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Evidence-based Series #1-10 Version 2.2006: Section 1

Management of Ductal Carcinoma in Situ of the Breast: A Clinical Practice Guideline

*W. Shelley, D. McCreedy, C. Holloway, M. Trudeau, S. Sinclair,
and the Breast Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: September 19, 2006
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The full Evidence-based Series #1-10 Version 2.2006 is comprised of 3 sections and is available on the CCO website (<http://www.cancercare.on.ca>)
PEBC Breast Cancer DSG page at:
<http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/>

Section 1: Clinical Practice Guideline

Section 2: Systematic Review

Section 3: Guideline Development and External Review – Methods and Results

Questions

- What is the optimal surgical management of ductal carcinoma in situ (DCIS) of the breast?
- Should breast irradiation be offered to women with DCIS, following breast-conserving surgery (defined as excision of the tumour with microscopically clear resection margins)? Are there patients who could be spared breast irradiation post–breast-conserving surgery for DCIS?
- What is the role of tamoxifen in the management of DCIS?

Target Population

These recommendations apply to women with DCIS.

Recommendations and Key Evidence

Surgical Management

Women with DCIS of the breast who are candidates for breast-conserving surgery should be offered the choice of breast-conserving surgery or total mastectomy.

Mastectomy with the option for reconstruction remains an acceptable choice for women preferring to maximize local control.

- No randomized trials designed to compare total mastectomy with breast-conserving surgery for DCIS were found. The National Surgical Adjuvant Breast Project (NSABP) B-06 trial (1) involved women with invasive malignancy. However, a small number of women entered were found, on pathology review, to have only DCIS. An analysis based on this subgroup of DCIS patients (2) found a trend towards a much higher local recurrence rate in patients who received breast-conserving surgery alone (9/21; 43%), compared with those who received either breast-conserving surgery plus radiotherapy (2/27; 7%) or mastectomy (0/28; 0%). Two meta-analyses (3,4), consisting mainly of non-randomized trials, also demonstrated higher local recurrence in patients treated by breast-conserving surgery alone versus those treated by mastectomy. One reported no significant differences in local recurrence rates between patients treated by breast-conserving surgery followed by radiotherapy and mastectomy, whereas the second showed improved local recurrence rates with mastectomy. To date, no survival benefit for either type of surgery has been reported. The expert opinion of the Breast Cancer DSG is that this non-randomized data supports the recommendation that breast-conserving surgery followed by radiation is an acceptable treatment option, in addition to mastectomy.

Qualifying Statements

- When breast-conserving surgery is performed, all mammographically suspicious calcifications should be removed and margins should be microscopically clear of DCIS.
- Mastectomy, with the option of reconstruction, is recommended for those women who have an area of DCIS large enough that breast-conserving surgery would leave them with an unacceptable cosmetic result.

Radiotherapy

Women with DCIS who have undergone breast-conserving surgery should be offered adjuvant breast irradiation.

Randomized trials of post-lumpectomy radiation versus observation in patients at relatively low risk of recurrence following surgery alone are ongoing. Until the results of those studies are available, these patients should be referred to a radiation oncologist for a thorough discussion of what is currently known about the potential benefits and toxicities of post-lumpectomy radiation in their particular situation.

- Three randomized trials (5-12) investigated the role of radiotherapy after breast-conserving surgery in patients with DCIS. In each, the risk of invasive and non-invasive ipsilateral recurrence was reduced with adjuvant radiotherapy. There were no significant differences in distant metastasis or overall survival.

Tamoxifen

While there is some evidence to suggest that tamoxifen is effective in the reduction of ipsilateral recurrence and contralateral incidence in women with DCIS, the absolute benefit is small and the evidence is conflicting.

Women should be informed of the option of five years of tamoxifen therapy and of the potential toxicities and benefits associated with tamoxifen.

- Two trials (12,13) investigated the role of tamoxifen versus no tamoxifen in addition to breast-conserving surgery and radiotherapy in the treatment of DCIS. The first demonstrated a significantly lower cumulative incidence of ipsilateral or contralateral breast malignancy for patients in the tamoxifen group versus those in the placebo group. In the second, tamoxifen treatment did not significantly reduce the incidence of either ipsilateral or contralateral breast malignancy.

Qualifying Statement

- In a subset analysis of one of the randomized studies (14), the beneficial effect of tamoxifen was most apparent in the estrogen receptor-positive patients. Therefore, if it is felt that a patient might benefit from tamoxifen for one of the above reasons, hormone receptor assessment could be considered in order to aid in the decision regarding tamoxifen treatment.
- Randomized studies suggest that women who are most likely to have a positive benefit/risk ratio with tamoxifen are those who are less than 50 years of age or who have positive resection margins and refuse further surgery. Women who have a contraindication to radiation or who refuse this treatment but still want to avoid mastectomy should also be considered for tamoxifen therapy.

Related Guidelines

- Practice Guideline Report #1-1: *Surgical management of Early Stage Invasive Breast Cancer.*
- Practice Guideline Report #1-2: *Breast Irradiation in Women with Early Stage Invasive Breast Cancer Following Breast Conserving Surgery.*

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Contact Information

For further information about this series, please contact **Dr. Wendy Shelley**; Kingston Regional Cancer Centre, 25 King St W, Kingston ON, K7L 5P9; Telephone: 613-544-2631 x4502; Fax: 613-546-8209; E-mail: wendy.shelley@krcc.on.ca.

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Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

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Evidence-based Series #1-10 Version 2.2006: Section 2

Management of Ductal Carcinoma in Situ of the Breast: A Systematic Review

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QUESTIONS

- What is the optimal surgical management of ductal carcinoma in situ (DCIS) of the breast?
- Should breast irradiation be offered to women with DCIS, following breast-conserving surgery (defined as excision of the tumour with microscopically clear resection margins)? Are there patients who could be spared breast irradiation post-breast-conserving surgery for DCIS?
- What is the role of tamoxifen in the management of DCIS?

INTRODUCTION

DCIS of the breast represents a heterogeneous group of diseases characterized by the proliferation of malignant epithelial cells that are confined within the basement membrane of the mammary ducts (1). The natural history of DCIS is poorly understood. Limited published information is available that is generalizable to current practice, because the clinical nature of DCIS has changed over the years. DCIS incidence increased significantly during the years that routine screening mammography became available. In the United States, the age-adjusted DCIS incidence rate increased from 2.4 per 100,000 women in 1973 to 15.8 per 100,000 women in 1992, an increase of 557% (2). At the present time, the vast majority of DCIS lesions are nonpalpable and are identified by microcalcifications discovered at the time of routine screening mammography.

The management of DCIS has evolved with the changing clinical nature of the disease and the emergence of new evidence. Originally, mastectomy was the standard operative procedure for patients presenting with DCIS. However, there has been a shift towards breast-conserving surgery (BCS). Radiotherapy has been recommended for women with DCIS following BCS, but, more recently, the role of adjuvant radiation for all subgroups has been questioned. In addition, the role of adjuvant tamoxifen therapy in women with DCIS is unclear. Given the increasing incidence and the wide spectrum of management options, the Breast

Cancer Disease Site Group (DSG) felt that DCIS of the breast was an appropriate topic for a practice guideline.

METHODS

This systematic review was developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC), using the methods of the Practice Guidelines Development Cycle (3). Evidence was selected and reviewed by three members of the PEBC Breast Cancer Disease Site Group (DSG), a radiation oncologist, a surgical oncologist, and a research methodologist.

This systematic review is a convenient and up-to-date source of the best available evidence on the management of DCIS of the breast. The body of evidence in this review is primarily comprised of randomized controlled trial data. That evidence forms the basis of a clinical practice guideline developed by the Breast Cancer DSG and published as Section 1 of this evidence-based series. The systematic review and companion practice guideline are intended to promote evidence-based practice in Ontario, Canada. The PEBC is editorially independent of Cancer Care Ontario and the Ontario Ministry of Health and Long-Term Care.

A practice guideline report on the management of DCIS of the breast was originally completed in January 1998 and published in *Cancer Prevention and Control* (4). Since the publication of the 1998 guideline, the medical literature has been monitored, and the results of additional randomized clinical trials have become available that have an impact on treatment recommendations. Therefore, the Breast Cancer DSG felt that the original guideline document and the new evidence should be integrated. This systematic review, and the evidence-based series of which it is a part, reflect the evidence up to March 2005 and include revised recommendations based on that evidence. This evidence-based series replaces the original report.

Literature Search Strategy

MEDLINE was searched to March 2006, using a disease-specific medical subject heading (MeSH) term ("carcinoma, intraductal, noninfiltrating") and treatment-specific MeSH terms ("radiotherapy", "mastectomy", or "tamoxifen"). The Excerpta Medica database (EMBASE) was also searched up to March 2006, using a disease-specific Excerpta Medica Tree (EMTREE) term ("intraductal carcinoma") and the same treatment-specific EMTREE term as for the MEDLINE search.

Issue 5 (2004) of the Cochrane Library, the Physician Data Query database (http://www.cancer.gov/search/clinical_trials/), and conference proceedings from the American Society of Clinical Oncology (1998 to 2005), the American Society for Therapeutic Radiology and Oncology (1998 to 2005), and the San Antonio Breast Cancer Symposium (2001 to 2005) were also searched. The Canadian Medical Association Infobase (<http://mdm.ca/cpgsnew/cpgs/index.asp>) and the National Guidelines Clearinghouse (<http://www.guideline.gov/>) were searched for existing evidence-based practice guidelines. Relevant articles and abstracts were selected and reviewed by three reviewers, and the reference lists from these sources were searched for additional trials, as were the reference lists from relevant review articles.

