These guidelines have been withdrawn

MOH clinical practice guidelines are considered withdrawn five years after publication unless otherwise specified in individual guidelines. Users should keep in mind that evidence-based guidelines are only as current as the evidence that supports them and new evidence can supersede recommendations made in the guidelines.

CLINICAL PRACTICE GUIDELINES

Breast Cancer

Ministry of Health

National Committee on Cancer Care

Mar 2004

MOH Clinical Practice Guidelines 4/2004

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Grades of recommendation

Grade	Recommendation
A (evidence levels Ia, Ib)	Requires at least one randomised controlled trial, as part of the body of literature of overall good quality and consistency addressing the specific recommendation.
B (evidence levels IIa, IIb, III)	Requires availability of well conducted clinical studies but no randomised clinical trials on the topic of recommendation.
C (evidence level IV)	Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates absence of directly applicable clinical studies of good quality.
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Breast Cancer

MOH Clinical Practice Guidelines 4/2004

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Statement of Intent

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

Adherence to these guidelines may not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Foreword

Breast cancer has remained the commonest cancer among women in Singapore over the last 30 years. In 2002, the Ministry initiated a national screening programme for breast cancer. The goal of this programme is to detect and treat breast cancer early so that our patients can achieve the best outcomes in terms of prolonged survival, reduced morbidity and better quality of life.

These clinical practice guidelines discuss the evidence for the many treatment options open to patients with ductal carcinoma in situ and invasive breast cancer. Strong evidence from randomised controlled trials underpins some recommendations made in the guidelines. Other recommendations are supported by lower levels of evidence and have a greater potential to change as expert opinion in these areas varies. It is therefore important to explain the benefits and risks of all treatment options carefully to patients and consider their attitudes to different treatments.

The guidelines also contain a section on the pathology of breast cancer. This section provides useful information for pathologists and surgeons on the conventions in handling and reporting of pathological breast specimens.

I hope you will find these guidelines useful in considering and advising on treatment options with your patients with breast cancer.

PROFESSOR TAN CHORH CHUAN
DIRECTOR OF MEDICAL SERVICES

Contents

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Ductal Carcinoma in Situ (DCIS)

GPP Mastectomy and breast conservation surgery and adjuvant radiotherapy are effective alternative treatments for ductal carcinoma in situ and the patient's preference should be considered in the choice of treatment. (pg 14)

GPP

A Nevertheless there are some cases in which breast conservation is contra-indicated, which include: (pg 15)

- Presence of multicentric tumours involving more than one quadrant of the breast.
- Diffuse malignant-looking microcalcifications throughout the breast.
- Factors unrelated to ductal carcinoma in situ but which may preclude the use of adjuvant radiotherapy may be considered relative contra-indications to breast conservation. These include collagen vascular disease such as scleroderma and systemic lupus, pregnancy and previous radiotherapy to the breast area.
- Reluctance of the patient to undergo radiotherapy. As many patients may have inaccurate preconceptions of the side effects and toxicity of radiotherapy, a referral to a radiation oncologist is recommended before the decision is taken to not offer breast conservation for this reason alone.

Grade A, Level Ib

A Indications for breast conservation surgery and adjuvant radiotherapy include mammography-detected ductal carcinoma in situ, or palpable ductal carcinoma in situ with no suggestion of multicentricity or diffuse microcalcification on pre-operative mammography. (pg 15)

Grade A, Level Ib

A No subgroup of ductal carcinoma in situ has been identified from randomised clinical trials that have not benefited from the addition of adjuvant radiotherapy. However, the addition of adjuvant radiotherapy to breast conservation surgery in small low grade ductal carcinoma in situ with clear margins of more than 1 cm adds minimal benefit in improving local control. For the group of patients where the benefit is small, the patient's attitude towards the risk and benefit of radiotherapy needs to be taken into consideration before radiotherapy is omitted. (pg 15)

Grade A, Level Ib

A Re-excision of margins should be undertaken when margin involvement is found on histological examination, or if malignant appearing microcalcification is seen in post-operative mammography. (pg 16)

Grade A, Level Ib

GPP Orientation of the surfaces of the excision specimen at the time of initial surgery will allow the re-excision of that margin which is involved alone, and decrease cosmetic deformity. (pg 16)

GPP

A The likelihood of axillary involvement in ductal carcinoma in situ is about 2-3%, and axillary dissection is therefore not recommended. (pg 16)

Grade A, Level Ib

GPP The role of sentinel node biopsy in ductal carcinoma in situ is not resolved and is not recommended. (pg 16)

GPP

A Routine use of tamoxifen in ductal carcinoma in situ is not indicated. (pg 16)

Grade A, Level Ib

C The routine use of more sophisticated means to detect tumour recurrence in the absence of clinical signs and symptoms, such as tumour markers, imaging for metastasis and liver function tests has not been shown to be useful or cost-effective and is discouraged. (pg 17)

Grade C, Level IV

C Post-operatively, the clinical review of the patient is recommended at three- to six-monthly intervals for three years, six-monthly to12-monthly for the second to fifth years, and annually thereafter. (pg 17)

Grade C, Level IV

A Post-operative mammography is required to ensure removal of all malignant microcalcifications for screen-detected ductal carcinoma in situ. (pg 17)

Grade A, Level 1b

GPP Surgery and post-operative radiotherapy changes usually resolve six months to a year after treatment and a repeat mammogram of the affected breast is recommended at the end of the first year. (pg 17)

GPP

C Following the mammography of the affected breast at the end of the first year post-treatment, annual to two-yearly mammography of both breasts is recommended. (pg 17)

Grade C Level IV

Invasive Breast Cancer: Surgical Therapy

A Breast conservation surgery and adjuvant radiotherapy and total mastectomy and axillary clearance are effective treatments for invasive breast cancer and the patient's preference should be considered in the choice of treatment. (pg 21)

Grade A, Level Ia

A Nevertheless there are some cases in which breast conservation is contra-indicated, which include: (pg 21)

- Presence of multicentric tumours involving more than one quadrant of the breast
- Diffuse malignant-appearing microcalcifications throughout the breast
- Persistent positive surgical margins following reasonable attempts for clear margins
- While there is no definite size that mandates mastectomy, a relative indication would be if surgical and radiological assessment

suggests that adequate margins cannot be obtained with an acceptable cosmetic result. (see section on Neoadjuvant Chemotherapy)

- Factors unrelated to breast cancer but which may preclude the use of adjuvant radiotherapy may be considered relative contra-indications to breast conservation. These include collagen vascular disease such as scleroderma and systemic lupus, pregnancy and previous radiotherapy to the breast area.
- Reluctance of the patient to undergo radiotherapy. As many patients may have inaccurate preconceptions of the side effects and toxicity of radiotherapy, a referral to a radiation oncologist is recommended before the decision is taken to not offer breast conservation for this reason alone.

Grade A, Level Ia

A Patients with lobular cancer subtype can be offered breast conservation, if there is a good chance that clear margins can be obtained and the presence of multi-centricity can be excluded. (pg 22)

Grade A, Level Ia

A Enlarged axillary nodes, whether fixed or mobile, are not a contra-indication to breast conservation surgery as no increase in local recurrence has been reported. (pg 22)

Grade A, Level Ia

A Central location is not a contra-indication to breast conservation surgery, as good control can be obtained with postoperative radiotherapy. (pg 22)

Grade A, Level Ia

A A positive family history should not prevent a woman from considering breast conservation surgery and adjuvant radiotherapy, as previously reviewed studies have not shown an increase in local recurrence with this option. (pg 22)

Grade A, Level Ia

A Re-excision of margins should be undertaken when margin involvement is found on histological examination, or if malignant appearing microcalcification is seen in post-operative mammography. (pg 22)

Grade A, Level Ib

GPP Orientation of the surfaces of the excision specimen at the time of initial surgery will allow the re-excision of that margin which is involved alone, and decrease cosmetic deformity. (pg 22)

GPP

B Level II axillary dissection to include the clearance of nodes under the pectoralis minor will provide accurate staging information and maintain local control in the axilla. In cases where fixed axillary nodes are found in pre-operative clinical examination, or the presence of gross extra-nodal spread at the time of axillary surgery, a level III clearance to include all nodes to the lateral border of the first rib may decrease the incidence of axillary recurrence. (pg 22)

Grade B, Level IIb

C The routine use of more sophisticated means to detect tumour recurrence, such as tumour markers, imaging for metastasis and liver function tests has not been shown to be useful or cost-effective and is discouraged. (pg 23)

Grade C, Level IV

C Post-operatively, the clinical review of the patient is recommended at three- to six-monthly intervals for three years, six-monthly to twelve-monthly for the second to fifth years, and annually thereafter. (pg 23)

Grade C, Level IV

C Following the mammography of the affected breast at the end of the first year post-treatment, annual to two-yearly mammography of both breast is recommended. (pg 23)

Grade C, Level IV

Invasive Breast Cancer: Adjuvant Cytotoxic and Hormonal Therapies

GPP There is currently no data to support the use of raloxifene (EVISTA) as adjuvant hormonal therapy in early breast cancer and use for adjuvant treatment in breast cancer is not recommended. (pg 26)

GPP

A Adjuvant treatments are recommended for the risk groups and patient groups as shown in the following table: (pg 27)

Patient group	Risk Group	
	Minimal/Low	**Intermediate/High**
Premenopausal		
ER or PR positive	Tamoxifen or None	Chemotherapy + Tamoxifen or Ovarian ablation + Tamoxifen
ER and PR negative	None	Chemotherapy
Post-menopausal		
ER or PR positive	Tamoxifen or None	Chemotherapy + Tamoxifen or Tamoxifen
ER and PR negative	None	Chemotherapy

Grade A, Level Ib

Adjuvant Radiotherapy for Invasive and Non-invasive Breast Cancer

A Post-mastectomy radiotherapy should be offered to a patient with T3 or T4 primary tumours, or with four or more lymph nodes involved. (pg 31)

Grade A, Level Ia

A All patients undergoing breast conservation surgery for invasive and non-invasive breast cancer should be offered adjuvant radiotherapy. (pg 31)

Grade A, Level Ia

GPP All patients eligible for breast conservation should be referred for a radiation oncology consultation if the fear of breast conservation is radiation treatment. (pg 31)

GPP

B Radiation treatment should be given in the management of locally advanced tumours. (pg 31)

