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Guideline 8-11

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

Patient Indications for Mohs Micrographic Surgery

C. Murray, D. Sivajohanathan, T. Hanna, S. Bradshaw, N. Solish, B. Moran, R. Hekkenberg, A. Wei, T. Petrella and the Melanoma Disease Site Group

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An assessment conducted in November 2023 deferred the review of Guideline 8-11. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 8-11 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/52161

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Patient Indications for Mohs Micrographic Surgery

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

a. To describe evidence-based indications for Mohs micrographic surgery (MMS);
b. To assess Mohs outcomes such as cure rates and recurrence rates, as well as quality of life (QOL) and complications;
c. To assess whether volume of patients treated affects outcomes of MMS.

TARGET POPULATION

Adults with a diagnosis of skin cancer.

INTENDED USERS

Clinicians involved in the assessment and treatment of patients with skin cancer.

NOTE: Terms used throughout this guideline are as how individual trials and studies reported them. Although this guideline sought to include guidance for all types of skin cancer, comparative studies that met the inclusion criteria were mainly non-melanoma skin cancers. A few comparative studies on other types of skin cancers (i.e., atypical fibroxanthoma, dermatofibrosarcoma protuberans, sebaceous carcinoma, melanoma in situ, and invasive melanoma) were found and are also discussed.

Aside from MMS, other methods of intraoperative peripheral and deep circumferential margin analysis exist and are expected to also provide advantages in comparison to standard excision. However, this guideline focuses exclusively on MMS, WLE, and radiation and did not cover other methods of non-MMS forms of frozen section marginal control. Further, this guideline refers to radical radiotherapy and does not consider adjuvant radiotherapy in its literature review nor does it address metastatic disease.

RECOMMENDATIONS

Recommendation 1
Surgery (with postoperative or intraoperative marginal assessment), or radiation for those who are ineligible for surgery, should remain the standard of care for patients with skin cancer given the lack of high-quality, comparative evidence.
Qualifying Statements for Recommendation 1
• Eligibility for surgery depends on disease stage, surgical considerations, aesthetic outcomes, patient comorbidities, and patient preference. • There are various clinical situations where it may be considered appropriate for referral to a radiation oncologist. Based on standards of care and clinical experience, the Working Group suggests that the following clinical situations may be appropriate for referral for radical radiotherapy: 1. Where there is patient preference based on the expected cosmetic or functional outcomes of surgery or anxiety related to surgery; 2. Cases with increased risk of recurrence or extensive subclinical spread with surgery.

Further indications for patients with skin cancer that would be eligible for radiation is beyond the scope of this guideline.

- A multidisciplinary approach is also suggested for high-risk cases.
- For characteristics of patients who would be considered appropriate for referral to a Mohs surgeon, please refer to Recommendation 2.

Recommendation 2

MMS is recommended for those with histologically confirmed recurrent basal cell carcinoma (BCC) of the face, and is appropriate for primary BCCs of the face that are >1 cm, have aggressive histology, or are located on the H zone of the face (Figure 1-1).

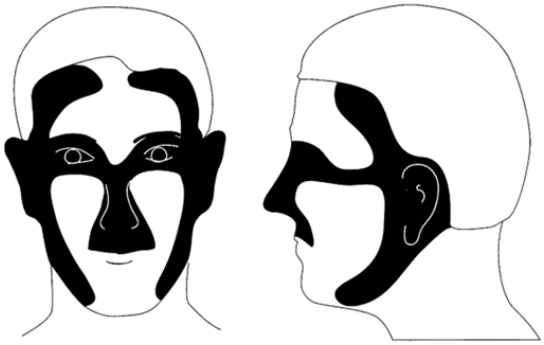

Figure 1-1. Facial H zone [1]

Qualifying Statements for Recommendation 2

- There are situations in which MMS may be considered in patients outside of the above recommendation: smaller tumours (<1 cm in diameter) where tissue sparing is of functional or cosmetic significance (this includes tumours in patients with a genetic predisposition to multiple skin cancers, such as Gorlin syndrome); complex tumours that may necessitate margin-controlled surgery; or immunosuppressed patients.
- Patients with complicated BCC or locally advanced BCC should be considered for multidisciplinary assessment by dermatologists, surgical specialists, medical, and radiation oncologists.
- Examples of aggressive histology include basosquamous, morpheaform/sclerosing, micronodular, or infiltrative, as well as lesions with perineural invasion.
- The Working Group recognizes that much of the literature used to inform recommendations is based on BCC; however, based on clinical experience and expert opinion, the Working Group suggests that there are some instances in which patients with squamous cell carcinoma (SCC) may follow the same indications for BCC. However, in cases where SCC is deemed high risk, the need for evaluation by a multidisciplinary team (i.e., dermatologists, surgical specialists, medical, and radiation oncologists) should be considered.
- Patients with aggressive or high-risk nonmelanoma skin cancer may benefit from methods, such as MMS or other intraoperative margin-controlled surgery, which lower recurrence rates. Radiation is also a valuable option in high-risk patients who may have a contraindication to surgery or who may need adjuvant therapy in high-risk disease.
- Patients with dermatofibrosarcoma protuberans, atypical fibroxanthoma, and sebaceous carcinoma have shown benefit in the use of MMS over wide local excision (WLE). The results of these studies are subject to selection bias and were not adequately powered. However, the Working Group notes that although methodologically strong evidence does not exist for rarer types of skin cancer, MMS should be considered on a case-by-case basis.

- Patients with invasive melanoma or melanoma in situ have shown no survival or recurrence benefit in the use of MMS over WLE. These retrospective studies were not adequately powered. A recent guideline by Cancer Care Ontario on primary excision margins in cutaneous melanoma has been published. Please refer to Guideline 8-2 Version 2 for recommended surgical margins in this population.

Recommendation 3
MMS should be performed by physicians who have completed a degree in medicine or equivalent, including a Royal College of Physicians and Surgeons of Canada Specialist Certificate or equivalent, and have received advanced training in MMS.
Qualifying Statements for Recommendation 3
• MMS is a surgical technique requiring specific training in the assessment of frozen section histology to detect cutaneous malignancies, the surgical skills of cancer removal, and the reconstruction of cosmetically sensitive areas of the face and other complex areas. • Advanced training is defined as having a recognized MMS fellowship through the American College of Mohs Surgery, or equivalent accrediting body.

Reference

1. Smeets NWJ, Krekels GAM, Ostertag JU, Essers BAB, Dirksen CD, Nieman FHM, et al. Surgical excision vs Mohs' micrographic surgery for basal-cell carcinoma of the face: Randomised controlled trial. Lancet. 2004;364(9447):1766-72.

Patient Indications for Mohs Micrographic Surgery

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

d. To describe evidence based indications for Mohs micrographic surgery (MMS);
e. To assess Mohs outcomes such as cure rates and recurrence rates, as well as quality of life (QOL) and complications;
f. To assess whether volume of patients treated affects outcomes of MMS.

TARGET POPULATION

Adults with a diagnosis of skin cancer.

INTENDED USERS

Clinicians involved in the assessment and treatment of patients with skin cancer.

NOTE: Terms used throughout this guideline are as how individual trials and studies reported them. Although this guideline sought to include guidance for all types of skin cancer, comparative studies that met the inclusion criteria were mainly non-melanoma skin cancers. A few comparative studies on other types of skin cancers (i.e., atypical fibroxanthoma, dermatofibrosarcoma protuberans, sebaceous carcinoma, melanoma in situ and invasive melanoma) were found and are also discussed.

Aside from MMS, other methods of intraoperative peripheral and deep circumferential margin analysis exist and are expected to also provide advantages in comparison to standard excision. However, this guideline focuses exclusively on MMS, WLE, and radiation and did not cover other methods of non-MMS forms of frozen section marginal control. Further, this guideline refers to radical radiotherapy and does not consider adjuvant radiotherapy in its literature review nor does it address metastatic disease.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1
Surgery (with postoperative or intraoperative marginal assessment), or radiation for those who are ineligible for surgery, should remain the standard of care for patients with skin cancer given the lack of high-quality, comparative evidence.
Qualifying Statements for Recommendation 1
• Eligibility for surgery depends on disease stage, surgical considerations, aesthetic outcomes, patient comorbidities, and patient preference. • There are various clinical situations where it may be considered appropriate for referral to a radiation oncologist. Based on standards of care and clinical experience, the Working Group suggests that the following clinical situations may be appropriate for referral for radical radiotherapy: 1. Where there is patient preference based on the expected cosmetic or functional outcomes of surgery or anxiety related to surgery; 2. Cases with increased risk of recurrence or extensive subclinical spread with surgery. Further indications for patients with skin cancer that would be eligible for radiation is beyond the scope of this guideline.

- A multidisciplinary approach is also suggested for high-risk cases.
- For characteristics of patients who would be considered appropriate for referral to a Mohs surgeon, please refer to Recommendation 2.

Key Evidence for Recommendation 1

- The evidence comes from three retrospective, comparative studies comparing surgical excision (SE) with radiotherapy in patients with squamous cell carcinoma (SCC) of the lip. There is no evidence comparing MMS with radiation.
- First, the trial by de Visscher et al. [1] reported similar local recurrence rates for surgery and radiotherapy (3.6% and 4.4%, respectively; p>0.05) in previously untreated patients. Both arms differed statistically in terms of tumour size, differentiation grade, and years of follow-up; patients in the radiotherapy group had a greater tumour size than patients in the surgery group. Regional recurrence rates were significantly lower after surgery than after radiotherapy (4.8% and 12.2%, respectively; p=0.03) though only tumour size carried significance in adjusted analysis.
- The remaining two studies present unclear methods and results should be interpreted with caution. Babington et al. [2] reported recurrence rates of 53% and 19% for surgery and radiotherapy, respectively. A p-value was not reported. Twenty percent of patients were previously treated elsewhere and many were referred with recurrent disease; however, the distribution of these patients within the current surgery and radiation arms is unclear. Polytomous regression analysis reported that a close (≤2 mm) or positive margin in the surgery group predicted local recurrence (p=0.05).
- Last, the study by Sarachev et al. [3] reported local recurrence rates of 3.1% and 4.3% for surgery and radiotherapy, respectively. A p-value was not reported. This study provided minimal information on patients who received radiotherapy or about the comparability of treatment groups.

Interpretation of Evidence for Recommendation 1

- There was agreement among the members of the Working Group that the overall certainty of the evidence was very low and was not generalizable to the entire target population. The Working Group believed that this evidence was insufficient to make recommendations changing the standard of care.
- The overall quality of the evidence was deemed very low because of indirectness and risk of selection bias in all three studies.
- The Working Group considered recurrence rate to be the most important outcome, followed by QOL, complications, and cosmesis. Some patient input was sought and patients identified that all of the outcomes mentioned would be important to them in making any treatment decisions. However, few studies collected or reported on QOL, complications, and cosmesis data.

Recommendation 2

MMS is recommended for those with histologically confirmed recurrent basal cell carcinoma (BCC) of the face, and is appropriate for primary BCCs of the face that are >1 cm, have aggressive histology, or are located on the H zone of the face (Figure 2-1).

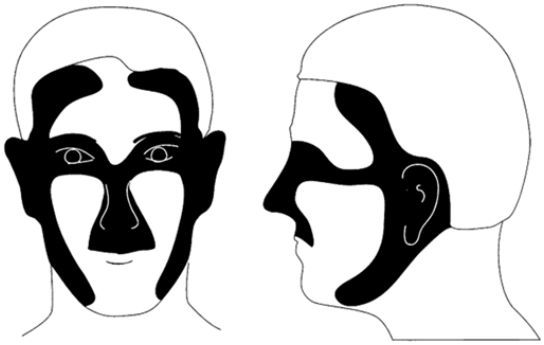

Figure 2-1. Facial H zone [4]

Qualifying Statements for Recommendation 2

- There are situations in which MMS may be considered in patients outside of the above recommendation: smaller tumours (<1 cm in diameter) where tissue sparing is of functional or cosmetic significance (this includes tumours in patients with a genetic predisposition to multiple skin cancers, such as Gorlin syndrome); complex tumours that may necessitate margin-controlled surgery; or immunosuppressed patients.
- Patients with complicated BCC or locally advanced BCC should be considered for multidisciplinary assessment by dermatologists, surgical specialists, medical, and radiation oncologists.
- Examples of aggressive histology include basosquamous, morpheaform/sclerosing, micronodular, or infiltrative, as well as lesions with perineural invasion.
- The Working Group recognizes that much of the literature used to inform recommendations is based on BCC; however, based on clinical experience and expert opinion, the Working Group suggests that there are some instances in which patients with SCC may follow the same indications for BCC. However, in cases where SCC is deemed high risk, the need for evaluation by a multidisciplinary team (i.e., dermatologists, surgical specialists, medical, and radiation oncologists) should be considered.
- Patients with aggressive or high-risk nonmelanoma skin cancer (NMSC) may benefit from methods, such as MMS or other intraoperative margin-controlled surgery, which lower recurrence rates. Radiation is also a valuable option in high-risk patients who may have a contraindication to surgery or who may need adjuvant therapy in high-risk disease.
- Patients with dermatofibrosarcoma protuberans (DFSP), atypical fibroxanthoma (AFX), and sebaceous carcinoma have shown benefit in the use of MMS over wide local excision (WLE). The results of these studies are subject to selection bias and were not adequately powered. However, the Working Group notes that although methodologically strong evidence does not exist for rarer types of skin cancer, MMS should be considered on a case-by-case basis.
- Patients with invasive melanoma or melanoma in situ have shown no survival or recurrence benefit in the use of MMS over WLE. These retrospective studies were not adequately powered. A recent guideline by Cancer Care Ontario (CCO) on primary excision margins in cutaneous melanoma has been published. Please refer to Guideline 8-2 Version 2 for recommended surgical margins in this population.

