Evidence-based Series 1-1 Version 3—Education and Information 2015

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

Surgical Management of Early-Stage Invasive Breast Cancer

Members of the Breast Cancer Disease Site Group

An assessment conducted in January 2015 put Evidence-based Series (EBS) 1-1 Version 3 in the Education and Information section. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes.

Evidence-based Series (EBS) 1-1 Version 3, the resulting review report, consists of the following 4 parts:
1. Guideline Overview
2. Summary
3. Full Report
4. Document Assessment and Review Tool

and is available on the CCO website (http://www.cancercare.on.ca)
PEBC Breast Cancer Disease Site Group page at:
http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/breast-ebs/.

Release Date: September 15, 2011

For information about the PEBC and the most current version of all reports, please visit the CCO website at http://www.cancercare.on.ca/ or contact the PEBC office at:
Phone: 905-527-4322 ext. 42822   Fax: 905-526-6775   E-mail: ccopgi@mcmaster.ca

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Evidence-based Series 1-1 Version 3

Surgical Management of Early-Stage Invasive Breast Cancer

Guideline Report History

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<th>GUIDELINE VERSION</th>
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<th>PUBLICATIONS</th>
<th>NOTES AND KEY CHANGES</th>
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<td>1966 to 1996</td>
<td>Full Report</td>
<td>Peer review publication¹ Web publication Not applicable (NA)</td>
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<td>1996 to 2003</td>
<td>New data added to original Full Report</td>
<td>Peer review publication² Updated Web publication</td>
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Evidence-based Series 1-1 Review Update 2011

Surgical Management of Early-Stage Invasive Breast Cancer

Guideline Review Summary

Review Date: November 19, 2010

The 2003 guideline recommendations are ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW
Evidence-based Series History
This guidance document was originally released by the Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO) in 1996. The first update was released in January 2003. In November 2010, the PEBC guideline update strategy was applied and the new updated document released in September 2011. The Summary and the Full Report in this review update are the same as in the January 2003 version.

Update Strategy
Using the Document Assessment & Review Tool (at the end of this document) as the updating strategy, the PEBC review includes an updated search of the literature, review and interpretation of the new eligible evidence by clinical experts from the authoring guideline panel, and consideration of the guideline and its recommendations in response to the new available evidence.

DOCUMENT ASSESSMENT AND REVIEW RESULTS
Questions Considered
1. In the surgical management of patients with early-stage invasive breast cancer (stage I and II), who are candidates for breast conservation therapy, how does breast conservation therapy compare to modified radical mastectomy in terms of survival, disease recurrence and quality of life?
2. What is the optimum management of the axilla?
Literature Search and New Evidence
The new search (June 2002 through May 2010) yielded five relevant new publications from five randomized controlled trials (RCTs) whose initial publications were already included in the original document. Brief results of these publications are shown in the Document Assessment & Review Tool at the end of this report.

Impact on Guideline and Recommendations
The new data supports existing recommendations for Guideline Question 1 (Q1) (mastectomy versus breast conserving surgery). Hence, the Breast Cancer DSG ENDORSED the 2003 recommendations on mastectomy versus breast conserving surgery.

The opinion was that the consideration of evidence and recommendations relevant to guideline Q2 had been addressed more fully in a complementary guidance document developed in 2009 (EBS 17-5: Sentinel Lymph Node Biopsy in Early-stage Breast Cancer). Therefore, a search for new literature with respect to this question was not conducted, and the recommendations regarding this question are no longer relevant to this document, as noted in the recommendations section (page vi) of this report.
Surgical Management of Early-Stage Invasive Breast Cancer

Members of the Breast Cancer Disease Site Group


Report Date: January 2003

SUMMARY

Guideline Questions

• In the surgical management of patients with early-stage invasive breast cancer (Stage I and II) who are candidates for breast conservation therapy, how does breast conservation therapy compare to modified radical mastectomy in terms of survival, disease recurrence and quality of life?

• What is the optimum management of the axilla?

Target Population
Women with early-stage (Stage I and II) invasive breast cancer who are eligible for either breast conservation therapy or mastectomy.

Recommendations

• Women who are eligible for breast conservation therapy should be offered the choice of either breast conservation therapy with axillary dissection or modified radical mastectomy.

NOTE: While the previous version of this document contained recommendations for the optimal management of the axilla, these recommendations have been superseded by those found in a more recent PEBC guidance document, EBS 17-5: Sentinel Lymph Node Biopsy in Early-stage Breast Cancer. Therefore, the recommendations for the optimal management of the axilla have been deleted from this version of this guideline; readers are referred to document EBS 17-5 for recommendations on this issue.

Qualifying Statements

• With no difference in survival or distant recurrence, the choice between breast conservation therapy with axillary dissection and modified radical mastectomy should be dependent upon patient preference where appropriate.
• Each patient should be fully informed of the risks and benefits of each procedure.
• Patients should be aware that breast conservation therapy involves tumour excision with clear margins, axillary dissection, and adjuvant breast irradiation.
• Patients who choose breast conservation therapy should be aware that there is also the potential need for further surgery, possibly a mastectomy, in cases of local recurrence.
• Evidence surrounding quality of life after surgery is conflicting, but there is some evidence suggesting that women who receive breast-conserving therapy may have higher body self image than those who undergo mastectomy.
• In some instances, preoperative chemotherapy can shrink a large primary tumour and allow for breast conservation therapy. However, in such circumstances, there may be an increased risk of local breast cancer recurrence following breast irradiation.

Methods
The literature was searched using MEDLINE (through June 2002), and the Cochrane Library (Issue 2, 2002). The Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society of Radiation Oncology, article bibliographies, and personal files were also searched to June 2002.

Evidence was selected and reviewed by six members of the Practice Guidelines Initiative Breast Cancer Disease Site Group and methodologists. This practice guideline has been reviewed and approved by the Breast Cancer Disease Site Group, which is comprised of surgeons, medical oncologists, radiation oncologists, epidemiologists, pathologists, a medical sociologist, and a patient representative.

External review by Ontario practitioners was obtained through a mailed survey. Final approval of the practice guideline report has been obtained from the Practice Guidelines Coordinating Committee.

The Practice Guidelines Initiative has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature and where appropriate, integration of this literature with the original guideline information.

Key Evidence
• Eleven large randomized trials that followed participants for up to 20 years did not detect significant differences in overall survival or in rates of distant recurrence between breast-conserving surgery and mastectomy.
• Six randomized trials, spanning four decades, detected absolute improvements in survival rates ranging from 4% to 16% with axillary node dissection compared to no axillary dissection. Meta-analysis of results from the six trials detected a significant survival benefit of 5.4% (95% confidence interval, 2.7% to 8.0%; p<0.01) for axillary node dissection. However, evolving treatment modalities may diminish the effect of the survival benefit.

Related Guidelines
• Practice Guidelines Initiative’s Evidence Summary #13-1: Treatment of Lymphedema Related to Breast Cancer (under development).
• Evidence-based Series (EBS) #17-5 Sentinel Lymph Node Biopsy in Early-stage Breast Cancer.
Contact information

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or

Dr. Maureen Trudeau; Co-chair, Breast Cancer Disease Site Group; Toronto-Sunnybrook Regional Cancer Centre, 2075 Bayview Ave, Toronto ON, M4N 3M5; Telephone 416-480-5145; FAX 416-217-1338; E-mail: maureen.trudeau@tsrcc.on.ca.

The Practice Guidelines Initiative is sponsored by:
Cancer Care Ontario & the Ontario Ministry of Health and Long-term Care.
Visit [http://www.cancercare.on.ca](http://www.cancercare.on.ca) for all additional Practice Guidelines Initiative reports.
PREAMBLE: About Our Practice Guideline Reports

The Practice Guidelines Initiative (PGI) is a project supported by Cancer Care Ontario (CCO) and the Ontario Ministry of Health and Long-Term Care, as part of the Program in Evidence-based Care (PEBC). The purpose of the Program is to improve outcomes for cancer patients, to assist practitioners to apply the best available research evidence to clinical decisions, and to promote responsible use of health care resources. The core activity of the Program is the development of practice guidelines by multidisciplinary Disease Site Groups of the PGI using the methodology of the Practice Guidelines Development Cycle. The resulting practice guideline reports are convenient and up-to-date sources of the best available evidence on clinical topics, developed through systematic reviews, evidence synthesis, and input from a broad community of practitioners. They are intended to promote evidence-based practice.

This practice guideline report has been formally approved by the Practice Guidelines Coordinating Committee, whose membership includes oncologists, other health providers, patient representatives and Cancer Care Ontario executives. Formal approval of a practice guideline by the Coordinating Committee does not necessarily mean that the practice guideline has been adopted as a practice policy of CCO. The decision to adopt a practice guideline as a practice policy rests with each regional cancer network that is expected to consult with relevant stakeholders, including CCO.

Reference:

For the most current versions of the guideline reports and information about the PEBC, please visit the CCO Web site at: http://www.cancercare.on.ca
For more information, contact our office at:
Phone: 905-527-4322 ext. 42822 Fax: 905-526-6775
E-mail: ccopgi@mcmaster.ca

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I. QUESTIONS
In the surgical management of early-stage invasive breast cancer (Stage I and II), how does breast conservation therapy compare to modified radical mastectomy in terms of survival, disease recurrence, and quality of life? What is the optimum management of the axilla?

II. CHOICE OF TOPIC AND RATIONALE
The Provincial Breast Cancer Disease Site Group (DSG) chose the surgical management of early-stage breast cancer as a priority for guideline development in 1995 because of the importance of the topic and the reported geographic variation in practice. Since the original practice guideline report was completed in February 1996, the medical literature has been monitored for new evidence relevant to this practice guideline. With changes in practice, updated results from surgery trials, and more recent evidence on axillary dissection, sentinel-node biopsy and quality of life, it was felt that the original guideline document should be revised to reflect the current state of the art in the surgical management of early-stage invasive breast cancer.

