular fossa (n=105) Hypofractionated regimen (98.5% of patients) • Total dose: 30Gy • Schedule: 6Gy fractions twice weekly over 2.5 weeks	• 5y axillary control rate*: 88%	• 5y OS*: 51% • 5y DFS*: 43% • 5y DMFS*: 46%	• Arm edema was the most common complication (21%; n=42/200; Grade not reported) • 5y treatment related complication rate ○ Grade 1: 14% ○ Grade 2: 18% ○ Grade 3: 0% • Grade 1 adverse events: fibrosis (n=2), rib fracture (n=1) • Grade 2 adverse events: brachial plexopathy (n=1,

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Median F/U: 59 months (range, 5.9-283 months)				resolved completely), radiation pneumonitis in adjacent lung (n=1, resolved completely)
Chang et al, 2006 [1] Sample size: n=56 • 27 with primary disease and 29 with recurrence Treatment: wide local excision plus RT Primary site: head and neck (87%), axilla (5%), upper torso (4%), groin (2%), upper extremity (2%) Median F/U: 4.4 years (range, 7.2-173 months)	RT indication: Close or positive margins, gross disease, satellitosis, disease recurrence, ≥3 positive LNs, >3cm LN diameter, ECE, cervical LN involvement RT field: Primary site and regional LNs where appropriate Hypofractionated regimen (n=41/56, 73.2%) • Total dose: 30Gy • Schedule: 5 fractions of 6Gy twice weekly for 2.5 weeks Conventional regimen (n=14/56, 25.0%) • Total dose: 60Gy (median) • Schedule: once-daily fraction of 2Gy (median)	• 5y in-field LRCR: 87%	• 5y OS: 46%	
Conill et al, 2009 [40] Sample size: n=77 (50 with primary LN disease, 27 with recurrent disease) Treatment: lymphadenectomy surgery plus RT Primary site: not reported	RT indication: ECE, ≥3 positive LNs, ≥3cm LN diameter, or LN recurrence RT field: Involved LN basins (cervical 15.6%, axillar 57.1%, groin 27.3%) Hypofractionated regimen (n=65/77, 84.4%) • Total dose: 30-36Gy • Schedule: 6Gy fractions twice weekly	• 5y in-field LRCR*: 90%	• Median OS: 26 months (95%CI, 18-34 months) • Median DMFS: 16 months (95%CI, 13-18 months)	

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Median F/U: not reported	Conventional regimen (n=12/77, 15.6%) • Total dose: 44-50Gy • Schedule: 2Gy fractions five times a week			
Sherriff et al, 2012 [22] Sample Size: n=49 (11 with no history of melanoma, 38 with LN recurrence) Treatment: nodal dissection plus RT Primary site: not reported Median F/U: 35 months (range, 3-140 months)	RT indication: size and number of involved LNs, close or involved margins, or ECE RT field: Involved LN basins (axilla 38.8%, head and neck 32.7%, ilio-inguinal 28.5%) Conventional regimen (n=36/49, 73.5%) • Total dose: 45Gy, 48Gy, or 50Gy • Schedule: 20 fractions over 4 weeks	• Patients followed 35 months (range, 3-140 months) • Local recurrence rate: 22.4% • Distant recurrence rate: 53.1%	• Median OS: 38.3 months	• 6 (12.2%) patients developed lymphedema • 1 patient required a skin graft following wound breakdown • 1 patient developed hearing loss following RT to the left neck
Stevens et al, 2000 [2] Sample size: n=174 total • n = 142 with recurrent nodal disease Treatment: excision plus RT Primary site: all 174 patients - head and neck (45%), trunk (27%), limbs (14%), occult (14%) Median F/U: 30 months (range, 6-116 months)	RT indication: Patients with metastases to regional LNs – positive margins, ECE, multiple positive LNs, large LNs, perineural or vascular extension, or parotid LN involvement RT field: Involved LN basins (n=142; neck 55%, axilla 34%, inguinal 8%, multiple regions 3%) Hypofractionated regimen (all patients) • Total dose: 30-36Gy • Schedule: 5-7 fractions twice weekly over 2.5 weeks	• 5y in-field recurrence rate (all patients): 11%	• 3y MFS for patients with recurrent melanoma: 39%	

Study, Population	RT Details	Control Rate	Survival	Adverse Events
Strojan et al, 2010 [12] Sample size: n=83 (76 with primary LN disease, 7 with regional recurrence after previous surgery) Treatment: • Nodal dissection: n=40 • Dissection plus RT: n=43 (higher risk factor patients) Primary site: not reported Median F/U: 2.1 years (range, 0.1-8.5 years)	RT indication: Results of the histopathologic examination of resected specimen RT field: Involved neck and parotid LNs Hypofractionated regimen (all RT patients) • Total dose: 60Gy (range, 47.8-78.8Gy) • Schedule: 5Gy fractions (range, 2-6Gy) over 20 days (range, 11-43)	• 2y RCR improved following RT (p=0.015) ○ Surgery: 56% (95%CI, 40-72%) ○ RT: 78% (95%CI, 63-92%)	• No difference in 2y OS ○ Surgery: 58% (95%CI, 42-73%) ○ RT: 51% (95%CI, 36-66%)	• Long-term complications assessed in patients who survived >6 months • No difference in rate of late toxic events between groups (p>0.05) ○ 27.8% (95%CI, 14.2-45.2%) patients who received RT reported 1 or more toxic events ○ Grade 1: 6 events ○ Grade 2: 4 events ○ Grade 3: 0 events

Abbreviations: CI, confidence interval; DFS, disease free survival; DMFS, distant metastasis free survival; DSS, disease specific survival; ECE, extracapsular extension; F/U, follow-up; Gy, Gray; LCR, local control rate; LN, lymph node; LRCR, local regional control rate; MFS, metastasis free survival; OS, overall survival; RCR, regional control rate; RT, radiation therapy; vs., versus; y, year.
Note: * indicates that the rate was calculated using an actuarial method.