Key Evidence for Recommendation 2

- The best evidence comes from two randomized controlled trials (RCTs) [4-8].
- MMS has not been shown to be inferior to WLE. Moreover, selected patient populations have been shown to have better outcomes with MMS.
- One RCT has been conducted comparing MMS with SE for BCC [4,6,8]. This RCT included, for primary BCC, patients with a facial tumour of at least 1 cm in diameter, located in the H zone, or of an aggressive histopathological subtype, and, for recurrent BCC, patients with a facial tumour recurring for the first or second time. For primary BCC, no statistically significant differences were found in the recurrence rates between MMS and SE at five years (p=0.397) [6] or 10 years (MMS, 4.4%; SE, 12.2%; p=0.100) [8]. In the management of recurrent BCC, recurrence rates were significantly lower for MMS than SE at both five years (p=0.021) [6] and 10 years (p=0.023) [8]. Aesthetic outcomes did not significantly differ between SE and MMS for both primary and recurrent BCC [4]. However, for tumours that required more than one SE (primary BCC, 18%; recurrent BCC, 32%) or at least two Mohs' stages for complete excision, defects after SE were significantly larger than those after MMS for both primary (p<0.001) and recurrent (p=0.026) BCC [4]. Cosmetic results were significantly poorer as the defect size increased for primary and recurrent BCC. A significant difference was found in the number of complications between MMS (8%) and SE (19%) for patients with recurrent BCC (p=0.021). No difference in complications was found for patients with primary BCC (p=0.681). Although the results were not statistically significant for recurrence rates after 10 years of follow-up for patients with primary BCC, the Working Group suggests that clinicians consider the value of cosmesis in addition to recurrence rates.
- The second RCT involved 30 patients with high-risk BCC. This RCT reported that the median area of surgical defects was significantly smaller after MMS when compared with standard surgery (MMS, 116.6 mm^2; SE, 187.7 mm^2; p<0.001) [7]. This trial closed prior to accrual completion as the predetermined endpoint demonstrating a significant difference, a mean defect diameter greater than 1.5 times, was reached.
- Three observational studies (one prospective and two retrospective) compared MMS with SE in patients with BCC and SCC [9-11]. Two studies found no statistical difference in recurrence rates between MMS and SE [9,11], while the third did not report a p-value [10]. However, these studies were not powered to detect differences and the design of the studies allowed for selection bias. The retrospective study by van der Eerden et al. [11] found that defects were smaller after MMS in recurrent NMSC of the nose (p=0.038). This remained true after adjusting for localization and for primary or recurrent disease (p=0.008).
- In the retrospective single-arm study by Flohil et al. [12], a multivariate analysis of patients with BCC of the head and neck who had received MMS found that BCCs located in the H zone, tumours >10 mm, aggressive tumours subtypes, and recurrent tumours remained significantly associated with requiring two or more stages of MMS. Tumour size (≥21 mm), recurrent tumours, and tumours in the H zone remained significant predictors for extensive subclinical tumour spread.
- In another retrospective single-arm study by Batra et al. [13] of 1131 Mohs cases with malignant skin tumours, a multivariate analysis found that the most significant predictors of extensive subclinical spread included any type of BCC on the nose, increasing pre-operative size (≥10 mm), recurrent BCC on the nose, and location on the ear or eyelid.
- Retrospective, comparative studies have shown benefit in the use of MMS over WLE in patients with DFSP in three studies. In one, the difference was statistically significant (p=0.016) [14]; the other two, one of which used the Mohs Tubingen technique, did not report a p-value [15,16]. Retrospective, comparative studies on AFX (p-value not

reported) [17], and sebaceous carcinoma (p-value not reported) [18] have also shown benefit in the use of MMS over WLE. The results of these studies are subject to selection bias and were not powered to detect differences between treatment groups.
- Two retrospective, comparative studies have shown no benefit in the use of MMS over WLE in patients with invasive melanoma [19] or melanoma in situ [20]. These studies were not powered to detect differences between treatment groups.

Interpretation of Evidence for Recommendation 2

- There was agreement among the members of the Working Group that the overall certainty of the evidence was moderate for NMSC but very low for other types of skin cancer. The Working Group concluded that evidence with very low overall certainty was insufficient to make definitive recommendations.
- The best evidence comes from two RCTs [4-8]. Based on these RCTs, the overall quality of the evidence was deemed moderate.
- The Working Group considered recurrence rate to be a critical outcome, and QOL, complications, and cosmesis to be important outcomes. Some patient input was sought and patients identified that all of the outcomes mentioned would be important to them in making any treatment decisions. However, few studies collected or reported on QOL, complications, and cosmesis data. The Working Group believes the desirable effects (i.e., decreased recurrence rates) are large compared with the undesirable effects (i.e., complications and adverse cosmetic outcomes) in patients with recurrent BCC. For patients with primary BCC, there may be minimal decrease in recurrence rates with MMS, but a moderate decrease in defect size and few undesirable effects (i.e., complications). Therefore, the Working Group believes the desirable effect of smaller defect size outweighed the undesirable effects. For patients with non-BCC, the desirable effects are uncertain. However, given that the risk of undesirable effects is anticipated to be small, it is anticipated that patients with a higher risk of recurrence may benefit from MMS compared with SE and may be considered on a case-by-case basis.
- The available evidence is difficult to generalize to all patients with skin cancer because it did not adequately cover non-BCC skin cancers; however, the Working Group recommends, based on expert opinion, that those skin cancers be considered on a case-by-case basis.

Recommendation 3

MMS should be performed by physicians who have completed a degree in medicine or equivalent, including a Royal College of Physicians and Surgeons of Canada (RCPSC) Specialist Certificate or equivalent, and have received advanced training in MMS.

Qualifying Statements for Recommendation 3

- MMS is a surgical technique requiring specific training in the assessment of frozen section histology to detect cutaneous malignancies, the surgical skills of cancer removal, and the reconstruction of cosmetically sensitive areas of the face and other complex areas.
- Advanced training is defined as having a recognized MMS fellowship through the American College of Mohs Surgery, or equivalent accrediting body.

Key Evidence for Recommendation 3

- No studies were found comparing the surgical volume of MMS or training with patient outcomes.
- This recommendation was based on the acknowledgement by the Working Group of the unique specialized skills required for successful conduct of MMS procedures that would not be acquired in a current RCPSC specialist certificate.

IMPLEMENTATION CONSIDERATIONS

The Working Group considered these recommendations to be the best possible recommendations given the currently available data and recognized that this guideline will not introduce any new feasibility issues than already exist. It is important to note that MMS is only available in a few urban centres in Ontario (i.e., Toronto, Kingston, and Ottawa), making access to MMS an issue for many patients. There are a limited number of Mohs surgeons in the province, which in part can be attributed to a lack of hospital resources and funding for jobs for clinicians with the appropriate MMS training; these issues have resulted in long wait times. The Working Group recognizes that the mentioned barriers and inequities already exist within the clinical community. These recommendations would validate and align with what providers are currently implementing and would not add new costs to the system. The Working Group believes the outcomes valued in the guideline would align with patient values and that patients would view these recommendations as acceptable.

Patient Indications for Mohs Micrographic Surgery

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, CCO. The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

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

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

BACKGROUND FOR GUIDELINE

Currently in Ontario, the management of aggressive NMSC is often guided by local resources as MMS is only available in few urban centres. The lack of an evidence-based guideline on this topic coupled with a need to develop indications to ensure appropriate patients are deriving benefit and that patients are being treated equitably across the province resulted in the development of this guideline.

GUIDELINE DEVELOPERS

This guideline was developed by the MMS GDG (Appendix 1), which was convened at the request of the Melanoma Disease Site Group (DSG) and the Surgical Oncology Program.

The project was led by a small Working Group of the MMS 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 Mohs surgery, radiation oncology, dermatology, medical oncology, head and neck surgery, pathology, cytology, and health research methodology. Other members of the MMS GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [21,22]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [23] 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 costs, 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

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

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

The following criteria were used to select potentially relevant guidelines:

- Guideline databases and websites were searched using the following keyword "Mohs"
- Only evidence-based guidelines published after 2012 (i.e., less than five years old) were considered to ensure currency.

This search did not yield a guideline that could be adapted or endorsed.

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 or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC 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

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

PATIENT AND CAREGIVER-SPECIFIC CONSULTATION GROUP

Four participated as Consultation Group members for the MMS GDG. They reviewed copies of the project plan and provided feedback on its comprehensibility, appropriateness and feasibility to the Working Group's Health Research Methodologist. The Health Research Methodologist relayed the feedback to the Working Group for consideration.

ACKNOWLEDGEMENTS

The MMS GDG would like to thank the following individuals for their assistance in developing this report:

- Oleh Antonyshyn, Fulvia Baldassarre, Melissa Brouwers, Laurie Elit, Danny Enepekides, Bill Evans, Sheila McNair, Norma Varela, Emily Vella, Jensen Yeung, and David Zloty for providing feedback on draft versions.
- Ruth Chau and Kristy Yiu for conducting a data audit.
- Sara Miller for copy editing.

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Section 4: Systematic Review

INTRODUCTION

Skin cancer is the most common cancer in Canada. Skin cancer may be divided into cutaneous melanoma, NMSC, and cutaneous lymphoma. Although there are many types of NMSC, the vast majority of cases are either BCC or SCC, so many consider NMSC to be synonymous with the combination of BCC and SCC. In Canada, there were an estimated 6500 new cases of melanoma and 76,100 cases of NMSC in 2014, with 77% of NMSC cases being BCC and 23% being SCC. NMSC accounts for at least 40% of all new cancer cases in Canada but is likely underestimated since most provincial and territorial cancer registries do not routinely collect incidence data on NMSC [24]. These cancers are difficult to register because they may be diagnosed and/or treated in a variety of settings that do not report to the provincial and territorial cancer registries.

NMSC may range from slow-growing superficial skin growths, to invasive, destructive, and fatal metastatic tumours. The majority of BCCs are nonaggressive and may be treated with locally destructive or standard excisional techniques. A smaller percentage of BCC may be invasive in the skin and soft tissues causing local destruction and functional impairment, particularly on the head and neck. An even smaller percentage of BCC may be significantly destructive and progress to regional spread and even metastasis. SCC has the same spectrum of disease severity; however, SCC is much more likely to become aggressive and lead to metastasis and death. More aggressive NMSCs require therapy that will ensure complete removal of the cancerous cells while sparing injury to normal tissue, particularly in functionally or cosmetically sensitive locations. More effective treatments, with higher cure rates and less disturbance of normal tissue, will improve patient QOL, minimize morbidity, and prevent the cost and morbidity of secondary therapies.

Primary NMSC is a contiguous tumour, meaning the cancerous cells start from a central focus and grow outward while remaining attached. For this reason, surgical excision with accurate margin analysis is expected to predict cure. As NMSC becomes more aggressive, the growth may be more difficult to detect but if the true margins are evaluated, an experienced pathologist will determine surgical success in the vast majority of cases. If a NMSC has been treated previously, there is a chance the tumour has been divided into more than one focus and rendered discontiguous. However, the cancerous cells typically remain within the treatment location. NMSC may spread via lymphatics to distant sites, but this guidance document will not address the management of metastatic disease.

There are a variety of terms used for excision in the literature. These include but are not limited to SE, standard SE (SSE), conventional excision (CE), and WLE. These terms will be defined below.

SE resects skin and underlying soft tissue around a skin cancer in an attempt to remove all of the malignant cells and achieve clear margins (i.e., a peripheral and deep rim of normal tissue). The process involves an initial evaluation of the skin lesion and an estimate made of the size, shape, and depth of the tumour. A border of normal skin around the tumour is marked for excision with a scalpel. The clinical margins of excision (i.e., the width and depth of the border beyond the clinical tumour) are chosen based on how accurately the surgeon can estimate the extent of the tumour, and the known success rates of various clinical margins for the tumour in question.

SSE, or CE, resects skin and the tissue is then sent for postoperative marginal assessment (POMA). The specimen is oriented, either with a suture or another marker to assist the pathologist, and placed in formalin for POMA. The histology report should comment on the type of skin cancer, the relevant malignant features that impact prognosis, the method of margin evaluation, the involvement of the surgical margins with cancerous cells, and the location or orientation of any positive margins. In most cases, the method of margin evaluation is a breadloaf technique vertically sectioning the specimen. The breadloaf technique, sometimes referred to as on edge margins, examines less than 1% of the true margin.

WLE is a surgical excision using postoperative marginal assessment, which usually has a predetermined margin width based on clinical studies. While technically synonymous with SSE, the word 'wide' in WLE may be confusing the some readers because in some cases the width of excision is only a few millimetres.

Other histologic processing techniques, such as en-face, pre-excision scouting, or staged perimeter are more effective at examining the true margins and predicting cure. However, these techniques are more time intensive and are more commonly used with intraoperative margin analysis (IOMA) as described below.

IOMA, in contrast with POMA, is a surgical excision technique of resecting the skin and deep tissue around and underneath a tumour that is very similar to SSE. The difference is, instead of sending the specimen in a container for histologic assessment at a later time, IOMA is performed at the time of resection and before reconstruction. The specimen is anatomically oriented to identify where tumour may remain along a margin of resection. If cancerous cells remain at any deep or peripheral margin, the anatomic locations corresponding to the positive margins are specifically identified and designated for further resection.

Most methods of SE-IOMA, which include intraoperative frozen sections and MMS, involve en-face processing of tissue. In comparison to breadloaf or on edge margins, en-face margins process the outside face of the specimen to visualize the margins. This takes more time to process but may render close to 100% of the margin for examination, in comparison to often <1% for breadloafing.

MMS is the most common method of SE-IOMA in North America. MMS is an outpatient procedure that has two main components: a) the removal of skin cancer in a minor surgical room, and b) the rapid processing of the specimen by an onsite, dedicated histology laboratory. Using current methods, a surgical excision is performed under local anesthetic with close margins. The specimen is immediately marked with a series of dyes that correspond to the patient's anatomic defect represented by an individualized map. A central debulk may be removed and further tested for upstaging in high-risk cases. The resected area is managed for hemostasis and kept clean and bandaged while the specimen is brought to the laboratory for immediate processing. The histotechnologist mounts the specimen in a horizontal-oblique fashion, which is a version of en-face that allows the peripheral and deep margins to be visualized at the same time. Mohs processing is akin to taking the three-dimensional pie crust (the peripheral and deep margins) and flattening it out to view as a two-dimensional image.

The details of how the specimen is histologically processed to allow complete evaluation of the peripheral and deep margins are beyond the scope of this guideline. Once available for review, which commonly takes between 20 min and 1 h, the Mohs surgeon assesses the histologic slides for evidence of malignancy at the margins. The exact locations of any remaining cancerous cells are mapped on the anatomic diagram, which guides the Mohs surgeon in resecting more tissue from those areas only. The process repeats until all margins are deemed clear of malignancy and only then will the patient move to the next step in the process, reconstruction.

The MMS method, like all IOMA techniques, assumes a prior biopsy has established the diagnosis. Although en-face techniques such as MMS are specifically designed to examine the

peripheral and deep margins of skin specimens with skin cancer, it is also sometimes valuable to have the bulk of the specimen processed for prognostic reasons. In these cases, a central debulk may be sent for pathologic analysis, which may incorporate immunohistochemical analysis if required.

In this review, we consider WLE, CE, and SSE to technically mean the same thing. We will use WLE as default, but if a source study uses another term, such as SSE, we will use that term to remain accurate when describing the study.

In situations where patients are not eligible for surgery, radical radiotherapy is used. This systematic review does not consider adjuvant radiotherapy in its literature review and excludes brachytherapy as it is not routinely performed for skin cancer in Ontario.

The lack of an evidence-based guideline on this topic coupled with a need to develop indications to ensure appropriate patients are deriving benefit and that patients are being treated equitably across the province resulted in the development of this guideline.

The Working Group of the Melanoma DSG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. In the absence of high-quality clinical trials, treatment decisions are made with the best available evidence and expert opinion. This review considers the role of the following interventions for skin cancer: MMS, WLE, and radiation. This guideline does not address treatments typically employed for lower-risk skin cancers such as destructive techniques (e.g., electrodesiccation and curettage, cryotherapy, photodynamic therapy, topical therapy, injectable treatments). Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1. Does MMS provide better outcomes than WLE in patients with skin cancer?
    a) Cure rates, recurrence rates
    b) QOL
    c) Complications, cosmesis

2. In patients with skin cancer, what are the clinical characteristics or indications that identify groups of patients who derive greater benefit from MMS?

