MINISTRY OF HEALTH
MANATŪ HAUORA

Management of Early Breast Cancer

New Zealand GUIDELINES GROUP
Te Rōpū Rarangi Tohutohu
Promoting Effective Health and Disability Services

Evidence-based
Best Practice
Guideline

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Funding and independence

This guideline was funded by the Ministry of Health. The development of the guideline was researched and written by NZGG employees or contractors. Appraisal of the evidence, formulation of recommendations and reporting are independent of the Ministry of Health.

Statement of intent

NZGG produces evidence-based best practice guidelines to help health care practitioners, policy-makers and consumers make decisions about health care in specific clinical circumstances. The evidence is developed from systematic reviews of international literature and placed within the New Zealand context.

While NZGG guidelines represent a statement of best practice based on the latest available evidence (at the time of publishing), they are not intended to replace the health practitioner's judgment in each individual case.

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Cover concept: The cover image of pounamu, inspired by the whakataukī, has been chosen for its traditional reference to inner peace, the highest form of beauty.

The Mangopare design incorporates both the koru (a symbol of the continuity of life) and the hammerhead shark (a symbol of strength and tenacity).

Pounamu carved by: Ric Moor, Rapahoe.

Copies of the guideline and summary are available online at www.nzgg.org.nz – click on 'Publications' then 'Guidelines and Reports' then 'Cancer' – or through Wickliffe on (04) 496 2277. Order No: HP: 4809 (guideline).

He tatau pounamu, e kore e ngaro

Inner peace and beauty (the door of greenstone), is never lost

Endorsements

The following organisations have endorsed the content of this guideline:

ROYAL AUSTRALASIAN
COLLEGE OF SURGEONS

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About the guideline

Purpose

The purpose of this guideline is to provide an evidence-based summary of best practice in the management of early breast cancer in order to promote best clinical practice in relation to the care and management of women with early breast cancer. The recommendations are based on clinical effectiveness and other considerations (including quality of life), but not on an analysis of cost effectiveness or quality of life years gained.

The need for the guideline

The New Zealand Cancer Control Strategy Action Plan 2005–2010 identified the development of guidelines for cancer as an essential step in achieving national consistency and quality in cancer services.[1] The establishment of a programme for the ongoing development of formal guidelines for cancer care was specified in this plan.[1] This guideline was commissioned by the Ministry of Health to meet this identified need.

In 2005, breast cancer was the most common site of cancer registration for women, with an age-standardised rate of 92 cases per 100,000 females. Breast cancer was also the leading cause of cancer death among New Zealand women (647 deaths, 17.1% of female cancer deaths), with an age-standardised mortality rate of 21.7 per 100,000 females.[2] Internationally, New Zealand has high breast cancer incidence and mortality.[3] Compared with other Organisation for Economic Co-operation and Development (OECD) countries, New Zealand has the sixth highest death rate for female breast cancer.[3]

This guideline has been developed to ensure practitioners are aware of and implement optimal evidence-based treatments.

Scope of the guideline

The guideline covers the period from a person's diagnosis through to treatment for early breast cancer, and includes recommendations for follow-up. The guideline specifically addresses the management of women with ductal carcinoma in situ and invasive adenocarcinoma of the breast of clinical stages I, II and IIIA. Men with stage I, II and IIIA breast cancer are also included. Appendix A provides further details of clinical staging for reference. Please note that while this guideline has used the term 'women' in its recommendations, individual clinical judgments should be utilised to determine where a recommendation applies to men.

It should be noted that the management of women with more advanced breast cancer is beyond the scope of the guideline, so has been excluded. The evidence for breast cancer screening and diagnosis investigations and for the effectiveness of granulocyte colony-stimulating factor (G-CSF) were also beyond the scope of this guideline. Furthermore, the guideline does not cover all clinical scenarios or medical emergencies.

The Guideline Development Team (GDT) recommends that monitoring adherence to the guideline recommendations should occur as part of the implementation process.

Target audience

The guideline is intended primarily for the providers of care for women with early breast cancer. It is also expected that the guideline will have implications for health service provider organisations and funders, and may be accessed by women with early breast cancer.

The New Zealand Guidelines Group (NZGG) is committed to involving consumers in the development of all NZGG guidelines. Consumers are a part of the GDT, helping to determine the clinical questions to be included in the guideline, reviewing the evidence and forming the guideline recommendations.

Treaty of Waitangi

NZGG acknowledges the importance of the Treaty of Waitangi to New Zealand, and considers the Treaty principles of partnership, participation and protection as central to improving Māori health. As part of its commitment to the Treaty, NZGG explicitly involves Māori consumers and health care practitioners in all its work. Māori health needs and outcomes should be considered and explicitly addressed throughout the guideline process.

NZGG's commitment to improving Māori health outcomes means we work as an organisation to identify and address Māori health issues relevant to each guideline. In addition, NZGG works to ensure Māori participation is a key part of the guideline development process. It is important to differentiate between involving Māori in the guideline development process (the aim of which is to encourage participation and partnership), and specifically considering Māori health issues pertinent to that guideline topic at all stages of the guideline development process. Although Māori participation in guideline development aims to ensure the consideration of Māori health issues by the guideline team, this is no guarantee of such an output; the entrenched barriers Māori may encounter when involved in the health care system (in this case guideline development) need to be addressed. NZGG attempts to challenge such barriers by specifically identifying points in the guideline development process where Māori health must be considered and addressed. In addition, it is expected that Māori health is considered at all points in the guideline in a less explicit manner.

Guideline development process

NZGG follows specific structured processes for guideline development. A general description of these processes in relation to this guideline is in this section, with further details outlined in Chapter 11, *General section: methods* and the NZGG *Handbook for the preparation of explicit evidence-based guidelines*.[4]

In brief, NZGG convened the multidisciplinary GDT comprising members nominated by a diverse range of stakeholder groups. Five, one- or two-day, face-to-face meetings of the full GDT were held, where evidence was reviewed, based on 44 clinical questions, and recommendations were developed. The 44 clinical questions relate to those key areas about which the GDT believed practitioners required practical guidance to improve outcomes for patients. The questions were used to inform the search of the published evidence, from which the GDT derived systematic evidenced-based statements for best practice. The different types of evidence appraised included, but was not limited to, existing guideline research, systematic reviews and randomised controlled trials.

Full methodological details are in Chapter 11, *General section: methods*. This chapter also includes details of the GDT and lists the organisations that provided feedback during public consultation on the guideline.

Summary

Key messages

- As Māori and Pacific peoples often cite communication with health care providers as a barrier to care, practitioners should provide information to Māori and Pacific peoples, preferably face-to-face and supported with appropriate written information
- It is important to provide timely and appropriate information, tailored for the individual woman at all stages of the cancer journey using a variety of formats if required
- Women should be made aware that the degree of benefit varies according to prognostic factors and the absolute benefit of therapy, and that this should be weighed against the side effects of treatment, both prior to therapy, and while treatment is ongoing
- All women with early breast cancer should have their case discussed at a multidisciplinary team meeting
- Workforce development, especially of Māori and Pacific health care practitioners is a priority
- Where available, women should be given the opportunity to participate in high quality clinical trials
- Women should receive treatment, where possible, within specified timeframes to optimise the effectiveness of treatment
- Some treatment options are dependent upon a woman's menopausal status
- Some treatments are dependent upon the expression of target receptors by a woman's breast cancer (hormone receptor or HER2 status)

Summary of recommendations

This is a summary of the recommendations developed by the Guideline Development Team (GDT). The recommendations are grouped under headings and subheadings which correspond to individual chapters and sections within the chapter. Some recommendations appear in more than one section for completeness. Good practice points developed by the GDT can be found in the relevant section of each chapter in the main body of the guideline. Further details of the clinical questions the GDT asked about treatment effectiveness, recommendation grading and other methodology can be found in Chapter 11, *General section: methods*.

Grading of recommendations

The New Zealand Guidelines Group grades of recommendation are as follows.

Key to recommendations	Grade
The recommendation is supported by good evidence (based on a number of studies that are valid, consistent, applicable and clinically relevant)	A
The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence)	B
The recommendation is supported by international expert opinion	C
The evidence is insufficient, evidence is lacking, of poor quality or opinions conflicting, the balance of benefits and harms cannot be determined	I
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

General principles of care

Communication and information provision

Recommendations

	Grade
Practitioners should give a woman with early breast cancer information about her diagnosis, treatment options (including risks and benefits) and support services	C
Information should be tailored to each woman's individual situation throughout her cancer journey, including follow-up	C
Practitioners, in consultation with the woman, should determine the level and amount of information that will be most effective in enabling her to understand her condition and treatment options	C

Psychosocial support

Recommendations

	Grade
Psychosocial support should be available to all women with early breast cancer	A
Cognitive behavioural therapy should be available for women with early breast cancer experiencing an anxiety disorder or depression	A

Role of multidisciplinary team

Recommendation

	Grade
All women with early breast cancer should be managed by a multidisciplinary team	A

Considerations for Māori and Pacific peoples

Refer to the relevant good practice points in the chapter.

Staging

Routine staging investigations

Recommendations

	Grade
In asymptomatic women with early operable breast cancer (T1–2, N0–1), routine screening for metastatic disease is not required For women with stage I breast cancer, preoperative chest X-ray is not routinely indicated for staging purposes	A
Bone scintigraphy, liver scans and thoracic imaging should be considered for patients with more advanced but operable disease (T3, N1–2) if it will affect treatment	B
Clinical staging based on history and physical examination should be routinely performed prior to treatment	C

Staging continued...

Use of magnetic resonance imaging

Recommendation

	Grade
Magnetic resonance imaging (MRI) should be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful. These include: Preoperative • Invasive lobular carcinoma • Suspicion of multicentricity • Lesions of the breast (ie, T0N+) not detectable on other clinical or imaging modalities • Genetic high risk • Women with breast implants • Aged younger than 40 years • Assessment following neoadjuvant treatment • Women with dense breasts Postoperative • Diagnosis of recurrence	A

Surgery for early invasive breast cancer

Note: These recommendations apply to early invasive breast cancer. Recommendations for ductal carcinoma in situ are listed separately.

Mastectomy versus breast conserving surgery and radiotherapy

Recommendations

	Grade
All women with early stage invasive breast cancer who are candidates for breast conserving surgery should be offered the choice of breast conserving surgery or mastectomy	A
The choice of surgery should be tailored to the individual, who should be fully informed of the options, and who should be made aware that radiotherapy is required following breast conserving surgery and that further surgery may be required if the margins are positive or close	A
A woman with early stage invasive breast cancer should be informed of the benefits and harms of radiotherapy prior to making a decision regarding breast conserving surgery or mastectomy	A

continued over...

Recommendations continued...

	Grade
Mastectomy rather than breast conserving surgery should be considered if: • 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 • there is multifocal/multicentric disease or extensive malignant microcalcification on mammogram which can not be adequately cleared with an acceptable cosmetic result with breast conserving surgery • there is a contraindication to local radiotherapy (eg, previous radiotherapy at this site, connective tissue disease, severe heart and lung disease, pregnancy) • fitness for surgery is an issue • patient choice	A
Breast conserving surgery can be considered for a woman with a centrally located tumour, although it may require excision of the nipple and areola, which may compromise cosmesis	A

Margins of excision for breast conserving surgery

Recommendations

For invasive breast cancer only	Grade
Breast conserving surgery requires the complete excision of the tumour with clear margins and an acceptable cosmetic result following excision and radiotherapy	C
Detailed pathological assessment of the distance of the invasive carcinoma from all margins should be made	C
A circumferential or radial margin of greater than or equal to 2 mm should be achieved where possible	C
For women with margin widths of less than 2 mm several factors should be considered in determining whether re-excision is required. These include: • age • tumour histology (lymphovascular invasion, grade, extensive in situ component, tumour type eg, lobular carcinoma) • which margin is approximated by tumour (smaller margins may be acceptable for deep and superficial margins) • extent of cancer approaching the margin	C

Surgery for early invasive breast cancer continued...

Quadrantectomy versus lumpectomy

Recommendation

For invasive breast cancer only	Grade
Quadrantectomy is not routinely recommended as breast conserving surgery due to adverse cosmetic results In most cases quadrantectomy is not required to achieve complete excision	B

Management of the axilla

Effectiveness of nodal excision

Recommendations

For invasive breast cancer only	Grade
Assessment of axillary lymph node status should be undertaken for most early invasive breast cancers in order to stage the disease, to minimise the risk of loco-regional recurrence and assist in the planning of adjuvant therapy	A
Axillary node dissection is normally recommended in a woman with clinically involved nodes or breast cancer greater than 3 cm or multifocal disease These criteria and the role of sentinel node-based management in this setting are currently the subject of ongoing clinical trials (SNAC2, and limited data from NSABP B32 and ALMANAC trials)	A
Sentinel lymph node biopsy should be offered as a suitable alternative to axillary dissection in a woman with: • a unifocal tumour of diameter less than or equal to 3 cm; and • a clinically negative axilla, including consideration of imaging findings	B
Women should be informed regarding side effects of axillary node dissection, including seroma formation, altered sensation in the arm, lymphoedema and possible reduced shoulder movement long term	A
Axillary node dissection levels I and II (and level III nodes where indicated) should be undertaken in all women with clinically node-positive disease	A
Due to lack of evidence no recommendations were made for the effectiveness of excising the supraclavicular and internal mammary chain nodes versus no excision	I

Diagnostic accuracy of sentinel lymph node biopsy

Recommendations

	Grade
Sentinel lymph node biopsy should be offered as a suitable alternative to axillary dissection in a woman with: • a unifocal tumour of diameter less than or equal to 3 cm; and • a clinically negative axilla, including consideration of imaging findings	B
A woman should be informed of the potential risks and benefits of the sentinel lymph node biopsy technique and procedure	C
A woman should be informed of the potential for an unsuccessful sentinel lymph node biopsy or a false negative result	C
The team performing the sentinel lymph node biopsy should comprise a surgeon, nuclear physician (where available), pathologist, anaesthetist and appropriate nursing support	C
The surgeon performing sentinel lymph node biopsy should be appropriately trained and experienced in the technique	B
Where possible lymphatic mapping with preoperative lymphoscintigraphy in combination with intraoperative use of the gamma probe and blue dye should be used to locate the sentinel node	B
Where a combination technique for the sentinel lymph node biopsy procedure is unavailable, use of blue dye or radioisotopes alone is appropriate	B
Detailed, definitive histological assessment of the sentinel node is recommended to detect metastatic disease	C
Intraoperative assessment of the sentinel node should be confirmed with a definitive histological assessment to reduce the risk of a false negative result	B
For definitive assessment of a sentinel node (if the initial haematoxylin and eosin-stained section is negative) four sections at 500 microns through each 2 mm slice should be cut and three sections should be stained with haematoxylin and eosin with one randomly chosen section submitted for cytokeratin immunohistochemistry	C

Surgery for early invasive breast cancer continued...

Effectiveness of sentinel lymph node biopsy compared with axillary dissection

Recommendations

	Grade
Sentinel lymph node biopsy should be offered as a suitable alternative to axillary dissection in a woman with: • a unifocal tumour of diameter less than or equal to 3 cm; and • a clinically negative axilla, including consideration of imaging findings	B
A woman should be informed of the potential risks and benefits of the sentinel lymph node biopsy technique and procedure	C
A woman should be informed of the potential of an unsuccessful sentinel lymph node biopsy or a false negative result	C
If the sentinel node is not identified at the time of sentinel lymph node biopsy, axillary dissection should be performed	B
If a positive sentinel node is identified, axillary dissection is recommended with due consideration of the risks and benefits to the individual	B
If a negative sentinel node is identified, clinical follow-up of the axilla is recommended	B
The team performing the sentinel lymph node biopsy should comprise a surgeon, nuclear physician (where available), pathologist, anaesthetist and appropriate nursing support	C
The surgeon performing sentinel lymph node biopsy should be appropriately trained and experienced in the technique	B
Surgeons and anaesthetists should be aware of the possibility of adverse reactions in some patients during the sentinel lymph node biopsy procedure	C
For a woman with a positive non-axillary node (eg, internal mammary, supraclavicular or infraclavicular nodes) radiotherapy to those nodes should be considered	C

Axillary clearance after sentinel lymph node biopsy

Refer to the relevant good practice point in the chapter.

Breast reconstruction

Recommendations

	Grade
A woman being prepared for a mastectomy should be informed of the option of breast reconstruction and, if appropriate, should discuss the option with a surgeon trained in reconstructive techniques prior to the surgery	C
The use of immediate or delayed breast reconstruction is an important means of enhancing body image and self-confidence after mastectomy and both options should be available to women in the public and private sectors in New Zealand	C

Venous access and risk of lymphoedema

Refer to the relevant good practice points in the chapter.

Radiotherapy

Radiotherapy in addition to breast conserving surgery

Recommendation

For invasive breast cancer only	Grade
A woman should be offered radiotherapy following breast conserving surgery for early invasive breast cancer unless there is a particular contraindication	A

Radiotherapy in addition to mastectomy

Recommendations

For invasive breast cancer only	Grade
A woman at high risk of loco-regional recurrence post-mastectomy (ie, 4 or more nodes positive in axilla, tumour size greater than 5 cm, close margins) should have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist, and should receive radiotherapy unless there is a particular contraindication	A
A woman at moderate risk of loco-regional recurrence (1–3 nodes positive in axilla, high grade tumours, lymphovascular invasion or young age) should have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist, and the woman should be referred for a discussion regarding radiotherapy	B
There is no evidence for the routine use of radiotherapy for women at lower risk of local recurrence post-mastectomy. These women should have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist	B

Radiotherapy continued...

Addition of boost dose of radiotherapy to radiotherapy and breast surgery

Breast conserving surgery alone

Recommendations

	Grade
A boost radiotherapy dose should be considered for all women with early invasive breast cancer treated with radiotherapy and breast conserving surgery, in particular: • women younger than 50 years of age	A
Consideration should be given to adverse events (eg, fibrosis) caused by additional radiation when planning treatment	A

Mastectomy alone

Recommendation

	Grade
Due to lack of evidence no recommendations were made for the routine use of boost dose radiotherapy after mastectomy and radiotherapy	I

Fractionation schedules

Partial or accelerated partial versus whole breast radiotherapy

Recommendation

	Grade
Due to a lack of evidence no recommendations were made for the routine use of partial or accelerated partial breast radiotherapy for women following breast conserving surgery	I

Hypofractionated radiotherapy

Recommendation

	Grade
Radiotherapy treatment for early invasive breast cancer should use an accepted regimen such as:	
• 50 Gy in 25 fractions over 5 weeks	A
• 45 Gy in 20 fractions over 5 weeks	B
• 42.5 Gy in 16 fractions over 3.5 weeks for those with small or medium breasts, not requiring boost or nodal radiation	B
• 40 Gy in 15 fractions over 3 weeks*	B

* It should be noted that the data for long-term follow-up in the latter three schedules of this recommendation is still awaited

Nodal irradiation

Recommendations

	Grade
Ipsilateral supraclavicular fossa Radiotherapy to the ipsilateral supraclavicular fossa should be given in a woman who is at high risk (4 or more positive axillary nodes)	B
Axilla Radiotherapy to the axilla should be considered when: • no axillary dissection has occurred • there has been inadequate surgery, although this may add to morbidity • a high number or percentage of nodes are involved, or where there are positive margins or major extra-nodal spread or it is considered likely that residual breast cancer has been left in the axilla	B
Internal mammary chain Radiotherapy to the internal mammary chain should be considered for women who have a positive internal mammary node on sentinel node biopsy Routine use of radiotherapy to the internal mammary chain is not recommended	C

Systemic therapy: chemotherapy regimens

Adjuvant therapy

Refer to the relevant good practice points in the chapter.

Anthracycline-based regimens

Recommendations

	Grade
Anthracycline-based regimens should be considered for adjuvant chemotherapy as they are more effective than standard cyclophosphamide, methotrexate and fluorouracil (CMF) regimens	A
The absolute benefits of anthracycline-based regimens should be balanced against the side effects on an individual basis when planning management	B

Taxane-based regimens

Recommendation

	Grade
Inclusion of a taxane as part of adjuvant chemotherapy should be considered in all cases where chemotherapy is contemplated	A

Trastuzumab-based regimens

Recommendations

	Grade
An improvement in overall survival is confirmed only by trials where the duration of trastuzumab was one year. This duration of treatment is considered the standard of care* and should be offered to all women receiving adjuvant trastuzumab for HER2-positive breast cancer * Based on the current evidence for clinical effectiveness	A
A woman prescribed trastuzumab should have their cardiac function monitored regularly (eg, 3 monthly) using Multi Gated Acquisition (MUGA) scans or echocardiography** **Left Ventricular Ejection Fraction (LVEF) is a good clinical indicator of left ventricular systolic function. Damage to the heart muscle during myocardial infarction or as a result of cardiotoxicity from chemotherapy impairs the heart's ability to eject blood and results in a decreased ejection fraction. The ejection fraction is an important prognostic indicator with a significantly reduced LVEF typically resulting in poorer prognosis	B

Preoperative chemotherapy

Recommendations

	Grade
Preoperative chemotherapy may be considered where a woman with a large breast tumour has a preference for breast conserving surgery	A
Preoperative chemotherapy is recommended for a woman with inflammatory or inoperable locally advanced breast cancer without evidence of systemic spread	A

Systemic therapy: endocrine therapies

Accuracy of oestrogen and progesterone receptor scores

Recommendations

	Grade
Every primary breast carcinoma should be submitted for oestrogen and progesterone receptor assay	C
Pathology reports should formally state both the proportion of positive nuclei and intensity of staining for oestrogen receptor and progesterone receptor to which a simple scoring system (eg, Allred) can be applied	C

Endocrine therapy as an adjunct to chemotherapy

Recommendations

	Grade
In premenopausal women with hormone receptor positive breast cancer, endocrine therapy should be considered	A
In hormone receptor negative breast cancer, endocrine therapy offers no benefit and should be avoided due to the risk of side effects	A
At the time of this review there was no randomised controlled trial evidence to support the use of ovarian function suppression (LHRH agonists or oophorectomy) in conjunction with an aromatase inhibitor in premenopausal women. This is not recommended outside the remit of a clinical trial	A
When both endocrine therapy and chemotherapy are to be administered the chemotherapy should be administered first	C
In women considering oophorectomy a trial of at least one month of a LHRH agonist is recommended to allow an assessment of the tolerability of such treatment before committing to an irreversible procedure	C

Systemic therapy: endocrine therapies continued...

Addition of chemotherapy to endocrine therapy ± surgery ± radiotherapy

Recommendations

	Grade
For a woman with hormone receptor negative breast cancer adjuvant chemotherapy should be considered	A
For a premenopausal woman with hormone receptor positive breast cancer, chemotherapy (including an anthracycline and/or a taxane) followed by tamoxifen should be considered	A
For a postmenopausal woman with hormone receptor positive breast cancer the use of chemotherapy in addition to endocrine therapy should be considered, taking into account the overall benefits and risks of treatment* * Benefits in those aged over 70 years are uncertain	A
When both chemotherapy and endocrine therapy are to be administered the chemotherapy should be administered first	C

Effectiveness of one endocrine therapy over another

Recommendations

	Grade
Oophorectomy is an acceptable treatment option but is associated with high morbidity and long-term adverse effects	A
A LHRH agonist in addition to tamoxifen should be considered for a woman at high risk of recurrence (aged younger than 40 years), who is not postmenopausal (at least 3 months of amenorrhoea) after chemotherapy	B
In a woman considering oophorectomy, a trial of at least one month of a LHRH agonist is recommended to allow an assessment of the tolerability of such treatment before committing to an irreversible procedure	C

Aromatase inhibitors

Recommendations

	Grade
Aromatase inhibitors should form at least part of the treatment regimen when adjuvant endocrine therapy is prescribed to postmenopausal women with hormone receptor positive early breast cancer, unless contraindications to their use exist	A
Adjuvant endocrine therapy for postmenopausal women with hormone receptor positive early breast cancer should comprise treatment for 5 years with either an aromatase inhibitor alone or with a sequence of an aromatase inhibitor and tamoxifen. Women already on tamoxifen for 2–3 years should switch to an aromatase inhibitor	A
Adjuvant endocrine therapy should be given for a duration of at least 5 years	A
The use of tamoxifen alone as adjuvant therapy for postmenopausal women is recommended only when an aromatase inhibitor is contraindicated or has been tried and was not tolerated Tamoxifen for 5 years remains the standard of care in premenopausal women with hormone receptor positive breast cancer	A
Premenopausal women who have completed 5 years of tamoxifen and have become menopausal should be given the option of extended therapy with an aromatase inhibitor	A
Extended (or 'late') use of an aromatase inhibitor after 5 years of tamoxifen is recommended only for those women with hormone receptor positive breast cancer who have completed a 5-year course of tamoxifen and become suitable for treatment with an aromatase inhibitor late in that course (eg, having become reliably menopausal after the time when a switch policy would have been considered)	A
Measurement of oestrogen and gonadotrophin levels is recommended before initiating treatment with an aromatase inhibitor where there is a chance that the woman is still premenopausal Note: Particular care is required for younger women just post chemotherapy or on tamoxifen, as amenorrhoea can occur when normal premenopausal ovarian oestrogen production is present. Tamoxifen leads to elevated gonadotrophin levels even in the presence of normal premenopausal ovarian endocrine function	A
Aromatase inhibitors should be prescribed with caution for women in their forties with chemotherapy-induced premature ovarian failure	B

Systemic therapy: endocrine therapies continued...

Role of adjuvant bisphosphonates

Survival

Recommendation

	Grade
Due to the lack of consistent evidence no recommendations were made regarding use of oral bisphosphonates for the reduction of osseous metastases in early breast cancer	I

Bone density

Recommendations

	Grade
Women who are osteoporotic and on adjuvant endocrine therapy which enhances loss of bone density or who have undergone premature treatment-induced menopause should receive a bisphosphonate	A
Women who are osteopenic and on adjuvant therapy which enhances loss of bone density, or who have undergone premature treatment-induced menopause should be considered for a bisphosphonate, especially in the presence of other risk factors: prior non-traumatic fracture, aged over 65 years, family history, tobacco use, low body weight	C
Postmenopausal women taking aromatase inhibitors are recommended to commence treatment with bisphosphonates if the T-score is <-2.0, or <-1.0 in the presence of a vertebral fracture. Secondary causes of osteoporosis should be excluded and standard lifestyle advice on smoking and exercise, calcium supplementation and adequacy of vitamin D intake should also be provided	C
Women with premature menopause due to chemotherapy, ovarian function suppression or oophorectomy and postmenopausal women receiving adjuvant therapy with an aromatase inhibitor should have bone density monitored at least every 2 years following a baseline DEXA (dual energy X-ray absorptiometry) scan of the spine and hip	C
Frequency of bone mineral density monitoring should be tailored to the individual. If baseline T-score >-1.0 further monitoring of bone density may not be necessary	C
A woman with early breast cancer at risk of bone mineral loss should be provided with appropriate advice for good bone health. This includes, but is not limited to: • a healthy diet • cessation or continuing abstinence from smoking • maintenance of a healthy body mass index • regular exercise • calcium • adequate vitamin D levels	C

Ductal carcinoma in situ

Mastectomy compared with breast conserving surgery: ductal carcinoma in situ

Recommendation

	Grade
When making the choice between breast conserving surgery and mastectomy the following factors should be considered in discussion with the woman: • ratio of the size of the tumour to the size of the breast and tumour location in terms of acceptable cosmesis • the presence of multifocal/multicentric disease or extensive malignant microcalcification on mammogram which cannot be adequately cleared with an acceptable cosmetic result with breast conserving surgery • potential contraindications to local radiotherapy (eg, previous radiotherapy at this site, connective tissue disease, severe heart and lung disease, pregnancy) • fitness for surgery • patient choice	C

Margins of excision for breast conserving surgery: ductal carcinoma in situ

Recommendations

	Grade
Ductal carcinoma in situ (DCIS) extending up to a margin of excision requires further surgery – either wider excision or mastectomy to achieve clear margins in the absence of contraindications	A
Detailed pathological assessment of the distance of the in situ carcinoma from the margins should be made	C
A circumferential or radial margin of greater than or equal to 2 mm should be achieved where possible	C
For women with margin widths of less than 2 mm several factors should be considered in determining whether re-excision is required. These include: • age • size, grade, and the presence or absence of comedo necrosis • which margin is approximated by DCIS (smaller margins may be acceptable for deep and superficial margins as by definition DCIS does not go into muscle or subcutaneous fat) • extent of DCIS approaching the margin	C

Ductal carcinoma in situ continued...

Management of the axilla: ductal carcinoma in situ

Recommendations

	Grade
Axillary dissection should not be performed for women with ductal carcinoma in situ	I
In a woman with a larger volume and higher grade ductal carcinoma in situ or where there is suspicion of invasive disease or for women undergoing mastectomy, sentinel lymph node biopsy to stage the axilla may be considered	B

Radiotherapy in addition to breast conserving surgery: ductal carcinoma in situ

Radiotherapy and breast conserving surgery: ductal carcinoma in situ

Recommendation

For ductal carcinoma in situ only	Grade
A woman who has undergone breast conserving surgery for ductal carcinoma in situ should have their case discussed at a multidisciplinary meeting with a radiation oncologist and/or should be offered consultation with a radiation oncologist	A

Addition of boost dose of radiotherapy to radiotherapy and breast conserving surgery: ductal carcinoma in situ

Recommendation

	Grade
Due to lack of evidence no recommendations were made for the routine use of a boost dose of radiotherapy in women with ductal carcinoma in situ	I

Systemic therapy: endocrine therapies

Refer to the relevant good practice point in the chapter.

Follow-up

Radiological follow-up

Recommendations

	Grade
Regular mammography should be used in order to detect recurrence or new breast cancers at an early stage in patients who have undergone previous treatment for breast cancer	A
A woman should have her first post-treatment mammogram one year after her first diagnostic mammogram or 6 months after radiotherapy, and annually thereafter	A

Clinical follow-up

Recommendations

	Grade
Continuity of care for those with breast cancer is encouraged and should be undertaken by a clinician (eg, breast specialist, breast physician, nurse practitioner) experienced in the surveillance of breast cancer and in breast examination, including the examination of irradiated breasts	B
Continuity of care may be shared with a general practitioner in appropriate circumstances (ie, ready access to specialist support)	C

Special issues

Genetic testing

Recommendations

	Grade
All women from high risk families* should be offered referral to their regional genetics centre for information on genetic testing * Important risk factors include: early onset breast cancer, multiple affected family members, male breast cancer, bilateral breast cancer, ovarian cancer, Ashkenazi Jewish ancestry, or a known BRCA1 or BRCA2 mutation in the family	C
Genetic counselling should be undertaken by a health practitioner with appropriate training (a certified genetic counsellor or medical geneticist)	C
Pre-test genetic counselling should include discussion of the following: • aim of testing, inheritance, accuracy of the test (sensitivity and specificity) • timeframe for providing results • uncertainty of cancer risk estimates with a mutation • possible test results (positive, negative, uninformative or variant of unknown clinical significance) • implications for the individual and family including clinical management options, psychosocial impact of testing, potential risks of discrimination (eg, by life and health insurers); and • alternative options to testing	C
Genetic testing aimed at identifying a mutation in a family should be offered to an affected family member. If a mutation is identified, predictive testing can then be offered to adult at-risk family members	C
Women or men with an estimated probability of 20% or greater of carrying a BRCA1 or BRCA2 mutation (probability estimated by use of models such as BRCAPRO or BOADICEA, and clinical judgment) should have access to genetic testing	C
Interpretation of test results and estimation of cancer risks for the family should take into account pedigree information, the analytical and clinical validity of the test methodology, and the penetrance and nature of the detected mutation	C

Prophylactic treatment

Recommendations

	Grade
A woman with a significant family history of breast cancer or who is known to carry a BRCA1 or BRCA2 gene mutation should be offered the option of prophylactic mastectomy. Prophylactic salpingo-oophorectomy should also be discussed	C
A woman with a significant family history of breast cancer or who is known to carry a BRCA1 or BRCA2 gene mutation should have genetic counselling in a specialist cancer genetics clinic	C
For premenopausal women with a significant family history of breast cancer or who are known to carry a BRCA1 or BRCA2 mutation, information about bilateral salpingo-oophorectomy as a potential risk-reducing strategy for breast cancer should be made available	C
In women considering risk-reducing bilateral salpingo-oophorectomy, the lack of efficacy of screening should be discussed	C

Participation in clinical trials

Refer to the relevant good practice point in the chapter.

