CancerCare Manitoba
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Practice Guideline: Disease Management

Consensus Recommendations for Management of Malignant Melanoma

Effective Date: June 2016

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes in terms of survival and quality of life through the development, dissemination, implementation and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This practice guideline was created through the efforts of a large interdisciplinary group from CCMB in collaboration with community partners. Members of the CCMB Skin Cancer Disease Site Group (DSG), including dermatologists, plastic surgeons, surgical oncologists, medical oncologists and radiation oncologists, have participated in its development.

The Skin Cancer DSG will review and update this document every three years, unless emerging evidence from scientific research, or practice issues requiring urgent resolution dictate a need for immediate change in content.

Purpose

This document is intended as a guide to facilitate a common approach to the clinical management of malignant melanoma.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers and dieticians at CCMB, and Community Oncology Program sites (Community Cancer Program Network (CCPN) sites, Uniting Primary Care and Oncology (UPCON) clinics and WRHA Community Oncology Program sites).

Disclaimer

This guideline document should be viewed as an evidence-based practice tool, and as such, it does not represent an exhaustive text on the subject of malignant melanoma. Clinicians are advised to use it in their practice concomitantly with information from other evidence-based sources.

Use of this guideline in the clinical setting should not preclude use of the practitioner's independent clinical judgment, nor should it replace consultation with the appropriate oncology specialist when indicated (example: medical oncologist, radiation oncologist, family practitioner in oncology (FPO), nurse practitioner/clinical nurse specialist, pharmacist, psychosocial oncology professional and dietician).

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under his/her care, and ideally this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

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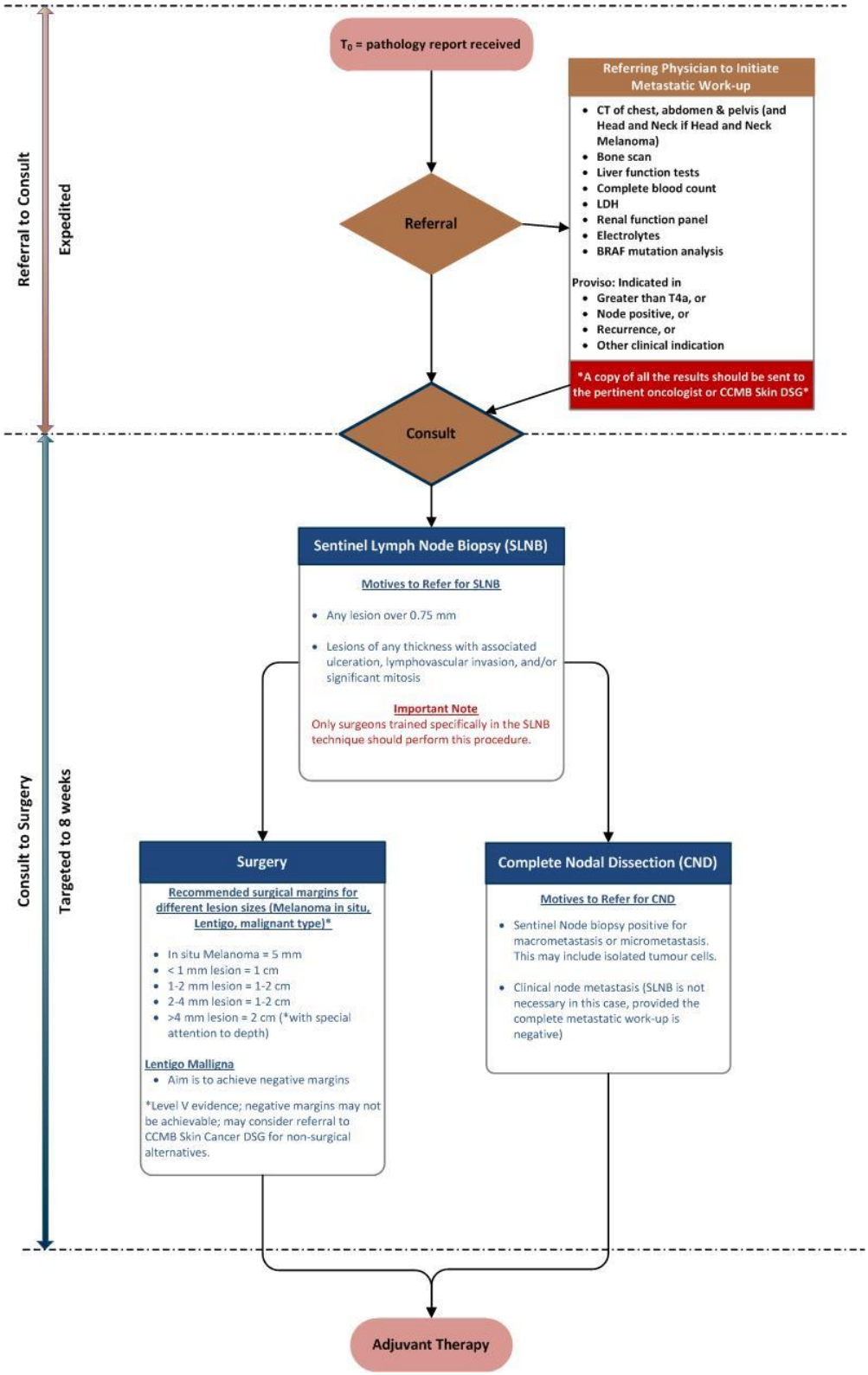