3. Does MMS provide better outcomes than radiation in patients with skin cancer?
    a) Cure rates, recurrence rates
    b) QOL
    c) Complications, cosmesis

4. Does WLE provide better outcomes than radiation in patients with skin cancer?
    a) Cure rates, recurrence rates
    b) QOL
    c) Complications, cosmesis

5. Does surgical volume of MMS predict for better outcomes in patients with skin cancer?

METHODS

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

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. This included original systematic reviews and systematic reviews published as a component of practice guidelines. The MEDLINE (1946 to August 4, 2017) and EMBASE (1974 to August 4, 2017) databases, as well as the Cochrane Database of Systematic Reviews (2005 to August 4, 2017) were searched for published systematic reviews. The full search strategy is available in Appendix 2.

Search for Primary Literature

In the absence of any relevant, comprehensive systematic reviews, a search was conducted for primary literature. The MEDLINE and EMBASE databases were searched for published RCTs as well as prospective and retrospective comparative and noncomparative studies based on the inclusion criteria for each question outlined below. Questions involving MMS were searched beginning 1970 as it was known to be the beginning of the modern Mohs technique, while the question involving WLE and radiation was searched beginning 1990 as it was known that no relevant studies existed before this time. The full search strategy is available in Appendix 2. Reference lists of included primary literature were screened for additional, relevant citations.

- Years covered:
    - Questions 1, 2, 3, and 5 – 1970 to August 4, 2017
    - Question 4 – 1990 to August 4, 2017

Literature Search Strategy

Study Selection Criteria and Process

For the following research questions:
1. Does MMS provide better outcomes than WLE?
3. Does MMS provide better outcomes than radiation?

Inclusion Criteria
•RCTs, prospective and retrospective comparative studies comparing MMS with WLE or with radiation with ≥30 participants in each arm reporting on any of the following outcomes: recurrence rate, cure rate, QOL, complications, and cosmesis; and
•Studies assessing adult patients with skin cancer.

Exclusion Criteria
•Studies with brachytherapy as a type of radiation. If studies included mixed types of radiation in the radiotherapy arm, studies with ≥20% of patients receiving brachytherapy were excluded; or
•Abstracts of nonrandomized studies; or
•Papers or abstracts not available in English; or
•Letters and editorials that reported clinical trial outcomes; or
•Papers and abstracts published before 1970.

For the following research question:
2. In patients with skin cancer, what are the clinical characteristics or indications that identify groups of patients who derive greater benefit from MMS?

Inclusion Criteria
•RCTs, prospective and retrospective comparative studies (comparing MMS with surgery or radiation) with ≥30 participants in each arm;

•Prospective or retrospective single-arm studies of MMS with ≥100 participants which have conducted a multivariate analysis; and
•Studies assessing adult patients with skin cancer.

Exclusion Criteria
•Abstracts of nonrandomized studies; or
•Papers or abstracts not available in English; or
•Letters and editorials that reported clinical trial outcomes; or
•Papers and abstracts published before 1970.

For the following research question:
4. Does WLE provide better outcomes than radiation?

Inclusion Criteria

- Randomized controlled trials, prospective and retrospective comparative studies comparing surgery with radiation with ≥30 participants in each arm reporting on any of the following outcomes: recurrence rate, cure rate, QOL, complications, and cosmesis; and
- Studies assessing adult patients with skin cancer.

Exclusion Criteria

- Studies with brachytherapy as a type of radiation. If studies included mixed types of radiation in the radiotherapy arm, studies with ≥20% of patients receiving brachytherapy were excluded; or
- Abstracts of nonrandomized studies; or
- Papers or abstracts not available in English; or
- Letters and editorials that reported clinical trial outcomes; or
- Papers and abstracts published before 1990.

For the following research question:
5. Does surgical volume of MMS predict for better outcomes?

Inclusion Criteria

- RCTs, prospective and retrospective comparative studies (comparing MMS with surgery or radiation) with ≥30 participants in each arm assessing surgical volume in relation to any of the following outcomes: recurrence rate, cure rate, QOL, complications, and cosmesis;
- Prospective or retrospective single-arm studies with ≥100 participants assessing surgical volume in relation to any of the outcomes listed above; and
- Studies assessing adult patients with skin cancer.

Exclusion Criteria

- Abstracts of nonrandomized studies; or
- Papers or abstracts not available in English; or
- Letters and editorials that reported clinical trial outcomes; or
- Papers and abstracts published before 1970.

A review of the titles and abstracts that resulted from the search was conducted by one reviewer (DS). For items that warranted full-text review, one reviewer (DS) reviewed each item.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data extraction was conducted by one reviewer (DS) and audited by a second independent auditor (KY).

Important quality features, such as statistical power calculations, sample size, methods of randomization, allocation concealment, blinding, intention to treat analysis, and source of funding were extracted for randomized studies. Criteria from the Cochrane Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool were used to assess the risk of bias for all non-randomized studies.

Criteria from the GRADE method were used to assess the aggregate quality of the evidence for RCTs and non-RCTs. Four factors were assessed for each outcome in each comparison: risk of bias, inconsistency, indirectness, and imprecision.

Synthesizing the Evidence

A meta-analysis was not planned due to the heterogeneity across trials.

RESULTS

Search for Existing Systematic Reviews

No relevant systematic reviews were identified. Systematic reviews were excluded for not including study types of interest and including studies with less than 30 patients on each arm among other differences in the inclusion criteria.

Search for Primary Literature

In the absence of any relevant systematic reviews, the primary literature search was undertaken as planned.

Literature Search Results

A total of two relevant RCTs [4-8], three prospective comparative studies [9,25-30], 14 retrospective comparative studies [1-3,10,11,14-20,31,32] and two retrospective single-arm studies [12,13] were included. Table 4-1 summarizes the characteristics of the included studies by question and results of the included studies are presented in Tables 4-2 and 4-3. A PRISMA flow diagram of the complete search is available in Appendix 3. Three studies, which met the inclusion criteria, provided conflicting results within their publications (e.g., values were reported differently in the abstract and main text, reported values were different between the tables and main text) and as a result will not be discussed [33-35].

Due to the absence of studies comparing MMS with radiation, an additional research question was later added to compare surgery with radiation. Further, once the MMS data were obtained for the question on patient indications, a decision to include single-arm studies with multivariate analyses was made.

Table 4-1. Studies selected for inclusion

Study	Type of skin cancer	Intervention	Number of skin tumours evaluated	Inclusion criteria	Exclusion criteria	Notes	Included for research question
Randomized controlled trial							
Smeets NWJ (2004) [4] Mosterd K (2008) [6] Van loo E (2014) [8] Essers B (2007) [5]	BCC of the face	SE MMS	Primary tumours 198 MMS, 199 SE Recurrent tumours 99 MMS, 102 SE	Primary BCC: At least one untreated, histologically confirmed, facial tumour of at least 1 cm in diameter, located in the H zone; or an aggressive histopathological subtype (morpheaform, micronodular, BCC with squamous differentiation, trabecular, infiltrative) Recurrent BCC: At least one histologically confirmed, facial tumour recurring for the first or second time	Patients with a life expectancy of less than 3 years.	Surgical team of dermatologists who had equal experience in SE and MMS.	1 and 2
Muller FM (2009) [7]	BCC	SE MMS	15 pts 15 pts	Patients with a clinical diagnosis of a nodular BCC less than 1 cm in diameter at least 1 cm away from the eyelids and nose.	Patients who were immunosuppressed; tumours that were superficial, recurrent, morpheic, or infiltrative; inability to comply with instructions.	A dermatology trainee undergoing training in dermatologic surgery performed all excision in SE group. An experienced Mohs surgeon performed MMS.	1 and 2
Prospective, comparative							
Asgari MM (2009) [36] Chren MM (2004) [28] Chren MM (2007) [27]	Nonmelanoma skin cancer	Excision MMS	Each publication evaluated a different subgroup of patients	Patients with a final histopathologic diagnosis of non-recurrent NMSC in 1999 and 2000 at a university-affiliated dermatology practice or the nearby affiliated Veterans Affairs Medical Center.	Patients younger than 18 years; if their records were protected because they were employees; if they had a previous skin cancer diagnosed during the study period.	-	1 and 2

Study	Type of skin cancer	Intervention	Number of skin tumours evaluated	Inclusion criteria	Exclusion criteria	Notes	Included for research question
Chren MM (2011) [29] Chren MM (2013) [9]							
O'Neill J (2014) [30]	-	Excision MMS	353 tumours 1525 tumours	Patients undergoing any dermatologic surgery procedure at Advanced Dermatology & Cosmetic Surgery, Florida and Wake Forest University Dermatologic Surgery, North Carolina.	-	-	1 and 2
Bordeaux JS (2011) [26]	-	SE MMS	542 tumours 1369 tumours	All patients presenting to the University of Massachusetts Medical School Dermatology Clinic from March 15, 2006 to June 15, 2007 undergoing MMS or scalpel-based excisional surgery requiring sutures.	Patients undergoing punch biopsies, electrodessication and curettage, shave biopsies, and shave excisions.	Surgeries performed by 4 general dermatologists, 2 fellowship trained MMS attendings, and 2 MMS fellows.	1 and 2
Retrospective, comparative studies							
van der Eerden PA (2010) [11]	NMSC (BCC and SCC)	Conventional excision MMS	709 tumours 795 tumours	All patients treated for NMSC from 1990-2008 in one tertiary referral centre.	-	One facial plastic surgeon and 5 histopathologists.	1 and 2
Jebodhsingh KN (2012) [32]	Periocular BCC	Mohs frozen sections negative margins Permanent sections with negative margins Permanent sections with	43 pts 259 pts 87 pts	All patients who had surgery for periocular BCC performed by a single surgeon, between January 1, 1995 and January 1, 2005, at McMaster University in Hamilton, ON.	-	-	1 and 2

Study	Type of skin cancer	Intervention	Number of skin tumours evaluated	Inclusion criteria	Exclusion criteria	Notes	Included for research question
		positive margins					
Hou JL (2014) [18]	Sebaceous carcinoma	WLE MMS	26 tumours 35 tumours	Patients with sebaceous carcinoma seen at one institution between January 1, 1992 and April 20, 2012.	-	-	1 and 2
Chin-Lenn L (2013) [19]	Melanoma of the face	WLE MMS	91 pts 60 pts	Patients registered by the Alberta Cancer Registry as diagnosed with invasive melanoma of the face from 1997 to 2007.	In situ component only; melanomas of the scalp, ear, neck, or mucosal membranes; histologically positive margins; follow-up duration less than 2 months or incomplete data	A single physician performed all MMS.	1 and 2
Nosrati A (2017) [20]	Melanoma in situ	WLE MMS	385 pts 277 pts	Patients with a biopsy demonstrating melanoma in situ treated with either WLE or MMS	Patients with invasive disease or multiple melanoma		1 and 2
Paradisi A (2008) [14]	DFSP	WLE MMS	38 pts 41 pts	81 consecutive patients with DFSP treated at 3 institutions between February 1990 and December 2005.	-	-	1 and 2
Lowe GC (2016) [15]	DFSP	WLE MMS	104 pts 82 pts	Patients with primary and recurrent DFSP treated at the Mayo Clinic from January 1, 1955 through March 31, 2012.	Patients not surgically treated with WLE or MMS.		1 and 2
Veronese F (2017) [16]	DFSP	WLE Mohs Tubingen	62 pts 73 pts	Patients with histologically confirmed DFSP at two institutions in Italy between January 1997 and December 2014.	-	-	1 and 2
Ang GC (2009) [17]	AFX	WLE MMS	23 tumours 59 tumours	All cases of AFX treated at an institution from 1980 to 2004.	-	-	1 and 2

Study	Type of skin cancer	Intervention	Number of skin tumours evaluated	Inclusion criteria	Exclusion criteria	Notes	Included for research question
			91 pts				
Cook Jr. BE (1999) [10]	Malignant eyelid tumours	SE + frozen section SE w/o frozen section MMS	87 pts 52 pts 32 pts	Olmstead County residents who had a newly diagnosed malignant eyelid tumour between Jan 1, 1976 and Dec 31, 1990, inclusive.	-	-	1 and 2
Hansen JP (2008) [31]	SCC in situ (Bowen's disease)	Elliptical excision MMS	109 tumours 83 tumours	Patients with a histologically confirmed diagnosis of Bowen's disease seen at the University of Iowa Hospitals and Clinics Department of Dermatology between Jan 1999 and Jan 2003.	Tumours associated with HPV, found on mucous membranes or genitalia or found within or at the margins of an invasive skin malignancy (such as SCC or BCC).		1 and 2
Babington S (2003) [2]	SCC of the lip	Surgery Radiotherapy	51 pts 62 pts	Patients with histologically confirmed SCC arising from the vermilion of the lip and were treated with radical intent during 1980 to 2000 at Westmead Hospital.	-	Radiotherapy included orthovoltage and superficial radiation therapy.	4
de Visscher J (1999) [1]	SCC of the lower lip	Surgery Radiotherapy	166 pts 90 pts	Previously untreated patients with stage I primary SCC of the lower lip between 1980 and 1994 at Medical Centre Leeuwarden and Radiotherapie Institute Friesland.	-	Radiotherapy included orthovoltage, electron beam therapy, contact therapy, and brachytherapy.	4
Sarachev E (2001)	SCC of the lower lip	Surgery	184 pts	Patients with stage I SCC of the lower lip from South	-	-	4

Study	Type of skin cancer	Intervention	Number of skin tumours evaluated	Inclusion criteria	Exclusion criteria	Notes	Included for research question
[3]		Radiotherapy	592 pts	Bulgaria between 1985 and 1999.			
Retrospective, single-arm studies							
Batra RS (2002) [13]	Malignant skin tumours	MMS	1131 tumours	Patients with malignant skin tumours referred for MMS at the Department of Dermatology at the Beth Israel Deaconness Medical Center between July 1996 and July 1999.	-	All patients excised by the same Mohs surgeon.	2
Flohil SC (2013) [12]	BCC	MMS	1464 tumours	BCCs located in the head and neck and treated with MMS between January 2006 and December 2009 at the Department of Dermatology of the Erasmus MC University Medical Center.	-	Performed by a Mohs surgeon and a dermatopathologist.	2

Abbreviations: AFX: Atypical fibroxanthoma, BCC: Basal cell carcinoma, DFSP: dermatofibrosarcoma protuberans, HPV: human papillomavirus, MMS: Mohs micrographic surgery, NMSC: nonmelanoma skin cancers, pts: patients, SCC: squamous cell carcinoma, SE: surgical excision, WLE: wide local excision, w/o: without; -: not reported

Study Design and Quality

Quality of Individual Trials

RCTs

Quality characteristics were assessed for both RCTs and are reported in Appendix 4. All published reports of the trials were searched for the necessary information. Power and required sample size were calculated and reported in both trials [4,6-8]. The RCT by Smeets et al. [4] consisted of a five-year and 10-year follow up with 205 tumours lost to follow-up at five years and 380 tumours at 10 years. While this study noted it followed the intention to treat principle, the number of patients randomized to their respective treatment groups were not used in the calculations but rather the number of patients that received treatment.

