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CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF BREAST CANCER

(2ND EDITION)

MINISTRY OF HEALTH MALAYSIA

ACADEMY OF MEDICINE MALAYSIA

These guidelines are updates to the existing CPG on Breast Cancer in 2002. Since the issuance of these guidelines, there have been recent advancements in the aspects of screening, diagnosing and management of breast cancer especially in pharmacotherapy

These guidelines are meant to be guide for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every health care provider is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

This guidelines were issued in 2010 and will be reviewed in 2014 or sooner if new evidence becomes available.

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Electronic version available on the following websites:
http://www.moh.gov.my
http://www.acadmed.org.my

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GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The development group for this Clinical Practice Guidelines (CPG) consisted of breast and endocrine surgeons, oncologists, radiologists, pathologists, palliative physicians, geneticists, family medicine specialists, a clinical psychologist, public health physicians, a nursing lecturer, a nurse manager and a member of breast cancer group support. They were from the Ministry of Health (MOH), Ministry of Higher Education, private healthcare institution and non-governmental organisations. There was an active involvement of the review committee during the process of development of these guidelines.

Literature search was carried out at the following electronic databases: PUBMED/ MEDLINE, Cochrane Database of Systemic Reviews (CDSR), International Health Technology Assessment websites, Journal full text via OVID search engine, guidelines databases. (Refer Appendix 1 for Search Terms) In addition, the reference lists of all retrieved articles were searched to identify relevant studies. Experts in the field were also contacted to obtain further studies. All searches were conducted between 24 March 2009 through 20 February 2010.

Reference was also made to other guidelines on management of breast cancer such as National Institute for Clinical Excellence (NICE) 2009 Breast Cancer Screening - Early and Locally Advanced Breast Cancer: Diagnosis and Treatment, NICE 2009 Advanced Breast Cancer: Diagnosis and Treatment, New Zealand Guidelines Group (NZGG) 2009 Management of Early Breast Cancer, Scottish Intercollegiate Guidelines Network (SIGN) 2005 Management of Breast Cancer in Women, Federaal Kenniscentrum voor de Gezondheidszorg (KCE) 2006 Breast Cancer Screening, National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology 2008 Breast Cancer, National Health and Medical Research Council (NHMRC) 2001 CPG for the Management of Early Breast Cancer. These CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) prior to them being use as references.

The clinical questions were developed under ten major subtopics and members of the development group were assigned individual questions within these subtopics. (Refer Appendix 2 for Clinical Questions) The group members met a total of 35 times throughout the development of these guidelines. All literatures retrieved were appraised by at least two members and presented in the form of evidence tables and discussed during development group meetings. Later, all statements and recommendations formulated were agreed upon by both the development group and review committee. Where evidence was insufficient, the recommendations were derived by consensus of the development group and review committee. These CPG are based largely on the findings of systematic reviews, meta-analyses and clinical trials retrieved with local practices taken into consideration.

The articles were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation in these guidelines was modified from Grades of Recommendation of the Scottish Intercollegiate Guidelines Network (SIGN).

The draft guidelines were externally reviewed and posted on the MOH Malaysia website for comment and feedback. These guidelines had also been presented to the Technical Advisory Committee for CPG and the Health Technology Assessment (HTA) and CPG Council MOH Malaysia for review and approval.

OBJECTIVE

To provide evidence-based recommendations for the optimal care of women with breast cancer and women at risk of breast cancer

CLINICAL QUESTIONS

Refer Appendix 2

TARGET POPULATION

Inclusion criteria

- Women with early, advanced and metastatic breast cancer and women at risk of breast cancer

Exclusion criteria

- Non epithelial breast malignancy
- Specific groups with breast cancer – breast cancer in elderly, breast cancer in pregnancy, pregnancy after breast cancer, hormone replacement therapy after breast cancer and male breast cancer

TARGET GROUP/USER

These guidelines are applicable to all healthcare professionals who are involved in the management of patients with breast cancer:-

- General Practitioner/Family Medicine Specialist
- Breast Care Nurse/Oncology Nurse/Palliative Nurse/Community Nurse
- General Surgeon
- Breast and Endocrine Surgeon
- Radiologist
- Radiotherapist/Oncologist
- Pathologist/Histopathologist
- Palliative Care Physician
- Geneticist
- Psychiatrist/Psychologist/Psycho-oncologist
- Counsellor
- Pharmacist
- Physiotherapist/Occupational Therapist
- Dietician
- Breast Cancer Support Group

HEALTHCARE SETTINGS

Outpatient, inpatient and community settings

PROPOSED CLINICAL AUDIT INDICATORS FOR QUALITY MANAGEMENT

Percentage of newly diagnosed breast cancer patients receiving initial treatment within two months of presentation

$$= \frac{\text{Newly diagnosed breast cancer patients receiving initial treatment within two months of presentation}}{\text{All compliant newly diagnosed breast cancer patients}} \times 100\%$$

Percentage of eligible breast cancer patients post-surgery commencing chemotherapy within two months

$$= \frac{\text{Eligible breast cancer patients post-surgery commencing chemotherapy within two months}}{\text{All breast cancer patients post-surgery requiring chemotherapy}} \times 100\%$$

Percentage of local recurrence of breast cancer within two years

$$= \frac{\text{All patients with local recurrence of breast cancer within two years}}{\text{All patients with surgery for breast cancer}} \times 100\%$$

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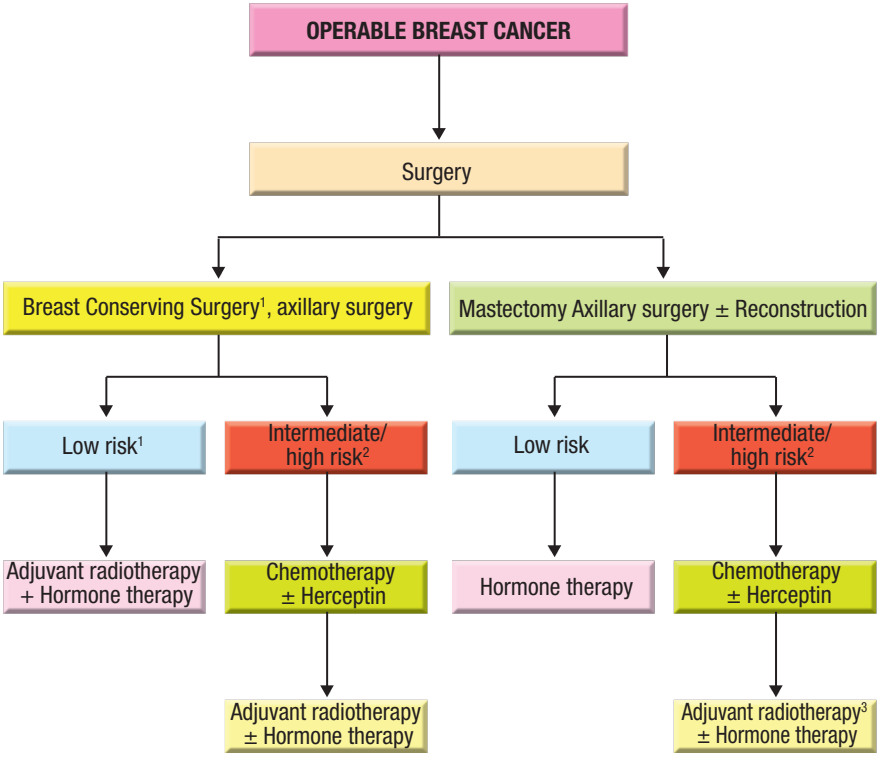
ALGORITHM FOR TREATMENT OF OPERABLE BREAST CANCER



[1]If the surgical margin is 2 mm, several factors should be considered in determining whether re-excision is required. These includes:

- Age
- Tumour histology (lymphovascular invasion, grade, extensive in-situ component and tumour type such as lobular carcinoma)
- Which margin is approximated by tumour (smaller margins may be acceptable for deep and superficial margins)
- Extent of cancer approaching the margin

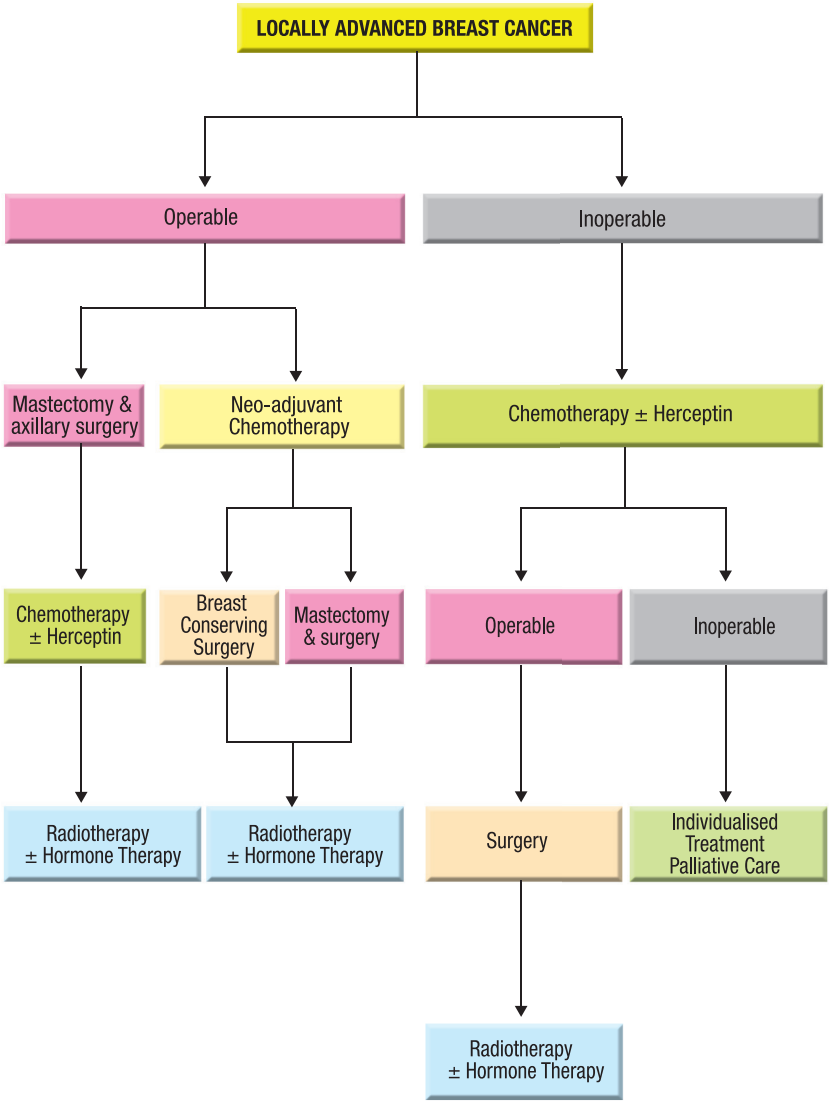
[2]Risk Stratification

Low risk	Intermediate risk	High risk
pN0 and all of the following criteria: • size of tumour max 2 cm • Grade 1 • no lymphovascular invasion • ER-/PR-positive • HER2- negative • age ≥ 35 years old	pN0 and at least 1 further criteria: • size of tumour > 2 cm • Grade 2/3 • vessel invasion present • HER2 over-expression • age < 35 years old • or pN+(N1-3) and HER2-negative	• pN+(N1-3) and HER2 over-expression or • pN+ (N ≥ 4)

[3] Indication for adjuvant radiotherapy

- 4 or more lymph nodes
- Positive margin
- ± 1-3 lymph nodes
- ± Node negative disease with high risk of recurrence with 2 or more risk factors such as
  - presence of lymphovascular invasion, tumours greater than 2 cm, grade 3 tumours, close resection margin (< 2 mm) and premenopausal status

ALOGRITHM FOR TREATMENT OF LOCALLY ADVANCED BREAST CANCER



1. INTRODUCTION

The National Cancer Registry (NCR) 2006 reported that there were 3,525 female breast cancer cases in Malaysia and this made it the most commonly diagnosed cancer in women (29.9 % of all new cancers). Breast cancer was the commonest cancer in all ethnic groups and in all age groups in females from the age of 15 years onwards. The overall Age-Standardised Incidence Rate (ASR) was 39.3 per 100,000 population.[1, level III]

The incidence of breast cancer increased steadily starting from age of 30 years with a peak age specific incidence rate in the 50 - 59 age groups. The situation is similar amongst the Malays, Chinese, and Indians. The incidence rate then declined in the older age groups. Of the cases diagnosed in 2003, 33.6% (one-third) were in women between 40 and 49 years of age. The Chinese women had the highest incidence with an ASR of 46.4 per 100,000 population followed by Indian women with an ASR of 38.1 per 100,000 population and Malay women with an ASR of 30.0 per 100,000 population. Compared to the 2003 - 2005, the ASR is lower for all races, but the age-specific incidence patterns are very similar (Refer to Table 1, Table 2 and Figure 1).[1, level III]

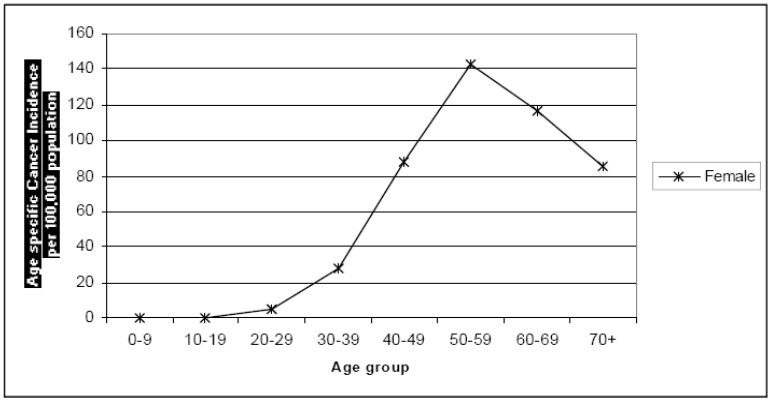
Table 1: Female Breast Age-Specific Cancer Incidence per 100,000 Population, by Ethnicity and Sex, Peninsular Malaysia 2006

		Age groups (year)								
		0 - 9	10 - 19	20 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70+	CumR
Female	**Malay**	0	0.2	3.2	27	73.8	114.7	78.9	43.4	3.2
	Chinese	0	0	4.9	26.9	96.6	176.7	143.3	118.8	5
	Indian	0	0	3.2	16.7	82.3	111.1	138.3	140.5	4.3

Table 2: Female Breast Cancer Incidence per 100,000 Population (CR) and Age-Standardised Incidence (ASR), by Ethnicity and Sex, Peninsular Malaysia 2006

Ethnic group	Female			
	No	%	CR	ASR
Malay	1,539	47.6	25.3	30.4
Chinese	1,375	42.5	53.2	46.4
Indian	320	9.9	34.9	38.1

Figure 1: Female Breast Age-Specific Cancer Incidence per 100,000 Population by Sex, Peninsular Malaysia 2006



1.1 Risk Factors

There are a number and variety of risk factors that cause the complex multifaceted nature of breast cancer. The risk factors are summarised in Table 3.