Inclusion Criteria

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria:

- The management of DCIS of the breast was evaluated using a randomized controlled trial or a meta-analysis of non-randomized and/or randomized trials.
- Reported outcomes included overall or disease-free survival, local recurrence (invasive or non-invasive), breast conservation, distant recurrence, toxicity, or quality of life.

- Clinical trial results were reported in full papers or abstracts. Although data presented in meeting abstracts may not be as reliable and complete as that from papers published in peer-reviewed journals, abstracts can be a source of important evidence from randomized trials and add to the evidence available from fully published studies. These data often appear first in meeting abstracts and may not be published for several years. Evidence-based clinical practice guidelines addressing this topic were also eligible for inclusion.

Exclusion Criteria

Articles were excluded if they met the following criteria:

- Trial results were published in a language other than English.
- Publication occurred prior to 1983. Because our understanding of DCIS biology has evolved substantially since the maturation of screening mammography, trials published prior to this date are not relevant to current clinical practice.

Synthesizing the Evidence

Because the randomized trials on the management of DCIS of the breast were clinically heterogeneous, their results were not pooled.

RESULTS

Literature Search Results

The following publications were eligible for inclusion in the systematic review of the evidence:

- One subgroup analysis (5) of patients found to have DCIS on pathology review of a randomized trial designed to address the role of BCS in early-stage invasive breast cancer (6). Two meta-analyses on the surgical management of DCIS, comprised predominantly of non-randomized prospective and retrospective studies (7,8).
- Three randomized trials (reported in eight articles) that evaluated the use of adjuvant radiotherapy in patients who had undergone BCS for DCIS (9-16).
- Two randomized trials (reported in three articles) that investigated the use of tamoxifen in patients with DCIS who had undergone BCS and adjuvant radiotherapy (13,16,17).
- Six practice guidelines relevant to the management of DCIS of the breast (reported in seven sources) (18-24).

Outcomes

Mastectomy versus BCS for DCIS

Unfortunately, no randomized trials designed to compare mastectomy with BCS for DCIS were found. Data were available from the National Surgical Adjuvant Breast Project (NSABP) B-06 trial, a randomized trial designed to address the role of BCS in patients with early-stage invasive breast cancer (6). According to the pathology review, 76 patients with DCIS had been allocated to the three treatment groups, mastectomy, BCS only, and BCS with adjuvant radiation. These cases were followed, and results were published in a separate report (5). The majority of lesions were palpable, with an average size of 2.2 cm; only one lesion was found incidentally with mammography. At an average follow-up of 83 months, the rate of ipsilateral breast cancer recurrence was 43% (9/21) in the BCS only group and 7% (2/27) in the BCS plus radiotherapy group. There were no local failures in the mastectomy group (0/28). Radiotherapy following BCS was the only significant predictor of reduced local breast recurrence ($p=0.01$). There were two deaths due to breast cancer in the BCS-only group, no deaths in the BCS plus radiation group, and one death in the mastectomy group. Given that all patients were initially randomized in a trial of early invasive disease, this study may have limited generalizability. The small number of patients limits the power of this study to detect meaningful differences in survival.

A published meta-analysis by Peng Yin et al included 24 published reports, comprised mainly of clinical series, retrospective studies, and prospective non-randomized studies of patients with DCIS who were treated by mastectomy or BCS (7). Six of the 24 reports were published prior to 1983. The confidence profile method with the random effect hierarchical model was used to pool the data. The outcome of interest was the rate of local recurrence (defined as a chest wall recurrence for patients treated by mastectomy or a recurrence in the breast for patients treated by BCS) and death. New contralateral breast cancers were not included in the analysis. Local recurrence rates were corrected for the length of follow-up and compared for patients treated by mastectomy and BCS with and without irradiation. In total, 2,407 patients were included. At five years, local recurrence was higher for patients treated with BCS, with or without radiation, (21.5%; 95% confidence interval [CI], 14.0% to 30.7%) versus those treated by mastectomy (4.6%; 95% CI, 2.3% to 7.6%). In the studies reporting on patients treated by BCS plus radiation, the risk of local recurrence was 10.6% (95% CI, 5.6% to 16.9%). Mortality rates at five years were similar for patients treated by BCS or mastectomy (4.2%; 95% CI, 1.4% to 8.5% and 3.9%; 95% CI, 1.7% to 6.8%, respectively).

Similarly, Boyages et al conducted a meta-analysis of published reports of studies of patients with DCIS (8). Case series, retrospective studies, and prospective studies were included. Only one trial included in the BCS analysis (NSABP B-06, described above) and two trials included in the BCS plus radiotherapy analysis (NSABP B-06, described above and NSABP B-17, described below), were randomized. Six of the studies included were published prior to 1983. The summary recurrence rate and 95% confidence intervals for each treatment category were calculated using random and fixed effects models. The random effects model was employed where statistically significant heterogeneity between studies existed. Meta-analysis yielded statistically different summary local recurrence rates of 1.4%, 8.9%, and 22.5% in patients with DCIS treated by mastectomy, BCS plus radiotherapy, or BCS alone, respectively (Table 1).

Table 1. Pooled local recurrence rates by treatment (Boyages et al) (8).

Treatment	Number of studies	Average of median follow-ups per study (months)	Absolute local recurrence rate*	95% CI
Mastectomy	21	80	1.4%	0.7% to 2.1%
BCS + radiotherapy	19	62	8.9%	6.8% to 11.0%
BCS alone	17	68	22.5%	16.9% to 28.2%

Abbreviations: BCS, breast-conserving surgery; CI, confidence interval.

*Patients with high-grade tumours, necrosis, comedo subtype, or positive margins were more likely to benefit from radiotherapy following BCS.

Radiotherapy Following Breast-Conserving Surgery for DCIS

The European Organization for Research and Treatment of Cancer (EORTC) 10853 trial explored the role of radiotherapy after BCS for patients with DCIS. A peer-reviewed publication reported the results of this trial at a median follow-up of two years (9), but a more recent abstract reported results at a median follow-up of 10.2 years (25). A total of 1,010 women with DCIS measuring less than or equal to 5 cm were treated by BCS and were randomized to no further treatment or to radiotherapy, 5000 cGy in 25 daily fractions in five weeks. Resection margins were microscopically free of disease. Twenty-one percent were detected clinically, and the mean diameter was 21 mm (9). At a median follow-up of 10.2 years, the 10-year local relapse-free rate was 75% for patients receiving no further treatment compared with 85% for patients receiving adjuvant radiotherapy (hazard ratio [HR], 0.55; 95% CI, 0.41 to 0.73; log rank, p<0.0001).

At a median follow-up of two years, the radiotherapy group, relative to the no-further-treatment group, had a reduced risk of invasive recurrence from 8% to 4% (HR, 0.60; 95% CI, 0.37 to 0.97) and non-invasive recurrence from 8% to 5% (HR=0.65; CI, 0.41 to 1.03) (9). These differences continued to be significant at a median follow-up of 10.2 years ($p=0.006$ and $p=0.009$, respectively; exact risks not reported) (25). There were no significant differences in contralateral incidence, distant metastasis, death, or event-free survival. A multivariate analysis found a significant difference in the risk of local recurrence due to no further treatment as opposed to radiotherapy (HR, 1.74; 95% CI, 1.28 to 2.42), after controlling for young age, symptomatic detection, intermediately or poorly differentiated DCIS, solid or cribriform growth pattern, and doubtful margins.

A separate published report on a prognostic factor analysis in this study on a subset of 775 patients who had central pathology review confirmed DCIS without invasion (10). Median follow-up was 5.4 years. Treatment group, age, method of detection, nuclear grade, necrosis, architecture, size, margin status, histologic grade, and Van Nuy's classification were the factors examined in a multifactor analysis. Under the Van Nuy's classification system, low/moderate grade lesions (nuclear grade I or II) are split into two groups by the absence (Group I) or the presence (Group II) of comedo-type necrosis. High nuclear grade (grade III) is defined as Group III. Age ≤ 40 years, clinical detection, cribriform or solid/comedo architecture, close, involved or unknown margins, and no postoperative radiation were all risk factors for local recurrence.

Multivariate analysis was not done for each treatment group but, in the single factor analysis, all subgroups had an observed lower incidence of local recurrence in the radiated group compared to the non-radiated group. Two subgroups in the radiated group had local recurrence rates $\geq 20\%$ —those ≤ 40 years of age, a 23% recurrence rate, and those with involved, close, or unspecified resection margins, a 20% recurrence rate.

The NSABP B-17 trial was also designed to evaluate the role of radiotherapy after BCS in women with DCIS (11-13). In this 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. Although the fact has been reported that approximately 90% of lesions were 2cm or less in size, with a mean size of 1.2cm, the debate has been whether size was accurately assessed on this study (26) or an underestimate. Only 8% were detected clinically. 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; $p=0.80$).

The overall incidence of contralateral malignancy was only reported by treatment arm in the 1998 report after a median follow-up of eight years. At that time, the incidence of invasive or in situ contralateral disease was 5.4% in the lumpectomy group (4.9% invasive and 0.5% in situ) and 6.0% in the lumpectomy plus radiation group (3.6% invasive and 2.4% in situ). The 2001 report gave the rate of contralateral breast disease only as a first event rather than at any time, with the rate being 5.8 per thousand patients per year in the lumpectomy group and 8.4 in the radiation group ($p=0.26$).