The RCT by Muller et al. [7] was ended early because the predetermined stopping rule was met (i.e., the mean defect diameter in one group was greater than 1.5 times that in the other group). The primary outcome of this trial was the size of defect after MMS or standard surgery and while patient or clinical blinding was not possible, the calculation of defect sizes was performed by an individual unaware of defect sizes.

Non-RCTs

This document includes 17 non-randomized comparative studies that were each assessed using the ROBINS-I tool and are reported in Appendix 5. All published reports of the studies were searched for the necessary information. Overall, nine [11,14,15,17-19,26,28,32] of the included nonrandomized studies were assessed as having a serious risk of bias and eight [1-3,10,16,20,30,31] as having a moderate risk of bias.

Quality of the Aggregate Evidence

According to GRADE, observational studies without special strengths of important limitations provide low-quality evidence.

The best evidence for WLE compared with MMS and for patient indications for MMS comes from two RCTs, which were used to assess the overall quality. The quality of the evidence is moderate, marked down for risk of bias.

The quality of the aggregate evidence for WLE compared with radiotherapy is very low and was marked down due to risk of bias (retrospective studies) and indirectness.

Outcomes

Question 1: Does MMS provide better outcomes than WLE? a) cure rates, recurrence rates; b) QOL; c) complications, cosmesis

Seventeen comparative studies (two RCTs, three prospective and 11 retrospective) were found that compared MMS with WLE.

a) Cure rates, recurrence rates

One RCT [4,6,8], one prospective comparative trial [9] and 11 retrospective comparative studies [10,11,14-20,31,32] reported on recurrence rates.

One RCT compared MMS and SE [4,6,8]. This RCT studied the effect of MMS and SE in primary and recurrent BCC of the face. No statistically significant differences were found in the recurrence rates between MMS and SE for primary BCC at five years (MMS, 2.5%; SE, 4.1%; p=0.397) [6] or 10 years (MMS, 4.4%; SE, 12.2%; p=0.100) [8]. However, for recurrent BCC, recurrence rates were significantly lower for MMS than SE at both five years (MMS, 2.4%; SE, 12.1%; p=0.015) [6] and 10 years (MMS, 3.9%; SE, 13.5%; p=0.023) [8]. It is important to note that approximately 35% to 40% of tumours completed follow-up at 10 years. For those with primary BCC, the mean age of patients being lost to follow-up was significantly higher than

patients who completed the 10-year follow-up (p<0.001). When controlling for possible confounding factors (i.e., tumour localizations in the H zone, previous therapy, first or second recurrent BCC, tumour size, and aggressive histological subtype) in a regression analysis, treatment modality remained statistically significant (p=0.038).

In a prospective comparative study by Chren et al. [9] for nonrecurrent NMSC (i.e., BCC and SCC), there was no statistical difference in the hazard of tumour recurrence for MMS compared with SE in adjusted models or in propensity-matched pairs at five years.

Of the 11 retrospective studies, median follow-up ranged from 16 months to 10 years. Three retrospective studies reported on BCC and SCC [10,11,32]. The first study [11] reported no difference in recurrence rates between those treated with MMS and SE (p=0.78); however, the majority of patients with tumours on the nose or biopsy-proven aggressive BCC were treated with MMS. The second study [10] to report on BCC and SCC (90.8% of patients with BCC, 8.6% of patients with SCC, and 0.6% with malignant melanoma) found that patients treated with MMS had lower recurrence rates (3.1%) when compared with patients treated with excision with frozen section control (5.7%) but higher excision rates when compared with patients treated with excision without frozen section control (0%). A p-value was not reported. The third study by Jebodhsingh et al. [32] found a statistically significant difference for recurrence-free survival rates between patients who had Mohs frozen section with negative margins (92%; 95% confidence interval [CI], 81 to 100), permanent sections with positive margins (80%; 95% CI, 66 to 93]) and permanent sections with negative margins (87%; 95% CI, 76 to 98]; p=0.030). However, when adjusted for age the p-value was not statistically significant (p=0.088). It is also important to note patients were not distributed equally among the three groups with 67% of patients belonging to the permanent sections with negative margins group and that patients who received Mohs surgery were considered to have more serious cases.

Of the eight remaining studies, three studies [14-16] looked at DFSP. The study by Paradisi et al. [14] found that in patients with DFSP, those who received MMS had significantly lower local recurrence rates (0%; 95% CI, 0.0 to 8.6) than those who received WLE (13.2%; 95% CI, 4.4 to 28.1; p=0.016). No patients were found to have distant or regional metastases and characteristics of patients were not significantly different between the two arms. In the study by Lowe et al. [15], the recurrence rate in patients who received WLE was 30.7% while the recurrence in rate in patients who received MMS was 3.0%. Recurrence-free survival rates at four, 10, and 15 years were significantly higher with MMS (p<0.001). Postoperative defect sizes were significantly lower with MMS (mean ± standard deviation [SD], 8.8±5.5 cm) than with WLE (mean ± SD, 10.7±4.3 cm; p=0.004), The third study on DFSP [16] compared WLE with the Mohs Tubingen technique – a slow Mohs-like technique. In that study, 90.4% of the tumours were primary and 9.6% were nonprimary. After a median follow-up time of 4.7 years for patients who received WLE and nine years for those who received the Mohs Tubingen technique, the recurrence rates were 8.1% and 5.5%, respectively. A p-value was not reported.

In studying AFX, Ang et al. [17] found lower recurrence rates in patients treated with MMS (0%) compared with WLE (8.7%); however, a p-value was not reported. Further, the median size of tumours treated using MMS were larger than those treated using WLE (1.5 cm and 1.0 cm, respectively; p=0.02). Similarly, in a study by Hou et al. [18] on primary sebaceous carcinoma, lower recurrence rates were reported in patients treated with MMS (2.9%) than in patients treated with WLE (3.8%); however, a p-value was not reported. Hansen et al. [31] studied Bowen's disease and estimated five-year recurrence rates of 6.3% (95% CI, 2.4 to 14.7) for MMS, 9.0% (95% CI, 3.7 to 19.4) for shave excision, and 5.5% (95% CI, 2.2 to 12.4) for elliptical excision.

Last, two studies reported on melanoma [19,20]. Chin-Lenn et al. [19] reported on invasive melanoma and found no statistically significant differences for local (MMS, 6.2%; WLE, 7.7%; p=0.58) and regional (MMS, 8.7%; WLE, 18.9%; p=0.37) five-year recurrences rates

between WLE and MMS. The treatment arms were not balanced with MMS being used more frequently in women (p=0.02) and those with melanoma on the nose (p=0.001). Nosrati et al. [20] reported on patients with melanoma in situ and found no statistically significant difference in recurrence rates between patients who received WLE and MMS (p=0.07). There were significant differences in anatomic site of tumour between patients who received MMS and WLE (p<0.001). The majority of the patients who received MMS had tumours on the head and neck while the majority of the patients who received WLE had tumours on the trunk or extremities.

b) QOL

One prospective comparative study reported on QOL.

In the study by Chren et al. [27], 633 patients from the original prospective cohort were used to study QOL outcomes using the 16-item version of Skindex but the methods for selecting this subset was not clear. SE and MMS did not differ in their effects on any domain of tumour-related QOL (i.e., symptoms, emotions, or functioning), even after patients were matched for propensity of treatment. Using a larger subset of patients from the original prospective cohort (n=834), Asgari et al. [25] measured long-term satisfaction (i.e., 12 months after therapy) to an item derived from the 18-item Patient Satisfaction Questionnaire (i.e., I am completely satisfied with the treatment of my skin problem). In the 315 patients treated with excision or MMS, the odds of higher long-term satisfaction was independently associated with younger age, better pretreatment mental health status and skin-related QOL, and treatment with MMS.

c) Complications and cosmesis

One RCT reported on both complications and cosmesis while another reported on cosmesis, three prospective comparative studies reported on complications, and one retrospective comparative study reported on cosmesis.

The RCT by Smeets et al. [4] found that aesthetic outcomes did not significantly differ between SE and MMS for both primary and recurrent BCC. However, for tumours that required more than one SE or at least two MMS stages for complete excision, the mean defect size after incomplete excision was significantly larger than after MMS for both primary (SE, 8.66±4.15 mm^2; MMS, 4.86±7.55 mm^2); p<0.001) and recurrent (SE, 14.52±15.28 mm^2; MMS, 7.95±8.11 mm^2; p=0.026) BCC. Cosmetic results were significantly poorer as the defect size increased for primary (p<0.001) and recurrent (p=0.001) BCC. In another RCT involving 30 patients with high-risk BCC, the median area of surgical defects was significantly smaller after MMS when compared with standard surgery (MMS, 116.6 mm^2; SE, 187.7 mm^2; p<0.001) [7]. This trial was stopped early, following the predetermined rule of stopping if there was a major difference in the mean defect diameter with one group being greater than 1.5 times than the other.

In a parallel study to the RCT by Smeets et al. [5], patients who consented were asked to participate in an interview a few weeks before the surgery and six months postoperatively. In 222 patients (133 with primary BCC and 89 with recurrent BCC), no statistically significant difference was found in perceptions on facial aesthetics between patients who underwent MMS and SE. Patients in both groups believed they had improved in time with regards to all four facial aesthetic parameters (i.e., perceptions of size, the conspicuousness, the subjective burden on facial appearance, and the extent to which the facial site is regarded as making the appearance less beautiful) (p<0.05). This RCT also found a statistically significant difference in the number of complications between MMS (8%) and SE (19%) for patients with recurrent BCC (p=0.021) [4]. However, no difference in complications was found for patients with primary BCC (p=0.681). The most common complications for both primary and recurrent BCC included wound infection and necrosis of grafts or flaps.

One retrospective study reported on cosmesis and noted that defects were smaller after MMS only in recurrent tumours on the nose (median defect size: MMS, 2.4 mm^2; CE, 5.6 mm^2;

p=0.038) [11]. The defects after MMS were significantly smaller compared with defects after SE after adjusting for localization and primary or recurrent disease (p=0.008).

Two prospective trials that reported on complications in patients receiving SE or MMS did not provide detailed patient characteristics or type of skin cancer [26,30]. The first trial [30] compared patients who received MMS with non-MMS patients and reported that patients who received MMS were more likely to have a risk of 'suspicion of infection' than those who receiving non-MMS surgery (odds ratio, 4.07; 95% CI, 1.52 to 10.91; p=0.005). The second trial [26] reported that treatment type (i.e., MMS or SE) was not associated with bleeding (p=0.07) or infection (p=0.97).

Question 2: In patients with skin cancer, what are the clinical characteristics or indications that identify groups of patients who derive greater benefit from MMS?

In addition to the studies and data presented in Question 2, subgroup analyses conducted in the RCT comparing MMS with SE and two case series of patients who have received MMS and had performed multivariate analyses were included for this question.

In the RCT by Smeets et al. [4], 18% of primary BCC and 32% of recurrent BCC in the surgical group were incompletely excised after the first excision [4]. Primary BCC with aggressive histopathology were more likely to undergo incomplete excision than those with nonaggressive histopathology (p=0.022). In a subgroup analysis by histological subtype for recurrent BCC at 10 years of follow-up, cumulative recurrence-free survival was significantly lower in patients with aggressive recurrent BCC who received SE (80.7%) than in patients who received MMS (96.1%) (p=0.021) [8]. It is important to remember that approximately 35% to 40% of tumours completed follow-up at 10 years.

The study by Flohil et al. [12] examined 1464 patients with BCC of the head and neck who had received MMS [12]. In a multivariate analysis, BCCs located in the H zone, tumours larger than 10 mm, aggressive tumour subtypes, and recurrent tumours remained significantly associated with two or more stages of MMS. Tumour size (≥21 mm), recurrent tumours, and H zone remained significant predictors for extensive subclinical tumour spread.

In another retrospective study of 1131 Mohs cases with malignant skin tumours, a multivariate analysis found that the most significant predictors of extensive subclinical spread included BCC on the nose (p=0.002), increasing pre-operative size (≥10 mm), and recurrent BCC on the nose [13].

Question 3: Does MMS provide better outcomes than radiation? a) cure rates, recurrence rates; b) QOL; c) complications, cosmesis

No comparative studies were found between MMS and radiation.

Question 4: Does WLE provide better outcomes than radiation? a) cure rates, recurrence rates; b) QOL; c) complications, cosmesis

a) Cure rates, recurrence rates

Three retrospective comparative studies were found that compared surgery with radiation [1-3]. All three studies included patients with SCC of the lip.

The first trial studied SCC on the lower lip and reported local recurrence rates of 3.6% and 4.4% for surgery and radiotherapy, respectively, in previously untreated patients (p>0.05) [1]. Radiation consisted of orthovoltage, electron beam therapy, contact therapy, or brachytherapy, while surgical treatment consisted of full-thickness V- or W-shaped excision and primary closure. Both arms differed statistically in terms of tumour size, differentiation grade, and years of follow-up, with patients in the radiotherapy group having a greater tumour size than patients in the surgery group. Regional recurrence rates were significantly lower after surgery (4.8%) than after radiotherapy (12.2%; p=0.04). A multivariate analysis was conducted; however, statistical significance was set at the 0.10 level for reasons not specified. When using a statistical significance level of 0.05, tumour size was prognostic for developing regional metastasis (p=0.03).

The remaining two studies are considered to be of very low quality. The study by Babington et al. [2] reported recurrence rates of 53% and 19% for surgery and radiotherapy, respectively. Twenty percent of patients were previously treated elsewhere and many were referred with recurrent disease; however, the distribution of these patients within the current surgery and radiation arms is unclear. Patients in the radiation arm received either orthovoltage or superficial radiation therapy. Polytomous regression analysis reported that a close (≤2 mm) or positive margin in the surgery group predicted local recurrence (p=0.05). The last study [3] reported local recurrence rates of 3.1% and 4.3% for surgery and radiotherapy, respectively. However, it provided minimal information on patients who received radiotherapy or about the comparability of treatment groups.

b) QOL
None of the studies reported on QOL.

c) Complications, cosmesis
None of the studies reported on cosmesis.

Question 5: Does surgical volume of MMS predict for better outcomes?

No studies were found that examined surgical volume of MMS with any of the outcomes of interest.