1.1.1 Gender

Female has higher risk to develop breast cancer than their male counterparts. The rate for male to develop breast cancer was 1.15 per 100,000 men years compared to female at 42.6 per 100,000 women years.[2, level III]

1.1.2 Age

The risk increases from the age of 40 years old for pre-menopausal group and 50 years old for the post menopausal group.[3, level II-2; 4, level II-2; 5, level II-2]

1.1.3 History of Neoplastic Disease of the Breast

- Prior history of breast cancer carries an elevated risk of developing new primary breast cancer.[6, level III; 7, level II-2]
- Person with breast carcinoma in situ (lobular carcinoma in situ and ductal carcinoma in situ) are at high risk to develop invasive breast carcinoma.[8, level II-2; 9, level III; 10, level III]
- Person with breast tissue biopsy showing proliferative disease with and without atypical cells has an increased risk to develop future breast cancer. Benign breast disease with atypical hyperplasia lesion carries the highest risk to develop breast cancer.[3, level II-2; 4, level II-2; 5, level II-2]

1.1.4 Family History

Family history of breast cancer is an independent risk factor. The risk is higher in women with breast cancer among young first degree relatives. Sister carries more risk than mother.[9, level III; 11, level II-2; 12, level II-3; 13, level II-3; 14, level II-2]

Carriers of BRCA1 and BRCA2 genetic mutation are at high risk to develop future breast cancer. (Refer to Section 11.2 on Familial Breast Cancer)

1.1.5 Radiation Exposure

- Multiple exposures of therapeutic radiation to the chest for cancer at an early age (less than 20 years old) pose a high risk of developing breast cancer.
- Contralateral breast cancer has been shown to develop after exposures of high dose radiation used during radiotherapy for breast cancer.
- Patients with Hodgkin's disease receiving radiotherapy at high doses are at high risk to develop breast cancer.
- Screening using mammography has not been shown to significantly affect the breast cancer status.[15, level III; 16, level II-2; 17, level II-3; 18, level II-3]

1.1.6 Reproductive Factors

- First full-term pregnancy more than 30 years old.[19, level II-2; 20, level II-2]
- Nulliparity.[9, level III; 21, level II-2; 22, level II-2; 20, level II-2]
- Breastfeeding for duration more than 12 months is protective of breast cancer.[23, level III; 24, level II-3; 9, level III; 21, level II-2]
- Oral contraceptive use poses a mild increase of breast cancer risk especially if it is use before the first full term pregnancy. However, the risk is lower with low dose preparation. [25, level II-2; 26, level II-2]
- Unopposed estrogen use in hysterectomised women mildly increases the risk of breast cancer and only after longer term use (> 15 years).[27, level I; 28, level II-2]
- Combination hormone replacement therapy has a mild risk for breast cancer.[29, level I]
- Age at menopause of more than 55 years old.[20, level II-2]
- Age at menarche less than 12 years old.[19, level II-2; 22, level II-2]

1.1.7 Breast Density

Higher breast density from mammography. The risk ranges from two times in scattered fibroglandular density to four times in an extremely dense breast.[30, level II-2; 5, level II-2]

1.1.8 Lifestyle

- A body mass index of more than 25 has an increased risk to develop breast cancer with higher death rate. Small waist and waist-hip ratio (WHR) give a significant protection against breast cancer in pre-menopausal women.[31, level II-2; 32, level II-1; 33, level II-2]
- Alcohol (especially beer) consumed more than 10 g/day especially among post-menopausal women is a risk factor for developing invasive breast cancer.[34, level 1I-2; 35, level II-2; 36, level II-2]
- Moderate to vigorous exercise of more than seven hours in a week of physical activity was inversely related to breast cancer.[37, level II-3; 38, level II-2; 39, level II-3]

Table 3: Stratifications of Risk Factors

Low Risk (RR 1.0 - 1.4)	Moderate Risk (RR 1.5 - 2.0)	High Risk (RR > 2.0)
• Alcohol consumption	• Increasing age from 40 years old	• Personal history of invasive breast cancer
• Reproductive factors: o Increasing age at first full term pregnancy > 30 year o Hormone replacement therapy o Oral contraceptive pill usage	• Reproductive factors: o Early menarche (< 12 year old) (RR 1.02) o Late menopause (> 55 year old) (OR 2.4) o Nulliparity	• Lobular Carcinoma In Situ (LCIS) and Ductal Carcinoma In Situ (DCIS)
• Obesity	• Benign breast disease with proliferation without atypia	• Benign breast disease with atypical hyperplasia
	• Dense breast	• Ionising radiation from treatment of breast cancer, Hodgkin's disease, etc.
		• Carrier of BRCA1 and 2 genetic mutation
		• Significant family history i.e. first degree family with breast cancer

Adapted from:

- Weir R, Day P and Ali W. Risk factors for breast cancer in women. A systematic review NZHTA REPORT June 2007; 10(2); level I
- Cancer Genetic Services In Scotland – Management of Women with a Family History of Breast (internet communication, 13 jan 2010 at Cancer, www.sehd.scot.nhs.uk/mels/HDL2007_08.pdf level III
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- Slattery ML, Kerber RA. A comprehensive evaluation of family history and breast cancer risk, The Utah Population Database. JAMA; 19993; 270:1563-8

2. SCREENING

2.1 Screening on General Population

Benefit of breast self-examination (BSE) appears to be ineffective in reducing breast cancer mortality.[40; 41]
The effectiveness of CBE is equivocal.[42] The current evidence is insufficient to assess the additional benefits and harms of clinical breast examination (CBE).[43]

The Cochrane Systemic Review (SR) of eight Randomised Clinical Trials (RCTs) (n=600,000), comparing the effects of mammography screening, found that three trials with adequate randomisation did not show a significant reduction in breast cancer mortality at 13 years follow up (RR=0.90, 95% CI 0.79 to 1.02); while four trials with suboptimal randomisation showed a significant reduction in breast cancer mortality (RR=0.75, 95% CI 0.67 to 0.83). The RR for all seven trials combined was 0.81, 95% CI 0.74 to 0.87. The trials with adequate randomisation did not find an effect of screening on cancer mortality, including breast cancer, after 10 years follow up (RR=1.02, 95% CI 0.95 to 1.10) or on all-cause mortality after 13 years follow up (RR=0.99, 95% CI 0.95 to 1.03). The SR concluded that screening is likely to reduce breast cancer mortality. As the effect was lowest in the adequately randomised trials, a reasonable estimate is a 15% reduction corresponding to an absolute risk reduction of 0.05%. Screening led to 30% over-diagnosis and overtreatment, or an absolute risk increase of 0.5%. It is not clear whether screening does more good than harm.[44, level I]

The results of the Ontario Health Technology Assessment assessing five health technology assessments, two Preventive Services Task Force reports, one Cochrane SR and eight RCTs showed that screening mammography in women aged 40 to 49 years at average risk for breast cancer is not effective in reducing mortality.[45, level I]

Results of evaluation on the role of various imaging modalities used in the screening and diagnosis of breast cancer revealed that mammography is the only imaging technique that has a significant impact on screening of asymptomatic individuals for breast cancer. Breast ultrasound and breast magnetic resonance imaging (MRI) are frequently used adjuncts to mammography in treatment planning and staging and not for screening.[46, level III]

Another Cochrane SR of two large population based studies from Russia and Shanghai (n=388,535) on screening for breast cancer by regular self-examination (self-breast examination/SBE) or clinical breast examination (CBE) found that there was no statistically significant difference in breast cancer mortality between the groups (RR=1.05, 95% CI 0.90 to 1.24). In Russia, more cancers were found in the breast self-examination group than in the control group (RR 1.24, 95% CI 1.09 to 1.41) while this was not the case in Shanghai (RR 0.97, 95% CI 0.88 to 1.06). Almost twice as many biopsies (n=3,406) with benign results were performed in the screening groups compared to the control groups n=1,856, RR=1.88, 95% CI 1.77 to 1.99. The review alsoss concluded that these two large trials did not suggest a beneficial effect of screening by BSE but suggested increase in harms in terms of increased numbers of benign lesions identified and biopsied. The review concluded that screening by BSE or physical examination cannot be recommended. However, women who continue with BSE or wish to be taught the technique should be informed on lack of supporting evidence from the two major studies for them to make informed decision.[40, level I]

Elmore et al. reviewed breast cancer screening in the community and new screening modalities. The results from this SR demonstrated significant reductions of 20% to 35% in mortality from breast cancer for women aged 50 to 69 years and slightly less in women aged 40 to 49 years at 14 years of follow up. Results from seven population-based community screening programmes in the United States on 463,372 screening mammography revealed an overall sensitivity of 75.0% and specificity of 92.3%. Review on CBE screening revealed an overall estimate for sensitivity of 54% (95% CI 48 to 60) and specificity of 94% (95% CI 90 to 97). MRI had not been studied in the general opulation as a screening tool. This study concluded that in the community, mammography remains the main screening tool and CBE and BSE are less effective.[41, level I]

Thistlethwaite et al. examined the evidence for screening CBE and found that it had a low sensitivity (54%) but high specificity (94%).The highest sensitivity of CBE appeared to be in women aged 50 - 59 years old while it is lowest in women aged 40 - 49 years old. Training of clinicians may account for a 27 - 29% difference in sensitivity and 14 - 33% difference in specificity. However, a negative examination does not exclude the presence of breast cancer. The effect of CBE on mortality from breast cancer is still unclear.[42, level III]

A recent SR by US Preventive Task Force (USPTF) 2009 recommended biennial screening mammography for women aged 50 to 74 years. The decision to start regular, biennial screening mammography before the age of 50 years should be an individual one and take patient context into account, including the patient's values regarding specific benefits and harms. The evidence was insufficient to assess the additional benefits and harms of screening mammography in women 75 years or older. The USPTF suggests against teaching BSE and the current evidence is insufficient to assess the additional benefits and harms of CBE beyond screening mammography in women 40 years or older. The evidence was also insufficient to assess the additional benefits and harms of either digital mammography or MRI instead of film mammography as screening modalities for breast cancer.[43, level I]

Although there is no evidence on the effectiveness of breast self-examination (BSE), the practice of BSE has been seen to empower women and encourage them to take responsibility for their own health. Therefore, BSE is recommended for raising awareness among women at risk rather than as a screening method.[47]

RECOMMENDATION
Mammography may be performed biennially in women from 50 – 74 years of age. **(Grade A)**
Breast cancer screening using mammography in low and intermediate risk women aged 40 – 49 years old should not be offered routinely. **(Grade A)**
Women aged 40 – 49 years should not be denied mammography screening if they desire to do so. **(Grade C)**
BSE is recommended for raising awareness among women at risk rather than as a screening method. **(Grade C)**

2.2 Screening on High Risk Group

A review by Nelia Alfonso on 49 published papers from 1989 - 2007 concluded that among screening strategies for high-risk women, MRI screening in addition of mammography should be recommended for women who meet at least one of the listed criteria under high risk group in **Table 3**. It should begin annually at the age of 30 years old and continue for as long as the woman is in good health, as suggested by most guidelines such as National Comprehensive Cancer Network (NCCN), American Cancer Society (ACS) and US Preventive Task Force (USPTF).[48, level II-2]

Based on a SR of 11 nonrandomised studies on the sensitivity, specificity, likelihood ratios and post-test probability associated with adding MRI to annual mammography screening of women at very high risk for breast cancer, Ellen et al. concluded that screening women at very high risk for breast cancer with both MRI and mammography might rule out cancerous lesions better than mammography alone. The summary negative likelihood ratio and the probability of a BI-RADS-suspicious lesion (given negative test findings and assuming a 2% pretest probability of disease) were 0.70 (95% CI 0.59 to 0.82) and 1.4% (95% CI 1.2% to 1.6%) for mammography alone and 0.14 (95% CI 0.05 to 0.42) and 0.3% (95% CI 0.1% to 0.8%) for the combination of MRI plus mammography, using a BI-RADS score of 4 or higher as the definition of positive.[49, level II-1]

While lifetime risk of breast cancer for women diagnosed with LCIS may exceed 20%, the risk of invasive breast cancer is continuous and only moderate in risk in the 12 years following local excision. Only one MRI screening study included a selected group of women with LCIS which showed a small benefit over mammography alone in detecting cancer. This benefit was not seen in patients with atypical hyperplasia.[50, level II-3] The results of MRI screening for breast cancer in high-risk patients with LCIS and atypical hyperplasia, as reviewed by Port et al., showed that those who had MRIs were younger ($p < 0.001$) with stronger family history of breast cancer ($p = 0.02$). In MRI-screened patients, 55 biopsies were recommended in 46/182 (25%) patients in which 46/55 (84%) biopsies were based on MRI findings alone. The yield of MRI screening overall was cancer detection in 6/46 (13%) of biopsies, 5/182 (3%) of MRI screened patients and 5/478 (1%) of total MRIs. Therefore, MRI screening generated more biopsies for a large proportion of patients, and facilitated detection of cancer in only a small highly selected group of patients with LCIS.[51, level III]

RECOMMENDATION
Screening women at high risk for breast cancer should be done from the age of 30 years with both MRI and mammography as it is more effective than mammography alone. **(Grade B)**
MRI screening should not be performed in patients with lobular carcinoma in situ and atypical hyperplasia. **(Grade B)**

3. REFERRAL TO SURGICAL/BREAST CLINIC

Only two retrospective studies addressed issue on referral to surgical/breast clinic. The first study provided evidence on the success of categorising patients into urgent and non-urgent cases. It was noted that 46.7% (n=6,678) of the referrals originated from fast-track referrals and the remainder 53.3% (n=7,625) came via routine referrals. 71.7% of the referrals met the referral criteria. Out of the appropriate referrals, 14.4% were cancers compared to only 0.55% of the inappropriate referrals ($p < 0.001$). 91.8% of the total breast cancer patients came from fast-track clinics while 8.2% from routine referrals. Apart from that, 16.4% of the patients seen in the fast-track clinic were detected with breast cancer compared to only 1.3% from routine referrals ($p < 0.001$).[52, level III]

In another retrospective study, 21 (19.4%) cancers were diagnosed from 108 urgent referrals. Out of these, 92 patients were given an urgent appointment because of the presence of high-risk criteria in which 21 (22.8%) cancers were detected. Out of 162 given routine appointments, only two were diagnosed with cancer. In addition to the assessment by referring physicians, certain high-risk criteria are helpful to select patients who should be seen urgently. The mean waiting time was 19 days and 154 days for urgent referral and routine appointments respectively.[53, level III]

Criteria for early referral [53, level III]
• Age > 40 years old women presenting with a breast lump
• Lump > 3 cm in diameter at any age
• Clinical signs of malignancy

4. ASSESSMENT/DIAGNOSIS IN SPECIALIST CLINIC

4.1 Triple Assessment

Triple assessment which consists of clinical assessment, imaging (ultrasound and/or mammography) and pathology (cytology and/or histology) is an established method for the diagnosis of breast cancer in many parts of the world.[54; 55]

The Belgian guidelines recommend that all patients presenting with breast symptom should have a full clinical examination and where a localised abnormality is present, patients should have mammography and/or ultrasonography followed by core biopsy and/or fine needle aspirate cytology depending on the clinician's, radiologist's and pathologist's experience. They also state that if a lesion is considered malignant following clinical examination, imaging or cytology alone, where possible should have histopathological confirmation of malignancy before any definitive surgical procedure. Young women (< 40 year old) presenting with breast symptoms which are strongly suspicious of breast cancer should be evaluated by means of the triple test approach to exclude or establish a diagnosis of breast cancer.[55]

The NICE guidelines states that in most cases whether symptomatic or screen detected, the diagnosis of breast cancer is made by triple assessment (clinical examination, mammography and/or ultrasonography imaging with core biopsy and/or fine needle aspiration cytology.[54]

In a more recent cross sectional study (n=50) on accuracy of triple test score (physical examination, mammography and fine needle aspirate cytology) in the diagnosis of palpable breast lump on women above 35 years old, the accuracy of triple test score was 98%, sensitivity 100%, specificity 95.2%, positive predictive value (PPV) 96.7% and a false positive rate of 3.3%.[56, level III]

4.2 Diagnostic Accuracy of Ultrasound and Mammography Together Compared With Ultrasound or Mammography Alone

Studies have shown that adjunct ultrasound to mammography improves the diagnostic yield of breast cancer. Corsetti et al. evaluated the contribution of ultrasound in detecting breast cancer in women with dense breasts and negative mammography among 25,572 self referred women. The study found that ultrasound screening of mammography negative dense breast contributed an additional 20% cancer detection rate in asymptomatic women compared to mammography alone with a higher contribution among women younger than 50 years old.[57, level III]

In another cross-sectional study (n=999 symptomatic women) on the complementary role of ultrasound to mammography, the sensitivity of mammography was 56.6% (95% CI 44.3 to 64.2) while the sensitivity of adjunct ultrasound was 80.8% (95% CI 70.5 to 86.9). Adjunct ultrasound was found to be significantly more sensitive in cancer detection compared to mammography alone ($p < 0.001$). There was no significant difference in specificity of adjunct ultrasound versus mammography alone. The specificity of mammography was 99.4% (95% CI 98.6 to 99.8) while the specificity of adjunct ultrasound was 99.1% (95% CI 98.85 to 99.6).[58, level III]