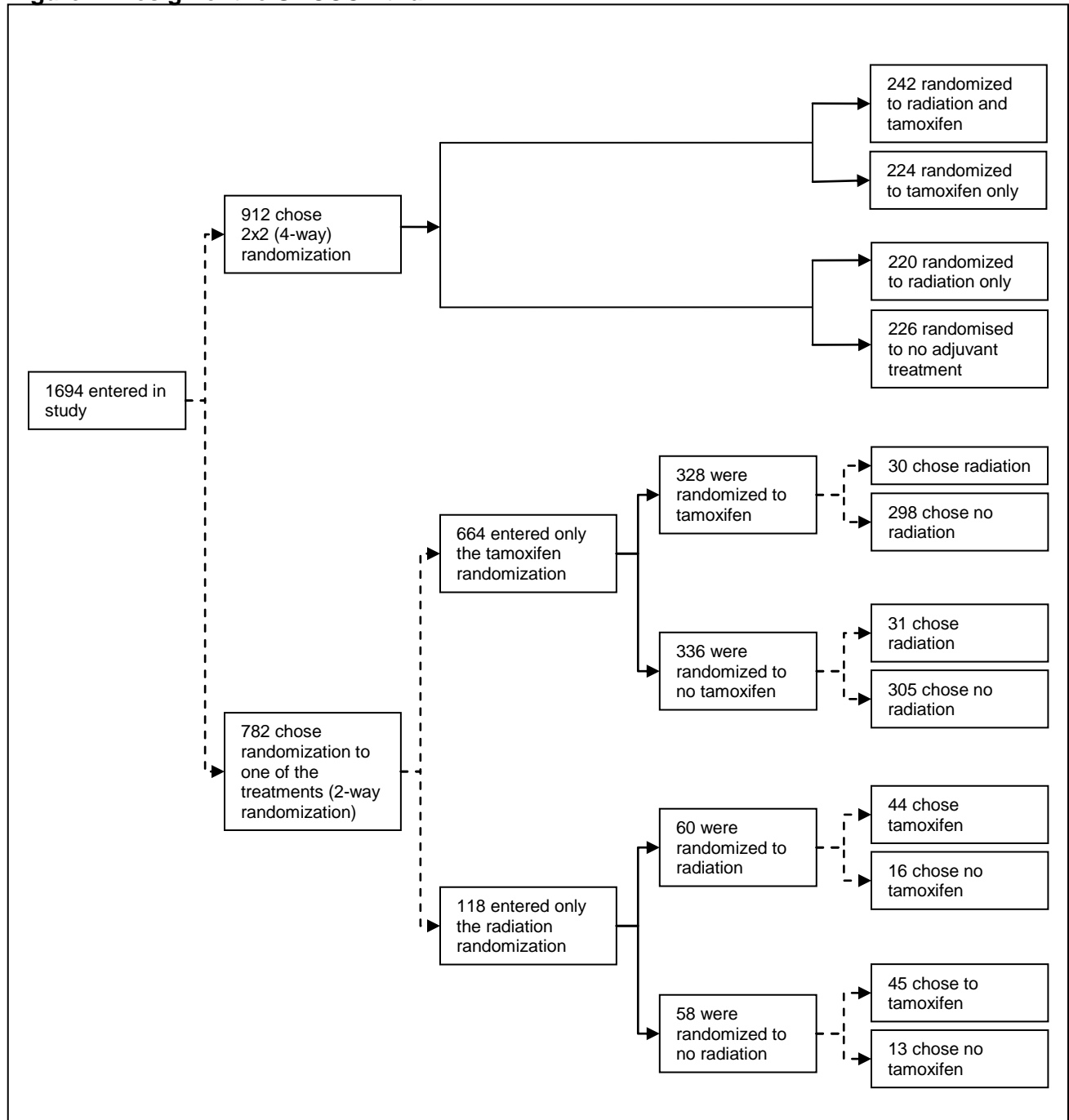
The NSABP initially did a pathologic prognostic factor analysis after five years of follow-up (15) and updated this analysis after eight years of follow-up on a larger group of patients (N=623) who had had central pathology review (14). The pathologic factors examined were comedo necrosis, histologic type, margin status, lymphoid infiltrate, nuclear grade, focality, cancerization, stroma, and tumour size. In a multifactor analysis, only the presence of moderate to marked comedo necrosis was a significant predictor of breast recurrence. The average annual hazard rates for recurrence were lower for all nine pathologic characteristics in the radiated compared to the non-radiated group. When patients were subdivided according to the

Van Nuy's classification, again, recurrence rates were lower in all three groups if the patients had received radiation.

In the United Kingdom Coordinating Committee on Cancer Research (UKCCCR) trial, a complex, modified, 2x2 factorial design (Figure 1) was used to evaluate radiotherapy and tamoxifen in women with completely excised DCIS (16). Women were recruited from breast screening centres, and so the majority (90.5%) were over 50 years of age. Resection margins that were radiologically and histologically free of disease were required. Partway through the study, the decision was made to include patients with microinvasion (< 1 mm in diameter), and these patients made up 3% of the study population. Surgeons and their patients could either choose to enter the four-arm study (no postoperative treatment, tamoxifen alone, radiation alone, or radiation and tamoxifen) or to be randomized only to tamoxifen versus no tamoxifen or radiation versus no radiation. If a patient chose to participate only in the tamoxifen randomization, she could choose whether or not to receive radiation. Similarly, if she entered only the radiation randomization, she could choose whether or not to receive tamoxifen. For the purposes of the analyses, only the patients randomized to tamoxifen versus no tamoxifen were included in the tamoxifen comparison (i.e., patients who entered the radiation part of the study and chose to take tamoxifen were not included in the tamoxifen comparison). The same was true for the radiotherapy comparison.

A total of 1,694 eligible patients were entered into the study, 912 in the four-arm comparison, an additional 664 in the tamoxifen comparison (603 chose not to receive radiation and 61 chose radiation), and an additional 118 in the radiotherapy comparison (89 chose tamoxifen and 29 chose no tamoxifen). The results of the tamoxifen comparison are described in the following section, *Tamoxifen and Radiotherapy versus Radiotherapy Alone*.

Figure 1: Design of the UKCCCR trial.



Abbreviations: UKCCCR, United Kingdom Coordinating Committee on Cancer Research.
 Adapted from Houghton et al (16).
 Dotted lines indicate that allocations were by choice; solid lines indicate random allocation.

A total of 1,030 patients are included in the radiation comparison (912 in the four-arm randomization and 118 in the two-arm randomization). Of these, 522 were randomized to receive radiation, 5000 cGy in 25 daily fractions in five weeks, and 508 were randomized to no radiation. Fifty-four percent in the group who received radiation and 51% in the group that did not receive radiation also 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 (Table 2).

Table 2: Incidence of breast events in patients in the radiotherapy comparison (UKCCCR trial).

Type of event	Randomized to radiotherapy (%)	Randomized to no radiotherapy (%)	HR (95% CI)	p-value
Ipsilateral				
Invasive	3	6	0.45 (0.24, 0.85)	0.01
DCIS	3	7	0.36 (0.19, 0.66)	0.0004
Invasive or DCIS	6	14	0.38 (0.25, 0.59)	<0.0001
Contralateral				
Invasive	2	1	1.50 (0.53, 4.22)	0.44
Invasive or DCIS	2	2	0.82 (0.34, 1.18)	0.65
Total invasive	5	7	0.62 (0.37, 1.04)	0.07
Total DCIS	3	9	0.31 (0.17, 0.56)	<0.0001
Total invasive or DCIS	7	16	0.43 (0.29, 0.63)	<0.0001

Abbreviations: DCIS, ductal carcinoma in situ; HR, hazard ratio; UKCCCR, United Kingdom Coordinating Committee on Cancer Research.

Taken from Houghton et al (16).

Tamoxifen and Radiotherapy versus Radiotherapy Alone

The NSABP B-24 randomized trial investigated the role of tamoxifen, 20 mg daily for five years, versus placebo in addition to BCS and radiotherapy in the treatment of DCIS in 1,804 women (13,17). The majority of patients presented with mammographically detected DCIS (83%), tumours less than or equal to 1cm (84%) and negative margins (75%). Of the 1804 randomized patients, 564 (31.3%) did not complete the assigned therapy (269 on placebo and 295 on tamoxifen). Side effects of treatment was given as the reason for treatment discontinuation in 98 placebo patients and 146 tamoxifen patients. At a median follow-up of 6.9 years, the cumulative seven-year incidence of ipsilateral or contralateral breast malignancy was lower for patients in the tamoxifen group versus those in the placebo group (10.0% vs. 16.9%, p=0.0003). The lower incidence was seen primarily in invasive disease (4.4% vs. 8.5%, p=0.0009). Data broken down by ipsilateral recurrence and contralateral incidence are summarized in Table 3.

Table 3: Cumulative incidence of breast cancer events at seven years (NSABP B-24 trial).

Type of recurrence	Breast cancer events		Rate ratio (95% CI)	P-value
	Placebo (%)	Tamoxifen (%)		
Ipsilateral				
Invasive	5.3	2.6	0.53 (0.32-0.86)	0.01
Non-invasive	5.8	5.0	0.85 (0.56-1.29)	0.48
Contralateral				
Invasive	3.2	1.8	0.64 (0.35-1.17)	0.16
Non-invasive	1.6	0.6	0.32 (0.09-0.93)	0.03

Abbreviation: NSABP, National Surgical Adjuvant Breast Project.

Taken from Fisher et al (13).

The overall seven-year survival rate was 95% for both groups. A substantial number of patients had positive (16%) or unknown (10%) margins for DCIS, and others were known to have residual suspicious calcifications. The recurrence rate in those with negative margins was lower and the effect of tamoxifen less. For those receiving tamoxifen versus placebo, the absolute risk of ipsilateral breast recurrence (invasive or DCIS) was 7.0% versus 8.8% in the margin-negative group and 10.6% versus 14.1% in the unknown or margin-positive group, respectively.

At five years of follow-up, two placebo patients had developed deep vein thrombosis compared with nine tamoxifen patients, and one placebo patient had suffered a non-fatal pulmonary embolus compared with two tamoxifen patients. At seven years of follow-up, three placebo patients had developed endometrial cancer compared with seven tamoxifen patients.