Guideline Recommendations

1. i) *Time from initial referral to CancerCare consult* will be expedited, with the caveat that select patients may require pre-planning before any procedure can be done.
   ii) *Time from CancerCare consult to surgery* will be targeted to 8 weeks; this however is only true for local procedures and sentinel node biopsies.

   Note: T_0 is the time when the pathology report is received.

2. Patients should be allocated to the respective surgeons, based on the site of the lesion.

3. Referral to the surgical oncology team for Sentinel Lymph Node Biopsy (SLNB) consideration should be made for:
   a. Any lesion over 0.75 mm
   b. Lesions of any thickness with associated ulceration, lymphovascular invasion, and/or significant mitosis

4. Only surgeons trained specifically in the SLNB technique should perform this procedure.

5. Patients should be referred for Complete Nodal Dissection (CND) when:
   a. A sentinel node biopsy is positive for macrometastasis or micrometastasis. Consideration given to isolated tumour cells
   b. There is clinical nodal metastasis (SLNB is not necessary in this case, provided the complete metastatic work up is negative)

6. Specific surgical (clinical) circumferential margin goals should be achieved *(See Section VI for details)*

   Note: Lentigo maligna should aim to achieve negative margins.

7. i) *BRAF* mutation analysis of the pathology specimen should be considered for thick primary and node positive tumours.

   ii) *CKIT* mutation analysis should be considered for ocular and mucosal melanomas.

8. Metastatic work-up should be ordered by the referring physician, when referring patients for systemic therapy. It does not need to be completed before referral, only initiated. Metastatic work-up includes:
   a. CT of Chest, Abdomen and Pelvis (CT or Head and Neck if Head and Neck Melanoma)
   b. Bone scan
   c. Liver function tests
   d. CBC
   e. Lactate dehydrogenase (LDH)
   f. Renal function panel
   g. Electrolytes
   h. *BRAF* mutation analysis

   Provisio: Indicated in
   - Greater than T4a, or
   - Node positive, or
   - Recurrence, or
   - Other clinical indication

CancerCare Manitoba

Disease Management Recommendations

Consensus Recommendations for Management of Malignant Melanoma

I. Introduction

Melanoma is a skin cancer that arises from the malignant transformation of melanocytes. Melanoma accounts for only 4-5% of all skin cancers but has the highest death rate amongst skin cancers. The incidence of melanoma is rising faster than any other malignancy. The median age of diagnosis is 45-55 years, with males and Caucasians making up the majority of cases. The estimated incidence of melanoma in 2011 was 5,500 new cases nationally and 160 cases provincially. Estimated mortality rates for 2011 were 950 patients nationally and 30 patients provincially.[1] The graph below illustrates that while incidence is increasing, mortality rates remain steady in Manitoba.[2]