Table 4-2. Outcomes for WLE vs. Mohs

Study	Type of tumours & number of patients evaluated	Median follow-up	Recurrence rates	Re-excision rates	Complications	Cosmesis/QOL
Randomized controlled trials (2 trials, 5 publications)						
Smeets NWJ (2004) [4]	pBCC SE, 199 MMS, 198 rBCC SE, 102 MMS, 99	-	Not extracted as 5- and 10-year follow-up data are available.	pBCC 35 incompletely excised; 31 re-excised[1] rBCC 31 incompletely excised; 25 re-excised[2]	14% 12% p=0.681 19% 8% p=0.021 Common complications for pBCC: wound infection, necrosis of grafts or flaps, or a combination of both. Common complications for rBCC: wound infection, necrosis of grafts or flaps, or postoperative bleeding.	Aesthetic outcomes did not differ between MMS and SE in pBCC or rBCC. Mean defect size: pBCC (SE vs. MMS; p=0.386) rBCC (SE vs. MMS; p=0.598) For tumours that needed more than one SE or at least 2 MMS stages for complete eradication, defects after MMS were significantly smaller for both primary and recurrent BCC.
Mosterd K (2008) [6]	pBCC SE, 134 MMS, 125 rBCC SE, 59 MMS, 75	5 yr	4.1%; 2.5% p=0.397 12.1% 2.4% p=0.021	-	-	-

Study	Type of tumours & number of patients evaluated	Median follow-up	Recurrence rates	Re-excision rates	Complications	Cosmesis/QOL
Van loo E (2014) [8]	pBCC SE, 69 MMS, 71 rBCC SE, 36 MMS, 42	10 yr	 12.2% 4.4% p=0.100 13.5% 3.9% p=0.023	-	-	-
Essers B (2007) [5]	pBCC, 133 pts rBCC, 89 pts	6 mths	-	-	-	No statistically significant difference in perceptions on facial aesthetics between patients who underwent MMS or SE. Patients in both groups generally believed they improved in time with regards to all four facial aesthetic parameters[3] ($p<0.05$)
Muller FM (2009) [7]	BCC SE, 15 pts MMS, 15 pts	-	-	-	-	Median area of surgical defects: SE, 187.7 mm^2 MMS, 116.6 mm^2 $p<0.001$
Prospective, comparative (3 studies, 5 publications)						
Chren MM (2007) [27]	NMSC – BCC & SCC SE, 251 pts MMS, 246 pts	-	-	-	-	SE and MMS did not differ in their effects on any domain of tumour-related QOL[4], even after patients (n=399) were matched for propensity of treatment.

Study	Type of tumours & number of patients evaluated	Median follow-up	Recurrence rates	Re-excision rates	Complications	Cosmesis/QOL
Chren MM (2011) [29]	NMSC – BCC & SCC SE, 309 tumours MMS, 172 tumours	-	 4.2% 3.5%	14 incompletely excised; 11 re-excised[5]	-	-
Chren MM (2013) [9]	NMSC – BCC & SCC SE, 571 pts MMS, 556 pts	7.4 yrs[6] (3.0-8.8)	 3.3% (95% CI, 1.6-4.9) 1.7% (95% CI, 0.4-3.0) p=not significant			
O'Neill J (2014) [30]	Non-Mohs, 822 MMS, 1546[7]	-	-	-	Patients who received MMS were more likely to have a risk of 'suspicion of infection' than those who received non-Mohs surgery (OR, 4.07; 95% CI, 1.52-10.91; p=0.005).	-
Bordeaux JS (2011) [26]	SE, 542 MMS, 1369	-	-	-	Procedure type (MMS or SE) was not significantly associated with bleeding (p=0.07) or infection (p=0.97).	-
Retrospective, comparative (7 studies, 7 publications)						
van der Eerden PA (2010) [11]	NMSC CE, 709 MMS, 795	 16 mths 24 mths	 0.99% 0.75% p=0.78	-	-	No significantly different defect sizes on most locations. Defects smaller after MMS only in recurrent tumours on the nose (p=0.038). Significantly smaller defects after MMS after

Study	Type of tumours & number of patients evaluated	Median follow-up	Recurrence rates		Re-excision rates	Complications	Cosmesis/QOL
							adjusting for localization and primary or recurrent disease (p=0.008).
Jedodhsingh KN [32]	Periocular BCC Mohs frozen sections negative margins, 43 pts Permanent sections with negative margins, 259 pts Permanent sections with positive margins, 87 pts	27 mths	Recurrence-free rate 92% (95% CI, 81-100) 87% (95% CI, 76-98) 80% (95% CI, 66-93)		-	-	-
Hou JL (2014) [18]	Primary SC WLE, 26 MMS, 35	-	3.8% 2.9%[8]		-	-	-
Chin-Lenn L (2013) [19]	Invasive melanoma WLE, 91 pts MMS, 60 pts	 49 mths 47.5 mths	Local 5 yr, 7.7% 5 yr, 6.2% p=0.58	Regional 5 yr, 18.9% 5 yr, 8.7% p=0.37	-	-	-
Nosrati A (2017) [20]	Melanoma in situ WLE, 385 pts MMS, 277 pts	8.6 yrs (0.2-37)	5 yr, 4.1% (95% CI, 2.5-6.8) 15 yr, 7.3% (95% CI, 4.8-11.0) 5 yr, 1.1% (95% CI, 0.4-3.4) 15 yr, 5.0% (95% CI, 1.4-17.3)		-	-	

Study	Type of tumours & number of patients evaluated	Median follow-up	Recurrence rates		Re-excision rates	Complications	Cosmesis/QOL
Paradisi A (2008) [14]	DFSP WLE, 38 pts MMS, 41 pts	Average, 4.8 yrs (range, 2-10) 5.4 yrs (range, 2-15)	Local 13.2% (95% CI, 4.4-28.1) 0% (95% CI, 0.0-8.6) p=0.016	No patients with distant or regional metastases.	-		Postoperative defect size greater for WLE than MMS, not significant
Lowe GC (2017) [15]	DFSP WLE, 104 pts MMS, 82 pts	Mean 5.7 yrs 4.8 yrs	30.8% 3.0%		-	-	-
Veronese F (2017) [16]	DFSP WLE, 62 pts Mohs Tubingen, 73 pts	4.7 yrs 9 yrs	8.1% 5.5%		-	-	-
Ang GC (2009) [17]	AFX WLE, 23 MMS, 59[9] 91 pts	8.7 yrs (1.5-26.3) 4.5 yrs (1.0-16.1)	8.7% 0%		-	-	-
Cook Jr. BE (1999) [10]	Malignant eyelid tumours SE + frozen section control, 87 pts SE without frozen section control, 52 pts MMS, 32 pts	6.5 yrs (0-18.6)	5.7% 0% 3.1% p=not reported		-	-	-

Study	Type of tumours & number of patients evaluated	Median follow-up	Recurrence rates	Re-excision rates	Complications	Cosmesis/QOL
Hansen JP (2008) [31]	Bowen's disease Elliptical excision, 109	Mean 31.5 ± 18.7 (2-70)	5 yr, 5.5% (95% CI, 2.2-12.4)	-	-	-
	Shave excision, 79	33.4 ± 18.1 (4-72)	5yr, 9.0% (95% CI, 3.7-19.4)			
	MMS, 83	26.3 ± 17.5 (2-66)	5yr, 6.3% (95% CI, 2.4-14.7)			

[1] Three received MMS
[2] Five received MMS and one received photodynamic therapy
[3] Perception of size the facial site, the conspicuousness of the facial site, the subjective burden by the facial site on the facial appearance and the extent to which the facial site is regarded as making the appearance less beautiful
[4] Quality of life domains from Skindex – symptoms, emotions and functioning
[5] Two received electrodessication and curettage, five received additional excision, four received MMS and three had no information was available about subsequent treatment
[6] Includes patients who received destruction
[7] Includes 21 patients who received modified Mohs surgery
[8] Calculated from those with documented recurrence
[9] Data available for 58 tumours treated with MMS

Abbreviations: AFX: Atypical fibroxanthoma, BCC: basal cell carcinoma, CE: conventional excision, CI: confidence interval, DFSP: dermatofibrosarcoma protuberans, MMS: Mohs micrographic surgery, mths: months, NMSC: nonmelanoma skin cancers, OR: odds ratio, pBCC: primary basal cell carcinoma, pts: patients, QOL: quality of life, rBCC: recurrent basal cell carcinoma, SCC: squamous cell carcinoma, SE: surgical excision, WLE: wide local excision, yr(s): year(s), -: not reported

Table 4-3. Outcomes for Radiation vs. Surgery

Study	*Number of patients & type of tumours*	*Median follow-up*	*Recurrence rate*		*Complications*	*Aesthetics*
Retrospective, comparative						
Babington S (2003) [2]	SCC of the lip Surgery, 51 Radiotherapy, 62	54 mths (0-189)	53% 19%		12 pts died of disease; 2 died following cardiac arrest; one postoperatively after neck dissection	-
de Visscher J (1999) [1]	SCC of the lower lip Surgery, 166 Radiotherapy, 90	55 mths (6-160) 75 mths (12-166)	**Local** 3.6% 36 mths (8-48)[1] 4.4% 12 mths (8-32)[1] p>0.05	**Regional** 4.8% 26 mths (8-54)[1] 12.2% 24 mths (8-81)[1] p=0.03	2 pts treated by both surgery and radiotherapy died of pulmonary metastases after 25 and 30 mths, respectively; 2 pts died of intercurrent disease after 4 and 8 mths, respectively, one pt died of complications of treatment after salvage neck dissection.	-
Sarachev E (2001) [3]	SCC of the lower lip Surgery, 184 Radiotherapy, 592		**Local** 3.1% 4.3%	**Regional** 4.4% 5.2%	-	-

[1] Median follow-up
Abbreviations: mths: months, pts: patients, SCC: squamous cell carcinoma

Ongoing, Unpublished, or Incomplete Studies

There were no ongoing, unpublished, or incomplete studies found that met the inclusion criteria of this guideline. This search was conducted on August 4, 2017 at clinicaltrials.gov. However, a systematic review protocol was found was found that seeks to examine the effectiveness of MMS compared with other treatment modalities such as excisional surgery, curettage and electrodessication, and radiation therapy, as well as such as topical 5-fluorouracil and imiquimod immunotherapy in the management of NMSC [37].

DISCUSSION

Skin cancer is the most common malignancy in Ontario, and accounts for significant health resource allocation. Superficial, nonaggressive neoplasms may be successfully managed by a number of techniques, and are not the subject of this guideline. Aggressive forms of skin cancer represent a small portion of overall disease, but effective management of these malignancies reduces the risk of disease progression, which may lead to significant morbidity. MMS uses frozen section histology to analyze tumour margins intraoperatively in order to guide complete tumour removal, while sparing injury to normal adjacent tissue. Other methods of intraoperative peripheral and deep circumferential margin analysis exist and are expected to also provide advantages in comparison to standard excision. However, this guideline focuses exclusively on MMS, WLE, and radiation and did not cover other methods of non-MMS forms of frozen section marginal control.

Conservative or narrow margins using standard surgical technique raise the possibility of an incomplete removal, leading to more treatment or delayed recurrent disease. Wider margins risk greater scarring coupled with disfigurement or dysfunction. The benefit of complete marginal analysis is to guide tissue removal during the procedure, to limit the resection of normal tissue. Greater assurance of marginal status at the time of resection allows the surgeon a greater ability to plan reconstruction with confidence.

The members of the Working Group believed that while it is important to acknowledge current treatment practices and patterns of care, the recommendations should be based on the best available evidence. The Working Group members agreed that recurrence rates, complications of therapy, cosmesis, and QOL are acceptable outcomes and are important to patients as well. A Patient and Caregiver Consultation Group confirmed these outcomes to be of importance.

Few well-designed trials have compared MMS with other methods of treating skin cancer. MMS has been compared with SSE, otherwise known as POMA or WLE, and most of these trials have indicated lower recurrence rates with MMS for various skin cancers [4,6,8,14,17,18] although many do not provide p-values. However, most studies have not controlled for important patient or tumour characteristics, thus rendering an effective comparison impossible. Selection bias is also an issue in these studies as patients were chosen for type of treatment based on institutional guidelines. Often, MMS was chosen for the more complex cancers [14,18], but remained at least as effective. Further, retrospective studies had low patient numbers and were not powered to detect differences between groups.

The most important research used to guide the Working Group's recommendations was the RCT comparing MMS with WLE in patients with facial, high-risk primary BCCS, and recurrent BCCs [4,6,8]. High-risk primary BCC was defined as being a BCC of at least 1 cm in size, having aggressive histology (micronodular, morpheaform, BCC with squamous differentiation, infiltrative) or being located on the H zone of the face. Recurrent BCC were those that had failed at least one previous treatment. SE was performed with a 3 mm margin. Positive margins after SE lead to a re-excision, and subsequent positive margins went on to receive MMS. Overall, 3.5% of primary BCC and 17% of recurrent BCC from the SE arm were treated with MMS instead

of SE, although these cases remained in the SE arm for statistical analysis based on intention to treat [4]. MMS was also initially treated with a 3 mm margin, whereas positive margins were treated during the same procedure with subsequent levels until clear.

Despite the histologic subtypes being more aggressive on average in the groups who were treated with MMS, defects were significantly larger in patients after an incomplete excision in comparison to those patients with multiple Mohs stages, and this was true for primary ($p<0.001$) and recurrent BCC ($p=0.026$) [4]. Cosmetic results were significantly poorer as the defect size increased for primary and recurrent BCC although aesthetic outcomes did not differ between MMS and SE in primary BCC or recurrent BCC.

Although a significant number of patients were not available for final analysis, the 10-year follow-up provided valuable data. For primary BCC, MMS had a recurrence rate of 4.4% versus 12.2% in the SE arm ($p=0.100$) [8]. Although this is not statistically significant, the lower number of recurrences in primary BCC following MMS was thought to be relevant by the members of the Working Group, especially given the 3.5% cross-over rate. For recurrent BCC, recurrence rates were 3.9% for MMS compared with 13.5% for SE, which was statistically significant ($p=0.023$), despite a 17% cross-over rate.

Recurrent BCC had more complications with SE (19%) as compared with MMS (8%), ($p=0.021$) [4]. The members of the Working Group recommend MMS for recurrent facial BCC, based on the statistically significant reduction in recurrence. High-risk tumours, as defined by aggressive histology or location in the H-zone of the face that are at least 1 cm in size should also be considered for MMS, based on the trend of reduced recurrence. The evidence reporting lower complication rates and smaller defect sizes with MMS further support these recommendations. Two retrospective studies of patients who received MMS that conducted multivariate analyses further supported these recommendations. One study found that BCCs located in the H zone, tumours larger than 10 mm, aggressive tumours subtypes, and recurrent tumours remained significantly associated with two or more stages of MMS, while tumour size (≥21 mm), recurrent tumours, and H zone location remained significant predictors for extensive subclinical tumour spread [12]. The second found that the most significant predictors in patients with malignant skin tumours of extensive subclinical spread included BCC on the nose ($p<0.002$), increasing preoperative size (≥10 mm), and recurrent BCC on the nose [13].

Much of the evidence used to inform recommendations were based on BCC, with few retrospective studies assessing other skin cancers, creating a gap in evidence and literature on the effectiveness of MMS in these skin cancers. However, in other skin cancers residing in locations where re-excision or a larger defect size could endanger function or cosmesis, consideration should be given to margin-controlled removal. This is based on the few retrospective comparative studies of various skin cancers and the Working Group's expert understanding of the pathobiologic similarity of these malignancies to BCC.