A subgroup analysis was done on the 628 patients for whom estrogen-receptor (ER) status was known (327 placebo and 301 tamoxifen) (27). Seventy-seven percent of the tumours were ER positive, and the risk ratio (RR) of recurrent or new breast pathology with tamoxifen was 0.41 in the ER-positive patients, (95% CI, 0.25-0.65; p=0.0002). In the ER-negative patients, the RR was 0.80 (p=0.5), but the authors point out that the number of events in the ER-negative group was too small (36) to rule out a clinically meaningful benefit (95% CI for RR, 0.41-1.56).

In the UKCCCR trial, 1,576 patients were included in the tamoxifen analyses, 912 in the four-arm randomization and 664 in the two-arm randomization (16). Seven hundred ninety-four patients were randomized to tamoxifen and 782 to no tamoxifen. Only 34% of the tamoxifen group and 32% of the no-tamoxifen group received radiation. Of the 794 patients randomized to receive tamoxifen, 86 (11%) stopped taking the drug before five years or took it for less than the time they were on the trial. After a median follow-up of 52.6 months, there was no statistically significant difference in the occurrence of ipsilateral or contralateral invasive carcinoma or DCIS (Table 4), but there was a difference in the overall incidence of DCIS (ipsilateral and contralateral combined).

Table 4: Incidence of breast events in patients in the tamoxifen comparison (UKCCCR trial).

Type of event	Randomized to tamoxifen (%)	Randomized to No tamoxifen (%)	HR (95% CI)	p-value
Ipsilateral				
Invasive	6	4	1.31 (0.84, 2.03)	0.23
DCIS	7	10	0.74 (0.52, 1.04)	0.08
Invasive or DCIS	13	15	0.90 (0.69, 1.17)	0.42
Contralateral				
Invasive	1	2	0.66 (0.30, 1.46)	0.30
Invasive or DCIS	1	3	0.52 (0.25, 1.07)	0.07
Total invasive	7	6	1.11 (0.76, 1.63)	0.59
Total DCIS	7	11	0.68 (0.49, 0.96)	0.03
Total invasive or DCIS	14	18	0.83 (0.64, 1.06)	0.13

Abbreviation: DCIS, ductal carcinoma in situ; HR, hazard ratio; UKCCCR, United Kingdom Coordinating Committee on Cancer Research.

Taken from Houghton et al (16).

In a comparison between NSABP B-24 and the UKCCCR results, the authors of the UKCCCR noted that only 33% of the patients in their tamoxifen comparison also received radiation. Of these 523 patients who also received radiation, no difference was observed in the incidence of subsequent invasive cancer or DCIS between those who did and did not receive

tamoxifen. In the 1,053 patients who did not receive radiation, the only difference was seen in the incidence of the combination of ipsilateral and contralateral DCIS (Table 5).

Table 5: Incidence of breast events in patients in the tamoxifen comparison, stratified by whether or not they received radiotherapy (UKCCCR trial).

Type of event	Randomized to tamoxifen (%)	Randomized to no tamoxifen (%)	HR (95% CI)	p-value
Patients not receiving radiotherapy (N=1053)				
Ipsilateral invasive	5	4	1.32 (0.81, 2.14)	0.26
Ipsilateral DCIS	6	9	0.73 (0.51, 1.06)	0.10
Total invasive	5	5	1.11 (0.72, 1.72)	0.64
Total DCIS	6	10	0.68 (0.47, 0.97)	0.03
Total invasive or DCIS	12	15	0.80 (0.61, 1.05)	0.11
Patients receiving radiotherapy (N=523)				
Ipsilateral invasive	1	1	1.25 (0.43, 3.61)	0.68
Ipsilateral DCIS	1	1	0.75 (0.28, 2.02)	0.57
Total invasive	2	1	1.11 (0.50, 2.48)	0.80
Total DCIS	1	1	0.75 (0.28, 2.02)	0.57
Total invasive or DCIS	3	3	0.95 (0.51, 1.77)	0.88

Abbreviation: DCIS, ductal carcinoma in situ; HR, hazard ratio; UKCCCR, United Kingdom Coordinating Committee on Cancer Research.

Taken from Houghton et al (16).

In the UKCCCR study, only 9.5% of patients were less than 50 years of age, compared with 33.5% of patients in the NSABP B-24 study. Data by age on the NSABP study was only available for ipsilateral breast malignancy. For this endpoint, the benefit of tamoxifen in both studies was more apparent in women 50 years of age or less (Table 6).

Table 6: Effect of tamoxifen in patients by age at randomization: a comparison of the UKCCCR and the NSABP B-24 trial results.

	Randomized to tamoxifen (%)	Randomized to no tamoxifen (%)	HR (95% CI)	p-value
≤ 50 years				
DCIS or invasive events				
Total UK events	18	26	0.62 (0.30, 1.28)	0.19
UK ipsilateral invasive or DCIS	13	22	0.52 (0.23, 1.20)	0.12
B-24 ipsilateral invasive or DCIS*	11	16	0.62 (0.41, 1.06)	0.09
>50 years				
DCIS or invasive events				
Total UK events	14	17	0.85 (0.65, 1.11)	0.24
UK ipsilateral invasive or DCIS	13	14	0.95 (0.71, 1.26)	0.72
B-24 ipsilateral invasive or DCIS*	5	7	0.78 (0.49, 1.29)	0.36

Abbreviation: DCIS, ductal carcinoma in situ; HR, hazard ratio; NSABP, National Surgical Adjuvant Breast Project; UKCCCR, United Kingdom Coordinating Committee on Cancer Research.

Taken from Houghton et al (16).

* The UKCCCR authors calculated 95% CI and p-values for the B-24 trial by using binomial approximations.

The above studies provide some tamoxifen toxicity data, but the NSABP study P-1 provides detailed data, stratified by patient age, on a large sample of well women considered to be at higher than average risk of developing breast cancer (28). In order to determine if tamoxifen could decrease the likelihood of developing breast cancer, 13,388 women were

randomized to placebo versus tamoxifen, 20 mg daily for five years.. Median follow-up was 54.6 months. The numbers of serious events by treatment arm and by age are given in Table 7, along with the risk ratios and 95% confidence intervals. The largest differences in the number of the serious adverse events appeared to be in women over 50 years of age, although the absolute number of adverse events is small with tamoxifen, as is the incremental risk.

Table 7: Toxicity on tamoxifen versus placebo, NSABP P-1 prevention trial.

Type of Event	Number of Events		RR	RR 95% CI
	Placebo (out of 6,707)	Tamoxifen (out of 6,681)		
Endometrial cancer	15	36	2.53	1.35 to 4.97
Age≤49	8	9	1.21	0.41 to 3.60
Age≥50	7	27	4.01	1.70 to 10.90
Stroke	24	39	1.59	0.93 to 2.77
Age≤49	4	3	0.76	0.11 to 4.49
Age≥50	20	35	1.75	0.98 to 3.20
Pulmonary embolism	6	18	3.01	1.15 to 9.27
Age≤49	1	2	2.03	0.11 to 119.62
Age≥50	5	16	3.19	1.12 to 11.15
Deep vein thrombosis	22	35	1.60	0.91 to 2.86
Age≤49	8	11	1.39	0.51 to 3.99
Age≥50	14	24	1.71	0.85 to 3.58

Abbreviations: NSABP, National Surgical Adjuvant Breast Project; RR, relative risk.
Adapted from Fisher et al (28)

Practice Guidelines on the Management of DCIS

Six relevant, evidence-based practice guidelines (reported in seven sources) were identified (18-24). Table 8 summarizes the main recommendations or statements from each guideline, grouped according to surgical, radiation, or tamoxifen therapy. The fact that the tamoxifen recommendations/statements were made prior to the publication of the UKCCCR trial is important to note.

Table 8: Clinical practice guidelines relevant to the management of DCIS.

Source (reference)	Country of Origin	Date last updated	Recommendation/statement		
			Surgical	Radiation	Tamoxifen
National Breast Cancer Centre (18)	Australia	2003	Excision must obtain clear margins. If margins are involved, further excision is required.	Radiotherapy after complete local excision reduces invasive recurrence. For women with good prognostic features, the overall clinical benefit may be small.	Not addressed.
National Comprehensive Cancer Network (19)	USA	2003	Women with DCIS that is not amenable to margin-free excision should receive mastectomy; otherwise BCS is recommended.	Whole breast irradiation with boost to tumour bed is recommended for women with negative margins. Selected patients with DCIS may be appropriately treated with BCS without irradiation.	Tamoxifen for five years should be considered for patients treated with BCS and radiotherapy or patients treated with BCS alone.
Canadian Breast Cancer Initiative (20,21)	Canada	2001	Mastectomy is recommended for those with large lesions where BCS would produce an unacceptable cosmetic effect or where there is persistent margin involvement after 2 or more attempts at excision.	BCS should usually be followed by radiotherapy, but in cases of small low-grade lesions with clear margins, radiotherapy may be omitted, after a careful discussion with the patient regarding options and risks.	Tamoxifen is a reasonable option for women who want to minimize their risk of recurrence and are willing to accept the risk of tamoxifen toxicity. The potential benefits and risks of tamoxifen for each individual patient should be discussed with that patient.
The Royal College of Radiologists (22)	United Kingdom	1999	Extensive or multifocal DCIS should be treated by mastectomy.	Radiotherapy after BCS reduces the rate of local recurrence, particularly in women with high-grade lesions or positive margins.	The role of tamoxifen remains conjectural.
The Scottish Intercollegiate Guideline Networks (23)	Scotland	1998	Mastectomy is recommended for patients with DCIS greater than 4cm or those with disease affecting more than one quadrant.	Radiotherapy should be considered following BCS with wide local excision.	Not addressed.
New Zealand Guidelines Group (24)	New Zealand	1997	Excision with clear margins is the treatment goal. To achieve this, either mastectomy or BCS may be performed.	Radiotherapy should normally be given following BCS.	Not addressed

Abbreviations: BCS, breast conserving surgery; DCIS, ductal carcinoma in situ.