Research Question 5: Does a standard RT fractionation schedule provide equivalent disease control compared with a hypofractionated schedule?

The systematic review did not identify any studies that directly compared a standard fractionation schedule to a hypofractionated schedule. Standard fractionation schedules are defined as those that deliver ≤ 2.5Gy per fraction daily for at least 20 fractions. In an effort to answer this research question, the reviewers compared the control rates and rates of adverse events for studies that used a hypofractionated schedule with studies that used a standard fractionation schedule (Table 4-5). The TROG RCT [9,10], as well as three retrospective cohort studies [5,17,22] reported on patients following adjuvant RT with a standard fractionation schedule, while 12 retrospective cohort studies [2,3,6,11-13,16,18-20,23,24] reported on patients who received a hypofractionated schedule. When comparing the publication dates of the two groups of studies, studies that used a hypofractionated schedule were older than studies that used a standard fractionation schedule (Table 4-5). Both local and regional control rates do not appear to differ when comparing the groups of studies (Table 4-5). Similarly, the rates of Grade 2 and Grade 3 adverse events appears to be the same for hypofractionated [11,12,18-20,24] and standard fractionation [17] schedules (Table 4-5); however, for standard fractionation schedule studies, only one retrospective cohort study [17] reported on long-term adverse events, making it difficult to compare adverse events.

Table 4-5. Control rate and rate of adverse events for hypofractionated compared with standard fractionation schedules.

	Number of Studies [refs] and Publication Year Range	Local and Regional Control Rate Range	Rate of Grade 2 and Grade 3 Adverse Events
Hypofractionated Schedule	12 retrospective cohort studies [2,3,6,11-13,16,18-20,23,24] published 2000 through 2010	LCR: 87% - 94% RCR: 74% - 94%	Grade 2: 9% - 25% Grade 3: 0% - 5%
Standard Fractionation Schedule	1 RCT [9,10] and 3 retrospective cohort studies [5,17,22] published 2011 through 2014	LCR: 78% - 95% RCR: 85% - 90%	Grade 2: 22% Grade 3: 0%

Note: Included studies reported on 2-year, 3-year, 5-year and 10-year control rates.
Abbreviations: LCR, local control rate; RCR, regional control rate.

Ongoing, Unpublished, or Incomplete Studies

One recruiting study was identified by a search of https://clinicaltrial.gov. The TROG Neurotropic Melanoma of the Head and Neck (RTN2) RCT will compare surgery alone to surgery plus adjuvant RT (NCT00975520).

DISCUSSION

Historically, melanoma was believed to be a radio-resistant tumour, but *in vitro* studies using melanoma cell lines have verified that melanoma cells are radiation responsive [21]. This finding has led to the use of adjuvant RT for locoregional disease control by targeting micrometastatic disease post-resection. As such, there is little evidence and even less guidance on the use of adjuvant RT for melanoma patients. First-line curative treatment for melanoma involves surgical resection with wide margins. Local recurrence after wide local excision with adequate clear margins is rare and occurs in fewer than 5% of cases [4]. However, specific features, including the desmoplastic subtype, positive margins, location on the head or neck,

recurrent disease, and thick primary lesions with ulceration and satellitosis, are all associated with high risk for primary tumour recurrence [4]. Recurrence rates of 23% to 48% have been reported for desmoplastic melanomas, while local recurrence rates can rise up to 17% when melanomas are located on the head and neck and to 14% to 16% when satellitosis features are present [4]. In-transit melanoma recurrence rates are also high [7], and a retrospective review of patients who were diagnosed with in-transit recurrence as a first site of recurrence indicated that 21.5% of these patients progress to regional node metastasis and 42.5% progress to distant metastasis [8]. For all patients with stage III melanoma, even after wide excision and complete lymph node dissection, the risk of local relapse is 15%, and as high as 30% to 50% for patients who possess high risk features [21]. The features associated with high risk of nodal relapse include extracapsular lymph node extension, multiple involved lymph nodes, cervical lymph node location, or recurrent disease [4].