III. METHODS
Guideline Development
This practice guideline report was developed by the Practice Guidelines Initiative (PGI), using the methodology of the Practice Guidelines Development Cycle (1). Evidence was selected and reviewed by six members of the PGI’s Breast Cancer Disease Site Group and methodologists.

The guideline is a convenient and up-to-date source of the best available evidence on the surgical management of early-stage breast cancer, developed through systematic reviews, evidence synthesis, and input from practitioners in Ontario. It is intended to enable evidence-based practice. The Practice Guidelines Initiative is editorially independent of Cancer Care Ontario, and the Ontario Ministry of Health and Long-term Care.

External review by Ontario practitioners was obtained through a mailed survey consisting of items that address the quality of the draft practice guideline report and recommendations, and whether the recommendations should serve as a practice guideline. Final approval of the original guideline report has been obtained from the Practice Guidelines Coordinating Committee.
The PGI has a formal standardized process to ensure the currency of each guideline report. This consists of periodic review and evaluation of the scientific literature, and where appropriate, integration of this literature with the original guideline information. This document replaces the practice guideline report on the surgical management of early-stage breast cancer originally completed in 1996 (2).

Guideline History
A PGI practice guideline on the surgical management of early-stage invasive breast cancer was originally completed on February 14th 1996 and published in Cancer Prevention and Control 1997;1(1):10-17. In 2001/2002, the Breast Cancer DSG revised the guideline to reflect the current evidence. This guideline report reflects the evidence up to June 2002 and includes revised recommendations based on that evidence. The recommendation concerning breast conservation therapy versus mastectomy is similar to that made in 1996, but new recommendations dealing with axillary lymph node dissection and sentinel lymph node biopsy have been added.

Literature Search Strategy
The literature was searched using MEDLINE (through June 2002) and the Cochrane Library (Issue 2, 2002). The Physician Data Query (PDQ) database, clinical trial and practice guideline Internet sites, abstracts published in the proceedings of the annual meetings of the American Society of Clinical Oncology and the American Society of Radiation Oncology, article bibliographies, and personal files were also searched to June 2002.

The search strategy combined disease-specific terms (breast neoplasms/ or breast cancer.tw. or mammary neoplasms/) and treatment-specific terms (mastectomy/ or mastectomy.tw,sh. or mastectomy or segmental/ or lumpectomy.tw. or breast conserv:.tw. or conserv:.tw. or sentinel.tw or axilla:.tw.) with design-specific terms (meta-analysis.pt,sh,tw. or randomized controlled trial:.sh,pt,tw. or randomized controlled trials/ or random:.tw.). The literature search was not restricted by language.

Inclusion Criteria
Articles were eligible for inclusion in the systematic review of the evidence if they were randomized controlled trials comparing breast conservation therapy versus mastectomy or were randomized trials on the surgical management of the axilla. Trials investigating the efficacy and safety of sentinel lymph node biopsy were also eligible. Outcomes of interest included overall or disease-free survival, local recurrence, distant recurrence, and quality-of-life. Both abstract and full reports were eligible.

Evidence-based practice guidelines, meta-analyses, systematic reviews, and economic analyses addressing the guideline questions were also included in the guideline report.

Synthesizing the Evidence
Survival data from six randomized trials were combined using the meta-analysis software package, Metaanlyst (J. Lau, Boston, MA). Results were expressed as odds ratios (OR), where OR <1.0 for the occurrence of a specific event favours breast conservation therapy and OR >1.0 favours mastectomy.

IV. RESULTS

Literature Search Results
- In the surgical management of early-stage invasive breast cancer, eleven randomized
controlled trials (3-14), four meta-analyses (2,15-17), and four guidelines (18-21) comparing the effect of breast-conserving therapy versus mastectomy on overall survival or recurrence were identified and reviewed.

- In the surgical management of the axilla, six randomized controlled trials (9,10,22-30), one meta-analysis (31), two clinical practice guidelines (21,32) on axillary dissection, and one randomized trial on axillary node sampling (33) were identified and reviewed.
- One meta-analysis (34) and one clinical practice guideline (35) on sentinel lymph node biopsy were also included in this guideline report.
- In comparing quality-of-life in patients undergoing breast conservation therapy versus mastectomy, 13 papers reporting quality-of-life data from randomized trials (36-48), one systematic review (49), and one meta-analysis (50) were identified.

### Systematic Review of the Evidence

**Surgical management - breast conservation therapy versus mastectomy**

**Randomized controlled trials**

Key results of the eleven randomized trials comparing breast conservation therapy with mastectomy in women with early-stage breast cancer are summarized in Table 1. Six of the eleven randomized trials are considered the standard in the field (3-8). Of the remaining five trials, the Guy’s Hospital series had significant methodological irregularities (9,10) and results from three trials reported in the meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group (11,12) were never published.

With the exception of the two Guy’s Hospital trials (9,10), there were no reports of significant differences in overall survival, disease-free survival, or distant disease-free survival in any of the studies comparing breast-conserving surgery and mastectomy.

**Table 1: Randomized trials comparing breast conservation therapy to mastectomy.**

<table>
<thead>
<tr>
<th>Study group/ Author/ Year</th>
<th>Comparison**</th>
<th># of Patients</th>
<th>Years of follow-up</th>
<th>Overall Survival</th>
<th>Disease-free survival</th>
<th>Local recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IGR</td>
<td>tumourectomy + radiation modified radical mastectomy</td>
<td>88</td>
<td>15</td>
<td>73%</td>
<td>55%</td>
<td>9%</td>
</tr>
<tr>
<td>Arriagada (3) 1996</td>
<td></td>
<td>91</td>
<td>15</td>
<td>65%</td>
<td>44%</td>
<td>14%</td>
</tr>
<tr>
<td>NSABP B-06 Fisher (4) 1995</td>
<td>lumpectomy lumpectomy + radiation total mastectomy</td>
<td>634</td>
<td>12</td>
<td>58%</td>
<td>47%</td>
<td>37%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>628</td>
<td>12</td>
<td>62%</td>
<td>49%</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>589</td>
<td>12</td>
<td>60%</td>
<td>50%</td>
<td>NR</td>
</tr>
<tr>
<td>NCI</td>
<td>lumpectomy + radiation modified radical mastectomy</td>
<td>121</td>
<td>10</td>
<td>77%</td>
<td>72%</td>
<td>5%</td>
</tr>
<tr>
<td>Jacobson (5) 1995</td>
<td></td>
<td>116</td>
<td>10</td>
<td>75%</td>
<td>69%</td>
<td>10%</td>
</tr>
<tr>
<td>DBCG</td>
<td>breast-conserving surgery total mastectomy</td>
<td>430</td>
<td>6</td>
<td>79%</td>
<td>70%</td>
<td>2%</td>
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<tr>
<td>Blichert-Toft (6) 1992</td>
<td></td>
<td>429</td>
<td>6</td>
<td>82%</td>
<td>66%</td>
<td>---</td>
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<tr>
<td>EORTC</td>
<td>breast-conserving surgery modified radical mastectomy</td>
<td>455</td>
<td>8</td>
<td>71%</td>
<td>64%</td>
<td>11%</td>
</tr>
<tr>
<td>Van Dongen (7) 1992</td>
<td></td>
<td>424</td>
<td>8</td>
<td>73%</td>
<td>70%</td>
<td>8%</td>
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<tr>
<td>Study group/Author/Year</td>
<td>Comparison**</td>
<td># of Patients</td>
<td>Years of follow-up</td>
<td>Overall Survival</td>
<td>Disease-free survival</td>
<td>Local recurrence</td>
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<td>Milan Veronesi (8) 1990</td>
<td>quadrantectomy + radiation modified radical mastectomy</td>
<td>352[349]</td>
<td>13[13]</td>
<td>71%[69%]</td>
<td>NR[NR]</td>
<td>3%[2%]</td>
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<tr>
<td>Guy’s Hospital Hayward (9) 1977</td>
<td>wide excision + radiation total mastectomy + radiation</td>
<td>122[130]</td>
<td>6[10]</td>
<td>NR[NR]</td>
<td>NR[NR]</td>
<td>30%[40%]</td>
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<tr>
<td>Guy’s Hospital Atkins (10) 1972</td>
<td>wide excision + radiation total mastectomy + radiation</td>
<td>184[192]</td>
<td>NR[NR]</td>
<td>88%[85%]</td>
<td>NR[NR]</td>
<td>NR[NR]</td>
</tr>
<tr>
<td>Naples D’Aiuto (11)</td>
<td>breast-conserving surgery mastectomy</td>
<td>170[170]</td>
<td>NR[NR]</td>
<td>88%[85%]</td>
<td>NR[NR]</td>
<td>NR[NR]</td>
</tr>
<tr>
<td>CRC, UK (12) 1995</td>
<td>breast-conserving surgery mastectomy</td>
<td>71[74]</td>
<td>NR[NR]</td>
<td>80%[82%]</td>
<td>NR[NR]</td>
<td>NR[NR]</td>
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<td>BMFT 01, Germany (12)</td>
<td>breast-conserving surgery mastectomy</td>
<td>41[31]</td>
<td>NR[NR]</td>
<td>90%[95%]</td>
<td>NR[NR]</td>
<td>NR[NR]</td>
</tr>
</tbody>
</table>

* indicates a significant difference at p<0.05
** axillary dissection was carried out in all patients except for the breast conservation arms in the two Guy’s Hospital trials.

Long-term results of the NSABP B-06 (in abstract form) and EORTC trials are now available (13,14). Data from 15-year follow-up of the NSABP B-06 trial participants continue to show no significant difference between breast conservation therapy and mastectomy in overall survival, disease-free survival, or distant disease-free survival (13). At ten years, results from the EORTC trial (14) also show no significant differences in survival (65% versus 66%, p=0.11) or distant metastasis-free rates (61% versus 66%, p=0.24) between breast conservation and mastectomy; however, rates of loco-regional recurrence were significantly higher in the breast conservation arm (20% versus 12%, p=0.01).