Areas in which no recommendations developed

The following areas were subject to general discussion only and no recommendations were developed:

- pregnancy
- use of complementary therapies.

1 Introduction and guideline context

Overview

The guideline begins with a description of the context of breast cancer in New Zealand following a summary that includes all recommendations in the guideline (good practice points are found with the recommendations in specific chapters). The remainder of the guideline is then structured to mirror the clinical journey of the woman with early breast cancer, progressing from chapters on general principles of care and staging to chapters on interventions (including breast surgery, radiotherapy, chemotherapy and endocrine therapy) and follow-up. The treatment of women with a diagnosis of ductal carcinoma in situ is addressed in a separate chapter, and a further chapter addresses additional issues for special consideration that the Guideline Development Team (GDT) identified as of importance. Some of these issues were identified during guideline development after the formal systematic reviews had been conducted and where this is the case the relevant sections are based on non-systematic reviews of the evidence and the expert opinion of the GDT.

The major sections within each chapter reflect specific clinical questions (see Chapter 11, *General section: methods*). Each section includes a summary of the evidence identified that met inclusion criteria and a summary of the findings, and concludes with the recommendations and good practice points developed.

Breast cancer epidemiology

Breast cancer is a significant health issue for New Zealanders and is the leading cause of cancer mortality in New Zealand women. In 2005, breast cancer was the most common site of cancer registration for women (2458 cases, 27.4% of all female registrations), with an age-standardised rate of 92 cases per 100,000 females. Breast cancer was also the leading cause of cancer death among New Zealand women (647 deaths, 17.1% of female cancer deaths), with an age-standardised mortality rate of 21.7 per 100,000 females.[2]

The cumulative survival rate after adjusting for expected causes of death is approximately 82% after five years. Internationally, New Zealand has high breast cancer incidence and mortality.[3] Compared with other Organisation for Economic Co-operation and Development (OECD) countries, New Zealand has the sixth highest death rate for female breast cancer.[3]

While the incidence of both female and male breast cancer is increasing in New Zealand,[5] the female breast cancer mortality rate has reduced by 19% over the last decade, mirroring international trends. This reduction is generally attributed to earlier detection and the greater use and effectiveness of adjuvant treatment.[6]

Ethnic disparities

Ethnic disparities in health care have long been documented in New Zealand[7] and breast cancer mortality is no exception.[8, 9] A study investigating indigenous disparities in New Zealand, Australia, Canada and the United States showed New Zealand age-standardised mortality rates for Māori were 18.9 per 100,000 population compared with 12.9 per 100,000 non-Māori, reflecting a relative risk for Māori women 1.5 times that of non-Māori women. The mortality rates were higher for both groups (Māori and non-Māori) than any other country studied.[10]

Breast cancer is the most common site of cancer with an age-standardised rate of 105.8 per 100,000 females for Māori and 100.3 per 100,000 for Pacific peoples in 2005.[2] The age-standardised mortality rate for Māori was 21.1 per 100,000 females.[2]

Māori women compared with non-Māori women were more likely to be diagnosed with breast cancer and, after diagnosis, were two-thirds more likely to die as a result. This was particularly notable for women younger than 60 years.[11] Māori women were also more likely to be diagnosed at a later disease stage.[12]

Breast cancer was also the leading cause of cancer death in 1996–2000 among Pacific women aged under 65 years. In this period, breast cancer registration rates for Pacific women were similar to that of the total New Zealand population for all ages, but mortality rates were higher.[13] Pacific women experienced an approximate three-fold increase in breast cancer mortality in the 20 years from 1980 until 1999.[14]

Among Asian peoples, registration rates (standardised rate ratios) for breast cancer were significantly higher for Indian and 'Other Asian' women than for Chinese women.[15] In 1998–2002, in women aged 45 years and over, breast cancer mortality rates were significantly lower for Chinese women in New Zealand compared with the rate in the total New Zealand population. Breast cancer registration rates were lower in all three Asian ethnic groups than in the total population in 1997–2001.

Breast cancer control in New Zealand

Cancer control strategies have been developed in several countries in recent years, including Australia, the United States of America, Canada and New Zealand. These strategies aim to decrease the incidence, morbidity and mortality associated with cancer, and promote cancer prevention, access to care and timely treatment. The strategies are designed to provide a systematic and integrated approach to the provision of cancer care services. The New Zealand Cancer Control Strategy aims to provide a high-level framework for reducing the incidence and impact of cancer in New Zealand and reducing inequalities.[16]

The Cancer Control Action Plan outlines actions necessary for achieving the goals and objectives of the Cancer Control Strategy from 2005 to 2010. Specific areas for action included primary prevention, screening, early detection, diagnosis and treatment, rehabilitation and support, and palliative care. The strategy and action plan also address workforce development, research, data collection and analysis.[1]

Breast cancer surveillance in New Zealand

The New Zealand Cancer Registry is a national registry of all new primary malignant cancer cases administered by the New Zealand Health Information Service. The registry includes information on each cancer case (such as site, stage and pathology), as well as demographic information (such as age, gender and ethnicity). This information is gathered from laboratory reports, discharge reports from public and private hospitals, death certificates and autopsy reports.[8, 12] A statutory requirement for cancer laboratories to report to the registry was introduced by the Cancer Registry Act 1993 and came into force under the Cancer Registry Regulations 1994. Enforcement of the Act has contributed to improvements in the quality and completeness of information in the registry.

Between December 1998 and June 2004, the New Zealand breast cancer screening programme – BreastScreen Aotearoa – offered publicly funded mammography to all New Zealand women without symptoms of breast disease aged 50 to 64 years, with the aim of reducing mortality from breast cancer. From 1 July 2004, women aged 45 to 49 years and 65 to 69 years also became eligible for publicly funded mammography. One of the essential requirements of an effective screening programme is that women who have cancers detected subsequently receive optimal treatment. This guideline has been developed to help ensure practitioners are aware of and implement optimal evidence-based treatments.

Risk factors

Women

The complex multifaceted nature of breast cancer is reflected in the number and variety of risk factors that have been identified. The main risk factors for breast cancer are being a woman and increasing age.

Recognised as additional established risk factors for breast cancer are:

- past history of breast cancer[17]
- family history of breast or ovarian or related cancers[18, 19]
- older age at birth of first child[18, 19]
- selected precursor lesions of breast cancer (including atypical ductal hyperplasia, lobular carcinoma in situ and ductal carcinoma in situ)[17]
- increased breast density[17]
- heavy alcohol intake[17]
- nulliparity[17]
- postmenopausal obesity[17] and higher than optimal body mass index[20]
- hormone replacement therapy[17]
- current or recent use of oral contraceptives[17]
- high total energy intake[17]
- radiation exposure
- Jewish ancestry.

A study conducted over 10 years (1988–1997) investigated cancer mortality by occupation among New Zealand women. Higher breast cancer mortality rates were noted in clerical workers, sales workers and teachers.[21]

Genetic factors

A family history of breast cancer and especially in a premenopausal close relative, is a strong risk factor for the development of breast cancer.[22] Although most breast cancers occur in women with no family history, the chance that a woman living in more developed countries will develop the disease increases as the number of affected first-degree relatives increases.[23]

Several heritable genetic mutations associated with increased risk of breast cancer have been discovered. The best known of these are mutations of the BRCA1 and BRCA2 genes, which are associated with an eight- to nine-fold higher risk for breast cancer.[24] However, BRCA1 and BRCA2 mutations explain only 1% to 2% of all breast cancers and have a frequency of only 1 in 1000 women in the general population.

Men

Breast cancer is uncommon in men with an incidence of approximately 1% of that in women.[5] The National Institute of Clinical Excellence cancer referral guidance[18] identified that breast cancer was more common in men over the age of 50 years. Testicular abnormalities (undescended testis, congenital inguinal hernia, orchidectomy, orchitis, testicular injury), infertility, Klinefelter syndrome, positive family history, BRCA gene mutations, benign breast conditions (nipple discharge, breast cysts, breast trauma), radiation exposure and Jewish ancestry were cited as risk factors. The evidence for the significance of any risk factor in the estimation of disease risk in symptomatic men is unknown.[25]

Delay

There is limited published New Zealand data on delays to breast cancer treatment and delays through the treatment process. BreastScreen Aotearoa quality standards stipulate that 90% of women should normally receive their first surgical treatment within 20 working days of receiving their final diagnostic results. BreastScreen Aotearoa patient figures show that this result is being achieved for only 57.7% of Māori women and 71.2% of non-Māori women (personal communication Madeleine Wall, BreastScreen Aotearoa, 23 July 2008).

Urban versus rural residence

Rural centres are perceived as being at a disadvantage in the appropriate management of women with breast cancer compared with inner city hospitals, because of a lack of resources. A 2007 study[26] investigating the effect of urban versus rural residence on stage at diagnosis and survival, found no disparity in breast cancer outcomes for New Zealand women based on location of residence. This study confirmed earlier work showing no regional differences in outcomes for breast cancer patients.[27]

Cultural considerations

Cultural awareness and considerations are important within the New Zealand health care context. Specific issues relevant to Māori and Pacific peoples are discussed in Chapter 2, *General principles of care*.

2 General principles of care

This chapter addresses general principles of care for women with early breast cancer, including:

- communication and information provision
- psychosocial support
- the role of the multidisciplinary team and identified coordinator of care
- considerations for Māori and Pacific peoples.

Introduction

A diagnosis of cancer has a huge impact on the individual and their family/whānau. A patient-centred approach needs to provide for the psychological as well as the physical requirements of the individual, and support their family/whānau.

Communication skills are fundamental to the development of an effective relationship between the woman with early breast cancer and the health practitioner, as is a multidisciplinary approach to care, which ensures that the patient remains the centre of care. Treatment is planned in a timely fashion with input from all relevant disciplines. Information can be provided to the individual with early breast cancer or their family/whānau in a number of ways.

Three clinical questions were developed to assess the best approaches in the areas of psychosocial support, communication and information provision, and multidisciplinary care (see Chapter 11, *General section: methods*), which form the basis of this chapter.

In addition, issues in relation to culturally appropriate care of Māori and other ethnic groups within the New Zealand population emerged as important areas for discussion within the development of the guideline. This content is also included in this chapter, along with corresponding good practice points developed on the basis of expert opinion.

Communication and information provision

Background

Both the person facing a diagnosis and treatment for cancer and their family/whānau are faced with a formidable quantity of information. The quantity, timing and format in which this information is transmitted influences levels of distress, anxiety and quality of life.[28] The information needs of any patient should be individually determined and reassessed at different stages of the clinical pathway.[28]

Body of evidence

Due to the nature of the evidence, a non-systematic review was undertaken on effective advice, communication and information provision for people with early breast cancer. Evidence included:

- National Breast Cancer Centre (NBCC) – *Clinical practice guidelines for the psychosocial care of adults with cancer* (2005)[29]
- National Institute of Clinical Excellence (NICE) – *Guidance on supportive and palliative care: research evidence* (2004)[30]
- National Health and Medical Research Council (NHMRC) – *Clinical practice guidelines for the management of early breast cancer* (2001)[31]
- Kinnersley et al. – *Interventions before consultations to help patients address their information needs by encouraging question asking* (2008)[28]
- Cancer Society of New Zealand – *A national stocktake and review of a selection of consumer cancer information resources* (2006).[32]

Summary of findings

Communication skills

The NBCC guidelines[29] highlighted the importance of specific practitioner communication skills to enhance patient recall and understanding, improve patient satisfaction and reduce emotional distress at specific stages of the patient journey (including diagnosis, discussion of prognosis and discussion of treatment options). The NBCC guidelines[29] also emphasised the importance of privacy and the presence of a support person at diagnosis and when discussing prognosis. The provision of information through a variety of acceptable and appropriate media for the individual was found to be important at all stages of the patient journey and decision-making processes. It was noted that communication during clinical care is not limited solely to details of the illness and treatment, but extends into other areas (eg, demographic factors, media information, family and friends, body image concerns and personal beliefs about treatment). These areas are discussed in more detail on the NBCC website (www.nbocc.org.au).

Communication skills training

The NICE guidance on supportive and palliative care[30] evaluated the role of communication skills training for health professionals. Communication skills training was shown to alter health professionals' attitudes and improve methods of eliciting concerns and offering information. Those training programmes that appeared to be most effective were learner-centred, provided a safe environment for reflection and self-awareness, had defined core competencies, were led by suitably trained and experienced professionals, and provided constructive feedback.

Exploring and responding to specific concerns

It is important to ascertain the individual's perception of their general psychological and emotional well-being, as well as their physical well-being, and explore any specific concerns or sources of distress (eg, anxiety, depression, interpersonal functioning, coping with physical symptoms, body image and sexuality).

Patients may find it difficult to formulate and articulate questions during consultations and it has been suggested that prompt sheets or coaching may be effective.[28] The NBCC[29] developed verbal prompts to assist practitioners when raising specific concerns with people who have cancer (see Appendix B).

Information provision

Information provided to women with early breast cancer should be current and of a high quality.[31]The nature, level and format of the information provided at each stage of the pathway should be dependent on numerous factors including educational, cultural and ethnic factors and on the individual's requirements.[31]The NICE guidance[30] noted the high value placed on face-to-face interactions by both the patient and carer. Even when face-to-face communication skills are effective, the individual may not be able to recall all of the information they were provided with during the consultation.[29] Repetition through various media may facilitate recall.[29]

The NICE guidance[30] provided a comprehensive list of interventions that have been found to be of use in enhancing effective communication. This includes written, audio, visual and educational information and health professional involvement. The emphasis was on coping with the disease, psychological adjustment, symptom management, continuity of care and behaviour change. One practical suggestion recommended was encouragement for the patient to take notes or record the consultation to aid their later review of the information provided.[30]

The *National stocktake and review of a selection of consumer cancer information resources*[32] undertaken by the Cancer Society of New Zealand identified a large volume of material available to the consumer in numerous formats and from a wide variety of organisations. The stocktake also identified gaps in specific information areas. These gaps included: information in culturally appropriate formats, on complex treatments, on alternative and complementary therapy, on survivorship and on late effects of treatment, and in the timing of information provision to patients.

Several websites provide information and resources to women and their family/whānau about breast cancer and treatment. See Appendix C for further information.

Language

The Guideline Development Team (GDT) considers that where English is not the individual's first language, an appropriately trained interpreter should be available in addition to a family/whānau or staff member. Written information in a variety of formats and languages should also be available.

Development of recommendations

The GDT based its recommendations on a non-systematic review of available evidence and selected areas of importance.

The GDT noted that those diagnosed with early breast cancer needed to be accurately and fully informed of their disease and treatment options. Information should be provided on an individually tailored basis with educational, cultural and ethnic factors taken into consideration. Different options are available to provide this information and the most

appropriate method should be selected in discussion with the person with early breast cancer. Repetition of information through additional media or the presence of a support person may help retention of information.

Recommendations

	Grade
Practitioners should give a woman with early breast cancer information about her diagnosis, treatment options (including risks and benefits) and support services	C
Information should be tailored to each woman's individual situation throughout her cancer journey, including follow-up	C
Practitioners, in consultation with the woman, should determine the level and amount of information that will be most effective in enabling her to understand her condition and treatment options	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice points

Practitioners should receive training in effective communication skills	✓
Practitioners, in consultation with the woman, should determine the preferred format and timing of information provision	✓
A woman with early breast cancer should be encouraged to take a support person to consultations to provide support and to assist in retaining information	✓
A woman with early breast cancer should be encouraged to take notes or record a consultation	✓
Practitioners should ask the woman what she has understood, to determine how well information has been absorbed. Reflective, open-ended questions (eg, 'We have just covered a lot of information, what have you understood from this discussion?') should be used whenever new information is introduced	✓
Practitioners should be aware that information provided to a woman with early breast cancer may often need to be repeated	✓
A woman with early breast cancer should be given adequate time and opportunities to discuss and absorb information and ask questions	✓
Service providers and practitioners should ensure that high quality evidence-based information resources are available for women with early breast cancer in a variety of formats and languages	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Psychosocial support

Background

The diagnosis of cancer brings with it uncertainty about the future. This section addresses the issue of psychosocial support for women with early breast cancer and their families. The NBCC guidelines[29] comprehensively overview the key emotional issues for consideration when treating a person with early breast cancer. These issues include emotional, social and psychological issues; physical issues associated with quality of life, illness and treatment side effects; practical and financial issues; and more specific cultural and existential factors involved in dealing with a diagnosis of early breast cancer. Further details can be accessed on the NBCC website (www.nbocc.org.au).

Much of the data identified in the literature focused on psychological interventions such as counselling, psychotherapy, educational interventions and support groups, and this is reflected in the content of this section. Counselling encompasses supportive care delivered by a range of health professionals and may include supportive listening, the provision of practical information and education, instruction in relaxation therapies, assistance with communication and relationship problems, training in assertiveness and advice on problem-solving. Educational interventions aim to reduce feelings of inadequacy, confusion, helplessness and loss of control by providing information about the disease process, coping with the disease and the resources available. Individual psychotherapy is a one-to-one interaction between therapist and patient aiming to decrease distress and improve self-esteem, and help overcome the personal challenges of breast cancer.

It is estimated that up to 30% of women diagnosed with breast cancer will develop psychological morbidity (eg, an anxiety or a depressive disorder) within one year of diagnosis.[33–36] These psychological problems affect not only the patient but also their family.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

The Scottish Intercollegiate Guidelines Network (SIGN) guideline[37] considered both group-based and individual interventions. The Belgian guideline[38] also identified randomised controlled trials (RCTs) reporting on group interventions, individual interventions, couple and family interventions, and telemedicine interventions (eg, computer and telephone-based interventions). Many individual trials were hampered by methodological limitations and small sample sizes, and reporting on outcomes was heterogeneous. The NHMRC guideline[31] was based on meta-analysis and RCTs. The NBCC guidelines[29] considered individual and group therapies. (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Four additional meta-analyses and systematic reviews were identified. Bantum et al. (2007)[39] identified 18 RCTs evaluating psychological therapy for women with breast cancer that included both group and individual interventions. Chow et al. (2004)[40] identified eight RCTs that included psycho-educational therapy, supportive group therapy and individual psychotherapy. Smedslund et al. (2004)[41] identified eight RCTs and five non-RCTs of education, social support, psychotherapy, skills training, relaxation or their combinations.

(The studies were considered to be of high quality.) Osborn et al. (2006)[42] identified six RCTs of cognitive behavioural therapy that included women with breast cancer. (The study was considered to be of very high quality.)

Summary of findings

Psychosocial distress

The NBCC guidelines for the psychosocial care of adults with cancer included a checklist (see Box 2.1) that can be used to identify cancer patients at higher risk of psychosocial distress.[29] Caregivers (especially a spouse) are also at significant risk of psychological morbidity, are often neglected by the health professionals, and frequently report being unaware of the extent of the services available to them.[43]

Box 2.1 Checklist to identify cancer patients at a higher risk of psychosocial distress

Personal factors	Disease and treatment factors
• Younger age	• Advanced stage of disease
• Single, separated, divorced, widowed	• Poorer prognosis
• Living alone	• More treatment side effects
• Having children younger than 21 years	• Greater functional impairment and disease burden
• Economic adversity	• Lymphoedema
• Poor marital functioning	• Chronic pain
• Past psychiatric treatment, especially for depression	• Fatigue
• Cumulative stressful life events	
• History of alcohol or other substance abuse	

Source: National Breast Cancer Centre. Clinical practice guideline for the psychosocial care of adults with cancer. Campertown, NSW: 2005.

Adapted with permission from: National Breast and Ovarian Cancer Centre. Information provided by NBOCC is not intended to be used as a substitute for an independent health professional's advice. NBOCC does not accept any liability for any injury, loss or damage incurred by use of or reliance on the information. NBOCC develops material based on the best available evidence however NBOCC cannot guarantee and assumes no legal liability or responsibility for the currency or completeness of the information.

Support groups

Some groups offer mutual support to others with cancer. They may be face-to-face, telephone, email or web-based groups.[44] Better awareness between these groups and health professionals might help to improve the uptake and potential benefits of such groups.[44]

Role of multidisciplinary team

All members of the treatment team play a role in providing support and opportunities for women to disclose their concerns, feelings and fears. The NBCC guideline states that women in particular placed value on support provided by the doctors involved in their immediate care. The role of the breast care nurse was considered to be vital within the treatment team as it resulted in a reduction in psychological morbidity.[31]

Individual psychological interventions

Individual interventions that included telemedicine (telephone and computer interventions) produced significant improvements in mood, coping and distress in the short term. However, the sustainability of these benefits was equivocal. Psychological interventions implemented by clinical psychologists resulted in improved outcomes, compared with the same intervention delivered by other professionals.[45–47] Cognitive behavioural therapy resulted in short-term benefits in the reduction of depression and anxiety and both short- and long-term effects on quality of life in individual therapy.[42] The data from these studies are drawn from a general population of patients with cancer that included women with breast cancer. The NBCC guidelines[29] concluded that, where indicated, women with early breast cancer should be informed about the benefits of individual and group therapies, and asked whether they would like a referral or require assistance in arranging an appointment.

Group psychological interventions

Cognitive behaviourally focused group therapy was associated with a reduction in depression and mood disturbance, and an increase in quality of life. However, the sustainability of these benefits was equivocal.[37] Group interventions were more likely to provide support and understanding from women facing similar circumstances compared with individual interventions.[39] The findings of these studies are drawn from a general population of patients with cancer, which included women with breast cancer.

Overall survival

There is no evidence that psychosocial support or interventions influenced the survival of patients with breast cancer.[37, 40]

Development of recommendations

Based on NZGG's systematic review of the published evidence and expert opinion of the GDT members, the GDT noted the good quality evidence generally supported the use of psychosocial interventions.

Such interventions lead to an improvement in quality of life, functional adjustment and rehabilitation and a reduction in anxiety, depression and emotional stress, although there is no current evidence for influence on survival. The choice of intervention may depend on the needs of the individual and their social context. All women facing a diagnosis of early breast cancer will undergo a range of emotions and should be reassured that these are 'normal'.

The emotions extend to, and affect, the woman's spouse or partner, children and other family/whānau members, and friends. These significant others may provide the woman with support and may require support themselves. Health care professionals should be alert to potential psychosocial problems and be able to offer appropriate referrals or advice.

Individuals from culturally and linguistically diverse backgrounds often experience difficulties in accessing and utilising existing health care services. There is a need to develop culturally appropriate support systems, particularly for Māori and Pacific women.

The GDT's opinion was that behavioural therapy may be useful where there are issues for a woman with breast cancer concerning self-worth and body image (eg, sexuality), and may serve to limit or prevent the development of depression, anxiety or other mental health conditions.

Recommendations

	Grade
Psychosocial support should be available to all women with early breast cancer	A
Cognitive behavioural therapy should be available for women with early breast cancer experiencing an anxiety disorder or depression	A

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice points

Psychosocial support should be available for partners/spouses/children of those with early breast cancer	✓
Supportive care and psychological therapy offered should reflect the needs of the individual and their social context	✓
Men diagnosed with breast cancer have particular psychological issues and needs that should be considered	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Role of multidisciplinary team and identified coordinator of care

Background

Optimal therapy for early breast cancer should be undertaken by a multidisciplinary team. The team may include surgeons, radiologists, radiation and medical oncologists, pathologists, geneticists, counsellors, breast physicians, specialist nurses, physiotherapists, general practitioners and other health care professionals. The team should actively seek and consider input from the woman with cancer. Multidisciplinary care may be provided in an integrated treatment centre or be accomplished elsewhere by consultation among professionals. The participation of the multidisciplinary team in patient care is a requirement under the New Zealand Cancer Control Strategy.[16] Multidisciplinary teams help ensure that women with cancer receive all appropriate and necessary treatment modalities, that expert discussion and consensus occur in difficult clinical scenarios, and patients do not receive conflicting information from different sources.

Body of evidence

The systematic review undertaken on the effectiveness of the multidisciplinary team and coordinators of care identified the following evidence that met the inclusion criteria.

In relation to this topic the SIGN guideline[37] focused on the role of the breast cancer nurse specialist as a coordinator of care. Although no RCTs were identified, a cohort study and a multicentre implementation study were included in the SIGN guideline review. The NHMRC guideline[48] included two cohort studies and a comparative study. The Belgian guideline[38] was based on a previous guideline[49] and expert opinion. (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Two systematic reviews were identified as meeting the inclusion criteria. A Cochrane Collaboration systematic review[50] identified five RCTs (no meta-analysis was conducted due to heterogeneity) evaluating the effectiveness of individual interventions carried out by breast care nurses on quality of life outcomes for women with breast cancer. Houssami (2006) identified 14 observational studies that assessed the extent and quality of evidence on how multidisciplinary care contributed to clinical outcomes in breast cancer, and whether these influenced survival.[51] (Both reviews were considered to be of high quality.)

Three additional primary studies were identified. A population-based longitudinal study by Morris et al. (2008) aimed to quantify the extent to which multidisciplinary team formation and surgical site specialisation in breast cancer had been implemented and whether these changes were associated with improvements in the outcome of breast cancer patients.[52] (The study was considered to be of high quality.) Chang et al. (2001) evaluated the effect of the multidisciplinary approach to the management of breast carcinoma.[53] Chan et al. (2006) followed a cohort who were surgically treated for breast carcinoma and evaluated the applicability of the multidisciplinary approach to the management of patients with breast cancer.[54] (These two studies were considered to be of low quality.)

Summary of findings

Effectiveness of multidisciplinary teams

The evidence indicated that a multidisciplinary breast clinic provided an accurate and effective means of establishing a correct diagnosis in women referred with breast symptoms.[38] The multidisciplinary approach was considered to be an efficient, cost-effective way to care for women with breast cancer[54, 55] and was noted to provide useful second opinions.[53] The NHMRC guideline reported that referral pathways were more likely to be streamlined with an multidisciplinary team approach and there were educational benefits to clinicians.[55]

Survival

The reviewed evidence indicated that the survival of women with breast cancer was better if they were treated by a specialist who has access to a full range of treatment options in a multidisciplinary approach.[52, 55]

Role of breast care nurse specialist

The role of the breast care nurse specialist was found to be well established within the multidisciplinary team. There was some evidence to suggest that breast care nurse specialists improved the continuity of care, information and support for women from diagnosis to follow-up[37] and were useful in the identification of anxiety and depression.[50]

Development of recommendations

Based on NZGG's systematic review of the published evidence the GDT noted that participation in multidisciplinary teams was found to be valuable for the management of those with early breast cancer. Interdisciplinary communication was found to alter management and ultimately improved patient outcomes. Additional benefits noted by the GDT included interdisciplinary collaboration, education and the development of management guidelines. The multidisciplinary team was considered an efficient way to combine input from a variety of health professionals on a large volume of cases.

The GDT also noted that the benefits of the multidisciplinary team approach included increased survival, increased patient satisfaction with care, improved perception of management of care, and increased access to information, including psychosocial and practical support. The GDT noted that most studies on multidisciplinary teams were observational or retrospective, and potentially susceptible to bias.

Similarly, it is generally held by medical specialists and consumers that an identified coordinator of care (eg, a breast care nurse or breast physician) is of benefit to offer guidance and support from diagnosis through treatment and follow-up. This coordinator role is especially important when a woman is changing treatment modalities or after completion of therapy, times when the woman may experience particular feelings of vulnerability. The identified coordinator of care could also play an important role in the identification of psychosocial problems and in providing patient education.

Recommendation

	Grade
All women with early breast cancer should be managed by a multidisciplinary team	A

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice points

A multidisciplinary team should consider the input from the woman with early breast cancer	✓
Every specialist involved in early breast cancer care should regularly participate in a multidisciplinary team meeting	✓
A coordinator of care is recommended for each woman with early breast cancer to facilitate the treatment pathway and provide guidance and support from diagnosis through to follow-up	✓
The multidisciplinary team and coordinator of care should provide culturally appropriate advice and support	✓
The outcomes of multidisciplinary team meetings should be clearly documented in the medical records and communicated to the individual woman	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Considerations for Māori and Pacific peoples

This content was based on expert opinion from representatives of the relevant cultural groups within New Zealand. Several issues were considered to be important in the New Zealand context specifically for Māori and Pacific peoples.

Some of these issues relate to the clinical consultation but not all require addressing at the first consultation. Time prior to making treatment decisions was identified as important to allow for consultation with friends, family/whānau and support groups. Flexibility in the amount and content of information provided was also noted as necessary to meet the specific needs of individual women. Routine questioning of a woman about her ethnic background offers an opportunity for the health practitioner to discuss individual cultural preferences in relation to health care, in addition to gathering appropriate ethnicity data.[56]

A prospective cohort study in New Zealand found differences in breast cancer biological characteristics between ethnic groups.[57] There is a tendency towards larger, higher-grade tumours with more positive lymph nodes in New Zealand Māori and Pacific peoples. The authors of this study suggest that improving access to screening mammography and treatment services, and education, and addressing cultural safety issues would be beneficial. A large retrospective cohort study from the United States of America investigating breast cancer stage, treatment and survival by race and ethnicity found differences in treatments received were likely to be the result solely of socioeconomic and cultural factors.[58]

Such contributors to disparities are reversible, and the New Zealand health system faces the challenge of offering practical solutions to reduce these differences and reduce ethnic inequalities in breast cancer outcomes.

Māori

The NZGG guideline *Suspected cancer in primary care* provides the following summary of the barriers for Māori when accessing care.[59]

Traditionally, Māori tend to have a more holistic view of health than the majority of the New Zealand population. Māori belief systems, such as views about reliance on the whānau, individual mana, death and dying, and practices associated with tapu/noa, continue to influence health behaviour. These views may influence preferences for care, individual help-seeking behaviour and responses to health care providers.[60]

Empirical qualitative research has identified barriers to care from a Māori perspective. Based on this research, a conceptual framework was developed to address the issue. The framework comprises four key areas: costs of care, communication, structural barriers and cultural fit. Specific barriers within each key area identified by this research are presented in Box 2.2.

Barriers to care will vary according to the specific context. In addition, there is likely to be overlap between the key areas (eg, structural barriers can increase costs and communication barriers will be compounded when cultural differences between a Māori patient and a health care provider exist). Each of these barriers is greater for nga hunga hauā (Māori with disabilities). Māori with significant disabilities comprise one of the most vulnerable populations, and the impact of multiple barriers can be overwhelming for this group.[60]

Box 2.2 Specific examples of barriers to care from a Māori perspective

Barrier	Specific examples
Costs of care[i,ii]	Direct: • consultation cost[ii,iii] • prescription charges[iii] • cost of general practitioner house call Indirect: • loss of wages (time off work)[iii] • perception of 'value for money' • financial cost of travel to receive care • ability to travel (childcare issues)[iii]
Communication[iv]	Health literacy Lack of knowledge of available services Experience of unfavourable attitudes to Māori
Structural barriers[ii]	Distance to travel for care[v] Appointment availability at a suitable time Waiting times System inflexibility Physical barriers Lack of choice of provider (eg, Māori health care practitioner)
Cultural fit[ii]	Perceptions of being patronised, treated with a lack of respect and/or racism[vi,vii] Previous bad experiences[i,iv,vi] Perceptions of illness and death Unfulfilled preference for a Māori health care practitioner Disempowerment (culturally appropriate 'shyness')[i] Feeling uncomfortable in unfamiliar (non-Māori) settings Lack of acknowledgment of whānau/Māori processes (eg, desire for whānau to take prime responsibility and a preference to suffer rather than be a burden)

Sources:

i Ellison-Loschmann L and Pearce N. Am J Public Health 2006;96:612–7.

ii Baxter J. Barriers to health care for Māori with known diabetes. Te Rōpū Rangahau Hauora a Ngāi Tahu; 2002.

iii Bolitho S, Huntingdon A. Nurs Prax N Z 2006;22:23–33.

iv Walker T, Signal L, Russell M, et al. NZ Med J 2008;121(1279).

v Brabyn L, Barnett R. NZ Med J 2004;117(1199):U996.

vi CBG Health Research Limited. Improving access to primary health care: an evaluation of 35 reducing inequalities projects. Birkenhead, NZ: 2005.

vii Harris R, Tobias M, Jeffreys M. Lancet 2006;367:2005–09.