The primary literature search for this systematic review identified only one recent RCT and 19 older retrospective cohort studies. Although the RCT was of moderate quality, based on the retrospective design of the cohort studies, the majority of the available literature in this area is of low quality. Most of the included retrospective studies included mixed melanoma subtypes, mixed RT doses and schedules, and a mixture of primary and recurrent disease patients, making it difficult to draw conclusions for individual melanoma subtypes, primary compared with recurrent disease, and for standard fractionation compared with hypofractionated schedules. The results section has been organized to reflect studies identified to inform each research question; however, the following discussions, as well as the drafted Recommendations, have pooled melanoma subtypes based on the identified literature in order to limit redundancy,

An additional issue related to the retrospective design of the included studies was the introduction of substantial performance bias. Since the studies were retrospective, when cohort studies compared patient records of those who did receive adjuvant RT with those who did not, baseline characteristics were different as patients in the adjuvant RT arm received the treatment based on high risk features, leading to a biased comparison of the groups after treatment. Any improvement in locoregional control or survival as a consequence of adjuvant RT in these studies is, thus, believed to be of a larger magnitude than reported.

Patients with Primary Melanoma and Recurrence at the Primary Site

Three identified retrospective single-arm cohort studies assessed the use of adjuvant RT to the primary site after resected curative treatment [1-3]. Unfortunately, two of these cohort studies reviewed the medical records of both primary and recurrent disease populations [1,2], while the third, which focused on primary melanoma, only assessed patients with head and neck melanomas [3]. The cohort study that focused on primary head and neck melanomas determined that adjuvant RT led to a 94% five-year LCR and a five-year OS rate of 58% [3]. However, interpretation of the impact of RT on local control is limited as only one had a positive margin in this series. The study also reported a five-year Grade 1 complication-free survival of 82%, 94% for Grade 2 complications, and 99% for Grade 3 complications [3]. Of the two cohort studies that assessed both patients with primary melanoma and recurrent disease at the primary site, one found a 87% five-year LRCR and a five-year OS rate of 46% for all patients [1], while the other study found a five-year in-field recurrence rate of 11% for all enrolled patients [2]. Based on this limited evidence provided by the cohort study that assessed the use of adjuvant RT in a high-risk melanoma population (head and neck), when adequate clear margins are unachievable, adjuvant RT may be a reasonable option. The NCCN [34], Alberta Health Services (AHS) [30], and the Dutch Working Group on Melanoma (DWG) [33] similarly direct healthcare providers to consider adjuvant RT for patients with close margins or at high risk for recurrence.

The literature search did not identify any studies that assessed the role of adjuvant RT for melanoma that has recurred at the primary melanoma site. As there was no evidence to inform this recommendation, the Working Group, upon approval from the Disease Site Group (DSG), used a consensus approach to draft this recommendation. Since rates of local recurrence have been found to be higher after a first recurrence [4], radiation oncologists within the Working Group considered the high risk of further recurrence in this population, paired with their clinical expert opinion to draft a recommendation. This recommendation was then voted upon and approved by the entire Working Group. In the expert opinion of the Working Group, if adequate clear margins are unachievable, adjuvant RT may be considered for patients with recurrence at the primary site. Similar recommendations for considering adjuvant RT for locally recurrent melanoma have been proposed by AHS [30], BAD [32], and NCCN [34].

The literature search did not identify any studies that specifically assessed the role of adjuvant RT in patients with primary melanoma plus satellites. Two retrospective cohort studies included to inform the recommendation for primary melanoma included patients with satellites, but one study only included three such patients [2], while the other reported satellitosis was an RT indication without indicating how many individuals fit this criterion [1]. As there was no evidence to inform this recommendation, the Working Group, upon approval from the DSG, used a consensus approach to draft this recommendation. Radiation oncologists within the Working Group considered the 14% to 16% local recurrence rates for tumours with satellitosis following surgery alone [4], as well as their clinical expert opinion to draft a recommendation. This recommendation was then voted upon and approved by the entire Working Group. In the expert opinion of the Working Group, further surgery is the preferred option for these patients, but if adequate clear margins are unachievable, adjuvant RT can be considered. Both AHS [30] and the DWG [33] similarly recommend that adjuvant RT be considered for patients with satellitosis.

Patients with Desmoplastic/Neurotropic Melanoma

The desmoplastic subtype is associated with a high risk for recurrence [4]. Two retrospective cohort studies compared the medical records of patients diagnosed with desmoplastic melanoma who were either treated with resection or resection plus adjuvant RT and found that five-year LCRs were significantly improved following adjuvant RT [5,6]; however, the one that reported on survival found no difference in 10-year DSS [6]. Following hypofractionated adjuvant RT, patients with desmoplastic melanoma experienced a high rate of moderate (9.9%) and severe (8.5%) adverse events. Moderate adverse events included hypothyroidism, delayed wound healing, edema, xerostomia, and keratoconjunctivitis sicca, while severe events included osteoradionecrosis, nonhealing scalp wound, and skin graft failure [6]. Unfortunately, the study did not indicate the primary melanoma location or RT field specific for those patients who experienced an adverse event, but examination of the reported events indicates that moderate and severe adverse events occurred in the head and neck regions. Adjuvant RT can be considered for patients with desmoplastic melanoma, but caution should be used when the RT field includes the head and neck region.

Patients with In-Transit and In-Transit Recurrent Melanomas

The literature search did not identify any systematic reviews or primary studies that assessed the role of adjuvant RT in stage III melanoma populations after undergoing resection for in-transit primary melanomas or in-transit recurrent melanomas. As there was no evidence to inform this recommendation, the Working Group, upon approval from the DSG, used a consensus approach to draft this recommendation. Radiation oncologists within the Working Group considered the high rate of in-transit recurrence, the overall survival and progression rate of in-transit melanomas, and their clinical expert opinion to draft a recommendation. This

recommendation was then voted upon and approved by the entire Working Group. In the expert opinion of the Working Group, adjuvant RT may be considered for patients with in-transit and in-transit recurrent melanomas on a case by case basis. This recommendation aligns with recommendations posed by AHS [30], ACN [31], BAD [32], and DWG [33].