Results of the first year screen in the American College of Radiology Imaging Network (ACRIN 6666) comparing screening breast ultrasound and mammography to mammography alone in women with high risk of breast cancer, the diagnostic yield of mammography was 7.6 per 1000, mammography and ultrasound was 11.8 per 1000 with a supplemental yield of 4.2 per 1000 (95% CI 1.1 to 7.2). The diagnostic accuracy of mammography alone was 0.78 (95% CI 0.67 to 0.87) but higher for mammography and ultrasound at 0.91 (95% CI 0.84 to 0.96). The PPV of biopsy recommendation after full workup of mammography was 22.6% (95% CI 14.2 to 33), ultrasound alone was 8.9% (95% CI 5.6 to13.3) and combined ultrasound and mammography was 11.2% (95% CI 7.8 to 15.6).[59, level III]

In a study by Bhate et al. on 203 symptomatic women, ultrasound was offered to all women and for those above 35 years old, an additional mammography was also performed. The study found that mammography led to a diagnosis of breast cancer in 4.4% of women. The study also recommended ultrasound to be the initial assessment in the evaluation of symptomatic women below the age of 35 years old instead of 40 years old.[60, level III]

RECOMMENDATION
Patients presenting with a breast symptom should be evaluated with a full clinical examination, mammography and/or ultrasound followed by biopsy, either fine needle and/or core biopsy. **(Grade C)**
Adjunctive ultrasound assessment improves breast cancer detection in women of all ages and where possible should be offered to all symptomatic breast patients. **(Grade C)**
In young women (< 35 years old), ultrasound should be used as the initial imaging modality as part of the triple assessment. **(Grade C)**

4.3 Pre-operative Assessment of the Breast

4.3.1 Pre-operative Magnetic Resonance Imaging of Early Breast Cancer

In a woman with early or locally advanced breast cancer, MRI may be considered if there is a likelihood that it can lead to a change in surgical management.[61]

Effective assessment prior to primary treatment ensures appropriate treatment. Pre-operative MRI has been suggested to be potentially useful in selected clinical situations. The Belgian guidelines reported that MRI is a sensitive procedure for the diagnosis of breast cancer with sensitivities ranging from 86 - 98%. However the low quality of evidence does not advocate the routine use of MRI for the diagnosis and staging of breast cancer.[55]

Similarly, the New Zealand guidelines concluded that MRI demonstrates some benefits in accuracy over conventional imaging modalities. This may lead to change in surgical management with more extensive tissue removal although subsequent pathology may not always justify the MRI result.[61]

In a recent prospective cohort (n=349) of women with invasive breast cancer who were eligible for breast-conserving therapy, pre-operative contrast enhanced magnetic MRI of the breast which influenced the rate of incomplete tumour excision. MRI detected larger extent of breast cancer in 19 women (11.0%) leading to treatment change [mastectomy (8.7%) or wider excision (2.3%)]. This study concluded that pre-operative MRI did not significantly ($p = 0.17$) affect the overall rate of incomplete tumour excision. However in women with Invasive Ductal Carcinoma (IDC), pre-operative MRI yielded significantly ($p = 0.02$) lower rates of incompletely excisions.[62 level II-2]

In a retrospective study (n =160) of women with operable breast cancer (stages Tis to T4), an additional 30 cases (18.75%) were diagnosed correctly using pre-operative MRI, which went undetected by clinical palpation, mammography, and breast ultrasound. However 14 cases (8.75%) turned out to be false positive. It was concluded that preoperative breast MRI detects additional invasive carcinoma and changes surgical management of operable breast cancer.[63, level III]

The New Zealand guidelines recommended that MRI should be considered in clinical situations where other imaging modalities are unreliable or inconclusive. These include: invasive lobular cancer; suspicion of multicentricity; genetic high risk (BRCA1 or BRCA2); patients with T0 N+ disease; patients with breast implants/foreign bodies; diagnosis of recurrence; follow up of neo-adjuvant treatment; women with dense breasts.[61]

RECOMMENDATION

MRI should not be routinely performed in the pre-operative assessment of patients with biopsy proven invasive breast cancer or DCIS. **(Grade B)**

MRI may be considered in clinical situations where other imaging modalities are unreliable or inconclusive which include:

- Invasive lobular cancer
- Suspicion of multicentricity
- Genetic high risk (BRCA1 or BRCA2)
- Patients with T0 N+ disease
- Patients with breast implants/foreign bodies
- Diagnosis of recurrence
- Follow up of after neo-adjuvant treatment
- Women with dense breasts **(Grade B)**

5. BASELINE STAGING INVESTIGATION

The American Joint Committee on Cancer (AJCC) Cancer Staging Manual (7th Edition) has been used for staging of cancers in these guidelines. (Refer to **Appendix 3**)[64,]

5.1 Early Breast Cancer

Early breast cancer is breast cancer that has not spread beyond the breast or the axillary lymph nodes. This includes ductal carcinoma in situ and stage I, stage IIA and stage IIB.

The Belgian guidelines concluded that there is no good evidence to support routine screening for metastases for patients with early breast cancer who are asymptomatic and with negative clinical findings. Although the imaging modalities such as chest x-ray (CXR), liver ultrasound and bone scintigraphy are relatively inexpensive, these imaging are not recommended for asymptomatic women with intra ductal tumour, pathological stage I disease and early operable breast cancer (T1-2, N0-1).[55]

Imaging investigations including CXR, bone scan, liver ultrasound and computerised tomography (CT) scan have low diagnostic yields and should be used only when clinically indicated such as symptoms of lung disease, a palpable liver, abnormal liver function test, bone pain or bony tenderness.[61]

The New Zealand guidelines recommended that patients with symptoms or positive clinical findings of metastases at a particular site will need appropriate investigation. In addition, in those with more advanced but operable disease (T3, N1-2) or in whom neo-adjuvant treatment is considered, further investigation is needed to exclude distant metastases. Patient at high risk of harbouring distant metastases (such as triple negative patients and young patients < 35 years old) should also be staged aggressively. However, these guidelines did not recommend routine bone scintigraphy for patients presenting with metastatic disease if CT of the thorax, abdomen and pelvis had been performed. Bone scintigraphy should be reserved for patients with symptoms suggestive of bone metastases at sites not imaged by CT and who had normal plain films of the symptomatic sites. There is insufficient evidence to determine whether fluorodeoxyglucose -positron emission tomography (FDG-PET) or bone scintigraphy is superior in detecting osseous metastases from breast cancer. However FDG-PET had a higher specificity and might better serve as a confirmatory test.[61]

A retrospective study (n=221) of patients with primary operable breast cancer showed that routine pre-operative staging with bone scan and liver ultrasound were not helpful. Bone scan had a false positive value of 12% and PPV of 19% while liver ultrasound had a false positive value of 3% and PPV of 33%. The author concluded that these investigations should be reserved for patients with symptoms suggestive of metastases, abnormal blood test and high risk patients.[65, level III]

RECOMMENDATION
In patients with early asymptomatic operable breast cancer, intraductal tumour and pathological stage I, screening (CXR, liver ultrasound, CT scan and bone scintigraphy) for metastasis should not routinely be performed. **(Grade C)**
In patients presenting with symptoms suggestive of bone metastases, bone scintigraphy should be used if CT of the thorax, abdomen and pelvis or plain radiograph of the symptomatic site are negative. **(Grade C)**

5.2 Advanced Breast Cancer

Locally advanced breast cancer (LABC) includes breast cancers with large primary tumors of more than 5 cm or those with skin and/or chest wall involvement, and with or without regional lymph node involvement (Stage 3a, 3b and 3c).

If advanced breast cancer is suspected either clinically or on initial imaging, the routine practice is to confirm the diagnosis and to assess the extent of the metastatic disease with more imaging (staging). This includes assessment of bony and visceral metastases such as plain radiograph, ultrasound, bone scintigraphy, CT, MRI and positron emission tomography/computerised tomography (PET/CT).[66]

MRI and FDG-PET were equal to or better than scintigraphy in visualising osteolytic bone metastases rather than osteoblastic lesions. Whole body MRI was found to be better than FDG-PET in detecting distant metastases particularly in the abdominal organs, brain and bone.[66]

There is insufficient evidence to support the choice of one imaging modality over another. The choice of the modality will depend on the availability of resources.[66]

RECOMMENDATION
In patients presenting with clinically advanced breast cancer, further imaging modalities such as chest x-ray, liver ultrasound, and/or CT scan should be offered to assess the extent of disease depending on the available resources. **(Grade C)**
CT (with bone window) or MR or bone scintigraphy may be offered to assess presence and extent of metastases in the axial skeleton. **(Grade C)**
The risk of pathological fracture in the extremities may be assessed using bone scintigraphy and/or plain radiography. **(Grade C)**

5.3 Positron Emission tomography (PET) or PET/CT in Staging

Unlike other imaging modalities, FDG labelled with positron emitting flourine provides functional information. Most malignant tumours have a higher glucose metabolism than normal tissue and take up more FDG-PET. Therefore, they show up as areas of increased activity. When CT is fused with PET, functional information can be located anatomically.[66]

The NICE guidelines recommended that PET/CT should only be used to make new diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease[54]. Whereas, the New Zealand guidelines recommended PET scan as a confirmatory test in diagnosing bony metastases as it was noted that PET scan had a higher specificity compared to bone scintigraphy.[61]

PET scan is not indicated in the diagnosis of breast cancer, axillary staging and in the follow-up of breast cancer. However, PET scan can be useful for the evaluation of metastatic disease in invasive breast cancer.[55]

A cross-sectional study (n=183) evaluated the preoperative diagnostic accuracy between FDG-PET/CT and axillary ultrasonography (AUS) in detecting axillary lymph node metastasis primary operable breast cancer. The diagnostic accuracy of FDG-PET/CT was shown to be nearly equal to AUS in terms of sensitivity (64.4% vs 54.2%), specificity (94.4% vs 99.2%) and overall accuracy (84.7% vs 84.7%). However the author concluded that considering the limited sensitivities, the high radiation exposure by FDG-PET/CT and costs of the examination, AUS is a more cost-effective imaging tool.[67, level III]

A prospective study (n=80) showed that the sensitivity, PPV and accuracy of FDG-PET for the detection of axillary lymph node metastasis were 44%, 89% and 72% respectively. It was concluded that FDG-PET could not replace histological staging using sentinel lymph node biopsy (SLNB) in patients with breast cancer.[68, level II-2]

In a retrospective study by Taira et al. (n=90) it was found that the positive detection rate on FDG-PET/CT was insufficient to determine the indication for sentinel node biopsy (sensitivity 48%, specificity 92%, PPV 72% and NPV 81%).[69, level III]

Another retrospective study (n=46) evaluated the role of PET/CT for tumour staging and recurrence. It demonstrated that the accuracy of diagnosis of tumour recurrence by PET/CT is 83% for patient-based and 96% for site-based. It was concluded that PET/CT was a sensitive and an accurate imaging modality, superior to CT for the diagnosis of tumour recurrence and for the definition of extent of disease.[70, level III]

A comparative study (n=34) of women with increased tumour markers showed that the combination of PET/CT was superior to PET or CT alone. CT had sensitivity of 92% and specificity of 78%, PET had a sensitivity of 88% and specificity of 78%, and combination of PET/CT sensitivity was 96% and specificity at 89%.[71, level II-3]

PET/CT was superior to conventional imaging procedures for detection of distant metastases. Although FDG-PET and CT provided similar diagnostic accuracy, this was often found to be complementary. This study demonstrated that for conventional imaging the sensitivity was 43% and specificity was 98% whereas, CT had a sensitivity of 83% and specificity of 85%, and FDG-PET had a sensitivity of 87% and specificity of 83%.[72 , level III]

Tevfik carried out a study on 271 women with biopsy-proven primary breast cancer looking at the efficacy of FDG-PET in detecting primary tumour, axillary lymph node and distant metastases. It was found that there was variation in diagnostic accuracy based on tumour size. The sensitivity increased with increasing tumour size i.e. T1a at 53%, T1b at 63%, T1c at 80% and T2 & T3 at 92%. For axillary lymph node metastasis, the sensitivity was 41% in pN1, 67% in pN2 and 100% in pN3, while specificity was 89% for pN0 stage. It was concluded that FDG-PET could detect axillary lymph node metastases in high axillary node stages.[73, level II-3]

A study done by Huang et al. on the estimation of radiation dose and cancer risk for whole body PET/CT scanning for the Hong Kong and U.S population showed that the effective dose for protocol A, B and C were 13.45, 24.79 and 31.91mSV for female and 13.65, 24.80 and 32.18mSv for male patients. The lifetime attributable risks (LARs) for cancer incidence were between 0.231% and 0.514% for a 20 years old U.S. woman and between 0.163% and 0.323% for 20 years old man. LARs was 5.5% - 20.9% higher for the Hong Kong population. This was attributed to a longer life expectancy and higher baseline cancer incidence in the organs sensitive to radiation in Hong Kong population. The induced cancer risks decreased when age at exposure increased. PET/CT examination resulted in increased patient radiation exposure compared to stand alone PET or CT examination, as the effective dose was the combination of the dose from PET and CT.[74, level III]

RECOMMENDATION
PET or PET/CT scan should not be offered to make the diagnosis of malignancy in breast tumours or for axillary staging or in the follow up of breast cancer patients**. (Grade C)**
PET/CT scan may be used in patients whose imaging is suspicious but not diagnostic of metastic cancer. **(Grade C)**

6. LABORATORY DIAGNOSIS

6.1 Fine Needle Aspiration Cytology (FNAC) vs Core Biopsy (CB)

A retrospective study of screen detected breast cancers (n=763) found that combining FNAC and CB resulted in improvement in accuracy, when the sensitivity increased from 93% for CB alone to 98% for combined FNAC and CB. This study concluded that combined FNAC and CB may be offered for diagnosis of breast cancer where facilities and expertise are available.[75, level III]

In contrast, an earlier comparative study of symptomatic patients (n=112) found that FNAC when performed in addition to CB did not provide useful additional information (sensitivity for FNAC was 90% and CB was 99%). The authors concluded that CB had a high accuracy rate which could not be improved upon by adding FNAC.[76, level III]

A prospective study of suspicious breast lesions (n=264) showed that FNAC and CB had similar accuracy rates when the lesions were $\leq$ 2 cm or $\geq$ 5 cm in size (sensitivity for FNAC was 85.6% and CB was 88.3%). This study also concluded that for lesions between 2 - 5 cm, CB was more accurate than FNAC (sensitivity for FNAC was 89.1% and for CB was 92.4%). However when combined, FNAC and CB had a sensitivity of 97.5%.[77, level II-3]

A comparative analysis of CB and FNAC (n=50) for breast cancer (clinically or mammographically detected) revealed that sensitivity for FNAC was 78.15% and CB 96.5% while specificity for FNAC was 94.44% and CB was 100%. However, CB had a higher inadequate sample rate. Thus the authors concluded that FNAC and CB cannot be treated as mutually exclusive, but must complement each other. While FNAC may be the preferred initial procedure to obtain diagnostic information, CB may be appropriate for impalpable breast lesions.[78, level II-3]

A locally conducted retrospective study (n=436) on the method of initial diagnosis in breast cancer showed that the accuracy of FNAC was 87% versus CB of 99%. However the author concluded that the ideal method of biopsy is dependent on the physical characteristics of the lump as well as the expertise available locally. Therefore FNAC was a reliable and relevant method for diagnosis of breast cancer and CB may be used as a second line method for diagnosis. Excision should be considered as the last option.[79, level III]

In a study (n=39) using concurrent trucut biopsy and FNAC for breast cancer, it was demonstrated that FNAC had a statistically significant higher detection rate compared to CB (90% vs 67%, $p \leq 0.02$). There was no false negative in FNAC. A total of nine cases reported positive in FNAC were negative in CB. The authors were of the opinion that CB was technically more difficult to perform with higher morbidity.[80, level III]

RECOMMENDATION
Fine needle aspiration cytology may be considered as the initial method of pathological assessment for palpable breast lumps where facility and expertise are available. **(Grade C)**
Core biopsy may be used as a complement for pathological diagnosis if the fine needle aspiration cytology is equivocal. **(Grade C)**
Core biopsy in combination with Fine needle aspiration cytology may be used where facility and expertise are available. **(Grade C)**

6.2 Human Epidermal Growth Factor Receptor 2 (HER-2) Testing In Breast Cancer

HER-2 testing may be performed by various methods including immunohistochemistry (IHC), fluorescent in-situ hybridisation (FISH), chromogenic in-situ hybridisation (CISH) and silver-enhanced in-situ hybrid (SISH).

