

ADJUVANT RADIATION THERAPY FOR INVASIVE BREAST CANCER

Date Developed: June, 2008

Last Revised: April, 2012

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.⁽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 (removal of the cancerous area and a small amount of surrounding tissue). Mastectomy may be necessary based on tumour location and the size or shape of the patient's breast, or it may be the patient's preference despite being eligible for breast conserving surgery. If a patient is eligible and chooses to have breast conserving surgery, 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.

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

GUIDELINE QUESTIONS

- For patients with T1, T2, T3, T4 invasive breast cancer, what is the optimal radiotherapy treatment after surgery (breast conserving or mastectomy) according to lymph node status (positive or negative)?
- How should a radial margin of excision of less than 2 mm be handled for patients with T1, T2 invasive breast cancer who are node negative and treated with breast conserving surgery?
- For patients with any stage of invasive breast cancer treated who have had neoadjuvant chemotherapy, what is the optimal radiotherapy treatment after surgery (breast conserving or mastectomy)?

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

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 OR mastectomy.

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 invasive breast cancer who have had breast-conserving surgery or a mastectomy.

RECOMMENDATIONS

Recommendations about the optimal use of radiotherapy following breast-conserving surgery for patients with invasive breast cancer are presented in Table 1.

Table 1 Radiotherapy recommendations for invasive breast cancer following surgery

Type of breast cancer	Surgery	
	Breast-conserving	Mastectomy
T1/T2 and node negative	<ul style="list-style-type: none"> • Adjuvant whole breast radiotherapy alone (no regional nodal RT) is recommended • Partial breast radiotherapy investigational as part of clinical trial if available, or in very select patients off trial • For margins <2 mm, re-excision recommended (close margins at fascia is an exception) • Radiotherapy boost recommended: In all women <40 yrs regardless of margin. In women >40 yrs, boost individualized based on risk assessment 	<ul style="list-style-type: none"> • No adjuvant radiotherapy recommended, even if resection margins close. Adjuvant RT can be considered when margin positive, but benefit not defined
T1/T2 and node positive	<p>Adjuvant WBRT recommended in all cases</p> <p>Regarding regional nodal irradiation (RNI):</p> <ol style="list-style-type: none"> 1. Isolated tumour cells in nodes (N0 as per TNM staging): <ul style="list-style-type: none"> ➢ RNI not recommended 2. SNB positive micromets without AND: <ul style="list-style-type: none"> ➢ RNI individualized based on risk assessment 3. SNB micromets with completion AND: <ul style="list-style-type: none"> ➢ RNI not recommended 4. SNB macromets without AND: <ul style="list-style-type: none"> ➢ RNI individualized based on risk assessment (**surgical management to be discussed with surgeons) 5. SNB macromets with AND: <ul style="list-style-type: none"> ➢ RNI recommended 	<ol style="list-style-type: none"> 1. Isolated tumour cells in nodes (N0 as per TNM staging): <ul style="list-style-type: none"> ➢ No adjuvant radiotherapy recommended 2. SNB micromets without AND: <ul style="list-style-type: none"> ➢ Chest wall with RNI individualized, based on risk assessment 3. SNB micromets with completion AND: <ul style="list-style-type: none"> ➢ No adjuvant radiotherapy recommended 4. SNB macromets without AND: <ul style="list-style-type: none"> ➢ Chest wall and RNI individualized based on risk assessment (**surgical management to be discussed with surgeons) 5. SNB macromets with AND: <ul style="list-style-type: none"> ➢ Chest wall and RNI recommended
T3/T4 and node negative or node positive	<ul style="list-style-type: none"> • Radiotherapy to breast/chest wall and RNI recommended 	<ul style="list-style-type: none"> • Radiotherapy to breast/chest wall and RNI recommended

Type of breast cancer	Surgery	
	Breast-conserving	Mastectomy
(Any stage) Treated with neoadjuvant chemotherapy	Radiotherapy to breast recommended regardless of final pathology. RNI individualized based upon presenting clinical stage.	<ul style="list-style-type: none"> Radiotherapy to chest wall and RNI recommended regardless of final pathology based on clinical stage, EXCEPT for T1/T2N0 (pre-chemo) treated with <u>mastectomy</u>

DISCUSSION

Most of the North American and European guidelines ⁽²⁻⁸⁾ recommend radiotherapy after breast conserving surgery for early stage invasive breast cancers.

The Early Breast Cancer Trialists' Collaborative Group (the "Oxford Review") reported that radiotherapy reduces the rate of local recurrence by about two-thirds and also reduces the number of deaths due to breast cancer. They however reported no statistically significant survival benefit from post-mastectomy radiotherapy, for either node-positive or node-negative women.⁽⁹⁾ Similar results were later reported by another meta-analysis of 15 RCTs in 2004.⁽¹⁰⁾ The NSABP trial B-21⁽¹¹⁾ 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%).

