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Adjuvant Radiation Therapy for Invasive Breast Cancer

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Alberta Health Services
CancerControl Alberta

Clinical Practice Guideline BR-005 – Version 5
www.ahs.ca/guru

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.[1] Invasive breast cancer usually requires surgical treatment, as well as treatment after surgery, including radiation. Two options exist for breast surgery: mastectomy (removal of the entire breast) and breast conserving surgery (BCS) (removal of the cancerous area and a small amount of surrounding tissue). Mastectomy may be necessary based on tumour location, size and/or shape of the patient's breast; or it may be the patient's preference despite being eligible for BCS. If a patient is eligible and chooses to have BCS, a margin of normal breast tissue around the tumour is required to avoid additional surgery. The first place for breast cancer to spread is the lymph nodes. Thus, the goal of surgery is to remove cancer from both the breast and the lymph nodes.

BCS plus RT is called breast conserving therapy and is used to reduce the likelihood of cancer recurrence. Radiation is generally recommended for patients who have had BCS for invasive breast cancer. Standard treatment includes a course of external-beam radiation therapy to the whole breast after BCS. However, this type of radiation requires several treatment sessions. The purpose of this guideline is to establish a standard of care for RT to patients with invasive breast cancer following BCS or a mastectomy.

Guideline Questions

1. For patients with T1, T2, T3, T4 invasive breast cancer, what is the optimal RT treatment after surgery (BCS or mastectomy) according to lymph node status (positive or negative)?
2. How should a positive margin be handled for patients treated with BCS?
3. For patients with invasive breast cancer treated with neoadjuvant chemotherapy, what is the optimal radiotherapy treatment after surgery (BCS or mastectomy)?
4. For left-sided breast cancer patients, can cardiac irradiation be minimized?

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 OR mastectomy.

Subsequent updates to the guideline are the result of deliberations of Alberta radiation oncologists at the 2012 to 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 invasive breast cancer who have had BCS or a mastectomy.

Recommendations

Recommendations about the optimal use of RT following BCS for patients with invasive breast cancer are presented in Table 1.

Table 1. Radiotherapy Recommendations for Invasive Breast Cancer Following

Type of Breast Cancer Surgery	Breast-conserving*	Mastectomy
T1/T2 and node negative	• Adjuvant whole breast radiation therapy (WBRT) alone (no regional nodal radiation therapy [RT]) is recommended • Partial breast radiotherapy investigational as part of clinical trial if available, or in very select patients	• No adjuvant radiotherapy recommended, if negative margins are achieved. Adjuvant RT can be considered when margin positive, but benefit not defined
T1/T2 and node positive	Adjuvant WBRT recommended in all cases Regarding regional nodal irradiation (RNI): • Isolated tumour cells in nodes (N0 as per TNM staging): o RNI not recommended • Sentinel lymph node biopsy (SLNB) positive micromets: o RNI individualized based on risk assessment o Warrant a discussion with a radiation oncologist: • Macrometastatic nodal disease: o RNI recommended	o Isolated tumour cells in nodes (N0 as per TNM staging): o No adjuvant RT recommended • SLNB positive micromets warrant a discussion with a radiation oncologist: o Chest wall with RNI individualized, based on risk assessment • Macrometastatic nodal disease: o Chest wall and RNI recommended
T3/T4 and node negative or node positive	• Radiotherapy to breast and RNI recommended	• Radiotherapy to chest wall and RNI recommended
Treated with neoadjuvant chemotherapy	• Radiotherapy to breast recommended regardless of final pathology Regarding RNI: • Clinical stage T1/T2N0: o No RNI recommended • Clinical stage II (T1/T2N1 or T3N0): o RNI based on consultation with radiation oncologist and degree of pathologic response • Clinical stage III/Locally advanced breast cancer (T1-T4N2-3, T3N1): o RNI recommended	• Clinical stage T1/T2N0: o No adjuvant radiotherapy recommended • Clinical stage II (T1/T2N1 or T3N0): o Adjuvant radiotherapy individualized based on consultation with radiation oncologist and degree of pathologic response • Clinical stage III/Locally advanced breast cancer (T1-T4N2-3, T3N1): o Chest wall and RNI recommended

Left-sided breast cancer	Deep inspiration breath hold (DIBH) during adjuvant radiation therapy should be an available treatment option to minimize cardiac dose.

Discussion

The AMAROS trial showed a significant role for RT in treating patients with positive sentinel lymph node biopsies (SLNB). The study randomized (n=1425) SLNB-positive patients to receive axillary node dissection (n=781) or regional RT (n=681). The majority of patients (93%) had only 1 or 2 positive nodes and had systemic therapy (97%). Only a quarter of patients had N1mic SNLB-positive nodes, and 10% in both arms had RT to internal mammary chain lymph nodes. No significant differences in regional recurrence, distant metastases, or overall survival were observed. However, there were significantly fewer cases of lymphedema reported in the group receiving regional RT (14% vs. 28%; p<0.001 at a median follow-up 6.1 years).[2]

Most of the North American and European guidelines recommend RT after BCS for early stage invasive breast cancers.[3-8] RT is not required if mastectomy was performed, except where negative margins were not achieved. 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 ductal carcinoma in situ, whereas a negative margin is a margin with no ink on the tumour, and that no further differentiation is required.[5]