Patients who are predisposed to rapidly advancing malignancy, such as those who are immunosuppressed, may benefit from margin-controlled surgery. Those with a genetic predisposition to multiple skin cancers, such as Gorlin's syndrome, who may develop vast numbers of malignancies and thus benefit from skin-sparing techniques, should be considered for MMS in nonsuperficial lesions.

The members of the Working Group propose that where tissue sparing is crucial or an elevated risk of morbidity from recurrence exists, MMS should be considered.

There are no well-designed trials comparing WLE or MMS with radiation. Retrospective studies comparing WLE and radiation did not identify significant advantages with either method and were not controlled for risk factors. Untangling the reasons for why either treatment was chosen was not possible. No studies compared MMS with radiation for any of the outcomes of interest. One study did compare WLE with radiation and concluded surgery resulted in superior cosmesis; however, brachytherapy was used in more than 20% of patients and thus did not meet

our inclusion criteria [38]. The members of the Working Group agreed there was no evidence supporting a change to the current standard of care between WLE and radiation.

Radiation is most helpful when surgery is contraindicated, the tumour is in a location where radiation can access without causing secondary injury, and the delayed effects of treatment are anticipated to be minor. Surgery is relatively contraindicated when the patient is either psychologically or medically unprepared for a local anesthetic procedure that may be complicated by bleeding or temporary incapacity. When tumours reside in locations where surgery would be technically challenging and likely result in significant functional impairment, radiation should be an option. Lesions that are widespread or discontiguous may benefit from radiation therapy, as compared with surgical options. Patients who have failed margin-controlled surgery should be evaluated for factors that would predict further surgical incomplete resection, and considered for radiation if identified as poor surgical candidates. Referrals for radiotherapy should be forwarded to units with extensive experience in the delivery of radiation that maximizes skin cancer clearance while minimizing injury to normal skin. Radiation fields are wider than the predicted size of the cancer and thus affect surrounding normal skin. Estimating the depth and width of the radiation required, like estimating surgical margins, is often challenging. Wider and deeper fields are often chosen, especially for cancers with subclinical spread or aggressive features. Although newer fractionated methods reduce injury, therapy raises the risk of secondary skin malignancy and impairs skin function in the irradiated field. This may result in poor wound healing if surgery is required at the site in the future. Repeat radiation is typically contraindicated for new cancers within a previously irradiated field. Radiation, like surgery, may injure nearby structures such as tear ducts, and cause cosmetic concerns such as alopecia. For these reasons, radiation may be most appropriate for older patients who are less likely to have delayed complications such as secondary malignancies or fibrosis within an irradiated field requiring surgery. Older patients are also more likely to have comorbidities that may raise the risk of surgical options, or prefer palliative radiation as an option.

For patients with complex or advanced skin cancers, a multidisciplinary approach is recommended. Collaboration among medical oncologists, radiation oncologists, surgeons, pathologists, and dermatologists will often provide options that may work synergistically to support the goals of the patient and family.

MMS requires specialized training in resection, expertise in the histologic interpretation of frozen section pathology, and the reconstruction of complex facial defects. There are no studies that compared outcomes between procedures performed by differing levels of expertise or experience, but it is the Working Group's expert opinion that the skill set needed to operate at a high standard would require a RCPSC Certificate, or equivalent, and successful completion of an accredited fellowship in MMS, such as the American College of Mohs Surgery or equivalent accrediting body. No studies were also found where surgical volume of MMS predicted for outcomes.

Access to MMS in Ontario was identified by the Working Group to be a significant barrier to care for most patients. MMS currently uses the infrastructure of a hospital to provide the required facilities. These centres only exist in large urban centres and are not able to meet the demands of the increasing number of complex facial skin cancers in Ontario.

The current recommendations do not introduce new indications for MMS, but rather provide the evidence that has been used to develop triage models for skin cancer management. This guidance document also helps to clarify areas where data are lacking, and form the basis of future trials examining clinically relevant questions.

CONCLUSIONS

The standard of care for patients with skin cancer is surgery (with postoperative or intraoperative marginal assessment), or radiation for those who are ineligible for surgery. Given the lack of high-quality, comparative evidence, there is no reason to change this standard of care. Eligibility for surgery depends on disease stage, surgical considerations, aesthetic outcomes, patient comorbidities, and patient preference. Mohs micrographic surgery is another surgical technique used in patients with skin cancer. It is recommended for those with histologically confirmed recurrent BCC of face, and is appropriate for primary BCCs that are greater than 1 cm on the face, have aggressive histology, or are located on the H zone of the face. The evidence comes largely from two RCTs. Based on the clinical expert opinion of the Working Group, there are other situations where MMS may be indicated in patients. These include smaller tumours (<1 cm in diameter) where tissue sparing is of functional or cosmetic significance, in complex tumours that may necessitate margin-controlled surgery, or in aggressive or high-risk NMSC. MMS should be performed by physicians who have completed a degree in medicine or equivalent, including an RCPSC Specialist Certificate or equivalent, and have received advanced training in MMS.

Patient Indications for Mohs Micrographic Surgery

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 20 members of the GDG Expert Panel, 17 members cast votes and none abstained, for a total of 85% response in July 2017. Of those that cast votes, 13 approved the document (76.5%). 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. H zone is a term that is used repeatedly; it may be useful to define it.	We have added an image showing the H zone within the recommendations.
2. I think you need to differentiate somewhere that MMS is not standard for melanoma and that it is predominantly used in NMSC.	We have inserted the following statement in the qualifying statements, "Patients with invasive melanoma or melanoma in situ have shown no benefit in the use of MMS over WLE. These retrospective studies were not adequately powered. A recent guideline by Cancer Care Ontario (CCO) on primary excision margins in cutaneous melanoma has been published. Please refer to this guideline for recommended surgical margins in this population."
3. This does not seem specific to an MMS guideline. It covers all treatments of skin cancer (WLE, MMS, radiation), whereas the guideline title refers only to MMS.	The objectives for this guideline are specific for MMS. However, in order to write a guideline on MMS and to determine when it is appropriate we needed to include other treatments for comparisons. A guideline on skin cancer would be much broader and include other techniques such as curettage, electrodessication, cryosurgery, etc.
4. It would be valuable to have input in these guideline from a specialty-trained dermatopathologist. At the institutions I have trained at and am now practicing, our dermatopathologists do not call margins for melanoma on frozen section due to concerns such as artifact from the freezing process that can obscure interpretation.	Our Working Group included one pathologist. There is another guideline developed by CCO that covers surgical margins in cutaneous melanoma. We have inserted a reference to that guideline.
5. "NMSC may spread via lymphatics to distant sites, but this guidance document will not address the management of metastatic disease." This should be stated at the outset of the guidelines.	We have inserted a preamble to the beginning of this guideline that includes, "Further, this guideline refers to radical radiotherapy and does not consider adjuvant radiotherapy in its literature review nor does it address metastatic disease."
Regarding recommendation 1: ***Surgery (most commonly WLE, or MMS), or radiation for those who are ineligible for surgery, should remain the standard of care for patients with skin cancer given the lack of high quality, comparative evidence.***	
6. I do not think this is an accurate statement, nor a clear statement. MMS is not acceptable	Please see Response 2.

as standard of care for resection of melanoma based on current evidence.	
7. Other destructive modalities (curettage, electrodessication, cryosurgery) are often effective for smaller, low-risk tumours.	This guideline does not cover these destructive modalities as the objective of this guideline was to identify when MMS is appropriate, not to cover all treatment options for skin cancer. We have added a preamble to the recommendations to acknowledge this.
8. I agree in principle, and with review of the literature, with this statement. I do think that it may be somewhat too general as a first recommendation. This is basically endorsing all of the current available treatments without clarifying the role of multidisciplinary input or specifying within the recommendation the various surgical approaches and how they differ. "Surgery" is a broad and nebulous term. I can appreciate that it is clarified in the qualifying statements; however, a clearer definition within the Recommendation wording itself is preferred.	We have modified the recommendation to read as follows, "Surgery (with postoperative or intraoperative marginal assessment), or radiation for those who are ineligible for surgery, should remain the standard of care for patients with skin cancer given the lack of high-quality, comparative evidence."
Regarding the following qualifying statement for Recommendation 1: ***Based on standards of care and clinical experience, the Working Group suggests that clinical situations with any of the following features may be considered appropriate for referral to a radiation oncologist:*** ***1.Where there is patient preference based on the expected cosmetic or functional outcomes of surgery or anxiety related to surgery;*** ***2.When the patient is on anticoagulation with significant risks of bleeding with surgery and when stopping/modifying anticoagulation carries medical risks;*** ***3. In clinical situations where the intent is palliative;*** ***4.Cases with increased risk of recurrence with (further) surgery:*** ***a. Discontiguous lesions where marginal assessment is very difficult;*** ***b. High-risk histologic features: perineural invasion, lymphatic invasion, vascular invasion, in transit metastasis or histologic subtype suggesting a high risk for surgical recurrence;*** ***c. Extensive disease: Large tumour diameter, thick lesions, or deep invasion where surgical resection is likely to cause significant morbidity;*** d. ***Poorly defined borders (e.g., selected recurrent lesions)***	
9. Some skin cancer subtypes are not very radiation sensitive or radiation can cause significant comorbidities. Patients should be educated about the risks.	The statement regarding radiation has been modified to, "There are various clinical situations where it may be considered appropriate for referral to a radiation oncologist. Based on standards of care and clinical experience, the Working Group suggests that clinical situations with the following may be appropriate for referral for radical radiotherapy: 1. Where there is patient preference based on the expected cosmetic or functional outcomes of surgery or anxiety related to surgery; 2. Cases with increased risk of recurrence or extensive subclinical spread with surgery.
10. Should the degree of medical risk be defined, a small risk for blood clot is still better than dying of metastatic skin cancer	
11. What data support this criterion? Most Mohs surgeons perform surgery without stopping anticoagulation.	
12. I suggest these following indications should be stated as reasons for adjuvant radiation after surgery, not for radiation alone	
13. I would not say the first line of treatment after surgery for in-transit metastases is radiation. We have many other treatments	

that are much more effective and with better evidence.	
14. You should clarify adjuvant versus primary radiation. I am assuming that this refers to adjuvant radiation for high-risk tumours, as radiation alone would not likely be curative.	
Regarding recommendation 2: ***MMS is recommended for those with histologically confirmed recurrent basal cell carcinoma (BCC) of face, and is appropriate for primary BCCs that are >1 cm on the face, have aggressive histology, or are located on the H zone of the face.***	
15. I think the requirement for a histologically confirmed BCC should be optional in certain cases. Many BCCs are clinically obvious and requiring a biopsy delays timely referral for MMS and exposes the patient to, potentially, more morbidity. Practically, I do not know how you can make this part of a guideline, but I would suggest it be explored.	The Working Group understands that the risk of misdiagnosis is too high and as a result recommends cases be histologically confirmed.
16. I believe that the 1 cm criterion for referral to MMS is too large. Depending on the location, even 5 to 6 mm should warrant MMS as a consideration. I know this is alluded to by the Working Group, but perhaps it should be stated explicitly in the recommendation.	This has already been addressed in the qualifying statements.
17. Consideration should also be given to BCCs with ill-defined margins, those in immunosuppressed patients, those in patients with a genetic predisposition to multiple skin cancers, such as Gorlin's, where tissue sparing is desired, or in SCC, to be assessed on a case-by-case basis.	The qualifying statement for Recommendation 1 has been modified to the following to include immunosuppressed patients, "There are situations where MMS may be considered in patients outside of the above recommendation: smaller tumours (<1 cm in diameter) where tissue sparing is of functional or cosmetic significance **(this includes tumours in patients with a genetic predisposition to multiple skin cancers, such as Gorlin's)**; complex tumours that may necessitate margin controlled surgery; **or immunosuppressed patients.**"
18. Do you want to specifically say – not appropriate for melanoma, melanoma in situ or SCC or Merkel cell?	Please see Comment 2.
19. A note could also be made on accessibility to expert follow-up and secondary care as an indication for Mohs. This may be due to patient compliance, distance to care, or patient insight. The salvage rate in recurrent (persistent) NMSC is excellent, but I believe that the functional and cosmetic results are better if caught early.	There is a resource implementation phase after the completion of this guideline that would address these concerns.
20. The recommendations should highlight the facial subunits that are best suited for a Mohs micrographic approach; specifically, eyelid, nasal ala, medial and lateral canthus, some lip lesions.	We have added an image showing the H-zone within the recommendations.
Regarding the following statement: **Although the results were not statistically significant for recurrence rates after 10 years of follow-up for patients with primary BCC, the Working Group suggests that clinicians consider the value of cosmesis (i.e., defect size) in addition to recurrence rates.**	

21. This is not totally correct. Cosmesis depends not only on size of the defect, but also the location on the face, and how the defect is closed (primarily, skin graft, flap, secondary intention). I assume that this statement comes from the RCT by Smeets – how did it rate cosmesis, and were there enough cases to compare cosmetic outcome after surgery based on the method of closure? I would leave it at "…that clinicians consider the value of cosmesis in addition to recurrence rates"	We agree and the suggested changes have been made.
General comments	
22. DFSP has a high risk of local recurrence with inadequate local treatment and it can dedifferentiate to a fully malignant fibrosarcoma over time. As the authors point out, the evidence to support MMS for DFSP is of low quality and subject to bias. All sarcomas in Ontario should be managed according to the CCO Provincial Sarcoma Management Plan.	The Working Group has looked at the evidence as well as the CCO Provincial Sarcoma Management Plan. We have determined that our qualifying statement aligns with it and does not contradict it. Further, we added another member to our Expert Panel who specializes in treating skin sarcomas. She was satisfied with the wording of the qualifying statements as, "Patients with dermatofibrosarcoma protuberans (DFSP), atypical fibroxanthoma (AFX), and sebaceous carcinoma have shown benefit in the use of MMS over wide local excision (WLE). The results of these studies are subject to selection bias and were not adequately powered. However, the Working Group notes that although methodologically strong evidence does not exist for rarer types of skin cancer, MMS should be considered on a case-by-case basis."
23. "Irradiated fields are typically resistant to subsequent radiation for new cancers within the field." I would reword this to say "Repeat radiation is typically contraindicated for new cancers within a previously radiated field." Irradiated fields are not "resistant" to subsequent radiation, but one does not typically re-irradiate due to concerns of late toxicity, depending on factors such as time since previous radiation, dose/fractionation received, volume treated, etc.	We agree and the suggested changes have been made.
24. I would further recommend a research question that examines patients who are immunosuppressed, as this is a growing cohort of patients with NMSC, specifically SCC.	We have modified the qualifying statement to address patients with immunosuppression – please see Response 12. However, a research question in this area cannot be added to this guideline at such a late stage. This may be included in future guidelines.
25. Recent guidelines for melanoma in situ (via CCO) are suggesting increasing margins to 0.5 cm to 1 cm ideally, based on a systematic review.	Yes, we have inserted the following statement in the qualifying statements for Recommendation 1, "A recent guideline by Cancer Care Ontario on primary excision margins in cutaneous melanoma has been published. Please refer to this guideline for recommended surgical margins in this population."