Additional Considerations for the Management of DCIS of the Breast

Evidence from randomized trials or meta-analyses is not available for a number of issues relevant to the management of DCIS. The following sections address these additional considerations, using expert opinion and non-randomized evidence from a non-systematic literature search. This information is intended to aid the practitioner and his/her patient in the management of DCIS of the breast and does not form the basis for the recommendations.

Technical Factors for Breast-Conserving Surgery for the Treatment of DCIS

The management of DCIS lesions requires close cooperation between the surgeon, radiologist, and pathologist. At present, the majority of patients with DCIS will be identified by mammographic abnormality. Preoperative confirmation of the diagnosis is by core needle biopsy is desirable. A preoperative mammogram with magnification views will often delineate the extent of microcalcifications. In most cases, excision will require preoperative localization by the radiologist, using a hooked wire or a similar device. Bracketing wires may aid in marking the extent of the lesion.

Complete excision of the lesion should be achieved, as studies have shown that positive or indeterminate resection margins increase the risk of local recurrence (15,20,29). A specimen radiograph is recommended for those who have image-guided resections, to ensure that the lesion has been excised. Careful pathologic assessments of the margins should be made, as well as determination of the presence of comedo necrosis and grade, as these factors are predictive of risk for recurrence. If there is any doubt about the completeness of the excision, a postoperative mammogram is recommended. If the excision has been incomplete, a re-excision can be carried out.

With respect to the need for axillary dissection, retrospective data suggest that the incidence of occult microinvasion and positive nodes relates to the size of the primary lesion. Microinvasion is unlikely in lesions of <5 cm (30), and axillary dissection is not indicated. However, areas of DCIS >5.5 cm are associated with invasion in 48% of patients (31). Most women with such areas of DCIS will require a mastectomy for complete excision. Current guidelines for the management of invasive disease recommend axillary staging. If sentinel node biopsy is to be selected as the approach of choice for axillary staging, consideration should be given to sentinel node biopsy at the time of a mastectomy for extensive DCIS. Axillary staging performed after a mastectomy requires axillary lymph node dissection, as sentinel node biopsy is not feasible. If the final pathology after the mastectomy reveals DCIS only, there is no indication for treatment alterations, regardless of the finding of isolated tumour cells (metastases < 0.2 mm) in the sentinel node, since the excellent prognosis of these patients is unlikely to be improved. Clinicopathologic studies have not demonstrated a relationship between axillary micrometastases (<0.2 cm) and prognosis in pure DCIS (32).

As with invasive disease, there are a number of contraindications for BCS. Patients with large tumours or small breasts may not have a satisfactory cosmetic result and may be better served by a simple mastectomy with the option of breast reconstruction. Also, patients with DCIS >5cm were not included in the EORTC study (9), and only four patients in the NSABP B-17 study had lesions greater than 3 cm (12). In the NSABP B-24 study, only 4% of patients had lesions greater than 2 cm (17). Therefore, the local control rates reported in these studies may not be generalizable to patients with larger lesions. The presence of multiple tumours in the breast and the appearance of extensive microcalcifications are also relative contraindications to breast-conserving therapy.

Dose and Fractionation Schedule of Breast Irradiation Following Breast-Conserving Surgery

Dose/Fractionation schedule

All three randomized trials (9,11-13,16) in DCIS used the same dose, fractionation schedule, 5000 cGy in 25 fractions in five weeks. No randomized trials have compared different dose/fractionation schedules in DCIS. One published study compared two different fractionation regimens in women with resectable invasive breast cancer following lumpectomy. The Ontario Clinical Oncology Group 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 (33). 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. Cosmetic outcome was also comparable, with an excellent or good cosmetic outcome of 76.8% in the 16-fraction arm and 77.4% in the 25-fraction arm (absolute difference, -0.6%; 95% CI, -6.5% to 5.5%). Grade 2 or 3 skin toxicity was 66% in the 16-fraction arm and 60% in the 25-fraction arm (absolute difference, 6%; 95% CI, -0.3% to 10%). Four cases of radiation pneumonitis (two in each arm) and one case of rib fracture (in the 25-fraction arm) occurred.

Boost

None of the DCIS studies used an additional “boost” dose to the tumour bed, and no study compared breast radiation alone to breast radiation plus a boost in DCIS. Such studies have, however, been done in patients with invasive breast cancer. There have been four randomized trials in patients with resectable invasive disease, comparing whole breast irradiation to whole breast radiation plus a boost to the tumour bed. Three of these studies were in patients with microscopically clear resection margins, and the fourth included some patients with positive resection margins (34-37). Table 8 summarizes the studies and their results.

Three of the studies showed a statistically significant decrease in local recurrence with the addition of the boost (Table 9). The EORTC “boost vs. no boost” (36) and Lyon trials (35) reported no significant difference in overall survival, and the Nice trial (34) reported no significant difference in cancer-specific survival. The Nice and Lyon trials did not report prognostic factor analyses. In a multivariate analysis, the Budapest boost trial (37) found age < 40 years, positive or close resection margins, and a high mitotic index to be predictive of local recurrence. The EORTC study found young age, a palpable tumour at presentation, and progesterone receptor-negative tumours to be predictive of local recurrence in a multivariate analysis, with “young age” being the strongest predictor. Table 10 provides the five-year actuarial breast recurrence rates by treatment arm and age.

The Lyon, EORTC, and Budapest studies reported cosmetic outcomes. The Lyon study reported no cases of grade 3 telangiectasia and a 5.9% incidence of grade 1 or 2 telangiectasia in the no-boost arm and 12.4% in the boost arm ($p=0.003$). The physician assessment score was good to excellent in 85% of patients, and the patient self-assessment after two years was good to excellent in 90%, with no significant difference in the treatment arms for these outcomes. In the EORTC study, cosmetic assessment, based on photographs, was done in a subset of 731 patients by a panel (38). A relative breast retraction score was also calculated on 1,141 patients, again based on photographic assessment. A good to excellent score was given to 71% in the boost group and 86% in the no-boost group ($p=0.0001$); the breast retraction score was 8.6% and 7.6%, respectively ($p=0.04$). The Budapest study reported 17.3% grade 2 or 3 late effects, according to the RTOG/EORTC scale, in those who received a boost and 7.8% in those who did not ($p=0.03$) and a good to excellent overall score of 85.6% in the boost group versus 91.3% in the no-boost group ($p=0.14$).

Table 9: Randomized trials of whole breast irradiation versus whole breast irradiation with a boost in women with invasive breast cancer.

Lead author, year (ref).	Trial name	Margin status	Median follow-up (years)	Treatment arms	N	Crude breast recurrence rate (%)	p-value	Five-year breast recurrence rate (%)	p-value
Teissier et al, 1998 (34)	Nice trial	Clear	6.1	50Gy/25 whole breast 50Gy/25 whole breast +10Gy/5 boost (electron or proton)	664	6.8 4.3	0.13	NR	NA
Romestaing et al, 1997 (35)	Lyon trial	Clear	3.3	50Gy/20/5wk whole breast 50Gy/20/4wk +10Gy/4 boost (electron)	503 521	4.0 1.9	NR	4.5 3.6	0.044
Bartelink et al, 2001 (36)	EORTC "boost vs. no boost" trial	Clear	5.1	50Gy/25 whole breast 50Gy/25 whole breast +16Gy/8 boost (electron, proton, or implant)	2,657 2,661	6.8 4.1	NR	7.3 4.3	<0.001
Polgar et al, 2002 (37)	Budapest boost trial	some patients had positive margins	5.3 (min. 3 yrs)	50Gy/25 whole breast 50Gy/25 whole breast +16Gy boost (electron or implant)	103 104	15.5 6.7	NR	15.1 7.3	0.049

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer; N, number of patients.

Table 10: EORTC five-year actuarial breast recurrence rates by age group at randomization.

Age group	Randomized to no boost (%)	Randomized to boost (%)	p-value
≤40 years	19.5	10.2	0.002
41-50 years	9.5	5.8	0.02
51-60 years	4.2	3.4	0.07
>60 years	4.0	2.5	0.14

Abbreviations: EORTC, European Organization for Research and Treatment of Cancer.
Adapted from Bartelink et al (36)

Omission of radiotherapy following breast-conserving surgery in low-risk patients

The two randomized trials (10,14) that analyzed prognostic factors did not identify a subgroup that had the same low recurrence rates with or without radiation. However, the numbers of patients in many of the subgroups were small, and the power to detect clinically meaningful differences or interaction was low. There are no published reports of studies that randomized patients at low risk of local recurrence to observation versus adjuvant radiation to determine if any patients might be treated without adjuvant radiation therapy. A number of non-randomized studies are available that attempt to describe a low-risk population.

In 1995, Silverstein reported on a series of 425 consecutive patients (including a retrospective series of 208 cases reported in 1990 (39)) to which a new pathologic classification (the Van Nuys DCIS classification, described above) was prospectively applied (30). Over the course of the study, non-randomized treatment options included, initially, mastectomy; then, BCS plus adjuvant radiation; and later, BCS alone. The option of follow-up only after BCS with clear margins became available in 1989, and most patients, when presented with this option, accepted it. The study presented results from these historical treatment cohorts with an overall median follow-up of 6.5 years. The disease-free survival at eight years was significantly different among all three groups: Group I (nuclear grade I or II without comedo-type necrosis), 93%; Group II (nuclear grade I or II with comedo-type necrosis), 84% (I vs. II, $p=0.05$); and Group III (high nuclear grade), 61% (II vs. III, $p=0.003$). Failures were primarily due to local recurrence. One patient in each of Groups II and III died of breast cancer (p =not stated OR non-significant?).