Adapted with permission from: P Jansen. Māori consumer use and experience of health and disability and ACC services. Mauri Ora Symposium, Wellington; April 2006.

Originally published in: New Zealand Guidelines Group. Suspected cancer in primary care. Wellington: 2009.

Pacific peoples

The term 'Pacific peoples' describes a diverse group of New Zealand-born individuals and migrants from South Pacific nations, who identify with one or more of the Pacific cultures either due to ancestry (family) or heritage (ie, Tuvalu people have resided in Samoa for generations due to Pacific migration).

Traditionally, Pacific cultures are oriented towards the social group and concepts of holistic health care.[61] Pacific peoples have many similarities between cultural beliefs, customs, values and traditions, but they also have differences. The Tongan culture has an important matriarchal influence with the oldest sister of a male being the most important member of the immediate or extended family. By contrast, Samoa has matai, which is a chief system (often male) that can be family- or village-based. Being aware of similarities and differences between certain cultures will assist practitioners to understand the values and beliefs of the Pacific patient.

Language may be a barrier to accessing information about relevant services and to accessing information within health service interactions.[62] Doctors responding to the National Primary Care Medical Survey rated 22% of Pacific patients attending primary care as not fluent in English.[63] It can be difficult to determine who may require an interpreter so the use of professional interpreter services should be offered to women in all clinical settings where there is any question of understanding. The use of non-professional interpreters is discouraged, as this has been suggested to influence the treatment outcome for patients.[64] A US study found that foreign-born Pacific patients were less likely to receive breast conserving surgery than US-born Pacific patients even when diagnosed in the earliest stages. Both groups were less likely than European breast cancer patients to receive breast conserving surgery. This study concluded that language and lack of access to regular health care may have contributed to these treatment disparities.[65] There are increasing numbers of Pacific primary care providers within New Zealand, and offering referral to one of these services for ongoing care may improve the woman's health care access in the long term.

Some Pacific people seek traditional methods of healing first or concurrently with their Western medical treatments.[66, 67] Traditional healers are an integral part of the Pacific community or family and are often well respected.[68] Christianity is a large part of many Pacific cultures and may influence health behaviour.[61] Providing a non-judgmental approach to the use of traditional and alternative treatments will assist with patient rapport and compliance.

Pacific women are less likely to access non-Pacific support groups. Pacific-specific support groups for women should be established, especially in the main cities of New Zealand that have sufficient population and numbers of Pacific women diagnosed with early breast cancer. It is not appropriate that Pacific women are grouped together with Māori women as the two groups have different cultural beliefs and issues. There needs to be further work to develop culturally appropriate psychosocial support for Pacific women.

Language

Health practitioners should not rely on family members to act as interpreters. Patients from non-English-speaking backgrounds should be provided with a proficient and professional interpreter at each consultation.

Workforce development

Two recent qualitative studies[69, 70] highlight the need to increase the Māori workforce, including Māori oncology nurses and a liaison person to help navigate across the cancer control continuum.

Providers of cancer care services should develop a workforce plan so that over time their staff composition reflects the community they serve. This may help to reduce the cultural barriers to cancer care services for Māori.

The quality of cancer care services for Māori can be improved through cultural competence training of all health professionals, including staff such as receptionists and administration staff.

Key factors in successful programmes to increase Māori health workforce recruitment and retention include Māori leadership, mentorship and peer support; and comprehensive support within study programmes and in the transitions between school, university and work.[71]

Māori- and Pacific-specific cancer services

Recent qualitative research suggests that the work of Māori providers should be extended and further resourced because of its importance in ensuring quality cancer control services for Māori.[69, 70]

Māori health providers are effective providers of cancer care for Māori because of their grounding in a Māori or iwi (tribal) world view, their style of practice and their support for Māori.[70] Māori providers provide practical support to Māori experiencing cancer and are a conduit between the woman with cancer and the cancer control system.

Māori- and Pacific-specific cancer services or service components should be delivered by existing Māori or Pacific providers or in partnership with Māori or Pacific providers.

Ethnicity data quality

There is evidence that questions the reliability of some ethnicity records in primary care.[11, 72]

Furthermore, Cormack et al.[9] identified that Māori cancer registrations and deaths were undercounted by about 17% and 6%, respectively for 1996–2001. However, using the 'ever-Māori' method for classifying ethnicity produced estimates accurate to within 1%.

The GDT considered that there should be consistency in the collection of ethnicity data, quality improvement initiatives around ethnicity recording and a consistent, systematic way of analysing data. These are important issues for accurately identifying disparity and for service planning and evaluation. Ethnicity data collection should follow the current Ministry of Health protocols.[56]

Development of recommendations

Based on the expert opinion of the GDT and the representatives of the appropriate ethnic groups the following good practice points were developed.

Good practice points

Data including the ethnicity of patients with early breast cancer should be recorded in a national database	✓
Health practitioners and others providing cancer care should receive training and support in culturally competent, patient-centred care	✓
Workforce development should target the training of more Māori and Pacific care providers including breast care nurses and coordinators of care	✓
Māori- and Pacific-specific cancer services or service components should be delivered by existing Māori or Pacific providers or in partnership with Māori or Pacific providers	✓
An invitation for women to bring whānau/family/support should be included with clinic appointment information	✓
Adequate time should be allocated to provide culturally appropriate care and to meet the needs of the woman with early breast cancer in an appropriate environment	✓
Practitioners should be aware of culturally sensitive issues such as exposure of the body	✓
Practitioners should consult with Māori and Pacific women with early breast cancer about preferences for care, including final disposal of tissue or body parts surgically removed	✓
To ensure effective communication for Pacific peoples and others whose first language is not English, competent interpreters and/or coordinators of care should be provided Acknowledgement and respect for a woman's beliefs regarding traditional health care practices are important	✓
Consideration should be given to allocating additional time for cross-cultural consultation, especially for those consultations requiring an interpreter	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

3 Staging

This chapter outlines the evidence and recommendations in relation to staging in early breast cancer and includes:

- routine staging investigations
- preoperative magnetic resonance imaging (MRI).

Introduction

A person with early breast cancer should be staged clinically according to the International Union Against Cancer (UICC) Tumour, Nodes and Metastases (TNM) classification[73] (see Appendix A) to define the anatomical extent of the disease (clinical tumour size, nodal status and clinical evidence of metastasis) and facilitate the planning of subsequent management. Planning of appropriate treatment relies on effective assessment prior to primary treatment. Routine use of specialised staging investigations for women with early breast cancer is not indicated. However, it must be recognised that staging tools are continually evolving and will become increasingly sophisticated.

Two clinical questions were developed to assess appropriate approaches to staging for early breast cancer (see Chapter 11, *General section: methods*).

Routine staging investigations

Background

Breast cancer patients should all undergo a clinical staging 'work-up' at the time of diagnosis (ie, assessment of clinical tumour size and loco-regional node involvement and a general physical examination) along with a history to check for possible symptoms of distant disease, such as fatigue, weight loss and bony aches or pains. Several staging investigations may also be used, including bone scintigraphy, liver imaging, chest X-ray, computerised tomography (CT), positron emission tomography (PET), and serum biomarkers (eg, CA 15-3). In relation to blood tests, some adjuvant therapies may be contraindicated in the presence of liver disease, and in the literature there is an incidence of hypercalcaemia in asymptomatic women from a variety of causes.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

The sources of evidence for the Scottish Intercollegiate Guidelines Network (SIGN) guideline[37] were not explicit for this topic. The staging section of the Belgian guideline[38] was based on two guidelines, the SIGN guideline[37] and the Cancer Care Ontario guideline,[74] in addition to Zuiden (2005).[75] The Australian National Health and Medical Research Council (NHMRC) guideline[31]included a 1997 update of recommendations from

the American Society of Clinical Oncology for the use of tumour markers in breast cancer. (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

One additional meta-analysis by Shie (2008) was identified.[76] This meta-analysis included six cohort studies (four prospective and two retrospective studies) examining the diagnostic properties of PET and bone scintigraphy in the detection of bone metastases in patients with breast cancer. (The study was considered to be of high quality.)

Five additional primary studies were identified. Hwa (2008) made a comparative evaluation of serum biomarkers (eg, CA 15-3, tissue polypeptide antigen [TPA], tissue polypeptide specific antigen [TPS], mucin-like cancer-associated antigen [MCA] and carcinoembryonic antigen [CEA]) from women with and without breast cancer, and evaluated the effectiveness of these biomarkers in the detection of primary breast cancer and lymph node metastatic status.[77] (The study received a QUADAS score of 9/14. For details about the QUADAS system, see Chapter 11, *General section: methods*). Both Silowska (2006)[78] and Baskic (2007)[79] compared serum biomarkers in women with breast cancer at various stages of the disease and considered the usefulness of these tests in evaluating the efficacy of treatment. (The studies received a QUADAS score of 7/14.) Aslan (2006) compared 5 mm CT and conventional X-ray in the detection of osseous metastases in invasive breast cancer, where bone scan was a 'gold' standard.[80] (The study received a QUADAS score of 9/14.)

Other data

The St Gallen Consensus 2007, the annual meeting of an international expert panel on breast cancer, considered the issue of routine staging investigations for breast cancer.[81]

Summary of findings

Radiographic screening for metastases

Routine bone scintigraphy, liver ultrasonography and chest radiography for metastatic disease are not indicated in an asymptomatic person with negative clinical findings and early operable breast cancer (T1–2, N0–1, see Appendix A for TNM classification) or ductal carcinoma in situ (DCIS).[37, 74, 75] However, women with symptoms suggestive of metastases at a particular site do require appropriate investigation, as do women with more advanced, but operable disease (T3, N1–2) in order to exclude distant metastases, and those for whom neoadjuvant treatment is considered.[37, 38]

Aslan (2006) found no significant differences between CT (sensitivity 71.8%, specificity 100%, positive likelihood ratio [PLR] ∞, negative likelihood ratio [NLR] 0.28) and X-ray (sensitivity 65.6%, specificity 100%, PLR ∞, NLR 0.34) in the detection of osseous metastases.[80] CT with 5 mm slices was not superior to X-ray when confirming suspicious lesions and in the diagnosis of metastatic lesions detected by bone scintigraphy. A larger series comparing different slice thickness of CT was suggested to clarify the issue.

In a large case series of 6628 body CT scans that included images of at least 2426 patients with breast cancer reviewed over a nine-year period, the authors reported that including the pelvis in the CT scan had an extremely low yield (0.7%) for pelvic metastases.[82] Pelvic CT led to 204 additional radiological examinations, including 186 pelvic sonographic

examinations and 50 additional surgical procedures. These investigations were associated with cancer in 16.4% of cases (n=39). The authors recommended against routine inclusion of the pelvis in staging CT scans.

It remained inconclusive whether fluorodeoxyglucose (FDG) PET scanning (PLR 11.5, NLR 0.2) or bone scintigraphy (PLR 3.7, NLR 0.27) was superior in detecting bone metastases from breast cancer. FDG PET had a higher specificity (93% vs 79%) and might better serve as a confirmatory test than bone scintigraphy and be potentially used to monitor response to therapy.[76]

Serum biomarkers for the screening of metastases

The evidence identified was from small case-control studies. There was no high-quality evidence to support the routine use of biochemical tests, including tumour markers such as CA 15-3, TPA, TPS, MCA and CEA for the staging of breast cancer.

Staging for those at higher risk of metastases

Observational data indicated that specific subsets of patients (patients with triple negative breast cancer and young patients) harbour a higher risk of distant metastases, so suggest that these groups should be staged more aggressively. This has not been recommended by previous guidelines.[37, 38] A retrospective observational study[83] of 516 newly diagnosed women with invasive breast cancer reported an overall detection rate of 6.3% for bone metastases by bone scintigraphy, 0.7% for liver metastases by liver ultrasonography, and 0.9% for lung metastases by chest radiography.

Imaging investigations including chest X-ray, bone scan, liver ultrasound, and chest and liver CT had a low diagnostic yield and should be used only when clinically indicated (ie, symptoms of lung disease, a palpable liver, abnormal liver function tests, bone pain or bony tenderness). Serological tests for cancer-specific antigens, such as CEA and CA 15-3, are non-specific and unreliable as indices of active disease.[31]

International expert opinion

The St Gallen Consensus noted that the benefits of extensive routine staging investigations have not been established.[81]

Development of recommendations

Based on the New Zealand Guidelines Group's (NZGG's) systematic review of the published evidence, the Guideline Development Team (GDT) noted that the evidence for the effectiveness of routine staging investigations to detect metastases is sparse. All included guidelines concurred that there was no evidence to support routine screening for metastatic disease in asymptomatic patients with early breast cancer.[31, 37, 38] Only patients with signs or symptoms suggestive of metastases or at higher risk of distant metastases (eg, triple negative, larger tumour size or positive axillary nodes) require investigation.

There was some evidence that a combination of various serum biomarkers was valuable in the prediction of metastases in early breast cancer patients. Inclusion of the pelvis in staging CT scans resulted in a significant false positive rate and consequent unnecessary further investigations for women. There was inconclusive data as to the superiority of PET or bone scintigraphy in detecting osseous metastases from breast cancer. Only one study compared CT with X-ray in the detection of osseous metastases.

Recommendations

	Grade
In asymptomatic women with early operable breast cancer (T1–2, N0–1), routine screening for metastatic disease is not required For women with stage I breast cancer, preoperative chest X-ray is not routinely indicated for staging purposes	A
Bone scintigraphy, liver scans and thoracic imaging should be considered for patients with more advanced but operable disease (T3, N1–2), if it will affect treatment	B
Clinical staging based on history and physical examination should be routinely performed prior to treatment	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice points

Routine preoperative serum biomarkers are not recommended unless there are clinical indications (ie, comorbidity, preoperative chemotherapy, more advanced breast cancer)	✓
Preoperative full blood count, renal function tests, liver function tests and calcium levels are recommended for assessment of fitness for surgery and adjuvant drug therapies	✓
Screening for metastatic disease should be reconsidered after pathology results are available	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Preoperative magnetic resonance imaging

Background

MRI visualises tissues in the body with the use of a strong magnetic field aided by use of specific contrast agents. Recent studies have suggested several potential uses in the 'work-up' of women with newly diagnosed breast cancer.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

With specific regards to this topic, the SIGN guideline[37] was based on cohort studies, case-control studies and expert opinion. The Belgian guideline[38] was based on a previous guideline and prospective cohort studies. (Both guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Two additional meta-analyses were identified. Mann et al. (2008) identified 18 studies reporting on the use of MRI in patients with histologic proof of invasive lobular carcinoma.[84] Houssami (2008) identified 19 studies (n=2610) in a meta-analysis to determine the accuracy and impact of breast MRI in the context of local staging, with a focus on detection of multifocal and/or multicentric cancer not identified on conventional imaging.[85] (Both systematic reviews were considered to be of high quality.)

Two additional prospective cohort studies were identified. In the study conducted by Deurloo et al. (2006) all 155 patients underwent mammography, ultrasonography and MRI, the results of which were used to decide whether the patient was advised to undergo breast conserving surgery or mastectomy.[86] The surgical excision was performed by taking the result of the MRI examination into account. (The study received a QUADAS score of 10/14.) Van Goethem et al. (2007) determined the role of MRI in the detection and assessment of the extent of tumours with extensive in situ component (EIC+) in 233 patients.[87] (The study received a QUADAS score of 11/14.)

One retrospective non-randomised analysis of a cohort of patients from a single institution was identified that assessed the potential value of integrating breast MRI into the clinical evaluation of women with newly diagnosed, early-stage invasive breast carcinoma or DCIS.[88] (The study was considered to be of high quality.) All studies included histopathology as a reference standard.

Other data

Relevant other data included international expert opinion from the St Gallen Consensus,[81] a conference report of the COMICE trial[89] (abstract only) and a multicentre randomised trial of MRI planning for breast conserving treatment for breast cancer.

Summary of findings

Diagnostic value of magnetic resonance imaging

MRI was shown to be of benefit in symptomatic patients with implants, where ultrasound results were not diagnostic[37] and in women with metastatic deposits in axillary nodes where no primary cancer was identified.[37]

The Belgian guideline[38] reported insufficient evidence for the routine use of MRI for diagnosis and staging of breast cancer. MRI can be considered in specific clinical situations where other imaging modalities are unreliable or have been inconclusive,[38, 84] and where there are indications that MRI is useful (eg, invasive lobular carcinoma, suspicion of multicentricity, genetic high risk [BRCA1 or BRCA2], patients with T0N+ disease [see Appendix A for the TNM classification], patients with breast implants, diagnosis of recurrence, follow-up of neoadjuvant treatment).[38]

Deuloo et al. (2006) noted that the use of MRI increased the detection rate of a suspicious abnormality (99%) when compared with mammography (96%) or ultrasound (96%).[86] Younger patients with spiculated or irregular tumour margins and a large discrepancy in tumour extent measured at mammography and at ultrasound had a 50% probability (3.2 times higher) of inaccurate assessment of tumour extent with conventional imaging and correct assessment by MRI (PLR 1, NLR 1).[86] MRI in patients considered eligible for breast conserving surgery had complementary value over conventional imaging to assess tumour extent in approximately 23% of the patients.

Having evaluated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), PLR, NLR to predict invasive cancer with DCIS, Van Goethem et al. (2007) concluded that compared with mammography (20%, 96%, 64%, 76%, 5, 0.83, respectively) and ultrasound (14%, 94%, 48%, 74%, 2.3, 0.91, respectively), MRI was superior in the assessment of total tumour size and in the prediction of intraductal spread in EIC+ carcinomas (50%, 90%, 65%, 82%, 5, 0.55, respectively).[87]

The sensitivity of MRI for invasive lobular carcinoma was reported as 93.3%, compared with 83% for ultrasound and 86% for mammography, and 81.5% for physical examination.[84] The correlation with pathology ranged from 0.81 to 0.9.

No differences in overall survival, cause-specific survival, freedom from distant metastases or local failure were identified between MRI and no MRI groups in a cohort of 756 women with invasive breast cancer or DCIS.[88]

Effect of magnetic resonance imaging on surgical management

In 32% of patients, additional ipsilateral lesions were detected by MRI and surgical management was changed in 28.3% of cases of which 88% were judged necessary based on pathology.[84]

MRI staging resulted in more-extensive breast surgery, in some cases due to identification of more-extensive cancer, but in other cases due to a false positive result that may result in unnecessarily radical surgery, even mastectomy, for some women. There is also concern that, even for women in whom MRI correctly detects additional cancer foci, conversion to more extensive surgery may have little long-term clinical benefit because the additional disease may have been adequately treated with standard adjuvant therapy.[85] MRI incremental accuracy differed according to the reference standard, decreasing from 99% to 86% as the quality of the reference standard increased. The PPV to detect additional disease was 66% (95% CI 52–77); true positive to false positive ratio 1.91 (95% CI 1.09–3.34). The conversion rate from wide local excision to mastectomy as a result of MRI findings was 8.1% (95% CI 5.9–11.3), and from wide local excision to more extensive surgery was 11.3% in multifocal/multicentric disease (95% CI 6.8–18.3).[85] Randomised trials are needed to determine the clinical value of detecting additional disease that changes surgical treatment in women with early breast cancer.[85]

The UK NIHR HTA multicentre open-label COMICE trial[89] considered whether adding an MRI scan to conventional triple assessment (mammogram, ultrasound and biopsy) assisted loco-regional staging, and thereby reduced re-operation rates, for patients with primary breast cancer scheduled for wide local excision. Women with biopsy-proven primary breast cancer who were scheduled for wide local excision based on the triple assessment with mammogram, ultrasound and biopsy were randomised to receive additional MRI (n=817) or not (n=808). Although the median size of index lesion was identical across groups, the women who underwent MRI tended to have larger excisions (70.55 g vs 63.69 g, p=NS). The MRI group of women were more likely to go on to have mastectomy instead of the previously planned wide local excision (7.1% vs 1.2%), with no difference in re-operation rates (18.75% vs 19.33%, odds ratio 0.96, 95% CI 0.75–1.24, p=0.7691). The only significant predictors of re-operation were younger age and lobular cancer, not MRI. MRI had a relatively low effectiveness, with a PPV of 61.8% and a NPV of 83.7%. MRI changed management for 6.1% of patients, but 28% of multifocal disease was not confirmed pathologically. MRI also correctly detected additional cancerous lesions in 4.8% of patients. Additional imaging had no impact on survival or quality of life.

The results of the COMICE trial indicate no significant benefit in terms of reduction in re-operation rates by the addition of MRI to conventional triple assessment for this patient group. The COMICE trial data was identified by the GDT as of relevance. The data reported is from a conference abstract, so has not been subject to formal critical appraisal.

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted that MRI demonstrates some benefits in accuracy over conventional imaging modalities. This may in turn lead to a change in surgical management, with more extensive breast tissue removal, although subsequent pathology may not always justify the MRI result. MRI may be of benefit as a diagnostic tool when other imaging modalities are inconclusive. The GDT also noted the randomised trial evidence for the role of MRI as a screening tool for those with a very strong family history or known to be BRCA1 or BRCA2 positive. The GDT notes that women with dense breasts should also be considered for MRI when other imaging modalities have been inconclusive or unreliable.

Recommendation

	Grade
Magnetic resonance imaging (MRI) should be considered in specific clinical situations where other imaging modalities are not reliable, or have been inconclusive, and where there are indications that MRI is useful. These include: Preoperative • Invasive lobular carcinoma • Suspicion of multicentricity • Lesions of the breast (ie, T0N+) not detectable on other clinical or imaging modalities • Genetic high risk • Women with breast implants • Aged younger than 40 years • Assessment following neoadjuvant treatment • Women with dense breasts Postoperative • Diagnosis of recurrence	A

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice point

In a woman with early breast cancer magnetic resonance imaging should be considered where there is a moderate likelihood that it can lead to a change in management	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

4 Surgery for early invasive breast cancer

This chapter presents content in relation to breast surgery for early invasive breast cancer, including:

- mastectomy versus breast conserving surgery and radiotherapy
- margins of excision for breast conserving surgery
- management of the axilla in early invasive breast cancer
  - effectiveness of nodal excision
  - accuracy of sentinel lymph node biopsy (SLNB)
  - effectiveness of SLNB
  - axillary clearance after SLNB
- breast reconstruction
- venous access and risk of lymphoedema.

For relevant information on ductal carcinoma in situ (DCIS), see Chapter 8, *Ductal carcinoma in situ*.

Introduction

Breast cancer is usually treated surgically with either breast conserving surgery (BCS) or mastectomy, and assessment of axillary lymph nodes. Axillary lymph node status remains the single most significant prognostic factor (though this may be surpassed by molecular markers in the near future) and is an important step in the staging of breast cancer, and helps select adjuvant therapy. Surgical removal of the nodes is a treatment in its own right, reducing the risk of local recurrence and may influence breast cancer survival.

Eight clinical questions were developed to assess the best approaches for breast surgery in early breast cancer (see Chapter 11, *General section: methods*).

Mastectomy versus breast conserving surgery and radiotherapy

Background

The aim of surgery for early invasive breast cancer is to eradicate the primary tumour and any local extension, with a view to achieving local disease control. There are several well-established procedures for surgical treatment of early breast cancer.

- Wide local excision (excision of a tumour with a margin of clearance of both invasive and in situ disease). Usually with this procedure, the surgeon endeavours to take an approximate 1 cm macroscopic clearance. The goal is to achieve complete excision with an adequate microscopic clearance all around the tumour
- Segmental excision or sector resection (as above, but the excision incorporates tissue from the nipple right out to the periphery of the breast in a segmental shape). This and quadrantectomy are particularly useful for disease over a segmental distribution such as an extensive in situ component

- Quadrantectomy involves a similar excision to segmental excision but a whole quadrant of the breast is removed
- Mastectomy refers to removal of the entire breast. Mastectomy is often subclassified as simple, total or modified radical (removal of pectoral fascia plus at least levels I and II axillary dissection). A skin-sparing mastectomy is completed as part of a breast reconstruction procedure and entails preservation of some of the skin envelope that would normally be removed with the total mastectomy

Wide local excision, partial mastectomy, quadrantectomy and segmentectomy are usually referred to as BCS. The primary surgical aim is optimal breast cancer outcome, taking into consideration individual patient and disease factors. Radiotherapy is used as an adjunct to BCS.

The decision whether to recommend BCS and radiotherapy or mastectomy will depend on a range of factors. These factors may include, but are not limited to:

- the size of the tumour relative to the size of the breast precluding an acceptable cosmetic result
- the location of the tumour, for example, a centrally placed tumour is not a contraindication to BCS although it may necessitate removal of the nipple and areola, which may compromise cosmesis for some women
- the presence of multifocal or multicentric disease
- the presence of extensive malignant-type microcalcifications on mammography, indicating disease is too extensive for BCS
- previous high-dose radiotherapy to the region
- the presence of scleroderma (contraindicating postoperative radiation therapy)
- pregnancy
- fitness for surgery and/or radiotherapy
- the woman's own preferences, having taken consideration of the above factors
- advice from a radiation oncologist on the feasibility of radiotherapy.

Body of evidence

The systematic review undertaken to answer this question identified the evidence below, which met the inclusion criteria.

Four clinical guidelines met the inclusion criteria with relation to this question. The Scottish Intercollegiate Guidelines Network (SIGN) guideline[37] included four primary studies and the Cancer Care Ontario guideline.[90] In reference to the issue of BCS and radiotherapy versus mastectomy, the Belgian guideline[38] was based on two previous guidelines and one meta-analysis.[37, 91, 92] The Australian National Health and Medical Research Council (NHMRC) guideline[31] was based on an Early Breast Cancer Trialists' Collaborative Group (EBCTCG) review[93] and three individual trials[94–96] and also reported on psychological outcomes.[97–99] The British Medical Journal (BMJ) clinical guideline[100] was based on two systematic reviews, Morris et al. (2005) and the EBCTCG review.[93] Three randomised controlled trials (RCTs) included in the reviews have now reported 20-year follow-up results.[94, 96, 101] The BMJ clinical guideline also evaluated the evidence from Sacchini et al. (1991)[102] relating to differing extent of local excision in BCS.[100] (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

The EBCTCG (2005) review,[93] included in both the BMJ clinical evidence review[100] and NHMRC guideline,[31]was identified as a useful reference source for inclusion.

Summary of findings

Table 4.1 illustrates the patient population and outcomes of studies comparing mastectomy with BCS and radiotherapy in terms of tumour size, overall survival, disease-free survival and local recurrence.

Table 4.1 Randomised trials comparing mastectomy with breast conserving surgery and radiotherapy

Study group/ author/year	Comparison*	Maximum tumour diameter	No. of patients	Years of follow-up	Overall survival	Disease-free survival	Local recurrence
IGR Arriagada 1996[103]	Tumourectomy + radiation	2 cm	88	15	73%	55%	9%
	Modified radical mastectomy		91		65%	44%	14%
NSABP B-06 Fisher 1995[96]	Lumpectomy	4 cm	634	12	58%	47%	37%**
	Lumpectomy + radiation		628		62%	49%	11%
	Total mastectomy		589		60%	50%	NR
NCI Jacobson 1995[104]	Lumpectomy + radiation	5 cm	121	10	77%	72%	5%
	Modified radical mastectomy			116	75%	69%	10%
DBCG Blichert-Toft 1992[95]	Breast conserving surgery + radiation	5 cm	430	6	79%	70%	2%
	Total mastectomy		429		82%	66%	–
EORTC Van Dongen 1992[105]	Breast-conserving surgery + radiation	5 cm	455	8	71%	64%	11%
	Modified radical mastectomy		424		73%	70%	8%
Milan Veronesi 1990[94]	Quadrantectomy + radiation	2 cm	352	13	71%	NR	3%
	Modified radical mastectomy		349		69%	NR	2%

Notes:

* Axillary dissection was carried out in all patients

** Indicates a significant difference at $p<0.05$

NR = not reported

Sources:

IGR = Institute Gustave-Roussy Breast Cancer Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; NCI = National Cancer Institute; DBCG = Danish Breast Cancer Cooperative Group; EORTC = European Organisation for Research and Treatment of Cancer; CRC UK = Cancer Research Campaign United Kingdom; BMFT = Bundesministerium für Forschung und Technologie

Overall survival and recurrence

BCS and radiotherapy offer the same survival benefits as modified radical mastectomy in women with stage I or II breast cancer who are candidates for BCS.[93] No significant differences in survival were identified between BCS plus radiotherapy and mastectomy. There were no reports of significant differences in overall survival, disease-free survival or distant disease-free survival in any of the studies summarised in Table 4.1 comparing BCS plus radiotherapy and mastectomy.

The EBCTCG (2005) overview of randomised trials of local treatment has clearly shown that local recurrence may impact on patient survival.[106] For every four additional local recurrences at five years, one woman will have died by the 15-year follow-up. This means that women at higher risk for local recurrence may require more radical surgery and/or radiotherapy treatments. Additional surgery after BCS may be required if margins are positive or close.[37] Further details on margins of excision for BCS are in the section entitled, 'Margins of excision' in this chapter.

Other outcomes

Psychological well-being

There is no evidence for a substantial difference in postoperative psychological health between women who have had BCS plus radiotherapy and those who have had mastectomy.[31] There is some evidence to indicate that women having BCS plus radiotherapy have a better body self-image than those who undergo mastectomy.[31]

Cosmesis

Breast conserving surgery and radiotherapy was contraindicated if the ratio of the size of the tumour to the size of the breast would not result in acceptable cosmesis.[31, 37] In BCS, cosmesis may also be affected by the central situation of a tumour that may necessitate surgical excision of the nipple or areola.[37] The Guideline Development Team (GDT) notes that tumour location in the lower or inner breast is also a more difficult site to achieve good cosmesis.

Radiotherapy

Radiotherapy is usually administered as an adjunct to BCS. However, BCS is contraindicated in situations where there has been previous radiotherapy to the site.[31, 37] For details of adverse effects associated with radiotherapy, see Chapter 5, *Radiotherapy*, specifically the section entitled, 'Radiotherapy in addition to breast conserving surgery'.

Development of recommendations

Based on the New Zealand Guidelines Group's systematic review of the published evidence, the GDT concluded that for stages I and II breast cancer, BCS and radiotherapy results in no difference in outcomes compared with mastectomy in terms of overall survival. For women at high risk of local recurrence (eg, based on margins, tumour type, presence of lymphovascular invasion, lymph node involvement, young patient age, lack of use of radiotherapy and dose of radiotherapy and other adjuvant therapies), evidence from the

EBCTCG review[93] indicated that long-term survival outcomes are worse, highlighting the need to tailor local therapy to an individual woman's circumstances. Mastectomy is the preferred option for BRCA gene mutation carriers as it is associated with lower recurrence rates. The GDT noted that local recurrence can occur following mastectomy and BCS plus radiotherapy, and that women should be made aware of this risk.

With respect to timing of treatment, the GDT agreed that there should be a recommended number of days within which a woman should undergo surgery following diagnosis. The GDT did note that there were specific instances where there might be delays in meeting this timeline, including receipt of neoadjuvant treatment, fitness for surgery, additional staging requirements, high genetic risk, consideration of breast reconstruction, and individual patient choice.