Stage III Melanoma Patients with High Risk for Lymph Node Relapse and All Patients with Nodal Recurrence

An RCT conducted by the TROG enrolled patients at high risk for lymph node field relapse and randomized them to either adjuvant RT with standard fractionation or an observational arm [9,10]. Patients were ineligible for enrollment if they were diagnosed with impalpable lymph node field relapse, including those detected by sentinel lymph node biopsy. The TROG RCT reported a 52% to 56% relative reduction in relapse for patients who received adjuvant RT, but no difference in OS or RFS. This RCT built upon several older retrospective cohort studies in stage III patients that reported either improved RCRs [12], or no difference [15-17]. When only considering retrospective studies that evaluated adjuvant RT in patients following recurrence within the lymph node basin, one large cohort study reported improved five-year RCRs for cervical and axilla lymph nodes following adjuvant RT [11]. Two additional retrospective studies found no difference in control rates when comparing patients who did and did not receive adjuvant RT [13,14]; however, both studies also found that patients with worse prognostic features were offered adjuvant RT and no adjustment was made to compensate for these confounding factors. None of the identified studies reported a difference in OS when comparing those who did and did not receive adjuvant RT, but according to multivariate analysis, one retrospective study that focused on patients with nodal relapse found that both five-year DSS and DMFS were improved following adjuvant RT [11].

Publication of 73-month follow-up from the TROG RCT indicated that patients in the RT arm experienced worse regional symptoms, increased limb volumes, and common Grade 2 through 4 long-term RT toxicity [10]. However, a validated QoL tool (FACT-G) indicated no differences in QoL between the RT and observation groups [10]. Unfortunately, QoL and lymphedema data were incomplete for patients who experienced distant relapse and, thus, conclusions only apply to the period before distant relapse. Due to the limited adverse event data provided by the TROG RCT, the older retrospective cohort studies were used to inform the rate of long-term toxicities. Retrospective studies that compared patients who did and did not receive adjuvant RT, found either that the five-year rate of lymphedema was higher following adjuvant RT compared with surgery alone [11], or that the rate of lower extremity lymphedema following adjuvant RT to the inguinal lymph nodes to not be different than for patients who only received dissection [14]. A single-arm retrospective cohort study reported a five-year Grade 2 and Grade 3 complication rate that is dependent upon the lymph node disease site, with higher rates in lymphedema and all complications highest after RT to the groin, followed by axillary lymph nodes, then cervical nodes, and, finally, epitrochlear nodes [18]. Other single-arm cohort studies reported a five-year Grade 2 complication rate of 10% following adjuvant RT to cervical lymph nodes [19] and 18% following adjuvant RT to axillary lymph nodes [20]. The rate of reported adverse events is substantial; however, after wide excision and complete lymph node dissection for all stage III melanoma, the risk of local relapse for these patients is 15% [21]. Additionally, the presence of high-risk features may increase the rate of subsequent nodal recurrence after surgery alone to 30% to 50% [4]. Adjuvant RT is a reasonable option for patients at high risk for nodal recurrence, but clinicians should weigh the locoregional control benefits against the increased probability of long-term toxicities for each patient.

Adjuvant RT Fractionation Schedules

Hypofractionated RT regimens, which deliver a higher dose per fraction, were developed to compensate for the historical belief that melanoma was relatively radio-resistant compared with other types of cancers. However, more recent radiobiological and clinical studies [25,26,36], as well as earlier *in vitro* studies [21], have confirmed that melanoma are radiation responsive. Due to the high rates of adverse events reported with hypofractionated schedules, newer studies have adapted a conventional standard fractionated schedule. Standard fractionation schedules are defined as those that deliver ≤2.5 Gy per fraction daily for at least 20 fractions. Unfortunately, the systematic review of the primary literature did not identify any studies that directly compared control rates or rate of adverse events for a standard fractionated schedule and a hypofractionated schedule. When comparing studies that reported use of a standard fractionated schedule [5,9,10,17,22] with studies that reported use of a hypofractionated schedule [2,3,6,11-13,16,18-20,23,24], LCRs and RCRs appear to be similar. Thus, it can be concluded that a standard fractionation schedule potentially provides equivalent disease control when compared with the older hypofractionated schedules.

The rate of Grade 2 or Grade 3 adverse events for all identified studies ranged from 9% to 30%. Attempting to compare studies that reported on standard fractionating with studies that reported on hypofractionated schedules proved difficult as only one standard fractionating study [17] reported on rate of adverse events. The study only included 86 patients in total, with 60 receiving adjuvant RT [17]. Of the 60 that received adjuvant RT, 15 (22%) patients reported a Grade 2 toxic event, which is similar to the 9% to 18% of Grade 2 adverse events reported in the hypofractionated schedule studies [2,3,6,11-13,16,18-20,23,24]. Even though the limited data identified could not be used to compare adverse events for the two schedules, based on their expert opinion, the Working Group suggests a lower probability of adverse events with a lower radiation dose per fraction. The Working Group believes that standard fractionation schedules should be considered.