In 1996, Silverstein et al reported on another prognostic schema, the Van Nuys Prognostic Index (VNPI) (40). In a cohort of 333 DCIS patients treated with BCS (195 by excision only and 138 by excision plus radiation therapy) at the Breast Centre, Van Nuys and the Children's Hospital, San Francisco, California, three independent risk factors for local recurrence were identified: tumour size (>4.1, 1.6-4.0, <1.5 cm); margin width (<1, 1-9, >10 mm), and the previously described Van Nuys pathologic classification (I, II, and III). Scores of 1 (best) to 3 (worst) were assigned for each of the three predictors and totalled to give an overall VNPI score ranging from 3 to 9. The scoring system was applied to the original cohort, and cut-off points were determined by statistical analysis to identify three separate risk groups: low, VNPI score 3 or 4; intermediate, VNPI score 5 to 7; and high, VNPI score 8 or 9. Table 11 shows the risks for recurrence, with and without radiotherapy following BCS.

Table 11: Cumulative risk of ipsilateral breast recurrence (invasive and noninvasive) at eight years related to VNPI score.

VNPI Score	No Radiotherapy		Radiotherapy	
	Number at risk	Rate of local recurrence (%)	Number at risk	Rate of local recurrence (%)
3,4 (low)	76	3	25	0
5-7 (intermediate)	106	32	103	15
8,9 (high)	13	100	10	65

Abbreviations: VNPI, Van Nuys Prognostic Index.

The results suggest that patients at a low risk of recurrence do not benefit from adjuvant radiation, those in the intermediate group do benefit, and those in the high-risk group benefit but remain at substantial risk of recurrence.

In 1999, Silverstein et al reported the pathological results for 469 women with DCIS, 213 who received radiotherapy after BCS and 256 who received no further treatment (41). For patients with margins >10 mm, there was no benefit from radiation therapy in terms of rates of recurrence at eight years (RR, 1.14; 95% CI 0.10 to 12.64; p=0.92), and for patients with margins ranging from 1 to <10 mm, there was no reported benefit from radiotherapy (RR, 1.49; 95% CI; 0.76 to 2.90; p=0.24). However, radiation therapy was of significant benefit for patients with margins <1 mm (RR, 2.54; 95% CI, 1.25 to 5.18; p=0.01). Table 12 summarizes the results of this analysis.

Table 12: Influence of margin width on local control by patient radiotherapy status.

Margin width	No Radiotherapy		Radiotherapy		Relative risk	P-value
	# Patients	# Local recur.	# Patients	# Local recur.		
≥10mm	93	2	40	1	1.14 (0.10, 12.64)	0.92
1 to <10mm	124	23	100	15	1.49 (0.76, 2.90)	0.24
<1mm	39	13	73	21	2.54 (1.25, 5.18)	0.01

Abbreviations: recur., recurrences.

In 2003, Silverstein updated the prognostic index, based on an analysis of 706 DCIS patients treated with breast-conserving therapy (42). In this analysis, age was also identified as an independent prognostic factor in the multivariate analysis, along with tumour size, margin width, and pathologic classification. Based on this new scoring system, women with scores of 4, 5, or 6 had no significant difference in 12-year local recurrence-free survival, whether or not they had radiation treatment. Those with scores of 7, 8, or 9 had improved local control rates when treated with radiation. Those with scores of 10, 11, or 12 had improved local control with radiation but still had an unacceptably high local recurrence rate of 50% at five years with BCS and radiation.

All four studies suggest that different risk groups, which require different management strategies, may be identified (30,40-42). The approach is technically demanding, requiring intensive tissue processing to document the size of the lesion and extent of margins. Specimens are resected en bloc, and the whole specimen is submitted for histologic examination. Each of the six margins is inked and the specimen is then serially sectioned at 2 mm to 3 mm intervals. The interpretation of the results was limited because of the non-randomized historical comparisons and small patient subgroups evaluated.

Other recent studies have attempted to identify and treat highly selected patients with BCS only. Several of these studies have demonstrated late recurrence, especially with low-grade lesions after longer follow-up. Lagios et al reported on a prospective series of 79 patients treated with local excision only (43). Patients were given the option of no further therapy if the

original lesion was detected mammographically and found to be less than 25 mm in size, and postoperative mammograms confirmed no residual microcalcifications. The patients were accrued from 1972 to 1987. In an initial report after 48 months follow-up, a total of eight (10.1%) local recurrences were noted. After 124 months average follow-up, a total of 13 (17%) recurrences had developed, six invasive and seven non-invasive (44). While keeping in mind the limitations of comparisons across studies, in a similar cohort of patients treated with breast irradiation and followed for a similar period, no recurrences were noted in 20 patients (45).

Wong et al (46) reported a single-arm study of wide excision (≥ 1 cm) alone in DCIS patients, grade 1 or 2 with mammographic size ≤ 2.5 cm. Patients did not receive tamoxifen. The accrual goal was 200, but the study was stopped early with 158 patients accrued, because of a high local failure rate. At a median follow-up of 40 months, the actuarial five-year rate of local failure as first site of failure was 12% (13/158; crude recurrence rate, 8.2%). Nine patients recurred with DCIS and four with invasive disease.

The Radiation Therapy Oncology Group initiated a randomized trial (47) of post-lumpectomy radiation versus observation in patients felt to be at relatively low risk of recurrence with surgery alone (unicentric, non-palpable, < 2.5 cm, nuclear grade 1 or 2, with necrosis in < 1 ducts, margins ≥ 3 mm, clinically node negative, plus or minus tamoxifen). The planned sample size was 1790, but accrual was slower than expected and was stopped in July 2006, after 636 patients had been accrued. Despite the smaller sample size, we should still obtain valuable information from this study as the data matures.

The Institute of Cancer Research in the United Kingdom started a similar study in 2004 with a planned sample size of 2000, accrued over five years. Those study results too will help clarify the role of post-lumpectomy radiation in this low-risk patient population (48) (See Table 13. Ongoing phase III trials).

Pathologic Classification of DCIS

Several pathologic DCIS classification systems, based primarily on nuclear grade and/or necrosis, have been proposed to identify lesions more likely to recur or progress to invasive cancer in women treated by BCS (30,49,50). Evidence exists to support the clinical relevance of this approach, showing that high nuclear grade and/or necrosis, particularly extensive comedo necrosis are associated with a higher risk of early local recurrence following BCS (30,31,51). However, no classification system to date has been useful in predicting whether local disease is likely to recur as in situ or invasive carcinoma.

A Breast Health Institute-sponsored panel of experts representing the disciplines of surgical pathology, surgery, breast imaging (radiology), radiation oncology, and biostatistics was convened in 1997 to reach a consensus on the pathologic classification of DCIS (52). Although a single classification system for DCIS was not endorsed at this meeting, the recommendation was that the pathologist should clearly report the nuclear grade of the lesion and the presence or absence of necrosis. If a specific grading system for DCIS is used, this should be stated in the pathology report. The report should also include the architectural patterns present, since this may be clinically important. Studies have shown, for instance, that the micropapillary pattern, when present in pure form, tends to be more extensive (53-55).

The issue of consistency among pathologists in categorizing DCIS has been addressed in a few studies, using the newer classification systems (49,51,56-60). In general, the greatest consistency is achieved using classification systems based primarily on nuclear grade, particularly the Van Nuys scheme. Use of a synoptic report is recommended (52,61).

DISCUSSION

In the surgical management of DCIS, the choice between mastectomy and BCS should be dependent upon patient preference and the results of clinical, mammographic, and pathologic evaluation. Mastectomy is indicated for patients at high risk of recurrence with BCS

and radiation. High-risk factors include large size tumours (>5cm), particularly those with positive margins. While optimal margin widths for patients having BCS and radiation are not specifically known, close lateral margin widths of <1 mm have been associated with higher local recurrence rates in some studies. Patients with smaller areas of DCIS with resection margins \leq 1 mm or positive resection margins are also at a higher than average risk of recurrence. Mastectomy with the option of reconstruction is also an acceptable choice for women preferring to maximize local control. Given the importance of breast conservation for the patient and the potential for salvage, BCS and radiation is an equally acceptable option for eligible women with DCIS.

There are currently three prospective randomized trials (9-16) that support the routine use of radiation following BCS for patients with DCIS of the breast. Radiation resulted in reduced rates of breast recurrence (both invasive and non-invasive) and mastectomy. Patients should be made aware of the duration of radiation and its toxicity before making a choice between total mastectomy and BCS. All three studies used the dose-fractionation schedules of 5000 cGy in 25 fractions in five weeks, which should be considered the standard; however, the OCOG randomized trial in patients with invasive breast cancer showed that the shorter fractionation schedule of 4250 cGy in 16 fractions was as effective as and no more toxic than 5000 cGy in 25 fractions. We could find no radiobiological evidence to suggest that DCIS responds differently to radiation than invasive disease. The Breast Cancer DSG therefore felt it would be reasonable to offer this shorter fractionation schedule to those women with DCIS who preferred the convenience of a shorter overall treatment time.