Recommendations

	Grade
All women with early stage invasive breast cancer who are candidates for breast conserving surgery should be offered the choice of breast conserving surgery or mastectomy	A
The choice of surgery should be tailored to the individual, who should be fully informed of the options, and who should be made aware that radiotherapy is required following breast conserving surgery and that further surgery may be required if the margins are positive or close	A
A woman with early stage invasive breast cancer should be informed of the benefits and harms of radiotherapy prior to making a decision regarding breast conserving surgery or mastectomy	A
Mastectomy rather than breast conserving surgery should be considered if: • 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 • there is multifocal/multicentric disease or extensive malignant microcalcification on mammogram which can not be adequately cleared with an acceptable cosmetic result with breast conserving surgery • there is a contraindication to local radiotherapy (eg, previous radiotherapy at this site, connective tissue disease, severe heart and lung disease, pregnancy) • fitness for surgery is an issue • patient choice	A
Breast conserving surgery can be considered for a woman with a centrally located tumour, although it may require excision of the nipple and areola, which may compromise cosmesis	A
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice points

Breast conserving surgery should be used with caution in known BRCA gene carriers as it may result in high local recurrence rates	✓
A woman with early breast cancer should be informed that local recurrence can occur with either breast conserving surgery or mastectomy	✓
Women should undergo surgery within 20 working days of receiving the final diagnostic result. There may be specific instances where very complex decisions need to be made and/or where women require longer: • women receiving neoadjuvant treatment • women undergoing non-surgical treatment (eg, women unfit for surgery) • women at high risk requiring further staging investigations • women at high genetic risk • women considering breast reconstruction • patient choice	✓
Local therapy should be tailored to the individual to reasonably minimise the risk of local recurrence	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Margins of excision for breast conserving surgery

Background

In women undergoing BCS, completeness of excision minimises the risk of local recurrence. However, there is ongoing debate about the actual width of margin that is necessary for complete excision, varying from one cell to greater than 10 mm.[107] Margins are just one factor in the assessment of the risk of local recurrence. Other factors include tumour type, the presence of lymphovascular invasion, lymph node involvement, patient age, the use and dose of radiotherapy and other adjuvant therapies.[107] A detailed description of pathological requirements for early invasive breast cancer is in Appendix D.

Body of evidence

A systematic review revealed limited evidence relevant to this question, and the main conclusions were based on the expert advice supplied by the GDT and additional evidence from SIGN,[37] the BMJ clinical guideline[100] and the NHMRC guideline,[31] which made limited reference to margins of excision. One retrospective cohort study (Smitt et al., 1995) reported by the BMJ clinical guideline investigated the relationship between completeness of excision and local recurrence after breast conservation in 16 centres. (All of the guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Other data

See also Bleicher and Morrow's (2007)[108] review of the management of close margins in invasive breast cancer.

Summary of findings

There is clear evidence that leaving involved margins results in unacceptably high local recurrence rates. There is ongoing, unresolved debate about how great a margin of excision is necessary, particularly as there are no good RCTs that answer this question. Previous guidelines emphasise the need for 'clear' margins and acceptable cosmesis,[31, 37] but do not provide definitive guidance by way of an actual measurement. Bleicher and Morrow (2007) point out that a 'clear' margin varies considerably, from no tumour cells in direct contact with the inked specimen edge to several centimetres of normal breast tissue.[108]

In data reported by Smitt et al. (1995) from 16 centres evaluating completeness of excision and local recurrence, 13 centres found that incomplete excision significantly increased the risk of local recurrence compared with complete excision (relative risk 1.03, 95% CI 1.03–1.05).[100] The three centres not reporting increased rates of local recurrence after incomplete excision gave higher doses of radiotherapy (65–72 grays [Gy]) to those with involved margins. Two centres also used re-excision, and women with involved margins had only focal margin involvement.[100]

Development of recommendations

Based primarily on expert opinion the GDT noted that detailed assessment of the distance of the tumour from both the radial or circumferential margins and from the superficial and deep margins should be made.

Recommendations

For invasive breast cancer only	Grade
Breast conserving surgery requires the complete excision of the tumour with clear margins and an acceptable cosmetic result following excision and radiotherapy	C
Detailed pathological assessment of the distance of the invasive carcinoma from all margins should be made	C
A circumferential or radial margin of greater than or equal to 2 mm should be achieved where possible	C
For women with margin widths of less than 2 mm several factors should be considered in determining whether re-excision is required. These include: • age • tumour histology (lymphovascular invasion, grade, extensive in situ component, tumour type, eg, lobular carcinoma) • which margin is approximated by tumour (smaller margins may be acceptable for deep and superficial margins) • extent of cancer approaching the margin	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Quadrantectomy versus lumpectomy

Background

Quadrantectomy is similar to segmental excision (see section entitled, 'Background' under 'Mastectomy versus breast conserving surgery' for further information on surgical procedures) but a whole quadrant of the breast is removed. Lumpectomy is the surgical removal of a tumour, with minimal removal of surrounding tissue.

Body of evidence

A systematic review revealed limited evidence relevant to this topic. The BMJ clinical guideline 2006[100] reported data from one retrospective cohort study[109] that compared lumpectomy with quadrantectomy. (The guideline was given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.) One RCT (Milan II)[110] was found comparing quadrantectomy, axillary dissection and external beam radiotherapy (50Gy plus 10 Gy boost) (QUART) with tumorectomy and axillary dissection followed by external beam radiotherapy (45Gy) and a 15Gy boost with 192Ir implantation (TART).

Summary of findings

The results of both studies were consistent with quadrantectomy improving local recurrence rates compared with less radical BCS. The retrospective cohort study examining this issue found significantly more local recurrences with lumpectomy than with quadrantectomy (7% with lumpectomy vs 2% with quadrantectomy), but a major factor associated with local recurrence in the lumpectomy group was incomplete excision.[100] The view expressed in the BMJ clinical guideline is that there is no evidence of any benefit of quadrantectomy over lumpectomy, providing that complete excision is achieved.[100]

Mariani et al, (1998)[110] also found that a better local control can be obtained with the more extensive surgical resection. Using Cox regression models a significant difference between groups was detected for intrabreast tumour recurrence (IBTR) ($p<0.0001$), but not for distant metastases and overall survival. The unadjusted hazard ratio (HR) estimate for the TART versus QUART group was HR 2.81 (95% CI -1.77–4.47), $p<0.0001$ denoting an approximately three-fold increase in the hazard of occurrence of the event for TART women.

Five and ten-year estimates of crude cumulative incidence of IBTR were 4.7% and 7.4% in the QUART group, and 11.6 and 18.6% in the TART group. The difference was not substantially affected by patient or disease characteristics. For women undergoing a breast conserving operation on recurrence, the rate of second IBTR reoccurrence was relatively high, when compared with the rate of IBTR occurrence as first event.

The authors conclude that in treating small breast cancers it seems sensible to adopt a strategy of breast conserving surgery with sufficient margins of healthy tissue such as quadrantectomy followed by radiotherapy, which has proven to have a cumulative 10-year IBTR incidence less than 8% in routine practice, and in the case of local recurrence, the option of mastectomy should be considered by the surgeon and discussed with the patient, especially when the recurrence occurs early after surgery.

Development of recommendations

Despite the evidence for better outcomes with quadrantectomy for local recurrence the GDT notes that more extensive surgery in the breast does have a negative impact on cosmetic outcomes. The important issue is to achieve complete local excision with adequate margins. Because extensive DCIS may follow roughly a segmental distribution, some surgeons prefer to utilise a segmental or quadrant approach in these cases to help ensure adequate margins.

Recommendation

For invasive breast cancer only	Grade
Quadrantectomy is not routinely recommended as breast conserving surgery due to adverse cosmetic results In most cases quadrantectomy is not required to achieve complete excision	B

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Management of the axilla in invasive breast cancer: effectiveness of nodal excision

Background

Axillary surgery is currently required for adequate staging and treatment of early invasive breast cancer. The aims of axillary surgery are to eradicate local disease thereby minimising local recurrence and possibly influencing survival, and to determine prognosis in order to guide adjuvant therapy.

Axillary surgery may be by sentinel lymph node biopsy (SLNB), axillary dissection or axillary sampling. This section includes content on the effectiveness of axillary sampling and axillary dissection. SLNB is covered in a subsequent section in this chapter. Axillary lymph node dissection (ALND) comprises the removal of one, two or three levels of nodes relative to the pectoralis minor muscle. Axillary sampling aims to remove at least four nodes, usually from the lower axilla. Sampling potentially may miss nodes and understage the axilla, and if lymph nodes are positive, must be followed by radiotherapy. Axillary lymph node dissection tends to avoid the need for axillary radiotherapy and reduces the risk of axillary recurrence, but for lymph node-negative women is associated with a higher risk of surgical morbidity, especially lymphoedema.[31]

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

Four clinical guidelines met the inclusion criteria in relation to the clinical questions on the effectiveness of nodal excision. The recommendations of the SIGN guideline (2005)[37] were based on existing clinical guidelines.[31, 74] The Belgian guideline[38] made recommendations based on data from two sources.[111, 112] The BMJ clinical guidelines (2007)[113] included two systematic reviews[93, 114] and one RCT.[115] The International Society of Geriatric Oncology (ISGO) guideline

identified three RCTs, a survival analysis and a review of adults aged 60 years and over.[116] (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Two additional primary trials were identified.[117, 118] The International Breast Cancer Study Group (IBCSG) compared axillary clearance with no axillary clearance[117] in 473 postmenopausal node-negative women aged over 60 years, and Forrest (1995) compared mastectomy and lower axillary node sampling with mastectomy and complete axillary node clearance in 417 patients.[118] (The trials were considered to be of high quality.)

Two further trials, National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04[119] and a trial published by Louis-Sylvestre et al. (2004),[120] and a meta-analysis by Orr (1999)[121] were identified by the GDT for inclusion. A further guideline, the National Breast and Ovarian Cancer Centre (NBOCC) guideline (2008),[122] was identified.

Summary of findings

The SIGN guideline reported no consensus regarding the best way to manage the axilla but recommended that axillary surgery should be performed in all patients with invasive breast cancer. Procedures include axillary node sampling, axillary node clearance and SLNB.[37, 122]

Survival and recurrence

Chetty et al. (2000) reported that axillary sampling was not associated with significantly worse survival compared with axillary clearance, and rates of node positivity were similar in both groups.[113] Other studies have shown that sampling understages the axillary nodes in approximately 10% of women and axillary recurrence rates are higher for women with positive nodes on sampling unless axillary radiotherapy is given.[113] The Edinburgh trials reported no difference in loco-regional recurrence with axillary sampling plus radiotherapy compared with axillary clearance.[113]

Both the EBCTCG (1995)[93] review and Forrest (1995)[118] found no significant difference between axillary sampling or axillary clearance in terms of mortality or recurrence over 10 years' follow-up. A non-significant increase in the rate of loco-regional relapse was observed for those treated by axillary node clearance, this being due primarily to increased relapse on the non-irradiated chest wall (clearance 21% vs sampling 12% in those with node-positive disease).[118] Forrest (1995) concluded that if adequate sampling revealed non-involved nodes, routine postoperative irradiation was not necessary.

IBCSG Study 10-93 compared axillary dissection with no axillary surgery for older women with clinically clear axillary nodes. The study was powered for quality of life endpoints but showed that at six years, a similar proportion of patients in each group experienced recurrence, appearance of a secondary tumour or death (67% in the axillary clearance group vs 66% in the group without axillary clearance). Death from any cause at six years was also similar in both groups (75% in the axillary clearance group and 73% in the group without axillary clearance).[117]

The ISGO guideline[116] reported evidence from three RCTs and a survival analysis indicating no difference in outcome in older patients with small tumours without palpable lymph nodes when ALND was omitted. The guideline also cited a review conducted in older women.

This review concluded that ALND should be used when there is clinical suspicion of axillary lymph node involvement or high-risk tumours, since adjuvant treatment could depend on the pathological results of the ALND.

The NSABP B-04 trial[119] (for 20-year follow-up) compared the effectiveness of three different modes of treatment in women with clinically negative lymph nodes: radical mastectomy (including resection of axillary nodes), total mastectomy (sparing the axillary nodes) plus loco-regional/axillary irradiation and total mastectomy with no axillary irradiation. As a result of the general acceptance of that study, prophylactic axillary node dissection for women with clinically negative axillae is considered diagnostic, but not therapeutic, by many oncologists. Nevertheless, NSABP B-04 is considered to be underpowered to exclude a small survival advantage.

A Bayesian meta-analysis of six RCTs published in 1999 by Orr[121] showed that prophylactic axillary node dissection improved survival, ranging from 4% to 16%, corresponding to a risk reduction of 7% to 46%. Combining the six trials showed an average survival benefit of 5.4% (95% CI 2.7–8.0, probability of survival benefit >99.5%).[121] Orr concluded that axillary node dissection improved survival in women with operable breast cancer, although trial limitations prevented the extrapolation to T1a tumours (see Appendix A for TNM classification).[121]

The trial conducted by Louis-Sylvestre et al.[120] reported more loco-regional recurrence after radiotherapy than after axillary dissection but no difference in overall mortality.

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.[123]

No evidence was identified on the effectiveness of excising the axillary, supraclavicular and internal mammary chain nodes compared with no excision.

Adverse events

The rate of arm swelling was significantly higher following axillary clearance than after axillary sampling.[115] Arm lymphoedema rates were highest for axillary dissection plus axillary radiotherapy (12–60%) and lowest for axillary sampling alone (0–21%).[114] Restricted arm movement and arm pain were significantly more common early post-surgery in those with axillary clearance (39% and 23%) than in those without (15% and 7%), but no difference in quality of life was found after one year of follow-up.[117] Other adverse events that have been identified include seroma formation, altered sensation in the arm, and reduced shoulder movement in the long term.[122]

Development of recommendations

The systematic review of the published evidence highlighted the importance of accurate assessment and management of the axillary nodes in women with early breast cancer. The GDT noted that several adverse events are associated with the management of the axilla and that women should be advised of the benefits and potential harms associated with each procedure. The GDT also concluded that axillary sampling has now been largely superseded by sentinel lymph node-based management.

Additional good practice points were formulated by the GDT in other important areas relating to axillary surgery, including the role of the multidisciplinary team, the role of radiotherapy, and the preservation of the intercostobrachial nerve.

Recommendations

For invasive breast cancer only	Grade
Assessment of axillary lymph node status should be undertaken for most early invasive breast cancers in order to stage the disease, to minimise the risk of loco-regional recurrence and assist in the planning of adjuvant therapy	A
Axillary node dissection is normally recommended in a woman with clinically involved nodes or breast cancer greater than 3 cm or multifocal disease These criteria and the role of sentinel node-based management in this setting are currently the subject of ongoing clinical trials (SNAC2, and limited data from NSABP B32 and ALMANAC trials)	A
Sentinel lymph node biopsy should be offered as a suitable alternative to axillary dissection in a woman with a: • unifocal tumour of diameter less than or equal to 3 cm; and • clinically negative axilla, including consideration of imaging findings	B
Women should be informed regarding side effects of axillary node dissection, including seroma formation, altered sensation in the arm, lymphoedema and possible reduced shoulder movement long term	A
Axillary node dissection levels I and II (and level III nodes where indicated) should be undertaken in all women with clinically node-positive disease	A
Due to lack of evidence no recommendations were made for the effectiveness of excising the supraclavicular and internal mammary chain nodes versus no excision	I
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice points

For invasive breast cancer only	
The results of axillary surgery, and any unusual or difficult cases, should be discussed at a multidisciplinary team meeting	✓
Radiotherapy to the axilla may be considered as an alternative to surgery for a woman who is unfit for or who declines axillary surgery	✓
For women undergoing axillary dissection, the intercostobrachial nerve should be preserved where this does not compromise cancer clearance	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Diagnostic accuracy of sentinel lymph node biopsy

Background

ALND at level I, II or III comprises the surgical removal of a significant proportion of lymph nodes from the axilla. ALND has been associated with significant morbidity including longer postoperative stay, the need for an axillary drain, longer recovery, postoperative pain, limitation in shoulder movement and, in particular, lymphoedema.[31]

SLNB is a minimally invasive technique that is associated with reduced morbidity. The sentinel node is the first lymph node to which tumour cells are likely to spread from the primary breast tumour. The sentinel node is located by injecting a dye or radioactive isotope or both around the primary tumour and locating the lymph node/s to which the detection agent travelled. When identified, the sentinel node/s can be surgically excised and pathologically evaluated to determine whether tumour cells are present. If the sentinel node is positive, then ALND is usually performed. This process is called sentinel lymph node-based management of the axilla.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

The NBOCC guideline[122] identified 11 RCTs on SLNB. Five evaluated different technical aspects of the procedure. Six trials addressed the accuracy of the technique and morbidity (see Table 4.2). All of the trials in Table 4.2 were randomised trials that excluded women with clinically positive nodes, women with multicentric/multifocal tumours, pregnant or breastfeeding women, women with known allergies to radioisotopes or blue dye, and women with previously treated breast cancer or axillary surgery on the affected breast. (The guideline was given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Four systematic reviews were identified that met inclusion criteria. Cox (2000) conducted a cross-sectional study of 1147 breast cancer patients with a suspicion of node-negative breast cancer and a subsequent meta-analysis of women undergoing SLNB.[136] The Cox systematic review demonstrated significant heterogeneity between the 12 studies. (The systematic review was considered to be of low quality.) Fraile (2000) evaluated the technical success rate and sensitivity of SLNB compared with ALND in trials including 50 or more women.[137] Miltenburg (1999) evaluated the technical success of SLNB followed by ALND in 912 patients in 13 studies.[138] (These systematic reviews were considered to be of high quality.) Kim (2005) reviewed 69 studies of 10,454 patients who underwent complete ALND after SLNB, regardless of the results of SLNB. (This systematic review was considered to be of very high quality.)[139]

Table 4.2 Randomised trials comparing sentinel lymph node biopsy with axillary lymph node dissection reported in the National Breast and Ovarian Cancer Centre guideline

Trial name	Population	SLNB (no. of patients)	ALND (no. of patients)	SLNB group (method of sentinel node detection)	ALND group	Outcome measures reported by trial
Milan[124, 125]	Women with primary breast cancer, aged 40–75 years, cancer ≤2 cm, BCS performed before SLNB or ALND	259	257	SLNB (isotope) to ALND if sentinel node positive	SLNB to ALND	Axillary metastases, disease free and overall survival, detection rate
ALMANAC[126]	Women and men aged <80 years with clinically node-negative invasive breast cancer	495	496	SLNB (blue dye ± isotope) to ALND or axillary radiotherapy if sentinel node positive	Standard axillary treatment (ALND or four node sampling)	Arm and shoulder morbidity, QOL, detection rate
SNAC I[127–129]	Women with histologically or cytologically confirmed invasive breast cancer ≤3 cm	544	544	SLNB (blue dye ± isotope) to ALND if sentinel node positive	SLNB to ALND	Arm volume, QOL, detection rate
NSABP B-32[130–132]	Women with operable invasive breast cancer and clinically negative nodes	2804	2807	SLNB (blue dye ± isotope) to ALND if sentinel node positive	SLNB to ALND	QOL, false negative rate, detection rate
Cambridge[133]	Patients with ≤3 cm invasive node-negative breast cancer	143	155	SLNB (blue dye ± isotope) to ALND if sentinel node positive	ALND	Physical and psychosocial morbidity
GIVOM[134, 135]	Patients aged <80years with ≤3 cm node-negative breast cancer	352	345	SLNB (isotope) to ALND if sentinel node positive	SLNB to ALND	Detection, accuracy, QOL, overall and disease-free survival

Note: BCS = breast conserving surgery; QOL = quality of life; SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection

Source: National Breast and Ovarian Cancer Centre. Recommendations for the use of sentinel node biopsy in early (operable) breast cancer. Surrey Hills, NSW: 2008.

Seven primary studies were identified that met inclusion criteria. Krag et al. (2007) reported on the NSABP B-32 randomised trial,[132] which evaluated sentinel lymph node resection followed by immediate conventional axillary lymph node dissection of remaining non-sentinel lymph nodes and sentinel lymph node resection without axillary lymph node dissection if sentinel lymph nodes were negative on intraoperative cytology and histological evaluation in 5611 patients. Martin (2005) conducted a cross-sectional study of SLNB performed in 4116 patients using blue dye alone, radioactive colloid alone or both at the discretion of the surgeon followed by completion levels I and II ALND.[140] Veronesi et al.[124, 125] reported on the Milan trial, a prospective randomised trial in which all patients (n=516) underwent either quadrantectomy or wide local excision and had sentinel node biopsy. Tafra (2001)[141] conducted a multicentre study of 529 patients undergoing SLNB using a combination of blue dye and technetium sulphur colloid (Tc99). Bergkvist (2001)[142] reported on a prospective multicentre study of 498 patients with unifocal breast cancer who underwent SLNB with blue dye plus or minus probe followed by ALND. McMasters (2000)[143] conducted a multicentre study of 806 patients who had undergone SLNB followed by completion levels I and II ALND using single agent blue dye alone or radioactive colloid alone compared with a combination of both agents. (All of the trials were considered to be of high quality.)

Summary of findings

Seven trials reported high success rates (90–98%) for the localisation of the sentinel node in both the SLNB and ALND groups:

- SNAC1[128, 129]
- GIVOM[135]
- NSABP B-32[130]
- ALMANAC[126, 144]
- Tafra et al.[141]
- Bergkvist et al.[142]
- McMasters et al.[143]

The accuracy of SLNB (ie, the ability of SLNB to correctly predict the status of the axillary nodes as positive or negative) could be reported only in trials that performed SLNB followed by ALND in the control arm. These trials included:

- Milan[124, 125]
- SNAC1[128, 129]
- NSABP B-32[130–132]
- GIVOM[135]
- Tafra et al.[141]
- Bergkvist et al.[142]
- McMasters et al.[143]

The systematic review by Fraile concluded that SLNB has been shown to be a practical alternative to ALND.[137] Fraile states that as a result of the detailed pathological assessment performed on the sentinel nodes, in some cases nodal metastases may be found on SLNB that would be missed with routine ALND.

Increased age was found to be a factor in the failure to identify a sentinel node.[141, 143]

Accuracy/false negative rate

Table 4.3 summarises the sensitivity, specificity, and positive and negative likelihood ratio data on the accuracy of SLNB.

Table 4.3 Accuracy of sentinel lymph node biopsy

Author	Comparison/ technique	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio
Krag 2007[132] (NSABP B-32 trial)	SLNB alone	60.4%	82%	3.35	0.45
	SLNB + ALND	90.2%	70%	3.0	0.14
Cox 2000[136]	SLNB	98.2%	100%	–	–
Fraile 2000[137]	SLNB compared with ALND	91%	85%	6.0	0.1
Martin 2005[140]	SLNB followed by ALND	92%	100%	∞	0.08
Miltenberg 1999[138]	SLNB followed by ALND	98%	66.7%	2.94	0.03
Veronesi 2003/2006[124, 125] (Milan trial)	SNB followed by axillary dissection	99%	100%	∞	0.01
	ALND	91%	100%	∞	0.09
McMasters 2000[143]	SLNB by injection technique				
	Single agent	89.1%	100%	∞	0.1
	Dual agent	94.2%	100%	∞	0.058
	All techniques	92.2%	100%	∞	0.78

Note: SLNB = sentinel lymph node biopsy; ALND = axillary lymph node dissection

The false negative rates in the GIVOM study,[134, 135] with no training protocols, was higher at 15.7% than in the Milan[124, 125] (8.8%), SNAC1[128] (5.5%) and NSABP B-32[132] (9.7%) trials. Tafra et al.,[141] Bergkvist et al.[142] and McMasters et al.[143] reported false negative rates of 13%, 11% and 11.8%, respectively.

The false negative rate of SLNB decreases with the increasing number of sentinel nodes removed (NSABP B-32).[132] However, the added benefit of a lower false negative rate for the removal of more than four sentinel nodes from the axilla is very small.

Training and experience

The NBOCC guideline[122] and Kim's[139] 2005 systematic review both noted the importance of surgeons being trained and experienced in the technique. Lower false negative rates and higher sensitivity and accuracy were noted in trials where surgeons were required to have previously performed a minimum number of SLNBs followed by ALND.[122, 139] This finding is in contrast to that of trials such as the GIVOM trial,[134, 135] which did not require formalised training or experience.

The SNAC1 trial[128, 129] protocol stated that the surgeon performing the SLNB procedure should have completed at least 20 consecutive procedures, with greater than 90% success rate in locating the sentinel node. Tafra et al.[141] noted that accuracy increased and false negatives decreased when a surgeon had performed 30 or more procedures.

The NBOCC guideline[122] recommends that the team performing the SLNB should comprise a surgeon, a nuclear physician, a pathologist, an anaesthetist, as well as appropriate nursing support.

Technique

The NBOCC guideline[122] included five randomised trials that evaluated technical aspects of the SLNB procedure. Trials conducted by Hung et al. (2005), Meyer-Rochow et al. (2003) and Radovanovic et al. (2004) suggest that a combination of radioisotope and blue dye may be associated with a higher rate of sentinel lymph node detection than blue dye method alone. McMasters et al. (2000) reported a lower false negative rate in dual agent injection (5.8%) than with single agents (11.8%). All of these RCTs involved relatively small numbers of women. The systematic review by Kim,[139] which reviewed 69 studies involving 10,454 women, also demonstrated higher sentinel lymph node identification rates and lower false negative rates with use of the combination of radiotracer and blue dye than with either technique alone.

The use of each method in isolation also provided good detection and accuracy (see Table 4.3), although randomised trial data for blue dye alone is limited. Bergkvist et al.[142] reported that the detection rate using the gamma probe alone was 84% compared with blue dye alone at 67%. Two additional studies cited by the NBOCC guideline,[122] Rodier et al. (2007) and Povoski et al. (2006), reported that peritumoural, periareolar and intradermal injection sites were all effective for detecting the sentinel node in the axilla.

Studies suggest that the highest sentinel lymph node detection rates and lowest false negative rates are achieved with the combination of preoperative lymphoscintigraphy with intraoperative use of the gamma probe and blue dye.[122]

Pathology

The NBOCC pathology guidelines[145] state that there is strong evidence that the greater the number of sections examined, the greater the chance of detecting metastases. These pathology guidelines also indicate that where intraoperative assessment is required, cytological imprints and/or a frozen section assessment may be undertaken.

The precise pathology protocol and, in particular, the section numbers examined, varies widely from study to study. The NBOCC pathology guidelines recommended that for definitive assessment, if the initial haematoxylin and eosin-stained section is negative, four sections should be cut at 500 microns through a 2 mm sliced node,

three stained with haematoxylin and eosin, with one randomly chosen section submitted for cytokeratin immunohistochemistry.[145] The NBOCC guideline[122] noted that the detection of metastatic disease was enhanced through the detailed, definitive histological assessment of the sentinel node.

There is a potentially high risk of false negative rates with intraoperative assessment.[130–132, 134, 135] Confirmation with definitive histology reduces this false negative rate.[122]

Development of recommendations

The statements and recommendations for SLNB in early breast cancer are based primarily on latest evidence from RCTs, with some additional points from systematic reviews and meta-analyses. It should be noted that of the RCTs, only the ALMANAC[126, 144] and the NSABP B-32[130–132] studies included tumours over 3 cm in size, and in these studies 75% and 80% of women, respectively, had tumours less than or equal to 2 cm in size. There is not adequate evidence regarding SLNB for women with larger or multifocal cancers. Therefore, these recommendations apply to women with clinically negative nodes (including consideration of imaging findings) and with unifocal tumours less than or equal to 3 cm in diameter.

The GDT emphasises the need to discuss the potential harms and benefits with the woman prior to undergoing the SLNB procedure, as well as the potential for an unsuccessful SLNB or false negative result.

Recommendations

	Grade
Sentinel lymph node biopsy should be offered as a suitable alternative to axillary dissection in a woman with a: • unifocal tumour of diameter less than or equal to 3 cm; and • clinically negative axilla, including consideration of imaging findings	B
A woman should be informed of the potential risks and benefits of the sentinel lymph node biopsy technique and procedure	C
A woman should be informed of the potential for an unsuccessful sentinel lymph node biopsy or a false negative result	C
The team performing the sentinel lymph node biopsy should comprise a surgeon, nuclear physician (where available), pathologist, anaesthetist and appropriate nursing support	C
The surgeon performing sentinel lymph node biopsy should be appropriately trained and experienced in the technique	B
Where possible lymphatic mapping with preoperative lymphoscintigraphy in combination with intraoperative use of the gamma probe and blue dye should be used to locate the sentinel node	B
Where a combination technique for the sentinel lymph node biopsy procedure is unavailable, use of blue dye or radioisotopes alone is appropriate	B

continued over...

Recommendations continued...

	Grade
Detailed, definitive histological assessment of the sentinel node is recommended to detect metastatic disease	C
Intraoperative assessment of the sentinel node should be confirmed with a definitive histological assessment to reduce the risk of a false negative result	B
For definitive assessment of a sentinel node (if the initial haematoxylin and eosin-stained section is negative) four sections at 500 microns through each 2 mm slice should be cut and three sections should be stained with haematoxylin and eosin with one randomly chosen section submitted for cytokeratin immunohistochemistry	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

The results of the ongoing SNAC2 trial, which evaluates the accuracy of sentinel node biopsy in large and/or multifocal tumours, are awaited. (SNAC2 is a multicentre randomised trial of sentinel node-based management compared with axillary clearance in operable early breast cancer at the University of Sydney, NHMRC Clinical Trials Centre.)

Effectiveness of sentinel lymph node biopsy compared with axillary dissection

Background

Although sentinel lymph node-based management results in less morbidity than ALND does,[124, 126] it is associated with a risk of leaving positive lymph nodes in the axilla (the false negative rate) with the possibility that this might result in understaging of the axilla, omission of adjuvant therapies in some cases, local recurrence and possibly poorer cancer outcomes. This section reviews the evidence for the effectiveness of sentinel lymph node-based management and ALND.

Body of evidence

The systematic review undertaken to answer this question identified the following evidence that met the inclusion criteria.

Two clinical guidelines met the inclusion criteria. The International Society of Geriatric Oncology[116] was based on four publications from three RCTs,[124, 146–148] one survival analysis[149] and one review.[146] The NBOCC guideline (2008) on sentinel node biopsy[122] was based on 11 RCTs, five of which evaluated different technical aspects of the procedure. Six trials reported in the NBOCC guideline addressed the accuracy of the technique and morbidity (see Table 4.2 for details). (Both guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

One additional cohort study by Naik et al.[150] was identified that addressed this topic. The study focused on axillary local recurrence for those undergoing SLNB followed by ALND in sentinel node-positive patients. (The trial was considered to be of high quality.)

Summary of findings

Overall and disease-free survival

The NBOCC guideline[122] on sentinel node biopsy reported on overall and disease-free survival in three trials (Milan, GIVOM, ALMANAC), with equivalent rates in both the SLNB and ALND groups. None of these trials was adequately powered to show equivalence of the two operative techniques either for local recurrence or for survival outcomes and follow-up was short. The Milan Trial reported five-year data but the ALMANAC trial only reported on 12 months follow-up. Further follow-up and meta-analysis of long-term results of the RCTs are required to ascertain if SLNB results in poorer overall and disease-free survival compared with ALND.

Risk of recurrence

The long-term risk of regional recurrence is at present unknown. The maximum reported duration of follow-up amongst the RCTs is currently limited to five years.[122] In the cohort study reported by Naik et al.[150] axillary local recurrence occurred in 0.25% of patients with sentinel lymph node-based management and appeared to be at least equivalent to ALND.

Adverse events/morbidity

SLNB is associated with significantly lower morbidity when compared with ALND for incidence of arm lymphoedema, pain, disability and sensory deficit.[122] Allergic reactions, although not common, have been associated with the use of blue dye.[122] No adverse events associated with the dose of radiation administered during the SLNB procedure have been reported.

Non-axillary sentinel nodes

SLNB, in particular where preoperative lymphscintigraphy and peritumoral injection are used, identifies nodes outside the axilla, most commonly in the internal mammary nodes, but sometimes in intramammary or supraclavicular positions. There is limited evidence to determine the value of excising non-axillary sentinel nodes.[122] It is known that the finding of a positive internal mammary node may influence further therapy and has the same prognostic significance as a positive axillary node. Women with both a positive axillary and internal mammary node have a poorer prognosis than women with one or other alone. If a positive internal mammary node is found, it does indicate the need for consideration of radiotherapy to this region. In the opinion of the GDT, radiotherapy should be considered, if a positive non-axillary node is identified.

Other outcomes

There is limited or no trial data available on the effectiveness of SLNB compared with axillary dissection for several subgroups, including:[122]

- women with tumours greater than 3 cm
- 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.