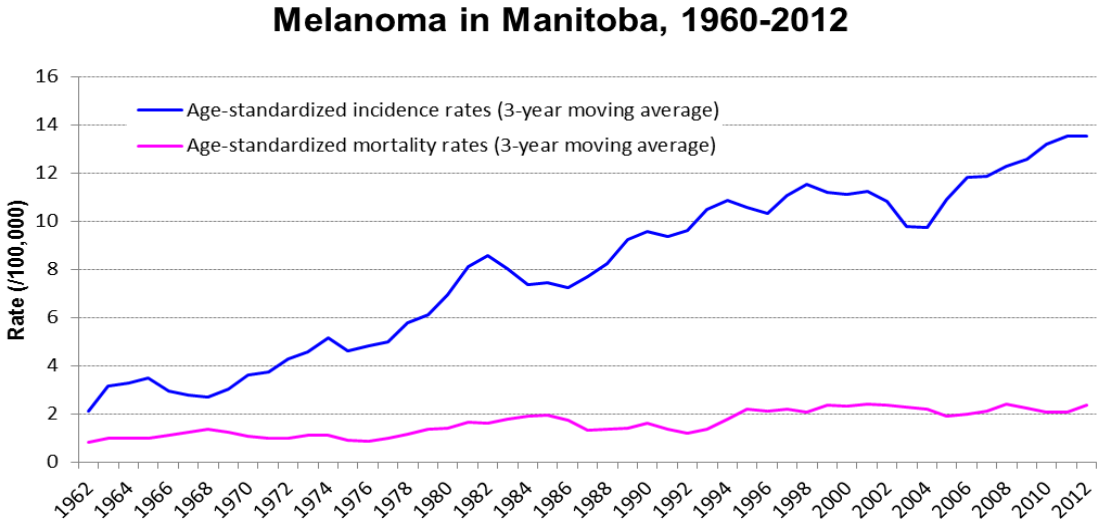

Figure 1. Age-standardized incidence and mortality rates of melanoma in Manitoba from 1960 to 2012.[2]

References

1. Canadian Cancer Society's Steering Committee on Cancer Statistics, *Canadian Cancer Statistics 2011,* Toronto, ON: Canadian Cancer Society; 2011.
2. Manitoba Cancer Registry, personal communication, May 12, 2015.

II. Scope of Guideline

Aim and Purpose

Development of this guideline was undertaken for the purpose of knowledge translation of the current standards in practice for treatment of melanoma in Manitoba. The overall aim of the development is to improve the standard of care received by this patient population, through application of evidence-based interventions and promotion of best practices.

Clinical Questions
What is the acceptable time interval from referral to surgical management?
Which patients are candidates for sentinel lymph node biopsy?
Who is to perform the surgery based on anatomic location?
What are acceptable surgical margins?
What patient imaging and/or laboratory work-up should be done?
Which patients should be referred to medical oncology?
Which patients should be referred to radiation oncology?

Consensus Panel

Consensus Panel	
Oncology Subspecialties CancerCare Manitoba/University of Manitoba	1 Dermatologist, Skin Cancer DSG Chair 1 Medical Oncologist, Skin Cancer DSG 1 Radiation Oncologist, Skin Cancer DSG 4 Surgical Oncologists, Skin Cancer DSG
Surgery University of Manitoba	2 Plastic Surgeons

Patient Population and Healthcare Setting

The recommendations in this guideline are applicable to the care of adult (18 years or older; male or female) patients with malignant melanoma. These recommendations are intended for use in both inpatient and outpatient settings.

End-Users

This guideline is written for use by clinicians providing care for the above mentioned patient population. Intended primarily for use by medical clinicians, the guideline may be of interest to trainees, allied healthcare staff, healthcare administrators, policy-makers and possibly members of the general public.

III. Guideline Methodology

Clinical Research Question Development

The Skin Cancer DSG chair and one other physician selected topics with the guiding factor being effect on outcome.

2012 Meeting Format and Consensus Process

A meeting was held in February 2012 in Winnipeg, Manitoba. Invitees were physicians playing key roles in the management of malignant melanoma, including surgeons, medical oncologists and radiation oncologists. The evidence was presented and discussion on each topic followed. Consensus was obtained by a show of hands among attendees.

