ADJUVANT RADIATION THERAPY
FOR DUCTAL CARCINOMA IN SITU

Effective Date: May 2015

The recommendations contained in this guideline are a consensus of the Alberta Provincial Breast 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

Breast cancer is the most frequently diagnosed type of cancer for women in Alberta. There were 2,333 new cases of breast cancer in Alberta women and 385 deaths due to the disease in 2012, the most recent year for which these data are available. Ductal carcinoma in situ (DCIS) of the breast is a heterogeneous group of proliferative cellular lesions that have the potential to become invasive. DCIS is usually treated by surgically removing the cancer – mastectomy or breast-conserving surgery (BCS). After surgery, radiation therapy (RT) has commonly been recommended for many patients. The purpose of this guideline is to establish a standard of care for radiation, post-surgery for breast cancer patients with DCIS.

GUIDELINE QUESTIONS

- What is the optimal RT treatment after surgery (BCS or mastectomy) for patients with DCIS?
- For patients with DCIS, how should a close radial margin of excision be handled following BCS?

DEVELOPMENT PANEL

The recommendations contained in this guideline were developed by the Alberta Provincial Breast Tumour Team. Members of the Alberta Provincial Breast Tumour Team include medical, radiation and surgical oncologists, as well as nurses, pathologists and pharmacists. Evidence in support of the guidelines was selected and reviewed by a working group from the Tumour Team and a Knowledge Management Specialist from the Guideline Resource Unit. A detailed description of the methodology followed during guideline development can be found in the Guideline Resource Unit Handbook.

This guideline was originally developed in June 2008. This guideline was revised in April 2012, and June 2015.

SEARCH STRATEGY

The original guideline was developed by searching MEDLINE (1966 through April 2008), EMBASE (1980 through April 2008), Cochrane Library, American Society of Clinical Oncology (ASCO) abstracts, and the CANCERLIT database. The search included practice guidelines, systematic reviews, meta-analyses, randomized controlled trials, and clinical trials. The search terms included breast, cancer* OR carcinoma OR tumour*, radiation OR radiotherapy, surgery OR conservation surgery, DCIS OR Ductal carcinoma in Situ.

Subsequent updates to the guideline are the result of deliberations of Alberta radiation oncologists at the 2012 and 2015 Annual Provincial Breast Tumour Team Meetings considering new evidence. A full systematic review of the literature and revamp of the guideline will be conducted in advance of the 2016 Annual Breast Tumour Team Meeting.

TARGET POPULATION

These recommendations apply to adult patients with DCIS who have had BCS or a mastectomy.
RECOMMENDATIONS

For breast cancer patients with DCIS, recommendations are presented in Table 1 for the standard of care for adjuvant RT following surgery.

Table 1  Adjuvant RT for Patients with DCIS

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>BCS</th>
<th>Mastectomy</th>
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<tbody>
<tr>
<td>Adjuvant whole breast radiotherapy (WBRT) recommended</td>
<td></td>
<td>No adjuvant RT recommended, even if resection margins close. Adjuvant RT can be considered when margin positive but benefit not defined</td>
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<tr>
<td>Partial breast RT investigational as part of clinical trial if available</td>
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<tr>
<td>For positive margins (ink on margin), re-excision recommended (close margin at fascia is an exception)</td>
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<tr>
<td>Pathologic/radiologic correlation required with margin width less than 2 mm; re-excision may be considered if there is discordance and based on individual case details</td>
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<tr>
<td>For close margins not treated with re-excision, the role of RT boost is not well defined</td>
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DISCUSSION

In 2014, a multidisciplinary panel of breast experts conducted a meta-analysis of margin width, and determined that a positive margin is a margin with ink on invasive carcinoma or DCIS, whereas a negative margin is a margin with no ink on the tumour, and that no further differentiation is required. If any controversy or uncertainty with regards to margins exists, the patient should be presented at rounds.

In the European Organization for Research and Treatment of Cancer (EORTC) 10853 trial, 1,010 women with DCIS measuring <5 cm were randomized to RT or no RT. At a median follow-up of 10.5 years, the 10-year local relapse-free rate was 74% for patients receiving no further treatment compared with 85% for patients receiving adjuvant RT (hazard ratio [HR], 0.53; 95%, confidence interval [CI], 0.40-0.70, log rank, p<0.0065). At a median follow-up of 10 years, the RT group, relative to the no-further-treatment group, had a reduced risk of invasive recurrence from 8% to 4% (HR=0.58; CI, 0.39-0.86). There were no significant differences in contralateral incidence, distant metastasis, death, or event-free survival.