Development of recommendations

Based on the New Zealand Guidelines Group's systematic review of the published evidence, the GDT concluded that SLNB was an effective technique compared with ALND with an associated reduction in morbidity of the arm for women with primary breast cancer less than or equal to 3 cm in size and with clinically negative nodes. The GDT noted the limited duration of follow-up in RCTs and that further results over a longer period are required to determine the long-term benefits of cancer outcomes from using SLNB compared with ALND. The GDT also noted that recommendations to individuals should be based on their absolute risk of axillary node involvement and resulting absolute risk of a false negative SLNB. These factors should be discussed with the patient. Recommendations to individuals should also take into account any uncertainties about the long-term effects of SLNB.

Some recommendations in this section are reproduced from other sections that also address the broader topic of management of the axilla as deemed appropriate by the GDT for completeness.

Recommendations

	Grade
Sentinel lymph node biopsy should be offered as a suitable alternative to axillary dissection in a woman with a: • unifocal tumour of diameter less than or equal to 3 cm; and • clinically negative axilla, including consideration of imaging findings	**B**
A woman should be informed of the potential risks and benefits of the sentinel lymph node biopsy technique and procedure	**C**
A woman should be informed of the potential of an unsuccessful sentinel lymph node biopsy or a false negative result	**C**
If the sentinel node is not identified at the time of sentinel lymph node biopsy, axillary dissection should be performed	**B**
If a positive sentinel node is identified, axillary dissection is recommended with due consideration of the risks and benefits to the individual	**B**
If a negative sentinel node is identified, clinical follow-up of the axilla is recommended	**B**
The team performing the sentinel lymph node biopsy should comprise a surgeon, nuclear physician (where available), pathologist, anaesthetist and appropriate nursing support	**C**
The surgeon performing sentinel lymph node biopsy should be appropriately trained and experienced in the technique	**B**
Surgeons and anaesthetists should be aware of the possibility of adverse reactions in some patients during the sentinel lymph node biopsy procedure	**C**
For a woman with a positive non-axillary node (eg, internal mammary, supraclavicular or infraclavicular nodes) radiotherapy to those nodes should be considered	**C**
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

The long-term results, including adequately powered analyses of cancer outcomes, from several large RCTs comparing SLNB and ALND are being awaited:

- NSABP B-32[130, 131]
- SNAC1[128, 129]
- GIVOM[135]
- ALMANAC.[126, 144]

The results of the American College of Surgeons ACOSOG Z0011 trial,[151] which asked whether ALND is required after the finding of macrometastases on SLNB, are also awaited. However, accrual has been slow and recruitment has closed early as a result.

Some technical results have been published, including data on complications, quality of life and morbidity, but none of these studies can report on differences in recurrence and survival at this stage.

SNAC2 is currently recruiting and seeks to provide evidence on cancer outcomes for women with larger or multifocal tumours who are not so far included in randomised trials or are included only in very small numbers.

The European AMAROS trial is also currently recruiting and examines whether it is better to perform ALND or axillary radiotherapy for women with positive sentinel nodes.

Other important unanswered questions about the use of sentinel node biopsy in early breast cancer not already addressed in the trials detailed above relate to:

- accuracy in neoadjuvant treatment
- accuracy of sentinel node biopsy in recurrent breast cancer
- the significance of and appropriate approach to the non-axillary sentinel node
- optimal pathological methods for assessing the sentinel node
- the role and method of intraoperative assessment
- overall and disease-free survival following sentinel node biopsy (meta-analysis of RCTs with long-term follow-up).

Axillary clearance after sentinel lymph node biopsy

Background

For some women, a positive sentinel node or nodes will be the only positive node/s in the axilla. This raises the question of whether an ALND is always necessary after finding a positive node.

Body of evidence

As this area was not prioritised for a full systematic review, a non-systematic review and the opinion of the GDT were used in the development of the recommendations.

Summary of findings

For the purposes of the following discussion, micrometastasis includes isolated tumour cells unless otherwise stated.

Routine practice has been to perform an axillary node dissection if SLNB yields a node involved by cancer. Degnim et al.[152] reported that in SLNB with macroscopic metastasis or metastases to sentinel nodes, 45% to 75% of these women have involved non-sentinel nodes elsewhere in the axilla. Even for women with micrometastases (metastases ≤2 mm in size) the prevalence of positive non-sentinel nodes is reported to be 12% to 20%.[152, 153] Approximately half of these positive non-sentinel nodes will be macrometastases.[153]

The Belgian guidelines[38] suggest that if SLNB is not able to identify a positive node at the time of surgery, ALND is an alternative. For women with tumours greater than 3 cm or with clinically or ultrasonographically positive nodes, axillary dissection is mandatory.[38]

The likelihood of a positive non-sentinel node in the presence of micrometastatic disease in a sentinel node is related to several further factors. The likelihood of a positive non-sentinel node goes up according to the size of the micrometastasis in the sentinel node,[153, 154] in the presence of extra capsular extension of tumour in the sentinel node[155, 156] and with increasing number of involved sentinel nodes. The likelihood of a positive non-sentinel node decreases according to the number of negative sentinel nodes present.[157] Other authors have used the ratio of positive to negative sentinel nodes to give an indication of risk for involvement of non-sentinel nodes. Presence of lymphovascular invasion[154] and increasing primary tumour size[156] are also related to risk of involvement of non-sentinel nodes.

The Memorial Sloan Kettering Institute has produced a nomogram based on its own series of over 4000 SLNBs to help surgeons and women predict the likelihood of involvement of a non-sentinel node. However, not all subsequent authors have been able to reproduce this nomogram. The nomogram can be accessed from the Memorial Sloan Kettering Institute website (www.mskcc.org).

ALND is recommended for women identified as node-positive[116] and for those where disease (micro metastases or macrometastases) is found in the sentinel node. The ISGO guideline[116] reported that controversy exists regarding the need for ALND following a positive SLNB. However, the Belgian guideline recommended ALND level I and II if the SLNB is positive (<0.2 mm).[38]

At present the standard of care following a positive SLNB is generally regarded as axillary dissection unless there are exceptional circumstances. The issue of whether to do an axillary lymph node dissection following the finding of micrometastasis or metastases in a sentinel node or nodes is currently the subject of International Breast Cancer Study Group trial IBCSG 23-01 (a randomised trial of axillary dissection compared with no axillary dissection for patients with clinically node-negative breast cancer and micrometastases in the sentinel node).

Good practice point

Axillary lymph node dissection is recommended where positive nodes are identified on sentinel lymph node biopsy in a woman with early breast cancer Even if micrometastases only are found, because there is a significant incidence of positive non-sentinel nodes, axillary lymph node dissection should normally be performed unless the patient is entered into a randomised trial Note: The data from the IBCSG 23-01 trial is awaited. This trial compares axillary node dissection with no axillary node dissection in patients with micrometases ≤2 mm/tumour ≤5 cm/ tumour (International Breast Cancer Study Group)	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Further important questions relating to the use of SLNB in early invasive breast cancer that have yet to be answered by clinical research are listed at the end of the previous section entitled, 'Effectiveness of sentinel lymph node biopsy compared with axillary dissection'.

Breast reconstruction

Background

Breast reconstruction involves the use of a prosthesis or tissue from elsewhere in the body to rebuild a breast shape following mastectomy. Methods of reconstruction include tissue expansion, use of implants, pedicled flaps, and free tissue transfers. Immediate breast reconstruction occurs at the time of initial surgery, whereas delayed reconstruction requires a subsequent surgical procedure once a woman has recovered from initial surgery and any other adjuvant treatments. The use of immediate or delayed breast reconstruction is an important means of enhancing body image and self-confidence after mastectomy. However, decisions regarding whether to choose breast reconstruction and when this should be performed (immediate or delayed) are complex.

Body of evidence

The systematic review undertaken did not identify any studies comparing the effectiveness of immediate compared with delayed breast reconstruction. Some evidence regarding local recurrence and surgery was available in the SIGN guideline[37] and comparing immediate and delayed reconstruction in the Belgian guideline.[38] The Australian NHMRC 2001 guideline noted the psychological benefit of communicating benefits and disadvantages of each procedure.[31] (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Summary of findings

Recurrence

The SIGN guideline[37] reported that 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. These findings were based on observational studies.

Radiotherapy

The GDT noted that radiotherapy to the reconstructed breast may result in significantly worse cosmetic outcomes, especially when an implant has been used. If post-mastectomy radiotherapy is required, delayed reconstruction may be preferable to immediate reconstruction for this reason and because reconstruction can sometimes interfere with delivery of radiotherapy. It is also very difficult to use tissue expansion in irradiated tissue, so reconstructive surgery options become more limited after radiotherapy, and delayed reconstruction, on average, yields poorer results than immediate reconstruction. A further difficulty women and clinicians face is that it is frequently not possible to ascertain preoperatively which patients will need post-mastectomy radiotherapy, because full pathology results become available only after primary cancer surgery has been completed.

Other outcomes

The SIGN guideline[37] noted that breast reconstruction can yield psychological benefit. The guideline reported that immediate reconstruction produces better cosmetic results. These findings were based on observational studies.

The GDT noted that complications arising from immediate reconstruction may occasionally delay adjuvant therapy. The choice of surgery is dependent on several factors, including breast size, adequacy of skin flaps, and whether radiotherapy is planned or has previously been used. Additional surgery to the opposite breast may be required for the purpose of symmetry. Breast reconstruction may also help to reduce a woman's concern about her cancer, as reconstructive surgery repairs the site that serves as a constant reminder of the life-threatening nature of the disease. A woman preparing for mastectomy should discuss the option of breast reconstruction with a specialist surgeon and should be supported in her decision-making.

Development of recommendations

Based on the available evidence, the GDT noted the psychosocial effects of breast reconstruction and, in particular, that the relative merits of immediate compared with delayed surgery require further study. The GDT noted the importance of providing adequate information to women about the advantages and disadvantages of the procedures and timing of those procedures. In the absence of high-quality evidence from the literature, Box 4.1 has been prepared largely on the basis of the expert opinion of the GDT.

Box 4.1 Advantages and disadvantages of immediate compared with delayed breast reconstruction

	Advantages	Disadvantages
Immediate breast reconstruction	• Better cosmetic outcome • Psychological benefit of waking with a reconstructed breast • Easier to resume normal clothing attire	• Complications of breast reconstruction can sometimes delay chemotherapy or radiotherapy* • If women require radiotherapy, they have a poorer cosmetic outcome • Requires taking in a further amount of information and further decision-making at a time when women may not feel able to do so
Delayed breast reconstruction	• Does not interfere with adjuvant therapy • Enables the woman to focus on her cancer treatment at the time of initial diagnosis and avoid having to consider additional information and decisions at a time when she may not feel able to do so • Allows more time to consider different reconstruction options	• Cosmetic outcomes are on average poorer than immediate reconstruction • Requires more operations than immediate reconstruction • Tissue expansion not possible or very limited if chest wall radiotherapy has been used

* Neo-adjuvant chemotherapy may avoid the possibility that a complication of immediate breast reconstruction delays adjuvant therapy

Recommendations

	Grade
A woman being prepared for a mastectomy should be informed of the option of breast reconstruction and, if appropriate, should discuss the option with a surgeon trained in reconstructive techniques prior to the surgery	C
The use of immediate or delayed breast reconstruction is an important means of enhancing body image and self-confidence after mastectomy and both options should be available to women in the public and private sectors in New Zealand	C

Good practice points

Breast reconstruction may be immediate or delayed. If it is immediate, discussion of breast reconstruction should include the fact that a complication may occasionally delay adjuvant chemotherapy or radiotherapy	✓
Neo-adjuvant chemotherapy may avoid the possibility that a complication of immediate breast reconstruction delays postoperative chemotherapy	✓
A woman should be provided with information on the advantages and disadvantages of breast reconstruction	✓
A woman who chooses to have a mastectomy with or without reconstruction should be supported in that decision	✓
If post-mastectomy radiotherapy is likely women should be aware that this may impact on the cosmetic outcome of breast reconstruction	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Venous access and risk of lymphoedema

Background

A potential consequence of early breast cancer surgery and/or radiotherapy is the development of lymphoedema. This is a chronic condition in which there is swelling of the affected arm or breast with associated physical and psychological morbidity, including:

- the swelling itself
- pain and heaviness of the arm or breast
- increased risk of cellulitis
- decreased functional capacity
- decreased quality of life.

Body of evidence

The systematic review undertaken to address the question of whether venous access to the arm on the side of axillary surgery increases the risk of lymphoedema identified the following evidence that met the inclusion criteria.

Clark et al.[158] conducted a prospective observational study for risk factors for breast cancer-related arm lymphoedema. (The study was considered to be of low quality.) The remaining evidence is based on international expert opinion, specifically a 2006 article by Cole.[159]

Summary of findings

Lymphoedema is a significant clinical problem, with Clark et al.[158] reporting an incidence of one in five women developing the condition following treatment for breast cancer. Risk factors for lymphoedema cited by Clark and colleagues include hospital skin puncture, mastectomy and increased body mass index, and the need for these to be considered in clinical practice is highlighted.

Additional risk factors noted by the GDT include a woman having undergone axillary surgery and/or radiotherapy; an infection in the arm; having a high body mass index; having any other injury to the arm, including insect bites and sunburn; increased age; undertaking air travel; and positive axillary node status.

International expert opinion

Cole[159] concluded that blood pressure measurements and non-accidental skin puncture procedures on the ipsilateral limb to the axillary node surgery should be avoided. Patients who have had unilateral axillary node surgery should be encouraged to offer the contralateral arm for non-accidental skin puncture procedures. Cole considered that by raising awareness and taking precautions to avoid injury, the likelihood of lymphoedema could be reduced. Lymphoedema can be both physically and psychologically distressing and serve as a reminder of the woman's cancer diagnosis. Further research on non-accidental skin puncture procedures as a risk for lymphoedema is vital.

Development of recommendations

The GDT noted a paucity of data for this question, which makes it difficult to draw any strong conclusions. Further research is required.

The GDT also noted that although the use of the contralateral arm is preferred, this imposes a higher risk of vascular complications in that arm, including pain, chemical phlebitis, fixed flexion deformities of the limb and deep vein thromboses. The alternative of using a central venous access device also imposes an additional scar on the anterior chest wall, and risks serious infections, catheter-related thromboses, with a significant number of central venous access devices having to be removed prematurely.

The GDT acknowledges that making a decision for non-accidental skin puncture in the affected limb involves several considerations, including the risk of delaying chemotherapy to insert central venous catheters, risk factors for the development of lymphoedema, and the predicted level of benefit from chemotherapy for that individual.

The GDT also noted that women should be advised about lymphoedema prevention and the support services available. Further information and support in relation to lymphoedema is available through the Cancer Society of New Zealand website (www.cancernz.org.nz) and from www.vascular.co.nz/lymphoedema.htm, an internet website that includes information on lymphoedema. (Note: The evidence base for the information on these websites has not been assessed by NZGG.)

Good practice points

In a woman who has undergone axillary surgery and/or radiotherapy health practitioners should avoid, if possible: • taking blood from the associated arm • obtaining blood pressure readings from the associated arm • insertion of cannula, injection or vaccination in the associated arm	✓
There are a number of risk factors associated with lymphoedema to consider: • a woman having undergone axillary surgery and/or radiotherapy • infection in the arm • high body mass index • having any other injury to the arm, including insect bites and sunburn • increased age • undertaking air travel • positive axillary node status	✓
A woman should be advised about lymphoedema prevention and support services available nationally and locally	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

5 Radiotherapy

This chapter presents content in relation to radiotherapy and breast surgery and radiotherapy scheduling in women with early invasive breast cancer and includes:

- radiotherapy in addition to breast surgery
  - breast conserving surgery
  - mastectomy
- addition of boost dose of radiotherapy to radiotherapy and breast surgery
  - breast conserving surgery
  - mastectomy
- fractionation schedules
  - partial/accelerated
  - hypofractionated
- nodal irradiation.

For relevant information on ductal carcinoma in situ (DCIS), see Chapter 8, *Ductal carcinoma in situ*.

Introduction

In early breast cancer, all detectable cancer is, by definition, restricted to the breast (and, in those with node-positive disease, the local lymph nodes) and can be removed surgically. However, clinically undetected deposits of neoplastic disease may remain, either locally or at distant sites that eventually develop into clinically detectable recurrence. Local deposits can be treated with radiotherapy, and there have been many randomised controlled trials (RCTs) on the effects of radiotherapy on local recurrence, distant recurrence and overall survival (OS).

Six clinical questions were developed to assess best approaches to radiotherapy for early breast cancer (see Chapter 11, *General section: methods*).

Radiotherapy in addition to breast conserving surgery

Background

Whole breast irradiation (WBI) following breast conserving surgery (BCS) is used routinely in those with early invasive breast cancer to achieve local disease control.

Body of evidence

The systematic review undertaken identified the following evidence on the addition of radiotherapy to BCS compared with BCS alone that met the inclusion criteria.

The Scottish Intercollegiate Guidelines Network (SIGN) guideline,[37] the British Medical Journal (BMJ) clinical guidelines[100] and the Belgian guideline,[38] included the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) systematic reviews[106, 123] (All the guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

The search identified three additional primary RCTs,[160–162] all of which included older women. Pōtter et al.[160] examined a subgroup of postmenopausal women randomised to radiotherapy compared with no radiotherapy following BCS plus tamoxifen or anastrozole. Schnapper and Hughes[161] reported on the eight-year follow-up of women aged 70 years or over who underwent lumpectomy and tamoxifen plus or minus radiotherapy. Prescott et al.[162] evaluated the addition of radiotherapy to BCS and endocrine therapy in women aged over 65 years. (All three of the RCTs were considered to be of high quality.)

Summary of findings

Survival

The EBCTCG reported the15-year risk of death from breast cancer as 30.5% for the addition of radiotherapy compared with 35.9% with no additional radiotherapy (corresponding to an absolute reduction of 5.4% SE 1.7).[106]

Radiotherapy may be as effective as surgery or tamoxifen at increasing survival and decreasing recurrence.[100] As expected, there were no significant differences in distant metastases, all-cause mortality or breast cancer-specific mortality with the addition of radiotherapy in individual smaller series with shorter-term follow-up.[161]

Recurrence

The risk of recurrence following BCS was significantly reduced by radiotherapy, from 26% with no radiotherapy to 7% with the addition of radiotherapy, based on data from 10 trials including 7300 patients.[106] This corresponds to a proportional reduction in local recurrence of 70% with radiotherapy (recurrence rate ratio 0.3). A reduced incidence of recurrent invasive breast cancer was also reported following radiotherapy in older women on endocrine therapy, though the benefits seen are much less than for younger women.[161, 162]

Other outcomes

Adverse effects associated with radiotherapy can be both acute and long term. Acute effects include fatigue, skin erythema and occasional skin breakdown, oedema, tenderness, pneumonitis and inconvenience.[106]

Radiotherapy requires women to attend a radiation oncology service daily during the week for as many days as there are fractions to be delivered – most commonly five days a week for five weeks. This is a considerable inconvenience and cost for some women, and for women who live some distance from such units, it may take them away from their usual support networks, friends and family.

Late effects of radiotherapy include breast fibrosis, breast pain, telangiectasis, lung fibrosis, late cardiac morbidity, radionecrotic rib fracture, increased risk of contralateral breast cancer and non-breast cancer mortality.[37, 106] Many of the studies that contributed data to these analyses utilised older radiotherapy regimens, and the risk of these adverse outcomes especially cardiac, lung and rib fracture are not thought to be as great using modern radiotherapy techniques.

Quality of life data from one RCT conducted in women aged over 65 years found no overall difference between those women receiving radiotherapy and the no radiotherapy group.[162]

Development of recommendations

Based on the New Zealand Guidelines Group's (NZGG's) systematic review of the published evidence, the Guideline Development Team (GDT) concluded that radiotherapy following BCS yields a major decrease in ipsilateral breast recurrence, local nodal recurrence, disease-free survival and mortality. The GDT developed a good practice point relating to the timeliness of treatment, in keeping with current health targets (see 'Health targets: shorter waiting times for cancer treatment' on the Ministry of Health website).[163]

Recommendation

For invasive breast cancer only	Grade
A woman should be offered radiotherapy following breast conserving surgery for early invasive breast cancer unless there is a particular contraindication	A
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice point

Radiotherapy should ideally commence within 8 weeks of completion of surgery or chemotherapy	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Radiotherapy in addition to mastectomy

Background

A significant number of individuals will undergo mastectomy for early breast cancer. Even after mastectomy, loco-regional recurrence, particularly on the chest wall may be a major problem for some women.[106] Factors that contribute to an increased risk of loco-regional recurrence include large tumour size, increasing involvement of axillary nodes, lymphovascular involvement and positive resection margins.

Body of evidence

The systematic review undertaken identified the following evidence on the addition of radiotherapy to mastectomy compared with mastectomy alone that met inclusion criteria.

Three guidelines met the inclusion criteria. The SIGN guideline,[37] BMJ clinical guideline[100] and Belgian guideline[38] included the EBCTCG systematic reviews,[106, 123] which examined data from 34 RCTs comparing mastectomy with mastectomy followed by radiotherapy in approximately 16,000 women. (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Two primary studies were identified. Killander et al.[164] reported a trial of postmenopausal women with stage II invasive breast cancer undergoing modified radical mastectomy randomised to receive postoperative radiotherapy alone, radiotherapy plus tamoxifen, or tamoxifen alone. (The study was considered to be of high quality.) Two publications, by Nielsen et al.[165] and Overgaard et al.[166] were identified relating to a single RCT conducted by the Danish Breast Cancer Cooperative Group. This trial evaluated radiotherapy and chemotherapy compared with chemotherapy alone following total mastectomy and partial axillary dissection in women aged under 70 years considered to be high risk based on tumour size (>5 cm) and/or positive axillary nodes and/or invasion of the skin or pectoral fascia. (The studies were considered to be of high quality.)

Summary of findings

Survival

The EBCTCG meta-analysis[106] provided strong evidence of a significant increase in OS with post-mastectomy radiotherapy, with a 5% reduction in 15-year mortality (5.4% in women with node-positive disease). There was no significant difference in mortality in women with node-negative disease, but a small difference in local recurrence at five years in this subgroup (6% reduced to 2% with radiotherapy).

The Belgian guideline reported a clear survival benefit of radiotherapy in postmenopausal women with node-positive breast cancer treated with modified radical mastectomy and adjuvant radiotherapy.[38] In women with primary operable breast cancer, radiotherapy decreases recurrence and mortality after mastectomy in women who are node positive or at high risk of recurrence, but may increase mortality in node-negative women.[100]

Loco-regional recurrence

The Belgian guideline concluded that post-mastectomy radiotherapy resulted in a decreased rate of local tumour recurrence.[38] The EBCTCG meta-analysis,[106] reported an absolute reduction in local recurrence at five years of 17% in women with node-positive disease post-mastectomy with axillary clearance from 23% with no radiotherapy to 6% with the addition of radiotherapy. In women with node-negative disease, there was a reduction in five-year local recurrence from 6% to 2% with radiotherapy.

Killander et al.[164] and Nielsen et al.[165] reported a reduced rate of loco-regional recurrence in the radiotherapy group compared with the no radiotherapy group. Overgaard et al.[166] concluded that post-mastectomy radiotherapy significantly and substantially improved loco-regional control and OS in all women with node-positive disease. However, though showing the greatest benefits for post-mastectomy radiotherapy, the Danish trial[165, 166] has been criticised for poor axillary surgery, with fewer than average axillary nodes removed and much higher local recurrence rates in the no radiotherapy group than other series with more thorough axillary surgery.[167]

Adverse effects

Adverse effects associated with radiotherapy are detailed in the previous section entitled, 'Radiotherapy in addition to breast conserving surgery'.

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted the reported reduction in loco-regional recurrence with post-mastectomy radiotherapy. This reduction was more pronounced in women with node-positive rather than node-negative disease. Breast cancer mortality was also reduced in women with node-positive disease who had mastectomy plus axillary clearance with radiotherapy. The GDT defined high risk of loco-regional recurrence as four or more nodes positive in axilla, tumour size greater than 5 cm and close margins; whereas moderate risk was defined as one to three nodes positive in axilla, high grade tumours, lymphovascular invasion or young age.[31, 100]

The GDT acknowledged that treatment methods, especially the radiotherapy target areas, and the dose and duration of adjuvant systemic therapies have changed with time. In particular, the heart and great vessels and other adjacent organs receive much less irradiation with improved modern planning techniques and equipment. This may limit the generalisability of some of the findings related to adverse effects of these treatments. The general dosing recommendation was for 50 gray (Gy) delivered in 25 fractions of 2 Gy over five weeks.

The GDT also noted that women should be informed of potential benefits and harms associated with postoperative radiotherapy.

Recommendations

For invasive breast cancer only	Grade
A woman at high risk of loco-regional recurrence post-mastectomy (ie, 4 or more nodes positive in axilla, tumour size greater than 5 cm, close margins) should have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist, and should receive radiotherapy unless there is a particular contraindication	**A**
A woman at moderate risk of loco-regional recurrence (1–3 nodes positive in axilla, high grade tumours, lymphovascular invasion or young age) should have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist, and the woman should be referred for a discussion regarding radiotherapy	**B**
There is no evidence for the routine use of radiotherapy for women at lower risk of local recurrence post-mastectomy. These women should have their case discussed at a multidisciplinary meeting with a radiation oncologist present, or discussed with a radiation oncologist	**B**

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Addition of boost dose of radiotherapy to radiotherapy and breast surgery

Background

WBI following BCS is standard practice in early invasive breast cancer. However, a significant risk of loco-regional recurrence remains. An additional boost dose of radiation to the tumour bed may reduce recurrence, but may also be associated with an increased risk of adverse effects.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

Two primary research publications reported results from the European Organisation for Research and Treatment of Cancer trial EORTC 22881–10882.[168, 169] Participants were randomised to receive or not receive a boost radiotherapy dose of 16 Gy to the original tumour bed. (The trial was considered to be of high quality.)

Summary of findings

Overall survival

No differences were identified in OS between the boost radiotherapy dose and no boost radiotherapy groups.[168, 169]

Loco-regional recurrence

EORTC results reported by Bartelink et al.[169] showed a significantly reduced risk of local recurrence as the first event in the boost radiotherapy dose group (4.3%) compared with 7.3% in the no boost radiotherapy group. Salvage mastectomies were reduced by 41% in the boost radiotherapy dose group as a result of the difference in local recurrence. Absolute risk reduction of recurrence was greatest for participants aged 40 years or younger (19.5% without boost radiotherapy dose vs 10.2% with boost radiotherapy dose). For women aged over 50 years, the benefits were less, with a 0.8% reduction in risk of recurrence seen at five years.

Adverse events

Severe fibrosis was significantly increased in the boost radiotherapy dose group at 10 years (4.4% vs 1.6%, $p<0.0001$). Moderate to severe fibrosis was also more commonly observed in the boost radiotherapy dose group (28.1% vs 13.2%, $p<0.0001$).[169]

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted that addition of boost dose radiotherapy (10–16 Gy) leads to improved loco-regional control, although no improvement in OS has been demonstrated. The GDT also noted that the main adverse effect of boost radiotherapy is severe to moderate fibrosis. Women with early breast cancer should be advised of the benefits and risks of treatment, including boost dose radiotherapy. The GDT formulated a good practice point regarding the value of the addition of boost dose radiotherapy for women with positive margins.

Recommendations

	Grade
A boost radiotherapy dose should be considered for all women with early invasive breast cancer treated with radiotherapy and breast conserving surgery, in particular: • women younger than 50 years of age	A
Consideration should be given to adverse events (eg, fibrosis) caused by additional radiation when planning treatment	A
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice point

A boost radiotherapy dose should be considered for women with positive margins	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Addition of boost dose of radiotherapy to radiotherapy and mastectomy

Body of evidence

No clinical guidelines or other secondary literature was identified that fulfilled the eligibility criteria for the review question. No primary trials were identified that addressed this topic. Given the lack of studies identified, the search was extended to include studies published from 1996. This extended search did not identify any studies of relevance.

Summary of findings

There was no evidence identified.

Development of recommendations

The GDT acknowledged that there is no evidence for use of boost dose radiotherapy after mastectomy and standard radiotherapy, so made no recommendations supporting its routine use in women with early breast cancer. A good practice point was developed by the GDT in relation to boost dose radiotherapy and women with positive margins.

Recommendation

	Grade
Due to lack of evidence no recommendations were made for the routine use of boost dose radiotherapy after mastectomy and radiotherapy	I
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice point

A boost dose should be considered on an individual basis for those with positive margins	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Fractionation schedules

Partial or accelerated partial versus whole breast radiotherapy

Background

Unlike WBI, partial breast irradiation (PBI) refers to irradiation of a limited volume of breast tissue around the tumour bed. PBI may be achieved using:

- intracavitary brachytherapy or balloon catheter devices
- interstitial brachytherapy
- intraoperative techniques using electrons or X-rays at 50 kVp
- external beam radiotherapy.

WBI typically delivers a radiation dose of 2 Gy with each treatment, typically over five to seven weeks. PBI techniques may deliver a standard schedule of fractionated therapy or deliver a larger than standard dose of radiation therapy with each treatment, allowing the overall duration of treatment to be shortened.

Accelerated PBI (APBI) shortens a five- to seven-week course of WBI to four to five days. The use of APBI has potential advantages including:[170]

- a reduction in treatment-related toxicity because of a lower radiation dose to adjacent organs, such as the heart and great vessels and lung
- increased utilisation of BCS
- a reduction in radiotherapy waiting times, treatment time and travelling
- a greater chance of preserving the breast should a recurrence occur elsewhere in the breast
- easier integration with chemotherapy schedules because radiotherapy time will be shorter.

There are also potential disadvantages to the use of APBI, including:[170]

- an increased risk of breast recurrence
- increased late toxicity, with resultant poor cosmesis
- more inconvenience for the woman as some techniques may require a second anaesthetic or a further invasive procedure
- some techniques require operator expertise and specialised equipment that may not be available in all centres.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

The BMJ guideline[100] was based on one systematic review that compared intraoperative and standard postoperative radiotherapy after BCS in two RCTs.[171, 172] (The guideline was given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

The Blue Cross Blue Shield Association Health Technology Appraisal was based on a systematic review by Rothenburg et al.[173] and the RCT by Polgar et al.[174] comparing the use of APBI with WBI following BCS. The systematic review included one earlier small RCT by Polgar et al.[175] and six non-randomised trials.[176–181] (The health technology appraisal was considered to be of high quality.)

The 2007 open-labelled trial by Polgar et al.[174] that compared PBI and WBI following adjuvant therapy met inclusion criteria. (The trial was considered to be of high quality.)

Summary of findings

Survival

There was no difference in disease-specific survival[171, 174] or OS[172, 174] shown between PBI and WBI at the five- to eight-year follow-up.

Loco-regional recurrence

In one earlier study (1996), there was a significantly increased recurrence rate in PBI at the eight-year follow-up compared with WBI (19.6% vs 9.9%).[171] Other studies reported no significant differences between PBI and WBI in local recurrence[172, 174] and distant recurrence.[172] The Blue Cross Blue Shield appraisal concluded that there was insufficient evidence as to the effectiveness of APBI compared with whole breast external beam radiotherapy in reducing recurrence and mortality.[173]

Several ongoing clinical trials in progress are evaluating different partial breast radiotherapy techniques. These should provide more rigorous evidence in the next five to 10 years.

- The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-39/RTOG 0413 trial is in the recruitment phase. It will compare WBI with or without boost or PBI after lumpectomy with a 10-year follow-up. The PBI will be delivered via one of three methods: multi-catheter brachytherapy; single catheter interstitial brachytherapy or three-dimensional conformal external beam radiation
- The targeted intraoperative radiotherapy trial (TARGIT) is currently in the recruitment phase. It will compare BCS plus either WBI with or without a boost dose or single fraction intraoperative radiotherapy targeted to the tumour bed
- The Groupe Europeen de Curietherapie – European Society for Therapeutic Radiology and Oncology (European GEC-ESTRO) trial was activated in 2005 with 1170 subjects recruited. The study compares WBI with high dose rate/pulsed dose rate multi-catheter interstitial brachytherapy
- The RAPID trial by the Ontario Clinical Oncology Group was activated in 2006 with 2128 subjects recruited. The study compares PBI using three-dimensional conformal external beam radiotherapy with WBI
- The IMPORT LOW trial by the Medical Research Council, United Kingdom was activated in 2006. It compares intensity modulated accelerated PBI with WBI

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted the limited evidence to determine the effectiveness of PBI or APBI compared with WBI and that the results of ongoing large scale phase III studies (eg, the NSABP B39 and RAPID trials) should help determine the answer in the future. Insufficient evidence was found overall on less than WBI after BCS. Studies are addressing whether PBI may be equivalent or preferable for selected women.