Low local recurrence has been reported by the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial with 20 years of follow-up of women (tumour size ≤ 4 cm node negative or positive) randomized to radical mastectomy, BCS with radiation or BCS alone.⁽¹²⁾ This trial however found no difference in survival between the three groups at 12-20 years of follow up.⁽¹²⁻¹⁵⁾ Similar results have been reported by other authors with different follow up intervals and varying doses of radiation.^(8,16-18) 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.^{(15,19) (15,19)} 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 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

Most trials did whole breast irradiation with doses of 45-50 Gy, and a boost to the primary site was employed in majority of the trials.^(12,22,24-28) In the National Surgical Adjuvant Breast and Bowel Project (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.

Side effects of radiotherapy

The side effects of modern breast radiotherapy are modest including altered pigmentation, ⁽²⁹⁾ breast discomfort, and firmness. ^(11, 30) The risk of cardiac disease is generally low with modern radiotherapy techniques. ^(11, 31, 32) Several studies report an association between radiotherapy and cardiovascular morbidity, including myocardial infarction and congestive heart failure. ^(33, 34) 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. ^(35, 36)

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). ⁽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 radiation treatment is currently estimated to be approximately one per thousand women receiving radiotherapy. ⁽³⁷⁾

If nodal radiotherapy is delivered, the volume of skin irradiated is increased as in 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.

GLOSSARY OF ABBREVIATIONS

Acronym	Description
ALND	axillary lymph node dissection
BCS	breast conserving surgery
FNA	fine needle aspiration
IM	internal mammary
ITC	isolated tumour cells
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.

REFERENCES

- (1) Canadian Cancer Society, Statistics Canada, Provincial/Territorial Cancer Registries, Public Health Agency of Canada. Canadian Cancer Statistics 2011. 2011; Available at: <http://www.cancer.ca/~media/CCS/Canada%20wide/Files%20List/English%20files%20heading/PDF%20-%20Policy%20-%20Canadian%20Cancer%20Statistics%20-%20English/Canadian%20Cancer%20Statistics%202011%20-%20English.ashx>. Accessed 04/03, 2012.
- (2) Whelan T, Olivotto I, Levine M, Health Canada 's Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. Clinical practice guidelines for the care and treatment of breast cancer: breast radiotherapy after breast-conserving surgery (summary of the 2003 update). CMAJ 2003 Feb 18;168(4):437-439.
- (3) Canadian Association of Radiation Oncologists. Breast radiotherapy after breast-conserving surgery. The Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. CMAJ 1998 Feb 10;158 Suppl 3:S35-42.
- (4) National Comprehensive Cancer Network. Breast Cancer. Version 2.2006. 2006; Available at: www.nccn.org/professionals/physician_gls/PDF/breast.pdf.
- (5) Scottish Intercollegiate Guidelines Network. Breast cancer in women: a national clinical guideline recommended for use in Scotland. 1998; Available at: <http://www.sign.ac.uk/pdf/sign29.pdf>. Accessed 12/19, 2005.
- (6) Collins JP, Simpson JS. Guidelines for the surgical management of breast cancer. Council of the Royal Australasian College of Surgeons. Aust N Z J Surg 1998 Mar;68 Suppl:1-28.
- (7) Recht A, Edge SB, Solin LJ, Robinson DS, Estabrook A, Fine RE, et al. Postmastectomy radiotherapy: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001 Mar 1;19(5):1539-1569.
- (8) American College of Radiology. Practice guideline for the breast conservation therapy in the management of invasive breast carcinoma. J Am Coll Surg 2007 Aug;205(2):362-376.
- (9) Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer. An overview of the randomized trials. N Engl J Med 1995 Nov 30;333(22):1444-1455.

- (10) Fisher B, Redmond C. Lumpectomy for breast cancer: an update of the NSABP experience. National Surgical Adjuvant Breast and Bowel Project. *J Natl Cancer Inst Monogr* 1992;(11)(11):7-13.
- (11) Vinh-Hung V, Verschraegen C. Breast-Conserving Surgery With or Without Radiotherapy: Pooled-Analysis for Risks of Ipsilateral Breast Tumor Recurrence and Mortality. *J Natl Cancer Inst* 2004;96(2):115.
- (12) Fisher B, Bryant J, Dignam JJ, Lawrence Wickerham D, Mamounas EP, Fisher ER, et al. Tamoxifen, Radiation Therapy, or Both for Prevention of Ipsilateral Breast Tumor Recurrence After Lumpectomy in Women With Invasive Breast Cancers of One Centimeter or Less. *Journal of Clinical Oncology* 2002 October 15, 2002;20(20):4141.
- (13) Fisher B, Bauer M, Margolese R, Poisson R, Pilch Y, Redmond C, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. *N Engl J Med* 1985 Mar 14;312(11):665-673.
- (14) Fisher B, Anderson S, Redmond CK, Wolmark N, Wickerham DL, Cronin WM. Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1995 Nov 30;333(22):1456-1461.
- (15) Uppsala-Orebro Breast Cancer Study Group. Sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Natl Cancer Inst* 1990 Feb 21;82(4):277-282.
- (16) Liljegren G, Holmberg L, Bergh J, Lindgren A, Tabar L, Nordgren H, et al. 10-Year results after sector resection with or without postoperative radiotherapy for stage I breast cancer: a randomized trial. *J Clin Oncol* 1999 Aug;17(8):2326-2333.
- (17) Clark RM, Whelan T, Levine M, Roberts R, Willan A, McCulloch P, et al. Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst* 1996 Nov 20;88(22):1659-1664.
- (18) Holli K, Saaristo R, Isola J, Joensuu H, Hakama M. Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: results of a randomized study. *Br J Cancer* 2001 Jan;84(2):164-169.
- (19) Liljegren G, Holmberg L, Adami HO, Westman G, Graffman S, Bergh J. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. *J Natl Cancer Inst* 1994 May 4;86(9):717-722.
- (20) Veronesi U, Luini A, Del Vecchio M, Greco M, Galimberti V, Merson M, et al. Radiotherapy after breast-preserving surgery in women with localized cancer of the breast. *N Engl J Med* 1993 Jun 3;328(22):1587-1591.
- (21) Overgaard M, Hansen PS, Overgaard J, Rose C, Andersson M, Bach F, et al. Postoperative radiotherapy in high-risk premenopausal women with breast cancer who receive adjuvant chemotherapy. Danish Breast Cancer Cooperative Group 82b Trial. *N Engl J Med* 1997 Oct 2;337(14):949-955.