Literature Search

An extensive literature search was undertaken in 2012 for articles pertaining to the chosen topics. One trial by Morton et al., a retrospective analysis conducted by Leiter et al. and one guideline from the European Dermatology Forum form the basis of the recommendations in this guideline, along with supplemental material providing critique and additional evidence. [1,2,3]

As guidelines are considered 'living' documents and must be kept abreast of the evidence, an updated literature search was performed in 2015. PubMed was systematically searched for clinical practice guidelines and relevant primary literature. Searches were limited to human studies, English language and published within the past 3 years. An updated version of the guideline from the European Dermatology Forum was identified, with the updates corroborating the recommendations stated in this guideline. [4]

Internal and External Review

Internal and external peer review were pursued, the results of which are appended to these guidelines. The internal review process was consensus-based and completed by the working group. An external review was conducted by a dermatologist from the BC Cancer Agency, a family physician in oncology from CancerCare Manitoba, a family physician in oncology from Western Manitoba Cancer Centre, and a surgical oncologist from Tom Baker Cancer Centre in Alberta. All reviewers completed a full review of the guideline document and submitted a standardized practitioner feedback survey (adapted from Brouwers and colleagues).[5] Feedback was reviewed and discussed by the working group. Decisions to incorporate any changes into the guideline were consensus-based (acceptance, rejection, or acceptance with modifications).

Maintenance

At CancerCare Manitoba clinical practice guidelines are considered 'living' documents which require ongoing evaluation, review and update. Re-evaluation of this guideline is planned for 2018. The working group will revise and update the document as needed, with any critical new evidence brought forward before this scheduled review.

References

1. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med*2006;355(13):1307-17.
2. Leiter U, Buettner P, Bohnenberger K, et al. Sentinel lymph node dissection in primary melanoma reduces subsequent regional lymph node metastasis as well as distant metastasis after nodal involvement. *Ann Surg Oncol* 2010;17(1):129-37.
3. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma: European consensus-based interdisciplinary guideline. *Eur J Cancer* 2010;46(2):270-83.
4. Garbe C, Peris K, Hauschild A, et al. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline – update 2012. *Eur J Cancer* 2012;48(15):2375-90.
5. Brouwers MC, Graham ID, Hanna SE, et al. Clinicians' assessments of practice guidelines in oncology: the CAPGO survey. *Int J Technol Assess Health Care* 2004;20(4):421-6.

IV. Acceptable Time Intervals and Appropriate Surgical Clinics

Efforts were made to streamline the care of patients with melanoma.

Recommendations

Consensus was reached on the following items:

i. *Time from initial referral to CancerCare consult* will be expedited, with the caveat that select patients may require preplanning before any procedure can be done.

ii. *Time from CancerCare consult to surgery* will be targeted to 8 weeks; this however, is only true for local procedures and sentinel node biopsies.

Note: T_0 is the time when the pathology report is received.

Consensus was reached to allocate patients to surgeons based on the site of the melanoma:

Plastic Surgeons - face, scalp, hands, fingers, feet, toes and difficult cosmetic reconstructions

Head and Neck Surgeons – head, neck, mucosal*

Surgical Oncology – trunk, extremity, perianal, anal*

Gyne-Oncology – vulva

Uro-Oncology – penis, scrotum

***Note:** Including invasive melanomas requiring sentinel node biopsies

V. Sentinel Lymph Node Biopsy and Complete Nodal Dissection

A. Sentinel Lymph Node Biopsy

The rationale behind pursuing sentinel lymph node biopsy (SLNB) is that although no survival advantage has been demonstrated, it may provide therapeutic information, allow eligibility of patients for clinical trials, and most significantly it provides prognostic information. Due to its inherent prognostic value, a lesion greater than 4 mm in size does not require SLNB. The recommendations below are based on consensus of the expert working group.

Recommendations

The question of referral for SLNB requires the understanding that one qualifier alone does not necessarily warrant SLNB. Likewise, lack of qualifiers does not necessarily exclude SLNB. Instead it is the contribution of these factors to the overall patient picture that is important, thus **all patients should be reviewed by the Skin Cancer surgical oncology team for consideration.**

1. Referral to the surgical oncology team for SLNB consideration should be made for:
    a. Any lesion over 0.75 mm
    b. Lesions of any thickness with associated ulceration, lymphovascular invasion, and/or significant mitosis
2. Only surgeons trained specifically in the SLNB technique should perform this procedure.