CONCLUSIONS

Although early diagnosis and surgical resection remains the first-line treatment for melanoma, for high risk patients, adjuvant RT may be a reasonable option. Adjuvant RT is associated with reduced locoregional recurrence, but has no impact on OS; as such, its disease control benefits must be weighed against the increased probability of long-term skin and regional toxicities, and potentially reduced QoL. Standard fractionation schedules should be considered to reduce the potential for adverse events.

CONFLICT OF INTEREST

Information regarding conflict of interest declarations can be found in Appendix 1.

The Use of Adjuvant Radiation Therapy for Curatively Resected Cutaneous Melanoma

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Guideline Development Group (GDG) Expert Panel and the Program in Evidence-Based Care (PEBC) Report Approval Panel (RAP) (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 12 members of the GDG Expert Panel, 10 members cast votes and two abstained, for a total of 83.3% response in August 2015. Of those that cast votes, 10 approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

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

Comments	Responses
1. One comment I have is rewording this qualifying statement from Recommendation 5: Patients at high risk for lymph node relapse are defined as those with large lymph nodes (≥3cm), multiple involved lymph nodes (≥4), extracapsular extension, or prior recurrent disease. To "in the studies, patients at high risk…." would that be true? I'm thinking that patients who don't fit that criteria are still considered high risk – for instance SLNB positive patients are considered high risk if 2 lymph nodes, etc	The first Qualifying Statement for Recommendation 5 has been rewritten to include both historical definitions of high risk as well as the characteristics used by TROG RCT so that no high risk patient is missed.
2. I would alter the qualifying statement of Recommendation 5 to be dependent on nodal basin. Would consider adjuvant RT for nodes ≥2cm, or ≥2nodes. Also as per TROG trial, patients with even one parotid node.	The first Qualifying Statement for Recommendation 5 has been rewritten to include both historical definitions of high risk as well as the characteristics used by TROG RCT.
3. In Recommendation #5, the second bullet, I think we should add: "no impact on relapse free nor overall survival" as per the TROG trial.	The second Qualifying Statement for Recommendation 5 has been altered to include this comment.
4. Do we want to have a statement on prioritization and timing of RT when adjuvant systemic RCTs are available or when IFN is planned?	The Working Group believed that this was an important point, but the literature was not searched to inform this question, so the Working Group do not feel confident in addressing the issue.
5. I think it would be worthwhile to mention somewhere in the guideline's discussion that the TROG adjuvant trial only enrolled patients with palpable/clinically detectable disease, not patients with occult lymph node metastases where disease burden is lower overall (ie SLNB detected).	Statements to address this comment were added to the Discussion.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in July 2015. The RAP conditionally approved the document on July 28, 2015. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

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

Comments	Responses
1. I personally would like to see reference to the need for discussion of these cases in a multidisciplinary case conference as well as reference to practitioners discussing the potential benefits and risks of adjuvant RT with their patients and taking patient values into consideration	A Recommendation Preamble was added to Section 1 and 2. The Preamble statements suggest discussion of these cases at a multidisciplinary case conference as well as adequate discussion with potential patients about the benefits and harms of adjuvant RT.
2. The qualifying statement for Recommendation 3 looks like it would also pertain to the other recommendations, no?	This Qualifying Statement was moved from Recommendation 3 and added to a Further Qualifying Statement section.
3. The questions are clearly articulated. However, it would be helpful, at least to readers less familiar with melanoma to provide a description of desmoplastic/neurotrophic melanoma and the reason that it is specifically identified as a subtype of melanoma within this review	The Working Group believed that since members of the multidisciplinary melanoma team comprised the Target Users for this guideline, a description of desmoplastic/neurotropic melanoma was unnecessary.
4. A table showing the melanoma staging system, perhaps as an Appendix would be helpful to the reader less familiar with melanoma.	The Working Group believed that since members of the multidisciplinary melanoma team comprised the Target Users for this guideline, inclusion of the melanoma staging system was unnecessary.
5. The criteria for selection of the literature for this review were well described but this reviewer was unclear as to why the inclusion start date of 2000 was chosen. Some explanation should be provided for this decision.	Since the Working Group knew *a priori* that the evidence base for this guideline was going to be mostly retrospective cohort studies with patients treated in the 1980s through the early 2000s, it was believed that searching farther back than 2000 would only identify older treatment regimens and would not inform current recommendations.
6. One reviewer expressed concern about endorsement of RT based on expert opinion with little/no evidence and because of the toxicities involved and potential implications for access.	The Working Group understood this position and believed that the Recommendation Preamble that includes suggestions to discuss these cases in multidisciplinary case conferences as well as adequate discussion with potential patients would help to ensure RT was offered to only appropriate patients.
7. Systemic therapies are mentioned but there is no reference to any PEBC guideline on adjuvant systemic therapy. If there is one, it might be useful to add. There may also be some value in referencing the use of IL-2 in the management of in-transit melanoma as this has recently been recommended for funding by pCODR at the request of the provincial DSG.	PEBC guideline 8-1 version 4, which addresses adjuvant systemic therapy for melanoma patients, has been added to the Related Guidelines heading in Section 2 of this report. Although the Working Group agrees that there would have been value in including reference to the use of IL-2 in the management of in-transit melanoma, this was believed to be outside the scope of this report. A guideline that will address management of in-

	transit melanomas is currently being planned by the DSG.