Meta-analyses
Our original practice guideline report (2) presented our meta-analysis of survival data on 4073 patients from six randomized trials comparing breast-conserving surgery with mastectomy (3-8) (see Table 1 for further information). The pooled analysis revealed no significant differences in overall survival (p=0.68) between the two treatment options. Although eleven trials were originally identified in the literature search, five trials were excluded from our analysis. The Guys’ Hospital Trials (9,10) used radiation levels that were lower than current standards and the axillae were not cleared in the breast conservation arm. In addition, even though the two series were virtually identical, survival of patients with Stage I disease in the mastectomy arm varied substantially between trials. The trial by D’Aiuto et al (11) was published only in abstract form.

In 1995, the Early Breast Cancer Trialists’ Collaborative Group published a meta-analysis of data from 4891 women who participated in nine randomized controlled trials of mastectomy versus breast-conserving surgery plus radiotherapy (12). They reported a non-significant odds reduction for mortality of -2% (standard error, 7), which represented a 2% increase in the odds of...
death in the mastectomy group compared with the breast conservation therapy group (p=0.7).

In 1997, Morris et al published a meta-analysis (15), using a combination of individual patient data and published results from six randomized trials. They report pooled odds ratios for mortality of 0.90 (95% confidence interval [CI], 0.74 to 1.09) at 5 years after randomization and 0.91 (95% CI, 0.78 to 1.05) at 10 years.

In 1998, abstract data from another meta-analysis by Morris et al reported long-term data from three randomized controlled trials (16). After up to 20 years follow-up, no significant differences were detected between the mastectomy and the breast-conservation arms in survival (log rank p=0.95) or in distant recurrence (log rank p=0.61).

**Practice guidelines**

Four evidence-based practice guidelines provide recommendations on the surgical management of early-stage breast cancer (17-21).

In July 1997, the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer recommended breast-conserving surgery followed by radiotherapy, in general, for women with Stage I or II breast cancer (17). The guideline also stated that women should be given a choice between breast-conserving therapy and mastectomy, and that this choice should take into account the personal circumstances and preferences of the patient. The recommendations were based on evidence from six randomized controlled trials (3-8), which showed equivalence between breast-conserving therapy and mastectomy with respect to distant recurrence and overall survival. The guideline also described a group of patients for whom mastectomy should be considered.

In 1995, the Australian National Breast Cancer Centre (18) reviewed evidence from three randomized trials (3,7,8) and concluded that there was no difference in the rate of survival or distant metastases between women undergoing breast-conserving surgery and those receiving mastectomy. They recommended that women should be fully informed about the treatment options and should be invited to participate in selecting their treatment. Specific situations in which mastectomy might be preferred over breast-conserving surgery were listed. A draft of the 2000 update of this guideline recommended that, where appropriate, women should be offered a choice of either breast-conserving surgery or mastectomy (19). This updated guideline was based on the meta-analysis by the Early Breast Cancer Trialists’ Collaborative Group (12).

In 1997, the National Comprehensive Cancer Network Breast Cancer Guidelines (20) reviewed the results of three randomized trials (trials not referenced) and concluded that mastectomy and breast-conserving therapy were 'medically equivalent treatment options'. In their flow chart on the management of Stage I and II invasive breast cancer, they listed total mastectomy and lumpectomy with radiotherapy as options, noting that the latter was the preferred option Contraindications to breast conservation were listed.

In October 1998, a national clinical guideline on breast cancer was produced for use in Scotland by the Scottish Intercollegiate Guidelines Network (21). Based on the standard randomized trials (3-5,7,8), this guideline recommended that for women with tumours up to 4 cm in size, there is no survival difference for patients treated with mastectomy versus breast conservation.

**Axillary node dissection**

**Randomized controlled trials**

Results from six randomized trials of axillary node dissection versus no axillary node dissection (9,10, 22-30) are summarized in the meta-analysis described below.
Meta-analysis
In 1999, Orr published a meta-analysis based upon four decades of data from 2936 women who participated in six randomized trials comparing mastectomy, or lumpectomy plus radiation, with or without axillary dissection (31). Trials were eligible for inclusion if they included patient populations with Stage I or a combination of Stage I and II disease. In two trials, the mean tumour size was not reported; three trials reported average tumour sizes >3cm, with positive nodes in 39% to 54% of patients. The authors of the meta-analysis reported that it was unlikely that any of the patients had mammographically detected tumours and that adjuvant treatment with chemotherapy or tamoxifen would rarely have been used at the time these trials were conducted. The six trials reported an absolute survival benefit with axillary dissection ranging from 4% to 16%, which corresponds to a 7% to 46% relative reduction in risk of death. Orr reported a significant pooled survival benefit of 5.4% (95% CI, 2.7% to 8.0%; p<0.01) favouring axillary dissection. However, the results must be viewed with caution since this meta-analysis was based only on published data, rather than on individual-patient data. Also, procedures other than level I and II axillary node dissection were used in some of the studies. While this meta-analysis suggests a significant survival benefit with axillary dissection, evolving approaches in surgical management, radiotherapy, adjuvant therapy and screening practices may limit the effect of the survival benefit on patients treated with current breast cancer therapy.

Practice guidelines
In 1998, a clinical practice guideline by the Canadian Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer included recommendations on axillary dissection (32). For accurate staging and reduction of risk of recurrence in the axilla, the guideline recommended that removal and pathological examination of level I and II axillary lymph nodes should be the standard practice in most cases of Stage I and II breast carcinoma. The guideline also reported that there is some justification for omitting this surgery if the risk of axillary metastasis is very low or the pathological findings will have no influence on therapy. It was also recommended that patients should be aware that there is recognized morbidity with axillary dissection, which can include post-operative pain, infection, reduced limb mobilization, and lymphedema.

The 1998 guideline by the Scottish Intercollegiate Guideline Network (21) recommended axillary surgery for all patients with operable invasive breast cancer, but the authors did not reach consensus on the best surgical management of the axillae. Sentinel node biopsy was not recommended as routine practice.

Axillary node sampling versus axillary node clearance
Randomized trial
A randomized trial by Chetty et al (33) compared 232 patients who received axillary node clearance to 234 patients who received axillary node sampling. After a relatively short median follow-up of 4.1 years, there were no significant differences between patients in the axillary node sample arm and those in the axillary clearance arm in terms of local (14 versus 15 patients), axillary (8 versus 7 patients) or distant recurrence (29 versus 29 patients). There were also no reported differences in 5-year survival rates (82.1% versus 88.6%; p=0.20, log rank test) or in disease-free survival (79.1% versus 76.0%, p=0.68).
**Sentinel lymph node biopsy versus axillary dissection**

In recent years, sentinel node biopsy has been introduced as an alternative to axillary dissection for the surgical staging of operable breast cancer. Sentinel node biopsy is widely used in the United States and is increasingly being used in Canada, despite the lack of data from randomized trials. With this technique, radioactive material and/or a blue dye is injected locally into the breast tissue that surrounds the tumour or biopsy cavity. This material is then taken up by the lymphatics and is traced with a handheld gamma probe or by following the blue dye to the first node or nodes draining the peritumoural breast tissue. This node—the *sentinel node*—is then removed and examined histologically for the presence of tumour cells. The histologic status of this sentinel node is thought to represent the histologic status of the whole lymphatic basin from which it has been removed; that is, a negative sentinel node suggests that other nodes in the axilla are also negative and a positive node(s) suggests that additional nodes may be positive.

While the concept of sentinel node biopsy is simple, the performance of the procedure to accurately locate, harvest and analyze the sentinel node in breast cancer is complex and challenging. It requires a team with members from nuclear medicine, surgery, and pathology and is only mastered after a substantial learning period. Surgical volume (i.e., number of cases) appears to be important in the success rate, as infrequent practice of the technique leads to higher failure rates (51). A positive node on sentinel biopsy (as identified by H&E staining) or failure to identify a sentinel node should be followed by an axillary dissection. There is evidence of therapeutic benefit of axillary node dissection in terms of both local control and survival. The extent of lymph node involvement also provides important prognostic information and may guide the selection of adjuvant treatment.

**Case series**

In 1999, Miltenburg et al published a meta-analysis of eleven case series published between 1993 and 1998 (34). Data were reported for 912 patients with breast cancer who had sentinel lymph node biopsy followed by axillary lymph node dissection. Overall, sentinel lymph nodes were successfully identified in 84% of patients and concordance with pathological results from axillary dissection was confirmed in 98% of patients. There was a 5% false-negative rate associated with sentinel lymph node biopsy. The highest identification rates were reached using either radiocolloid or dye and radiocolloid combined. In fact, between January 1991 and December 2000 over 50 studies (involving more than 9,000 women) have been reported (35). The studies were all case series, some prospective and some retrospective. In all of these studies, patients first had a sentinel node biopsy which was then followed by an axillary dissection. The false negative rate ranged from 0 to 22%. (This evidence is discussed in greater detail in the Canadian Breast Cancer guideline regarding sentinel lymph node biopsy [35]). It is important to understand that missing cancer cells in other lymph nodes may affect the treatment a patient receives after surgery and possibly the chances of breast cancer returning.

**Quality of life for patients who choose breast conservation therapy versus mastectomy**

**Randomized trials**

Thirteen papers on quality-of-life, using data from randomized trials of breast-conserving surgery versus mastectomy, have been published (36-47).

Poulsen et al reported on 184 women who participated in the Danish Breast Cancer Cooperative Group trial (36). Over an average follow-up of 31 months, no significant differences were found between the two types of surgery on measures of physical state, emotional state, social activities, work activities, body image, marital and sexual life, or level of anxiety.
Curran et al analyzed data from 278 women who participated in the European Organization for the Treatment of Cancer trial (37). Two years after surgery, women in the breast-conserving therapy group had better body image (p=0.001) and more satisfaction with treatment (p=0.001) than those in the mastectomy group; there was no significant difference between the two groups with respect to fear of cancer recurrence (p=0.236).

The remaining trials (38-48) are all described in the meta-analysis below.

Systematic Review
A systematic review by Irwig and Bennetts (49) included six randomized trials (all included in the meta-analysis described below) comparing quality of life after breast-conserving therapy with that after mastectomy. The authors deemed that the trial data was too heterogeneous to pool the results quantitatively. Five trials reported a significant difference in body image favouring breast conservation, while results measuring other quality of life outcomes (psychological, sexual, physical, fear of future, and global quality of life) were considered inconclusive.