Recommendation

	Grade
Due to a lack of evidence no recommendations were made for the routine use of partial or accelerated partial breast radiotherapy for women following breast conserving surgery	I

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice points

Partial breast radiotherapy for women after breast conserving surgery may be undertaken as part of a well conducted clinical trial	✓
Partial breast radiotherapy may be offered for individual women after breast conserving surgery where whole breast radiotherapy is deemed unsuitable	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Hypofractionated radiotherapy

Background

Typically, post-BCS radiotherapy is delivered over five weeks, in 25 treatment fractions to a total dose of 50 Gy. This may be followed by a further 10 Gy in five fractions.

Attempts have been made to deliver an effective dose of radiation in a shorter period in order to increase patient throughput and convenience for rural patients. However, concerns have been raised as to whether shorter fractionation schedules have equivalent outcomes in terms of local tumour control, cosmesis, OS and patient satisfaction. The concern with larger fraction sizes is based on radiobiological principles that state that the fraction size is the dominant factor in determining late side effects.[182] The aim of conventional fractionation at 2 Gy per fraction is to minimise late tissue damage whilst maximising tumour control.[182] Higher fraction size could lead to increased scarring and retraction of breast tissue, as well as skin atrophy (thinning) and telangiectasia (dilated blood vessels), and there is concern about late toxicity for the heart, especially in left-sided tumours in women undergoing radiotherapy.

Body of evidence

The systematic review undertaken on hypofractionation radiotherapy (with or without boost) identified the following evidence that met inclusion criteria.

Little evidence was available at the time of the development of the SIGN guideline[37] on dose fractionation for resectable invasive breast cancer.[183, 184] Schedules reported included 45 Gy in 20 fractions over five weeks, 50 Gy in 25 fractions over five weeks or 42.5 Gy in 16 fractions over three weeks. One RCT by Whelan et al. (2002) was identified that compared two of these fractionation regimens (25 fractions of 2 Gy over five weeks for a total dose of 50 Gy, or 16 fractions over three weeks for a total dose of 42.5 Gy) following lumpectomy. The study was of selected patients with small breasts, not requiring boost radiotherapy and with no nodal involvement, and did not address nodal irradiation. (The guideline was given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

The RCT described by Owen et al.[185] was a preliminary study of 1410 patients (to inform the design of a larger RCT, the START trial) using three fractionation dose schedules all administered over five weeks post-BCS:

- 50 Gy administered in 25 fractions of 2 Gy
- 39 Gy administered in 13 fractions of 3 Gy
- 42.9 Gy administered in 13 fractions of 3.3 Gy.

(The trial was considered to be of high quality.)

The START Trialists Group[186] reported on two multicentre RCTs, START A and START B. (Both trials were considered to be of high quality.) START A compared three fractionation schedules all administered for five weeks following BCS or mastectomy (n=2236):

- 50 Gy administered in 25 fractions of 2 Gy
- 39 Gy administered in 13 fractions of 3 Gy
- 41.6 Gy administered in 13 fractions of 3.2 Gy.

START B compared a hypofractionated and standard fractionation schedule administered following BCS or mastectomy (n=2215):

- 50 Gy administered in 25 fractions of 2 Gy over five weeks
- 40 Gy administered in 15 fractions of 2.67 Gy over three weeks.

Summary of findings

Survival

The SIGN guideline[37] reported data from the Whelan et al. (2002) study that found no significant difference in OS rate at the five-year follow-up with a hypofractionated compared with standard regimen. The START Trialists Group reported that in the START B trial[186] there were significant differences in disease-free and overall mortality rates in favour of the group who received the hypofractionated regimen (40 Gy in 15 fractions over 3 weeks). Further details are in Table 5.1. The authors anticipate that this effect will diminish over time, and the long-term follow-up of the trial continues.

Loco-regional recurrence

In the Whelan et al. (2002) study reported in the SIGN guideline,[37] no significant difference in local recurrence free rate at the five-year follow-up was seen (96.8% with 25 fractions vs 97.2% with 16 fractions; 95% CI 1.5–2.4).

At the five-year follow-up, Owen et al.[185] reported hazard ratios comparing 50 Gy to 42.9 Gy of 0.90 (95% CI 0.55–1.46) and 1.14 (95% CI 0.72–1.79) for 39 Gy compared to 50 Gy. After 10 years, the probability of recurrence was significantly greater in the 39 Gy than in the 42.9 Gy group (difference 3.7%, 95% CI 0.3–8.3, p=0.027). Owen et al.[185] concluded that the results were consistent with the hypothesis that fewer, larger fractions are at least as safe and as effective as 'standard' regimens but that the shorter schedule should be restricted to clinical trials.

At the five-year follow-up, the START Trialists Group[186] reported of the START B trial that the absolute difference in loco-regional recurrence could be up to 1.7% better and at most 1% worse with the hypofractionated regimen. The trial authors concluded that the delivery of 40 Gy in 15 fractions appeared to result in a loco-regional recurrence rate that was at least as favourable as the 'standard' 50 Gy in 25 fractions.

Other outcomes

Cosmetic results at five years were similar between fractionation schedules. However, in a 12-year update of the Whelan data, the incidence of moderate to severe late radiation morbidity (subcutaneous fibrosis) at 10 years doubled (8% vs 4%) in the shorter fractionation schedule.[187]

The START A trial[188] reported in a quality of life assessment that changes in breast appearance and breast hardness were the most commonly reported side effects. These side effects were less marked in the 39 Gy group and similar in the 41.6 Gy and 50 Gy groups, in contrast to those found at 10 years by Owen et al.[185] (11.2% for 42.9 Gy in 13 fractions of 3.3 Gy vs 6.4% for 50 Gy in 25 fractions of 2 Gy).

Both the START A and START B trials reported that the follow-up period of five years was too short to assess potential late normal tissue effects, such as cardiac damage.[186, 188] Follow-up continues for these trials. The long-term safety of the short fractionation schedule for the nodal areas has not been established.

Table 5.1 Early follow-up data (five years) for clinical outcomes following different fractionation schedules

Trial	No. of patients	Total dose (Gy)	Dose/ fraction (Gy)	No. of fractions	Five-year overall mortality % (95% CI)	Five-year local regional recurrence % (95% CI)	Five-year distant metastases % (95% CI)	Changes in breast appearance (photographic) % or HR (95% CI)
Owen (2006)	1410	50	2	25	–	7.9 (NR)	–	6.4
		39	3	13	–	9.1 (NR)	–	3.9
		42.9	3.3	13	–	7.1 (NR)	–	11.2
START A (2008)	2236	50	2	25	11.1 (8.7–13.4)	3.6 (2.2–5.1)	9.8 (7.5–12.0)	HR 1.09 (0.85–1.40)*
		41.6	3.2	13	11.3 (8.9–13.7)	3.5 (2.1–4.3)	9.5 (7.3–11.7)	
		39	3	13	10.7 (8.3–13.1)	5.2 (3.5–6.9)	11.9 (9.5–14.4)	HR 0.69 (0.52–0.91)**
START B (2008)	2215	50	2	25	11 (9.1–12.9)	3.3 (2.2–4.5)	10.2 (8.4–12.1)	HR 0.83 (0.66–1.04)
		40	2.67	15	8 (6.4–9.7)	2.2 (1.3–3.1)	7.6 (6.0–9.2)	

Notes: Gy = gray; CI = confidence interval; HR = hazard ratio; NR = Not reported

* 41.6 Gy vs 50 Gy

** 39 Gy vs 50 Gy

Development of recommendations

Based on NZGG's systematic review of the published evidence the GDT noted that there is currently insufficient evidence to identify one optimum fractionation schedule. The results of ongoing clinical trials will inform guidelines in the future. To minimise late tissue damage whilst maximising tumour control, the GDT supported the administration of boost dose radiotherapy at 2 Gy per fraction where indicated following a hypofractionated regimen. The GDT also noted that extended fractionation with smaller doses over five to six weeks should be considered in women with large breasts and postoperative side effects.

Recommendation

	Grade
Radiotherapy treatment for early invasive breast cancer should use an accepted regimen such as:	
• 50 Gy in 25 fractions over 5 weeks	A
• 45 Gy in 20 fractions over 5 weeks	B
• 42.5 Gy in 16 fractions over 3.5 weeks for those with small or medium breasts, not requiring boost or nodal radiation	B
• 40 Gy in 15 fractions over 3 weeks*	B
* It should be noted that the data for long-term follow-up in the latter three schedules of this recommendation is still awaited	
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice points

If boost radiotherapy is used after a hypofractionated regimen it should be at the standard 2 Gy per fraction	✓
Women with large breasts and those with significant postoperative induration, oedema, erythema, haematoma or infection should be considered for extended fractionation, with smaller daily doses over 5–6 weeks	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Nodal irradiation

Background

Radiotherapy to the regional nodes (supraclavicular, axillary and internal mammary) in early breast cancer has been given with the intent of reducing the risk of recurrence in these areas, but with an uncertain effect on survival. Most studies have used treatment to all nodal groups, rather than each group separately and these studies have generally utilised outdated radiation techniques. Possible disadvantages of radiotherapy to the regional nodes include an increased risk of:[189, 190]

- lymphoedema of the arm
- shoulder stiffness
- brachial plexopathy
- cardiac morbidity.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

Three clinical guidelines met the inclusion criteria. The 2005 SIGN guideline included evidence on irradiation of supraclavicular, axillary and internal mammary chain (IMC) nodes.[37] It was based on a 2001 American Society of Clinical Oncology (ASCO) guideline,[191] seven primary studies[192–198] and one overview of case studies and RCTs.[199]

The Belgian guideline[38] identified evidence on axillary and IMC irradiation based on three RCTs.[120, 200, 201] The BMJ guideline[100] identified evidence on regional nodal irradiation,[106] axillary irradiation[93] axillary irradiation[93] and ipsilateral supraclavicular fossa/chest wall irradiation.[106] (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Summary of findings

Loco-regional recurrence

Radiation to all loco-regional nodes

The BMJ guideline[100] reported that radiation to all loco-regional nodes improved recurrence rates.

Supraclavicular and chest wall

No RCTs or systematic reviews of radiotherapy to the ipsilateral supraclavicular fossa compared with no radiotherapy were identified in the BMJ guideline.[100] The data available was from trials of radiotherapy to the chest wall and supraclavicular nodes compared with no radiotherapy to either. The SIGN guideline[37] reported that three primary studies (Kuske et al. 1996; Ewers et al. 1992; Ragaz et al. 2005) showed higher levels of supraclavicular nodal failure and loco-regional failure in unirradiated compared to irradiated persons. The SIGN guideline also reported that post-mastectomy disease-free survival was significantly increased with the addition of radiotherapy. This difference, demonstrated in primary studies by McArdle et al. (1986) and Ragaz et al. (2005), was significant for people with four or more positive nodes. One systematic review reported that radiotherapy to the chest wall and lymph nodes was associated with reduced loco-regional recurrence.[100]

Axillary nodes

The 2001 ASCO guideline concluded that following adequate surgery by complete or level I or II axillary dissection, routine adjuvant radiotherapy to the axilla was unnecessary and may lead to increased morbidity.[37]

The RCTs by Veronesi et al. (2005) and Louis-Sylvestre et al. (2004) showed that axillary irradiation for women with node-negative cancer did not improve local recurrence rates or long-term survival.[38]

Internal mammary chain

Evidence for IMC irradiation was found to be conflicting. No benefit of IMC radiotherapy was reported by Freedman et al. (2000).[37] Studies by Lacour et al. (1983) and Veronesi et al.(1999) showed no improvement in survival for those undergoing IMC dissection in addition to standard radical mastectomy.[37] Yamashita et al. (1996) reported five-year disease-free survival to be similar between radical resection of IM and supraclavicular chain (57%), irradiation of the supraclavicular and IM nodes (53%) or no further surgery or irradiation in those areas (51%); although the risk of supraclavicular and/or IM recurrence was lowest in the irradiated group.[37]

However, two further studies identified after the NZGG systematic review reported positive outcomes with IMC irradiation. Arriagada et al. (1988) reported that in axillary node-positive patients IMC radiation led to reduced local recurrence rates even after IMC resection.[202] This translated into improved survival of 58% vs 48% at 10 years (n=1195). A recent study of IMC node biopsies in inner half tumours showed involvement in 10% rising to 21% if the axilla was positive and improved survival for IMC-positive women (68/663) compared with that seen for IMC-negative women with irradiation (n=663).[203]

Adverse effects

Potential shoulder stiffness and an increase in arm lymphoedema may occur with the combination of axillary dissection and axillary radiotherapy.[100]

Associated harms identified with radiation to the ipsilateral supraclavicular fossa included temporary upper oesophagitis, radiation pneumonitis and brachial plexopathy, but these were considered to be either rare or mild and temporary.[100]

Development of recommendations

Based on NZGG's systematic review of the published literature, the GDT noted that the RCTs showed a survival benefit for nodal irradiation to the IMC, supraclavicular fossa and axilla, when given as well as chest wall radiotherapy and compared with no radiotherapy to either. Because of the lack of evidence on the contribution to this benefit of the nodal radiotherapy component, the GDT noted that the reviewed guidelines were mostly unable to make any strong recommendations for the use of regional node radiotherapy.

Several adverse effects were associated with nodal irradiation (ie, lymphoedema, brachial plexopathy, shoulder pain and oesophagitis), and the GDT suggested that these should be discussed with the patient when making decisions regarding treatment options.

For further details and guidance on diagnosis of a positive node, see Chapter 4, *Surgery for early invasive breast cancer*.

Recommendations

	Grade
Ipsilateral supraclavicular fossa Radiotherapy to the ipsilateral supraclavicular fossa should be given in a woman who is at high risk (four or more positive axillary nodes)	B
Axilla Radiotherapy to the axilla should be considered when: • no axillary dissection has occurred • there has been inadequate surgery, although this may add to morbidity • a high number or percentage of nodes are involved, or where there are positive margins or major extra-nodal spread or it is considered likely that residual breast cancer has been left in the axilla	B
Internal mammary chain Radiotherapy to the internal mammary chain should be considered for women who have a positive internal mammary node on sentinel node biopsy Routine use of radiotherapy to the internal mammary chain is not recommended	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice points

Other indications for radiotherapy to nodal areas may be considered and the benefits and risks balanced	✓
It is reasonable to offer radiation to the internal mammary chain to those with inner half tumours particularly if the axilla is positive or lymphoscintigraphy shows drainage to internal mammary nodes	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

6 Systemic therapy: chemotherapy regimens

This chapter presents content in relation to chemotherapy for women with early invasive breast cancer and includes the role of:

- adjuvant therapy
- anthracycline-based regimens
- taxane-based regimens
- trastuzumab-based regimens
- preoperative chemotherapy.

Introduction

Unlike surgery and radiotherapy, which are local treatments, chemotherapy is a systemic therapy, potentially targeting cancer cells anywhere in the body where these agents can reach. Chemotherapy offers the opportunity to eradicate microscopic disease thereby curing some women who would otherwise have died from breast cancer. In other cases, cancer is not completely eradicated but recurrence is delayed. However, many women derive no benefit, either because they have cancers resistant to the regimens used or because they have no cancer left after local therapy. Most regimens also carry considerable toxicities that need to be weighed against potential benefits. Chemotherapy has traditionally been used after surgery as an adjuvant treatment for women at high enough risk of metastatic disease based on tumour factors such as nodal status, tumour size, grade, hormone and HER2/*neu* receptor status, and patient factors such as age and general health. Increasingly, interest has focused on preoperative treatment and the use of more sophisticated molecular tools for assessing risk of metastatic disease and likelihood of response to particular agents. The three main regimens, which are the subject of this chapter, are anthracycline-based regimens, taxane-based regimens and trastuzumab-based regimens.

Four clinical questions were developed to assess best practice in relation to chemotherapy (see Chapter 11, *General section: methods*).

Adjuvant therapy

This content on the role of adjuvant therapy is based largely on the 2005 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) systematic review[37] and best practice according to Guideline Development Team (GDT) expert opinion.

The concept of adjuvant therapy is a difficult one for many patients. It is often hard to convey the reasons for giving a treatment that cures only a minority of those who receive it, while the proportion having some benefit will depend on the overall risk of recurrence. Helping patients make choices about treatment is important, because chemotherapy usually impairs the patient's short-term quality of life. Decisions about adjuvant therapy not only require an assessment of prognostic and predictive factors, and therefore the potential benefits of treatment, but also the side effects of the treatment, the risks of which may vary from patient to patient, depending on their age and comorbidities.

Estimates of the benefits of adjuvant chemotherapy are made on the basis of patient age and prognosis derived from pathological features, such as tumour size, grade, the number of lymph nodes involved, hormone receptor status or the presence of human epidermal growth factor receptor 2 (HER2) protein overexpression or gene amplification.

The choice of chemotherapy and/or endocrine therapy as adjuvant treatment for early invasive breast cancer should be driven by endocrine responsiveness and risk of relapse. The effect of age on the benefit of chemotherapy is controversial, particularly for oestrogen receptor negative (ER -ve) tumours. There is uncertainty about what level of receptor expression is required for responsiveness to hormone manipulation. Breast tumours are generally considered to be hormone sensitive if more than 10% of the tumour stains for the oestrogen receptor or progesterone receptor, and less hormonally sensitive if the tumour does not.

Women with receptor positive tumours who receive chemotherapy should be considered for additional endocrine therapy at the completion of chemotherapy. Women with HER2-positive breast cancer are at greater risk of relapse than women with HER2-negative cancers with otherwise similar risk factors and these women should have special consideration for adjuvant chemotherapy.

The ability of postoperative adjuvant chemotherapy to reduce the risk of recurrence and death from breast cancer has been established by meta-analyses of randomised clinical trials.[204] These meta-analyses indicated that the use of adjuvant chemotherapy is associated with a reduction in the risk of relapse and death in women with early stage breast cancer. The proportional reduction in risk of relapse and death attributable to adjuvant chemotherapy is dependent on age at diagnosis but is independent of prognosis at point of diagnosis.[204] While who should receive adjuvant therapy was not a clinical question considered in this guideline, in discussion the GDT noted that adjuvant therapy should be considered for all patients with early stage breast cancer who have undergone surgery. This consideration should be conducted within the confines of a multidisciplinary team and the decision recorded. Timeliness of treatment is important and where adjuvant chemotherapy is planned, it should ideally commence within six weeks of completion of surgery.

Prognostic tools, such as Adjuvant! Online (www.adjuvantonline.com) and the Nottingham Prognostic Index (see Appendix E), are widely used to assist when considering adjuvant therapy. Adjuvant! Online is particularly useful when discussing adjuvant therapy with individual women. This online programme uses age and prognostic factors derived from pathological features of the breast cancer to predict the risk of death from breast cancer and the impact of chemotherapy and endocrine treatment on that risk. The information is displayed visually in a format that can be provided to the woman.

The final decision for or against adjuvant therapy must rest with the individual woman. For the woman to make a fully informed decision it is important that all the advantages and disadvantages for each possible type of adjuvant therapy have been discussed with her in sufficient detail.

Good practice points

Adjuvant therapy should be considered for all women with early invasive breast cancer who have undergone surgery	✓
Adjuvant therapy for an individual woman should be considered within the confines of a multidisciplinary team and the decision recorded	✓
Adjuvant chemotherapy should ideally commence within 6 weeks of completion of surgery	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Anthracycline-based regimens

Background

Until the 1990s, the most commonly used chemotherapy regimens for breast cancer were based on cyclophosamide, methotrexate and fluorouracil (CMF). Since this time, anthracycline-based treatments have largely supplanted CMF-based treatments because they have proven more efficacious, and in some cases can be delivered in a shorter timeframe and with fewer actual treatments required.

Body of evidence

The systematic review undertaken addressed the question of whether a multi-agent chemotherapy regimen centred on doxorubicin or epirubicin improved outcomes compared with a CMF regimen. The following evidence was identified that met the inclusion criteria.

The Scottish Intercollegiate Guidelines Network (SIGN) guideline[37] and the Belgian guideline[38] evaluated randomised comparisons between anthracycline-based and CMF-based regimens. Both guidelines included the National Cancer Institute of Canada clinical trial MA-5[205] comparing cyclophosphamide, epirubicin and fluorouracil (CEF) and CMF regimens. The British Medical Journal (BMJ) guideline[113] and SIGN guideline included the 2005 and 2008 EBCTCG systematic reviews.[204, 206] (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

One additional multicentre RCT, the Danish Breast Cancer Group Trial 89D,[207] was identified that randomised participants to receive either nine cycles of CMF or nine cycles of CEF therapy following resection of a grade I–III tumour with no distant metastases. (The study was considered to be of high quality.)

Summary of findings

Survival

The SIGN guideline,[37] Belgian guideline[38] and BMJ guideline[113] all noted that there was an improvement in survival following anthracycline-based regimens compared with standard CMF regimens. Ejlertsen et al.[207] concluded that anthracycline-based therapy resulted in an improvement in both disease free and overall survival (OS) at the 10-year follow-up and that this benefit was consistent regardless of age, nodal status, tumour size or hormone receptor status. The EBCTCG 2005 systematic review reported that anthracyclines were superior to standard CMF regimens, with a cancer death rate ratio of 0.84 SE 0.03).[37] The EBCTCG review also reported an absolute difference for 10-year probabilities of breast cancer mortality and overall mortality of approximately 3% at five years and 4% at 10 years in favour of anthracycline-based regimens.[37]

Recurrence

The SIGN guideline[37] and Belgian guideline[38] noted the reduced incidence of recurrence with using an anthracycline-based regimen. The EBCTCG 2005 systematic review reported that anthracycline-based regimens were superior to standard CMF regimens, with a recurrence rate ratio of 0.89 (SE 0.03) in favour of anthracycline-based regimens.[37] The EBCTCG review also reported an absolute difference for 10-year probabilities of recurrence of approximately 3% at five years and 4% at 10 years in favour of anthracycline-based regimens.[37]

Adverse effects

Toxicity associated with anthracycline-based regimens was considered acceptable.[37, 38, 207] The most commonly experienced adverse effects included:

- myelosuppression
- neutropenic sepsis
- alopecia
- nausea and vomiting
- mucositis
- cardiotoxicity, particularly with high cumulative doses.

Development of recommendations

Based on the New Zealand Guidelines Group's (NZGG's) systematic review of the published evidence the GDT noted that anthracycline-based regimens resulted in a significant reduction in breast cancer recurrence and increased OS compared with standard CMF regimens. The GDT also noted that several adverse effects were commonly associated with anthracycline-based regimens and that these should be discussed with the individual woman.

Recommendations

	Grade
Anthracycline-based regimens should be considered for adjuvant chemotherapy as they are more effective than standard cyclophosphamide, methotrexate and fluorouracil (CMF) regimens	A
The absolute benefits of anthracycline-based regimens should be balanced against the side effects on an individual basis when planning management	B

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Taxane-based regimens

Background

Taxanes have recently emerged as the most active cytotoxic compounds for breast cancer.[208] Taxanes used in the adjuvant setting include paclitaxel and docetaxel. Studies have investigated the benefit of combining taxanes with an anthracycline-based regimen or their sequential use following an anthracycline-based combination as adjuvant therapy for early breast cancer.

Body of evidence

The systematic review undertaken addressed the question of whether paclitaxel or docetaxel in addition to chemotherapy improved patient outcome. The following evidence was identified that met the inclusion criteria.

The SIGN[37] guideline identified limited data from one study (Cancer and Leukaemia Group B – CALGB 9344)[209] and the National Institute of Clinical Excellence (NICE) guideline[210] was based only on the British Cancer International Research Group BCIRG 001 trial.[211] The Belgian guideline,[38] BMJ clinical guideline,[113] Cancer Care Ontario clinical guideline[212] and five systematic reviews[208, 213–216] each included key trials (see Tables 6.1 and 6.2). Table 6.1 summarises trials investigating concurrent regimens, and Table 6.2 summarises trials investigating sequential regimens.

(The Cancer Care Ontario guideline was given the AGREE tool quality grading: strongly recommended. All other guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations. The meta-analyses/systematic reviews were considered to be of high quality. The NICE guideline[210] was based on a systematic review by Ward et al. 2006,[217] which was considered to be of high quality.)

The National Breast and Ovarian Cancer Centre (2008) guidance[122] was not evaluated as it was based only on the Ferguson et al. 2007 systematic review[213] already included.

Table 6.1 Trials using concurrent regimens

Trial name	No. of patients	Regimen
Docetaxel trials		
BCIRG 001[211]	1491	Doxorubicin + cyclophosphamide + docetaxel versus doxorubicin + fluorouracil + cyclophosphamide
ECOG 2197[218]	2889	Docetaxel + doxorubicin versus doxorubicin and cyclophosphamide
GEICAM 9805[219]	1040	Docetaxel + doxorubicin + cyclophosphamide versus fluorouracil + doxorubicin + cyclophosphamide
Paclitaxel trials		
ECTO[220]	901	Paclitaxel + doxorubicin then CMF versus doxorubicin then CMF
Kümmel et al. (2006)[221]	115	Epirubicin + paclitaxel then CMF versus Epirubicin + cyclophosphamide then CMF

Source: BCIRG = British Cancer International Research Group; ECOG = Eastern Cooperative Oncology Group; GEICAM = Grupo Español de Investigación del Cáncer de Mama (Spanish Breast Cancer Research Group); ECTO = European Cooperative Trial in Operable Breast Cancer

Table 6.2 Trials using sequential regimens

Trial name	No. of patients	Regimen
Docetaxel trials		
PACS 01[222]	1999	Fluorouracil + epirubicin + cyclophosphamide then docetaxel versus fluorouracil + epirubicin + cyclophosphamide
US Oncology 9734[223]	1016	Docetaxel + cyclophosphamide versus doxorubicin + cyclophosphamide
BIG 2-98[224]	2887	Docetaxel + doxorubicin then CMF versus doxorubicin then docetaxel then CMF versus doxorubicin + cyclophosphamide then CMF versus doxorubicin then CMF
Taxit 216[225]	972	Epirubicin then docetaxel then CMF versus epirubicin then CMF
Paclitaxel trials		
NSABP B-28[226]	3060	Doxorubicin + cyclophosphamide then paclitaxel versus doxorubicin + cyclophosphamide
CALGB 9344[209]	3170	Cyclophosphamide + doxorubicin then paclitaxel versus cyclophosphamide + doxorubicin
HeCOG[227]	1059	Epirubicin then paclitaxel then CMF versus epirubicin then CMF
GEICAM 9906[228]	1248	Fluorouracil + epirubicin + cyclophosphamide then paclitaxel versus fluorouracil + epirubicin + cyclophosphamide
MDACC[229]	524	Paclitaxel then fluorouracil + doxorubicin + cyclophosphamide versus fluorouracil + doxorubicin + cyclophosphamide

Source: BIG = British International Group; NSABP = National Surgical Adjuvant Breast and Bowel Project; CALGB = Cancer and Leukaemia Group B; HeCOG = Hellenic Cooperative Oncology Group; GEICAM = Grupo Español de Investigación del Cáncer de Mama (Spanish Breast Cancer Research Group); MDACC = M.D. Anderson Cancer Centre

Summary of findings

Overall and disease-free survival

There was a significant reduction in the risk of death reported in BCIRG 001 HR 0.70, 95% CI 0.53–0.91, p=0.008),[211] the Cancer and Leukaemia Group B CALGB 9344 trial (HR 0.82, 95% CI 0.71–0.95, p= 0.006),[209] PACS 01 (HR 0.77, 95% CI 0.56–0.94, p= 0.014)[222] HeCOG trial (HR 2.42, 95% CI 1.17–4.99, p=0.02)[227] with the addition of taxanes. Several reviews indicate that there is a significant improvement in disease-free survival and OS with the addition of a taxane.[208, 210, 213–215]

Concurrent regimens

The overall pooled estimate for concurrent schedule studies[211, 218, 220, 221, 224] showed a significant improvement in disease-free survival for women receiving taxane-based therapy (HR 0.82, 95% CI 0.71–0.94) in the Cancer Care Ontario guideline although there was no effect on OS.[212] However, in the Cochrane review[216] a significant improvement in both OS and disease-free survival was demonstrated for concurrent taxane-anthracycline regimens, respectively (HR 0.79, 95% CI 0.66–0.94; 0.79, 95% CI 0.70–0.90).[213]

Sequential regimens

Pooled estimates of disease free and OS showed a significant improvement for women receiving sequential taxane regimens[209, 222, 224–226, 228, 229] compared with their counterparts (disease-free survival HR 0.80, 95% CI 0.75–0.86; OS HR 0.83, 95% CI 0.76–0.91).[212] A significant improvement in both OS and disease-free survival was demonstrated for sequential taxane-anthracycline regimens (HR 0.82, 95% CI 0.75–0.90; HR 0.81 95% CI 0.76–0.88, respectively).[213]

Recurrence

A significant reduction in the risk of relapse (HR 0.72, 95% CI 0.59–0.88) was shown in the BCIRG 001 study[211] and the PACS 01 study (HR 0.82, 95% CI 0.69–0.99).[222] The addition of a taxane to an anthracycline-based regimen resulted in a statistically significant reduction in the risk of relapse (about a 17% relative risk reduction).[208]

Adverse effects

Reported adverse effects associated with taxane use include:[210, 212, 216]

- febrile neutropenia
- arthralgia
- diarrhoea
- stomatitis
- amenorrhoea
- asthenia
- myalgia
- leukopenia
- neurotoxicity, particularly peripheral neuropathy.

Incidences of febrile neutropenia were found to be reduced when granulocyte colony-stimulating factor (G-CSF) was added to the taxane arm.[212, 215] The increase in febrile neutropenia associated with taxane containing regimens was highest for concurrent regimens.[213]

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted that adding a taxane to adjuvant chemotherapy improved disease-free survival and OS. The GDT considered that due to the current lack of high-quality evidence regarding the use of G-CSF with taxane regimens no recommendation could be made at this time. A good practice point was developed to reflect the importance of informing women about the potential benefits and harms of taxane use.

Recommendation

	Grade
Inclusion of a taxane as part of adjuvant chemotherapy should be considered in all cases where chemotherapy is contemplated	A

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice point

A woman with early breast cancer should be informed about the benefits of adding a taxane to adjuvant chemotherapy and known side effects of taxanes. Information should be made available to assist in making an informed choice	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Trastuzumab-based regimens

Background

The drug trastuzumab (more commonly known under the trade name Herceptin®) is a humanised monoclonal antibody that acts by targeting breast cancer cells that overexpress the HER2/*neu* (erbB2) receptor protein or have a demonstrated amplification of the HER2 gene. Overexpression of this protein results in accelerated cell division and has been correlated with adverse prognostic factors such as large tumour size, high nuclear grade, and decreased expression of oestrogen and progesterone hormone receptors.[230] HER2 amplification has also been associated with reduced disease-free survival and OS for women with node-positive or node-negative disease.[231] Trastuzumab acts by binding to the cell protein receptors and thus inhibiting cell growth and the subsequent spread of the tumour.[231]

Quality assurance for HER2 testing

HER2 expression can be tested with immunohistochemistry, fluorescent in situ hybridisation (FISH) and bright field in situ hybridisation (which includes chromogenic in situ hybridisation and the recently introduced silver in situ hybridisation). Bright field in situ hybridisation shows correlation with FISH scoring but is still an evolving field, which should be kept under review (expert opinion). FISH and immunohistochemistry are the predominant techniques used currently in New Zealand.