Grade B, Level III

Neoadjuvant Therapy for Operable and Inoperable Breast Cancer

A In patients who desire breast conservation surgery, three to four cycles of anthracycline-based therapy after a biopsy of the tumour is recommended. Patients should be advised that a conversion to breast conservation may be possible in 20-30% of cases. If the tumour responds to chemotherapy, lumpectomy and axillary lymph nodes dissection, followed by radiotherapy may be considered if the patient meets the requirement for breast conserving therapy. (pg 34)

Grade A, Level Ib

B Breast conserving surgery may be followed by further individualized adjuvant chemotherapy such as additional anthracycline or taxane therapy. (pg 34)

Grade B, Level IIa

B If after 3-4 cycles of preoperative chemotherapy, the tumour fails to respond, or the response is minimal or if there is progression at any point, a mastectomy plus axillary dissection should be performed. Adjuvant therapy for these patients should be individualised, followed by radiation therapy as required. (pg 34)

Grade B, Level IIa

A After completion of all surgery, chemotherapy and radiation therapy, all patients with estrogen and/or progesterone receptor positive tumours should receive tamoxifen. (pg 35)

Grade A, Level Ib

B In patients with endocrine receptor positive tumours who are unfit or unwilling to receive chemotherapy, neoadjuvant endocrine therapy with third-generation aromatase inhibitors such as letrozole or anastrazole may be offered. (pg 35)

Grade B, Level IIa

C Initial treatment with anthracycline and/or taxane-based chemotherapy is recommended. (pg 35)

Grade C, Level IV

B For patients who respond to neoadjuvant chemotherapy, local therapy may consist of total mastectomy with axillary lymph node dissection or alternatively breast-conserving therapy can be considered in patients with a good partial or complete response to neoadjuvant chemotherapy.
(pg 35)

Grade B, Level IIa

C Patients with an inoperable stage IIIA or stage IIIB tumour, whose disease progresses during preoperative therapy, should be considered for palliative breast irradiation in an attempt to enhance local control. Further systemic adjuvant chemotherapy following local therapy is felt to be standard. (pg 35)

Grade C, Level IV

B After surgery, adjuvant radiation therapy to the chest wall and regional lymphatics is recommended. (pg 35)

Grade B, Level IIa

A Hormone therapy should be administered to patients whose tumours are estrogen receptor- or progesterone receptor-positive or of unknown hormone receptor status. (pg 35)

Grade A, Level Ib

A Elderly and frail patients are exceptions to the intensive multimodal approach. In such a patient with a receptor positive tumour, tamoxifen alone (20 mg/day) may be used to reduce tumour size with few or no side effects. (pg 36)

Grade A, Level Ib

1 Introduction

1.1 Aim and scope of guideline

Breast cancer is the commonest cancer among women in Singapore, and has been so for the last thirty years. The trend over time is that incidence is increasing, with the incidence rate in 1993-1997 being 2.3 times that in 1968-1972.

Breast cancer is probably the best studied of all adult malignancies in terms of number of study subjects accrued in large, multi-centre prospective randomised controlled trials with long follow-up results. Results from these studies have clarified the place of radical and conservative surgery, local and systemic adjuvant therapy, neoadjuvant systemic therapy, chemotherapy and endocrine modulators, in all their myriad combinations, in the treatment of this disease.

What has emerged from this plethora of information is the need for this and other cancers to be treated in a multi-disciplinary setting. This should involve surgeon, radiologist, medical oncologist, radiation oncologist and pathologist from the point of diagnosis before the options of further treatment are presented to the patient. The constitution of our workgroup recognises the place of such expertise in every phase of breast cancer management.

1.2 Guideline development

These guidelines were developed by a workgroup consisting of breast surgeons, a radiologist, medical and radiation oncologists, a pathologist and a nurse with an interest in breast cancer. Sub- specialists drafted their respective contributions based on evidence available in the literature up to March 2003. The various sections were discussed by the workgroup as a whole and the consensus opinion of the members of the workgroup was accepted as recommendations for best clinical practice.

1.3 Target group

These clinical practice guidelines have been drafted to assist women with breast cancer and their doctors to make decisions on managing

their disease. The focus of these guidelines is on breast cancer management. Recommendations on breast screening may be found in another Ministry of Health publication, the Health Screening Clinical Practice Guidelines.

The recommendations in these guidelines are evidence-based and apply to women of all ages with invasive breast cancer or ductal carcinoma in situ.

1.4 Review of Guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supercede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review 5 years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2 Ductal Carcinoma in Situ (DCIS)

2.1 Introduction

Ductal carcinoma in situ (DCIS) is defined as ductal malignancy with no breach of the basement membrane. The reported prevalence of DCIS depends on the uptake of screening mammography. In mature mammography screening programmes, DCIS constitutes up to 30% of all breast cancers detected.

Up to 50% of breast cancer recurrence following treatment of DCIS is invasive with its associated possibility of systemic spread and decreased survival. Treatment of DCIS is therefore guided by the incidence of invasive recurrence and the results of salvage therapy. The evaluation of results of trials on different DCIS treatment modalities is complicated by the changes in presentation of DCIS over time, different methods of mammographic and pathological evaluation, and the long natural history of this condition.

2.2 Supporting Literature

2.2.1 Mastectomy

No randomised controlled trials are available that have compared mastectomy to breast conservation. Four retrospective single-center studies with a median follow-up time exceeding 10 years have been reported.[1-4] All have documented a recurrence rate of 1-2%, suggesting that mastectomy is highly effective in the treatment of DCIS. Nevertheless, this may be over-treatment in the case of smaller tumours, particularly in the present setting of mammography-detected DCIS.

2.2.2 Breast conservation surgery and adjuvant radiotherapy (BCSRT)

Two large randomised controlled trials have compared the efficacy of breast conservation surgery (BCS) alone versus BCS with adjuvant radiotherapy (BCSRT).

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 study,[5-7] eligible patients required clear margins (defined as tumour cells not touching inked margins) and 80% of cases were mammographic detected lesions. The incidence of both invasive and non-invasive recurrence was markedly reduced by breast radiotherapy, with invasive recurrence of 3.9% in the irradiated group compared to 13.4% in the non-irradiated group ($p = 0.0005$). No significant difference in breast cancer survival was found with the addition of radiotherapy.

In the second trial, the European Organization for Research and Treatment of Cancer (EORTC) 10853 trial,[8,9] radiotherapy was found to improve the relapse-free survival from 84 to 91% at 5 years follow-up, with similar improvements in both in-situ and invasive recurrences.

Various clinical, pathological and radiological features have been identified which predict for recurrence and identify individuals for whom mastectomy should be offered as primary surgical treatment. A consistent predictor of recurrence found in several studies has been the presence of residual malignant microcalcifications following excision. In the few patients in whom such findings have been left untreated, a recurrence rate of 100% has been reported.[10]

2.2.3 Breast Conservation Surgery (BCS) alone

A number of studies have reported results following the use of breast conservation with clear margins alone with the omission of further adjuvant therapy. These subjects have generally been selected for small size, mammographic presentation only and wide surgical margins. The majority of recurrences occurred in patients with high grade DCIS, with nuclear grade 1 lesions having recurred in only 6% of patients.

Silverstein et al developed the Van Nuys Prognostic Index (VNPI),[11] a retrospectively derived risk index based on tumour size, extent of clear margins, pathological grade (based on nuclear grade and comedonecrosis). At 10 years follow-up, the low risk group was reported to have recurrence of 2% regardless of adjuvant therapy. More recently Silverstein et al[12] have suggested that any case of DCIS could be treated with wide excision of margins exceeding 1 cm, and with no benefit from further adjuvant treatment. However, in the absence of supporting data from randomised controlled trials, such an approach

has not been universally accepted. Furthermore, the retrospective basis of the data, with variations in surgical and pathological assessment over a 20-year period suggests that these findings cannot be taken as definitive.

2.2.4 Tamoxifen for DCIS

Given the success and high acceptability of tamoxifen in the treatment of invasive breast cancers, one large, prospective RCT[13] has examined the role of tamoxifen in the treatment of DCIS following local excision and post-operative radiotherapy. Patients were randomized to either receive tamoxifen 20 mg daily for 5 years or placebo following surgery and radiotherapy. Although there was no significant difference in breast cancer survival in the two arms, women in the tamoxifen group had fewer breast cancer events at 5 years than did those on placebo (8.2% vs 13.4%, p=0.0009). Well-known side effects of tamoxifen were also seen in the treatment arm, with endometrial cancer increasing from 0.45 to 1.53 per 1000 women per year and deep vein thrombosis from 0.2% to 1.0%.

2.3 Patient Evaluation

2.3.1 History

Breast specific elements of the history should include the family history of breast, ovarian and other malignancies that may suggest the presence of a hereditary syndrome. This will be more likely in the presence of early onset (breast cancer under 40 years of age) and bilateral disease.

The option of breast conservation and radiotherapy may be affected by a personal history of previous adjuvant therapy in the breast region, the presence of collagen vascular disease and the presence of previous breast implants, whether subcutaneous or sub-pectoral.

2.3.2 Physical Examination

A large majority of DCIS will present as mammographic abnormalities; the small minority of palpable DCIS can be evaluated along the same principles as palpable invasive breast cancers.

In the absence of physical abnormalities, the breast specific elements of the physical evaluation should include the volume, form and symmetry of the breasts. Reference should be made to preoperative mammograms in the assessment of the extent of disease and the possibility of adequate surgical margins with a cosmetically favourable outcome.

Palpable axillary and supraclavicular nodes suggest the possibility of under-staging and the presence of invasive disease. These can be evaluated with needle biopsy prior to definitive surgery.

2.3.3 Mammographic Evaluation

The most common presentation of DCIS is mammographic microcalcifications. The assessment of extent of disease should be carried out by surgeons and breast radiologists in a multidisciplinary setting. A recent mammogram, preferably within three months of surgery, should include standard craniocaudal and mediolateral oblique views. An effort should be made to determine the maximal extent of tumoural calcifications. Special views, including magnified and cone-compression films, can decrease the likelihood of underestimation of the extent of disease. Ultrasound may be helpful to determine the presence of nodular masses within the involved duct system which may indicate the presence of macroscopic invasive foci. Any such nodular lesions should be core biopsied if technically possible to determine whether they represent nodular DCIS or invasive carcinoma prior to definitive surgical treatment.

The use of other imaging abnormalities, especially magnetic resonance imaging (MRI), has not been established in the evaluation of DCIS.