Meta-analysis
An overview by Moyer (50) included a meta-analysis of ten randomized trials of mastectomy versus breast-conserving therapy (n= 941 patients). Results favouring breast-conserving therapy were reported in ten trials for psychological adjustment (mean weighted effect size [MWES], 0.060; standard deviation [SD], 0.66; p<0.001) and in three trials for social adjustment (MWES, 0.334; SD, 0.140; p<0.05). No significant differences were detected in seven trials measuring marital-sexual adjustment (p>0.05) or body/self image (p>0.05), or in six trials measuring cancer-related fears and concerns (p>0.05). The pooled effect size for global adjustment from three studies favoured mastectomy but was not statistically significant (MWES, -0.20; SD, 0.108; p>0.05).

SUPPLEMENTARY INFORMATION FOR PRACTITIONERS
The information below is not part of the systematic review of the evidence conducted to address the guideline questions posed on page one of this report. The Breast Cancer DSG has added discussion of technical factors, neoadjuvant chemotherapy, and relative contraindications to surgery in order to summarize current knowledge and opinion on these topics for practitioners.

Technical Factors Related to the Surgical Treatment of Early-Stage Breast Cancer
**Palpable lesions in the breast**
Any mass requiring excisional biopsy should be completely removed through a cosmetically acceptable incision placed directly over the mass. A margin of normal breast tissue should be included around the lump to ensure its complete removal. A breast lump proven to be malignant may be treated by wider surgical excision. The aim of lumpectomy is to completely excise the lesion along with a margin of normal breast tissue to ensure its complete removal. There is no firm consensus on the extent of the excision for resection, nor for the extent of margins to be free of the malignant process (52). There is a suggestion that local breast cancer recurrence rates were lower in the studies where quadrantectomy was performed versus similar studies on less extensive breast-conserving procedures (53). A larger excision may reduce the incidence of local recurrence but at the expense of cosmesis. Curvilinear incisions should be utilized in the natural lines of the skin in the upper quadrants of the breast. Radial incisions should not be performed in the upper quadrants. The specimen should generally be submitted intact (i.e. not bisected) directly for inking of the margins and other pathological processing. Suture approximation of
breast parenchyma or subcutaneous tissue should be avoided. Surgical drains should be omitted in breast-conserving surgical wounds. Superior cosmetic results are achieved with subcuticular skin closure techniques (54).

In the absence of further data, axillary dissection with removal of level I and II axillary nodes remains the standard of surgical care. This should ideally result in the identification of at least 10 nodes (55). At present, there is insufficient evidence to justify the omission of axillary dissection on the basis of primary tumour size alone. Axillary dissection might be omitted when the patient is clinically node negative and 1) has severe underlying co-morbid conditions and would not benefit from the axillary surgery or 2) if therapeutic decision-making, in terms of adjuvant therapy, is not affected (this may be particularly relevant in the elderly patient). If consideration is given to omitting axillary dissection, the patient should be aware of the rationale for this recommendation and the potential risks in terms of local recurrence.

If the pathologist reports microscopic involvement of the margins of resection with invasive cancer or DCIS, the patient is at increased risk for a local recurrence and re-excision or total mastectomy should be seriously considered. (This does not apply to lobular carcinoma in situ at the margins). The patient should be informed that the margins are positive.

**Non-palpable lesions**
With the increasing use of screening mammography, more patients are presenting to surgeons with suspicious imaging findings in association with a normal clinical breast examination. The management of these non-palpable lesions requires close cooperation between surgeon, radiologist, and pathologist. Minimally invasive tissue biopsy (core needle, vacuum-assisted) under ultrasound or stereotactic guidance has recently been used in the diagnosis of non-palpable lesions. This procedure does not obviate the need for excisional biopsy in all circumstances. Preoperative diagnosis of non-palpable lesions requiring excision is preferred where possible. Such information allows for wide excision of malignant lesions and reduces the total number of operative procedures required to achieve clear margins. The need for fewer operative procedures is correlated with reduced total tissue volume resected and superior cosmesis (56). Open surgical biopsy may be required to establish a diagnosis. In such cases, preoperative needle localization under local anaesthesia by the radiologist will be required using a hooked wire or similar device. The lesion should be excised completely, if possible. Specimen radiography is essential to ensure that the lesion has been excised. When performing specimen radiography, the use of compression devices may result in falsely close margins, particularly in specimens composed predominantly of fat, and should be avoided. As a rule, frozen section should be avoided because the amount of abnormal tissue may be limited and precise pathologic diagnosis may be difficult (57, 58). Further management should be deferred until the pathologist has carefully studied the permanent sections. If the excision has been incomplete, a re-excision should be carried out and an axillary lymph node dissection should be performed through a separate incision for all patients with invasive cancer.

Hormone receptor status should be assessed by performing immunohistochemistry on paraffin embedded sections using antibodies and standardized methodology that has been technically validated (59).

**Preoperative (Neoadjuvant) Chemotherapy for Operable Breast Cancer**
The concept of using preoperative chemotherapy in women with operable breast cancer is supported by several observations. First, in experimental animal models, removal of the primary tumour resulted in an increased growth of metastases and this alteration in growth kinetics of the
Secondary tumours could be abrogated by the administration of chemotherapy before removal of the primary tumour (58). Second, chemotherapy administered for locally advanced breast cancer could result in substantial shrinkage of tumours, such that tumours which were unresectable could now be surgically resected (61,62).

Results of non-randomized studies showed that chemotherapy administered before surgery resulted in high rates of clinical response (50-80%) but low rates of pathologic complete response (<5%) (63,64). These studies also suggested that reducing tumour size with chemotherapy allowed for breast-conserving surgery.

**Evidence from randomized trials**

Several early randomized trials evaluated preoperative chemotherapy for operable breast cancer (65,66), but their study designs were problematic and did not address the efficacy of preoperative chemotherapy compared to the same adjuvant chemotherapy administered postoperatively. A search of Medline from 1996 to June 2002 found three randomized trials that compared preoperative chemotherapy to postoperative chemotherapy (67-71).

In a trial conducted by Powles et al, 309 women were randomized to either four cycles of preoperative chemotherapy consisting of mitoxantrone and methotrexate, followed by four cycles of the same chemotherapy postoperatively, or eight cycles of the same chemotherapy after surgery (67). No difference was detected in disease-free survival (DFS) and overall survival (OS) between groups.

The NSABP B-18 trial also addressed this question (68-70). The primary objective of this trial was to determine whether preoperative chemotherapy (four cycles of adriamycin and cyclophosphamide) could improve DFS and OS compared to the same chemotherapy administered following surgery. Over 1,500 women participated in this trial. At a median follow-up of nine years, no difference was detected in disease-free or overall survival between treatment groups. The nine-year overall survival rate was 70% for the post-operative chemotherapy patients, compared to 69% for the pre-operative chemotherapy patients, and the disease-free survival was 53% compared to 55%. Secondary aims of the trial were: to determine whether preoperative chemotherapy resulted in more breast-conserving surgery and to examine the relationship between response to chemotherapy and DFS and OS. Sixty-seven percent of women in the preoperative chemotherapy group underwent lumpectomy compared to 60% in the postoperative chemotherapy group (p=0.002). This difference was particularly evident in women with tumours > 5cm in size, in whom the rates of lumpectomy were 22% and 8%, respectively. However, there was a significant increase in the rate of local recurrence in those who converted from proposed mastectomy to lumpectomy after pre-operative chemotherapy (15.9% local recurrence), compared to those who had lumpectomy as originally planned prior to randomization (9.9%) (p=0.04). This difference in local recurrence rate was no longer significant when adjusted for patient age and initial clinical tumour size (p=0.14). The overall response rate to preoperative chemotherapy was 80% (36% of patients achieved a clinical complete response and 44% a partial response). Of those women with a clinical complete response, 26% had a complete pathologic response. Both pathologic and clinical complete responses were associated with better DFS and OS, compared to patients whose tumours did not shrink with preoperative chemotherapy.

The EORTC conducted a study of four cycles of 5-FU, epirubicin and cyclophosphamide given preoperatively versus postoperatively, with the first postoperative cycle being given within 36 hours of surgery (71). Six hundred and ninety-eight patients with operable breast cancer were enrolled. After a median follow-up of 56 months, no significant difference in overall survival, progression-free survival, or locoregional recurrence was observed.
**Surgical issues associated with preoperative chemotherapy**

Preoperative chemotherapy does not improve DFS and OS compared to the more traditional approach of postoperative adjuvant chemotherapy. In some instances, preoperative chemotherapy can shrink a large primary tumour and allow for breast conservation therapy. However, in such circumstances there may be an increased risk of local breast cancer recurrence following breast irradiation. If preoperative chemotherapy is being considered, there are certain surgical issues that must be addressed (64). One relates to the difficulty in identification of the exact tumour location when a complete clinical response has occurred. Consideration should be given to placement of a marking clip in the tumour site at the time of initial biopsy. Another concern relates to the amount of breast tissue that needs to be removed at lumpectomy in patients with good tumour resolution. Because the frequency of apparent multifocality in resected specimens is inversely correlated with the magnitude of chemotherapy response, it would seem reasonable that breast-conserving surgery aim to excise residual disease with generous margins confirmed pathologically (72).

**Contraindications to Conservative Breast Surgery**

While the majority of patients with operable breast cancer are candidates for breast-conserving surgery, there are a few situations in which it may be contraindicated. Practitioners should consider the relative contraindications to surgery reviewed below when discussing treatment decisions with individual patients.

Some patients may decline conservative surgery for personal reasons and prefer a modified radical mastectomy. Before undergoing conservative surgery, all patients should be informed of the need for postoperative radiotherapy to the breast. If radiotherapy is not readily accessible, is contraindicated (for reasons such as prior radiation, pregnancy, severe cardiac or lung disease that could be worsened by radiation, scleroderma, or systemic lupus) or is declined by the patient, then conservative surgery is generally not recommended. In the case of pregnancy, lumpectomy could be carried out with breast irradiation delayed until after delivery.