In the National Surgical Adjuvant Breast Project (NSABP) protocol-B-17 trial, 818 DCIS patients with microscopically clear resection margins after BCS were randomized to RT, 5000 cGy in 25 fractions in five weeks, or observation. At a mean follow-up of 10.7 years, the 12-year cumulative incidence of invasive disease in the ipsilateral breast was reduced from 16.8% to 7.7% with RT (p=0.00001). The rate of non-invasive recurrence was also reduced from 14.6% to 8.0% with RT (p=0.001). There was no significant difference in overall survival for patients treated with BCS alone versus BCS plus RT (86% vs. 87%; relative risk [RR], 0.95; 95% CI, 0.63-1.45; p=0.80). In a separate peer review paper, Fisher et al. reported lower recurrence rates for all nine pathologic characteristics in the radiation group compared to the observed group.
In the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) trial, 1,030 patients were randomized after complete excision of DCIS to two (522 with RT and 502 without RT), and four arms (54% of the RT group received Tamoxifen and 51% in the non-RT group received Tamoxifen). After a median follow-up of 52.6 months, there was a significant decrease in ipsilateral DCIS and invasive disease and no significant difference in contralateral DCIS or invasive disease.

Dose/Fractionation Schedule and Acute Toxicity

The three randomized trials in DCIS used the same dose, fractionation schedule, and 5000 cGy in 25 fractions in five weeks. Whereas the Ontario Clinical Oncology Group (OCOG) trial randomized 1,234 women with invasive disease treated with BCS to a course of 5000 cGy in 25 fractions over five weeks or a course of 4250 cGy in 16 fractions over three weeks. At a median follow-up of 69 months, the five-year local recurrence-free survival was 97.2% in the long arm (absolute difference, 0.4%; 95% CI = -1.5%-2.4%). No difference was detected between arms in terms of disease-free or overall survival rates. The 16 fraction arm had better cosmetic outcome compared to the 25 fraction schedule (76.8% vs. 77.4%, absolute difference, 0.6%; 95% CI, -6.5%-5.5%). However, skin toxicity (Grade II or III) had a non-statistically significant higher incidence in the 16 fraction arm compared to the 25 fraction arm (absolute difference, 6%; 95% CI, -0.3%-10%), but there was no significant difference in the incidence of radiation pneumonitis. Only rib fracture in the 25 fraction arm was reported. This information suggests that the risk of toxicity from the 4250 cGy in 16 fractions protocol has a similar toxicity rate to the 5000cGy in 25 fractions protocol. There is no randomized data using the shorter fraction schedule in DCIS, but the OCOG data has been extrapolated to the DCIS population.

Side effects of radiotherapy

The side effects of modern breast RT are modest including altered pigmentation, breast discomfort, and firmness. The risk of cardiac disease is generally low with modern RT techniques. Several studies report an association between RT and cardiovascular morbidity, including myocardial infarction and congestive heart failure. In addition, a few studies have shown an increased risk of cardiovascular disease in patients who were treated with left-sided breast irradiation after breast-conserving therapy.

There is a higher risk of some malignancies in women receiving RT versus women not receiving RT. Increased RR was reported for lung cancer at 10-14 years and 15 or more years after initial breast cancer diagnosis (RR 1.62, 95% CI; 1.05-2.54 and RR 1.49, 95% CI; 1.05-2.14, respectively), for second breast cancer at 5-10 years (RR 1.34; 95% CI, 1.10-1.63) and 15 + years (RR 1.26; 95% CI, 1.00-1.59) and oesophageal cancer at 15 or more years (RR 2.19; 95% CI, 1.10-4.62). However given the protracted interval between treatment and the development of another neoplasm in the irradiated field, many of these studies are old. The risk of a second malignancy related to breast cancer RT treatment is currently estimated to be approximately one per thousand women receiving RT.
GLOSSARY OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>ASCO</td>
<td>American Society of Clinical Oncology</td>
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<tr>
<td>BCS</td>
<td>Breast-conserving surgery</td>
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<td>CI</td>
<td>Confidence interval</td>
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<td>CRT</td>
<td>Conformal radiotherapy</td>
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<td>DCIS</td>
<td>Ductal carcinoma in situ</td>
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<td>EORTC</td>
<td>European Organization for Research and Treatment of Cancer</td>
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<td>HR</td>
<td>Hazard ratio</td>
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<td>MRM</td>
<td>Modified radical mastectomy</td>
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<td>NSABP</td>
<td>National Surgical Adjuvant Breast Project</td>
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<td>OCOG</td>
<td>Ontario Clinical Oncology Group</td>
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<td>SLNB</td>
<td>Sentinel lymph node biopsy</td>
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<td>UKCCCR</td>
<td>United Kingdom Coordinating Committee on Cancer Research</td>
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<td>WBRT</td>
<td>Whole breast radiation therapy</td>
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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 Breast 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 Breast 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