A technology review based on 10 studies looking at HER-2 testing showed that the most cost-effective testing strategy is to screen all breast cancer cases with IHC, followed by FISH or CISH for IHC of 2+ (or of 2+ and 3+). FISH testing was more objective and predictive of response to anti-HER-2 therapy and had been advocated to confirm some or all positive IHC results. CISH is another promising and practical alternative to FISH that can be used in conjunction with IHC. Thus, it may represent an important addition to the HER-2 testing algorithm.[81, level III]

In a more recent study (n=72) by Pederson et al., dual CISH (using probe for HER-2 and centromere of chromosome 17) was shown to have 98.6% concordance and a correlation coefficient of 0.95 with FISH. The author concluded that further evaluation of its accuracy is still required before adopting into routine practice.[82, level III]

In another study (n=230), SISH was found to be an alternative for HER-2 testing. It had 96% concordance with CISH.[83, level III]

RECOMMENDATION
HER-2 test using immunohistochemistry should be performed for all invasive breast cancer cases. **(Grade C)**
Fluorescent in-situ hybridisation, silver-enhanced in-situ hybrid or chromogenic in-situ hybridisation should be used for confirmation when the immuno-histochemistry score is 2+ or 3+. **(Grade C)**

6.3 Pathology Reporting for Breast Cancer

An adequate pathology report for breast cancer must have the following minimum parameters: modified from [84, level III]

- Location (side and quadrant), maximum diameter, multifocality
- Tumour type (histology)
- Histological grade
- Lymph node involvement and total number of nodes examined
- Resection margins
- Lymphovascular invasion
- Non-neoplastic breast changes
- Hormone receptor status [estrogen-receptor/progesterone receptor (ER/PR)]
- HER-2 assessment

An audit (n=120) demonstrated that majority of the pathology reports did not fulfil the criteria set by College of American Pathologists.[85, level III]

In another audit conducted in Queensland looking at completeness of randomly selected histopathology reports (n=440) of newly diagnosed breast cancer, it was noted that 88% of synoptic (checklist) reports had all 7 criteria whereas only 27% of non-synoptic (free text format) reports had the same. Usage of synoptic reporting in laboratories varied depending on the workload (low at 82%, medium at 82% and high at 64%).[84, level III]

Similarly, an audit (n=100) done in the United Kingdom showed that the introduction of a standard proforma, that included 18 criteria outlined in the Royal College of Pathologists Minimum Dataset for breast cancer reports, led to a significant improvement ($p < 0.001$) in the completeness of breast cancer histopathology report (74% in the proforma versus 34% in the free text group).[86, level III]

RECOMMENDATION

A complete pathology report should have a minimum dataset.* **(Grade C)**

*Refer to Appendix 4 for detail

7. TREATMENT OF BREAST CANCER

7.1 Surgical Management for Women with Early Breast Cancer

Surgery is the mainstay of treatment for early breast cancer and consists of either breast conserving surgery (BCS) or mastectomy, and assessment of axillary lymph node.

A SR which included six randomised controlled trials (RCTs) with a 15 years follow up concluded that BCS and radiotherapy offer the same survival benefits as modified radical mastectomy in women with early breast cancer. (no significant differences in overall survival and disease free survival). Other outcome measures showed no evidence for a substantial difference in post-operative psychological health between women who have had either modality.[61]

RECOMMENDATION

All women with early breast cancer should be undergoes breast conserving surgery or mastectomy to obtain clearance of the cancer from the breast. **(Grade A)**

7.2 Contraindications of Breast Conserving Surgery (BCS)

Contraindications of BCS:

- The ratio of the size of the tumour to the size of the breast and location of the tumour would not result in acceptable cosmesis
- Presence of multifocal/multicentric disease clinically or radiologically
- Conditions where local radiotherapy is contraindicated (such as previous radiotherapy at the site, connective tissue disease and pregnancy)

BCS is increasingly accepted as a surgical technique for treatment of breast cancer since its introduction. However, mastectomy is required if there are absolute contraindications to BCS.

Six RCT recommended that BCS and radiotherapy were contraindicated if the ratio of the size of the tumour to the size of the breast would not result in acceptable cosmesis, if there are any contraindications to radiotherapy and presence multicentric/multifocal tumour.[61]

A retrospective study (n=1485) found that there was no difference in overall survival and disease free survival between BCS and mastectomy in centrally located tumours. In the same study, no difference was seen in BCS between centrally located tumour and peripheral tumours. [87, level II-2]

RECOMMENDATION

Breast conserving surgery is an option for a woman with a centrally located tumour, although it may require excision of the nipple and areola, which may compromise cosmesis. **(Grade A)**

7.3 Tumour Free Margin in Breast Conserving Surgery (BCS)

If the surgical margin is less than 2 mm, several factors should be considered in determining whether re-excision is required. These includes:

- Age
- Tumour histology (lymphovascular invasion, grade, extensive in-situ component and tumour type such as lobular carcinoma)
- Which margin is approximated by tumour (smaller margins may be acceptable for deep and superficial margins)
- Extent of cancer approaching the margin

Complete excision reduces the risk of local recurrence. However, there is an on-going debate on the optimal tumour free margin.

A SR revealed limited evidence in the optimal tumour free margin. There was no consistency regarding the optimal tumour-free tissue margin. There was an ongoing, unresolved debate about how great a margin of excision is necessary, particularly as there are no good RCTs that answer this question. However, there was clear evidence that leaving involved margins results in unacceptably high local recurrence rates.[61]

NICE evaluated a few RCTs and concluded that the crude local recurrence rate was 20 - 38% for margin 1 mm or less and 13 - 34% for a margin 2 mm or less. This crude local recurrence rate reduced to 13 - 19% with the addition of radiotherapy to 1 - 2 mm a margin. However, when a margin of 2 mm or more were achieved, the local recurrence rate was 2% (with radiotherapy) and 11% (without radiotherapy). This examination did not include the skin/superficial margin and fascial/deep margin as it may be impossible to obtain a 2 mm clearance.[54]

RECOMMENDATION

Complete excision of the tumour with clear margin (greater than or equal to 2 mm) is advised in breast conserving surgery. **(Grade A)**

7.4 Axillary Surgery in Early Breast Cancer

Axillary lymph node dissection (ALND) comprises of removal of one, two or three level of nodes relative to the pectoralis minor muscle. Typically 10 - 15 lymph nodes are retrieved and at least one section from each assessed by standard haematoxylin and eosin (H&E).[54]

The New Zealand guidelines highlighted the importance of accurate assessment and management of the axillary nodes in women with early breast cancer. The assessment should be undertaken for most early invasive breast cancers in order to stage the disease, minimise the risk of loco-regional recurrence and assist in planning of adjuvant therapy. Several adverse events are associated with the management of the axilla and women should be advised of the benefits and potential harms associated with each procedure. Axillary node dissection is more effective at lowering the risk of local recurrence than axillary node sampling, which in turn is more effective than no axillary surgery. No evidence was identified on the effectiveness of excision of the supra-clavicular and internal mammary chain nodes compared with no excision. [61]

7.4.1 Indications for Sentinel Lymph Node Biopsy (SLNB) in Breast Cancer

The New Zealand guidelines concluded that SLNB was an appropriate method of staging the axilla as there was no difference in axillary recurrence or overall survival. There was limited or no trial data available on the effectiveness of SLNB vs axillary lymph node dissection in the following subgroups:

- Women with tumours > 3cm
- Women with multicentric/multifocal tumours
- Women with clinically positive nodes
- Pregnant or breastfeeding women
- Women with known allergies to radioisotopes or blue dye
- Women with previously treated breast cancer or axillary surgery on the affected side

A woman should be informed of the potential for an unsuccessful SLNB or a false negative result.[61]

NZGG reviewed NBOCC guidelines and one SR and concluded that SLNB should be performed by surgeons who are trained and experienced in the SLNB. Another trial noted that the accuracy increased and false negative decreased when the surgeon performed 30 or more procedures.[61]

Apart from that, based on the same guidelines that included four RCTs and one SR evaluating technical aspect of SLNB, NZGG reported that combination radioisotope and blue dye is associated with a higher rate of sentinel lymph node detection than blue dye method alone.[61]

RECOMMENDATION
Sentinel node biopsy should not be carried out in women with clinically involved nodes. The safety and efficacy of sentinel node biopsy for breast cancer $>$ 3cm or multifocal disease has yet to be demonstrated in randomised controlled trials. As such, it is not recommended for these groups. **(Grade A)**
Sentinel lymph node biopsy may be offered to the following : • Unifocal tumour of $\leq$ 3cm • Clinically non-palpable axillary nodes **(Grade B)**
Sentinel lymph node biopsy should only be performed by surgeons who are trained and experienced in the technique.**(Grade A)**
Dual technique with isotope and blue dye in performing the sentinel lymph node biopsy is preferred. **(Grade A)**

7.5 Immediate Breast Reconstruction vs Delayed Breast Reconstruction

The choice of immediate or delayed reconstruction should be discussed within the team and with the patient.

There is very limited high quality evidence to address this issue whether the timing of breast reconstructive surgery alter the local recurrence rate and overall survival. However based on the NICE guideline, there is no difference in recurrence and survival following mastectomy with immediate reconstruction compared to mastectomy with no reconstruction.[54] Based on observational studies, breast reconstruction does not appear to be associated with an increase in the rate of local cancer recurrence or to impede the ability to detect recurrence if it develops. [61]

Expert opinion from NZGG Development Group noted that radiotherapy to the reconstructed breast may result in significantly worse cosmetic outcome, especially when an implant had been used.[61]

A retrospective study carried out in the MD Anderson Cancer Centre showed that of 32 patients who had radiation therapy after immediate free transverse rectus abdominis myocutaneous (TRAM) flap reconstruction had 87.5% of late complications compared to 8.6% in the 70 patients who had delayed free TRAM flap reconstruction after radiotherapy. Distorted contour due to flap contraction from radiation therapy required re-operation in 28% of these patients. These findings indicate that, in patients who are candidates for free TRAM flap breast reconstruction and need post-mastectomy radiation therapy, reconstruction should be delayed until radiation therapy is complete.[88, level III]

A retrospective review of 224 pedicled TRAM flaps reconstructions in 200 patients over a 10 year period found that active or former smoking and obesity contribute to a significant complication rate.[89, level III]

The Michigan Breast Reconstruction Outcome Study, a prospective cohort study of 326 patients, found that the most significant factors associated with higher complication rates were timing of reconstruction and body mass index. Both immediate breast reconstruction and obesity were associated with higher and major complication rates. The type of reconstruction, whether implant, pedicled TRAM or free TRAM, had no effect on complication rate.[90, level II-2]

The aim of immediate breast reconstruction is to improve well-being and quality of life for women undergoing mastectomy for breast cancer. A prospective study used the SF-36 Health Survey questionnaire to assess quality of life before and 12 months after mastectomy and immediate breast reconstruction together with patients' expectations of and satisfaction with the immediate breast reconstruction with implant. Scores for 76 participants were compared with those in 920 age-matched women from the general population. Pre-operative scores for emotional well-being and physical role functioning were lower than in the reference population, while after 12 months the scores in all domains had improved and were comparable with those in the reference population. Although many factors may influence quality of life, one year after breast cancer surgery with immediate reconstruction scores were equivalent to those of the normal population.[91, level II-2]

Two groups of consecutive patients from two different plastic surgical practice populations were evaluated to determine psychosocial differences between those who underwent immediate (n = 25) vs delayed (n=38) breast reconstruction. The relationship between timing of reconstruction and self-reported distress over the mastectomy experience revealed that only 25% of the women who underwent immediate repair reported "high distress" in recalling their mastectomy surgery compared with 60% of the delayed reconstruction group ($p = 0.02$).[92, level II-2]

RECOMMENDATION
Caution is required before offering immediate breast reconstruction to women who are active smokers or obese. **(Grade C)**
Discuss immediate breast reconstruction with all patients who are being advised to have a mastectomy and offer it except where significant co-morbidity or (the need for) adjuvant therapy may preclude this option. **(Grade C)**
In patients who are candidate for free flap breast reconstruction and need post-mastectomy radiation therapy reconstruction should be delayed until radiation therapy is completed. **(Grade C)**

7.6 Management of Locally Advanced Breast Cancer

7.6.1 Neo-Adjuvant chemotherapy in Locally Advanced Breast Cancer

Locally advanced breast cancer is invasive breast cancer that has one or more of the following features:

- large (typically bigger than 5 cm)
- spread to several lymph nodes in the axilla or other areas near the breast
- spread to several lymph nodes in the axilla such as the skin, muscle or ribs

However, there are no signs that the cancer has spread beyond the breast region or to other parts of the body.

The NICE guidelines found that there was no significant difference in overall survival (OS) and disease free survival (DFS) between neo-adjuvant chemotherapy and post-operative chemotherapy. However, better tumour response to chemotherapy was associated with better outcomes. The NICE guidelines also conclude that while giving neo-adjuvant chemotherapy to locally advanced breast cancer (LABC), adequate long-term local control by surgery and/or radiotherapy is still essential including those patients with complete clinical response. Many retrospective reviews suggest that radiotherapy reduces locoregional recurrence and improves survival in patients following neo-adjuvant chemotherapy and mastectomy.[54]

A study showed that neo-adjuvant chemotherapy can be given to downsize the tumour in an attempt for BCS or enable subsequent surgery for initially inoperable breast cancer. In addition to improving both operability and rates of BCS, neo-adjuvant chemotherapy also provides a valuable window to assess disease response to treatment and perform correlative tissue analyses.[93, level I]

7.6.2 Factors Affecting Response to Neo-Adjuvant Chemotherapy

Neo-adjuvant chemotherapy or primary systemic therapy is an established option for most patients with LABC. It is primarily utilised to optimise surgical outcomes for women with LABC.

A SR concluded that neo-adjuvant chemotherapy gives better clinical and pathological response in ER-negative tumours. Combinations of taxanes and anthracycline and the use of biological response modulators (herceptin) give high pathological complete responses (pCR) in HER-2 positive tumours. Other characteristics of tumours which respond well to chemotherapy include the non-lobular type, high grade histology, high Ki67 and luminal B. These tumour types have a higher chance of response and should be considered for neo-adjuvant chemotherapy. In contrast, tumours which show low response to chemotherapy (such as lobular type and low Ki67) should be considered for alternative approaches (such as neo-adjuvant endocrine therapy or mastectomy as initial treatment).[94, level I]

RECOMMENDATION

Neo-adjuvant chemotherapy or pre-operative systemic therapy can be offered to patients with operable locally advanced breast cancer who are not suitable candidates for BCS at presentation. **(Grade A)**

In locally advanced breast cancer that is inoperable, neo-adjuvant chemotherapy should be given to downsize the tumour to enable subsequent surgery. **(Grade A)**

7.7 Surgery for the Primary Tumour in Metastatic Breast Cancer

There is no RCT addressing surgery for the primary tumour in metastatic breast cancer. However, one retrospective study showed that surgical removal of the primary tumour was associated with a significantly longer survival time in patients with distant metastatic disease at diagnosis with 5-year survival rates of 24.5% with mastectomy and 13.1% without mastectomy ($p < 0.0001$).[95, level II-3]

Another retrospective study (n=111) concluded that improvement in local control may play a role in improving outcomes in women with stage IV breast cancer, and resection of in-breast tumours can help to achieve this.[96, level III]

RECOMMENDATION
Surgery of the primary tumour may be considered in stage IV breast cancer. **(Grade C)**

7.8 Resection of Metastases in Metastatic Breast Cancer

NICE guidelines concluded that there was no good evidence on the surgical treatment of metastatic brain disease from breast cancer. However, the guidelines suggested surgical therapy followed with whole brain radiotherapy in patients with single or small number of potentially resectable brain metastases, having good performance status and with no or well-controlled other metastatic disease.[66, level I]

For lung and liver metastasis, retrospective studies concluded that there was may be an overall survival benefit in selected cases. Yashimoto et al. had retrospectively followed up 90 patients who had surgery for lung metastases and concluded that surgery may benefit those with early breast cancer, disease free interval of more than three years and lesions of less than 2 cm.[97, level III]

Two small studies looking at liver metastasis from breast cancer showed no benefit in overall survival in patients with synchronous tumours, a short disease free interval and patients with an aggressive cancer.[98, level III; 99, level III]

RECOMMENDATION
Resection of limited metastastic disease may be considered in patients with advanced breast cancer in selected cases. **(Grade C)**

7.9 Systemic Therapy

7.9.1 Indications and Benefits of Adjuvant Chemotherapy in Early Breast Cancer

Breast cancer is recognised as a systemic condition even in early stage of the disease, with a significant risk of distant micro-metastases. As a result, adjuvant chemotherapy has an established role in eradicating these micro-metastases, thus improving survival.