Patients with large tumours (e.g., >5 cm) or a small volume breast may not have a satisfactory cosmetic result and may be better served by modified radical mastectomy followed by reconstruction. The presence of multiple tumours in more than one quadrant of the breast (multicentricity), the presence of diffuse malignant microcalcifications on mammography, or clinical signs of skin involvement are contraindications to conservative surgery, as is an inability to obtain clear margins with breast-conserving surgery. When conservative surgery is contraindicated, the preferred alternative treatment is usually modified radical mastectomy. However, for some patients, such as the elderly or those with co-morbid medical conditions, total (simple) mastectomy may be a satisfactory alternative.

**V. INTERPRETIVE SUMMARY**

For eligible candidates, surgical treatment options for early-stage invasive breast carcinoma include breast-conserving surgery plus radiation or mastectomy. Evidence from six randomized controlled trials has demonstrated comparable results from these treatment approaches, in terms of overall survival and disease-free survival.

Although evidence relating quality of life to the extent of breast surgery is conflicting, patients should be fully informed of the treatment implications involved with either breast-conserving surgery or mastectomy (i.e., potential need for additional surgery for persistent disease or the need for adjuvant radiation therapy following breast-conservation surgery).
There are patients with Stage I or II breast cancer who will require mastectomy because of their own personal preferences or because of the extent of the disease process in the breast which would obviate successful conserving surgery.

Evaluation of axillary lymph node pathology is an integral part of adjuvant treatment planning for most patients with Stage I and II breast cancer. Although the surgical treatment of the axillae in cases of early-stage breast cancer may or may not contribute significantly to a reduction in mortality in today's patient populations, it reduces the morbidity of axillary recurrence.

Axillary lymph node dissection is the current standard of surgical care. It carries significant risk of morbidity in terms of lymphedema and long-term post-surgical dysthesias. With no set criteria used to define lymphedema and a variety of assessment techniques in use, there is wide variation in reported rates of lymphedema following axillary dissection. Rates ranging from 2% to 70% have been reported (73). In a recent study (74), arm morbidity was assessed in 110 patients after partial mastectomy with axillary dissection and in most cases, irradiation (56). A total of 19% of patients developed lymphedema (defined as a >10% increase in arm volume), and 49% had reduced arm mobility (defined as a 15 degree impairment of shoulder mobility). After five years, 31% of patients continued to report some arm pain after breast conservation therapy.

However promising, investigations for axillary staging such as sentinel lymph node biopsy have not yet demonstrated acceptable specificity and sensitivity to be used routinely, outside the context of a clinical trial. While sentinel lymph node biopsy alone is currently not a standard practice, a position paper by McCready et al (75) recommends that surgeons consider acquiring the necessary equipment, training, and infrastructure to perform this technique. The surgeons should also develop collaborations with their colleagues in Pathology and Nuclear Medicine to assure proper handling and pathologic assessment of these nodes.

VI. ONGOING TRIALS

- The NSABP-32 trial is a phase III trial where clinically node-negative patients are randomized to sentinel lymph node biopsy (SLN) and axillary dissection or SLN alone (plus axillary dissection if SLN positive).
- The EORTC-10850 trial is a randomized trial that compares modified radical mastectomy versus tumour excision and hormonal therapy in patients aged 70 and over. A total of 100 evaluable patients will be recruited per treatment arm.
- The ACOSOG-Z0011 trial is a phase III randomized study where women with Stage I or IIA breast cancer with positive sentinel nodes receive axillary lymph node dissection versus no axillary dissection.
- The ACOSOG-Z0010 trial is a phase III prognostic study of sentinel node and bone marrow micrometastases in women with Stage I or IIA breast cancer.
- A randomized trial by the International Breast Cancer Study Group, compares axillary clearance versus tamoxifen in elderly women after surgery for early breast cancer.
- The American College of Surgeons is conducting an evaluation study of current methods in the treatment of patients with breast cancer. This study will include an assessment of sentinel lymph node biopsy.

The Breast Cancer DSG will monitor the literature for published results of these trials.

VII. DISEASE SITE GROUP CONSENSUS PROCESS

With no observed differences in overall survival or distant recurrence, the Breast Cancer DSG felt that for eligible candidates, the choice between breast conservation therapy and modified radical mastectomy should be based upon patient preference.
In order to make an informed decision, patients should be fully aware of the risks and benefits of each procedure. Breast conservation therapy typically involves tumour excision with clear margins, axillary dissection, and adjuvant breast irradiation. There is also a potential need for further surgery, possibly a mastectomy, in cases of local recurrence. A modified radical mastectomy involves the removal of the entire breast, including the nipple and areola complex, and the fascia over the pectoralis muscles while sparing the underlying muscles and innervation. Breast reconstruction is an option for patients who choose mastectomy.

The DSG agreed that there is insufficient evidence to make recommendations regarding sentinel lymph node biopsy alone at this time. The DSG acknowledged that some clinicians in Ontario are beginning to train for the procedure and are building expert teams in anticipation of the potential demand should sentinel node biopsy alone become standard practice. The DSG agreed that patients should be encouraged to participate in clinical trials investigating this procedure.

Given that quality-of-life measures are difficult to capture objectively, the DSG felt that the evidence surrounding quality of life after surgery was conflicting. While some evidence suggests that women who receive breast-conserving therapy may have higher body self image than those who receive mastectomy, other measures of psychosocial wellbeing were inconclusive.

VIII. EXTERNAL REVIEW OF THE PRACTICE GUIDELINE REPORT

Draft Practice Guideline

Based on the evidence described above, the Breast Cancer DSG drafted the following practice guideline:

Target population

Women with early-stage (Stage I and II) invasive breast cancer who are eligible for either breast conservation therapy or mastectomy.

Draft recommendations

Key recommendations

• Women who are eligible for breast conservation therapy should be offered the choice of either breast conservation therapy with axillary dissection or modified radical mastectomy.
• Removal and pathological examination of level I and II axillary lymph nodes should be the standard practice in most cases of Stage I and II breast carcinoma.
• There is promising but limited evidence that is not as yet sufficient to support recommendations regarding sentinel lymph node biopsy alone. Patients should be encouraged to participate in clinical trials investigating this procedure, however axillary dissection is the standard of care.

Qualifying statements

• With no difference in survival or distant recurrence, the choice between breast conservation therapy with axillary dissection and modified radical mastectomy should be dependent upon patient preference where appropriate.
• Each patient should be fully informed of the risks and benefits of each procedure.
• Patients should be aware that breast conservation therapy involves tumour excision with clear margins, axillary dissection, and adjuvant breast irradiation.
• Patients who choose breast conservation therapy should be aware that there is also the potential need for further surgery, possibly a mastectomy, in cases of local recurrence.
Evidence surrounding quality of life after surgery is conflicting, but there is some evidence suggesting that women who receive breast-conserving therapy may have higher body self image than those who undergo mastectomy.

Practitioner Feedback
Based on the evidence and the draft recommendations presented above, feedback was sought from Ontario clinicians in November 2001.

Methods
Practitioner feedback was obtained through a mailed survey of 201 practitioners in Ontario (42 Medical Oncologists, 41 Radiation Oncologists, and 118 Surgeons). The survey consisted of 21 questions about the quality of the practice-guideline-in-progress (PGIP) report and whether the draft recommendations should be approved as a practice guideline. Written comments were invited. Follow-up reminders were sent two weeks (post card) and four weeks (complete package mailed again) later. The Breast Cancer DSG reviewed the results of the survey.

Results
One hundred and thirty-one responses were received out of the 201 surveys sent (65% response rate). Responses include returned completed surveys as well as phone, fax, and e-mail responses. Of the practitioners who responded, 98 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 2.

Summary of written comments
Twenty-six respondents (27%) provided written comments. The main points contained in the written comments were:
1. The recommendations reflect current practice.
2. There was mixed feedback from practitioners on the role of sentinel node biopsy outside of clinical trials. Some practitioners urged the adoption of sentinel node biopsy by adequately trained surgeons. Others would like to see clear evidence of survival equivalence before adopting sentinel node biopsy as standard practice.
3. Should axillary dissection be completed if a positive node is found by sentinel node biopsy?
4. Some practitioners questioned the need for axillary node dissection in elderly women with receptor-positive cancers who would be receiving tamoxifen regardless of the results of the dissection.

Modifications/Actions
The following changes were made to the guideline report in response to issues 2-4 above:
- The issue of sentinel node biopsy alone, outside of a clinical trial, was discussed by the committee, as well as the reference by a number of practitioners to the Canadian practice guideline on sentinel lymph node (SLN) biopsy by the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The Canadian guideline recommends that axillary node dissection (AND) remains the standard of care and that, if a patient requests or is offered SLN biopsy alone, she needs to be made aware of the risks and benefits and what is and what is not yet known about the procedure. The Canadian guideline confirms that there are no data from randomized trials comparing outcomes from SLN biopsy to those with axillary node dissection and, therefore, participation in randomized trials is encouraged. Since there is
no evidence from randomized trials, the Canadian guideline is based on a consensus of the Steering Committee. The Ontario Breast Cancer DSG felt that, while this consensus statement was reasonable, SLN biopsy alone cannot be recommended in the absence of high-quality evidence. No change was made to the Ontario guideline.

- The rationale for full dissection when the sentinel lymph node is positive for metastatic disease was added to the guideline report.
- With regard to the omission of axillary node dissection in elderly hormone-receptor-positive patients receiving tamoxifen, it is recognized by the DSG that there may be some individual cases where the omission of axillary node dissection (AND) could be justified. This is discussed in section V of the guideline report. However, again there are no randomised data confirming that such patients do as well without, compared to with, axillary node dissection and so omission of AND cannot be recommended as standard care. The current International Breast Cancer Study Group clinical trial, comparing axillary clearance to tamoxifen in elderly women, addresses this question.