26. In the systematic review concerning c) Complications and cosmesis, it may be valuable to examine reconstructive techniques that are used in those studies (if reported) in particular as there are conclusions being drawn about defect size and cosmetic outcomes without specifying the reconstructions utilized.	The Working Group feels this is outside of the scope of this guideline.
27. I agree with the concluding statements in the following paragraphs and feel that there should be a clear emphasis set out in these guidelines (i.e., by putting these comments explicitly in the recommendations) for the following: "Patients who are predisposed to rapidly advancing malignancy, such as the immunosuppressed, **should be** strongly considered for margin-controlled surgery." "…where tissue sparing is crucial or an elevated risk of morbidity from recurrence exists, margin-controlled surgery **should be** considered.	The qualifying statement for Recommendation 1 has been modified to the following to include immunosuppressed patients, "There are situations where MMS may be considered in patients outside of the above recommendation: smaller tumours (<1 cm in diameter) where tissue sparing is of functional or cosmetic significance **(this includes tumours in patients with a genetic predisposition to multiple skin cancers, such as Gorlin's)**; complex tumours that may necessitate margin controlled surgery; **or immunosuppressed patients**."
28. There are persistent concerns about controlling the number of patients who have MMS to those where the margins are truly unclear for recurrent tumour, anatomical locations, or histology. The overall volume of NMSC patients would overwhelm any system both by time and financial constraints if the recommendations are too broad.	There is a resource implementation phase after the completion of this guideline that would address these concerns.
29. Need to discuss other margin assessment techniques as an option: 1. Staged perimeter or string approach 2. Frozen section margins, specifically with "en face" processing	We have augmented the introduction and discussion sections with other assessment techniques.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in April 2017. The RAP conditionally approved the document in April 2017. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

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

Comments	Responses
1. The discussion of the different types of skin cancer surgery could be further improved if the description of Mohs surgery was more detailed in terms of what equipment is used, how it is used, who does the histologic examination, and where is this actually done. This should be compared to the standard WLE approach. A description of the implications for operating room time compared to standard surgical approaches should also be included	We have augmented the introduction with these details.
2. The authors of this report seem to assume the reader of this guideline actually is knowledgeable of the management of skin cancers of the face. Terms such as the H zone are never explained nor is a detailed description of how Mohs surgery is actually performed. I would encourage the authors to augment the report with this information	We have added an image showing the H zone within the recommendations. We have also added a detailed description of MMS to the introduction.
3. The introduction would be improved by describing the different surgeries – MMS versus WLE versus excision versus CE. If SE is WLE, then I would use SE throughout the document and tables.	We have augmented the introduction with these details. Terms used throughout this guideline are as how individual studies and trials reported them.
4. What is the difference between the two groups in O'Neill and is excision the same as surgical excision in the next row?	Terms used throughout this guideline are as how individual studies and trials reported them.
5. Page 8 says you are only going to look at guidelines after 2012 forward. On page 12, you go back to 1970. The studies you include with the exception of two are all older than 2012. All the databases used, study types, and studies retrieved were appropriate. PRISMA diagram is good. Not sure why you restricted guidelines to after 2012.	We generally do not search for guidelines more than three years old due to the labour that it would take to incorporate new studies. We have added the following to the methods sections, "Questions involving MMS were searched beginning 1970 as it was known to be the beginning of the modern Mohs technique, while the question involving WLE and radiation was searched beginning 1990 as it was known that no relevant studies existed before this time."

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Eleven targeted peer reviewers from Ontario and across Canada who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group.

Five agreed to be the reviewers. Responses were received from four reviewers (Appendix 1). 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=4)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	1	0	1	2
2. Rate the guideline presentation.	0	0	0	2	2
3. Rate the guideline recommendations.	0	1	0	2	1
4. Rate the completeness of reporting.	0	1	0	1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	1	0	2	1
6. Rate the overall quality of the guideline report.	0	0	1	2	1
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.	1	0	0	2	1
8. I would recommend this guideline for use in practice.	1	0	0	1	2
9. What are the barriers or enablers to the implementation of this guideline report?	• Access to MMS • Accessibility of guideline to practitioners and patients • Accessibility and awareness of clinical experts in the field				

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

Comments	**Responses**
1. Reviewer states that plastic surgeons are underrepresented in this guideline (none on the Working Group and two of 23 on the Expert Panel) although they are the vast majority of surgeons managing cutaneous malignancies. Reviewer	We had two plastic surgeons on the Expert Panel, which is responsible for reviewing and approving the guideline. Through External Review (i.e., Targeted Peer Review and Professional Consultation), we consulted plastic surgeons. In Professional

makes a note that dermatopathologists are also under represented.	Consultation, we had four plastic surgeons provide feedback. Further, we have altered our Qualifying Statements for Recommendation 2 around specialties for multidisciplinary assessment from "surgical, medical, and radiation oncologists" to "surgical specialists, dermatologists, medical, and radiation oncologists". We had a dermatopathologist on the Working Group, as well as on the Expert Panel – please refer to Appendix 1. The articles referenced in this comment were excluded because they didn't meet eligibility criteria for this review as they're all non-comparative studies.
2. Reviewers states that the outcomes as well as cost effectiveness of intraoperative frozen sections versus MMS should be specifically analyzed and notes the following references: - Plast Surg (Oakv). 2014 Autumn; 22(3): 179–182. A reliable frozen section technique for basal cell carcinomas of the head and neck. Wisam Menesi, Edward W Buchel, and Thomas JE Hayakawa. - Eur J Ophthalmol. 2014 Jul-Aug;24(4):476-82. doi: 10.5301/ejo.5000405. Epub 2013 Dec 5. Outcome of 110 basal cell carcinomas of the eyelid treated with frozen section-controlled excision: mean follow-up over 5 years. Giordano Resti A, Sacconi R, Baccelli N, Bandello F. - Ophthal Plast Reconstr Surg. 2002 Nov;18(6):430-5. Management of periocular basal cell carcinoma with modified en face frozen section controlled excision. Wong VA1, Marshall JA, Whitehead KJ, Williamson RM, Sullivan TJ.	Assessing the cost-effectiveness of the various techniques is beyond the scope of this guideline. The references provided would have been excluded from our search as they are non-comparative studies. We have moved the following sentence from the Discussion to the Notes in Sections 1 and 2, "Aside from MMS, other methods of intraoperative peripheral and deep circumferential margin analysis exist and are expected to also provide advantages in comparison to standard excision. However, this guideline focuses exclusively on MMS, WLE, and radiation and did not cover other methods of non-MMS forms of frozen section marginal control."
2. Reviewer does not agree with the H zone of the face as an area necessitating frozen sections or Mohs and states that the presentation of intraoperative frozen sections are misleading and inaccurate. Reviewer believes it misrepresents those areas that are difficult to reconstruct, and where Mohs or intraoperative frozen sections are necessary. The indications for frozen section (SE-IOMA) are: 1. Pathological tumours (sclerosing BCC, etc.) 2. Recurrent tumours (postradiotherapy, post previous surgery) 3. Aggressive tumors (immunosuppressed patients, patient treated with radiotherapy for acne or tinea) 4. Those areas where tissue sparing is important to preserve function or cosmesis: eyelids, eyebrows (not included in H zone), nose, ear, upper lip and lower lip, (not included in H zone), upper cheeks (large defects cause ectropion and	Recommendation 2 regarding the use of MMS for the H zone of the face comes from the results of an RCT. While there is a lot of literature on this topic, we used the highest quality of evidence available (i.e., RCTs) to make recommendations. Please refer to the Qualifying Statements for Recommendation 2 where further indications for when MMS may be useful is mentioned based on clinical expertise and comparative evidence. We have moved the following sentence from the Discussion to the Notes in Sections 1 and 2, "Aside from MMS, other methods of intraoperative peripheral and deep circumferential margin analysis exist and are expected to also provide advantages in comparison to standard excision. However, this guideline focuses exclusively on MMS, WLE, and radiation and did not cover other methods of non-MMS forms of frozen section marginal control."

not included in H zone), labiomental fold (not included in H zone)	
3. Reviewer feels that given the number of qualifying statements for Recommendation 2, it should contain an additional sentence to accurately convey the role of MMS for other BCC types and less-common skin cancers. An example of a second sentence: "MMS may also be considered for less-common skin cancers as per the qualifying statements outlined below".	The Working Group understands this concern, however, would like to point the readers to the Qualifying Statements for Recommendation 2.
4. Reviewer feels reference studies 6, 9, and 15 have had their outcomes simplified and show a subtle bias away from MMS. The study design and quality section of the draft guidelines does address the studies outcomes in greater detail. However, the reviewer feels the simplifications are a reasonable compromise position and does not require any change in the primary recommendations.	Thank you for your comment.
5. Regarding the qualifying statement, "Patients with invasive melanoma or melanoma in situ have shown no survival or recurrence benefit in the use of MMS over WLE", the reviewers feels this statement is correct taken broadly. However, for melanoma in situ of the face, there is strong literature evidence that the recommended margin of 5 mm for melanoma in situ will prove inadequate in 14% to 35% of cases. A reference to CCO margins is then given, but does not address this concern. The current qualifying statement may wish to convey the desire that consideration be given to a WLE margin of 5-10 mm for melanoma in situ of the face, if MMS is not available, and if anatomic and functional considerations allow.	Determining margins was beyond the scope of this guideline. However, the recently published CCO Guideline 8-2 Version 2, as referenced in the Qualifying Statements for Recommendation 2, addresses this concern and notes that when possible, wide margins should be employed (i.e., 5mm-1cm for melanoma in situ), but recognizes that they may be difficult to achieve based on their anatomical location. In these instances margin-controlled excision may provide tissue sparing and improved tumour clearance.

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 surgeons and plastic surgeons with an interest in head and neck, as well as any clinicians with an interest in head and neck, melanoma, or skin in the PEBC database were contacted by email to inform them of the survey. Sixty-five professionals were contacted, all of which practice in Ontario. Nine (13.8%) responses were received. Three stated that they were no longer in active practice and one was not willing to participate. The results of the feedback survey from five people (four

plastic surgeons and one dermatologist) 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.

	N=5 (7.7%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	1	0	3	1
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.	0	1	1	2	1
3. I would recommend this guideline for use in practice.	0	1	0	1	3
4. What are the barriers or enablers to the implementation of this guideline report?	• Availability and access to MMS • Lack of resources – most hospitals in Ontario do not provide MMS • Access to Mohs training				

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

Comments	Responses
1. Two reviewers commented that there is no quality or cost-effectiveness/utility analysis associated with this guideline.	Assessing the cost-effectiveness of the various techniques is beyond the scope of this guideline.
2. One reviewer commented that H zone as a primary indicator for MMS is not borne out in clinical practice. The evidence for this recommendation is not convincing and that there is no mention of surgical excision with frozen check of the margins.	Recommendation 2 regarding the use of MMS for the H zone of the face comes from the results of an RCT. While there is a lot of literature on this topic, we used the highest quality of evidence available (i.e., RCTs) to make recommendations. Please refer to the Qualifying Statements for Recommendation 2 where further indications for when MMS may be useful is mentioned based on clinical expertise and comparative evidence.

CONCLUSION

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

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Appendix 1: Affiliations and Conflict of Interest Declarations

Table A1-1: Working Group Members

Name	Affiliation	Conflict of Interest
Scott Bradshaw Pathologist	Ottawa, ON	No conflict of interest declared
Tim Hanna Radiation Oncologist	Kingston General Hospital Kingston, ON	No conflict of interest declared
Rob Hekkenberg Head & Neck Surgeon		No conflict of interest declared
Benvon Moran Dermatologist Mohs surgeon	Kingston General Hospital Kingston, ON	No conflict of interest declared
Christian Murray Dermatologist Mohs surgeon	Women's College Hospital Toronto, ON	No conflict of interest declared
Teresa Petrella Medical Oncologist	Sunnybrook Health Sciences Centre Toronto, ON	No conflict of interest declared
Duvaraga Sivajohanathan Health Research Methodologist	Program in Evidence-Based Care, Cancer Care Ontario McMaster University Hamilton, ON	No conflict of interest declared
Nowell Solish Dermatologist Mohs surgeon	Women's College Hospital Toronto, ON	Has received grants/research support for nonresectable tumours with a hedgehog inhibitor; has been a principal investigator for a clinical trial with skin cancer patients ineligible for surgery and radiation;
Alice Wei Surgical Oncologist	Lead, Quality & Knowledge Transfer Surgical Oncology Program, Cancer Care Ontario Toronto, ON	Has received $5000 or more to act in a consulting capacity for Ethicon Inc.

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, and internal and external reviewers were asked to disclose potential conflicts of interest. The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline.