NICE guidelines did not specifically address this issue in its current edition as adjuvant chemotherapy is widely accepted internationally to be of significant proven benefit in women with breast cancer. The Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis of 194 un-confounded randomised controlled trials of adjuvant chemotherapy and hormonal therapy indicated that the use of anthracycline-based adjuvant chemotherapy is associated with a reduction 38% in the annual breast cancer death rate for women younger than 50 years of age and 20% for those between 50 and 69 years when diagnosed. The absolute benefit of chemotherapy varies according to patient age and underlying risk of recurrence. An estimate of the benefit of adjuvant chemotherapy can be made from the EBCTCG data [refer table 4].[54]

Table 4: Estimate of Benefit of Adjuvant Chemotherapy

Age	Risk	Absolute survival difference	Number needed to treat (NNT)
< 50	Low	4.6%	22
< 50	Intermediate	8.7%	12
< 50	High	15.1%	7
50 - 69	Low	2.4%	42
50 - 69	Intermediate	4.4%	23
50 - 69	High	7.4%	14

Adapted from EBCTCG Effect of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15 year survival: an observation of RCT. *Lancet* 2005; 365: 1687-1717

The advantage of adjuvant chemotherapy in post-menopausal patients is of smaller magnitude. The decision should be made after discussion with the patient and her family bearing in mind her age, co-morbidity, performance status & risk stratification (refer Table 5).

Table 5: Stratification for low, intermediate and high risk St. Gallen 2007

Low risk	Intermediate risk	High risk
pN0 and all of the following criteria: • size of tumour max 2 cm • Grade 1 • no vessel invasive • ER-/PR-positive • HER-2 negative • Age ± 35 years	pN0 and at least 1 further criterion: • size of tumour > 2 cm • Grade 2/3 • vessel invasion • HER-2 overexpression • age < 35 years old • pN+ (N1-3) and HER-2 negative	pN+ (N1-3) and HERs overexpression or pN+ (N > or = 4)

Adapted from Persing, M., and Große R. Current St. Gallen Recommendations on Primary Therapy of Early Breast Cancer. Breast Cancer. 2007; 2: 137-40

RECOMMENDATION
Adjuvant chemotherapy should be considered in all patients with early breast cancer. **(Grade A)**
Adjuvant chemotherapy should be offered to all women with any of the following risk factors especially in pre-menopausal women: • One or more positive axillary lymph nodes • ER negative disease • HER-2 3+ disease • Tumour size > 2 cm • Grade 3 disease **(Grade A)**

7.9.2 Indications and Benefits for Neo-Adjuvant Chemotherapy Compared to Adjuvant Chemotherapy in Early Breast Cancer

There is an option to offer chemotherapy prior to surgery in early breast cancer. This has the theoretical advantage of eradicating micro-metastases earlier in the course of the disease, in addition to the possibility of breast conserving surgery as opposed to mastectomy.

NICE guidelines commented on two SR. The first one, by Meiog 2007, reviewed ten RCTs involving 4,620 patients. The review did not find any difference in overall survival (HR=0.98, 95% CI 0.87 to 1.09). The subsequent SR by Rastogi 2008 also did not find any improvement in overall survival with neo-adjuvant compared to adjuvant chemotherapy (HR=0.99, 95% CI 0.85 to 1.16). However, in patients with locally advanced breast cancer who received primary chemotherapy, findings from a Cochrane SR and two other SRs suggested that better tumour response was correlated with better outcome. The applicability of these findings is limited because the majority of the patients had stage I and II disease. Pre-operative chemotherapy can be offered to those who are considering BCS. However, local recurrence is higher compared to mastectomy and this should be discussed with the patient. Seven studies in the SR reported a pathological complete response rate (pCR) of 4 - 29.2% with neo-adjuvant chemotherapy. Four RCTs reported overall survival data for 1,290 assessable patients and involving 381 deaths. There was a statistically significant difference in favour of pCR vs residual disease with HR=0.48 (95% CI 0.33 to 0.69).[54]

Gianni et al. reported on the results of a phase III RCTs evaluating the addition of paclitaxel to doxorubicin and followed by cyclophosphamide, methotrexate, and fluorouracil, as adjuvant or primary systemic therapy. There was no difference in overall survival between the adjuvant and neo-adjuvant chemotherapy arms in the study (HR=1.10, 95% CI 0.77 to 1.59).[100, level I]

RECOMMENDATION
Neo-adjuvant chemotherapy should not be routinely given to patients with early breast cancer. **(Grade A)**

7.9.3 Indications and Benefits of Taxane-Based Regimens Compared to Anthracycline-Based Regimens in Early Breast Cancer

Over the last decade, studies have shown significant benefits of taxane based chemotherapy regimens in metastatic disease. In the effort to further improve outcome in the adjuvant setting, taxanes have been investigated in numerous clinical trials.

NICE guidelines recommended the addition of docetaxel to an adjuvant chemotherapy regimen for patients with lymph node positive breast cancer. This was based on SR and meta-analysis. All of these studies confirmed an improvement in overall survival with the addition of a taxane to the adjuvant chemotherapy regimen.[54]

Ellis et al. evaluated the benefit of four cycles docetaxel after four cycles of 5-fluorouracil, epirubicin and cyclophosphamide (FEC) chemotherapy compared to eight cycles of FEC or cyclophosphamide, methotrexate, and fluorouracil Epi-(CMF). There was no difference in the five years disease free survival or overall survival despite recruiting 4,162 patients and a high proportion of patients with lymph node positive disease. However, the dose of epirubicin used in this trial was 60 mg/m^2 in the experimental arm and 60 mg/m^2 or 100 mg/m^2 in the control arm. The PACS01 trial assessed as part of the NICE guidelines evaluated three cycles of docetaxel after three cycles of FEC with epirubicin at a dose of 100 mg/m^2 and found a survival benefit of 4%.[101, level I]

Gianni et al. evaluated the addition of paclitaxel to an adjuvant doxorubicin and cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen in 904 patients. There was no difference in overall survival (HR=0.80, 95% CI 0.56 to 1.14). However, paclitaxel was given once every three weeks in this trial which is now not considered the optimal method of administering paclitaxel in the adjuvant setting.[100, level I]

Jones et al. published the updated results of the US Oncology Group study comparing four cycles of docetaxel and cyclophosphamide to doxorubicin and cyclophosphamide. After a median follow-up of 1,016 patients over seven years, there was a statistically significant survival difference in overall survival from 82% to 87% (HR=0.69, 95% CI 0.50 to 0.97).[102, level I]

Goldstein et al. compared doxorubicin and docetaxel to doxorubicin and cyclophosphamide in 2,882 patients and did not find any difference in disease free or overall survival. However, a lower dose of docetaxel (60 mg/m^2 every three weeks) was used. Furthermore, 66% of the patients recruited into this study had lymph node negative disease and the median size of the tumour was 2 cm. A suboptimal dose of docetaxel would not be expected to have a significant survival benefit in such a group of patients with good prognosis disease.[103, level I]

RECOMMENDATION
For women with lymph node positive breast cancer, a taxane (preferably Docetaxel) may be considered in the adjuvant chemotherapy regimen. **(Grade A)**

7.9.4. Indications and Survival Benefits for Anti-HER-2 Adjuvant Treatment in Early Breast Cancer

HER-2 is a transmembrane epidermal growth factor receptor that plays an important role in the growth signalling pathway for breast cancer. Over-expression of HER-2 or amplification of the gene has been associated with poorer prognosis. Trastuzumab has been shown to improve survival in the metastatic setting. More recent trials in the adjuvant setting have also demonstrated encouraging results.

NICE guidelines recommended the use of trastuzumab (herceptin) for patients with HER-2 3+ early breast cancer. This was based on three RCTs and a meta-analysis. Herceptin Adjuvant (HERA) trial evaluated the sequential use of herceptin after adjuvant chemotherapy in 5,102 women. With a median follow up of two years, a statistically significant improvement in overall survival was observed (HR=0.66, 95% CI 0.45 to 0.87). Romond found a similar improvement in overall survival with the addition of herceptin concurrently with adjuvant chemotherapy (HR=0.67, 95% CI 0.48 to 0.93). Using data from both trials, the NNT at two years was 56 and at three years were 40. The disease free survival was the primary end-point for both trials and this was also statistically significant with a difference of 8.4 - 11.7% at two years. Joensuu investigated nine weeks of herceptin with adjuvant chemotherapy and did not find a difference in overall survival. The meta-analysis included five RCTs and confirmed a overall survival benefit with the addition of herceptin to adjuvant chemotherapy (HR=0.66, 95% CI 0.55 to 0.78). [54]

RECOMMENDATION
Trastuzumab should be considered in women with HER-2 over-expressed or HER-2 gene amplified breast cancer having adjuvant chemotherapy. **(Grade A)**

7.10 Endocrine Therapy

7.10.1 Endocrine Therapy in Early Invasive Breast Cancer and Ductal Carcinoma in Situ (DCIS)

Endocrine therapy has a long established role in breast cancer. Over the last decade, it has been demonstrated to be of benefit in only in oestrogen receptor positive cancer.

Tamoxifen has been shown to improve survival in ER positive early invasive breast cancer with 15 years OS advantage of 9.2% (NNT=11). Five years of tamoxifen is superior to two years of tamoxifen.[54]

NICE guidelines reviewed two RCTs (DCIS-National Surgical Adjuvant Breast and Bowel Project (NSABP) B24 and UKCCCR) on tamoxifen. NSABP B24 showed a reduction in ipsilateral breast cancer where invasive breast cancer events of 2.1% in the tamoxifen arm vs 4.2% in the control arm, HR=0.56 (95% CI 0.32 to 0.95) and NNT=48. No difference in OS was seen. UKCCCR trial showed no difference in breast cancer events or OS. It was concluded that there is insufficient evidence to support the use of tamoxifen in DCIS.[54]

RECOMMENDATION
Tamoxifen should be offered to all women with ER positive invasive early breast cancer. **(Grade A)**
Hormonal therapy should not be used routinely in ductal carcinoma in situ. **(Grade A)**

7.10.2 Ovarian Suppression or Ovarian Ablation in Addition to Standard Adjuvant Therapy Consisting of Chemotherapy and Tamoxifen in Pre-Menopausal Breast Cancer Patients

There are some controversies with respect to the addition of ovarian suppression or ablation to chemotherapy and tamoxifen in pre-menopausal women with breast cancer. Some studies have suggested improved outcomes with this approach which were not confirmed by other investigators.

Based on two meta-analyses, NICE guidelines concluded that there was insufficient evidence to support the routine use of ovarian suppression or ablation in addition to chemotherapy and tamoxifen in pre-menopausal women with ER positive breast cancer. According to a recent meta-analysis there was a modest benefit for luteinizing-hormone-releasing hormone (LHRH) agonist with a HR=0.85 (95% CI 0.73 to 0.99) for death after recurrence in a subgroup analysis. However, tamoxifen was not employed as standard therapy after chemotherapy in several studies. This may have increased the magnitude of the benefit of LHRH agonists.[54]

A RCT of pre-menopausal women (n=910) treated with primary surgery and then offered LHRH agonist goserelin and tamoxifen compared to those who were just offered tamoxifen alone showed no benefit with the addition of goserelin in all events with ARR=2.8% (95% CI -7.7% to 2.0%) and breast cancer death with ARR=2.6% (95% CI -6.6% to 2.1%).[104, level I]

RECOMMENDATION

Adjuvant ovarian suppression or ablation should not be used routinely in addition to tamoxifen and chemotherapy in pre-menopausal women with ER positive early breast cancer. **(Grade A)**

7.11 Aromatase Inhibitors

In post-menopausal women, the main source of oestrogens is from the peripheral conversion of androgens by the aromatase enzyme. Inhibition of this enzyme will lead to further reduction in oestrogen level which may be of benefit in patients with oestrogen receptor positive breast cancer.

7.11.1 Benefits of Aromatase Inhibitors vs Tamoxifen in the Adjuvant Setting in Post-Menopausal Breast Cancer Patients

Based on the RCTs included in the NICE guidelines, there is no overall survival benefit with the use of aromatase inhibitors in the adjuvant setting. However, a significant improvement in overall survival was seen for the subset of node-positive patients in the letrozole group in the MA17 extended adjuvant trial (HR=0.61, 95% CI 0.38 to 0.98).[54]

An SR by Eisen et al. showed a disease free survival benefit for aromatase inhibitors in various upfront, switched and extended adjuvant trials with statistically significant HR ranging from 0.50 - 0.87.[54]

A durable disease free survival advantage of 4.8% and NNT of 21 was seen in the trial with the longest follow up data. This benefit was consistent with the other large randomised studies.[54]

RECOMMENDATION

Aromatase inhibitors may be considered as an option in post-menopausal women with ER positive early breast cancer as adjuvant hormonal therapy. **(Grade A)**

7.11.2. Benefits of Aromatase Inhibitors vs Tamoxifen in the Advanced Setting in Post-Menopausal Breast Cancer Patients

Based on a SR of 23 RCTs, there was an overall survival benefit in the use of aromatase inhibitors versus standard endocrine therapy. This was particularly seen in third generation aromatase inhibitors with statistically significant survival benefit (HR=0.87, 95% CI 0.82 to 0.93) and reduced breast cancer mortality (HR=0.91, 95% CI 0.86 to 0.96).[66]

A RCT (n= 371) with a median follow up of 29 months compared exemestane with tamoxifen as a first-line hormonal treatment of metastatic breast cancer in post-menopausal women. This trial demonstrated a progression free survival benefit of 4.1 months but no overall survival advantage HR=1.04 (95% CI 0.76 to 1.41). However, the author concluded that the follow up may be too short to show an overall survival difference.[105, level I]

RECOMMENDATION
Aromatase inhibitors may be considered as first line hormonal therapy in post-menopausal women with ER positive advanced breast cancer. **(Grade A)**

7.12 Radiotherapy

7.12.1 Post-Mastectomy Radiotherapy in Breast Cancer

In high risk patients who have had mastectomy, there is a significant risk of loco-regional relapse. Radiotherapy has been shown to improve loco-regional control but controversy existed regarding the survival benefit until recently.