Table 2. Practitioner responses to eight items on the practitioner feedback survey

<table>
<thead>
<tr>
<th>Item</th>
<th>Number (%)</th>
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<tbody>
<tr>
<td></td>
<td>Strongly agree or agree</td>
</tr>
<tr>
<td>2. The rationale for developing a clinical practice guideline, as stated in the “Choice of Topic” section of the report, is clear.</td>
<td>94 (96%)</td>
</tr>
<tr>
<td>3. There is a need for a clinical practice guideline on this topic.</td>
<td>88 (90%)</td>
</tr>
<tr>
<td>4. The literature search is relevant and complete.</td>
<td>87 (91%)</td>
</tr>
<tr>
<td>6. The results of the trials described in the report are interpreted according to my understanding of the data*.</td>
<td>92 (97%)</td>
</tr>
<tr>
<td>7. The draft recommendations in this report are clear.*</td>
<td>88 (97%)</td>
</tr>
<tr>
<td>8. I agree with the draft recommendations as stated.*</td>
<td>89 (93%)</td>
</tr>
<tr>
<td>20. This PGIP report should be approved as a practice guideline.*</td>
<td>80 (86%)</td>
</tr>
<tr>
<td>21. If this PGIP report were to become a practice guideline, how likely would you be to make use of it in your own practice?*</td>
<td>Very likely or likely</td>
</tr>
</tbody>
</table>

*Some practitioners did not answer these questions.

Practice Guidelines Coordinating Committee Approval Process

The practice guideline report was circulated to members of the Practice Guidelines Coordinating Committee (PGCC) for review and approval. All members of the PGCC returned ballots. Seven PGCC members approved the practice guideline report as written, one member approved the guideline and provided suggestions for consideration by the Breast Cancer DSG, and three members approved the guideline conditional on the DSG addressing specific concerns.

PGCC members noted the discussion of neoadjuvant chemotherapy and contraindications to conservative surgery that were included in the guideline report, and asked that recommendations or qualifying statements be formulated by the DSG to address these issues.
Modifications/Actions

The DSG’s intention was to keep the recommendations made in this guideline clearly focused on surgical issues (i.e., mastectomy versus lumpectomy and management of the axilla). The DSG included discussion of related issues, such as technical factors, neoadjuvant chemotherapy and contraindications as supplementary information for practitioners. These issues were outside the scope of the guideline questions and for this reason, were not included in the Results section of the guideline report. Instead, they appeared in separate sections later in the report. In order to make the context for the information clearer, it has been consolidated under a new section titled "Supplementary Information for Practitioners”.

The section on neoadjuvant chemotherapy does include evidence from randomized trials. The DSG added a qualifying statement about preoperative chemotherapy to the Practice Guideline. The DSG felt that it was not appropriate to include contraindications to conservative breast surgery in the recommendations or qualifying statements. The target population for the guideline includes only women with early-stage invasive breast cancer who are eligible for either breast conservation therapy or mastectomy. The contraindications discussed in the guideline report are relative rather than absolute contraindications.

IX. PRACTICE GUIDELINE

This practice guideline reflects the integration of the draft recommendations with feedback obtained from the external review process. It has been approved by the Breast Cancer DSG and the Practice Guidelines Coordinating Committee.

Target Population

Women with early-stage (Stage I and II) invasive breast cancer who are eligible for either breast conservation therapy or mastectomy.

Recommendations

• Women who are eligible for breast conservation therapy should be offered the choice of either breast conservation therapy with axillary dissection or modified radical mastectomy.
• Removal and pathological examination of level I and II axillary lymph nodes should be the standard practice in most cases of Stage I and II breast carcinoma.
• There is promising but limited evidence that is not as yet sufficient to support recommendations regarding sentinel lymph node biopsy alone. Patients should be encouraged to participate in clinical trials investigating this procedure; however, axillary dissection is the standard of care.

Qualifying statements

• With no difference in survival or distant recurrence, the choice between breast conservation therapy with axillary dissection and modified radical mastectomy should be dependent upon patient preference where appropriate.
• Each patient should be fully informed of the risks and benefits of each procedure.
• Patients should be aware that breast conservation therapy involves tumour excision with clear margins, axillary dissection, and adjuvant breast irradiation.
• Patients who choose breast conservation therapy should be aware that there is also the potential need for further surgery, possibly a mastectomy, in cases of local recurrence.
• Evidence surrounding quality of life after surgery is conflicting, but there is some evidence suggesting that women who receive breast-conserving therapy may have higher body self
image than those who undergo mastectomy.

- In some instances, preoperative chemotherapy can shrink a large primary tumour and allow for breast conservation therapy. However, in such circumstances, there may be an increased risk of local breast cancer recurrence following breast irradiation.

**Related Guidelines**
- Practice Guidelines Initiative’s Evidence Summary #13-1: Treatment of Lymphedema Related to Breast Cancer (under development)
- Evidence-based Series (EBS) #17-5 *Sentinel Lymph Node Biopsy in Early-stage Breast Cancer.*

**X. IMPLICATIONS FOR POLICY**
In 1999, a Canadian economic analysis was reported by Will et al on the economic benefits of increasing home-based postoperative care for patients undergoing either breast-conserving therapy or mastectomy. By increasing home-based postoperative care and introducing both ambulatory breast-conserving surgery and a two-day hospital stay for mastectomy, the authors report an estimated yearly savings of 24.8 million per year (in the worst case scenario) (76).

In 1997, Norum et al compared the economic costs of breast-conserving therapy versus mastectomy in Norway using a cost-minimising analysis (77). Reported costs for breast-conserving therapy versus mastectomy followed by reconstruction were $10,748 and $8,538, respectively.

**XI. JOURNAL REFERENCE**
This material has been published as “Surgical management of early stage invasive breast cancer: a practice guideline. *Can J Surg.* 2005 Jun;48(3):185-94” and is presented here by permission of the Canadian Journal of Surgery publisher © 2005 CMA Media Inc. http://www.cma.ca/staticContent/HTML/NO/12/cjs/vol-48/issue-3/pdf/pg185.pdf. CMA Media Inc. assumes no responsibility or liability for damages arising from any error or omission in the text or from the use of any information or advice contained in this material.

**XII. ACKNOWLEDGMENTS**
The Breast Cancer Disease Site Group would like to thank Dr. Doug Mirsky, Dr. David McCready, Dr. Nancy Down, Dr. Claire Holloway and Dr. Wendy Shelley for taking the lead in writing this practice guideline report.

For a full list of members of the PEBC Breast Cancer Disease Site Group, please visit the CCO website at [http://www.cancercare.on.ca](http://www.cancercare.on.ca).
REFERENCES


18. National Health and Medical Research Council Breast Cancer Centre. Clinical Practice


36. Poulsen B, Graversen HP, Beckmann J, Blichert-Toft M. A comparison of post-operative psychosocial function in women with primary operable breast cancer randomized to breast
74. Tengrup I, Tennvall-Nittby L, Christiansson I, Laurin M. Arm morbidity after breast-conserving


76. Will BP; Le Petit C; Berthelot JM; Tomiak EM; Verma S; Evans WK. Diagnostic and therapeutic approaches for nonmetastatic breast cancer in Canada, and their associated costs. Br J Cancer 1999;79:1428-36.

Appendix 1. Stage grouping for breast cancer (TNM staging).

Primary tumor (T)
- **TX**: Primary tumor cannot be assessed
- **T0**: No evidence of primary tumor
- **Tis**: Carcinoma in situ
  - Tis (DCIS) Ductal carcinoma in situ
  - Tis (LCIS) Lobular carcinoma in situ
  - Tis (Paget) Paget’s disease of the nipple with no tumor
  
  Note: Paget’s disease associated with a tumor is classified according to the size of the tumor.
- **T1**: Tumor ≤ 2 cm in greatest dimension
  - T1mic: Microinvasion ≤ 0.1 cm in greatest dimension
  - T1a: Tumor > 0.1 cm but not > 0.5 cm in greatest dimension
  - T1b: Tumor > 0.5 cm but not > 1 cm in greatest dimension
  - T1c: Tumor > 1 cm but not > 2 cm in greatest dimension
- **T2**: Tumor > 2 cm but not > 5 cm in greatest dimension
- **T3**: Tumor > 5 cm in greatest dimension
- **T4**: Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
  - T4a: Extension to chest wall, not including pectoralis muscle
  - T4b: Edema (including peau d’orange) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
  - T4c: Both T4a and T4b
  - T4d: Inflammatory carcinoma

Regional lymph nodes (N)
- **NX**: Regional lymph nodes cannot be assessed (e.g., previously removed)
- **N0**: No regional lymph node metastasis
- **N1**: Metastasis in movable ipsilateral axillary lymph node(s)
- **N2**: Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent* ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastasis
  - N2a: Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
  - N2b: Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the absence of clinically evident axillary lymph node metastasis
- **N3**: Metastasis in ipsilateral infraclavicular lymph node(s), or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the absence of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
  - N3a: Metastasis in ipsilateral infraclavicular lymph node(s) and axillary lymph node(s)
  - N3b: Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
  - N3c: Metastasis in ipsilateral supraclavicular lymph node(s)

Regional lymph nodes (pN)**
- **pNX**: Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
- **pN0**: No regional lymph node metastasis histologically, no additional examination for isolated tumor cells***
  - pN0(i-): No regional lymph node metastasis histologically, negative IHC
  - pN0(i+): No regional lymph node metastasis histologically, positive IHC, no IHC cluster > 0.2 mm
  - pN0(mol-): No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)
  - pN0(mol+): No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)
  - pN1mi: Micrometastasis (> 0.2 mm, none > 2.0 mm)
- **pN1**: Metastasis in one to three axillary lymph nodes and/or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent$
  - pN1a: Metastasis in one to three axillary lymph nodes
  - pN1b: Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent$
  - pN1c: Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent$
- **pN2**: Metastasis in four to nine axillary lymph nodes, or in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN2a Metastasis in four to nine axillary lymph nodes (at least one tumor deposit > 2.0 mm)
pN2b Metastasis in clinically apparent* internal mammary lymph nodes in the absence of axillary lymph node metastasis
pN3 Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral supraclavicular lymph nodes
pN3a Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit > 2.0 mm), or metastasis to the infraclavicular lymph nodes
pN3b Metastasis in clinically apparent* ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent§
pN3c Metastasis in ipsilateral supraclavicular lymph nodes

Distant metastasis (M)
MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

Abbreviations: IHC, immunohistochemistry; RT-PCR, reverse transcriptase polymerase chain reaction.