2.4 Recommendations

2.4.1 Surgery of the Breast

2.4.1.1 Mastectomy

GPP Mastectomy and BCSRT are effective alternative treatments for DCIS and the patient's preference should be considered in the choice of treatment.

GPP

A Nevertheless there are some cases in which breast conservation is contra-indicated, which include:

- Presence of multicentric tumours involving more than one quadrant of the breast.[10]
- Diffuse malignant-looking microcalcifications throughout the breast.[10]
- Factors unrelated to DCIS but which may preclude the use of adjuvant radiotherapy may be considered relative contra-indications to breast conservation. These include collagen vascular disease such as scleroderma and systemic lupus, pregnancy and previous radiotherapy to the breast area.[5,8,9]
- Reluctance of the patient to undergo radiotherapy. As many patients may have inaccurate preconceptions of the side effects and toxicity of radiotherapy, a referral to a radiation oncologist is recommended before the decision is taken to not offer breast conservation for this reason alone.[5,8,9]

Grade A, Level Ib

2.4.1.2 Breast conservation and adjuvant radiotherapy

A Indications for breast conservation surgery and adjuvant radiotherapy (BCSRT) include mammography-detected DCIS, or palpable DCIS with no suggestion of multicentricity or diffuse microcalcification on pre-operative mammography.[5-9]

Grade A, Level Ib

2.4.1.3 Breast Conservation alone

A No subgroup of DCIS has been identified from randomised clinical trials that have not benefited from the addition of adjuvant radiotherapy. However, the addition of adjuvant radiotherapy to breast conservation surgery (BCS) in small low grade DCIS with clear margins of more than 1 cm adds minimal benefit in improving local control. For the group of patients where the benefit is small, the patient's attitude towards the risk and benefit of radiotherapy needs to be taken into consideration before radiotherapy is omitted.[5-9, 11]

Grade A, Level Ib

2.4.1.4 Re-excision of margins

A Re-excision of margins should be undertaken when margin involvement is found on histological examination, or if malignant appearing microcalcification is seen in post-operative mammography.[5]

Grade A, Level Ib

GPP Orientation of the surfaces of the excision specimen at the time of initial surgery will allow the re-excision of that margin which is involved alone, and decrease cosmetic deformity.

GPP

2.4.2 Surgery of the axilla

A The likelihood of axillary involvement in DCIS is about 2-3%, and axillary dissection is therefore not recommended.[5-9]

Grade A, Level Ib

GPP The role of sentinel node biopsy in DCIS is not resolved and is not recommended.

GPP

2.4.3 Tamoxifen for DCIS

Tamoxifen provides risk reduction in recurrences in DCIS patients treated with breast conservation. Since a survival advantage has not been demonstrated, individual consideration of risks and benefits is important.[13]

A Routine use of tamoxifen in DCIS is not indicated.

Grade A, Level Ib

2.4.4 Surveillance

The purpose of post-treatment monitoring is twofold:

- Detection of recurrent disease or new tumours in ipsi- and contra-lateral breast
- Detection of progressive functional changes such as cosmetic deformity or difficulties in arm swelling or mobility

C The routine use of more sophisticated means to detect tumour recurrence in the absence of clinical signs and symptoms, such as tumour markers, imaging for metastasis and liver function tests has not been shown to be useful or cost-effective and is discouraged.[14]

Grade C, Level IV

C Post-operatively, the clinical review of the patient is recommended at three- to six-monthly intervals for three years, six-monthly to 12-monthly for the second to fifth years, and annually thereafter.[14]

Grade C, Level IV

A Post-operative mammography is required to ensure removal of all malignant microcalcifications for screen-detected DCIS.[8,9]

Grade A, Level 1b

It should be noted that mammographic features of cancer recurrence overlap with those following surgery and radiotherapy.

GPP Surgery and post-operative radiotherapy changes usually resolve six months to a year after treatment and a repeat mammogram of the affected breast is recommended at the end of the first year.[14]

GPP

C Following the mammography of the affected breast at the end of the first year post-treatment, annual to two-yearly mammography of both breasts is recommended.[14]

Grade C Level IV

3 Invasive Breast Cancer: Surgical Therapy

3.1 Introduction

Long-term results from numerous well-designed studies have clarified the position of various treatment modalities in invasive breast cancer. With increased public awareness and the implementation of the national breast cancer screening programme, breast cancer patients are expected to present earlier and hence be more likely to be suitable for and offered breast conservation surgery. Recent trials have also reported that neoadjuvant systemic therapy in operable breast cancer improves the breast conservation rate.

3.2 Supporting Literature

3.2.1 Total mastectomy and axillary clearance (TMAC) versus Breast conservative surgery with adjuvant radiotherapy (BCSRT)

Six large randomised controlled trials have confirmed the efficacy of BCSRT compared to TMAC.[15-23] All but one had a median follow-up in excess of 10 years, and have all shown no significant difference in disease-free survival. Four of the six trials reported no increase in regional recurrence rates.

Most regional recurrences were treated with mastectomy with no compromise in breast cancer survival.

It should be noted that total mastectomy does not eliminate the risk of local relapse. In the abovementioned randomised controlled trials, chest wall recurrence following TMAC was reported at 4-14% at 10 years follow-up. A meta-analysis of randomised controlled trials was carried out by the Early Breast Cancer Trialists' Collaborative Group[24] and showed no difference in overall survival between patients treated with TMAC or BCSRT. The local recurrence rate was 6.2% in the mastectomy group compared to 5.9% in women who had BCSRT.

3.2.2 Breast conservation surgery alone (BCS) versus Breast conservation surgery with adjuvant radiotherapy (BCSRT)

In addition to randomised controlled trials that have compared TMAC with BCSRT, ten randomised controlled trials have compared BCSRT with BCS alone.[25-33] Comparisons between these trials are difficult on account of their differences in stage of disease, definitions of clear margins and use of adjuvant systemic therapy and tamoxifen. Despite these differences, all trials have shown a benefit of adjuvant radiotherapy when added to BCS. A recent meta-analysis of these randomised controlled trials[24] estimated the absolute benefit of radiation on disease-free survival as 16% in the node negative patients (44.7% vs 28.6%, $p < 0.00001$) and 8% for the node positive patients (58% vs 49.8%, $p = 0.002$). Post operative irradiation has been found to benefit all groups of breast cancer patients treated.[29,32]

3.3 Patient Evaluation

3.3.1 History

Breast specific elements of the history should include the family history of breast, ovarian and other malignancies that may suggest the presence of a hereditary syndrome. This will be more likely in the presence of early onset (breast cancer under 40 years of age) and bilateral disease.

The option of breast conservation and radiotherapy may be affected by a personal history of previous adjuvant therapy in the breast region, the presence of collagen vascular disease and the presence of previous breast implants, whether subcutaneous or sub-pectoral.

In addition elements in this history should be obtained that may suggest the presence of metastatic disease, such as bone pain, pleuritic chest pain and abdominal discomfort.

3.3.2 Physical Examination

With breast cancer screening, an increasing proportion of invasive breast cancers is expected to have a normal physical examination.

The pre-operative approach to these patients should be managed along the same principles as non-palpable DCIS.

Elements in the physical examination should include factors that will indicate the suitability of BCS, as well as signs of more systemic or locally advanced disease. These include the size and location of the tumour, presence of multicentric or bilateral disease, the proportion of the tumour compared to the remaining breast volume, and the presence of axillary or supraclavicular lymph nodes. Locally advanced breast cancer is defined by the presence of skin ulceration and tumour satellites, peau d'orange, inflammatory breast cancer and fixed axillary nodes with ipsilateral arm lymphedema.

3.3.3 Mammographic Evaluation

The assessment of the extent of disease should be carried out by surgeons and radiologists in a multidisciplinary setting. Mammography is preferably carried out before needle or excision biopsy as these can alter the mammographic appearance and extent of the tumour. A recent mammogram, preferably within three months of surgery, should include standard craniocaudal and mediolateral oblique views of both breasts. An effort should be made to determine the maximal extent of tumoural calcifications. Special views, including magnified and cone-compression films, can decrease the likelihood of underestimation of the extent of disease. Up to 95% of tumours can be adequately selected on the basis of physical examination and mammography workup alone.

In general it is important to determine whether the index tumour is unifocal or multifocal prior to definitive surgery, in order to reduce the likelihood of early local recurrence, as well as the number of operations required for complete excision with clear margins. In addition to mammography, the use of ipsilateral breast ultrasound to assess the extent of disease may be helpful. Other imaging modalities, especially magnetic resonance imaging (MRI), while able to detect mammographically occult lesions, has not been shown to affect survival. Nevertheless MRI may be useful to detect multifocality in invasive lobular cancers, which are notoriously difficult to detect on conventional imaging and which have a relatively high (10-15%) incidence of multifocality.

3.4 Recommendations

3.4.1 Surgery of the Breast

A Breast conservation surgery and adjuvant radiotherapy (BCSRT) and total mastectomy and axillary clearance (TMAC) are effective treatments for invasive breast cancer and the patient's preference should be considered in the choice of treatment.[15-24]

Grade A, Level Ia

Multiple randomised studies have shown the efficacy of BCSRT to be equal to that of TMAC, in terms of both local recurrence and disease-free survival.

A Nevertheless there are some cases in which breast conservation is contra-indicated, which include:[24]

- Presence of multicentric tumours involving more than one quadrant of the breast
- Diffuse malignant-appearing microcalcifications throughout the breast
- Persistent positive surgical margins following reasonable attempts for clear margins
- While there is no definite size that mandates mastectomy, a relative indication would be if surgical and radiological assessment suggests that adequate margins cannot be obtained with an acceptable cosmetic result. (see section on Neoadjuvant Chemotherapy)
- Factors unrelated to breast cancer but which may preclude the use of adjuvant radiotherapy may be considered relative contra-indications to breast conservation. These include collagen vascular disease such as scleroderma and systemic lupus, pregnancy and previous radiotherapy to the breast area
- Reluctance of the patient to undergo radiotherapy. As many patients may have inaccurate preconceptions of the side effects and toxicity of radiotherapy, a referral to a radiation oncologist is recommended before the decision is taken to not offer breast conservation for this reason alone.