- (22) Blichert-Toft M, Nielsen M, Durning M, Moller S, Rank F, Overgaard M, et al. Long-term results of breast conserving surgery vs. mastectomy for early stage invasive breast cancer: 20-year follow-up of the Danish randomized DBCG-82TM protocol. *Acta Oncol* 2008;47(4):672-681.
- (23) Voogd AC, Nielsen M, Peterse JL, Blichert-Toft M, Bartelink H, Overgaard M, et al. Differences in risk factors for local and distant recurrence after breast-conserving therapy or mastectomy for stage I and II breast cancer: pooled results of two large European randomized trials. *J Clin Oncol* 2001 Mar 15;19(6):1688-1697.
- (24) Veronesi U, Cascinelli N, Mariani L, Greco M, Saccozzi R, Luini A, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002 Oct 17;347(16):1227-1232.
- (25) Arriagada R, Le MG, Rochard F, Contesso G. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. *J Clin Oncol* 1996 May;14(5):1558-1564.
- (26) Fisher B, Redmond C, Poisson R, Margolese R, Wolmark N, Wickerham L, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. *N Engl J Med* 1989 Mar 30;320(13):822-828.
- (27) Poggi MM, Danforth DN, Sciuto LC, Smith SL, Steinberg SM, Liewehr DJ, et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. *Cancer* 2003 Aug 15;98(4):697-702.
- (28) van Dongen JA, Voogd AC, Fentiman IS, Legrand C, Sylvester RJ, Tong D, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000 Jul 19;92(14):1143-1150.
- (29) Tho LM, McIntyre A, Rosst A, Gallagher C, Yap C, Ritchie DM, et al. Acute supraclavicular skin toxicity in patients undergoing radiotherapy for breast cancer: an evaluation of the 'T'-grip method of patient positioning. *Clin Oncol (R Coll Radiol)* 2006 Mar;18(2):133-138.
- (30) Delaney G. Recent advances in the use of radiotherapy to treat early breast cancer. *Curr Opin Obstet Gynecol* 2005;17(1):27.
- (31) Whelan T, MacKenzie R, Julian J, Levine M, Shelley W, Grimard L, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. *J Natl Cancer Inst* 2002 Aug 7;94(15):1143-1150.
- (32) Miller SR, Mondry T, Reed JS, Findley A, Johnstone PA. Delayed cellulitis associated with conservative therapy for breast cancer. *J Surg Oncol* 1998 Apr;67(4):242-245.
- (33) Correa CR, Litt HI, Hwang WT, Ferrari VA, Solin LJ, Harris EE. Coronary artery findings after left-sided compared with right-sided radiation treatment for early-stage breast cancer. *J Clin Oncol* 2007 Jul 20;25(21):3031-3037.

-
- (34) Hooning MJ, Botma A, Aleman BM, Baaijens MH, Bartelink H, Klijn JG, et al. Long-term risk of cardiovascular disease in 10-year survivors of breast cancer. *J Natl Cancer Inst* 2007 Mar 7;99(5):365-375.
- (35) Harris EE, Correa C, Hwang WT, Liao J, Litt HI, Ferrari VA, et al. Late cardiac mortality and morbidity in early-stage breast cancer patients after breast-conservation treatment. *J Clin Oncol* 2006 Sep 1;24(25):4100-4106.
- (36) Borger JH, Hooning MJ, Boersma LJ, Snijders-Keilholz A, Aleman BM, Lintzen E, et al. Cardiotoxic effects of tangential breast irradiation in early breast cancer patients: the role of irradiated heart volume. *Int J Radiat Oncol Biol Phys* 2007 Nov 15;69(4):1131-1138.
- (37) Roychoudhuri R, Evans H, Robinson D, Moller H. Radiation-induced malignancies following radiotherapy for breast cancer. *Br J Cancer* 2004;91(5):868.