

# **ADJUVANT RADIATION THERAPY FOR DUCTAL CARCINOMA IN SITU**

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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. In 2011, an estimated 2,100 women were diagnosed with breast cancer – an estimated 410 died.<sup>(1)</sup> Ductal carcinoma in situ (DCIS) of the breast is a heterogeneous group of proliferative cellular lesions that have the potential to become invasive.<sup>(2)</sup> DCIS is usually treated by surgically removing the cancer – mastectomy or breast conserving surgery. After surgery, radiation therapy 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 radiotherapy treatment after surgery (breast conserving or mastectomy) for patients with DCIS?
- For patients with DCIS, how should a radial margin of excision of less than 2 mm be handled following breast conserving surgery?

## 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 Utilization Resource Unit. A detailed description of the methodology followed during guideline development can be found in the [Guideline Utilization Resource Unit Handbook](#).

## SEARCH STRATEGY

The MEDLINE (1966 through April 2008), EMBASE (1980 through April 2008), 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. The search terms included breast, cancer\* OR carcinoma OR tumour\*, radiation OR radiotherapy, surgery OR conservation surgery, DCIS OR Ductal carcinoma in Situ.

For the 2012 update of this guideline recommendations were modified based on consensus discussion. However, no formal update of the literature was performed. A literature review will be conducted for the 2013 planned review.

## TARGET POPULATION

These recommendations apply to adult patients with DCIS who have had breast-conserving surgery or a mastectomy.

## RECOMMENDATIONS

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

**Table 1 Adjuvant radiotherapy for patients with DCIS**

| <b>Type of Surgery</b>  |   |
|---|---|
| <b>Breast Conserving Surgery</b>  | <b>Mastectomy</b>   |
| <ul style="list-style-type: none"> <li>• Adjuvant whole breast radiotherapy recommended</li> <li>• Partial breast radiotherapy investigational as part of clinical trial if available</li> <li>• For margins &lt;2 mm, re-excision recommended (close margin at fascia is an exception)</li> <li>• For margins &lt; 2 mm not treated with re-excision, role of RT boost not well defined</li> </ul> | <ul style="list-style-type: none"> <li>• No adjuvant radiotherapy recommended, even if resection margins close. Adjuvant RT can be considered when margin positive but benefit not defined</li> </ul> |

## DISCUSSION

In the European Organization for Research and Treatment of Cancer (EORTC) 10853 trial<sup>(3)</sup>, 1,010 women with DCIS measuring <5 cm were randomized to radiation or no radiation. 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 radiotherapy (hazard ratio [HR], 0.53; 95% CI, 0.40 to 0.70, log rank,  $p < 0.0065$ ). At the median follow-up of 10 years, the radiotherapy 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 to .86).<sup>(4)</sup> 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 radiotherapy, 5000 cGy in 25 fractions in five weeks, or observation.<sup>(5-8)</sup> 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 radiotherapy ( $p=0.00001$ ). The rate of non-invasive recurrence was also reduced from 14.6% to 8.0% with radiotherapy ( $p=0.001$ ). There was no significant difference in overall survival for patients treated with BCS alone versus BCS plus radiotherapy (86% versus [vs.] 87%; RR, 0.95; 95% CI, 0.63 to 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.<sup>(6, 9)</sup>

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 radiation and 502 without radiation), and four arms (54% of the radiation group received Tamoxifen and 51% in the non-radiation group received Tamoxifen).<sup>(10)</sup> 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<sup>(4-8, 10)</sup> in DCIS used the same dose, fractionation schedule, and 5000 cGy in 25 fractions in five weeks. Whereas the Ontario Clinical Oncology Group (OCOG)<sup>(11,12)</sup> 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, disease-free, and overall survival rates were 97.2% versus 96.8% (95% CI, -1.5% to 2.4%), 87.6% versus 91.0% ( $p=0.37$ ), and 97.8% versus 96.1% ( $p=0.78$ ) in the 16-fraction versus the 25-fraction arms, respectively. 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% to 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% to 10%), but there was no significant difference in the incidence of radiation pneumonitis and 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 very 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 radiotherapy are modest including altered pigmentation, <sup>(13)</sup> breast discomfort, and firmness.<sup>(14, 15)</sup> The risk of cardiac disease is generally low with modern radiotherapy techniques.<sup>(12, 15, 16)</sup> Several studies report an association between radiotherapy and cardiovascular morbidity, including myocardial infarction and congestive heart failure.<sup>(17, 18)</sup> 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.<sup>(19, 20)</sup>

There is a higher risk of some malignancies in women receiving radiotherapy vs. women not receiving radiotherapy. Increased relative risks (RR) was reported for lung cancer at 10-14 years and 15 or more years after initial breast cancer diagnosis (RR 1.62, 95% confidence interval [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 + years (RR 2.19, 95% CI 1.10-4.62).<sup>(21)</sup> 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 radiation treatment is currently estimated to be approximately one per thousand women receiving radiotherapy.<sup>(21)</sup>

### GLOSSARY OF ABBREVIATIONS

| Acronym | Description                    |
|---------|--------------------------------|
| BCS     | breast conserving surgery      |
| CRT     | conformal radiotherapy         |
| DCIS    | ductal carcinoma in situ       |
| MRM     | modified radical mastectomy    |
| SLNB    | sentinel lymph node biopsy     |
| WBRT    | whole breast radiation therapy |

### 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 Alberta Health Services, Cancer Care.

### MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2013. 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. Alberta Health Services – Cancer Care 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.

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