None of the randomized studies in DCIS added a boost to the tumour bed. Randomized trials of boost versus no boost in patients with invasive disease (34-37) have shown a decrease in local recurrence rates when a boost of 1000 to 1600 cGy is added, particularly in younger women or those with close or positive resection margins. Some DCIS studies (29,41,62) have shown increased recurrence rates in younger women and those with close resection margins who received standard postoperative whole breast radiation without a boost. The Breast Cancer DSG therefore felt it reasonable to consider the addition of a boost to the tumour bed in those DCIS patients who are felt to be at higher than usual risk of recurrence with standard whole breast radiation alone, provided the patients are willing to accept the possibility of a somewhat poorer cosmetic outcome.

Identifying a group of patients treated with BCS for DCIS who do not require adjuvant radiotherapy is not yet possible. Current data (39-42) suggest that age, tumour size, margin status, grade, and comedo-type necrosis are important predictors for local recurrence. These studies suggest that there may be different risk groups for local failure (e.g., low, intermediate, and high) where different treatments may be more desirable—low risk, BCS alone; moderate risk, BCS plus radiation; and high risk, total mastectomy plus or minus reconstructive surgery. Further evidence is necessary before making firm recommendations and prospective randomized trials looking at this question are ongoing. Until then, it is recommended that pathologic descriptions including assessment of size, margin status, nuclear grade, and evidence of comedo necrosis be reported more consistently. Patients interested in BCS alone should be made aware of what is currently known about the potential benefits and toxicities of post-lumpectomy radiation.

The NSABP-24 study (13,17) showed an overall decrease in invasive and in situ disease with the addition of tamoxifen to surgical excision followed by radiation, but most of the benefit appeared to be in younger women and those with positive or unknown resection margins. The UKCCCR (16) study showed no benefit with the addition of tamoxifen, but the study population consisted mostly of women over 50 years of age with clear resection margins. There was an observed benefit in the subset of women less than 50 years of age and also in those who did not receive radiation. Therefore, the Breast Cancer DSG felt that five years of tamoxifen is an option for DCIS patients, particularly in women less than 50 years of age, those with positive

resection margins who refuse further surgery, and those who refused or are unable to have radiation but want to avoid mastectomy. Patients and physicians need to consider the potential toxicities of tamoxifen as well as the possible benefits.

ONGOING TRIALS

Table 13 lists ongoing randomized trials that were identified through a systematic search of the U.S. National Cancer Institute Clinical Trials Database and that address questions of interest in this systematic review. Additionally, one study of note, identified through a non-systematic search of the database, is the E5194 study, National Library of Medicine (NLM) identifier NCT00002934 (63). This study is a prospective cohort study designed to examine the role of local excision alone in low-risk patients with DCIS characterized by low- or intermediate-grade tumours less than 2.5 cm in size or high-grade tumours less than 1 cm in size that have been resected with greater than 3 mm margins.

CONCLUSIONS

Women with DCIS of the breast who are candidates for BCS should be offered the choice of BCS or total mastectomy. Mastectomy with the option for reconstruction remains an acceptable choice for women preferring to maximize local control. Mastectomy, with the option of reconstruction, is recommended for those who have a large enough area of DCIS that BCS would leave the woman with an unacceptable cosmetic result. When BCS is performed, all mammographically suspicious calcifications should be removed, and margins should be microscopically clear of DCIS.

Women with DCIS who have BCS should be offered adjuvant breast irradiation to minimize the risk of recurrent neoplasia. Patients considered to be at relatively low risk of recurrence with surgery alone should be referred to a radiation oncologist for a thorough discussion of what is currently known about the potential benefits and toxicities of radiation in their particular situation.

While there is some evidence to suggest that tamoxifen is effective in the reduction of ipsilateral recurrence and contralateral incidence of neoplasia in women with DCIS, the absolute benefit is small and the evidence is conflicting. Women should be informed of the option of five years of tamoxifen therapy and of the potential toxicities and benefits associated with tamoxifen. Subset analyses of the randomized trials suggest that women who are most likely to have a positive benefit/risk ratio with tamoxifen are those who are less than 50 years of age or have positive or unknown resection margins, and this information can be considered in decision making. Those with positive estrogen-receptor tumours also seem to have the greatest benefit in the subset analysis of one of the studies. Therefore, if tamoxifen is felt to be of benefit for an individual patient, hormone-receptor assessment could be considered in order to aid in the decision regarding tamoxifen treatment. Postmenopausal women who opt for adjuvant tamoxifen should consider participating in the NSABP Trial B-35, comparing tamoxifen to anastrozole after lumpectomy and radiation.

CONFLICT OF INTEREST

None of the authors declared any potential or actual conflict of interest.

JOURNAL REFERENCE

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- Wright JR, Whelan TJ, McCready DR, et al. Management of ductal carcinoma in situ of the breast. *Cancer Prev Control*. 1998;2(6):312-19.

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Contact Information

For further information about this series, please contact **Dr. Wendy Shelley**; Kingston Regional Cancer Centre, 25 King St W, Kingston ON, K7L 5P9; Telephone: 613-544-2631 x4502; Fax: 613-546-8209; E-mail: wendy.shelley@krcc.on.ca.

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Table 13. Ongoing phase III trials.

Protocol ID and NLM Identifier	First Published	Trial Sponsor	Projected Accrual	Purpose
RTOG-9804, NCT00003857 (47)	June 1, 1999	NCI	1,790 within 6 years. Accrual Stopped in July 2006 after 636 patients randomized	<ul style="list-style-type: none"> ▪ Compare the efficacy of whole breast radiotherapy vs. observation with or without optional tamoxifen in decreasing or delaying the appearance of local failure (both invasive and in situ) and preventing the need for mastectomy in women with good-risk ductal carcinoma in situ (DCIS) of the breast. ▪ Compare distant disease-free survival of patients treated with these regimens.
NSABP-B-35, NCT00053898 (64)	January 26, 2003	NCI	1,500 per arm within 5 years, accrual complete	<ul style="list-style-type: none"> ▪ Compare the value of anastrozole vs. tamoxifen, in terms of preventing recurrence (i.e., local, regional, and distant recurrences and contralateral breast cancer), after lumpectomy and radiotherapy in postmenopausal women with ductal carcinoma in situ (DCIS). ▪ Compare subsequent disease occurrence, in terms of invasive breast cancer (local, regional, distant, or contralateral), ipsilateral and contralateral breast cancer (invasive and DCIS), and non-breast second primary malignancies, in patients treated with these drugs. ▪ Compare quality of life and symptoms of patients treated with these drugs. ▪ Compare quality-adjusted survival time of patients treated with these drugs. ▪ Compare the occurrence of osteoporotic fractures in patients treated with these drugs. ▪ Compare disease-free and overall survival of patients treated with these drugs.
CRUK-IBIS-II-DCIS, NCT00072462 (65)	October 25, 2003	Cancer Research UK	4,000 within 4 years	<ul style="list-style-type: none"> ▪ Compare the efficacy of adjuvant tamoxifen vs. anastrozole, in terms of local control and prevention of contralateral disease, in postmenopausal women with locally excised ductal carcinoma in situ. ▪ Compare side effect profiles of these drugs in these patients.

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Protocol ID and NLM Identifier	First Published	Trial Sponsor	Projected Accrual	Purpose
NSABP-B-39, NCT00103181 (66)	January 24, 2005	NCI	1,500 per arm within 2 years, 5 months	<p>Primary</p> <ul style="list-style-type: none"> ▪ Compare local tumour control in women with ductal carcinoma in situ or stage I or II breast cancer treated with adjuvant whole breast vs. partial breast irradiation. <p>Secondary</p> <ul style="list-style-type: none"> ▪ Compare overall survival, recurrence-free survival, and distant disease-free survival in patients treated with these regimens. ▪ Compare the cosmetic result in patients treated with these regimens. ▪ Compare fatigue and treatment-related symptoms in patients treated with these regimens. ▪ Compare perceived convenience of care in patients treated with these regimens. ▪ Compare acute and late toxic effects of these regimens in these patients.
96/84 Graham, NCT00138814 (67)	NR	St. George Hospital and Community Health Service, Sydney, New South Wales, Australia	NR	<ul style="list-style-type: none"> ▪ Compare boost versus no boost radiotherapy. (Patient population includes DCIS if completely excised.)
OCOG-2005-RAPID, NCT00282035 (68)	NR	Ontario Clinical Oncology Group	NR	<ul style="list-style-type: none"> ▪ Determine if accelerated partial breast irradiation, using 3D CRT, is as effective as whole breast irradiation following BCS in with DCIS or invasive non-metastatic breast cancer.
ICR-DCIS-II, NCT00077168 (48)	January 23, 2004	Institute for Cancer Research, UK	1,000 per arm within 5 years	<p>Primary</p> <ul style="list-style-type: none"> • Compare ipsilateral tumour relapse and metastases in women with completely excised low-risk hormone receptor-positive DCIS who are receiving adjuvant tamoxifen or anastrozole and treated with adjuvant radiotherapy versus observation. • Compare quality of life. <p>Secondary</p> <ul style="list-style-type: none"> • Determine minimal surgical margins required to minimize local recurrence. • Identify molecular markers that predict ipsilateral tumour recurrence.

Abbreviations: DCIS, ductal carcinoma in situ; NCI, National Cancer Institute (USA); NR, not reported.

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Evidence-based Series #1-10 Version 2.2006: Section 3

**Management of Ductal Carcinoma in Situ of the Breast:
Guideline Development and External Review –
Methods and Results**

*W. Shelley, D. McCreedy, C. Holloway, M. Trudeau, S. Sinclair,
and the members of the Breast Cancer Disease Site Group*

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Report Date: September 19, 2006
Replaces Original Report dated 1998

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The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO) (1). The PEBC mandate is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care.

The PEBC supports a network of disease-specific panels, called Disease Site Groups (DSGs) and Guideline Development Groups (GDGs), mandated to develop the PEBC products. These panels are comprised of clinicians, other health care providers, methodologists, and community representatives from across the province.