Grade A, Level Ia

The following are not contra-indications for BCSRT:

A Patients with lobular cancer subtype can be offered breast conservation, if there is a good chance that clear margins can be obtained and the presence of multi-centricity can be excluded.[24]

Grade A, Level Ia

A Enlarged axillary nodes, whether fixed or mobile, are not a contra-indication to BCS as no increase in local recurrence has been reported.[24]

Grade A, Level Ia

A Central location is not a contra-indication to BCS, as good control can be obtained with postoperative radiotherapy.[24]

Grade A, Level Ia

A A positive family history should not prevent a woman from considering BCSRT, as previously reviewed studies have not shown an increase in local recurrence with this option.[24]

Grade A, Level Ia

A Re-excision of margins should be undertaken when margin involvement is found on histological examination, or if malignant appearing microcalcification is seen in post-operative mammography.[16,25]

Grade A, Level Ib

GPP Orientation of the surfaces of the excision specimen at the time of initial surgery will allow the re-excision of that margin which is involved alone, and decrease cosmetic deformity.

GPP

3.4.2 Surgery of the axilla

B Level II axillary dissection to include the clearance of nodes under the pectoralis minor will provide accurate staging information and maintain local control in the axilla. In cases where fixed axillary nodes are found in pre-operative clinical examination, or the presence of gross extra-nodal spread at the time of axillary surgery, a level III clearance to include all nodes to the lateral border of the first rib may decrease the incidence of axillary recurrence.[25]

Grade B, Level IIb

The acceptance of the sentinel node biopsy as part of routine breast cancer management awaits the reporting of several large randomised controlled trials, and its use for the time being should be confined to research and accreditation protocols.

3.4.3 Surveillance

The purpose of post-treatment monitoring is twofold:

- Detection of recurrent disease or new tumours in ipsi- and contra-lateral breast
- Detection of progressive functional changes such as breast deformity, arm swelling or impaired mobility.

C The routine use of more sophisticated means to detect tumour recurrence, such as tumour markers, imaging for metastasis and liver function tests has not been shown to be useful or cost-effective and is discouraged.[34]

Grade C, Level IV

C Post-operatively, the clinical review of the patient is recommended at three- to six-monthly intervals for three years, six-monthly to twelve-monthly for the second to fifth years, and annually thereafter.[34]

Grade C, Level IV

C Following the mammography of the affected breast at the end of the first year post-treatment, annual to two-yearly mammography of both breasts is recommended.[34]

Grade C, Level IV

4 Invasive Breast Cancer: Adjuvant Cytotoxic and Hormonal Therapies

4.1 Introduction

Systemic adjuvant therapy is designed to eradicate the microscopic deposits that may have metastasized from the primary tumour so as to increase the chance of long term survival. Numerous large randomised controlled trials have demonstrated convincingly that adjuvant systemic therapy significantly reduces the likelihood of recurrence and death in patients with early invasive breast cancer.

There are two main types of adjuvant systemic therapy available: chemotherapy and hormonal therapy. The magnitude of the effect of different systemic adjuvant therapies on recurrence and death from early breast cancer is best estimated from the published overview analyses by the Early Breast Cancer Trialists Collaborative Group (EBCTCG).[35,36]

4.2 Literature Review

4.2.1 Polychemotherapy

Polychemotherapy reduces the annual odds of recurrence and death by 24% and 15% respectively, while the corresponding figures for hormonal therapy (tamoxifen) are 47% and 26%.[35,36] The absolute benefit in terms of the number of recurrences prevented and lives saved depends on the baseline risk of recurrence. The higher the risk the greater the absolute benefit. For example, 5 years of tamoxifen will prevent 5 deaths in node-negative breast cancer and 10 deaths in node-positive breast cancer for every 100 women treated.

The decision to utilize adjuvant systemic therapy requires the consideration of the risk of recurrence with local therapy alone and balancing that against the magnitude of benefit and the toxicity of adjuvant therapy. The decision making process should involve both the healthcare provider and the patient.

The overview analysis has demonstrated that polychemotherapy (>2 agents) reduces the annual odds of recurrence by 24% and the annual

odds of death by 15%. In women under age 50 years, the respective figures were 35% and 27%. This translates into an absolute improvement of 15% in disease-free survival and 12% in overall survival in node-positive patients less than 50 years old. Although definitive data of more prolonged treatment are lacking, four to six courses (3 to 6 months) of treatment appear to provide optimal benefits. Available data also indicate that adjuvant chemotherapy regimens that include an anthracycline (e.g. doxorubicin) result in a small but statistically significant improvement in survival compared to non-anthracycline-containing programmes.

There is currently no convincing evidence that more dose-intensive treatment programmes (high-dose chemotherapy requiring peripheral stem cell support) is associated with improved survival outcomes compared to polychemotherapy programmes at standard doses. However, dose-intensity is important to outcome in the standard dose ranges. Dose reduction and treatment delays for reasons other than unacceptable toxicity should therefore be avoided.

There is limited data to define the optimal use of adjuvant chemotherapy in women more that 70 years of age. Although the survival benefit is likely to be similar to younger women, there are legitimate concerns regarding the toxicity with chemotherapy in this patient population. The decision to treat these women with adjuvant chemotherapy will have to take these and other competing risks of mortality into consideration.

4.2.2 Hormonal Therapy

Adjuvant hormonal therapy is recommended for women whose breast tumour is positive for hormone receptors (estrogen and/or progesterone receptors; see Pathological Evaluation), regardless of age, menopausal status, and involvement of axillary lymph nodes or tumour size. Although the likelihood of benefit increases with increased expression of hormonal receptors, patients with any amount of receptors expression may still benefit and should not be denied hormonal therapy. Adjuvant hormonal therapy is NOT recommended for women whose cancers do not express hormone receptor.

Tamoxifen, a selective estrogen receptor modulator, is the most studied and commonly used adjuvant hormonal therapy. Based on the overview analysis, 5 years of tamoxifen reduces the relative odds of recurrence

and death by 47% and 26% respectively. It also halves the incidence of new contralateral breast cancer. The same effect is observed regardless of age and menopausal status of the woman. The current evidence suggests the optimal duration of treatment with tamoxifen is 5 years. Tamoxifen has been associated with a slight but definite increase in risk of endometrial cancer (0.4%) and venous thromboembolism (0.5-1.5%). In the majority of women, the benefits of tamoxifen far outweigh its risks.

Anastrazole is a non-steroidal aromatase inhibitor that acts by blocking the conversion of androgen to estrogen in the peripheral (including the tumour) tissue. The early result of a large randomised controlled trial[37] comparing anastrazole against tamoxifen alone, and tamoxifen plus anastrazole as adjuvant therapy is now available. Single agent anastrazole was found to be marginally superior to both tamoxifen alone and the combination of the two drugs. However, most of the major professional bodies consider the follow-up of this study (less than 5 years) still relatively short and they are of the view that it is premature to recommend anastrazole as the standard of care. Anastrazole could be an alternative for women who would otherwise benefit from hormonal therapy but unable to tolerate tamoxifen. Due to its mechanism of action, anastrazole should only be used in post-menopausal women.

Ovarian ablation, achieved by bilateral oophorectomy, radiotherapy or chemical suppression (with LHRH agonist or antagonist), has been shown to reduce the risk of recurrence and death in women less than 50 years of age with functioning ovaries and hormone receptor positive breast cancer. The magnitude of the benefits appears to be equivalent to that demonstrated with some chemotherapy regimes.

GPP There is currently no data to support the use of raloxifene (EVISTA) as adjuvant hormonal therapy in early breast cancer and use for adjuvant treatment in breast cancer is not recommended.

GPP

4.3 Risk Stratification

The following method of risk stratification is used:

	Risk Group	
Characteristics	**Minimal/Low (all characteristics must be present)**	**Intermediate/High (Presence of any of the characteristics)**
Lymph node	Negative	Positive
Tumour size	≤ 1 cm	>1 cm*
Hormonal receptors	ER and/or PR positive	ER and PR negative

ER = estrogen receptor
PR = progesterone receptor
* More than 3 cm for "Good prognostic" histological types (i.e. mucinous carcinoma, tubular carcinoma, typical medullary carcinoma).

In tumours of 1 cm or less, grade is not critical in the stratification of risk.[38]

4.3.1 Adjuvant Treatment Recommendations

A Adjuvant treatments are recommended for the risk groups and patient groups as shown in the following table:[35,36]

Patient group	**Risk Group**	
	Minimal/Low	**Intermediate/High**
Premenopausal		
ER or PR positive	Tamoxifen	Chemotherapy + Tamoxifen
	or	or
	None	Ovarian ablation + Tamoxifen
ER and PR negative	None	Chemotherapy
Post-menopausal		
ER or PR positive	Tamoxifen	Chemotherapy + Tamoxifen
	or	or
	None	Tamoxifen
ER and PR negative	None	Chemotherapy

Grade A, Level Ib

5 Adjuvant Radiotherapy for Invasive and Non-invasive Breast Cancer

5.1 Introduction

The indications for adjuvant post-operative radiotherapy depend on the surgery performed and on the pathological findings. Thus the sites of treatment and radiation dose can vary depending on the extent of surgery. It should be noted that adjuvant radiotherapy does not replace the need for histologically clear margins, which remains a predictor for local recurrence even following adjuvant radiotherapy. The role of radiation in the lymphatic drainage sites also depends on the type of axillary surgery which can vary from a full formal level III lymph node dissection to axillary sampling, sentinel node biopsy or no axillary surgery at all. Internal mammary irradiation remains a controversy until the results of the trials carried out by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) are available.

The role of radiation in locally advanced tumours includes treatment of an ulcerative bleeding tumour, adjuvant post-mastectomy radiotherapy or as part of breast conservation following neoadjuvant systemic therapy.

5.2 Literature Review

5.2.1 Post-mastectomy Radiotherapy

Many patients do not require radiotherapy following mastectomy. However, a subgroup of patients exists who have been inferred from prospective clinical trials to have a higher risk of relapse on the chest wall.[39,40,41] This risk remains significant despite the use of appropriate systemic therapy including anthracycline cytotoxics[39,40,42] and hormonal therapy.[41] It should also be noted that variation in surgical practice as to the extent of tissue removal might influence relapse.

Additionally recent meta-analysis of post-radical mastectomy radiotherapy prospective trials has demonstrated a cause-specific

survival benefit of 18%[43] and this is also supported by two more recent trials in pre-menopausal women[40,45] and one in postmenopausal women[3].