The EBCTCG Overview showed a survival benefit of 4.4% and local control benefit of 17% for node positive patients with the use of adjuvant radiotherapy post-mastectomy. This corresponded with a NNT of 23 for overall survival and 6 for local control. For those with node negative disease, there was a detrimental effect on the overall survival by 4.2% while local control improved by 4%. A meta-analysis by Gebski et al. that included only trials utilising optimal radiotherapy also showed a survival benefit of 6.4% with a NNT of 16. NICE guidelines recommended adjuvant chest wall radiotherapy for those post-mastectomy and at high risk of local recurrence including those with four or more lymph nodes involvement or involved resection margins. It also recommended against adjuvant radiotherapy for those with low risk of local recurrence.[54]

A recent SR (that included only modern radiotherapy techniques for patients with node negative disease) showed a highly significant improvement in the 10 years locoregional recurrence rate with a hazard ratio of 0.17 and more importantly there was no detrimental effect on overall survival.[106, level I]

RECOMMENDATION

Adjuvant radiotherapy should be offered to the following post-mastectomy patients with:

- ≥ Four lymph nodes
- Positive margin **(Grade A)**

Adjuvant radiotherapy can be offered to the following post-mastectomy patients with:

- 1 - 3 lymph nodes **(Grade B)**
- Node negative disease with high risk of recurrence with two or more risk factors such as presence of lymphovascular invasion, tumours greater than 2 cm, grade 3 tumours, close resection margin (< 2mm) and premenopausal status **(Grade B)**
- T3 and T4 tumours **(Grade C)**

7.12.2 Radiotherapy Post-Breast Conserving Surgery in Breast Cancer

There is 25 - 35% risk of local recurrence post-breast conserving surgery for breast cancer. Radiotherapy has been shown to significantly reduce this risk.

The EBCTCG SR showed a survival benefit of 8.2% and local control benefit of 30.1% for node positive patients with the use of adjuvant radiotherapy post-breast conserving surgery. This corresponded to a NNT of 13 for overall survival and four for local control. For those with node negative disease overall survival improved by 4.6% ($p = 0.06$) and local control benefit by 16.1%. The NNT for local control was 7. NICE guidelines recommended breast radiotherapy for those who had breast conserving surgery with clear margins.[54]

A recent RCT (n = 264) focusing on patients with favourable prognostic features with lower risk of recurrence (patients age older than 40, resection margin of at least 1 cm, tumour size 2 m or smaller, node negative, progesterone receptor positive, well to moderately differentiated, unifocal and low cell proliferation rate) showed an improvement of local control by 15% though there was no significant survival benefit.[107, level I]

A Cochrane SR on post-operative radiotherapy for DCIS for patients who had BCS showed an absolute reduction of 12% for ipsilateral breast events (DCIS and invasive recurrence). There was no survival benefit for this group of patients.[108, level I]

RECOMMENDATION

All patients with post-BCS should be offered adjuvant radiotherapy for both invasive breast cancer and ductal carcinoma in situ. **(Grade A)**

8. PSYCHOLOGICAL SUPPORT

8.1 Assessment of Distress

The diagnosis of breast cancer for women is undeniably distressing. In addition to the normal reactions to such a diagnosis, many women experience elevated levels of distress as the illness progresses.

For many women with breast cancer, their anxiety and depression go undetected. According to several RCTs, up to 45% of women diagnosed with breast cancer continue to experience clinical anxiety and depression many months into their illness; their distress, in turn, affects various realms of their illness experience including their physical, psychological and social functioning.[109]

SIGN guidelines recommended that breast cancer services should routinely screen for the presence of distress and risk factors for very high levels of distress from the point of diagnosis onwards (including during follow up review phases) through routinely administered self-report questionnaires. However, these questionnaires are not recommended for those who are not at high risk of developing emotional distress.[109]

A cross-sectional study looked at the utility of the Hospital Anxiety and Depression Scale (HADS) in detecting emotional distress among women diagnosed with breast cancer (n = 361). Results showed that HADS was able to differentiate women with major depressive disorders (MDD) from others: detection rate of MDD=0.94 (95% CI 0.91 to 0.97), sensitivity of 0.87 (95% CI 0.70 to 0.95), specificity of 0.85 (95% CI 0.81 to 0.89) and PPV of 0.35.[110, level III]

Another cross-sectional study (n=204) compared the validity and reliability of HADS and Structured Clinical Interview for DSM Disorders (SCID) in detecting emotional distress in women with breast cancer. For MDD the, area under the curve/AUC (total) was 0.77, AUC (depression) was 0.79 and AUC (anxiety) was 0.72. For Anxiety Disorders (ADs), the AUC (total) was 0.74, AUC (depression) was 0.74 and AUC (anxiety) was 0.70. When compared with SCID, the percentage of cases identified by HADS was 28% for MDD and 22% for ADs.[111, level III]

Thomas et al. conducted a survey looking at the validity and reliability of HADS (n=242) and Cronbach alpha for the depression subscale was 0.81, for the anxiety subscale was 0.71 and total HADS was 0.85.[112, level III]

A recent survey (n=227) compared Beck Depression Inventory Scale Short Form (BDI-SF) and the HADS in screening for depression in women with advanced metastatic breast cancer. Results showed, using a cut-off of 4, the BDI-SF had a sensitivity of 0.84, specificity of 0.63 and PPV of 0.52. But based on a cut-off of 11 on the HADs, the sensitivity was 0.16, specificity 0.97 and PPV 0.75.[113, level III]

RECOMMENDATION
Women diagnosed with breast cancer should be screened for emotional distress. **(Grade C)**
Validated self-assessment psychological tests such as Hospital Anxiety and Depression Scale, administered by a trained personnel may be used to screen for emotional distress at the time of diagnosis. **(Grade C)**

8.2 Cognitive Behaviour Therapy

Women with breast cancer cope with distress differently. However, a significant number of women fail to use effective coping strategies in dealing with the challenges of living with breast cancer. Research has found that individual therapy, such as Cognitive Behaviour Therapy (CBT), has been found to be useful in helping women to utilise effective coping strategies in dealing with their breast cancer.

SIGN guidelines recommended that CBT should be offered in groups or individual format to selected breast cancer patients with anxiety and depressive disorders. It should be also offered to those with localised, loco-regional and advanced stages of cancer.[109]

A meta-analysis based on 56 RCTs looked at the moderators of different psychosocial interventions for breast cancer patients. CBT led by psychologists was more effective in individual settings compared to group settings ($p < 0.05$). CBT was also found to be more effective after surgery or months after initial diagnosis than during medical treatment ($p < 0.01$).[114, level I]

An evaluation of a group CBT for women suffering from menopausal symptoms following breast cancer treatment using a single group with pre- and post-treatment assessment showed that scores in depressed mood, anxiety and sleep (WHOQOL) significantly improved, as did aspects of quality of life (SF 36) such as emotional role and limitation, energy and vitality, and mental health. Participants also reported significant reduction in hot flushes and night sweats following treatment (38% reduction in frequency and 49% in problem rating) at 6 weeks. Improvements were even maintained at three months follow up.[115, level III]

RECOMMENDATION
Cognitive behaviour therapy should be offered by trained personnel to women with breast cancers in an individual context, across all stages of disease, particularly for the emotionally vulnerable groups identified by the prior assessment of distress. **(Grade B)**
Cognitive behaviour therapy should be offered preferably right after diagnosis/surgery or months after diagnosis but not during medical treatment. **(Grade C)**

8.3 Psychosocial Support

Social support, whether tangible, informational or emotional, is essential for women to adjust to life with breast cancer. Support provided has to gear for the women's needs. Research has indicated that women who receive quality support have improved physical and emotional outcomes.

According to SIGN, group psychosocial interventions should be offered to women who feel it would suit their needs while supportive expressive therapy should be offered to women with advanced breast cancer.[109]

A RCT (n=227) was conducted to identify the effects of supportive expressive group therapy (SEGT) for women with metastatic breast cancer on survival and psychosocial outcomes. Ppatients were randomised to either intervention (SEGT and relaxation therapy, n=147) or relaxation only therapy (n=80). SEGT did not improve survival (median survival 24 mths in SEGT vs 18.3 in controls; univariate HR for death=0.92, 95% CI, 0.69 to 1.26. However, SEGT ameliorated and prevented new DSM-IV depressive disorders (p=0.002), reduced hopeless-helplessness (p=0.004), trauma symptoms (p=0.004) and improved social functioning.[116, level I]

Two hundred and twenty seven women who were surgically treated for regional breast cancer and waited for adjuvant therapy were recruited in a RCT. These women were assigned to either a psychological intervention (i.e. small patient groups which included strategies to reduce stress improve mood, alter health behaviours, and maintain adherence to cancer treatment and care) or no intervention. Results showed that total mood disturbance significantly decreased more in the intervention arm for patients with high initial cancer stress (F=4.13, $p < 0.05$) and similarly for anxiety (F=4.15, $p < 0.05$) and fatigue (F=5.14, $p < 0.05$). The patients in intervention arm also improved in overall dietary habits (F=5.01, $p < 0.05$) and decreased their smoking behaviour (F=4.52, $p < 0.05$). Results also showed significant improvement in immune responses in the intervention group ($p < 0.05$).[117, level I]

A quasi experimental study was conducted to assess the effectiveness of hospital support group. In this study, 94 who attended the support group were compared to those who declined (n=71). Results showed a significant difference in anxiety and depression between the groups ($p < 0.001$) and that participants in intervention group continued to have less anxiety at 12 months (OR=2.5, CI 95% 1.56. to 5.51).[118, level II-1]

A SR (n=13 RCTs) looked at the effects of psychosocial interventions on the quality of life of patients with advanced breast cancer. All trials used a randomisation procedure to allocate the psychosocial intervention. Out of 13 trials, 12 showed positive effects on one or more indicators of quality of life (QoL).[119, level I]

Arving et al. conducted a RCT comparing the effectiveness of psychosocial support provided by oncology nurses specially trained in psychological techniques, individual psychologists and standard care on quality of life, emotional well-being and life events among breast cancer patients. Consecutive patients with breast cancer (n=425) were considered. A total of 179 (62%) patients were randomised in blocks of nine into one of three groups and assessed at baseline: (a) individual nurse support [INS] (n=60), (b) Individual Psychosocial support [IPS] (n=60) or (c) standard care [SC] (n=59). Results showed the following: at 6 months follow up, systemic therapy side effects increased significantly in the IPS and SC groups but not the INS group ($p < 0.001$); more patients in the INS and IPS groups improved clinically significantly from in anxiety ($p < 0.01$), depression ($p < 0.05$) and in intrusion thoughts ($p < 0.001$). It was concluded that psychosocial support using techniques derived from cognitive behavioural therapy, such as relaxation and distraction, activity scheduling and ways to improve communication, was beneficial for breast cancer patients and that psychosocial support can be provided both by specially trained oncology nurses and psychologists.[120, level I]

RECOMMENDATION

Psychosocial support should be provided by trained personnel for women with breast cancer, particularly to those with high initial emotional distress. **(Grade A)**

8.4 Breast Care Nurse (BCN)

The role of a BCN is to provide treatment and management information and psychosocial support from the time of diagnosis and throughout women's treatment journey.

NICE guidelines suggested that adding the services of an advanced practice care nurse to standard care significantly reduced uncertainty, complexity, inconsistency and unpredictability without influencing quality of life or mood. Support from a BCN following cancer surgery alleviated depression over time but made no significant difference to anxiety. However, receiving support from the breast care nurse specialist before and after receiving a pre-surgical diagnosis significantly lowered clinically-relevant anxiety when measured two weeks after surgery regardless of eventual diagnosis. Evidence also showed that psycho-educational intervention, delivered by a BCN to women with breast cancer after primary treatment was effective thus providing a 'safe passage' from treatment to survivorship.[54]

New Zealand guidelines and the SIGN guidelines recommended that the role of a BCN was vital within the treatment team as it resulted in a reduction in psychological morbidity, improved the continuity of care, information and support for women from diagnosis to follow up and was useful to identify anxiety and depression.[61,109]

SIGN guidelines and Belgian guidelines stated that using a structured approach to psychological care allowed breast care nurse specialists to improve the continuity of care information and support the women receive from the time of diagnosis until follow up. All women with potential or known diagnosis of breast cancer should have access to a breast care nurse specialist for information and support at every stage of diagnosis and treatment. The BCN should have appropriate education and experience.[55,109]

An observational study that used a mixed method design with a random sampling (n=51) stated that BCN played an important role in providing relevant and necessary information and offered great support to women with breast cancer and thus improved patient outcomes.[121, level III] Another survey (n=544) found that women who received care from the breast cancer nurse were better informed ($p = 0.001$) and felt better supported compared to who had no breast nurse contact.[122, level III]

In another a retrospective survey by Scwajeer et al. (n = 50), women (93%) benefited from the BCN's intervention in general. Members of the multi-disciplinary team also confirmed the functions of BCN role. They identified the BCN contribution to the continuity of women's care as a major strength especially on the role for psychosocial support and information, a source of expert advice and were found to be helpful in the women's recovery.[123, level III]

RECOMMENDATION

All patients with breast cancer should be assigned to a breast care nurse who will support them throughout the diagnosis, treatment and follow up. **(Grade A)**

8.5 Psycho-education Programmes

Women with breast cancer experience anxiety related to their diagnosis and side-effects of cancer treatment. They need knowledge to cope with their diagnosis of breast cancer. Those who obtain up-to-date information on breast cancer treatments and management have an increased awareness of choices available to manage the disease and gain a sense of control. SIGN guidelines recommended that women with breast cancer should be offered audiotapes or follow up summary letters of important consultations.[109]

Santon et al. assessed the effectiveness of psycho-educational programme in improving physical and emotional well-being among women newly diagnosed with stage I or II breast cancer. The programme consisted of multiple sources of information such as standard printed material (CTL) vs CTL and also peer modelling videotape (VD) vs CTL, VD, psycho-educational counselling and informational workbook (EDU). Findings suggested that a peer-modeling videotape (VD) could accelerate the recovery of energy during the re-entry phase in women treated for breast cancer. A peer–modelling tape (VD) to be used with other psycho-educational programmes on is recommended for women upon their diagnosis of breast cancer.[124, level I]

Effect of the breast cancer educational Intervention (BCEI) studies on overall QoL was studied in 256 women with breast cancer within one year of diagnosis. The educational programme consisted of face to face education (thrice in six months), emotional support via telephone (thrice in six months), follow up education, and support and telephone discussions, written materials and audiotapes. It was found that BCEI was effective in enhancing QOL of women diagnosed with breast cancer.[125, level I]

Yates et al. evaluated the efficacy of a psycho-educational intervention in improving cancer- related fatigue for early stage breast cancer on 109 women using a RCT design. Preparatory education and support had the potential to assist women to cope with cancer-related fatigue.[126, level I]

The effect of a supportive care programme on anxiety level of women with suspected breast cancer during the diagnostic period was conducted using a longitudinal, quasi-experimental design. Findings suggested that a supportive care programme that incorporates informational and emotional support and follow up telephone consultations can decrease anxiety levels of women with suspected breast cancer.[127, level II-1]

Wolf used a focus group interview to explore experiences of women after undergoing breast reconstruction on how their information need could be met. A small sample (eight women) who were randomly selected wanted their decision-making to be guided by surgeon and recommended that the sources of information found to be relevant and helpful which included the surgeon, breast care nurse, photographs, and contact with other patients, written information, a tape of consultation and information videotapes.[128, level III]

One RCT by William and Schreier determined the effectiveness of informational audiotapes on self-care behaviours, state of anxiety and use of self-care behaviours. Findings suggested that informational audiotapes were effective teaching tools and can be an effective means for providing instructions about self-care behaviours and lowering anxiety.[129, level I]

Another RCT evaluated the usefulness of an educational video with regards to the patient's ability to recall and report side-effects of chemotherapy. All participants (n=30) in the intervention group were satisfied with the video and the video group had a higher recall of information (66.7%) compared to those (10%) who preferred discussion with nurse and written information. Findings suggested that the inclusion of a video in chemo education improved retention of information regarding chemo side effects.[130, level I]

Wilmoth et al. did a RCT to describe women's perceptions of the effectiveness of telephone support and educational materials on their adjustment to breast cancer. Participants who received telephone support for one year, in addition to educational materials, reported improvement in their attitudes toward their breast cancer and better relationships with their spouses compared to 38% in the control group.[131, level I]

RECOMMENDATION

Psycho-education programmes such as printed materials (given face to face/taken home), audiotape, peer modelling video tapes, telephone support and/or counselling should be provided for all women upon their diagnosis of breast cancer. **(Grade A)**

8.6 Palliative Care

Palliative care aims to maximise the quality of life in the time remaining for the patient with breast cancer.