Appendix D contains all pathology guidance summarised for this guideline, including further details on HER2 testing. Using the standard testing algorithm immunohistochemistry is performed initially. A score of zero or 1 is regarded as negative, 2+ is regarded as equivocal requiring further testing (currently FISH) and 3+ is regarded as positive. FISH testing is scored as a ratio of the number of copies of the HER2 gene identified to the number of copies of centromere 17 present. Less than 1.8 is regarded as negative, 1.8 to 2.2 is equivocal, and greater than 2.2 is regarded as positive. The 2007 American Society of Clinical Oncology (ASCO) guidelines[232] provide further details of testing and scoring criteria for immunohistochemistry and FISH. The Royal College of Pathologists of Australasia (RCPA) Quality Assurance Program[233] and the ASCO guidelines[232] emphasise the critical need for a high level of quality assurance in HER2 testing.

Body of evidence

The systematic review undertaken addressed the question of whether trastuzumab in addition to chemotherapy improved patient outcome. The following evidence was identified that met the inclusion criteria.

Four published clinical guidelines were identified. The NICE guideline,[234] Cancer Care Ontario guideline,[235] National Breast Cancer Centre guideline[236] and Belgian Health Care Knowledge Centre guideline[237] included a series of published and unpublished RCTs examining the use of adjuvant trastuzumab in early breast cancer (see Tables 6.3 and 6.4).

The published RCTs were:

- NSABP B-31[238]
- Intergroup N9831[238]
- HERA[239, 240]
- FinHer.[241]

The unpublished RCT was BCIRG-006.[242]

(The Cancer Care Ontario guideline was given the AGREE tool quality grading: strongly recommended. All other guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations. The NICE guideline[234] was based on a systematic review by Ward,[217] which was considered to be of high quality.)

Three meta-analyses were identified.[217, 243, 244] The meta-analyses included the trials described in Table 6.3, with the exception of the PACS 04 trial. The Viani et al.[243] meta-analysis did not include unpublished material. The FinHer trial[241] was subsequently excluded from the Bria et al.[244] systematic review due to the short duration of trastuzumab therapy, administration before chemotherapy, and small sample size. The main outcomes of the meta-analyses are reported in Table 6.5. (The systematic reviews were considered to be of high quality.)

Perez et al.[245] provided four-year follow-up data (median 2.9 years) from the combined American studies, National Surgical Adjuvant Breast and Bowel Project NSABP B-31 and Intergroup N9831 (unpublished).

Three additional RCTs were identified.[246–248] Buzdar et al.[246] randomised a small number of patients for a comparison of paclitaxel plus fluorouracil, epirubicin and cyclosphosphamide with and without trastuzumab weekly for 24 weeks (see Table 6.6). The E2198 trial conducted by Sledge et al.[247] was a small trial designed to test cardiac safety. The trial was underpowered and not intended to test the efficacy of trastuzumab. The PACS 04 trial conducted by Speilmann et al.[248] compared chemotherapy with chemotherapy plus sequential trastuzumab administered for one year. Treatment commenced six to seven weeks post chemotherapy and radiotherapy. The latter two trials were available in abstract form only. (The trials were considered to be of low quality.)

An additional 2008 review by Madarnas et al.[249] was identified after the formal search. This systematic review did not identify any additional RCTs, so was not formally appraised by NZGG.

Due to the current level of public debate focused on both published and unpublished (conference proceedings) data in this area, the GDT decided to review data from both sources. The GDT noted that the data identified in unpublished conference proceedings have not undergone a process of rigorous peer review and do not occupy the same space in scientific discussions as the peer-reviewed evidence.

Main conclusions of the reviewed evidence

Reduction of risk of recurrence, disease-free survival and overall survival

The Belgian guideline[237] concluded that use of trastuzumab results in a dramatic reduction in distant recurrence and improves two- or three-year disease-free survival from 75–78% to 86–89% in women with early stage breast cancer.

The NICE committee[234] agreed that trastuzumab reduces the risk of recurrence of HER2-positive breast cancers. It noted that the short-term follow up of the trials meant there was limited evidence regarding gains in OS and whether trastuzumab reduced or delayed recurrence. However, the NICE committee noted that earlier adjuvant studies with other breast cancer treatments showed that the prevention of recurrence results in later gains in OS. Therefore, clinical specialists had advised the NICE committee that it was reasonable to extrapolate that this relationship would hold true for trastuzumab. This view was subsequently validated by OS advantages seen from the addition of trastuzumab in three trials: BCIRG 006,[242] HERA,[239, 240] and the combined analysis of the concurrent taxane and trastuzumab arms of the NSABP B-31 and N9831 studies.[238, 245]

The NBCC guideline[236] noted that the efficacy of trastuzumab had not been demonstrated in women with both node-negative disease and a primary tumour size of less than or equal to 1 cm, as this group of patients was excluded from all of the trastuzumab studies. The GDT noted that there are data demonstrating that even small HER2-positive tumours lead to a high risk of recurrence.[241]

Further follow-up data from the HERA trial analysis (n=3387) concluded that one year of treatment with trastuzumab after adjuvant chemotherapy resulted in a significant OS benefit after a median follow-up of two years; and that the emergence of this benefit reinforces the importance of trastuzumab in the treatment of women with HER2-positive early breast cancer.[240]

The combined analysis of the two North American studies, NSABP B-31 and Intergroup N9831, comparing one year of trastuzumab initiated concurrently with chemotherapy with the same chemotherapy without trastuzumab, reported an OS and disease-free survival advantage (n=3676).[238, 245] This advantage remained evident at the four-year follow-up (unpublished data from conference proceedings). In contrast, there was no statistically significant survival advantage seen with the use of nine weeks of trastuzumab partnered with either docetaxel or vinorelbine prior to three cycles of chemotherapy with the FEC60 regimen in the FinHer trial (n=232).[241] The second interim analysis of a fourth (unpublished) study, BCIRG 006 (n=3222), also reported an OS advantage from 12 months of trastuzumab treatment, but the results of this analysis are available only as a conference abstract.[242]

The analysis of the risk–benefit ratio for mortality, recurrence and development of metastases in the Viani et al.[243] meta-analysis indicated that one year of adjuvant trastuzumab for women with HER2-positive early breast cancer should be recommended.

Duration of regimens

The HERA,[239, 240] NSABP B-31[238] and Intergroup N9831[238] trials reported benefits in disease-free survival and OS resulting from one year of treatment with trastuzumab. Both the Australian National Breast Cancer Centre (NBCC) guideline[236] and Cancer Care Ontario guideline[235] recommended that trastuzumab should be offered for one year to all patients with: HER2-positive node-positive or node-negative disease; tumour greater than 1 cm in size; primary breast cancer; and who are receiving or have received (neo)adjuvant chemotherapy.

The small FinHer trial[241] provided some evidence for improved disease-free survival resulting from nine weeks' treatment duration. The Belgian guideline[237] concluded that there was efficacy in both one year duration and nine weeks' duration of treatment. The Belgian guideline stated that trastuzumab resulted in a dramatic reduction in distant recurrence and improved two- or three-year disease-free survival from 75–78% to 86–89% in women with early stage breast cancer, when administered either nine weeks before anthracyclines or during one year after anthracyclines.

At present, the weight of the evidence supports one year of treatment with trastuzumab as this is the only duration of treatment associated with an OS benefit. The large number of women included in these trials (see Table 6.3) leads to precise estimates of effect that are not available for other durations of treatment.

Further clinical trials are under way to assess the issue of optimal duration of treatment, for example, HERA will compare 12 months with 24 months of treatment;[239, 240] PERSEPHONE will compare 12 months with six months of treatment, as will a trial run by the Hellenic Oncology Research Group (NCT00615602), and the SOLD trial aims to compare nine weeks with 12 months. The ALTTO trial (Adjuvant Lapatinib and/or Tratuzumab Treatment Optimisation) has four treatment arms, all of which provide 12 months of HER2-targeted therapy, namely 12 months of trastuzumab, 12 months of lapatinib, 12 months of trastuzumab and lapatinib, and three months of trastuzumab followed by nine months of lapatinib.

Adverse effects: cardiotoxicity

The most notable adverse effect associated with trastuzumab is cardiotoxicity, (severe congestive heart failure – New York Heart Association III/IV), with a reported incidence of 0.54% to 4.5% in trastuzumab groups compared with 0% to 1.8% in control groups.[237, 240, 243] Cardiotoxicity is strongly associated with an anthracycline-based regimen,[236, 237] especially in women aged over 50 years, with a reduced left ventricular ejection fraction (LVEF).[237]

The Australian NBCC[236] recommends that patients with pre-existing cardiac dysfunction (defined as LVEF ≤50%, a history of documented congestive heart failure, coronary artery disease with previous Q-wave myocardial infarction, angina pectoris requiring medication, uncontrolled hypertension, clinically significant valvular disease, or unstable arrhythmias) do not receive trastuzumab therapy. The NICE committee noted that uncertainties remained over long-term effects and the possible impact of trastuzumab therapy in women with a range of cardiac conditions or an LVEF of 55% or less.[234]

It is noted in the Belgian guideline[237] that in the small FinHer trial[241] (using a low epirubicin dose), no congestive heart failure was reported. The GDT noted that in routine clinical practice higher doses of epirubicin are considered standard and the risk of cardiac toxicity at these doses, administered subsequent to trastuzumab, is not known. Congestive heart failure associated with trastuzumab usually responds to cessation of trastuzumab[236] and/or treatment of the cardiac failure.[250]

Sequential versus concurrent regimens

Where one year of trastuzumab is to be administered, indirect comparisons between trials indicate that there is less cardiotoxicity when trastuzumab is given after the completion of chemotherapy. Whether there is any difference in effectiveness of trastuzumab used sequentially or concurrently with chemotherapy is yet to be determined.[235, 250] The Belgian guideline[237] noted that the pooled efficacy data of one year of trastuzumab appeared stronger (for disease-free survival) when trastuzumab was administered concurrently with a taxane after anthracycline chemotherapy. The unpublished sequential arm data of the North Central Cancer Treatment Group NCCTG (Intergroup) N9831[238, 245] trial has not been evaluated in this guideline, as only 20% of expected events were reported in the unplanned interim analysis.

Development of recommendations

Based on NZGG's systematic review of the published evidence the GDT concluded that trastuzumab has demonstrated benefits to patients with HER2-positive breast tumours. There is a dramatic reduction in distant recurrence and an improvement in two- or three-year disease-free survival in those women.

As the only trials to have demonstrated an improvement in OS are those that have administered trastuzumab for one year, and the large number of patients in these trials and homogeneity of effect provide confidence in this result, the GDT concluded that one year is indicated as the recommended duration of treatment. The GDT notes that the optimal duration of regimens is being explored in further trials.

In addition, the GDT notes that the efficacy of trastuzumab in women with tumours that are both less than 1 cm in size and node negative is uncertain because this subgroup was excluded from all trials, but that even small HER2-positive tumours lead to a high risk of recurrence.[251] The associated known side effects of trastuzumab, in particular cardiotoxicity, need to weighed against the benefits of therapy. For the great majority of patients the risks of cardiotoxicity appear to be outweighed by the benefits demonstrated in disease-free survival and OS.

The efficacy of sequential compared with concurrent regimens has not been ascertained, but both strategies have been shown to improve patient outcomes. Information comparing these strategies will be provided as data emerges from clinical trials currently under way. This issue may be addressed in further updates of this NZGG guideline.

To ensure quality of assessment of HER2 status, participation in external quality assurance programmes as supplied by the RCPA and/or United Kingdom National External Quality Assessment Service is strongly encouraged. The GDT based its recommendations on the available evidence at the time of guideline development. Consistent with clinicians worldwide, the GDT notes its focus on the use of OS as the most important indicator of treatment benefit. Patient survival is the ultimate outcome.

Recommendations

	Grade
An improvement in overall survival is confirmed only by trials where the duration of trastuzumab was one year. This duration of treatment is considered the standard of care* and should be offered to all women receiving adjuvant trastuzumab for HER2-positive breast cancer * Based on the current evidence for clinical effectiveness	A
A woman prescribed trastuzumab should have their cardiac function monitored regularly (eg, 3-monthly) using Multi Gated Acquisition (MUGA) scans or echocardiography** ** Left ventricular ejection fraction (LVEF) is a good clinical indicator of left ventricular systolic function. Damage to the heart muscle during myocardial infarction or as a result of cardiotoxicity from chemotherapy impairs the heart's ability to eject blood and results in a decreased ejection fraction. The ejection fraction is an important prognostic indicator with a significantly reduced LVEF typically resulting in poorer prognosis	B
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice point

In women with borderline cardiac function, it may be preferable to administer trastuzumab after the completion of chemotherapy. Whether there is any difference in the effectiveness of trastuzumab used sequentially or concurrently with chemotherapy is uncertain	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Further trials are awaiting report in the peer-reviewed published literature in relation to trastuzumab. These will provide information on the effectiveness of trastuzumab in combination with other agents, and in regimens using different sequencing and duration.

Table 6.3 Adjuvant trastuzumab in HER2-positive early breast cancer

Study	No. of patients	Regimen (number analysed)	Trastuzumab duration and sequence	Median follow-up duration reported to date
NSABP B-31*[238, 245]	1736	AC-T (n=872) AC-TH (n=864)	Concurrent 1 year	24 months
NCCTG (Intergroup) N9831*[238, 245]	2766	AC-T (n=971) AC-T-H (981) AC-T+H (n=814)	Sequential 1 year	
HERA[239, 240]	5102	Chemotherapy# – Observation (n=1698)		23 months
		Chemotherapy# – H (n=1703)	Sequential 1 year	
		Chemotherapy# – H (n=1701)	Sequential 2 years	
FinHer[241]	232 (HER2/ neu-amp)	Docetaxel -FEC (n=58)	Concurrently 9 weeks	36 months
		Docetaxel +H-FEC (n=54)		
		Vinorelbine -FEC (n=58)		
		Vinorelbine +H-FEC (n=62)		
PACS04**[248, 252, 253]	528	Chemotherapy# – H (n=260)	Sequential for 1 year	48 months
		Chemotherapy alone# (n=268)		
BCIRG-006***[242]	3222	AC- D (n= 1073) AC- D+H (n=1074) D+ Plat +H (n=1075)	Concurrently 1 year	36 months

Notes:

* Perez 2007 refers to data provided at the American Society of Clinical Oncology (ASCO) meeting 2007. Median follow-up 2.9 years

** Unpublished data, San Antonio Breast Cancer Symposia (SABCS) 2007. Note that 10% of women receiving FEC did not go on to receive trastuzumab. This was due to cardiotoxicity in 2%

*** Unpublished data, SABCS 2006

AC = doxorubicin + cyclophosphamide; T = paclitaxel; H = trastuzumab; FEC = fluorouracil + epirubicin + cyclophosphamide; D = docetaxel; Plat = carboplatin; # Chemotherapy regimen not specified; NSABP = National Surgical Adjuvant Breast and Bowel Project; NCCTG = North Central Cancer Treatment Group; HERA = Herceptin Adjuvant Trial; FinHer = Finland Herceptin Study; BCIRG = Breast Cancer International Research Group

Table 6.4 Main outcomes reported from key trials evaluating trastuzumab in HER2-positive early breast cancer

Study	Patient outcome HR (95% CI)				Adverse event HR (95% CI)			
	No. of patients recruited	Mortality	Recurrence	Disease-free survival (DFS) and overall survival (OS)	Symptomatic cardiotoxicity Grade III/IV congestive heart failure (CHF)	Asymptomatic cardiotoxicity, significant decrease in LVEF	Grade 3–4 cardiac event or death from heart failure	NYHA grade III/IV cardiac toxicity
Combined analysis^ NSABP B-31[238, 245] and NCCTG (Intergroup) N9831[238, 245]	Total n=2043 AC-T (n=1024) AC-TH (n=1019) Total n=1633 AC-T (n=819) AC-T-H (n=814)	AC-T group – 92 events; AC-TH group – 62 events. HR 0.67 (12.7–13.7) Absolute survival rate after 3 years was 91.7% in AC-T group and 94.3% in AC-TH group; at 4 years, the respective rates were 91.4% and 86.6%. NNT 55.26 (26.8–)	117/222 events in trastuzumab group, 235/397 events in control group. HR 0.47 (0.38–0.59); p<0.0001	261 events in the control group and 133 units in the trastuzumab group. HR 0.48 (0.39–0.59) DFS at 3 years was 75.4% in AC-T group and 87.1% in AC-TH group. At 4 years, the respective % was 67.1% and 85.3%. NNT 13.01 (9.28–21.76) 4 year OS 85.9% in AC-T and 92.6% in trastuzumab HR 0.63, (p<0.0004)	NSABP B-31 34/951 events of confirmed CHF in concurrent arm AC-TH NCCTG N9831 17/571 events in AC-TH	NSABP B-31 34% in trastuzumab arm had a significant decrease in LVEF (≥10% to below 55%) compared with 17% in the control group		At 24 months HR (95% CI) NR, NNT 65 (44–119)

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Table 6.4 continued...

Study	Patient outcome HR (95% CI)				Adverse event HR (95% CI)			
	No. of patients recruited	Mortality	Recurrence	Disease-free survival (DFS) and overall survival (OS)	Symptomatic cardiotoxicity Grade III/IV congestive heart failure (CHF)	Asymptomatic cardiotoxicity, significant decrease in LVEF	Grade 3–4 cardiac event or death from heart failure	NYHA grade III/IV cardiac toxicity
HERA[239, 240]	Total n=5090 Chemotherapy – observation (n=1693) Chemotherapy – H (n=1694)	A 24% relative reduction in mortality in the trastuzumab arm At 12 months HR 0.76 (0.47–1.23) for trastuzumab, NNT 211.17 (56.81 – ∞) At 48 months HR 0.66 (0.47–0.91); 59 [3%] events occurred in trastuzumab arm vs 90 [5%] events in the control arm	Patients surviving free from distant recurrence at 12 months: Control group n=171 (82.8%); trastuzumab group n=89 (90.6%). HR 0.49 (0.38 to 0.63; p<0.0001)	At 23 months 218 DFS events in the trastuzumab and 321 events in the control group. HR 0.64 (0.54–0.76; p<0.0001) Overall survival: 59 events in trastuzumab group; 90 events in control group HR 0.66 (0.47–0.91) p=0.01	At 12 months severe CHF; n=9/1677 [0.54%] in trastuzumab group and n=0/1710 [0%] in control group p=0.002	At 12 months 113 events in trastuzumab and 34 in control group (p<0.001)	At 12 months 132 events in trastuzumab and 75 in control group (p<0.001)	At 12 months 0.6% in the trastuzumab group; 0.1% in the control group HR (95% CI) NR. NNH 242 (125–3736) At 24 months Control group: n=0/1708 [0%] Trastuzumab group: n=10/1678 [0.6%] p<0.0001

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Table 6.4 continued...

Study	Patient outcome HR (95% CI)				Adverse event HR (95% CI)			
	No. of patients recruited	Mortality	Recurrence	Disease-free survival (DFS) and overall survival (OS)	Symptomatic cardiotoxicity Grade III/IV congestive heart failure (CHF)	Asymptomatic cardiotoxicity, significant decrease in LVEF	Grade 3–4 cardiac event or death from heart failure	NYHA grade III/IV cardiac toxicity
FinHer[241]	Total n=232 n=116 – trastuzumab group; n=116 – no trastuzumab group	(36 months follow-up) Trastuzumab group 23/115 (20%); no trastuzumab group 20/116 (17.2%) events HR 0.41 (0.16–1.08) NNT) 14.43 (9.97–∞)		DFS at 36 month follow-up Trastuzumab group 21/116 (81.9%); No trastuzumab group 18/116 (84.5%) events; HR 0.42 (0.21–0.83). OS at 36 month follow-up Trastuzumab group 23/115 (80%); No trastuzumab group 20/116 (82.8%) events; HR 0.41 (0.16–1.08). NNT (95% CI) NR				
PACS04[248]	Total n=528 Chemotherapy alone n=268; Chemotherapy – trastuzumab n=260	2/260 in treatment group versus 1/268 in control group RR 2.06 (0.61–6.99)	(48 months follow-up) Trastuzumab 8/260 (3.1%) Chemotherapy alone 14/268 (5.2%)	(48 months follow-up) Trastuzumab 59/260 (22.6%) Chemotherapy alone 70/268 (26.1%) DFS HR 0.86 (0.61–1.22)				

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Table 6.4 continued...

Study	Patient outcome HR (95% CI)				Adverse event HR (95% CI)			
	No. of patients recruited	Mortality	Recurrence	Disease-free survival (DFS) and overall survival (OS)	Symptomatic cardiotoxicity Grade III/IV congestive heart failure (CHF)	Asymptomatic cardiotoxicity, significant decrease in LVEF	Grade 3–4 cardiac event or death from heart failure	NYHA grade III/IV cardiac toxicity
BCIRG-006[242]	Total n=3222 AC-T (n= 1073) AC-TH (n=1074) TCH (n=1075)	(23 months follow-up) HR – NR, NNT (95% CI) 66.91 (not estimable) 36 months – death any cause (events) 80/1073 AC-T 49/1074 AC-TH 56/1075 TCH		(36 months follow-up) DFS AC-T group 192/1073 events; AC-TH group 128/1074 events; TCH group 142/1075 events. HR 0.49 (0.37–0.65), p<0.0001 OS AC-T group 80/1073 events; AC-TH group 49/1074 events; TCH group 56/1075 events			(23 months follow-up), Grade 3-4 cardiac left ventricular function HR (95% CI) NR NNH 72 (40–320) At 36 months (events) 4/1050 AC-T 20/1068 AC-TH 4/1056 TCH	

Notes:

* Perez 2007 refers to data provided at the American Society of Clinical Oncology (ASCO) Meeting 2007. Median follow-up 2.9 years

** Unpublished data, San Antonio Breast Cancer Symposia (SABCS) 2007. Note that 10% of women receiving FEC did not go on to receive trastuzumab. This was due to cardiotoxicity in 2%

*** Unpublished data, SABCS 2006

^ Due to the similarity between the concurrent regimen arms of the NSABP B-31 and NCCTG trials a joint analysis of data was conducted

\# Chemotherapy regimen not specified

AC = Doxorubicin + cyclophosphamide; T = paclitaxel ; H = trastzumab; FEC = fluorouracil + epirubicin +cyclophosphamide; D = Docetaxel; Plat = carboplatin; NSABP = National Surgical Adjuvant Breast and Bowel Project; NCCTG = North Central Cancer Treatment Group; HERA = Herceptin Adjuvant Trial; FinHer = Finland Herceptin Study; BCIRG = Breast Cancer International Research Group; LVEF = left ventricular ejection fraction; NNT = number needed to treat; NNH = number needed to harm

Table 6.5 Key results from the three meta-analyses evaluating trastuzumab in HER2-positive early breast cancer

Meta-analysis (included trials)	Patient outcome (HR/RR/OR; 95% CI)							Adverse events (HR/RR/OR; 95% CI)			
	Mortality	Recurrence	Disease-free survival	Metastases	Distant disease-free survival	Distant recurrence	Second tumours other than breast cancer	Symptomatic cardiotoxicity, Grade III/IV congestive heart failure	Asymptomatic cardiotoxicity, significant L-FEV drop	Grade 3–4 cardiac event or death from heart failure	NYHA grade III/IV cardiac toxicity
Viani et al. 2007[243] (NSABP B-31; N9831; FinHer; HERA; BCIRG 006)	n=9117 217/4555 (5%) in trastuzumab arm vs 392/4562 (8.5%) in control arm (p<0.00001), OR 0.52 (0.44–0.62)		Disease-free survival rates were 8.7% (400/4555) and 15.3% (700/4562) for trastuzumab arms and no transtuzumab arms, respectively; (p<0.00001); OR 0.53, (0.46–0.60)	Transtuzumab patients – 6% (276/4555) and no trastuzumab patients – 10.8% (497/4562); (p<0.00001); OR 0.53, (0.45–0.61)			n=6738 the likelihood of subsequent other tumours than breast cancer were 0.33-fold smaller in trastuzumab arms patients; (p=0.007); OR 0.33, (0.15–0.74 in 3 trials only)				203/4555 = 4.5% post trastuzumab, 86/4562 = 1.8% no trastuzumab OR 2.45 (1.89–3.16)

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Table 6.5 continued...

Meta-analysis (included trials)	Patient outcome (HR/RR/OR; 95% CI)							Adverse events (HR/RR/OR; 95% CI)			
	Mortality	Recurrence	Disease-free survival	Metastases	Distant disease-free survival	Distant recurrence	Second tumours other than breast cancer	Symptomatic cardiotoxicity, Grade III/IV congestive heart failure	Asymptomatic cardiotoxicity, significant L-FEV drop	Grade 3–4 cardiac event or death from heart failure	NYHA grade III/IV cardiac toxicity
Bria et al. 2006[214] (BIG; HERA; BCIRG 006; NSABP B-31; N9831; FinHer)	Trastuzumab group 232/9974 vs control group 276/9974 RR 0.66 (0.55–0.78); NNT 51 Absolute difference 1.96% (0.01–3.9)		Trastuzumab 633/9974 vs control group 801/9974 RR 0.63 (I 0.51–0.77); NNT 16 Absolute difference 6.0% (4.0–7.9)		RR 0.61 (0.54–0.70); NNT 21 Absolute difference 4.8% (2.8–6.7)			Trastuzumab 141/10955 vs control group 15/10955 RR 7.05 (3.88–12.83); NNH 62 Absolute difference 1.61% (0–3.4)	Trastuzumab 824/10955 vs control group 299/10955 RR 2.18 (1.45–3.27); NNH 14 Absolute difference: 7.20% (5.3–9.0)		
Ward et al. 2006[217] (HERA; NSABP B-31; N9831; FinHer; BCIRG 006)	OR 0.67 (0.52–0.87)		OR 0.50 (0.44–0.57)			OR 0.47 (0.39–0.56)				OR 5.54 (2.07–14.82)	

Table 6.6 Main results of additional study evaluating trastuzumab in HER2-positive early breast cancer

	Sample size	Disease-free survival at 1 year	Disease-free survival at 3 years
Buzdar et al. 2007[246]	n=42	Chemotherapy + trastuzumab 100% (95% CI 85.2–100); chemotherapy alone 94.7% (95% CI 85.2–100)*	Chemotherapy + trastuzumab 100% (95% CI 85.2–100); chemotherapy alone 85.3% (95% CI 67.6–100)*

Notes:

* T → FEC versus T+H → FEC+H

T = paclitaxel; H = trastzumab; FEC = fluorouracil + epirubicin + cyclophosphamide

Preoperative chemotherapy

Background

Primary systemic chemotherapy (preoperative) involves the administration of a chemotherapy regimen after diagnosis but prior to the definitive surgical intervention. Such an approach may be useful in shrinking large tumours to enable breast conserving surgery (BCS) instead of mastectomy and may assist in the identification of appropriate systemic regimens as the response of the original tumour can be observed clinically and on pathology.

Body of evidence

The systematic review undertaken addressed the effectiveness of preoperative (neoadjuvant) chemotherapy compared with adjuvant chemotherapy. The following evidence was identified that met the inclusion criteria.

Three clinical guidelines met the inclusion criteria. The SIGN guideline,[37] NHMRC guideline[48] and Belgian guideline[38] included a series of meta-analyses/systematic reviews and RCTs. (All of the guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

One Cochrane systematic review[254] identified 14 relevant RCTs. The systematic review by Stebbing et al.[113] identified five relevant RCTs. (Both systematic reviews were considered to be of high quality.)

Four additional primary studies were identified.[255–257] Rastogi et al.[255] included two NSABP protocols (B-18 and B-27). These studies compared preoperative and postoperative chemotherapy (B-18), and preoperative versus a combination of preoperative and postoperative chemotherapy regimens (B-27). van Nes et al.[256] compared preoperative and postoperative chemotherapy in an RCT. Boughey et al.[257] conducted a prospective case-series study aimed to determine the effect of preoperative compared with postoperative chemotherapy on the volume of tissue excised and the number of breast operations

in patients undergoing surgery for breast cancer. Wolmark et al.[258] compared preoperative and postoperative chemotherapy for OS and disease-free survival and evaluated the effect of preoperative chemotherapy on surgical management and recurrence. (All of the studies were considered to be of high quality.)

Summary of findings

Overall and disease-free survival

No additional benefit of neoadjuvant chemotherapy over the use of adjuvant chemotherapy in terms of disease-free survival or OS was identified.[48, 254–256, 258] The SIGN guideline[37] reported that in women aged over 70 years, there was a paucity of data on the benefit of adjuvant chemotherapy, with no clear evidence for or against its use, although there was data to suggest that the degree of benefit may be reduced with increasing age. The decision regarding which patients should be offered chemotherapy was dependent on a risk-benefit analysis made on the basis of their tumour details, age and type of therapy offered.[37, 38]

Recurrence

Wolmark et al.[258] reported that at the five-year follow-up, there were no statistically significant differences between neoadjuvant and adjuvant chemotherapy in the rates of loco-regional recurrence at any specific site. There was a strong correlation between age and rate of ipsilateral breast tumour recurrence (IBTR) ($p=0.00003$), with higher IBTR rates in women aged under 50 years (13.1%) compared with the rates of those aged 50 years and over (5.2%). A marginally statistically significant increase ($p=0.04$) was reported initially in the rate of IBTR found in patients who were converted from proposed mastectomy to lumpectomy after neoadjuvant chemotherapy compared with those patients who had a lumpectomy as initially planned before randomisation. This trend persisted through nine years of follow-up. The rate of IBTR was 15.9% in women downstaged to lumpectomies compared with 9.9% in women who received lumpectomies as originally planned.[258]

Effect on surgical management

Neoadjuvant chemotherapy was frequently offered to facilitate surgery in women with T3 tumours in whom mastectomy might be difficult or in women with T2–T3 tumours where BCS was not possible at presentation, but would be appropriate if the tumour were downstaged with neoadjuvant therapy.[37, 38, 113] Rastogi et al.[255] reported data from Fisher et al. (1997) suggesting that neoadjuvant chemotherapy can increase the overall breast conservation rate from 60% to 67%. The greatest increase was noted in women with tumours greater than 5 cm in size.

Mieog et al.[254] concluded that neoadjuvant chemotherapy permitted more BCS (a breast conservation rate of 8%), yet at the associated cost of increased loco-regional recurrence (a non-significant risk increase of 7.5%). van Nes et al.[256] also reported that BCS rates were increased with the use of neoadjuvant chemotherapy with no significant increase in loco-regional recurrence. The results overall suggest limited increase in the risk of loco-regional recurrence (approximately 2%) as long as surgery remains part of the treatment, even after complete tumour regression. Boughey et al.[257] reported that among patients treated with BCS for larger breast tumours, patients treated with neoadjuvant chemotherapy had less extensive resection compared with those treated with adjuvant chemotherapy, with no change in rates of re-excision.

Development of recommendations

Based on NZGG's systematic review of the published evidence the GDT noted that there appeared to be no benefits in terms of disease-free survival or OS in the use of preoperative (neoadjuvant) compared with postoperative (adjuvant) chemotherapy.

The GDT also noted the benefit of neoadjuvant chemotherapy for women with large tumours as it improved the rate of breast conservation. However, the GDT noted that the downstaging of the tumour through such therapy results in the loss of prognostic information and ability to predict absolute benefit of systemic treatment in an individual.

The GDT noted that there was an increased risk of loco-regional recurrence when preoperative chemotherapy was used to make BCS feasible, and that the risks as well as the benefits should be discussed with the individual.

Neoadjuvant chemotherapy enables observation of the response of a tumour to a particular systemic regimen. The degree of response is in itself of prognostic value. However, other traditional prognostic information especially regarding axillary nodal status, may be lost. This may influence other treatment decisions, and in particular may complicate radiotherapy decision-making.

Recommendations

	Grade
Preoperative chemotherapy may be considered where a woman with a large breast tumour has a preference for breast conserving surgery	A
Preoperative chemotherapy is recommended for a woman with inflammatory or inoperable locally advanced breast cancer without evidence of systemic spread	A

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice point

Practitioners should be aware that conversion from mastectomy to breast conserving surgery by preoperative chemotherapy may be associated with a higher risk of loco-regional recurrence	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

7 Systemic therapy: endocrine therapies

This chapter presents content in relation to endocrine therapy for women with early invasive breast cancer and includes the:

- accuracy of oestrogen and progesterone receptor scores
- role of endocrine therapy
  - endocrine therapy as an adjunct to chemotherapy
  - addition of chemotherapy to endocrine therapy ± surgery ± radiotherapy
  - effectiveness of one endocrine therapy over another endocrine therapy
- role of aromatase inhibitors
- role of bisphosphonates
  - survival
  - bone density.