The definition of the high risk subgroup that would benefit from adjuvant post-mastectomy radiotherapy remains controversial especially in the group of women with 1-3 axillary nodes positive.[39] Post-operative radiation was found to benefit women in which there was a high risk of loco-regional recurrence, including patients with large tumours of more than 5 cm in the greatest diameter (T3), T4 tumours, or positive surgical margins. When there are 4 or more lymph nodes involved after an axillary clearance, irradiation to the chest wall and supraclavicular regions are also indicated.

The limited randomized trial data that exists for women stratified into this 1-3 axillary node positive group suggests a benefit for radiotherapy. However, the data is less convincing with other large retrospective data sets.[39] For this group of women with 1-3 axillary node positive, the decision to offer adjuvant radiotherapy is based upon extrapolation from predictive factors (such as age, grade, estrogen receptor status and lymphovascular invasion) to determine women at relatively higher risk of locoregional relapse.[42,44]

The recently reported randomised Danish Breast Cancer Cooperative Group (DBCG) trials demonstrated a significant survival benefit with adjuvant radiotherapy for pre- and post-menopausal women.[40,41] The radiation treatment volume included regional nodal sites including the internal mammary chain (IMC), axillary and supraclavicular fossa (SCF) irradiation. However the contribution of IMC and axillary radiotherapy to the benefit of adjuvant therapy remains uncertain. The radiation therapy of both sites increases the potential morbidity of adjuvant treatment. With greater use of anthracycline systemic therapy and the knowledge that IMC radiotherapy adds additional cardiac volume to radiotherapy portals, concerns over cardiac morbidity exist.[39]

The EORTC and NCIC are conducting randomised trials investigating the use of IMC radiotherapy, and at present this site of prophylactic nodal irradiation will not be routinely offered. Similarly axillary radiotherapy post-dissection will be avoided for the majority of women other than those with extensive extranodal disease or incomplete dissection. In these situations discussion with the surgeon is also indicated, to determine the extent of axillary clearance.

The supraclavicular fossa is the major site of regional relapse in women, with both retrospective and limited prospective data confirming that cumulative SCF relapses exceed 15% in high-risk patients.[39,46,47] This site will be routinely treated in women with high-risk disease as indicated by nodal status.

As with any medical intervention, the benefit of post-mastectomy radiotherapy must be weighed against potential adverse effects of this therapy. Contemporary radiotherapy delivery employing image-based planning has substantially reduced potential cardiac damage, and an excess of cardiac deaths has not been reported in more recent trials.

5.2.2 Post Breast Conservation Surgery (BCS) Radiotherapy

Six randomised trials have now been published with long-term follow up demonstrating a significant disease-free survival (DFS) benefit with radiotherapy following BCS.[48,49,51-55] This benefit exists despite the use of appropriate systemic therapy.[49,55] The benefit in DFS is on the basis of improved local control, however, and no trial thus far demonstrates an overall survival benefit with postoperative radiotherapy.

Breast radiation is clearly appropriate after breast-conserving surgery to reduce the risk of ipsilateral breast relapse.[48] At the present time, no subgroup has been isolated to be considered at adequately low risk to not require radiotherapy following BCS. NSABP 21 accumulated data on minimal risk (<10 mm) breast cancer patients managed by complete local excision and tamoxifen versus adjuvant tamoxifen and radiotherapy following surgery. In the non-irradiated arm, a local failure rate of 16.5% at 8yrs compared with 2.8% with combined radiotherapy and tamoxifen,[49] confirming previous prospective data on minimal risk patients.[50]

5.2.3 Role of Irradiation in Neoadjuvant Therapy in Locally Advanced Breast Cancers

Radiotherapy is offered in locally advanced breast cancer (LABC) to improve local control and survival. Given the broad spectrum of LABC, the treatment decision should be individualised and discussed in a

multidisciplinary setting. Randomised trials are limited and the regimens are varied.[56-58] The role of a completion mastectomy is uncertain in women who initially had inoperable disease[57,59] as is the timing and volume of RT delivery after initial response.[60]

5.3 Recommendations

5.3.1 Post-Mastectomy Radiotherapy Recommendations

A Post-mastectomy radiotherapy should be offered to a patient with T3 or T4 primary tumours, or with four or more lymph nodes involved.[40-43]

Grade A, Level Ia

5.3.2 Radiotherapy Recommendations Following Breast Conserving Surgery

A All patients undergoing breast conservation surgery for invasive and non-invasive breast cancer should be offered adjuvant radiotherapy.[48,49,51-55]

Grade A, Level Ia

GPP All patients eligible for breast conservation should be referred for a radiation oncology consultation if the fear of breast conservation is radiation treatment.

GPP

5.3.3 Radiotherapy recommendations for locally advanced breast cancer

B Radiation treatment should be given in the management of locally advanced tumours.[56-58]

Grade B, Level III

6 Neoadjuvant Therapy for Operable and Inoperable Breast Cancer

6.1 Introduction

Despite improvements in the early diagnosis of breast cancer, locally advanced breast cancer (LABC), and cancers not amenable to breast conservation surgery (BCS) can be expected to account for up to 50% of cases in Singapore. While early experience with neoadjuvant chemotherapy in unresectable breast cancers resulted in tumour shrinkage amenable to consequent surgical excision, recent trials have shown the applicability of this approach in operable breast cancers as well. This may allow for women to select for breast conservation where mastectomy may have been initially required, or for smaller resection volumes resulting in improved cosmetic results.

In elderly patients who may not be suitable for systemic chemotherapy, recent trials using neoadjuvant endocrine manipulations show promise in a similar approach to hormone receptor positive tumours.

6.2 Literature Review

6.2.1 Neoadjuvant therapy for operable breast cancer (Stage I, II, IIIA - T3N1)

The National Surgical Adjuvant Breast and Bowel Project (NSABP) has reported the results of a large prospective randomised controlled trial[61] in which 1523 patients with T1-3, N0-1, M0 breast cancers were randomised to either surgery followed by 4 cycles of adriamycin cytoxin (AC) or 4 cycles of neoadjuvant AC followed by surgery. After 5 years of follow-up, no significant differences were noted in either local recurrence rates or overall survival. Of the patients receiving neoadjuvant chemotherapy, 67.8% were amenable to breast conservation surgery compared to 59.8% of patients with adjuvant chemotherapy ($p = 0.003$). Similar results were reported in a smaller RCT reported by van der Hage, et al.[62] These findings suggest that neoadjuvant chemotherapy may be an approach where more patients could avoid mastectomy for equally effective cancer control.

Nevertheless, in the NSABP group which was considered to be suitable for BCS after neoadjuvant chemotherapy, local recurrence rates at 5 years was 14.5% compared to 6.9% of patients who were considered BCS suitable prior to chemotherapy. While just short of being statistically significant ($p = 0.04$), these findings emphasise the practical problems in assessing the completeness of resection and extent of disease in this group of patients.

Neoadjuvant therapy for operable breast cancer has been limited mainly to the use of neoadjuvant chemotherapy. Recently, neoadjuvant endocrine therapy is emerging as an attractive alternative to chemotherapy, especially in hormone receptor-positive tumours and in patients who may be unable to unwilling to accept the chemotherapy toxicity. Nevertheless there have been no controlled trials that have compared neoadjuvant chemotherapy to hormone therapy to date.

The early studies using neoadjuvant hormone therapy have been carried out in the setting of inoperable cancer, or in the treatment of patients who were not fit for either radiotherapy or therapeutic surgery. More recently, several randomised trials have reported the efficacy of endocrine therapy given over a three to four month period in reducing tumour volume. These have employed a variety of endocrine modulators, including tamoxifen, and the third generation aromatase inhibitors, letrozole, anastrazole and exemestane.

6.2.2 Neoadjuvant Therapy for Inoperable Breast cancer

Multimodality therapy delivered with curative intent is the standard of care for patients with clinical stage IIIB and inflammatory disease.[63-67] There is a paucity of randomized controlled trials involving women with locally advanced disease, and there is uncertainty as to the optimum order of these treatments. Initial surgery is generally limited to biopsy, to permit the determination of histology, estrogen receptor and progesterone receptor status, with or without HER2/neu overexpression analysis.

6.2.3 Monitoring of Treatment Response

Monitoring of response is generally performed by clinical palpation. However, this may be misleading on occasion as some tumours may necrose with only slight changes in size, while others may apparently resolve with persistent impalpable viable tumour. Ultrasound and mammography have limited roles in evaluation of tumour resolution, though ultrasound may detect a residual mass in patients with apparently complete responses. Contrast enhanced MRI is known to be the most accurate imaging method for evaluation of the amount of residual viable tumour.

6.3 Recommendations

6.3.1 Neoadjuvant Therapy for Operable Breast Cancer

A In patients who desire breast conservation surgery, three to four cycles of anthracycline-based therapy after a biopsy of the tumour is recommended. Patients should be advised that a conversion to breast conservation may be possible in 20-30% of cases. If the tumour responds to chemotherapy, lumpectomy and axillary lymph nodes dissection, followed by radiotherapy may be considered if the patient meets the requirement for breast conserving therapy.[61,62]

Grade A, Level Ib

B Breast conserving surgery may be followed by further individualized adjuvant chemotherapy such as additional anthracycline or taxane therapy.[63-67]

Grade B, Level IIa

B If after 3-4 cycles of preoperative chemotherapy, the tumour fails to respond, or the response is minimal or if there is progression at any point, a mastectomy plus axillary dissection should be performed. Adjuvant therapy for these patients should be individualised, followed by radiation therapy as required.[63-67]

Grade B, Level IIa

A After completion of all surgery, chemotherapy and radiation therapy, all patients with estrogen and/or progesterone receptor positive tumours should receive tamoxifen.[61,62]

Grade A, Level Ib

B In patients with endocrine receptor positive tumours who are unfit or unwilling to receive chemotherapy, neoadjuvant endocrine therapy with third-generation aromatase inhibitors such as letrozole or anastrazole may be offered.[63-67]

Grade B, Level IIa

6.3.2 Neoadjuvant Therapy for Inoperable Breast Cancer

C Initial treatment with anthracycline and/or taxane-based chemotherapy is recommended.[66]

Grade C, Level IV

B For patients who respond to neoadjuvant chemotherapy, local therapy may consist of total mastectomy with axillary lymph node dissection or alternatively breast-conserving therapy can be considered in patients with a good partial or complete response to neoadjuvant chemotherapy.[68]

Grade B, Level IIa

C Patients with an inoperable stage IIIA or stage IIIB tumour, whose disease progresses during preoperative therapy, should be considered for palliative breast irradiation in an attempt to enhance local control. Further systemic adjuvant chemotherapy following local therapy is felt to be standard.[66]

Grade C, Level IV

B After surgery, adjuvant radiation therapy to the chest wall and regional lymphatics is recommended.[63-65]

Grade B, Level IIa

A Hormone therapy should be administered to patients whose tumours are estrogen receptor- or progesterone receptor-positive or of unknown hormone receptor status.[69]

Grade A, Level Ib

A Elderly and frail patients are exceptions to the intensive multimodal approach. In such a patient with a receptor positive tumour, tamoxifen alone (20 mg/day) may be used to reduce tumour size with few or no side effects.[69]

Grade A, Level Ib

7 Pathology of Breast Cancer

7.1 Handling of breast specimens

7.1.1 Surgical handling of specimens

A surgical specimen must be oriented as per an agreed protocol between the surgeon and the pathologist. Sutures or clips may be used. A convenient method is to have long sutures for lateral, short sutures for superior and medium sutures for medial margins. An added safety feature is to ink the posterior margin, in the event of loosened/lost sutures. For clinically impalpable and radiologically detected lesions, it is mandatory that a specimen radiograph be performed to confirm that the radiological abnormality has been sampled or removed. A copy of the radiology report, along with the specimen radiograph and the specimen should be transported to the pathology department. Specimens should never be incised by the surgeon before dispatch to the pathology department, as this may interfere with pathology assessment.