EXTERNAL REVIEW
External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Six targeted peer reviewers from Ontario who are considered to be clinical and/or methodological experts on the topic were identified by Adjuvant RT GDG. Three agreed to be the reviewers (Appendix 1) and responses were received from all three reviewers. Results of the feedback survey are summarized in Table 5-3. The 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=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				2	1
2. Rate the guideline presentation.			1	2	
3. Rate the guideline recommendations.		1	1	1	
4. Rate the completeness of reporting.				2	1
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?			1	1	1
6. Rate the overall quality of the guideline report.			1	2	
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.				3	
8. I would recommend this guideline for use in practice.				3	
9. What are the barriers or enablers to the implementation of this guideline report?	Barriers – due to the lack of available high-quality evidence to inform the recommendations, potential users may dismiss the conclusions as not useful Enablers – there were no enablers provided for the reviewers				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. The guideline obviously follows a template. Perhaps some hyperlinks could be changed to simply include information instead, where the additional information is short. For example rather than hyperlink to PEBC 8-2, just quote what the adequate margin is	The Working Group reviewed the guidelines for which there were hyperlinks to determine if this suggestion could be incorporated. Unfortunately, the recommendations within these guidelines are more complex and require context than what could be simply quoted within the current guideline.

within the document for each primary size or depth.	
2. I do not agree with the conclusion that high risk for primary site recurrence requires both + margins and at least one of the other high risk features to be present. The cited reference (4) [Ballo and Ang] does not support this conclusion. Their paper presents the stand alone factors (Table 2 of paper), also stating that a combination of risk factors likely elevates the risk further	The Working Group agrees that primary margins and the other high-risk features are stand-alone risk factors. As such, it was never intended for guideline users to conclude both positive margins and at least one high risk feature was required to define those at high-risk for primary site recurrence. The Qualifying Statement for Recommendation 1 has been reworded to make this clearer.
3. NCCN's latest review also supports Desmoplastic as a high risk factor for primary site recurrence, and also adds extensive neurotropism and the locally recurrent setting, but not head and neck location. I do not think the Ballo and Ang (4) paper concludes that head and neck location is an indication for adjuvant primary site radiation, and quotes a range of 5-17% (Table 1 of paper), much like Breslow thickness ≥ 4 mm 6-14%	Head and neck location has been included in this guideline as a high-risk factor for recurrence both based upon the 5-17% risk of recurrence, and also due to the difficulty in achieving clear resection margins for melanomas located in these areas.
4. Recommendation 5: It is not clear why size of ≥ 2 cm was used. The cited TROG trial used 3 or 4 cm depending on the location, and this is reaffirmed currently by NCCN 2015, as well as in the older Ballo and Ang review (reference 4) (3cm).	The Working Group greatly appreciates this feedback as this was a typo that originated when incorporating the Internal Review feedback. The Qualifying Statement for Recommendation 5 has been corrected and now indicates that large lymph nodes of ≥3 cm are a risk factor for lymph node relapse.

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 individuals in the PEBC database who had indicated interest in systemic therapy and melanoma, radiation and melanoma, surgery and melanoma, adjuvant therapy and melanoma, or adjuvant therapy and radiation, were contacted by email to inform them of the survey. Fifty-nine professionals who practice in Ontario were contacted. Eight (13.6%) responses were received with two stating that they did not have interest in this area. The results of the feedback survey from six people 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 (16.7%)	5 (83.3%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1 (16.7%)	2 (33.3%)	3 (50.0%)

3. I would recommend this guideline for use in practice.				4 (66.7%)	2 (33.3%)
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers - Old views about lack of radiosensitivity for melanoma, so this guideline will need a KT strategy to overcome some of those opinions that may still exist outside of cancer centres. Enablers – There were no enablers provided by the reviewers				

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. Recommendation 2 does not seem to be stating anything additional to what is trying to be stated in Recommendation 1.	Although Recommendation 1 and 2 are directed for slightly different melanoma populations, the Working Group agrees with this comment in that similar action is being recommended. However, Recommendation 1 is based on published clinical evidence, while Recommendation 2 is consensus opinion, and as such, pooling the recommendations is not appropriate.

CONCLUSION

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

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Appendix 1: Members of the Adjuvant RT Guideline Development Group

Working Group Members

Name and Expertise	Affiliation	Conflict of Interest
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Report Approval Panel Members

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Bill Evans, Medical Oncologist	Cancer Care Ontario Toronto, ON	No conflict declared
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Expert Panel Members

Name	Affiliation	Conflict of Interest
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Pablo Cano	Northeastern Ontario Regional Cancer Centre	
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Alexandra Easson	Princess Margaret Hospital	No conflict declared
Danny Ghazarian	Toronto General Hospital	No conflict declared
Caroline Hamm	Windsor Regional Cancer Centre	No conflict declared
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Gregory Knight	Grand River Regional Cancer Centre	Has earned more than $5000 in a single year on advisory boards
David McCready	Princess Margaret Hospital	No conflict declared
Christian Murray	Skin Surgery Centre, University of Toronto	No conflict declared
Xinni Song	The Ottawa Hospital Cancer Centre	No conflict declared
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Targeted Peer Reviewers