* "Clinically apparent" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.
** Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node" (eg, pN0(i+)(sn)).
*** Isolated tumor cells are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by immunohistochemical or molecular methods but which may be verified on hematoxylin and eosin stains. Isolated tumor cells do not usually show evidence of metastatic activity (eg, proliferation or stromal reaction).
§ Not clinically apparent" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.
¶ If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as N3b to reflect increased tumor burden.

Stage Grouping

0 Tis N0 M0
I T1* N0 M0
IIA T0 N1 M0
T1* N1 M0
T2 N0 M0
IIB T2 N1 M0
T3 N0 M0
III A T0 N2 M0
T1* N2 M0
T2 N2 M0
T3 N1 M0
T3 N2 M0
IIIB T4 N0 M0
<table>
<thead>
<tr>
<th>Stage</th>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIB</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>IIA</td>
<td>T1</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIIB</td>
<td>T2</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td>IIIC</td>
<td>Any T</td>
<td>N3</td>
<td>M0</td>
</tr>
<tr>
<td>IV</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>


* T1 includes T1mic.

### DOCUMENT ASSESSMENT AND REVIEW TOOL

<table>
<thead>
<tr>
<th>Number and title of document under review</th>
<th>EBS #1-1 Version 2.2003: Surgical Management of Early-Stage Invasive Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date of current version</td>
<td>January 21, 2003</td>
</tr>
<tr>
<td>Clinical reviewer</td>
<td>Dr. M. Brackstone</td>
</tr>
<tr>
<td>Research coordinator</td>
<td>Rovena Tey</td>
</tr>
<tr>
<td>Date initiated</td>
<td>May 11, 2010</td>
</tr>
<tr>
<td>Date and final results / outcomes</td>
<td>November 19, 2010: ENDORSED</td>
</tr>
</tbody>
</table>

Beginning at question 1, below, answer the questions in sequential order, following the instructions in the black boxes as you go.

1. Is there still a need for a guideline covering one or more of the topics in this document? Answer Yes or No, and explain if necessary:
   - **YES**
     - A guideline is still needed for guideline Q1 (surgical management - breast conserving vs. mastectomy)
     - For guideline Q2 (management of the axilla), a recent CCO guideline has just been published by Ralph George et al. 2009 (*Sentinel Lymph Node Biopsy in Early-stage Breast Cancer*)

   If No, then the document should be ARCHIVED¹ with no further action; go to 11. If Yes, then go to 2.

2. Are all the current recommendations based on the current questions definitive* or sufficient§, and have less than 5 years elapsed since the latest search? Answer Yes or No, and explain if necessary:
   - **NO**
     - Current recommendations in this guideline are >5 years since the last search (which was 2002) - since then there have been publications showing longer follow-up of the same RCTs referred to in this publication (such as NSABP B-06) which still show the same findings.
     - The recommendations of the management of the axilla are not sufficient since the standards have changed.

   If Yes, the document can be ENDORSED² with no further action; go to 11. If No, go to 3.

3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, providing references of known evidence:
   - **NO**
     - For guideline Q1 (breast conservation vs. mastectomy), where current publications and follow-up data supports the original findings, and there have been no new significant studies to change that finding.

   YES
     - For guideline Q2 (management of the axilla) - where this guideline states that axillary dissection is the standard of care, that is absolutely not true any longer and the standard of care is sentinel lymph node biopsy as described in the CCO guideline by Ralph George et al. 2009 (*Sentinel Lymph Node Biopsy in Early-stage Breast Cancer*)

   If Yes, the document should be taken off the Web site as soon as possible. A WARNING³ should be put in its place informing a user that the document is only available by email, with a brief explanation of the reasons. If No, go to 4.
4. Do current resources allow for an updated literature search to be conducted at this time? Answer Yes or No, and explain as necessary. Provide an expected date of completion of the updated search, if applicable:

<table>
<thead>
<tr>
<th>4. YES</th>
</tr>
</thead>
<tbody>
<tr>
<td>• There is a designated research co-ordinator at the PEBC to carry out the literature search</td>
</tr>
<tr>
<td>• Updated search to be completed by July 2010</td>
</tr>
</tbody>
</table>

If No, a DEFERRAL should be placed on the document indicating it cannot be updated at this time, but will be reviewed again on a yearly basis. If Yes, go to 5.

5a. List below any new, relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Changes are in **BOLD**.

- Q1 - Delete “quality of life” as an outcome because finding many studies reporting this is not expected
- Q2 - Delete entire Q2 because it has been addressed in a recently published CCO guideline by Ralph George et al 2009 (Sentinel Lymph Node Biopsy in Early-stage Breast Cancer)

**Original Questions:**

3. In the surgical management of patients with early-stage invasive breast cancer (Stage I and II) who are candidates for breast conservation therapy, how does breast conservation therapy compare to modified radical mastectomy in terms of survival, **and** disease recurrence **and quality of life**?

4. **What is the optimum management of the axilla?**

**Target Population:**

Women with early-stage (Stage I and II) invasive breast cancer who are eligible for either breast conservation therapy or mastectomy.

5b. List below any changes to the selection criteria in the original version made necessary by new questions, changes to existing questions, or changes in available evidence (e.g., limit a search to randomized trials that originally included non-randomized evidence). Changes are in **BOLD**.

- Delete inclusion of studies on management of axilla and sentinel lymph node biopsy
- Delete quality of life as an outcome of interest
- Restrict the updated search to only phase 3 RCTs, therefore exclude phase 1 and 2 trials.

**Inclusion criteria:**

Articles were eligible for inclusion in the systematic review of the evidence if they were randomized controlled trials comparing breast conservation therapy versus mastectomy **or** were randomized trials on the surgical management of the axilla.

Trials investigating the efficacy and safety of sentinel lymph node biopsy were also eligible. Outcomes of interest included overall or disease-free survival, local recurrence, **and** distant recurrence, **and quality-of-life**.

Both abstract and full reports were eligible.

Evidence-based practice guidelines, meta-analyses, systematic reviews, and economic analyses addressing the guideline questions were also included in the guideline report.

**Exclusion criteria:**

Phase 1 and 2 trials were excluded.
5c. Conduct an updated literature search based on that done for the current version and modified by 5a and 5b above. Report the results below.

Full Selection Criteria, including types of evidence (e.g., randomized, non-randomized, etc.):
Articles were eligible for inclusion in the systematic review of the evidence if they were randomized controlled trials comparing breast conservation therapy versus mastectomy.

Outcomes of interest included overall or disease-free survival, local recurrence, and distant recurrence.

Both abstract and full reports were eligible.

Evidence-based practice guidelines, meta-analyses, systematic reviews, and economic analyses addressing the guideline questions were also included in the guideline report.

Exclusion criteria:
Phase 1 and 2 trials were excluded.

Search Period:
• June 2002 to 18 May 2010, up to week 19 or week 1 May (Embase + Medline)
• 2007 to 2009 (ASCO Annual Meeting)
• 2007 to 2009 (San Antonio BC Symposium)

Brief Summary/Discussion of New Evidence:
Of 560 total hits from Medline + Embase, 235 abstracts from ASCO, and 126 hits from San Antonio conference abstract searches, and after manually scanning reference lists of relevant articles, 5 references representing 5 RCTs were found comparing breast conservation therapy versus mastectomy, all of which are full-text publications of the long-term follow-up of RCTs that are already included in the existing guideline.

<table>
<thead>
<tr>
<th>Interventions</th>
<th>Name of RCT</th>
<th>Population</th>
<th>Outcomes</th>
<th>Brief results</th>
<th>References</th>
</tr>
</thead>
</table>
| BCS + RT vs. modified radical mastectomy | IGR (France) group | Early BC (T1; N0 or N1; M0)                      | 22-y OS, distant metastases, recurrence | • Equivalence trial.  
• Groups did not differ for 22-y OS, distant metastases, or recurrence | (Arriagada R et al. 2003)     |
| BCS vs. mastectomy                     | DBCG-82TM       | Primary operable invasive early BC               | 20-y OS, 10-y RFS, pattern of recurrence | • Groups did not differ for 20-y OS, 10-y RFS, or pattern of recurrence       | (Blichert-Toft M et al. 2008)   |
| BCS vs. BCS + RT vs. total mastectomy  | NSABP B-06      | Stage 1 or 2 BC with tumours ≤ 4 cm              | 20-y OS, DFS, recurrence          | • All 3 groups did not differ for 20-y OS or DFS.  
• Recurrence for BCS vs. BCS+ RT = 39% vs. 14% (p < 0.001) | (Fisher B et al. 2002)        |
| BCS + RT vs. Patey modified radical mastectomy | NCI             | Stage 1 or 2 invasive BC (T1 or T2; N0 or N1; M0) | 1 = 18-y OS, DFS 2 = contralateral BC | • Groups did not differ for 18-y OS, DFS, or incidence of contralateral BC. | (Poggi MM et al. 2003)          |
| BCS + RT vs. radical (Halsted) mastectomy | Milan group     | Early BC with tumours ≤ 2 cm (stage T1, N0)     | 20-y mortality, 20-y recurrence, distant metastases | • Groups did not differ for 20-y mortality or distant metastases.  
• 20-y cumulative recurrence for BCS vs. mastectomy = 8.8% vs. 2.3% | (Veronesi U et al. 2002)      |

BC = breast cancer; BCS = breast conserving surgery; DFS = disease-free survival; OS = overall survival; RFS = recurrence-free survival; RT = radiotherapy; vs. = versus; 1 = primary endpoints; 2 = secondary endpoints
New References Identified (alphabetical order):


Literature Search Strategy:

