ADJUVANT RADIATION
FOR MALIGNANT MELANOMA

Effective Date: February 2014

The recommendations contained in this guideline are a consensus of the Alberta Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.
BACKGROUND

The role of adjuvant radiation therapy in the management of melanoma remains unclear. It should rarely be employed for definitive treatment of a primary melanoma site. The main role of adjuvant radiation is the treatment of the nodal basin after resection of regionally advanced melanoma. Several non-randomized studies have suggested that postoperative radiation to the neck or axilla after radical lymph node dissection decreases regional recurrence rates in node-positive patients.\(^1\text{-}^3\)

Until larger randomized trials are conducted, it is reasonable to consider postoperative radiation therapy in patients with gross extra-capsular extension or multiple involved lymph nodes.\(^4\)

GUIDELINE QUESTION

- Should adjuvant radiation therapy be offered to patients with early stage melanoma who have been rendered disease-free following the resection of cutaneous melanomas and who are at high risk for subsequent recurrence?
- Should adjuvant radiation therapy be offered to patients with advanced stage melanoma?
- Should adjuvant radiation therapy be offered to patients with recurrent melanoma?
- What considerations should be made when treating patients with radiation therapy?

DEVELOPMENT PANEL

This guideline was reviewed and endorsed by the Alberta Cutaneous Tumour Team. Members of the Alberta Cutaneous Tumour Team include medical oncologists, radiation oncologists, surgical oncologists, dermatologists, nurses, pathologists, and pharmacists. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the Guideline Utilization Resource Unit Handbook.

SEARCH STRATEGY

The MEDLINE (1966 through January 2011), CINAHL, Cochrane, ASCO Abstracts and proceedings, and CANCERLIT databases were searched. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. Search terms included: radiation or adjuvant radiation and malignant melanoma.

PubMed was again searched in 2013 for evidence on radiation therapy in cutaneous melanoma. The search term "melanoma" was used and results were limited to clinical trials, published between January 2012 and January 2013. Citations were hand-searched for studies pertaining to radiation therapy, resulting in one new phase III clinical trial. Updates to the National Comprehensive Cancer Network guideline (2013) on melanoma were cross referenced with this guideline as well. Following a review of the evidence by the Alberta Cutaneous Tumour Team, no changes to the recommendations were made.

Using the same search strategy, two relevant articles published between January 2013 and January 2014 were identified during the 2014 update. Following a review of the evidence by the Alberta Cutaneous Tumour Team, no changes were made to the recommendations.
TARGET POPULATION

The recommendations outlined in this guideline apply to adults over the age of 18 years with malignant melanoma. Different principles may apply to pediatric patients.

RECOMMENDATIONS

- Most patients with in-situ or early-stage melanoma (Stage 0; Stage 1A/B; Stage II, 1 mm thick with ulceration or Clark level IV, V or > 1 mm thick, any characteristic; and Stage III, sentinel node positive):
  - There is no recommendation for the use of adjuvant radiation therapy, as most of these patients will be cured by primary excision alone.  
  - Post-operative radiotherapy may be used after close or positive margins where further excision is not practical or possible, inoperative lentigo maligna, rapid or multiple recurrences or extensive perineural spread (as seen with Desmoplastic melanoma).
- Patients with Stage IIIC or Stage IV disease should be referred for the consideration of adjuvant radiation therapy to improve local and regional control of their disease.  
  - Stage IIIC with multiple nodes involved or extranodal extension: consider radiation therapy to nodal basin  
  - Stage III in transit: consider radiation therapy  
  - Stage IV Metastatic: if disseminated (unresectable) with brain metastases, consider radiation for symptomatic patients
- Consider the following for patients with recurrence: 
  - Recurrence (true local scar): base treatment on stage of recurrence  
  - Recurrence (local, satellitosis, and/or in-transit): consider radiation therapy  
  - Recurrence (nodal): consider adjuvant radiation therapy  
  - Recurrence (distant): if disseminated (unresectable) with brain metastases, consider radiation for symptomatic patients
- If Interferon is to be part of the treatment regimen:
  - Radiation should not be given concurrently.  
  - Interferon may act as a radiosensitizer, and patients receiving both may experience increased toxicities.  
  - Radiation therapy may be delayed until completion of the induction phase of interferon administration.

DISCUSSION

Surgery is the primary treatment of patients with stage I-III melanoma. However, high recurrence rates have prompted attempts to develop effective adjuvant therapies after primary local and regional surgical interventions.

Primary indications for consideration of adjuvant radiation include nodal extracapsular extension (ECE), large lymph node size, multiple lymph nodes involved with metastatic disease, and recurrent disease after prior nodal surgery. Regional recurrence rates after surgical dissection alone when any one of these features is present range from 30-50%, although higher rates have been reported.  

Additional high-risk
features include macroscopic nodal disease, positive margins and head and neck lymph node location and consideration for patients with positive nodal disease who refuse dissection.\textsuperscript{15-18}