Name	Affiliation	Conflict of Interest
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Name	Affiliation	Conflict of Interest
Carey Shenfield	Kingston General Hospital	No conflict declared
Woodrow Wells	Stronach Regional Cancer Centre	No conflict declared

Appendix 2: Literature Search Strategy

MEDLINE

1. Exp melanoma/
2. Melanoma.mp
3. melanoma:.mp
4. (malignant$ adj5 melanoma$).tw
5. Desmoplastic.mp
6. Neurotropic.mp
7. Satellite$.mp
8. (in adj transit$).mp
9. Lymph node.mp
10. (nodal adj basin).mp
11. Or/1-10
12. Exp radiotherapy, adjuvant/
13. (adjuvant radiotherapy or adjuvant therapy or radiation).tw
14. Radiotherapy, adjuvant/
15. Exp adjuvant radiotherapy/
16. (adjuvant adj2 radiotherapy).mp
17. (adjuvant adj2 radiation).mp
18. (post-operati$ adj2 radiotherapy).mp or (post-operati$ adj2 radiation).mp
19. (postoperati$ adj2 radiotherapy).mp or (postoperati$ adj2 radiation).mp
20. Or/12-19
21. 11 and 20
22. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
23. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt
24. random allocation/ or double blind method/ or single blind method/
25. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
26. or/22-25
27. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
28. (clinical trial or clinical trial, phase II or controlled clinical trial).pt
29. (27 or 28) and random$.tw.
30. (clinic$ adj trial$1).tw.
31. (singl$ or doubl$ or treb$ or tripl$).tw. adj (blind$3 or mask$3 or dummy).tw.
32. placebos/
33. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
34. (allocated adj2 random).tw.
35. Prospective study/
36. Retrospective study/
37. Cohort study/
38. (case adj control).mp
39. or/30-38
40. 26 or 29 or 39
41. 21 and 40
42. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt
43. 41 not 42
44. exp animal/ not human/
45. 43 not 44
46. Limit 43 to English
47. Limit 46 to yr="2000-2015"

EMBASE

1. Melanoma.mp
2. melanoma:.mp
3. (malignant$ adj5 melanoma$).tw
4. Desmoplastic.mp
5. Neurotropic.mp
6. Satellite$.mp
7. (in adj transit$).mp
8. Lymph node.mp
9. (nodal adj basin).mp
10. Or/1-9
11. Exp radiotherapy, adjuvant/
12. (adjuvant radiotherapy or adjuvant therapy or radiation).tw
13. Radiotherapy, adjuvant/
14. (adjuvant adj2 radiotherapy).mp
15. (adjuvant adj2 radiation).mp
16. (post-operati$ adj2 radiotherapy).mp or (post-operati$ adj2 radiation).mp
17. (postoperati$ adj2 radiotherapy).mp or (postoperati$ adj2 radiation).mp
18. Or/11-17
19. 10 and 18
20. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
21. randomization/ or single blind procedure/ or double blind procedure/

22. (randomi$ control$ trial? or rct or phase III or phase IV or phase 3 or phase 4).tw.
23. or/20-22
24. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
25. 24 and random$.tw.
26. (clinic$ adj trial$1).tw.
27. (singl$ or doubl$ or treb$ or tripl$).tw. adj (blind$3 or mask$3 or dummy).tw.
28. placebo/.
29. (placebo? or random allocation or randomly allocated or allocated randomly).tw.
30. (allocated adj2 random).tw.
31. Prospective study/
32. Retrospective study/
33. Cohort study/
34. (case adj control).mp
35. or/26-34
36. 23 or 25 or 35
37. 19 and 36
38. (editorial or note or letter erratum or short survey).pt or abstract report/ or letter/ or case study/
39. 37 not 38
40. animal/ not human/
41. 39 not 40
42. Limit 41 to English
43. Limit 42 to yr="2000-2015"

Appendix 3: Quality Assessment of Included Studies

Study [ref]	Patient Selection Criteria	Control of Confounding Factors	Summary of Limitations	Sources of Funding
Randomized Controlled Trial				
Burmeister et al, 2012 [9],Henderson et al, 2015 [10]	• Eligible patients randomly assigned with computer program (allocation concealment) • No blinding of participants or personnel	• Arms were balanced in terms of institution, lymph node field, number of involved nodes, maximum involved node diameter, and extent of extranodal spread	• Performance bias – patients could not be blinded due to therapy, but study conductors could have been blinded • Quality of life and lymphedema data not available after distant relapse; therefore, incomplete	National Health and Medical Research Council of Australia, Cancer Australia, Melanoma Institute Australia, Cancer Council of South Australia
Retrospective Cohort Studies				
Agrawal et al, 2009 [11]	• Review of melanoma databases at the University of Texas MD Anderson Cancer Center (MDACC) Department of Radiation Oncology and the Roswell Park Cancer Institute Department of Surgical Oncology	• Adjuvant RT offered to more patients with cervical recurrence compared to surgery, while surgery more often offered to axilla and inguinal LN recurrent patients	• Selection bias • Performance bias – patients received concurrent systemic therapy	Not reported
Ballo et al, 2003 [19]	• Review of melanoma databases at MDACC Department of Radiation Oncology	• Single-arm study of patients with RT indications	• Heterogeneity – mixed primary and recurrent disease melanoma population	Supported in part by grant awarded by the National Cancer Institute, US Department of Health and Human Services, and the Gilbert H. Fletcher Chair
Ballo et al, 2006 [18]	• Review of MDACC Department of Radiation Oncology and institutional patient databases	• Single-arm study of patients with RT indications	• Heterogeneity – mixed primary and recurrent disease melanoma population • Performance bias – patients received concurrent systemic therapy	Supported in part by grant awarded by the National Cancer Institute, US Department of Health and Human Services
Ballo et al, 2002 [23]	• Review of the MDACC Department of Radiation Oncology database	• Single-arm study of patients with RT indications	• Heterogeneity – mixed primary and recurrent disease melanoma population	Supported in part by grant awarded by the National Cancer