Medline

1. meta-analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$ or quantitative overview).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psychlit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliography$ or hand-search$ or relevant journals or manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. exp randomized controlled trials as topic/ or exp clinical trials, phase III as topic/ or exp clinical trials, phase IV as topic/
16. (randomized controlled trial or clinical trial, phase III or clinical trial, phase IV).pt.
17. random allocation/ or double blind method/ or single blind method/
18. (random$ control$ trial? Or rct or phase III or phase IV or phase 3 or phase 4).tw.
19. or/15-18
20. (phase II or phase 2).tw. or exp clinical trial/ or exp clinical trial as topic/
21. (clinical trial or clinical trial, phase II or controlled clinical trial).pt.
22. (20 or 21) and random$.tw.
23. (clinical$ adj trial$1).tw.
24. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy)).tw.
25. placebos/
26. (placebo? Or random allocation or randomly allocated or allocated randomly).tw.
27. (allocated adj2 random).tw.
28. or/23-27
29. practice guidelines/
30. practice guideline?.tw.
31. practice guideline.pt.
32. or/29-31
33. 7 or 8 or 9 or 14 or 19 or 22 or 28 or 32
34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. 33 not 34
36. limit 35 to english
37. limit 36 to human
38. exp breast neoplasms/
41. 39 and 40
42. 38 or 41
Embase
1. exp meta analysis/ or exp systematic review/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthesis$ or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp review/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-8
10. (cochrane or embase or psychlit or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliography or hand-search$ or relevant journals or manual search$).ab.
12. exp randomized controlled trial/ or exp phase 3 clinical trial/ or exp phase 4 clinical trial/
13. randomization/ or single blind procedure/ or double blind procedure/
14. (randomi$ control$ trial? Or rct or phase III or phase IV or phase 3 or phase 4).tw.
15. or/12-14
16. (phase II or phase 2).tw. or exp clinical trial/ or exp prospective study/ or exp controlled clinical trial/
17. 16 and randomS.tw.
19. (((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3 or dummy$))).tw.
20. placebo/
21. (placebo? Or random allocation or randomly allocated or allocated randomly).tw.
22. (allocated adj2 random).tw.
23. or/18-22
24. practice guidelines/
25. practice guideline?.tw.
27. or/24-26
28. 9 or 10 or 11 or 15 or 17 or 23 or 27
29. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
30. 28 not 29
31. limit 30 to english
32. limit 31 to human
33. exp breast neoplasms/
36. 34 and 35
37. 33 or 36
38. (early or stage I or stage 1 or stage 2 or stage II) and invasive).tw.
39. 37 and 38
40. (breast conservation or breast conserving or excision or lumpectomy or mastectomy or tumorectomy or quadrantectomy).mp.
41. 39 and 40
42. 32 and 41
43. (200223S or 2003$ or 2004S or 2005$ or 2006S or 2007$ or 2008$ or 2009$ or 2010$).ew.
44. 42 and 43

ASCO Annual Meeting - manually checked all abstracts from www.asco.org in the section: Breast cancer - local regional therapy

San Antonio Breast Cancer Symposium - mastectomy and (conservation or conserving), mastectomy and lumpectomy, mastectomy and (tumorectomy or tumorectomy), mastectomy and quadrantectomy (2007 and 2008); checked abstracts from www.sabcs.org in category: Breast conservation; surgery (2009)
<table>
<thead>
<tr>
<th>Q6</th>
<th>Is the volume and content of the new evidence so extensive such that a simple update will be difficult?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>6. NO</strong></td>
<td>• updated data supports prior guideline evidence</td>
</tr>
<tr>
<td>If Yes, then the document should be ARCHIVED with no further action; go to 11. If No, go to 7.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q7</th>
<th>On initial review, does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary? Answer Yes or No, and explain if necessary:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>7. YES</strong></td>
<td>• New data supports existing recommendations for Guideline Q1 (mastectomy vs. BCS)</td>
</tr>
<tr>
<td>• All 5 RCTs identified by the updated search represent publications showing further follow-up data for RCTs already referenced in the existing guideline and do not reveal any changes in study findings, thus would not dispute the existing guideline recommendations.</td>
<td></td>
</tr>
<tr>
<td>• All relevant subjects are addressed in existing guidelines so no new recommendations are necessary.</td>
<td></td>
</tr>
<tr>
<td>• Guideline 1-1 should be ENDORSED for the recommendations on mastectomy vs. BCS</td>
<td></td>
</tr>
<tr>
<td>If Yes, the document can be ENDORSED. If No, go to 8.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q8</th>
<th>Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed? Answer Yes or No, and explain if necessary, citing newly identified references:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>8. NO</strong></td>
<td>• New search supports current recommendations for Guideline Q1</td>
</tr>
<tr>
<td>• However, as identified in Q3, the existing recommendations for Guideline Q2 about management of the axilla is no longer valid and a warning note will be placed on the cover page of this guideline and readers will be directed to a reference of the CCO guideline by Ralph George et al. 2009 (Sentinel Lymph Node Biopsy in Early-stage Breast Cancer) that now answers that Q.</td>
<td></td>
</tr>
<tr>
<td>If Yes, a WARNING note will be placed on the web site. If No, go to 9.</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q9</th>
<th>Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>9. Not applicable.</strong></td>
<td>If Yes, the document update will be DEFERRED, indicating that the document can be used for decision making and the update will be deferred until the expected evidence becomes available. If No, go to 10.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q10</th>
<th>An update should be initiated as soon as possible. List the expected date of completion of the update:</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>10. Not applicable.</strong></td>
<td>An UPDATE will be posted on the Web site, indicating an update is in progress.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Q11</th>
<th>Circulate this form to the appropriate Disease Site Group for their approval. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSG Approval Date:</strong> November 19, 2010</td>
<td></td>
</tr>
</tbody>
</table>
DOCUMENT ASSESSMENT & REVIEW 5-STEP FLOW CHART

<table>
<thead>
<tr>
<th>STEPS</th>
<th>Outcomes</th>
<th>Action</th>
</tr>
</thead>
</table>


STEP 2: First teleconference to determine:
- the clinical relevance of the guideline,
- if a new literature search is needed, and
- if Yes, the search criteria.

1. Is there still a NEED for a guideline covering one or more of the topics in this document?
   - Yes: Archive
   - No: Continue

2. Are all the current recommendations based on the current questions definitive* or sufficient§, and have less than 5 years elapsed since the latest search?
   - Yes to all: Endorse
   - No: Proceed

3. Is there expected or known evidence that contradicts the current recommendations, such that they may cause harm or lead to unnecessary or improper treatment if followed?
   - Yes: Warning
   - No: Proceed

4. Do current resources allow for an updated literature search to be conducted at this time?
   - Yes: New search
   - No: Deferral

5. List any new and relevant questions that have arisen since the last version of the document. List any changes to the original research questions that now must be considered. Determine the search criteria.

STEP 3: A NEW literature search based on input from #5 will be conducted, and the result will be sent to the reviewers with a follow-up date.

Please note: No teleconference needed, IF the answers lead to one of these outcomes, PLUS the reviewer(s) complete & return the form with the answers & explanations.

Teleconference with the reviewer(s) will focus the discussion on #5: the search strategies, i.e., scope, key word(s), and inclusion and exclusion criteria.

RC emails DSG reviewer(s) the protocol

Discuss questions #1-5

RC conducts new search
FLOW CHART (cont.)

**STEPS** | **Outcomes** | **Action**
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**STEP 4:** Second teleconference to determine the ultimate status of the document

**#6.** Are the volume and content of the newly identified evidence such that a new document is necessary to address the topic?

- Yes: Archive

- No: **#7.** Does the newly identified evidence support the existing recommendations? Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?

  - Yes: **Endorse**

  - No: **#8.** Does any of the newly identified evidence, on initial review, contradict the current recommendations, such that the current recommendations may cause harm or lead to unnecessary or improper treatment if followed?

    - Yes: **Warning**

    - No: **#9.** Is there a good reason (e.g., new, stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline?

      - Yes: **Deferral**

      - No: **#10.** An update should be initiated as soon as possible. List the expected date of completion of the update.

**STEP 5:** Final outcome approval; Document Assessment & Review questions #11

**#11.** Circulate this form, the new evidence, and a draft document for approval by the appropriate DSG. Once approved, a copy of this form should be placed behind the cover page of the current document on the Web site. Notify the original authors of the document about this review.

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Please note: No teleconference needed, IF the reviewer(s) complete and return the form with answers & explanations.

Teleconference with the reviewer(s) to discuss the type of update, priority, and resources.
DOCUMENT ASSESSMENT AND REVIEW DEFINITIONS

Document Assessment and Review Terms

*DEFINITIVE RECOMMENDATIONS* - Definitive means that the current recommendations address the relevant subject area so fully that it would be very surprising to identify any contradictory or clarifying evidence.

§SUFFICIENT RECOMMENDATIONS* - Sufficient means that the current recommendations are based on consensus, opinion and/or limited evidence, and the likelihood of finding any further evidence of any variety is very small (e.g., in rare or poorly studied disease).

¶WARNING - A warning indicates that, although the topic is still relevant, there may be, or is, new evidence that may contradict the guideline recommendations or otherwise make the document suspect as a guide to clinical decision making. The document is removed from the Web site, and a warning is put in its place. A new literature search may be needed, depending on the clinical priority and resources.

Document Assessment and Review Outcomes

1. ARCHIVED - An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of the Web site and each page is watermarked with the phrase “Archived”.

2. ENDORSED - An endorsed document is a document that the DSG/GDG has reviewed for currency and relevance and determined to be still useful as guidance for clinical decision making. A document may be endorsed because the DSG/GDG feels the current recommendations and evidence are sufficient, or it may be endorsed after a literature search uncovers no evidence that would alter the recommendations in any important way.

3. DEFERRAL - A Deferral means that the clinical reviewers feel that the document is still useful and the decision has been made to postpone further action for a number of reasons. The reasons for the deferral are in the Document Assessment and Review Tool (Appendix 2).

4. UPDATE - An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.