Palliative care is an approach that improves the QoL of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems physical, psychosocial or spiritual in nature. Palliative care:

- provides relief from pain and other distressing symptoms
- affirms life and regards dying as a normal process
- intends neither to hasten or postpone death
- integrates the psychological and spiritual aspects of patient care
- offers a support system to help patients live as actively as possible until death
- offers a support system to help the family cope during the patients' illness and in their own bereavement

- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- will enhance quality of life, and may also positively influence the course of illness
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications

Source: WHO Definition of Palliative Care (internet communication 17 Feb 2010) at http://www. who.int/cancer/palliative/definition/en/

A SR was carried out to look at the effectiveness of palliative care or hospice care team. In this review, a meta-regression of 26 studies found slight positive effect (0.1), of palliative and hospice care team (PCHCT) on patient outcomes, independent of team make-up, patient diagnosis, country, or study design. On the other hand, a meta-analysis of 19 studies demonstrated small benefit on patients' pain (OR=0.38, 95% CI 0.23 to 0.64) and other symptoms (OR=0.51, 95% CI 0.30 to 0.88) but a non-significant trend towards benefits for satisfaction and therapeutic interventions. Data regarding home deaths were equivocal. While the meta-synthesis of all studies found wide variations in the type of service delivered by each team, there was no discernible difference in outcomes between city, urban, and rural areas. Evidence of benefit was strongest for home care.[132, level I]

A RCT of 322 patients with advanced cancer found that nurse-led palliative psycho-educational intervention improved quality of life and mood but no differences was seen in symptom intensity. [133, level I]

A multicentre RCT (n= 517) found that inpatient palliative care services improved satisfaction on care ($p = 0.04$) and communication ($p = 0.004$), reduced Intensive Care Unit admission ($p = 0.04$) and lower 6-month net cost savings of $4,855 per patient ($p = 0.001$) but there was no difference in symptom control and survival. There are several possible explanations for the effect of palliative care team on symptom control. First, patients in this study reported relatively low physical symptoms at study enrolment. The mean pain rating on a scale of 1 to 10 was 3.4 suggesting that pain was less than in other reported populations whose symptoms were more severe. Second, the average index hospitalisation length of stay after study enrolment was 4.9 days, a shorter time for the palliative care team to manage complex physical symptoms compared to studies with longer interventions. Finally, this patient population survived for a longer period of time indicating they might be earlier in their disease state than other inpatient palliative care patients.[134, level I]

RECOMMENDATION

The palliative care physician should be involved in management of advanced breast cancer. **(Grade A)**

9. FOLLOW UP

With regard to follow up schedule after treatment of breast cancer, NICE technology review 2002 advised that patients should be followed up in a hospital setting for a minimum of three years.[135, level III] The most recent guidelines did not mention the follow up period. It was concluded that the available studies were unable to indicate an ideal frequency of follow up. However, annual mammography and regular physical examination were recommended.[54]

Even though studies showed that mammography (MMG) had high sensitivity and specificity in detecting recurrent ipsilateral breast cancer and contra-lateral new cancer, but SR of observational studies concluded that routine follow up MMG did not directly improve survival in patients treated for breast cancer. In contrast, a separate meta-analysis concluded that detection of loco-regional or contra-lateral recurrence in asymptomatic patients during follow up or assessed by mammography improved survival compared to late symptomatic detection.[61]

Minimal requirement for regular follow-up of a primary breast cancer is a clinical review every three months for the first year, then six-monthly for five years, then an annual review thereafter.[136]

During follow up, history and physical examination should be carried out. Blood tests and diagnostic imaging have not been found to improve survival or quality of life more than does physical examination for detecting distant metastasis. The patient is also advised to carry out monthly breast self-examination.[137]

RECOMMENDATION

Regular follow up should be scheduled as follows:

- three monthly for the first year
- then six-monthly for five years
- then an annual review thereafter **(Grade C)**

Annual mammography should be offered to all patients with early breast cancer who has undergone treatment to detect recurrence or contra-lateral new breast cancer**. (Grade C)**

10. LIFESTYLE MODIFICATION IN BREAST CANCER SURVIVORS

In the Women's Intervention Nutrition Study (n=2,437), the effect of fat reduction intake in women with resected, early stage breast cancer receiving conventional cancer management was studied. Dietary fat intake at 12 months was significantly lower ($p <$ 0.001) in the intervention group with intake of 33.3 g/day (95% CI 32.2 to 34.5) vs 51.3 (95% CI 50.0 to 52.7) in the control group. A total of 277 relapse events (local, regional, distant, or ipsilateral breast cancer recurrence or new contralateral breast cancer) had been reported (9.8% of the intervention versus 12.4% of control group). The HR of relapse events was 0.76 in favour of the intervention group (95% CI 0.60 to 0.98). The author concluded that a lifestyle intervention of reducing dietary fat intake, with modest influence on body weight, may improve relapse free survival of breast cancer patients.[55]

The Women's Healthy Eating and Living (WHEL) RCT (n=3109) examined whether an increase in vegetable, fruit and fiber intake and a decrease in dietary fat intake reduced the risk of recurrent and new primary breast cancer and all causes mortality in women with previously treated early stage breast cancer. Over the mean 7.3-year follow-up, 16.7% women in the intervention group versus 16.9% in the comparison group experienced an invasive breast cancer event (adjusted HR=0.96; 95% CI 0.80 to 1.14). On the other hand, 10.1% in intervention group vs 10.3% in the control group died (adjusted HR=0.91, 95% CI 0.72 to 1.15). The DFS curves were virtually identical across groups. The study concluded that the adoption of a diet that was very high in vegetables, fruit and fiber, and low in fat did not reduce additional breast cancer events or mortality.[138, level I]

In a cohort study (n=3,846) examining whether high intake of animal fat was associated with increased breast cancer mortality and high intake of fibre was associated with decreased breast cancer mortality showed that in simple models adjusted for time since diagnosis, age, and energy intake, animal fat intake was associated with increased breast cancer death, while cereal fibre intake was associated with reduced breast cancer death. However, no association were found in fully adjusted models: the RR for increasing quintiles for animal fat was 1.00, 0.89, 0.86, 0.85, and 0.89 (95% CI 0.61 to1.28) while for cereal fibre, they were 1.00, 0.95, 0.76, 0.81, and 1.00 (95% CI 0.71 to 1.40). Results of simple models adjusted for physical activity were similar to those for full multivariate models. They showed that physical activity decreased the risk of death from breast cancer ($p < 0.001$).[139, level II-2]

RECOMMENDATION

Diet high in fibre and low in fat together with physical activity should be advised in women with breast cancer**. (Grade B)**

11. FAMILIAL BREAST CANCER

11.1 Genetic Counselling for Inherited Risk to Hereditary Breast and Ovarian Cancer

There are no population-based RCTs of risk assessment and genetic testing using the outcomes of incidence of breast and ovarian cancer or cause-specific mortality.

The USPSTF found good evidence that genetic counselling and genetic testing services improved important health outcomes and concluded that benefits substantially outweigh harms.[140]

Frank et al. examined the results for BRCA1 and BRCA2 genetic testing of > 10,000 women in USA and found that specific features of personal and family history could be used to assess the likelihood of identifying a mutation in BRCA1 or BRCA2 in individuals tested in a clinical setting. [141, level III] This is supported by Mann et al. who examined the results of BRCA1 and BRCA2 genetic testing of 822 families in Australia and found similar features could be used to assess the likelihood of identifying mutation carriers.[142, level III]

Thirthagiri et al. examined the results of BRCA1 and BRCA2 genetic testing of 187 individuals in Malaysia and found similar features can be used to assess the likelihood of mutation carriers in Asians but reported that existing risk prediction models underestimated the number of carriers in Asian cohorts.[143, level III]

As a result of the medical, legal and ethical implications of genetic testing, all genetic testing should be accompanied by appropriate pre- and post-genetic counselling which should be provided by suitably trained personnel.

There is currently no evidence to support the use of genetic testing of other genes or genetic loci in routine clinical practice.

RECOMMENDATION

Women whose family history is associated with an increased risk for deleterious mutations in BRCA1, BRCA2 or TP53 genes should be referred for genetic counselling and evaluation for genetic testing. This includes individuals with affected blood relatives with any one of the following family history patterns (These individuals should be from the same side of family):

- 2 or more first or second degree relatives on the same side of family with breast or ovarian cancer any age; or
- 2 or more first or second degree relatives on the same side of family with breast cancer, 1 of whom was diagnosed ≤ age 50 years old; or
- 1 first degree relative with breast cancer diagnosed ≤ age 40 years old; or
- 1 first degree relative with both breast and ovarian cancer at any age; or
- 1 first degree relative with bilateral breast cancer at any age; or
- 1 first degree relative with male breast cancer; or
- 2 or more first or second degree relatives on the same side of family with ovarian cancer at any age; or
- Family history of breast cancer in combination with other BRCA-related cancers, such as pancreas, prostate and oesophageal cancers on the same side of family; or
- Family history of early onset breast cancer in combination with other TP53-related cancers such as sarcomas and multiple cases of childhood cancers on the same of family. **(Grade C)**

Genetic counselling or routine breast cancer susceptibility gene testing for women whose personal or family history is not associated with an increased risk for deleterious genetic mutations should not be offered. **(Grade C)**

11.2 Interventions which Reduce the Incidence and Mortality of Breast and Ovarian Cancer in Women Identified as High Risk by Personal or Family History, Positive Genetic Test Results or Both

There is strong evidence that individuals with significant family history or pathogenic mutations in BRCA1 or BRCA2 have a significantly higher risk of breast and other related cancers.[144, level II-3; 145, level II-2]

Individuals with significant family history (see family history criteria in the recommendation 11.1) but with no pathogenic mutations in BRCA1 and BRCA2 remain high risk to familial breast and ovarian cancer and should therefore be offered appropriate counselling and clinical management based on their age and family history.[146, level III]

For individuals with pathogenic BRCA1 and BRCA2 mutations, have an inherited risk of breast, ovarian and a number of related cancers. For BRCA1 mutation carriers, the estimated lifetime risk of breast cancer ranges from 40% to 85%, and the estimated lifetime risk of ovarian cancer ranges from 20% to 65%.[144, level II-3; 145, level II-2] For BRCA2 mutation carriers, the breast cancer risk is similar, but the lifetime risk of ovarian cancer is approximately 20%.[144, level II-3; 145, level II-2] BRCA1 or BRCA2 mutation carriers also have a higher incidence of contralateral breast cancer within the first five years of follow up after the primary breast cancer i.e. 12 - 33% among BRCA1 or BRCA2 mutation carriers or (2.4 - 6.5% per year)[147, level II-3; 148, II-3; 149, level II-3; 150, level II-3; 151, level II-3; 152, level II-3, 153, level II-3] as compared to a 0.4 - 1% per year for breast cancer patients in general.[154, level II-3]

11.3 Intensive Screening

11.3.1 Breast Cancer

Intensive screening for breast cancer in BRCA mutation carriers is recommended by expert groups[155, level III], but there is currently no trial of the effectiveness of intensive screening in reducing mortality. MRI is more sensitive for detecting breast cancers (sensitivity of 77%) than mammography (sensitivity of 36%), ultrasound (sensitivity of 33%) or clinical breast examination alone (sensitivity of 9%).[156, level I; 157, level I]

11.3.2 Ovarian Cancer

Early ovarian cancer is asymptomatic and the available techniques have not been demonstrated to be effective for early diagnosis. Intensive screening for ovarian cancer in BRCA carriers is therefore not supported because of the current limitations in sensitivity and specificity of transvaginal ultrasounds and/or measurement of serum CA125 level.[157, level II-3; 158, level II-3] Risk reducing salpingo-oophorectomy (RRSO) is therefore strongly recommended to BRCA1/2 mutation carriers once childbearing is complete.

11.4. Chemoprevention

11.4.1 Tamoxifen, Raloxifene and Anastrazole

A number of large chemoprevention trials[159, level I;160, level I;161, level I; 162, level I] had shown that tamoxifen and raloxifene significantly reduced the overall risk of breast cancer, but this effect was observed only for oestrogen receptor-positive but not oestrogen receptor-negative tumours. Although the numbers are small, the data also suggested that tamoxifen may reduce the risk for breast cancer for BRCA2 carriers but not for BRCA1 carriers,[163, level II-3] and may also reduce the risk of contralateral breast cancer in BRCA carriers.[164, level II-3] Notably, there is no data on overall mortality benefit and use of tamoxifen associated with several adverse effects, including increased in thromboembolic events, stroke, endometrial cancer and gynaecological problems.[162, level I]

There is currently an ongoing large randomised trial addressing the efficacy of anastrazole in the prevention of breast cancer.[165, level I]

11.4.2 Oral Contraceptives

No RCT of oral contraceptives to prevent breast or ovarian cancer have been published. Although observational studies indicate that oral contraceptives are associated with reduced ovarian cancer in the general population and in BRCA1 and BRCA2 mutation carriers, it may not be associated with an increased risk of breast cancer.[166, level II-2; 167, level II-2; 168, level II-2]

11.4.3 Prophylactic Surgery

No RCT of prophylactic surgery have been conducted as this would not be ethical and therefore, conclusions can only be drawn from cohort studies which have intrinsic bias' that may lead to over- and/or under-estimation of effects.[140, level II-2]

11.4.4 Bilateral Prophylactic Mastectomy

All studies of prophylactic bilateral mastectomy in high risk women are consistent and indicate an 85 - 100% reduction in risk to breast cancer[169, level II-2;148, level II-2;170, level II-2; 171, level II-2; 140, level II-2; 150, level II-2] but there is insufficient evidence that bilateral prophylactic mastectomy (BPM) leads to improved survival. A small number of cohort studies had examined the possible harms associated with BPM and reported that the majority of women were satisfied with the procedure when combined with reconstructive surgery and reported of diminished concerns about breast cancer after BPM.[172, level II-2; 173, level II-2] Notably, a number of studies have reported the presence of occult tumours in up to 4% of at-risk breasts at the time of prophylactic surgery,[169, level II- 2; 174, level II-2] highlighting the need for careful pathological assessment at the time of surgery.

11.4.5 Contralateral Prophylactic Mastectomy

Whilst some studies have shown that BRCA carriers may have an increased risk of ipsilateral breast cancer, this has not been found in other studies. However, the majority of studies of consistently show that BRCA carriers have a higher risk of contralateral breast cancer compared to non-BRCA carriers.[147, level II-2; 148, level II-2; 149, level II-2; 150, level II-2; 151, II-2; 152, level II-2; 153, level II-2] Moreover, the majority of studies of prophylactic contralateral mastectomy in high-risk women are also consistent, indicating an 85 - 100% reduction in risk to breast cancer and increased overall survival.[147, II-2; 148, II-2; 150, II-2] A small number of cohort studies have examined the possible harms associated with contralateral prophylactic mastectomy (CPM) and reported that the majority of women are satisfied with the procedure and reported of diminished concerns about breast cancer after CPM.[175, II-2]

11.4.6 Bilateral Salpingo-oophorectomy

Risk reducing salpingo-oopherectomy (RRSO) remains the most effective risk reduction strategy for the prevention of BRCA1- and BRCA2-associated gynecological cancers. RRSO can lead to reduced risk for ovarian cancer of 85 - 100% and breast cancer of 53 - 68%.[176, level II-2; 177, level II-2; 144, level II-2; 178, level II-2] and at least in one study, bilateral prophylactic salpingo-oophorectomy (BPSO) was associated with an improvement in overall survival.[179, level II-2] Notably, a number of studies have shown that occult cancers occur in up to 6.3% of ovaries and fallopian tubes, and it is therefore recommended that extensive pathologic evaluation is conducted on resected ovaries and fallopian tubes, even when they appear macroscopically normal.[180, level II-2; 181, level II-2; 144, level II-2; 182, level II-2; 183, level II-2] Pre-menopausal high risk women are the most likely to benefit from prophylactic oophorectomy, but also the most likely to experience side effects from surgery, including the loss of fertility, loss of sexual function and increased osteoporosis,[184, level II-2] and therefore prophylactic oophorectomy is advised after completion of childbearing and from the age of 40 years old.

