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Surgical Management of Early-Stage Invasive Breast Cancer

Practice Guideline Report #1-1 Version 2.2003

Members of the Breast Cancer Disease Site Group

ORIGINAL GUIDELINE: January 21, 2003

This practice guideline report replaces an earlier version of the report that was completed in 1996 and published as:

Mirsky D, O'Brien SE, McCready DR, Newman TE, Whelan TJ, Levine MN and the Breast Cancer Disease Site Group. Surgical Management of Early Stage Invasive Breast Cancer (Stage I and II). *Cancer Prevention & Control, 1997*; 1(1): 10-17.

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.
- 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.

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 Practice Guideline Report #1-2: *Breast Irradiation in Women with Early-Stage Invasive Breast Cancer Following Breast Conserving Surgery.*
- Practice Guidelines Initiative's Evidence Summary #13-1: *Treatment of Lymphedema Related to Breast Cancer* (under development).

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The Practice Guidelines Initiative is sponsored by:
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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.[1] 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:

[1] Browman GP, Levine MN, Mohide EA, Hayward RSA, Pritchard KI, Gafni A, et al. The practice guidelines development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995;13(2):502-12.

For the most current versions of the guideline reports and information about the PGI and the Program, please visit our Internet site at:
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FULL REPORT

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 very 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, Metaannalyst$^{0.988}$ (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.

(Study group/ Author/ Year	Comparison**	# of Patients	Years of follow-up	Overall Survival	Disease-free survival	Local recurrence
IGR Arriagada (3) 1996	tumourectomy + radiation	88	15	73%	55%	9%
	modified radical mastectomy	91		65%	44%	14%
NSABP B-06 Fisher (4) 1995	lumpectomy	634	12	58%	47%	37%*
	lumpectomy + radiation	628		62%	49%	11%
	total mastectomy	589		60%	50%	NR
NCI Jacobson (5) 1995	lumpectomy + radiation	121	10	77%	72%	5%
	modified radical mastectomy	116		75%	69%	10%
DBCG Blichert-Toft (6) 1992	breast-conserving surgery	430	6	79%	70%	2%
	total mastectomy	429		82%	66%	---
EORTC Van Dongen (7) 1992	breast-conserving surgery	455	8	71%	64%	11%
	modified radical mastectomy	424		73%	70%	8%
Milan Veronesi (8) 1990	quadrantectomy + radiation	352	13	71%	NR	3%
	modified radical mastectomy	349		69%	NR	2%
Guy's Hospital Hayward (9) 1977	wide excision + radiation	122	6	NR	NR	30%*
	total mastectomy + radiation	130				8%
Guy's Hospital Atkins (10) 1972	wide excision + radiation	184	10	NR	NR	40%*
	total mastectomy + radiation	192				18%
Naples D'Aiuto (11)	breast-conserving surgery	170	NR	88%	NR	NR
	mastectomy	170		85%		
CRC, UK (12) 1995	breast-conserving surgery	71	NR	80%	NR	NR
	mastectomy	74		82%		
BMFT 01, Germany (12)	breast-conserving surgery	41	NR	90%	NR	NR
	mastectomy	31		95%		

* 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.

IGR, Institute Gustave-Roussy Breast Cancer Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; NCI, National Cancer Institute; DBCG, Danish Breast Cancer Cooperative Group; EORTC, European Organisation for Research and Treatment of Cancer; CRC UK, Cancer Research Campaign United Kingdom; BMFT, Bundesministerium fur Forschung und Technologie; NR = Not Reported

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 vs. 15 patients), axillary (8 vs. 7 patients) or distant recurrence (29 vs. 29 patients). There were also no reported differences in 5-year survival rates (82.1% vs.88.6%; $p=0.20$, log rank test) or in disease-free survival (79.1% vs. 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; $p>0.05$).

V. 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 pre-operative 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 tumor 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.

VI. 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.

VII. 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.

VIII. 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 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.

IX. 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 a 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

Item	Number (%)		
	Strongly agree or agree	**Neither agree nor disagree**	**Strongly disagree or disagree**
2. The rationale for developing a clinical practice guideline, as stated in the "*Choice of Topic*" section of the report, is clear.	94 (96%)	4 (4%)	0
3. There is a need for a clinical practice guideline on this topic.	88 (90%)	7 (7%)	3 (3%)
4. The literature search is relevant and complete.	87 (91%)	9 (9%)	0
6. The results of the trials described in the report are interpreted according to my understanding of the data*.	92 (97%)	3 (3%)	0
7. The draft recommendations in this report are clear.*	88 (97%)	3 (3%)	0
8. I agree with the draft recommendations as stated.*	89 (93%)	1 (1%)	6 (6%)
20. This PGIP report should be approved as a practice guideline.*	80 (86%)	8 (9%)	4 (4%)
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?*	Very likely or likely	Unsure	Not at all likely or unlikely
	89 (94%)	4 (4%)	2 (2%)

*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.

X. 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 Practice Guideline Report #1-2: Breast Irradiation in Women with Early-Stage Invasive Breast Cancer Following Breast Conserving Surgery.
- Practice Guidelines Initiative's Evidence Summary #13-1: Treatment of Lymphedema Related to Breast Cancer (under development)

XI. 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.

XII. JOURNAL REFERENCE

Publication in progress.

XIII. ACKNOWLEDGMENTS

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For a full list of members of the Cancer Care Ontario Breast Cancer Disease Site Group please visit the website of the Program in Evidence-based Care at http://www.ccopebc.ca/.

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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 (eg, 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 presence 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 (eg, 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

NOTE. Adapted with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the *AJCC Cancer Staging Manual, Sixth Edition* (2002) published by Springer-Verlag New York, www.springer-ny.com.
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
IIIA	T0 N2 M0
	T1* N2 M0
	T2 N2 M0
	T3 N1 M0
	T3 N2 M0
IIIB	T4 N0 M0
	T4 N1 M0
	T4 N2 M0
IIIC	Any T N3 M0
IV	Any T Any N M1

NOTE. Adapted with permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC Cancer Staging Manual, Sixth Edition (2002) published by Springer-Verlag New York, www.springer-ny.com.
* T1 includes T1mic.

Source: Singletary SE, Allred C, Ashley P, et al. Revision of the American Joint Committee on Cancer staging system for breast cancer. *J Clin Oncol* 2002 1;20(17):3628-36.