7.1.2 Pathological handling of specimens

7.1.2.1 Wide excision specimens

The specimens are oriented according to the marking sutures or clips, measured in three dimensions, weighed and marked with India ink or other similar pigments. The margins can be inked in different colours for identification under microscopic examination. The ink is allowed to dry and the specimen can be dabbed/dipped in Bouin's fixative for better adherence of marking solutions. The specimen is serially sliced along the short axis. The lesion is identified, measured in three dimensions and macroscopically described. The distance of the lesion from the radial (superior, inferior, medial, lateral), anterior (superficial) and posterior (deep) margins is measured and documented. The size of a lesion measured macroscopically should be checked against the size measured microscopically on the sections, especially for small lesions. A diagram of the specimen may be used as a guide to subsequent block taking. All excision margins, especially those within 10 mm of the lesion, should be examined histologically. For small specimens, all tissue should be blocked and processed.

7.1.2.2 Mastectomy specimens

These should be handled in the usual manner, documenting the size (in 3 dimensions), appearance, and location (quadrant) of the tumour. Three blocks of tumour, or four blocks of the cavity wall if the tumour had been previously removed, 1 block from each quadrant and the nipple should be sampled.

7.1.2.3 Axillary lymph nodes

All axillary lymph nodes found within the specimen should be submitted for microscopic examination. Small nodes must be wholly submitted. Larger nodes that do not reveal macroscopic tumour involvement also have to be totally examined, and can be serially sectioned and submitted in one or more blocks. For grossly involved nodes, only a representative section that contains the tumourous area need be submitted.

7.1.2.4 Sentinel lymph node

The sentinel lymph node should be serially sectioned, preferably at 2 mm intervals, and entirely submitted for histology.[70] It is still controversial if routine serial step-sectioning or immunohistochemistry should be recommended.

7.1.3 Pathological handling of excisions performed for radiologically detected lesions

It is important that the specimen be compared with the specimen radiograph, and that the area corresponding to the radiological abnormality is properly sampled. For small specimens, the entire specimen can be submitted for histological examination. For larger specimens, the area in question may be sampled, including sections from the relevant margins. Slice specimen radiography may be utilised to select the sections for processing.

In the event that the radiologic abnormality has been demonstrated on the specimen radiograph, but cannot be identified histologically, paraffin block radiography may be used to locate the lesion.

7.2 Intraoperative frozen sections

7.2.1 Indications

Intraoperative frozen sections are indicated:

- to confirm histological invasion in cases with a pre-operative cytological malignant diagnosis
- on a sentinel node to decide on the need for axillary dissection

Ideally a preoperative diagnosis of cancer should be made for optimal breast cancer counselling and to minimise the number of diagnostic surgical procedures.

The use of frozen section for the diagnosis of breast cancer is discouraged.[71]

7.3 Ductal carcinoma in situ (DCIS)

7.3.1 Classification of DCIS

There are several classification systems for DCIS advocated by various expert groups,[72-78] all of which rely on assessment of a combination of the following: architectural features, the presence or absence of necrosis, and nuclear grade.

It is recommended that DCIS be classified primarily by nuclear grade, as it correlates with recurrence after local excision,[79-81] and it appears to be a reproducible method.[82] Preliminary evidence has been put forward[7] for confluent necrosis as a feature which imparts a worse prognosis to low or intermediate nuclear grade lesions. Table 1 shows the nuclear grade classification of DCIS according to United Kingdom National Health Service Breast Screening Programme (NHSBSP) Guidelines.

Table 1 NHSBSP nuclear grade classification of breast DCIS[78]

High Nuclear Grade	Intermediate Nuclear Grade	Low Nuclear Grade
Pleomorphic, irregularly spaced, large nuclei, coarse chromatin, prominent nucleoli. Mitoses frequent and often abnormal. Growth pattern variable, often comedo type necrosis.	Cases which cannot easily be assigned to high or low nuclear grade. Usually some architectural polarization.	Monomorphic evenly spaced cells with roughly spherical centrally placed nuclei, inconspicuous nucleoli. Few mitoses, rare individual cell necrosis, architectural polarization.

Source: NHSBSP Publication No 3. Pathology reporting in breast cancer screening. 2nd edition, 1995.

Classification should be according to highest nuclear grade.

For pure DCIS lesions, the following six pathologic characteristics should be documented:

1. size
2. margins
3. nuclear grade
4. necrosis
5. architecture
6. calcifications

7.3.1.1 Size

For small DCIS tumours, the maximum diameter of the entire lesion is measured on the slide. For larger lesions, it may be necessary to estimate the extent by counting the number of specimen slices containing tumour, and multiplying by the average sliced section thickness. Referral to the gross specimen may be required. It is recognised that DCIS may show apparently uninvolved areas between involved ducts on the same

slide. In such cases, the longest distance between involved ducts should be recorded, including any intervening normal tissue.

7.3.1.2 Margins

The distance from each margin should be stated in millimeters when less than 10 mm. Margins more than 10 mm can be stated as ">10 mm". If DCIS is present at the margin, it should be reported specifying the margin involved.

7.3.1.3 Nuclear grade

Nuclear grade should be based on features classified by NHSBSP guidelines (see Table 1).

7.3.1.4 Necrosis

Two categories are recognised:

- necrosis not present or minimal, i.e. no central duct necrosis is present, but focal necrosis and isolated apoptotic cells may be present.
- necrosis present - central necrosis is identified in ducts (synonymous with what has previously been described as "comedo" type necrosis).

7.3.1.5 Architecture

Many tumours show more than one architectural/morphological pattern. The major architectural patterns of DCIS are comedo, cribriform, papillary, micropapillary and solid. Less common variants can also be encountered. The architecture of DCIS may be classified according to the dominant pattern, and if there is a significant component of another subtype, the term "mixed" pattern can be applied.

7.3.1.6 Calcification

No data are available to relate the presence or absence of calcification to outcome. The purpose of recording calcification within the lesion is

mainly to foster improved understanding of the relationship between radiological and pathological findings. Two categories are recognised:

- calcification present – specify whether necrosis associated or secretory in type.
- calcification absent.

The report should specify if the calcification is associated with DCIS or invasive carcinoma; or if the calcifications are benign in nature.

Note: Cancerisation of lobules is included in any assessment of DCIS.

7.4 Microinvasion

The differentiation between DCIS with microinvasion and invasive breast cancer associated with DCIS is an important one. The former probably has little indication for adjuvant therapy; the latter, if classified as an invasive breast cancer with extensive in situ component (EIC) requires not only larger margins of resection but possibly mastectomy. Unfortunately, there is no consensus as to what constitutes microinvasion. Silverstein reserved the term for lesions with very small foci of invasion, 1 mm or less in diameter.[83]

The currently accepted definition as adopted by the TNM system (T1mic) describes it as cancer cells extending beyond the basement membrane into adjacent tissues with no focus larger than 1 mm, using only the largest focus for classification.[84] This criterion is also recommended in the NHSBSP guidelines,[78] which adds the caveat that the invasive focus should enter the interlobular non-specialized stroma. It is believed that with this restrictive definition, microinvasive carcinoma has a prognosis similar to the accompanying high grade DCIS[85] with little risk of axillary nodal metastases, and hence a management policy similar to DCIS is advocated.[86]

7.5 Invasive breast carcinoma

7.5.1 Reporting of invasive carcinoma

All histology reports should document the following pathological characteristics:

1. Tumour size

2. Histological subtype
3. Histological grade
4. Margins of excision
5. Lymphovascular invasion
6. Adjacent breast tissue
7. Hormone receptor status

7.5.1.1 Tumour size

The tumour should be measured in three dimensions; and the single greatest dimension of the invasive tumour is used for determining histological size.[70] The size of the tumour measured grossly must be verified microscopically, and the microscopic measurement takes precedence if there is a discrepancy between the macroscopic and microscopic assessment of tumour size.

For cancers less than 1 cm, the size should be measured on the slide.

For cancers that are diffuse and poorly defined, an estimate of the tumour size is given, with explanatory comments.

In tumours with both invasive and in situ components, only the size of the invasive component is used for staging purposes.

When 2 or more discrete invasive tumours are present, each is measured and reported separately.

7.5.1.2 Histological subtype

Histologic subtyping of invasive carcinoma is of prognostic value,[87] and should be performed on optimally fixed material.

The commonest subtype is infiltrative ductal carcinoma, NOS (not otherwise specified). Less common histologic variants are invasive lobular, tubular, cribriform, medullary, mucinous and mixed cancers.

7.5.1.3 Histological grade

Grading provides prognostic information,[88] and involves the assessment of 3 morphologic components:

- Tubule formation
- Nuclear pleomorphism
- Mitotic activity

Each parameter is assigned a score of 1 to 3, and adding the scores gives the overall histological grade (Table 2).