RECOMMENDATION
Appropriate counselling and clinical management should be offered to individual with significant family history but with no pathogenic mutation in BRCA1 and BRCA2 as they remain at high risk to familial breast and ovarian cancer. **(Grade B)**
Screening women with high risk for breast cancer should be done from age of 30 years with both MRI and mammography as it is more effective than mammography alone **(Grade B)**
Risk reducing salpingo-oophorectomy should be offered to BRCA1/BRCA2 mutation carriers once childbearing is complete**. (Grade B)**
Bilateral prophylactic mastectomy should be offered to women with deleterious mutations in BRCA1/BRCA2. **(Grade B)**
Contralateral prophylactic mastectomy may be offered to women with breast cancer who have deleterious mutations in BRCA1/ BRCA2. **(Grade B)**
Individuals with deleterious mutations in BRCA1/BRCA2 should be managed by a multidisciplinary team. **(Grade C)**

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APPENDIXES

APPENDIX 1

SEARCH TERMS

The following free text word or MeSH terms were used either singly or in combination:
alcohol and breast cancer, age AND risk of breast cancer, radiation AND breast cancer, reproductive risk AND breast cancer, hormonal exposure AND breast cancer, obesity AND breast cancer, referral to breast clinic, benign breast disease AND breast cancer risk, benign breast disease AND breast cancer risk, physical activity AND breast cancer, effective method for breast cancer screening among population, "breast self examination" AND "breast cancer screening", "Clinical breast examination" AND "breast cancer screening", breast screening - high risk women MRI, magnetic resonance imaging AND Invasive lobular carcinoma, magnetic resonance imaging in atypical hyperplasia AND invasive lobular carcinoma, breast cancer AND ultrasound AND mammography, breast cancer OR breast disease AND diagnosis, breast cancer AND triple assessment, preoperative MRI AND breast cancer, PET CT AND "breast cancer" AND staging, PET CT AND "breast cancer" AND role, PET CT AND "breast cancer" AND diagnosis, "breast cancer" AND scintigraphy, PET AND PET/CT AND "breast cancer", PET CT, breast cancer, staging breast cancer, "metastatic breast cancer" AND Imaging, breast cancer and staging and CT thorax, breast cancer , staging, staging breast cancer, imaging breast cancer, staging AND "breast cancer", "breast neoplasm" OR "breast carcinoma" OR "breast cancer" AND "fine needle aspiration cytology" AND "core needle biopsy" OR "core biopsy" OR "needle biopsy" AND accuracy, FISH AND CISH, "breast carcinoma" OR "breast cancer" AND "minimum dataset" OR "synoptic report" OR "proforma report" , surgical treatment for early breast cancer, contraindications to breast conservative surgery, breast conserving surgery vs mastectomy, mastectomy vs breast conserving surgery, centrally located breast cancer, breast conserving surgery AND centrally located breast cancer, tumour free margin for breast cancer, sentinel node biopsy AND DCIS, sentinel node biopsy AND DCIS, timing of breast reconstruction, locally advanced breast cancer AND neo-adjuvant chemotherapy, locally advanced breast cancer AND neo-adjuvant chemotherapy, locally advanced breast cancer AND neo-adjuvant therapy, neo-adjuvant chemotherapy response AND breast cancer, surgery in metastatic breast cancer, Hepatic resection, liver metastases, breast cancer, breast neoplasms AND trastuzumab OR lapatinib, -breast neoplasms AND tamoxifen OR aromatase inhibitors, breast neoplasms AND goserelin, breast neoplasms AND tamoxifen OR aromatase inhibitors, radiotherapy, breast neoplasms, radiotherapy, breast neoplasms, "hospital anxiety AND depression scale" AND "breast cancer", CBT AND "breast cancer", "behavioral therapy" OR "cognitive therapy" AND "breast cancer", "psychological assessment" AND "breast cancer", distress AND assessment AND "breast cancer", BDI AND "breast cancer", Valid measures AND "breast cancer", psycho-education intervention And breast cancer, psycho-education materials AND breast cancer, information materials and breast cancer, breast cancer nurse, breast care nurse, breast cancer nurse specialist, breast cancer nurse, palliative care AND quality of life, follow-up schedule for breast cancer, lifestyle modification increase survival rate for breast cancer survivors, "lifestyle modification" AND "survival rate for breast cancer patients", "lifestyle modification" and "increase survival rate", women's healthy eating and living study, "dietary fat reduction" AND "breast cancer outcome"

CLINICAL QUESTIONS

Risk factor

- What are the risk factors of breast cancer?

Screening

- What is the most effective method of screening breast cancer among the general population?
- What is the most effective method of screening for breast cancer among the high risk group?

Referred

- What are the criteria for referral to breast clinic?

Radiology

- What is the diagnostic accuracy of ultrasound and mammography together compared with ultrasound or mammography alone in detecting breast cancer?
- What is the role of triple assessment in the diagnosis of breast cancer?
- What is the role of magnetic resonance imaging of the breast in the pre-operative assessment of patients with biopsy-proven DCIS or invasive breast cancer?
- What is the role of PET or PET/CT in patients with breast cancer?
- What is the recommended imaging modality to investigate the extension of the disease in patients with breast cancer?

Pathology

- In the diagnosis of breast cancer, is FNAC as accurate as core biopsy?
- What is the best method to test for HER-2 over expression in patients with breast cancer?
- What are the elements of an adequate pathology report for breast cancer?

Surgical Management

- What is the appropriate surgical management for women with early breast cancer?
- What are the contraindications to breast conserving surgery (BCS)? Is BCS amenable for centrally located tumour?
- What is the adequate tumour free margin in breast conserving surgery?
- What is the role of axillary surgery in early breast cancer? What are the indications for sentinel lymph node biopsy in breast cancer?

- Does the timing of breast reconstructive surgery alter the local recurrence rate and overall survival?
- What is the role of neoadjuvant chemotherapy in locally advanced breast cancer? Which subgroup will response better with neoadjuvant chemotherapy?
- What is the role of surgery for the primary tumour in metastatic breast cancer?
- Does removal of metastatic disease improve overall survival?

Oncology

- What are the indications and benefits of taxane-based regimens versus anthracycline- based regimens in early breast cancer?

- What are the indications and survival benefits for anti-HER-2 treatment in early or locally advanced breast cancer?
- In patients with early invasive breast cancer and DCIS, what is the effectiveness of endocrine therapy?
- In pre-menopausal breast cancer patients, what is the role of ovarian suppression or ovarian ablation?
- In post-menopausal breast cancer patients, what are the benefits of aromatase inhibitors versus tamoxifen in the adjuvant, neo-adjuvant and advanced setting?
- In patients who had mastectomy, does radiotherapy to the chest wall reduce the risk of local recurrence and improve overall survival?
- In patients who have had BCS, does radiotherapy to the breast reduce the risk of local recurrence and improve overall survival?

Psychology Support

- What assessments have been shown to be useful in identifying emotional and mental health status of women diagnosed with breast cancer?
- Is cognitive behaviour therapy (CBT) effective in improving emotional well-being and quality of life among women diagnosed with breast cancer?
- How effective is psychosocial support (such as supportive group therapy) and psycho-education materials in improving the well being and quality of life of women with breast cancer and their families, and to cope with their disease?
- How effective are psychoeducation materials in assisting breast cancer patients to cope with their diagnosed breast cancer?
- What is the role of breast cancer nurse specialist?
- What is the effect of palliative care compared to standard care in quality of life of cancer patients?

Follow Up

- What is the follow up schedule and procedures after treatment of breast cancer?
- Does lifestyle modification increase survival rate of breast cancer survivors?

Familial Breast Cancer

- Who should be offered genetic counselling for inherited risk to hereditary breast and ovarian cancer?
- Management of risk i.e. mastectomy, surveillance and chemoprevention in three groups of women: (a) affected BRCA carriers, (b) unaffected BRCA carriers and (c) high risk but no mutations in BRCA1 and BRCA2?

AJCC STAGING (TNM CLASSIFICATION) 7TH EDITION

Primary Tumour (T)		
The T classification of the primary tumour is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimetre. If the tumour size is slightly less than or greater than a cut-off for a given T classification, it is recommended that the size be rounded to the millimetre reading that is closest to the cut-off. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements respectively. In general, pathologic determination should take precedence over clinical determination of T size.		
TX	Primary tumour cannot be assessed	
T0	No evidence of primary tumour	
Tis	Carcinoma in situ	
	Tis (DCIS)	Ductal carcinoma in situ
	Tis (LCIS)	Lobular carcinoma in situ
	Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorised based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumour ≤ 20 mm in greatest dimension	
	T1mi	Tumour ≤ 1 mm in greatest dimension
	T1a	Tumour > 1 mm but ≤ 5 mm in greatest dimension
	T1b	Tumour > 5 mm but ≤ 10 mm in greatest dimension
	T1c	Tumour > 10 mm but ≤ 20 mm in greatest dimension
T2	Tumour > 20 mm but ≤ 50 mm in greatest dimension	
T3	Tumour > 50 mm in greatest dimension	
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)	
Note: Invasion of the dermis alone does not qualify as T4		
	T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
	T4b	Ulceration and/or ipsilateral satellite nodules and/or oedema (including peaud'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
	T4c	Both T4a and T4b
	T4d	Inflammatory carcinoma (see "Rules for Classification")

Regional Lymph Nodes (N)		
Clinical		
NX	Regional lymph nodes cannot be assessed (e.g. previously removed)	
N0	No regional lymph node metastases	
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)	
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected * ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases	
	N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
	N2b	Metastases only in clinically detected * ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected * ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	
	N3a	Metastases in ipsilateral infraclavicular lymph node(s)
	N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
	N3c	Metastases in ipsilateral supraclavicular lymph node(s)

* Note: Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine needle

Pathologic (pN)*	
pNX	Regional lymph nodes cannot be assessed (e.g. previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
Note: Isolated tumour cell clusters (ITC) are defined as small clusters of cells not greater than 0.2 mm, or single tumour cells, or a cluster of fewer than 200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by immunohistochemical (IHC) methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.	
pN0(i–)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm (detected by H&E or IHC including ITC)
pN0(mol–)	No regional lymph node metastases histologically, negative molecular findings RT-PCR)
pN0 (mol+)	Positive molecular findings (RT-PCR), ** but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases; or metastases in 1 - 3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected ***
pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
pN1a	Metastases in 1 - 3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
pN1b	Metastases in internal mammary nodes with micro-metastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected ***
pN1c	Metastases in 1 - 3 axillary lymph nodes and in internal mammary lymph nodes with micro-metastases or macro-metastases detected by sentinel lymph node biopsy but not clinically detected
pN2	Metastases in 4 - 9 axillary lymph nodes; or in clinically detected **** internal mammary lymph nodes in the absence of axillary lymph node metastases
pN2a	Metastases in 4 - 9 axillary lymph nodes (at least one tumour deposit greater than 2.0 mm)
pN2b	Metastases in clinically detected **** internal mammary lymph nodes in the absence of axillary lymph node metastases

pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected **** ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micro-metastases or macro-metastases detected by sentinel lymph node biopsy but not clinically detected *** ; or in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ten or more axillary lymph nodes (at least one tumour deposit greater than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected **** ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micro-metastases or macro-metastases detected by sentinel lymph node biopsy but not clinically detected ***
pN3c	Metastases in ipsilateral supraclavicular lymph nodes
Notes: * Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn)	
** RT-PCR: reverse transcriptase/polymerase chain reaction	
*** "Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination	
**** "Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macro-metastasis based on fine needle aspiration biopsy with cytologic examination	

Distant Metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumour cells in circulating blood, bone marrow, or other non-regional nodal tissue that are no larger than 0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm

ANATOMIC STAGE/PROGNOSTIC GROUPS			
Stage 0	Tis	N0	M0
Stage IA	T1*	N0	M0
Stage IB	T0	N1mi	M0
	T1 *	N1mi	M0
Stage IIA	T0	N1**	M0
	T1 *	N1 **	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1 *	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

APPENDIX 4

MINIMUM DATASET FOR THE HISTOPATHOLOGY REPORTING OF BREAST CANCER

Patient Name:.....

Registration Number:.....Laboratory Number: .....

Complete histopathological diagnosis: .....

Specimen: .....

* Tumour Location: .....

* Size: Invasive cancer: .....

* Tumour type: .....

* Histological Grade: .....

Tubule formation (score): .....

Nuclear grade (score): .....

Mitoses (score): .....

* DCIS in Specimen: Present / Absent

DCIS grade: .....

Percentage of DCIS in tumour: .....

DCIS in adjacent breast tissue: .....

* Resection margins involved: ☐ YES (DCIS/ Invasive) ☐ NO

Orientation of involved margin: .....

Distance of margin from tumour (mm): .....

* Calcification: ☐ Present ☐ Absent

* Lymphovascular invasion: .....

* Non-neoplastic breast : .....

* Hormone receptor status

*Estrogen receptors: Positive / Negative

Percentage of nuclei stained: .....

Intensity of staining : .....

* Progesterone receptors: ☐ positive ☐ negative

Percentage of nuclei stained: .....

Intensity of staining: .....

* HER-2 assessment: .....

Others: Please specify: .....

.....

* Axillary lymph node metastasis: ☐ Present ☐ Absent

Number of nodes involved / nodes examined: ..... / .....

Extracapsular lymph node involvement: .....

Micrometastasis: .....

LIST OF ABBREVIATIONS

ACS	American cancer society
ALND	Axillary lymph node dissection
ASR	Age-standardized incidence rate
AUC	Area under the curve
AUS	Axillary ultrasonography
BCEI	Breast cancer educational intervention
BCN	Breast care nurse
BCS	Breast conserving surgery
BDI-SF	Beck depression inventory short form
BI-RADS	Breast imaging-reporting and data system
BPM	Bilateral prophylactic mastectomy
BPSO	Bilateral prophylactic salpingo-oophorectomy
BRCA	Breast cancer gene mutation
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
BSE	Breast self examination
CB	Core biopsy
CBE	Clinical breast examination
CBT	Cognitive behaviour therapy
CI	Confidence interval
CISH	Chromogenic in-situ hybridisation
CMF	Cyclophosphamide, methotrexate and fluorouracil
CNB	Core needle biopsy
CPM	Contralateral prophylactic mastectomy
CT	Computerised tomography
DCIS	Ductal carcinoma in situ
DFS	Disease free survival
EBCTCG	Early breast cancer trialists collaborative group
ER/PR	Estrogen-receptor/progesterone receptor
FDG-PET	Fluorodeoxyglucose-positron emission tomography
FEC	5-fluorouracil, epirubicin, and cyclophosphamide
FISH	Fluorescent in-situ hybridisation
FNAC	Fine needle aspiration cytology
H&E	Standard haematoxylin and eosin

HADS	Hospital anxiety and depression scale
HER-2	Human epidermal growth factor receptor 2
HERA	Herceptin Adjuvant
IDC	Invasive ductal carcinoma
IHC	Immunohistochemistry
ILC	Invasive lobular carcinoma
INS	Individual nurse support
IPS	Individual psychosocial support
LABC	Locally advanced breast cancer
LAR	Lifetime attributable risk
LCIS	Lobular carcinoma in situ
LHRH	Luteinising-hormone-releasing hormone
LAR	Lifetime attributable risk
MDD	Major depressive disorders
MMG	Mammography
MRI	Magnetic resonance imaging
OS	Overall survival
PCHCT	Palliative and hospice care team
pCR	Polymerase chain reaction
PET/CT	Positron emission tomography/computerised tomography
PPV	Positive predictive value
QoL	Quality of life
RCT	Randomised control trial
RR	Relative risk
RRSO	Risk reducing salpingo-oopherectomy
SBE	Self breast examination
SCID	Structured clinical interview for DSM disorders
SEGT	Supportive expressive therapy
SISH	Silver-enhanced in-situ hybridisation
SLNB	Sentinel lymph node biopsy
SR	Systematic review
TRAM	Transverse rectus abdominis myocutaneous
USPTF	US Preventive Task Force
WHEL	Women's healthy eating and living
WHR	Waist hip ratio

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LEVELS OF EVIDENCE SCALE

LEVEL	STUDY DESIGN
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grade of recommendation relates to the strength of the evidence on which the recommendations are based. It does not reflect the clinical importance of the recommendations