Table A1-2: Report Approval Panel Members

Name	Affiliation	Conflict of Interest
Melissa Brouwers Scientific Director	Program in Evidence-Based Care, Cancer Care Ontario McMaster University Hamilton, ON	No conflict of interest declared
Laurie Elit Surgeon	Juravinski Cancer Centre Hamilton, ON	No conflict of interest declared
Bill Evans Medical Oncologist		No conflict of interest declared

Table A1-3: Expert Panel Members

Name	Affiliation	Conflict of Interest
Murray Allen Plastic Surgeon	Ottawa Hospital Ottawa, ON	Has received fee for service OHIP and administrative stipend university and hospital; has an extensive practice in skin cancer but has not been trained in or practices MMS; refers and accept referrals from a Mohs surgeon
Tara Baetz Medical Oncologist	Cancer Centre of Southeastern Ontario Kingston, ON	No conflict of interest declared
Elizabeth Barnes Radiation Oncologist	Sunnybrook Health Sciences Centre Toronto, ON	No conflict of interest declared
Salvatore (Sam) Cammisuli Dermatologist	Oshawa, ON	No conflict of interest declared
Pablo Cano Medical Oncologist	Sudbury Regional Hospital Sudbury, ON	No conflict of interest declared
Charles Catton Radiation Oncologist	Princess Margaret Hospital Toronto, ON	Chair of the CCO Provincial Sarcoma Services Oversight Committee
An-Wen Chan Dermatologist Mohs Surgeon	Women's College Hospital Toronto, ON	No conflict of interest declared
Alexandra Easson Surgeon	Princess Margaret Hospital Toronto, ON	No conflict of interest declared
Danny Ghazarian Pathologist	Toronto General Hospital Toronto, ON	No conflict of interest declared
Caroline Hamm Medical Oncologist	Windsor Regional Cancer Centre Windsor, ON	No conflict of interest declared
Barbara Heller Surgeon	St. Joseph's Healthcare Hamilton, ON	No conflict of interest declared
Jadranka Jambrosic Dermatologist/Pathologist	Toronto, ON	No conflict of interest declared

Jillian Macdonald Dermatologist Mohs Surgeon	Ottawa, ON	No conflict of interest declared
David McCready Surgeon	Princess Margaret Hospital Toronto, ON	No conflict of interest declared
Sudha Rajagopal Medical Oncologist	Credit Valley Hospital Mississauga, ON	No conflict of interest declared
Kathryn Roth Head and Neck Surgeon	London Regional Cancer Program London, ON	Employed as Kathryn Roth Medicine Professional Corporation through London Health Sciences Centre, St. Joseph's Hospital, Western University; paid in part as fee-for-service through OHIP for skin cancer excisions and use of frozen section margins where appropriate, no Moh's surgery offered; received $5000 or more from Hoffmann-La Roche Ltd for speaking, travel, educational grant for my department; approximately 60% of my clinical practice is skin cancer related; received educational grant from Hoffmann-La Roche Ltd, and Merck for support of Residents' Research Day for the Department of Otolaryngology - Head & Neck Surgery, Western University; received $5000 or more in educational grants in my role as the CPD director for our department
Xinni Song Medical Oncologist	Ottawa Hospital Ottawa, ON	No conflict of interest declared
John Toye Plastic Surgeon	Orillia, ON	No conflict of interest declared
Alexander Sun Radiation Oncologist	Princess Margaret Hospital Toronto, ON	No conflict of interest declared
Frances Wright Surgeon	Sunnybrook Health Sciences Centre Toronto, ON	Received a grant from Roche for a neoadjuvant melanoma trial

Table A1-4: Targeted Peer Reviewers

Name	Affiliation	Conflict of Interest
Oleh Antonyshyn Plastic Surgeon	Sunnybrook Health Sciences Centre Toronto, ON	No conflict of interest declared
Danny Enepekides Head & Neck Surgeon	Sunnybrook Health Sciences Centre Toronto, ON	No conflict of interest declared
Jensen Yeung Dermatologist	Sunnybrook Health Sciences Centre Toronto, ON	No conflict of interest declared
David Zloty Dermatologist Mohs Surgeon	Vancouver Coastal Health Vancouver, BC	No conflict of interest declared

Appendix 2: Literature Search Strategy

MEDLINE

1 exp Mohs Surgery/
2 Mohs.mp.
3 MMS.mp.
4 (micrographic adj2 surgery).mp.
5 or/1-4
6 exp animals/ not humans/
7 5 not 6
8 limit 7 to english language
9 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
10 8 not 9

EMBASE

1 exp Mohs Surgery/
2 Mohs.mp.
3 MMS.mp.
4 (micrographic adj2 surgery).mp.
5 or/1-4
6 exp animals/ not humans/
7 5 not 6
8 limit 7 to english language
9 (editorial or note or letter or short survey).pt. or letter/
10 8 not 9

A research question of radiation versus wide local excision was added post-hoc to this guideline. The search strategy for this question is below.

MEDLINE

1 (systematic adj (review: or overview:)).mp.
2 (meta-analy: or metaanaly:).mp.
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
7 or/1-6
8 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic:quality).ab.
9 (stud: adj1 select:).ab.
10 (8 or 9) and review.pt.

11 7 or 10
12 (guideline or practice guideline).pt.
13 exp consensus development conference/
14 consensus/
15 (guideline: or recommend: or consensus or standards).ti.
16 or/12-15
17 11 or 16
18 exp Melanoma/
19 melanoma.mp.
20 exp Carcinoma, Basal Cell/
21 (basal adj3 cell adj3 carcino$).mp.
22 exp Carcinoma, Squamous Cell/
23 (squamous adj3 cell adj3 carcino$).mp.
24 exp Carcinoma, Merkel Cell/
25 (Merkel adj3 cell adj3 carcino$).mp.
26 BCC.tw.
27 SCC.tw.
28 MCC.tw.
29 exp Hutchinson's Melanotic Freckle/
30 (lentigo adj maligna).mp.
31 exp Dermatofibrosarcoma/
32 (dermatofibrosarcoma adj protuberans).mp.
33 exp Sebaceous Gland Neoplasms/
34 (sebaceus adj carcinoma).mp.
35 exp Sweat Gland Neoplasms/
36 (microcystic adj adnexal adj carcino$).mp.
37 (atypical adj fibroxanthoma).mp.
38 (eccrine adj carcinoma).mp.
39 exp Paget Disease, Extramammary/
40 (extramammary adj2 Paget$).mp.
41 leiomyosarcoma.mp.
42 (primary adj5 cutaneous adj5 adenocarcino$).mp.
43 or/18-42
44 (wide adj local adj excision).mp.
45 WLE.mp.
46 exp General Surgery/
47 surgery.mp.
48 or/44-47
49 exp Radiotherapy/
50 exp Radiation/
51 radiation.mp.
52 radiotherapy.mp.
53 or/49-52
54 43 and 48 and 53
55 exp animals/ not humans/
56 54 not 55
57 limit 56 to english language
58 (comment or letter or editorial or note or erratum or short survey or news or newspaper article or case report or historical article).pt.
59 57 not 58

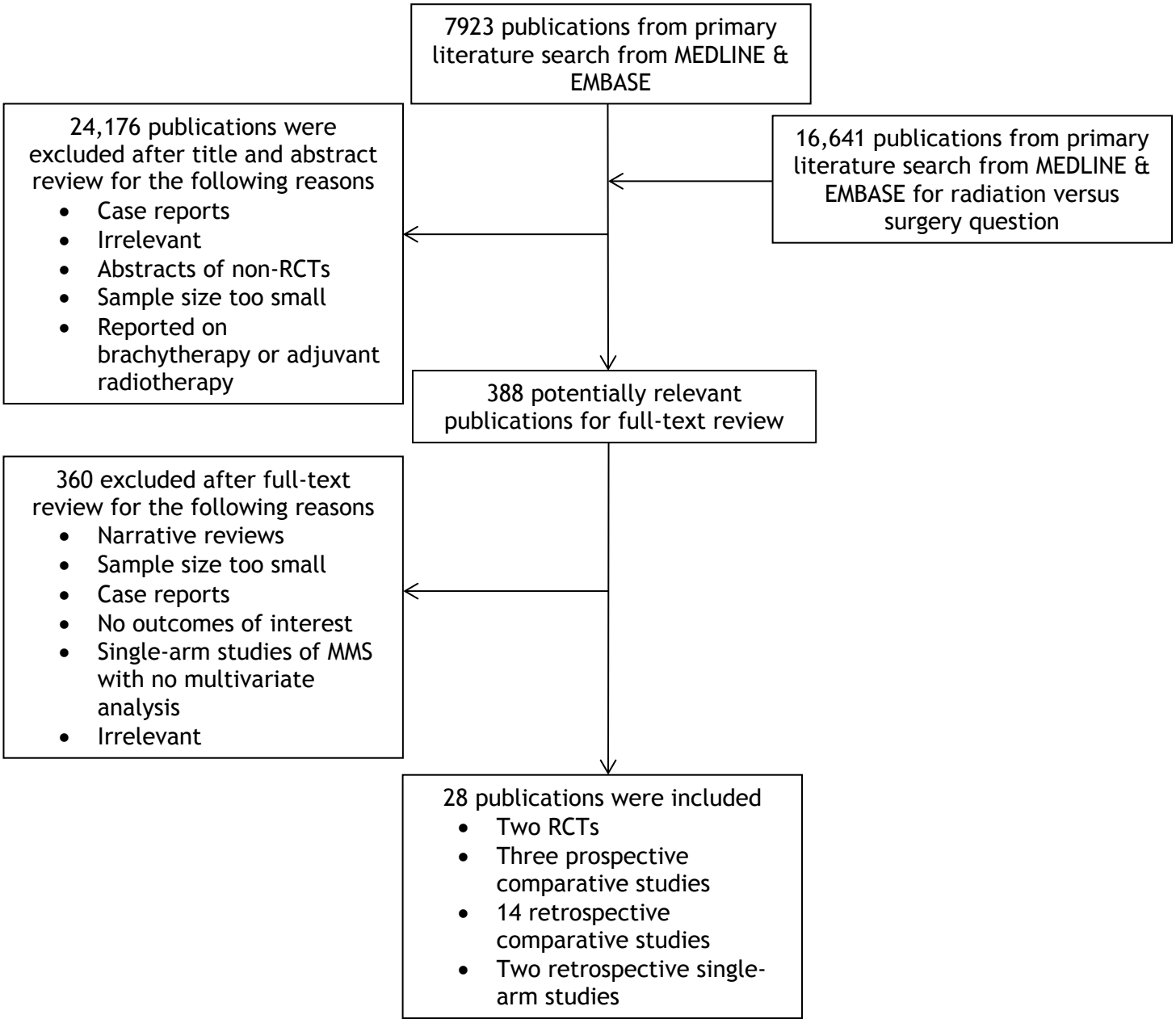
60 59 not 17
61 limit 60 to yr=1990-2016

EMBASE

1 (systematic adj (review: or overview:)).mp.
2 (meta-analy: or metaanaly:).mp.
3 (pooled analy: or statistical pooling or mathematical pooling or statistical summar: or mathematical summar: or quantitative synthes?s or quantitative overview:).mp.
4 (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
5 (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinhal or cinahl or science citation index or scisearch or bids or sigle or cancerlit or pubmed or pub-med or medline or med-line).ab.
6 (reference list: or bibliograph: or hand-search: or handsearch: or relevant journal: or manual search:).ab.
7 or/1-6
8 (selection criteria or data extract: or quality assess: or jadad score or jadad scale or methodologic:quality).ab.
9 (stud: adj1 select:).ab.
10 (8 or 9) and review.pt.
11 7 or 10
12 consensus development conference/
13 practice guideline/
14 *consensus development/ or *consensus/
15 *standard/
16 (guideline: or recommend: or consensus or standards).kw.
17 (guideline: or recommend: or consensus or standards).ti.
18 or/12-17
19 11 or 18
20 exp Melanoma/
21 melanoma.mp.
22 exp basal cell carcinoma/
23 (basal adj3 cell adj3 carcino$).mp.
24 exp squamous cell carcinoma/
25 (squamous adj3 cell adj3 carcino$).mp.
26 exp Merkel cell tumour/
27 (Merkel adj3 cell adj3 carcino$).mp.
28 BCC.tw.
29 SCC.tw.
30 MCC.tw.
31 exp malignant lentigo/
32 (lentigo adj maligna).mp.
33 exp dermatofibrosarcoma/
34 (dermatofibrosarcoma adj protuberans).mp.
35 exp sebaceous carcinoma/
36 (sebaceous adj carcinoma).mp.
37 exp sweat gland carcinoma/
38 (microcystic adj adnexal adj carcino$).mp.
39 exp fibroxanthoma/
40 (atypical adj fibroxanthoma).mp.

41 (eccrine adj carcinoma).mp.
42 exp Paget skin disease/
43 (extramammary adj2 Paget$).mp.
44 exp leiomyosarcoma/
45 leiomyosarcoma.mp.
46 (primary adj5 cutaneous adj5 adenocarcino$).mp.
47 or/20-46
48 exp Wide Excision/
49 (wide adj local adj excision).mp.
50 WLE.mp.
51 surgery.mp.
52 or/48-51
53 exp Radiotherapy/
54 exp Radiation/
55 radiation.mp.
56 radiotherapy.mp.
57 or/53-56
58 47 and 52 and 57
59 58 not 19
60 exp animals/ not humans/
61 59 not 60
62 limit 61 to english language
63 (editorial or note or letter or short survey).pt. or abstract report/ or letter/ or case study/
64 62 not 63
65 limit 64 to yr=1990-2016

Appendix 3: PRISMA Flow Diagram



Appendix 4: Quality Assessment of Randomized Controlled Trials

Table A4-1: Quality Assessment of Randomized Controlled Trials

Study	Allocation concealment	Randomization method	Primary outcome	Statistical power and required sample size	Blinding	ITT analysis	Loss to follow-up (# of pts)	Free of selective outcome reporting	Industry funding	Terminated early
Smeets NWJ (2004) [4] Mosterd K (2008) [6] Van loo E (2014) [8] Essers B (2007) [5]	Yes	A computer programme (Sampsize 2.0) randomly assigned patients to each group.	Recurrence rate	90% power to detect a 6.5% difference in RR of primary BCC (MMS 1.5% vs. SE 8.0%) and a 13.5% difference in RR of recurrent BCC (MMS 3.5% vs. SE 17.0%), one sided α= 0.05; 408 pts with primary and 204 pts with recurrent tumours were needed	No	No	205 tumours lost to follow-up at 5 years and 380 tumours lost to follow-up at 10 years.	No	No	No
Muller FM (2009) [7]	Yes	Opaque sealed envelopes containing the word “Mohs” or “Standard” written on a piece of paper were mixed together and an envelope was picked after a patient had given informed consent to the study.	Size of the defect	90% power to detect a significant difference of 10% in diameters, two sided α= 0.05; 80 patients needed Using the same assumptions, with 30 patients, we could see a 20% difference	No	Yes	No	No	No	Yes, because the predetermined stopping rule was met (i.e., the mean defect diameter in one group was greater than 1.5 times that in the other group)

Abbreviations: BCC, basal cell carcinoma; ITT, intention to treat; MMS, Mohs micrographic surgery; pts, patients; RR, relative risk; SE, surgical excision

Appendix 5: Evaluation of Non-Randomized Comparative Studies using Cochrane's ROBINS-I

Table A5-1: Evaluation of included non-randomized comparative studies using Cochrane's ROBINS-I

Study	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall
Ang GC (2009) [17]	Serious	Low	Low	Low	Low	Low	Low	Serious
Babington S (2003) [2]	Moderate	Low	Low	Low	Low	Low	Low	Low
Bordeaux JS (2016) [26]	Serious	Low	Low	Low	Low	Low	Low	Serious
Chin-Lenn L (2013) [19]	Serious	Low	Low	Low	Moderate	Low	Low	Serious
Chren MM (2004) [28]	Serious	Low	Low	Low	Low	Low	Low	Serious
Cook Jr. BE (1999) [10]	Moderate	Low	Low	Low	Low	Low	Low	Low
de Visscher J (1999) [1]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Hansen JP (2008) [31]	Moderate	Low	Low	Low	Low	Low	Low	Low
Hou JL (2014) [18]	Serious	Low	Low	Low	Low	Low	Low	Serious
Jebodhsingh KN [32]	Serious	Low	Low	Low	Low	Low	Low	Serious
Lowe GC (2016) [15]	Serious	Low	Low	Low	Low	Low	Low	Serious
Nosrati A (2017) [20]	Moderate	Low	Low	Low	Low	Low	Low	Moderate
O'Neill J (2014) [30]	Moderate	Low	Low	Low	Low	Low	Low	Moderate

Paradisi A (2008) [14]	Serious	Low	Low	Low	Low	Low	Low	Serious
Sarachev E (2001) [3]	Moderate	Moderate	Low	Low	Low	Low	Low	Moderate
van der Eerden PA (2010) [11]	Serious	Low	Low	Low	Low	Low	Low	Serious
Veronese F (2017) [16]	Moderate	Low	Low	Low	Low	Low	Low	Low

Abbreviations: ROBINS-I, Cochrane Risk Of Bias In Non-randomized Studies of Interventions