Study [ref]	Patient Selection Criteria	Control of Confounding Factors	Summary of Limitations	Sources of Funding
			• Performance bias – patients received concurrent systemic therapy	Institute, US Department of Health and Human Services
Ballo et al, 2004 [24]	• Review of the MDACC Department of Radiation Oncology database	• Single-arm study of patients with RT indications	• Performance bias – patients received concurrent systemic therapy	Not reported
Beadle et al, 2009 [20]	• Review of the MDACC Department of Radiation Oncology database	• Single-arm study of patients with RT indications	• Heterogeneity – mixed primary and recurrent disease melanoma populations • Performance bias – patients received concurrent systemic therapy	Not reported
Bibault et al, 2011 [17]	• Review of patient records	• More cervical and axillary LN patients offered RT, while fewer inguinal LN patients offered RT	• Selection bias	Not reported
Bonnen et al, 2004 [3]	• Review of the MDACC Department of Radiation Oncology database	• Single-arm study of patients with RT indications	• Missing some patient characteristic data	Supported in part by grant awarded by the National Cancer Institute, US Department of Health and Human Services, and the Gilbert H. Fletcher Chair
Chang et al, 2006 [1]	• Review of patient records at the University of Florida	• Single-arm study of patients with RT indications	• Performance bias – patients received concurrent systemic therapy • Heterogeneity – mixed primary and recurrent disease melanoma population and mixed RT regimens	Not reported
Conill et al, 2009 [40]	• Review of patient records	• Single-arm study of patients with RT indications	• Heterogeneity – mixed primary and recurrent disease melanoma population and mixed RT regimens • Performance bias – patients received concurrent systemic therapy	Not reported

Study [ref]	Patient Selection Criteria	Control of Confounding Factors	Summary of Limitations	Sources of Funding
			• Missing primary site data and follow-up time data	
Fuhrmann et al, 2001 [15]	• Review of patient records in the Fachklinik Hornheide, Munster, Germany and University Hospital of Tubingen	• Patients offered RT had thicker tumours – no adjustment	• Selection and detection bias • Heterogeneity – mixed RT regimens	Not reported
Gojkovic-Horvat et al, 2012 [14]	• Review of patient records	• Adjuvant RT offered to patients with higher risk factor	• Selection and detection bias • Heterogeneity - Mixed RT regimens • Missing primary tumour site data	Not reported
Guadagnolo et al, 2014 [6]	• Review of patient records at MDACC	• Not discussed	• Heterogeneity – mixed primary and recurrent disease melanoma population	No specific funding disclosed
Hamming-Vrieze et al, 2009 [13]	• Review of patient records at the Netherlands Cancer Institute, Amsterdam	• Adjuvant RT offered to patients with poorer prognosis factors	• Selection and detection bias	None reported
Moncrieff et al, 2008 [16]	• Review of patient records in the Sydney Melanoma Unit and Sydney Head and Neck Cancer Institute databases	• Patients at high risk for recurrence offered RT	• Selection and detection bias	Supported in part by a grant from the Melanoma Foundation of the University of Sydney
Sherriff et al, 2012 [22]	• Review of patient records from an existing radiotherapy database	• Single-arm study of patients with RT indications	• Heterogeneity – mixed primary and recurrent disease melanoma population • Missing primary tumour site data	None reported
Stevens et al, 2000 [2]	• Review of patient records from the Royal Prince Albert Hospital Department of Radiation Oncology	• Single-arm study of patients with RT indications	• Heterogeneity – mixed primary and recurrent disease melanoma population	None reported
Strojan et al, 2010 [12]	• Review of patient records from the Cancer Registry of Slovenia database	• Adjuvant RT offered to patients with poorer prognostic factors	• Selection and detection bias • Heterogeneity – mixed primary and recurrent disease melanoma population	Supported by a grant from the Slovenian Research Agency

Study [ref]	Patient Selection Criteria	Control of Confounding Factors	Summary of Limitations	Sources of Funding
			• Missing primary tumour site data	
Strom et al, 2014 [5]	• Review of patient records	• Adjuvant RT offered to patients with poorer prognostic factors – controlled by multivariate regression analysis	• Selection bias • Heterogeneity – mixed RT regimens • Missing histopathological data	No specific funding disclosed