The PEBC is well known for producing evidence-based practice guideline reports, using the methods of the Practice Guidelines Development Cycle (1,2). The PEBC reports consist of a comprehensive systematic review of the clinical evidence on a specific cancer care topic, an interpretation of and consensus agreement on that evidence by our DSGs and GDGs, the resulting clinical recommendations, and an external review by Ontario clinicians in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each clinical practice guideline report, through the routine periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original clinical practice guideline information.

The Evidence-based Series: A New Look to the PEBC Practice Guidelines

Each Evidence-based Series is comprised of three sections.

- *Section 1: Clinical Practice Guideline.* This section contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the DSG or GDG involved and a formalized external review by Ontario practitioners.

- *Section 2: Systematic Review.* This section presents the comprehensive systematic review of the clinical and scientific research on the topic and the conclusions reached by the DSG or GDG.
- *Section 3: Guideline Development and External Review: Methods and Results.* This section summarizes the guideline development process and the results of the formal external review by Ontario practitioners of the draft version of the clinical practice guideline and systematic review.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This evidence-based series was developed by the Breast Cancer DSG of CCO's PEBC. The series is a convenient and up-to-date source of the best available evidence on the management of ductal carcinoma in situ (DCIS) of the breast, developed through systematic review, evidence synthesis, and input from practitioners in Ontario.

Report Approval Panel

Prior to the submission of this Evidence-based Series report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. The Report Approval Panel did not identify any issues of concern and approved the report as submitted to them.

External Review by Ontario Clinicians

Following the review and discussion of Sections 1 and 2 of this evidence-based series and review and the approval of the report by the PEBC Report Approval Panel, the Breast Cancer DSG circulated the clinical practice guideline and systematic review to clinicians in Ontario for review and feedback. Box 1 summarizes the draft clinical recommendations and supporting evidence developed by the panel.

<p>BOX 1: DRAFT RECOMMENDATIONS (approved for external review June 1, 2006)</p> <p>Target Population These recommendations apply to women with DCIS.</p> <p>Recommendations and Key Evidence <i>Surgical Management</i></p> <p>Women with DCIS of the breast who are candidates for breast-conserving surgery should be offered the choice of breast-conserving surgery or total mastectomy.</p> <p>Mastectomy with the option for reconstruction remains an acceptable choice for women preferring to maximize local control.</p> <ul style="list-style-type: none"> ▪ No randomized trials designed to compare total mastectomy with breast-conserving surgery for DCIS were found. The National Surgical Adjuvant Breast Project (NSABP) B-06 trial (1) involved women with invasive malignancy. However, a small number of women entered were found, on pathology review, to have only DCIS. An analysis based on this subgroup of DCIS patients (2) found a trend towards a much higher local recurrence rate in patients who received breast-conserving surgery alone (9/21; 43%), compared with those who received either breast-conserving surgery plus radiotherapy (2/27; 7%) or mastectomy

(0/28; 0%). Two meta-analyses (3,4), consisting mainly of non-randomized trials, also demonstrated higher local recurrence in patients treated by breast-conserving surgery alone versus those treated by mastectomy. One reported no significant differences in local recurrence rates between patients treated by breast-conserving surgery followed by radiotherapy and mastectomy, whereas the second showed improved local recurrence rates with mastectomy. The expert opinion of the Breast Cancer DSG is that this non-randomized data supports the recommendation that breast-conserving surgery followed by radiation is an acceptable treatment option, in addition to mastectomy.

Qualifying Statements

- When breast-conserving surgery is performed, all mammographically suspicious calcifications should be removed and margins should be microscopically clear of DCIS.
- Mastectomy, with the option of reconstruction, is recommended for those women who have an area of DCIS large enough that breast-conserving surgery would leave them with an unacceptable cosmetic result.

Radiotherapy

Women with DCIS who have had breast-conserving surgery should be referred to a radiation oncologist for a discussion regarding the role of radiation in their treatment.

Women with DCIS who have undergone breast-conserving surgery should be offered adjuvant breast irradiation. Women with small (less than 2.5 cm.) grade I or II tumours that are completely resected with resection margins clear by ≥ 3 mm should consider participating in the National Cancer Institute of Canada Radiation Therapy Oncology Group (NCIC/RTOG) clinical trial exploring radiation versus wide excision alone.

- Three randomized trials (5-12) investigated the role of radiotherapy after breast-conserving surgery in patients with DCIS. In each, the risk of invasive and non-invasive ipsilateral recurrence was reduced with adjuvant radiotherapy. There were no significant differences in distant metastasis or overall survival.

Tamoxifen

While there is some evidence to suggest that tamoxifen is effective in the reduction of ipsilateral recurrence and contralateral incidence in women with DCIS, the absolute benefit is small and the evidence is conflicting.

Women should be informed of the option of five years of tamoxifen therapy and of the potential toxicities and benefits associated with tamoxifen. If post-menopausal women choose to accept adjuvant treatment, they should consider participation in the NSAPB study B-35, comparing tamoxifen to anastrozole following lumpectomy and radiation .

- Two trials (9,12,13) investigated the role of tamoxifen versus no tamoxifen in addition to breast-conserving surgery and radiotherapy in the treatment of DCIS. The first demonstrated a significantly lower cumulative incidence of ipsilateral or contralateral breast malignancy for patients in the tamoxifen group versus those in the placebo group. In the second, tamoxifen treatment did not significantly reduce the incidence of either ipsilateral or contralateral breast malignancy.

Qualifying Statement

- In a subset analysis of one of the randomized studies (14), the beneficial effect of tamoxifen was most apparent in the estrogen receptor-positive patients. Therefore, if it is felt that a patient might benefit from tamoxifen for one of the above reasons, hormone receptor assessment could be considered in order to aid in the decision regarding tamoxifen treatment.
- Randomized studies suggest that women who are most likely to have a positive benefit/risk ratio with tamoxifen are those who are less than 50 years of age or who have positive resection margins and refuse further surgery. Women who have a contraindication to radiation or who refuse this treatment but still want to avoid mastectomy should also be considered for tamoxifen therapy.

Methods

Feedback was obtained through a mailed survey of 109 practitioners in Ontario, including 54 surgeons, 31 radiation oncologists, and 24 medical oncologists. The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. The survey was mailed out on June 23, 2006. Follow-up reminders were sent at two weeks (post card) and four weeks (complete package mailed again). The authors reviewed the results of the survey.

Results

Forty-eight responses were received out of the 109 surveys sent (44.0% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the practitioners who responded, 38 (79.2%) indicated that the report was relevant to their clinical practice, and they completed the survey. Key results of the practitioner feedback survey are summarized in Table 1.

Table 1. Responses to eight items on the practitioner feedback survey.

Item	Number (%)		
	Strongly agree or agree	Neither agree nor disagree	Strongly disagree or disagree
The rationale for developing a guideline, as stated in the "Introduction" section of the report, is clear.	94.1%	2.6%	2.6%
There is a need for a guideline on this topic.	97.4%	0%	2.6%
The literature search is relevant and complete.	89.5%	7.9%	2.6%
The results of the trials described in the report are interpreted according to my understanding of the data.	92.1%	5.3%	2.6%
The draft recommendations in the report are clear.	92.1%	2.6%	5.3%
I agree with the draft recommendations as stated.	92.1%	2.6%	5.3%
This report should be approved as a practice guideline.	92.1%	2.6%	5.3%
If this report were to become a practice guideline, how likely would you be to make use of it in your own practice?	Very likely or likely	Unsure	Not at all likely or unlikely
	94.4%	5.6%	0%

Summary of Written Comments

Five respondents (13.2%) provided substantive written comments. The main points contained in the written comments, with the response of the authors, were:

- SUMMARY – One respondent suggested that the recommendation regarding mastectomy and BCS should be modified to stress that no survival benefit has been

found for either type of surgery. **RESPONSE** – A statement was added to the key evidence of the recommendation to this effect.

- **SUMMARY** – Two respondents pointed out that the NCIC/RTOG trial was no longer open, and that a recommendation that patients should be enrolled in it was not valid. **RESPONSE** – This portion of the recommendation was removed. The recommendation regarding radiation was also changed to address the management of those at relatively low risk of recurrence with surgery alone, given that this randomized trial is no longer open to accrual.
- **SUMMARY** – One respondent suggested that the document should strongly recommend the use of post-excision radiographs to rule out residual disease. **RESPONSE** – The writing committee did not feel that a strong recommendation for the use of post-excision radiographs was necessary. The committee felt that, if current state-of-the-art preoperative and specimen radiography was utilized and the specimen radiograph and microscopic examination was supportive of complete excision, a post-excision radiograph was not necessary. The committee felt that the sentence under the Technical Factors section on page 14, which reads, “If there is any doubt about the completeness of excision, a postoperative mammogram is recommended.” was sufficient. No change was made to the document, based on this comment.
- **SUMMARY** – One respondent stated that prescriptive recommendations with respect to the available trial were questionable, and the data supporting no “XRT” was soft. **RESPONSE** – As above for the comments regarding the closure of this study.
- **SUMMARY** – One respondent asked whether there was any data on compliance in the Tamoxifen studies. **RESPONSE** – Data on compliance was included in the relevant section of the Systematic Review.

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Contact Information

For further information about this series, please contact **Dr. Wendy Shelley**; Kingston Regional Cancer Centre, 25 King St W, Kingston ON, K7L 5P9; Telephone: 613-544-2631 x4502; Fax: 613-546-8209; E-mail: wendy.shelley@krcc.on.ca.

For information about the PEBC and the most current version of all reports, please visit the CCO Web site at <http://www.cancercare.on.ca/> or contact the PEBC office at:
Phone: 905-525-9140, ext. 22055 Fax: 905-522-7681

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