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that RT reduces the rate of local recurrence by about two-thirds and also reduces the number of deaths due to breast cancer. However, the authors reported no statistically significant survival benefit from post-mastectomy RT, for either node-positive or node-negative women.[9] Similar results were later reported by another meta-analysis of 15 randomized controlled trials (RCTs) in 2004.[10] The National Surgical Adjuvant Breast and Bowel Project (NSABP) trial B-21 randomized patients post-BCS to tamoxifen or RT, or both, and showed that the combination had the lowest recurrence rates (2.8%) followed by RT alone (9.3%).[11] Low local recurrence has been reported by the NSABP B-06 trial with 20 years of follow-up of women (tumour size $\leq$ 4 cm node negative or positive) randomized to radical mastectomy, BCS with RT or BCS alone.[12] This trial however found no difference in survival between the three groups at 12-20 years of follow-up.[10,12-14] Similar results have been reported by other authors with different follow-up intervals and varying doses of radiation.[15-18] In another trial, women with node-negative breast cancer, primary tumours ≤2 cm were randomized after sector resection to receive either breast irradiation (5000 cGy in five weeks to the whole breast) or no breast irradiation.[14,19] This trial reported no difference in survival with statistically significant lower recurrence rates (2.3% versus 18.4% respectively, p<0.0001) for patients randomized to the RT arm.
The Milan trial that randomized node-positive women with primary tumours <2.5 cm to wider excision quadrantectomy) with or without RT also reported a low recurrence rate for women on the RT arm.[20] Data from the Danish study update for pre-menopausal women with 1-3 positive nodes showed a survival benefit with cyclophosphamide, methotrexate, and fluorouracil (CMF) chemotherapy. There is

no survival data from the Danish study in post-menopausal women with 1-3 positive nodes treated with chemotherapy as they were all treated with tamoxifen. The Danish study has reported decrease in local recurrence in the women randomized to BCS with radiation compared to women with mastectomy alone.[21-23]

Dose/Fractionation schedule

The majority of trials examining WBRT delivered doses of 40-50 Gy to the whole breast, and a boost to the primary site when indicated.[12,22,24-28] In the NSABP B-06 trial, a dose of 50 Gy was delivered to the entire breast without a boost in patients with histologically negative margins. None of these trials with follow-up times of up to 20 years found any significant differences in overall or disease-free survival when comparing the different fractionation schedules.

Choosing Wisely Canada, a campaign to help physicians and patients engage in conversation about tests, treatments, and procedures, recommend that WBRT in 25 fractions as part of breast conservation therapy not be initiated in women who are 50 years of age or older with early stage invasive breast cancer without considering shorter treatment schedules.[29] While the radiation oncologists involved in publishing this guideline agree with Choosing Widely Canada, in some cases a hyperfractionated schedule is more favorable (e.g. immediate reconstruction, postoperative infections, unfavourable body habitus, etc.).

Side effects of radiotherapy

The side effects of modern breast RT are modest, including altered pigmentation,[30] breast discomfort, and firmness.[11,31] The risk of cardiac disease is generally low with modern radiotherapy techniques.[11,32,33] Several studies report as association between RT and cardiovascular morbidity, including myocardial infarction and congestive heart failure.[34,35] 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.[36,37]

There is a higher risk of some malignancies in women receiving RT versus women not receiving RT. 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 and 15 or more years (RR 1.34, 95% CI 1.10-1.63 and RR 1.26, 95% CI 1.00-1.59, respectively), and oesophageal cancer at 15 or more years (RR 2.19, 95% CI 1.10-4.62).[37] 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 is currently estimated to be approximately one per thousand women receiving RT.[38]

If nodal RT is delivered, the volume of skin irradiated is increased as is the potential volume of lung (and heart for left-sided tumours). The post-operative risk of lymphedema is approximately doubled if

the entire axilla is included. Risk of clinically significant pneumonitis is approximately one percent. DIBH has been shown effective in reducing cardiac doses for patients receiving adjuvant left breast radiotherapy, and available data suggest that these reductions likely result in reduced long-term cardiac morbidity and mortality.[39] Therefore, DIBH should be an available treatment option for patients being treated with adjuvant radiation therapy for left-sided breast cancers.

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Development and Revision History

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

This guideline was originally developed in June 2008. This guideline was revised in April 2012, March 2013, June 2014, and June 2015.

Maintenance

A formal review of the guideline will be conducted 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.

Abbreviations

ASCO, American Society of Clinical Oncology
BCS, Breast conserving surgery
CI, Confidence interval
CMF, Cyclophosphamide, methotrexate, and fluorouracil
DIBH, Deep inspiration breath hold
EBCTCG, The Early Breast Cancer Trialists' Collaborative Group
NSABP, National Surgical Adjuvant Breast and Bowel Project
RCT, Randomized controlled trial
RNI, Regional node irradiation
RR, Relative risk
RT, Radiation therapy
SNLB, Sentinel Lymph Node Biopsy
WBRT, Whole breast radiation therapy

Disclaimer

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.

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