A retrospective study by Ballo and colleagues involving 160 patients who had surgery followed by radiotherapy (30 Gy in 6 Gy fractions two times per week) revealed 10-year actuarial local, regional, and locoregional control rates of 94%, 94%, and 91%, respectively, and 10-year actuarial disease-specific, disease-free, and distant metastasis-free survival rates of 48%, 42%, and 43%, respectively.\textsuperscript{19,20} Similar control rates and survival rates have been reported from more recent retrospective studies.\textsuperscript{21-26} Strojan, et al. (2010) published retrospective data showing significant improvements in regional control at two years with the use of adjuvant radiotherapy (60 Gy in 2 Gy fractions five times per week) as compared to surgery alone (78 vs. 56%; P=.015) among patients with regionally advanced melanoma to the neck and/or parotid.\textsuperscript{23} A prospective randomized controlled trial by Agrawal, et al. (2009), among patients with clinically advanced, regional lymph node-metastatic disease (n=615), compared therapeutic lymphadenectomy and adjuvant radiotherapy with surgery alone and demonstrated a reduction in the regional recurrence rate (10.2 vs. 40.6%); furthermore, adjuvant radiotherapy was significantly associated with five-year regional control (P<.0001), distant metastasis-free survival (P=.0006), and disease-specific survival (P<.0001).\textsuperscript{27} A more recent randomized trial compared adjuvant radiotherapy (48 Gy in 20 fractions) with observation, following lymphadenectomy among 217 patients with nodal metastases and a high risk of recurrence (based on number of nodes involved, extranodal spread, and maximum size of involved nodes). After a median follow-up of 40 months, the risk of lymph-node field relapse was found to be significantly reduced in the adjuvant radiotherapy group (20 relapses in RT vs. 34 in observation; HR 0.56, 95% CI 0.32-0.98; p=.041). However, there were no differences in relapse-free survival (70 events vs. 73, HR 0.91, 95% CI 0.65-1.26; p=.56) or overall survival (59 deaths vs. 47, HR 1.37, 95% CI 0.94-2.01; p=.12).\textsuperscript{28} The axillary control rate with adjuvant radiotherapy versus surgery alone has been reported to be as high as 87%. However, the risk of adjacent-field recurrences with the use of radiotherapy (OR 4.27, 95% CI 1.25-14.57; p=0.02) should be considered when planning radiotherapy.\textsuperscript{29}

Current guidance from the National Comprehensive Cancer Network supports the use of adjuvant radiotherapy, based on lower level evidence. The guideline states that adjuvant radiation may be considered in special cases where adequate surgical treatment is not possible, for selected patients with desmoplastic melanoma with extensive neurotrophism, and for patients at significant risk of nodal basin relapse. The suggested regimen is 30-60 Gy (2-6 Gy per fraction) over 2.5-6 weeks.\textsuperscript{30}

**DISSEMINATION**

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

**MAINTENANCE**

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2016. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.
CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

REFERENCES


**APPENDIX**

**AJCC 2009 (7th Edition) Anatomic Stage Groupings for Cutaneous Melanoma**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Clinical Staging</th>
<th>Pathologic Staging</th>
<th>5-year Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis N0 M0</td>
<td>Tis N0 M0</td>
<td>100%</td>
</tr>
<tr>
<td>IA</td>
<td>T1a N0 M0</td>
<td>IA T1a N0 M0</td>
<td>95%</td>
</tr>
<tr>
<td>IB</td>
<td>T1b N0 M0</td>
<td>IB T1b N0 M0</td>
<td>90%</td>
</tr>
<tr>
<td>IIA</td>
<td>T2b T3a N0 M0</td>
<td>II A T2b T3a N0 M0</td>
<td>78%</td>
</tr>
<tr>
<td>IIB</td>
<td>T3b T4a N0 M0</td>
<td>IIB T3b T4a N0 M0</td>
<td>65%</td>
</tr>
<tr>
<td>IIC</td>
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<tr>
<td>III</td>
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<tr>
<td></td>
<td></td>
<td>IIIC T4a N1a T4a N2a</td>
<td>27%</td>
</tr>
<tr>
<td>IV</td>
<td>Any T Any N M1</td>
<td>IV Any T Any N M1</td>
<td>13%</td>
</tr>
</tbody>
</table>

*a* Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention, it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

*b* Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial (i.e., sentinel node biopsy) or complete lymphadenectomy. Pathologic stage 0 or IA patients are the exception; they do not require pathologic evaluation of their lymph nodes.
### AJCC 2009 (7th Edition) TNM Staging Categories for Cutaneous Melanoma 31

<table>
<thead>
<tr>
<th>T</th>
<th>Thickness (mm)</th>
<th>Ulceration Status/Mitoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
| T1  | ≤ 1.00         | a: without ulceration and mitosis < 1/mm²  
|     |                | b: with ulceration or mitoses ≥ 1/mm²     |
| T2  | 1.01-2.00      | a: without ulceration       |
|     |                | b: with ulceration          |
| T3  | 2.01-4.00      | a: without ulceration       |
|     |                | b: with ulceration          |
| T4  | > 4.00         | a: without ulceration       |
|     |                | b: with ulceration          |

<table>
<thead>
<tr>
<th>N</th>
<th>Number of Metastatic Nodes</th>
<th>Nodal Metastatic Burden</th>
</tr>
</thead>
<tbody>
<tr>
<td>N0</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>
| N1  | 1                          | a: micrometastasis^a  
|     |                            | b: macrometastasis^b  
| N2  | 2-3                        | a: micrometastasis^a  
|     |                            | b: macrometastasis^b  
|     |                            | c: in transit metastases/satellites without metastatic nodes |
| N3  | 4+ metastatic nodes, or matted nodes, or in transit metastases/satellites with metastatic nodes |

<table>
<thead>
<tr>
<th>M</th>
<th>Site</th>
<th>Serum LDH (lactate dehydrogenase)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M0</td>
<td>No distant metastases</td>
<td>not applicable</td>
</tr>
<tr>
<td>M1a</td>
<td>Distant skin, subcutaneous or nodal metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1b</td>
<td>Lung metastases</td>
<td>Normal</td>
</tr>
<tr>
<td>M1c</td>
<td>All other visceral metastases</td>
<td>Normal</td>
</tr>
<tr>
<td></td>
<td>Any distant metastases</td>
<td>Elevated</td>
</tr>
</tbody>
</table>

^a Micrometastases are diagnosed after sentinel lymph node biopsy.

^b Macrometastases are defined as clinically detectable nodal metastases confirmed pathologically.