Table 2 Histological grading of invasive breast cancer

Score	Tubule formation	Nuclear pleomorphism	Mitotic activity (for field diameter of 0.48 mm)
1	> 75% tubules	Mild: small nuclei, regular outline, uniform chromatin, little size variation.	0-6 mitoses/hpf (high power field)
2	10% to 75% tubules	Moderate: larger cells with visible nuclei and moderate variability in both size and shape.	7-12 mitoses/hpf
3	< 10% tubules	Marked: vesicular nuclei with prominent nucleoli, marked variation in size and shape, occasionally bizarre.	> 12 mitoses/hpf

Source: NHSBSP Publication No. 3. Pathology reporting in breast cancer screening. 2nd edition, 1995.

The field diameter of the individual microscope must be calibrated to provide an accurate scoring of the mitotic count.[78]

7.5.1.4 Margins

The distance of the invasive tumour from the margins of resection should be recorded, in particular, the closest margin and its distance.

If an associated DCIS extends nearer to the resection margin, this should also be measured and documented.

If there is extension of tumour to the excision margin, it would be preferable if the extent (focal or extensive) of involvement is expressed.

7.5.1.5 Lymphovascular invasion

As lymphatic and blood vessels cannot be reliably distinguished from each other histologically, vessel or lymphovascular invasion is used to describe tumour nests within endothelial-lined spaces.

Retraction artefact has to be discounted, and as this is most often seen in the midst of the tumour, assessment of lymphovascular invasion should be made at the periphery of the tumour mass.

Involvement of dermal vessels should be documented.

7.5.1.6 Adjacent breast tissue

DCIS, lobular carcinoma in situ (LCIS), atypical ductal or lobular hyperplasia in adjacent breast tissue should be evaluated.

In mastectomy specimens, the nipple is examined for Paget's disease.

7.5.1.7 Hormone receptor status

Estrogen and progesterone receptor determination is of predictive and prognostic value in invasive breast cancer. While biochemical methods were used in the past, current practice relies mainly on immunohistochemistry.

The immunohistochemical interpretation of estrogen receptor and progesterone receptor status requires establishing quality assurance and appropriate controls. It is not clear which is the best method of reporting estrogen receptor and progesterone receptor results, though it is recommended that the proportion of cells that demonstrate nuclear staining be documented[78] and the staining intensity also be recorded.

Estrogen/progesterone receptor immunostaining should be evaluated only on the invasive component of the tumour.

7.6 Other issues

7.6.1 Extensive DCIS/Extensive in situ carcinoma (EIC)

Extensive in situ cancer (EIC) is defined as

- presence of DCIS representing more than 25% of the main tumour mass and extending beyond the confines of the main mass; or
- patients with predominantly DCIS, with one or more areas of focal invasion.

Studies from the Joint Center for Radiation Therapy (JCRT) at the Harvard Medical School revealed that the main factor predictive of a breast cancer recurrence was an extensive intraductal component (EIC positive tumour).[89-91] More recent information, however, suggests that EIC is not an independent predictor of local recurrence when margin status is factored into the pathologic evaluation, suggesting that clear margins in excess of 1mm, followed by radiotherapy, was adequate in controlling local reccurence in tumours with associated EIC.[92]

7.6.2 Axillary lymph nodes

The total number of lymph nodes and the number affected by metastatic carcinoma must be recorded. The greatest dimension of the metastatic focus,[70] the presence or absence of extranodal extension should be documented.

7.6.3 cerbB2/HER2/neu status

cerbB2 overexpression occurs in about a third of breast cancers, and is associated with high histologic grade, reduced survival, and lower responsiveness to methotrexate based chemotherapy regimens.[70]

While the usefulness of routine cerbB2 determination of all breast cancers is debatable, there is an increasing demand for its evaluation, particularly with the availability of Herceptin treatment (that targets the cerbB2 cell membrane protein) for advanced breast cancer patients.

Determination of cerbB2 status is carried out by 2 main methods: immunohistochemistry (IMH) and fluorescence in situ hybridisation (FISH). Both methods have pros and cons, which are summarised in Table 3.

Table 3 Comparison of immunohistochemistry and FISH in cerbB2

Immunohistochemistry	Fluorescence in situ hybridization (FISH)
Advantages 1. Relatively simple technique, can be applied to paraffin embedded tissue. 2. Can be achieved in most laboratories. 3. Short procedure time. 4. Light microscopic interpretation that can be performed readily. 5. Correlated with outcome and treatment response.	Advantages 1. Highly specific reagents commercially available. 2. Can be applied to fixed embedded tissues. 3. Standardized positive threshold. 4. Results are quantitative. 5. Internal controls.
Disadvantages 1. Many antibodies available that vary in specificity and sensitivity. 2. Affected by nature, duration and efficiency of fixative penetration; method of antigen retrieval; use of positive and negative controls. 3. No universally accepted threshold for positivity. 4. No standardized scoring system.	Disadvantages 1. Available only in some laboratories. 2. Technically more difficult than immunohistochemistry. 3. Longer procedure time. 4. Fluorescence microscope required for interpretation, more time consuming. 5. Linkage to Herceptin response currently not known.

Source: Schnitt, 2001; Walker, 2000 [93,94]

While FISH is generally accepted as the gold standard for determining cerbB2 status, the technical difficulty and cost involved may be a deterrent to its routine use. An option would be to utilise IMH and subject the weakly positive cases to FISH. In such instances, it would be necessary that the individual laboratory establishes its correlation between IMH and FISH results.

8 Clinical Audit Parameters

The following clinical audit parameters, based on recommendations in these guidelines, are proposed:

- Percentage of women with breast cancer who were appropriately offered breast conservation surgery with adjuvant radiotherapy for management. (see page 21)

Treatment options offered to breast cancer patients and the treatment selected should be documented. In cases where breast conservation surgery with adjuvant radiotherapy was not the treatment of choice, the reasons or contraindications should be documented.

- Percentage of women with breast cancer who are clinically reviewed at appropriate intervals post-operatively. (see pages 17 and 23)

Clinical reviews of the patient should be documented. As recommended in the guidelines, the clinical review of the patient is recommended at three- to six-monthly intervals for three years, six-monthly to twelve-monthly for the second to fifth years, and annually thereafter.

- Percentage of women (with DCIS/invasive breast cancer) who have used tumour markers, imaging for metastasis and liver function tests to detect tumour recurrence. (see pages 17 and 23)

- Percentage of women with DCIS who had post-operative mammography (to ensure removal of all malignant microcalcifications). (see page 17)

- Percentage of women (with DCIS/invasive breast cancer) who had appropriate annual to two-yearly mammography of both breasts following the mammography of affected breast at the end of the first year post-treatment. (see pages 17 and 23)

- Percentage of women with ER/PR positive tumours given adjuvant hormonal therapy (i.e. tamoxifen). (see pages 25 and 27)

- Percentage of women with T3, T4 primary tumours, or with 4 or more lymph nodes involved, being offered post-mastectomy radiotherapy. (see page 31)

- Percentage of women who had undergone breast conservation surgery being offered adjuvant radiotherapy. (see page 31)

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of MCQs. This is an extension of the learning process and is not intended to "judge" your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

Instruction: Choose the best answer

1. In the treatment of unicentric DCIS, adequate surgical treatment would require:

   A. Microscopic clear margins
   B. Check mammography post-operatively to exclude the presence of residual microcalcifications
   C. Axillary dissection can be omitted in the absence of proven invasive cancer
   D. All of the above

2. The following elements should be sought in obtaining the history of a woman with breast cancer:

   A. Family history of ovarian cancer
   B. History of collagen vascular disease
   C. Symptoms like bone pain or abdominal discomfort, suggestive of metastatic disease
   D. All of the above

3. The following statements are true, except:

   A. The most common presentation of ductal carcinoma in situ (DCIS) is mammographic microcalcifications
   B. Sentinel node biopsy is not recommended in DCIS as yet.
   C. Tamoxifen should be standard treatment for all cases of DCIS.
   D. Diffuse malignant-appearing microcalcifications throughout the breast are a contraindication to breast conservation.

4. Post-operatively, re-excision of margins should be done in a woman with breast cancer:

   A. When margin involvement is found on histological examination
   B. If malignant-appearing microcalcification is seen in post-operative mammography.
   C. Both A & B are true
   D. None of the above is true

5. Which of the following is a contra-indication to breast conservative treatment for invasive breast cancer?

   A. Invasive lobular cancer subtype
   B. Mother with previous diagnosis of breast cancer
   C. Widespread malignant calcifications on mammogram
   D. Palpable axillary lymph nodes

6. Tamoxifen should be offered to patients with which of the following cancers

   A. All estrogen receptor positive tumours
   B. Invasive cancers with close margins
   C. Multicentric DCIS
   D. None of the above

7. Adjuvant radiotherapy should be offered to

   A. invasive breast cancer treated with breast conservation surgery
   B. DCIS treated with breast conservation surgery
   C. invasive cancer treated with total mastectomy, where more than 3 axillary nodes have evidence of metastasis
   D. all of the above

8. Frozen section for the diagnosis of breast cancer is recommended for

   A. confirmation of invasion when the diagnosis of cancer was initially made on fine needle aspiration cytology
   B. intra-operative assessment of surgically clear margins
   C. no preoperative diagnosis of breast cancer
   D. all of the above

9. Which of the following significantly increases the risk of breast cancer?

   A. Fibroadenoma
   B. Fibrocystic disease of the breast
   C. Duct papilloma
   D. None of the above

10. Which of the following measures are recommended for surveillance of patients following treatment of breast cancer?

   A. Physical examination and periodic mammography
   B. CEA, HER2 status
   C. Routine ultrasound liver and bone scans
   D. All of the above

Answers

1.	D	6.	A
2.	D	7.	D
3.	C	8.	A
4.	C	9.	D
5.	C	10.	A

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MOH CLINICAL PRACTICE GUIDELINES 4/2004
Breast Cancer

Ministry of Health

National Committee on Cancer Care

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Ductal Carcinoma in Situ (DCIS)

GPP Mastectomy and breast conservation surgery and adjuvant radiotherapy are effective alternative treatments for ductal carcinoma in situ and the patient's preference should be considered in the choice of treatment. (pg 14)

GPP

A Nevertheless there are some cases in which breast conservation is contra-indicated, which include: (pg 15)

- Presence of multicentric tumours involving more than one quadrant of the breast.
- Diffuse malignant-looking microcalcifications throughout the breast.
- Factors unrelated to ductal carcinoma in situ but which may preclude the use of adjuvant radiotherapy may be considered relative contra-indications to breast conservation. These include collagen vascular disease such as scleroderma and systemic lupus, pregnancy and previous radiotherapy to the breast area.
- Reluctance of the patient to undergo radiotherapy. As many patients may have inaccurate preconceptions of the side effects and toxicity of radiotherapy, a referral to a radiation oncologist is recommended before the decision is taken to not offer breast conservation for this reason alone.