B. Complete Nodal Dissection

Currently, Complete Nodal Dissection (CND) is the standard of care after a positive SLNB or if there is clinical nodal metastases. Like SLNB, the survival advantage of this procedure is unknown if the dissection is of a clinically normal nodal basin after a positive SLNB; however it has been shown to improve local regional disease control.

Recommendations

Patients should be referred for CND when:

a. A sentinel node biopsy is positive for macrometastasis or micrometastasis. Consideration given to isolated tumour cells.

b. There is clinical nodal metastasis.

Table 1. Multi-Centre Selective Lymphadenectomy Trial[1]

5-year Survival Data	Group 1	Group 2	HR (95% CI)	P-value
Melanoma specific survival	86.6% Observation Group	87.1% SLNB Group	0.92 (0.67-1.25)	p = 0.58
Disease free survival	73.1% Observation Group	78.3% SLNB Group	0.74 (0.59-0.93)	p = 0.009
Disease free survival	53.4% SLN Positive Group	83.2% SLN Negative Group	NR	p < 0.001
Melanoma specific survival	72.3% SLN Positive Group	90.2% SLN Negative Group	NR	p < 0.001
5 year survival	52.4% Observation Group with recurrence	72.3% SLN Positive Group with CLND	0.51 (0.32-0.81)	p = 0.004

Abbreviations: CI, confidence interval; CLND, clinically detected nodal relapse; HR, hazard ratio; NR, not reported; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy

Table 2. Retrospective Analysis[2]

Disease free survival	SLND 76.9% (95% CI, 72.6-81.2)	Non-SLND 67.8% (95% CI, 63.1-72.5)	p = 0.003
Overall survival within SLND group	SLN positive 64.9% (95% CI, 50.8-79)	SLN negative 88.4% (CI, 85.5-91.9)	p < 0.001
Overall 5-year survival for patients with recurrence	SLND 52.9% (95% CI, 38.0-67.8)	Non-SLND 42% (95% CI, 29.1-55.0)	p = 0.196
Hazard analysis	SLN positive patient is 3.4 times more likely to die from the melanoma (95% CI, 1.8-6.4)		p < 0.001
Multivariate Cox analysis	Non-SLND group patients with recurrence had significantly increased risk of death, RR 2.2 (95% CI, 1.2-3.8)		p = 0.009

Abbreviations: CI, confidence interval; RR, relative risk; SLN, sentinel lymph node; SLND, sentinel lymph node dissection

References

1. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. *N Engl J Med* 2006;355(13):1307-17.
2. Leiter U, Buettner P, Bohnenberger K, et al. Sentinel lymph node dissection in primary melanoma reduces subsequent regional lymph node metastasis as well as distant metastasis after nodal involvement. *Ann Surg Oncol* 2010;17(1):129-37.

VI. Surgical Margins and Lentigo Maligna

Recommendations

In an effort to establish standard goals in regards to surgical (clinical) margins consensus was reached on the following:

Table 3. Surgical Margins

Lesion Size	Margin Size
In Situ Melanoma	5 mm (when achievable)
< 1 mm	1 cm
1-2 mm	1-2 cm
2-4 mm	1-2 cm
> 4 mm	2 cm with special attention to depth

Margins are extended to the fascia, but not inclusive (unless fascia is clinically involved).
Lentigo maligna is a special case in regards to margins.

It is important to note that one cannot accurately infer a clinical margin from a pathological margin.

In regards to lentigo maligna, the aim is to achieve negative margins. There is no evidence to support stringent quantitative resection margins for lentigo maligna. As such, pathology reporting should not dictate clinical management.

VII. Tumour Markers

Recommendations

i) *BRAF* mutation analysis of the pathology specimen should be considered for thick primary and node positive tumours.

ii) *CKIT* mutation analysis should be considered for ocular and mucosal melanomas.

VIII. Adjuvant Therapy

Recommendations

A metastatic work-up should be ordered by the referring physician when referring patients for systemic therapy. It does not need to be completed before referral, only initiated.