Grade A, Level Ib

A Indications for breast conservation surgery and adjuvant radiotherapy include mammography-detected ductal carcinoma in situ, or palpable ductal carcinoma in situ with no suggestion of multicentricity or diffuse microcalcification on pre-operative mammography. (pg 15)

Grade A, Level Ib

A No subgroup of ductal carcinoma in situ has been identified from randomised clinical trials that have not benefited from the addition of adjuvant radiotherapy. However, the addition of adjuvant radiotherapy to breast conservation surgery in small low grade ductal carcinoma in situ with clear margins of more than 1 cm adds minimal benefit in improving local control. For the group of patients where the benefit is small, the patient's attitude towards the risk and benefit of radiotherapy needs to be taken into consideration before radiotherapy is omitted. (pg 15)

Grade A, Level Ib

A Re-excision of margins should be undertaken when margin involvement is found on histological examination, or if malignant appearing microcalcification is seen in post-operative mammography. (pg 16)

Grade A, Level Ib

GPP Orientation of the surfaces of the excision specimen at the time of initial surgery will allow the re-excision of that margin which is involved alone, and decrease cosmetic deformity. (pg 16)

GPP

A The likelihood of axillary involvement in ductal carcinoma in situ is about 2-3%, and axillary dissection is therefore not recommended. (pg 16)

Grade A, Level Ib

GPP The role of sentinel node biopsy in ductal carcinoma in situ is not resolved and is not recommended. (pg 16)

GPP

A Routine use of tamoxifen in ductal carcinoma in situ is not indicated. (pg 16)

Grade A, Level Ib

C The routine use of more sophisticated means to detect tumour recurrence in the absence of clinical signs and symptoms, such as tumour markers, imaging for metastasis and liver function tests has not been shown to be useful or cost-effective and is discouraged. (pg 17)

Grade C, Level IV

C Post-operatively, the clinical review of the patient is recommended at three- to six-monthly intervals for three years, six-monthly to 12-monthly for the second to fifth years, and annually thereafter. (pg 17)

Grade C, Level IV

A Post-operative mammography is required to ensure removal of all malignant microcalcifications for screen-detected ductal carcinoma in situ. (pg 17)

Grade A, Level 1b

GPP Surgery and post-operative radiotherapy changes usually resolve six months to a year after treatment and a repeat mammogram of the affected breast is recommended at the end of the first year. (pg 17)

GPP

C Following the mammography of the affected breast at the end of the first year post-treatment, annual to two-yearly mammography of both breasts is recommended. (pg 17)

Grade C Level IV

Invasive Breast Cancer: Surgical Therapy

A Breast conservation surgery and adjuvant radiotherapy and total mastectomy and axillary clearance are effective treatments for invasive breast cancer and the patient's preference should be considered in the choice of treatment. (pg 21)

Grade A, Level Ia

A Nevertheless there are some cases in which breast conservation is contra-indicated, which include: (pg 21)

- Presence of multicentric tumours involving more than one quadrant of the breast.

- Diffuse malignant-appearing microcalcifications throughout the breast.
- Persistent positive surgical margins following reasonable attempts for clear margins.
- While there is no definite size that mandates mastectomy, a relative indication would be if surgical and radiological assessment suggests that adequate margins cannot be obtained with an acceptable cosmetic result. (see section on Neoadjuvant Chemotherapy in the main text).
- Factors unrelated to breast cancer but which may preclude the use of adjuvant radiotherapy may be considered relative contra-indications to breast conservation. These include collagen vascular disease such as scleroderma and systemic lupus, pregnancy and previous radiotherapy to the breast area.
- Reluctance of the patient to undergo radiotherapy. As many patients may have inaccurate preconceptions of the side effects and toxicity of radiotherapy, a referral to a radiation oncologist is recommended before the decision is taken to not offer breast conservation for this reason alone.

Grade A, Level Ia

A Patients with lobular cancer subtype can be offered breast conservation, if there is a good chance that clear margins can be obtained and the presence of multi-centricity can be excluded. (pg 22)

Grade A, Level Ia

A Enlarged axillary nodes, whether fixed or mobile, are not a contra-indication to breast conservation surgery as no increase in local recurrence has been reported. (pg 22)

Grade A, Level Ia

A Central location is not a contra-indication to breast conservation surgery, as good control can be obtained with postoperative radiotherapy. (pg 22)

Grade A, Level Ia

A A positive family history should not prevent a woman from considering breast conservation surgery and adjuvant radiotherapy, as previously reviewed studies have not shown an increase in local recurrence with this option. (pg 22)

Grade A, Level Ia

A Re-excision of margins should be undertaken when margin involvement is found on histological examination, or if malignant appearing microcalcification is seen in post-operative mammography. (pg 22)

Grade A, Level Ib

GPP Orientation of the surfaces of the excision specimen at the time of initial surgery will allow the re-excision of that margin which is involved alone, and decrease cosmetic deformity. (pg 22)

GPP

B Level II axillary dissection to include the clearance of nodes under the pectoralis minor will provide accurate staging information and maintain local control in the axilla. In cases where fixed axillary nodes are found in pre-operative clinical examination, or the presence of gross extra-nodal spread at the time of axillary surgery, a level III clearance to include all nodes to the lateral border of the first rib may decrease the incidence of axillary recurrence. (pg 22)

Grade B, Level IIb

C The routine use of more sophisticated means to detect tumour recurrence, such as tumour markers, imaging for metastasis and liver function tests has not been shown to be useful or cost-effective and is discouraged. (pg 23)

Grade C, Level IV

C Post-operatively, the clinical review of the patient is recommended at three- to six-monthly intervals for three years, six-monthly to twelve-monthly for the second to fifth years, and annually thereafter. (pg 23)

Grade C, Level IV

C Following the mammography of the affected breast at the end of the first year post-treatment, annual to two-yearly mammography of both breasts is recommended. (pg 23)

Grade C, Level IV

Invasive Breast Cancer: Adjuvant Cytotoxic and Hormonal Therapies

GPP There is currently no data to support the use of raloxifene (EVISTA) as adjuvant hormonal therapy in early breast cancer and use for adjuvant treatment in breast cancer is not recommended. (pg 26)

GPP

A Adjuvant treatments are recommended for the risk groups and patient groups as shown in the following table: (pg 27)

Patient group	Risk Group	
	Minimal/Low	**Intermediate/High**
Premenopausal		
ER or PR positive	Tamoxifen or None	Chemotherapy + Tamoxifen or Ovarian ablation + Tamoxifen
ER and PR negative	None	Chemotherapy
Post-menopausal		
ER or PR positive	Tamoxifen or None	Chemotherapy + Tamoxifen or Tamoxifen
ER and PR negative	None	Chemotherapy

Grade A, Level Ib

Adjuvant Radiotherapy for Invasive and Non-invasive Breast Cancer

A Post-mastectomy radiotherapy should be offered to a patient with T3 or T4 primary tumours, or with four or more lymph nodes involved. (pg 31)

Grade A, Level Ia

A All patients undergoing breast conservation surgery for invasive and non-invasive breast cancer should be offered adjuvant radiotherapy. (pg 31)

Grade A, Level Ia

GPP All patients eligible for breast conservation should be referred for a radiation oncology consultation if the fear of breast conservation is radiation treatment. (pg 31)

GPP

B Radiation treatment should be given in the management of locally advanced tumours. (pg 31)

Grade B, Level III

Neoadjuvant Therapy for Operable and Inoperable Breast Cancer

A In patients who desire breast conservation surgery, three to four cycles of anthracycline-based therapy after a biopsy of the tumour is recommended. Patients should be advised that a conversion to breast conservation may be possible in 20-30% of cases. If the tumour responds to chemotherapy, lumpectomy and axillary lymph nodes dissection, followed by radiotherapy may be considered if the patient meets the requirement for breast conserving therapy. (pg 34)

Grade A, Level Ib

B Breast conserving surgery may be followed by further individualized adjuvant chemotherapy such as additional anthracycline or taxane therapy. (pg 34)

Grade B, Level IIa

B If after 3-4 cycles of preoperative chemotherapy, the tumour fails to respond, or the response is minimal or if there is progression at any point, a mastectomy plus axillary dissection should be performed. Adjuvant therapy for these patients should be individualised, followed by radiation therapy as required. (pg 34)

Grade B, Level IIa

A After completion of all surgery, chemotherapy and radiation therapy, all patients with estrogen and/or progesterone receptor positive tumours should receive tamoxifen. (pg 35)

Grade A, Level Ib

B In patients with endocrine receptor positive tumours who are unfit or unwilling to receive chemotherapy, neoadjuvant endocrine therapy with third-generation aromatase inhibitors such as letrozole or anastrazole may be offered. (pg 35)

Grade B, Level IIa

C Initial treatment with anthracycline and/or taxane-based chemotherapy is recommended. (pg 35)

Grade C, Level IV

B For patients who respond to neoadjuvant chemotherapy, local therapy may consist of total mastectomy with axillary lymph node dissection or alternatively breast-conserving therapy can be considered in patients with a good partial or complete response to neoadjuvant chemotherapy. (pg 35)

Grade B, Level IIa

C Patients with an inoperable stage IIIA or stage IIIB tumour, whose disease progresses during preoperative therapy, should be considered for palliative breast irradiation in an attempt to enhance local control. Further systemic adjuvant chemotherapy following local therapy is felt to be standard. (pg 35)

Grade C, Level IV

B After surgery, adjuvant radiation therapy to the chest wall and regional lymphatics is recommended. (pg 35)

Grade B, Level IIa

A Hormone therapy should be administered to patients whose tumours are estrogen receptor- or progesterone receptor-positive or of unknown hormone receptor status. (pg 35)

Grade A, Level Ib

A Elderly and frail patients are exceptions to the intensive multimodal approach. In such a patient with a receptor positive tumour, tamoxifen alone (20 mg/day) may be used to reduce tumour size with few or no side effects. (pg 36)

Grade A, Level Ib