The Metastatic Work-Up Includes:	
CT of Chest, Abdomen and Pelvis (CT of Head and Neck if Head and Neck Melanoma)	Lactate Dehydrogenase (LDH)
Bone Scan	Renal Function Panel
Liver Function Tests	Electrolytes
Complete Blood Count	BRAF mutation analysis

Note: CT orders should include a time to be done by. A copy of all results should be sent to the pertinent oncologist or CancerCare Manitoba Skin Cancer DSG.

A. Medical Oncology Role

Medical Oncology May Consider Seeing the Following Patients:
≥ T3b (2-4 mm lesion with ulceration)
N +
Metastatic +

B. Radiation Oncology Role

Radiation oncology may see the following *Melanoma in situ* patients:	
Incomplete resections	Poor surgical candidates
Close or involved margins (if surgical options exhausted)	

Radiation oncology may see the following patients:	
Nodal Involvement: ≥ 2 nodes for truncal and extremity, ≥ 1 node for head and neck	
Nodal Size > 3 cm	Extracapsular extension
Residual disease in nodal basin	Recurrent resected

Radiation oncology may provide palliative therapy for:	
Satellite/in-transit metastases*	Any symptomatic metastases
Inoperable mucosal melanoma	Brain metastases referral to Gamma Knife†

*Consider referral to surgical oncology for possible intralesional therapy

†Referral to HSC Gamma Knife

IX. Implementation and Dissemination

The value of guidelines truly lies in their implementation and use. For that purpose, consideration was given to implementation tools during the drafting of this guideline document. Several tools emerged:

CancerCare Resources

It was recognized that resources would be needed to distribute these guidelines to the community. For that purpose, the guideline will be accessible online through the CancerCare Manitoba website. Online availability will be preceded by an e-blast notification with the website embedded. Announcement of the guideline and updates will be through established communication channels provincially; through the Community Oncology Program to CCPN sites, UPCON clinics and WRHA Community Oncology Program sites. This guideline will also be provided to partner organizations and guideline reviewers in other provinces. Use of the guideline in clinic will be through the online version.

Presentation of the guideline's recommendations will be made available at rounds and conferences; Skin Cancer DSG case conference rounds, CCMB Hematology/Oncology Regional Grand rounds, Allied Health rounds (Patient Services Rounds), CCPN Community Cancer Care annual educational conference and at UPCON education and training events.

Clinical Implementation

At CancerCare Manitoba a central triage agent has been established to distribute patients to the appropriate surgical clinics based on the site of the melanoma.

A template consult sheet will be created to include information on patient demographics, location of the lesion, size and depth, and type of excision.

X. Contact Physicians and Contributors

Contact Physicians

Dr. Marni Wiseman
Dermatologist, CancerCare Manitoba

Contributors

Dr. Marni Wiseman (Committee Chair and Meeting Moderator)	Dr. Alok Pathak
Dr. Tom Hayakawa	Dr. Leif Sigurdson
Dr. Pamela Hebbard	Dr. Debrah Wirtzfeld
Dr. Ahmet Leylek	Dr. Ralph Wong
Dr. Ethel MacIntosh	Dr. Brent Zabolotny
Dr. Debjani Grenier	Dr. Justin Rivard
Dr. Arbind Dubey	

External Reviewers

Dr. Vincent Ho
Dermatologist, BC Cancer Agency

Dr. Mark Kristjanson
Family Physician in Oncology, CancerCare Manitoba

Dr. Erika Möeller
Family Physician in Oncology, Western Manitoba Cancer Centre

Dr. Greg McKinnon
Surgical Oncologist, Tom Baker Cancer Centre

Approved By

Dr. Vallerie Gordon, Medical Oncologist
Medical Director, CCMB Clinical Practice Guidelines Initiative

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XI. Conflicts of Interest

In accordance with the CCMB policy no. 01.001, “Conflict of Interest”, the authors of this guideline declare that no commercial support was received during the development of this guideline.

CancerCare Manitoba
675 McDermot Avenue
Winnipeg, Manitoba, Canada
R3E 0V9
www.cancercare.mb.ca

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