For further general content on the role of adjuvant therapy (both chemotherapy and endocrine therapy), see Chapter 6, *Systemic therapy: chemotherapy regimens*. For relevant information on ductal carcinoma in situ (DCIS), see Chapter 8, *Ductal carcinoma in situ*.

Introduction

Endocrine therapy reduces the influence of oestrogen on breast cancer cells preventing their growth and spread. It is a systemic treatment and may be effective regardless of where the cancer cells are located in the body. A proportion of patients presenting with early breast cancer will already have metastatic spread of disease. The role of adjuvant systemic therapy in the form of endocrine treatment, chemotherapy or targeted biological agents is to decrease the risk of metastatic disease and recurrence. Endocrine therapies include tamoxifen and aromatase inhibitors and treatments such as ovarian suppression and ablation.

Pathology assessment of a tumour specimen following surgery provides prognostic information including nodal status, histological grade of the tumour and tumour size. Predictors of tumour responsiveness to endocrine therapy include hormone receptor (oestrogen and progesterone) and human epidermal growth factor receptor 2 (HER2) status. Hormone receptor status is utilised to indicate a woman's likelihood of benefit from systemic endocrine regimens.

Seven clinical questions were developed in relation to endocrine therapy in women with early breast cancer (see Chapter 11, *General section: methods*).

Accuracy of oestrogen and progesterone receptor scores

Background

Every primary breast carcinoma should be submitted for oestrogen receptor (ER) and progesterone receptor (PR) assay.[122] A variety of semi-quantitative scoring systems are available for ER and PR testing. Scoring systems are applied following immunohistochemical staining of processed tissue, and should take into account both the proportion of cells that show staining and the intensity of that staining.

There are three main scoring systems.

- The Allred score (Quick score)[259] has been successfully used to predict response to endocrine treatment[260] and remains the only validated hormone receptor scoring system.[261] An Allred score of 3 or above (more than 1% of cells with weak staining) was identified as the optimal cut-off for determining positivity and predicting response to endocrine treatment. However, because most trials use a cut-off greater than 10% the benefit of adjuvant endocrine therapy when staining is less than 10% is unclear.
- Using the Histo-score (H-score) the strength of hormone receptor positivity is also calculated using the percentage and intensity of stained cells, but it is the product of the actual percentage and the intensity score (0–3) that produces the final score (maximum 300).[262] Women with 1% to 10% of cells with weak staining would be deemed hormone receptor negative whereas they would be positive using the Allred score.
- The J-score is calculated by examining only the percentage of immunohistochemical-stained cells.[262] A score of 3 indicates hormone receptor positivity, and a score of 0 indicates hormone receptor negativity. Diagnostic accuracy and reproducibility have not been calculated for this scoring system, but it has been compared with the Allred scoring system for concordance. This scoring system is new and further studies of J-score diagnostic accuracy and clinical validity are yet to be undertaken.

Body of evidence

The systematic review undertaken identified limited evidence. No information regarding the use of scoring systems for hormone receptors was included in the Scottish Intercollegiate Guidelines Network (SIGN) guideline,[37] Belgian guideline[38] or British Medical Journal (BMJ) clinical evidence guideline.[113]

Two primary studies were identified.[262, 263] Kurosumi et al.[262] studied the concordance of the Allred and J-score scoring systems. (The study was found to lack methodological quality and was considered to be of low quality.) Dowsett et al.[263] aimed to determine whether the level of ER and PR expression could predict time to recurrence after treatment with tamoxifen, anastrozole or a combination of the two as part of the Arimidex, Tamoxifen Alone or in Combination (ATAC) study. (This study was considered to be of high quality.)

Due to the lack of high-quality evidence, pathology guidance was also reviewed for comment about acceptable scoring systems.

Other data: international expert opinion

The St Gallen Consensus considered the issue of determining endocrine responsiveness at the 10th expert consensus meeting in March 2007. An expert panel reaffirmed the primary importance of determining endocrine responsiveness of the breast tumour as a first approach to selecting systemic therapy.[81] See Appendix F for the St Gallen Consensus definitions of disease responsiveness categories.

Summary of findings

Pathology guidance recommended the use of the Allred (Quickscore) scoring system.[264] The St Gallen Consensus[81] and the National Breast and Ovarian Cancer Centre guideline[122] recommended the same cut-off point (more than 1% of cells stained for ER) although the National Breast and Ovarian Cancer Centre recommended descriptive reporting. Kurosumi et al.[262] stated that the J-score was simple and easy to use although it may be difficult to detect and evaluate positive cell counts less than or equal to 1%. There was some suggestion that staining intensity should be taken into account.

Accuracy and reliability

Standardisation of immunohistochemical staining and scoring techniques is required for ER and PR immunohistochemistry. Fisher et al.[265] suggested that the 'all or none' approach for quantifying receptor status might be the most practically useful method and avoid 'the delusion of precision' offered by other methods.

Quality assurance

A recent article from the results of the RCPA Quality Assurance Program following an audit of laboratories reporting breast carcinomas emphasises the critical need for a high level of quality assurance in ER and PR testing.[233] There was a wide variation in reported immunohistochemistry results for ER, PR and HER2 in invasive breast cancer. These differences may influence patient treatment although no methodological or specific factors were identified to account for the differences. Participation in external quality assurance programmes as supplied by the RCPA and United Kingdom National External Quality Assessment Service was strongly advised.[233]

The Guideline Development Team (GDT) advises that optimal tissue handling and prompt fixation of the tumour specimen (preferably within one hour) are essential for accurate testing. Further details of pathological management of early breast cancer are in Appendix D.

Development of recommendations

Based on the New Zealand Guidelines Group's (NZGG's) systematic review of the published evidence the GDT noted that the Allred score is the only clinically evaluated scoring system for ER and PR testing. The GDT considers that a high level of quality assurance is required for ER and PR testing and that simple scoring systems are more reliable.

Recommendations

	Grade
Every primary breast carcinoma should be submitted for oestrogen and progesterone receptor assay	C
Pathology reports should formally state both the proportion of positive nuclei and intensity of staining for oestrogen receptor and progesterone receptor to which a simple scoring system (eg, Allred) can be applied	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice points

Participation in a quality assurance programme, such as the RCPA QAP or UK scheme, with an attainment of at least 'satisfactory' performance is recommended	✓
Optimal tissue handling and prompt fixation of the sample preferably within one hour (or as soon as possible) from incision of the lesion is required	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Role of endocrine therapy

Endocrine therapy has fewer known side effects than chemotherapy and is often recommended as first-line treatment for women with hormone receptor positive (ie, oestrogen receptor positive (ER +ve) or progesterone receptor positive (PR +ve)) disease. Endocrine therapy includes drug treatments (aromatase inhibitors [AIs], tamoxifen, ovarian function suppression with LHRH analogues) or surgical or radiotherapeutic ovarian ablation. The appropriate choice of agent depends on the endocrine responsiveness of the cancer, the risk of relapse and the menopausal status of the woman. Appropriately used, all the above-mentioned endocrine therapies are known to yield highly significant improvements in disease-free survival and overall survival (OS).

Endocrine therapy as an adjunct to chemotherapy

For content on endocrine therapy with aromatase inhibitors see the section entitled, 'Aromatase inhibitors' later in this chapter.

Body of evidence

The systematic review undertaken addressed the question of whether endocrine therapy (tamoxifen, ovarian suppression, ovarian ablation) as an adjunct to chemotherapy improved patient outcome. The following evidence was identified that met the inclusion criteria.

Four clinical guidelines met the inclusion criteria. The SIGN guideline,[37] Belgian guideline[38] and BMJ guideline[113] all included the 2005 meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG).[204] The SIGN guideline also included a previous guideline and the results of several randomised controlled trials (RCTs) that examined premenopausal and postmenopausal women with node-positive and node-negative disease. The Belgian guideline[38] included additional RCT evidence and made recommendations for women with invasive non-metastatic breast cancer. The BMJ guideline[113] included additional evidence on tamoxifen and aromatase inhibitors. The National Institute of Clinical Excellence (NICE) guideline[266] focused on the use of endocrine therapies in oestrogen-positive early breast cancer. The NICE guideline was based on a systematic review.[267] (All of the guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

The 2008 EBCTCG meta-analysis[268] included approximately 50 trials of tamoxifen compared with no tamoxifen, and the Early Breast Cancer Overview Group (EBCOG) meta-analysis[269] evaluated the use of LHRH agonists to enable ovarian suppression in 16 RCTs. The systematic review by Poole and Paridaens[270] examined evidence for the use of AIs and tamoxifen in the adjuvant treatment of postmenopausal women with hormone-sensitive breast cancer. (All of the meta-analyses and systematic reviews were considered to be of high quality.)

Four primary studies were identified that met the inclusion criteria.[271–274] Morales et al.[271] compared the efficacy of three years of tamoxifen following chemotherapy with chemotherapy alone in premenopausal and postmenopausal women with early stage breast cancer. Gordon et al.[272] examined the effect of the addition of one year of tamoxifen therapy following chemotherapy in women with node-positive early breast cancer following modified radical mastectomy. Bernhard et al.[273] recruited premenopausal women with lymph node-negative cancer and assessed quality of life and menopause-related symptoms in women treated with chemotherapy and goserelin. Kaufmann et al.[274] examined the effect of the addition of two years' treatment with goserelin following chemotherapy in premenopausal women with stage I–III breast cancer. (All of the primary studies were considered to be of high quality.)

An additional review by Goldhirsch et al.[275] was identified by the GDT as relevant. The review examined the role of adjuvant therapy in very young women (ie, aged under 35 years).

Other data: international expert opinion

The St Gallen Consensus considered the issue of appropriate adjuvant treatment for women with early breast cancer according to hormone receptor sensitivity and risk of relapse at the 10th expert consensus meeting in 2007.[81] See Appendix F for the St Gallen Consensus definitions of disease responsiveness categories.

Summary of findings: premenopausal women: hormone receptor positive

Tamoxifen

The EBCTCG[204] reported that for women with ER +ve disease, allocation to about five years of adjuvant tamoxifen reduced the annual breast cancer death rate by 31% (SE 3); this was largely irrespective of the use of chemotherapy, age, PR status or other tumour characteristics. The annual recurrence rate after five years of tamoxifen was almost halved (recurrence ratio rate 0.59, SE 0.03). Annual breast cancer mortality rates were similar during years zero to four and years 5 to 14, as were the proportional reductions in rate from five years of tamoxifen, so the cumulative reduction in mortality was more than twice as great at 15 years than at five years after diagnosis.[204]

The SIGN guideline[37] and BMJ guideline[113] reported that ovarian suppression, with or without tamoxifen, in premenopausal women (over 35 years) with moderate or high risk ER +ve tumours, is as effective as cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy alone and may be superior. The effect was irrespective of age, daily tamoxifen dose (20–40 mg) and whether chemotherapy had been given to both groups. A subgroup analysis showed that a greater reduction in recurrence rate with tamoxifen was found for women with ER +ve tumours after five years compared with after one to two years (recurrence rate ratio 0.82, SE 0.03, $2p<0.0001$; breast cancer death ratio 0.91, SE 0.04, $2p=0.01$).[113, 204] In premenopausal women, ovarian suppression and tamoxifen as adjuvant treatment was shown to improve five-year survival, even in women with unknown ER status.[276] The Belgian guideline concluded that tamoxifen substantially improved the 10-year survival of women with ER +ve tumours.[38]

The study by Morales et al.[271] reported that the benefits of tamoxifen were most apparent in the subgroup of patients with node-positive and hormone receptor positive tumours. The EBCTCG[204] meta-analysis showed that five years of treatment was better than less than five years' treatment, and 10 years' treatment showed a small advantage over five years' treatment.

The GDT highlights that as endocrine therapy is not effective for women whose cancers are ER -ve and PR -ve, receptor status should be determined to avoid giving these women unnecessary treatment.

Goldhirsch et al.[275] noted that premenopausal women aged under 35 years were more likely to have more advanced disease at diagnosis and a poorer five-year survival than older premenopausal women. Younger premenopausal women have a poorer outcome than older premenopausal women when treated with tamoxifen alone (RR for relapse was 1.91, 95% CI 1.21–3.01).[275] Differences in outcome according to age for no treatment and chemotherapy plus tamoxifen were similar, also showing a poorer outcome for younger premenopausal women. The relative risk for relapse with chemotherapy plus tamoxifen reported in studies ranged from RR 1.55, 95% CI 1.14–2.1 to RR 1.94, 95% CI 1.40–2.69.[275]

The addition of ovarian function suppression with or without an aromatase inhibitor to tamoxifen is the subject of ongoing trials (SOFT and TEXT; see details of ongoing studies at the end of this section).

Ovarian suppression and ablation

The EBCTG meta-analysis reported that allocation to ovarian ablation or ovarian suppression (n=8000 women) also significantly reduced breast cancer mortality (2p=0.04) and recurrence (2p=0.0001), but appeared to do so only in the absence of other systemic treatments.[204]

The EBCOG systematic review[269] concluded that when used as the only systemic adjuvant treatment, LHRH agonists reduced the recurrence by 28.4% and death after recurrence was reduced by 17.8%. However, these results were not considered statistically significant. The addition of LHRH agonists to tamoxifen, chemotherapy, or both, reduced recurrence by 28.4% (95% CI -50.5–3.5, p=0.08); and death after recurrence by 17.8% (95% CI -52.8–42.9, p=0.49)[269] Ovarian suppression with LHRH agonists showed similar effectiveness to chemotherapy (recurrence 3.9% increase, range 7.7% reduction to 17% increase; death after recurrence 6.7% reduction, range 20.7% reduction to 9.6% increase; NS).[269]

The EBCOG systematic review also reported a large (but non-significant) reduction in recurrence and mortality among premenopausal women younger than 40 years in a small study conducted by Baum et al. (2006).[269] The Belgian guideline[38] reported the addition of the LHRH agonist goserelin to tamoxifen in premenopausal women was effective and may be regarded as a treatment option for premenopausal women with endocrine responsive disease.

In a study comparing ovarian ablation by irradiation and surgery versus surgery alone, OS and recurrence-free survival were reported to significantly increase after 15 years in 2102 premenopausal women (OS 52% vs 46%, p=0.001; disease-free survival 45% vs 39%, p=0.0007).[113] The benefit was independent of nodal status.

There is currently insufficient evidence to recommend the use of an LHRH agonist in adjunct to chemotherapy or tamoxifen treatment. The role of LHRH agonists in these settings is currently the subject of RCTs.[269]

Premenopausal women: hormone receptor negative

The EBCTCG 2007 systematic review concluded that tamoxifen is of little relevance in premenopausal women with ER -ve disease.[268]

Kaufmann et al.[274] found no additional advantage of goserelin therapy for women with hormone receptor negative disease who had received chemotherapy. Bernhard et al.[273] reported that women who received chemotherapy plus goserelin showed the same effect on quality of life indicators as women who received chemotherapy alone. There was also a similar pattern in amenorrhoea, hot flushes and coping scores for chemotherapy plus goserelin compared with chemotherapy alone.

The EBCOG meta-analysis[269] indicated that LHRH agonists were ineffective in hormone receptor negative tumours.

Other outcomes: adverse effects

For details of adverse effects associated with the use of tamoxifen, see the section entitled, 'Adverse effects' under 'Aromatase inhibitors' later in this chapter.

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted that for women with hormone receptor positive breast cancer some form of endocrine therapy should be considered, with the treatment options dependent on menopausal status.

In premenopausal women with hormone receptor positive breast cancer, tamoxifen is beneficial, with or without chemotherapy. Ovarian suppression and/or ablation plus tamoxifen may be more effective than tamoxifen alone but definitive proof is lacking. It remains uncertain whether ovarian suppression adds benefit when given after chemotherapy in women receiving tamoxifen.

In women with hormone receptor negative breast cancer, endocrine therapy should be avoided.

Several adverse effects and toxicities associated with endocrine therapy should be considered alongside the financial costs of prolonged treatment.

Some recommendations in this section are reproduced from other sections in this chapter for ease of reference and completeness.

Tables 7.1 and 7.2 summarise treatment options based on endocrine responsiveness and risk of relapse.

Recommendations

Description	Grade
In premenopausal women with hormone receptor positive breast cancer, endocrine therapy should be considered	A
In hormone receptor negative breast cancer, endocrine therapy offers no benefit and should be avoided due to the risk of side effects	A
At the time of this review there was no randomised controlled trial evidence to support the use of ovarian function suppression (LHRH agonists or oophorectomy) in conjunction with an aromatase inhibitor in premenopausal women. This is not recommended outside the remit of a clinical trial	A
When both endocrine therapy and chemotherapy are to be administered the chemotherapy should be administered first	C
In women considering oophorectomy a trial of at least one month of a LHRH agonist is recommended to allow an assessment of the tolerability of such treatment before committing to an irreversible procedure	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice point

For a woman with a low risk of recurrence the option not to use endocrine or chemotherapy treatment may be considered	✓

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Ongoing studies include the:

- Suppression of Ovarian Function Trial (SOFT): a phase III trial evaluating the role of ovarian function suppression and the role of exemestane as adjuvant therapies for premenopausal women with endocrine responsive breast cancer[277]
- Tamoxifen and Exemestane Trial (TEXT): a phase III trial evaluating the role of exemestane plus GnRH analogue as adjuvant therapy for premenopausal women with endocrine responsive breast cancer (International Breast Cancer Study Group IBCSG 25-02 BIG 3-02).

Addition of chemotherapy to endocrine therapy ± surgery ± radiotherapy

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

Two guidelines, the SIGN guideline[37] and Belgian guideline,[38] met the inclusion criteria but contained little information regarding the comparative effectiveness of chemoendocrine and endocrine therapies, with the more comprehensive guideline in this area being the Belgian guideline.[38] This guideline included the EBCTCG (2005) chemotherapy and endocrine therapy meta-analysis.[204] A further guideline, the International Society of Geriatric Oncology (ISGO) guideline,[116] identified one RCT in a systematic review focusing on women aged over 60 years. This RCT (French Adjuvant Study Group FASG 08) compared weekly epirubicin plus tamoxifen with tamoxifen alone in a six-year follow-up. (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Poole and Paridaens[270] identified one 1996 meta-analysis by Gelber et al.[278] that evaluated the effectiveness of adjuvant chemotherapy plus tamoxifen compared with tamoxifen alone on quality-adjusted survival. (The systematic review was considered to be of high quality.)

Seven primary studies were identified that met the inclusion criteria. The ABC Chemotherapy trial[279] tested the addition of chemotherapy to prolonged tamoxifen treatment (with or without elective ovarian ablation or suppression in the premenopausal and perimenopausal group. (The study was considered to be of high quality.) The International Breast Cancer Study Group IBCSG Trial 11-93[280] compared the effectiveness of adjuvant chemotherapy plus ovarian function suppression (OFS) and tamoxifen with OFS and tamoxifen alone in premenopausal patients with node-positive hormone-sensitive early breast cancer. This study closed early due to poor accrual, so lacked statistical power. (The study was considered to be of low quality.) Namer et al.[281] reported data from two RCTs (FASG 02 and 07) that compared chemoendocrine therapy (epirubicin-based chemotherapy plus tamoxifen) with that of tamoxifen alone in postmenopausal women with endocrine-responsive early breast cancer and one to three positive nodes. (The combined analysis was considered to be of high quality.)

Viale et al.[282] presented a 2008 analysis of two RCTs (IBCSG VIII and IX). IBCSG VIII comparing the effectiveness of goserelin alone, CMF chemotherapy followed by goserelin, and CMF chemotherapy alone in premenopausal women. IBCSG IX was designed to compare the effectiveness of tamoxifen alone with that of CMF chemotherapy followed by tamoxifen in postmenopausal women. (The combined analysis was considered to be of high quality.)

An additional review by Goldhirsch et al.[275] was identified by the GDT as relevant. The review examined the role of adjuvant therapy in very young women (ie, women aged under 35 years).

Other data: international expert opinion

The St Gallen Consensus considered the issue of appropriate adjuvant treatment for women with early breast cancer according to hormone receptor sensitivity and risk of relapse at the 10th expert consensus meeting in 2007.[81] See Appendix F for the St Gallen Consensus definitions of disease responsiveness categories.

Summary of findings

Hormone receptor positive

The Belgian guideline[38] reported that tamoxifen substantially improved the 10-year survival of those with ER +ve tumours. In ER +ve disease, five years of adjuvant tamoxifen reduced mortality irrespective of use of chemotherapy, age, PR status or other tumour characteristics.[38] For women with ER +ve disease, chemoendocrine therapy was found to be more effective than endocrine therapy alone or chemotherapy alone. Chemotherapy (cyclophosphamide, doxorubicin, fluorouracil) added significant long-term benefits for disease-free survival and OS to tamoxifen, especially if tamoxifen followed chemotherapy in postmenopausal women with hormone receptor positive breast cancer, as reported in a 10-year follow-up study.[283]

The ISGO guideline[116] reported that the benefit of adjuvant chemotherapy in addition to endocrine therapy in hormone receptor positive breast cancer is likely to be higher in tumours that are not clearly hormone sensitive (eg, low levels of hormone receptors, an absence of ER or PR, high grade tumours), although no conclusive data is available.

The EBCTCG 2005 meta-analysis found that chemotherapy provides significant benefit in addition to tamoxifen alone in women with ER +ve breast cancer.[38] The magnitude of this benefit is much greater for women aged under 50 years than for women aged 50–69 years, with minimal additional benefit for the addition of chemotherapy for postmenopausal women with strongly hormone receptor sensitive breast cancer.[270, 275]

Evidence is lacking to show that the addition of chemotherapy to tamoxifen plus OFS provided additional benefit to premenopausal women with hormone-sensitive, node-positive breast cancer. In low-risk, node-positive, hormone-sensitive breast cancer the possibility that endocrine therapy alone may be sufficient remains an open question.

Hormone receptor negative

The EBCTCG (2008)[268] meta-analysis demonstrated no effect of tamoxifen on ER -ve cancers.

Treatment in premenopausal women

The ABC Chemotherapy Trial[279] found that compared with no chemotherapy, chemotherapy in combination with five years' tamoxifen treatment produced modest improvements in recurrence-free survival and OS. There was some indication that age mediated the effect of chemotherapy, although not significantly, with women aged under 40 years benefiting proportionally less from chemotherapy than tamoxifen, possibly because of less chance of ovarian suppression with chemotherapy in this age group.[279] Therefore, the GDT noted that it is especially important for young women with hormone receptor sensitive breast cancer that endocrine therapy is used.

It is known that very young women (ie, aged under 35 years) are less likely to experience permanent menopause as a result of chemotherapy.[275] Amenorrhoea of less than three months' duration or continuing regular menses during or after chemotherapy in those with hormone receptor positive breast cancer is associated with a higher risk of relapse.[275]

The SIGN guideline[37] reported that the addition of CMF chemotherapy to tamoxifen was found to be beneficial to premenopausal women with fewer than four axillary lymph glands involved. Aebi et al.[284] concluded there was a paucity of data on the addition of tamoxifen to chemotherapy in premenopausal women, although no evidence that it is not of additional benefit. Omission of endocrine therapy in younger patients may be especially detrimental to their outcome.

In premenopausal women with ER +ve tumours the EBCTCG 2005 meta-analysis reported that five years of adjuvant tamoxifen reduced mortality by 31%, largely irrespective of chemotherapy and of age (under 50 years, 50–69 years, 70 years and over), PR status or other tumour characteristics. Five years was significantly more effective than one to two years of tamoxifen ($2p<0.00001$ for recurrence; $2p=0.01$ for breast cancer mortality).[204] For middle-aged women with ER +ve disease, the breast cancer mortality rate was almost halved by six months of anthracycline-based chemotherapy followed by five years of adjuvant tamoxifen over the next 15 years. If mortality reductions of 38% (women aged under 50 years) and 20% (women aged 50–69 years) from such chemotherapy were followed by a further reduction of 31% from the administration of tamoxifen in the risks that remain, the final mortality reductions would be estimated as 57% and 45%, respectively.[204]

Viale et al.[282] concluded that chemotherapy was of no overall additional benefit, although there was a trend for a benefit in young patients. Tamoxifen is the recommended endocrine treatment option, while the additional role of ovarian function suppression with or without an aromatase inhibitor is the subject of ongoing trials.

Treatment in postmenopausal women

The efficacy of tamoxifen in prolonging disease-free survival and OS when used alone or in addition to chemotherapy is established.[270] The addition of chemotherapy to adjuvant tamoxifen may improve recurrence-free survival and OS for some but not all patients with ER +ve breast cancer. Adding chemotherapy does not significantly improve quality-adjusted survival compared with tamoxifen alone.[270]

Namer et al. (2006) reported a significant improvement in disease-free survival with chemoendocrine therapy compared with tamoxifen alone in postmenopausal women with positive nodes and endocrine-responsive early breast cancer (hazard ratio [HR] 0.46, 95% CI 0.01–0.91, $p=0.0008$).[281]

Other outcomes

In a quality of life sub-study, patients who had received chemotherapy were compared with patients who had not received chemotherapy.[279] Patients who had received chemotherapy had more side effects, such as vasomotor menopausal symptoms for the first nine months after randomisation. Variation in tolerability between chemoendocrine and endocrine therapy must be taken into account when choosing between treatment options for individual patients.[281]

Endocrine responsiveness and risk of relapse

The St Gallen Consensus[81] provided summary guidance on appropriate adjuvant treatment for women with early breast cancer according to endocrine responsiveness and risk of relapse. This information is in Tables 7.1 and 7.2.

Development of recommendations

Based on NZGG's systematic review of the published evidence the GDT noted that there is evidence that chemotherapy is of benefit in premenopausal and some postmenopausal women with hormone receptor positive breast cancer but that the degree of benefit lessens with increasing age and other tumour factors. Each case should be considered on an individual basis with the risks and benefits of treatment taken into account.

Current evidence indicates that anthracycline-based and taxane-based chemotherapy regimens are more effective than CMF, and some studies have suggested this could modify the effects seen with chemoendocrine therapy compared with endocrine therapy alone. The GDT noted that no studies reviewed included taxane-containing regimens. The comparative effects of chemoendocrine therapy compared with endocrine therapy alone on disease outcomes appears to vary depending on the ER status of the tumour and menopausal status of the patient. Differences in the menopausal status of patients, the hormone-receptor status of tumours, and the type of endocrine and chemotherapy regimens employed in the trials make it difficult to compare the studies. Boxes 7.1 and 7.2 illustrate treatment options based on endocrine responsiveness and risk of relapse.

Recommendations

	Grade
For a woman with hormone receptor negative breast cancer adjuvant chemotherapy should be considered	A
For a premenopausal woman with hormone receptor positive breast cancer, chemotherapy (including an anthracycline and/or a taxane) followed by tamoxifen should be considered	A
For a postmenopausal woman with hormone receptor positive breast cancer the use of chemotherapy in addition to endocrine therapy should be considered, taking into account the overall benefits and risks of treatment* * Benefits in those aged over 70 years are uncertain	A
When both chemotherapy and endocrine therapy are to be administered the chemotherapy should be administered first	C
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice point

For early invasive breast cancer	
For a woman with a low risk of recurrence the option not to use endocrine or chemotherapy treatment should be considered as the benefits may in some cases be outweighed by the side effects of treatment	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Other ongoing trials are evaluating the role of ovarian suppression and aromatase inhibitors in premenopausal women, for example, SOFT: a phase III trial evaluating the role of ovarian function suppression and the role of exemestane as adjuvant therapies for premenopausal women with endocrine responsive breast cancer.[277]

Box 7.1 Recommended treatment options in premenopausal women based on endocrine responsiveness and risk of relapse*

Risk	Endocrine responsiveness		
	Highly endocrine responsive	Incompletely endocrine responsive	Endocrine non-responsive
Low	Endocrine therapy or no adjuvant therapy if at very low risk of recurrence	Endocrine therapy or no adjuvant therapy if at very low risk of recurrence	No adjuvant therapy
Intermediate	Chemotherapy followed by endocrine therapy	Chemotherapy followed by endocrine therapy	Chemotherapy
High	Chemotherapy followed by endocrine therapy	Chemotherapy followed by endocrine therapy	Chemotherapy

* See Appendix F for definitions of risk and disease responsiveness categories

Source: Adapted from Goldhirsch et al. Annals on Oncology 2007;18:1133–1144.

Box 7.2 Recommended treatment options in postmenopausal women based on endocrine responsiveness and risk of relapse**

Risk	Endocrine responsiveness		
	Highly endocrine responsive	Incompletely endocrine responsive	Endocrine non-responsive
Low	Endocrine therapy or no adjuvant therapy if at very low risk of recurrence	Endocrine therapy or no adjuvant therapy if at very low risk of recurrence	No adjuvant therapy
Intermediate	Endocrine therapy or chemotherapy followed by endocrine therapy	Chemotherapy followed by endocrine therapy	Chemotherapy
High	Endocrine therapy or chemotherapy followed by endocrine therapy	Chemotherapy followed by endocrine therapy	Chemotherapy

** See Appendix F for definitions of risk and disease responsiveness categories

Source: Adapted from Goldhirsch et al. Annals on Oncology 2007;18:1133–1144.

Effectiveness of one endocrine therapy over another endocrine therapy

Background

Endocrine therapy for premenopausal women may include tamoxifen, ovarian suppression with LHRH analogues or ovarian ablation (surgical removal or irradiation). Aromatase inhibitors do not adequately block oestrogen production in premenopausal women, though trials are testing whether they may have a role in conjunction with ovarian suppression or ablation. The use of aromatase inhibitors is considered in a subsequent section within this chapter.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

The SIGN guideline evidence[37] was based on a previous guideline,[285] one meta-analysis[206] and two RCTs.[276, 286] The recommendations of the Belgian guideline[38] were based on a systematic review[287] and two additional RCTs.[288, 289] The guidelines focused on endocrine therapy. The BMJ guideline[113] was based on the data from one meta-analysis[206] and the EBCOG meta-analysis[269] comparing the addition of LHRH agonists with no LHRH agonists in 16 trials.

The Adjuvant Breast Cancer Trials Collaborative Group (ABCTCG) trial[279] compared adjuvant ovarian ablation with ovarian suppression. Baum et al.[289] presented data on the combined analysis of four studies from the Zoladex in Premenopausal Patients (ZIPP) study (ZIPP UK; ZIPP Stockholm; ZIPP SE Sweden; ZIPP GIVIO). (All of the guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations. The studies were considered to be of high quality.)

Summary of findings

Ovarian suppression: LHRH agonist/tamoxifen

Adjuvant endocrine therapy for premenopausal women in the form of ovarian suppression including tamoxifen was shown by Love et al. (2002) to improve five-year survival, even when given to a population for whom endocrine receptor status is unknown.[37] The EBCTCG review (1998) confirmed data to suggest that endocrine therapy is of no benefit to patients whose tumours do not express hormonal receptors. Kaufmann et al. (2003) reported that ovarian suppression in premenopausal women has been shown to be as effective as CMF chemotherapy alone and, when given in combination with tamoxifen, to be more effective.[37]

The systematic review by Sharma et al. (2005) concluded that combined tamoxifen and LHRH agonists (without chemotherapy) may be regarded as a treatment option for premenopausal women with endocrine-responsive disease.[38] This was particularly so in those women aged under 35 years. No trials compared chemotherapy with LHRH agonist with tamoxifen in both arms.

The EBCOG meta-analysis showed that combined tamoxifen and LHRH agonists was an effective treatment with or without other systemic therapy but no significant benefit could be shown in trials examining the addition of LHRH analogues to tamoxifen alone.[269] The addition of LHRH agonists to chemotherapy with or without tamoxifen showed significant reductions in recurrence (12.2%) and death (15%), but statistical significance was lost in meta-analysis of trials examining the addition of LHRH agonists to chemotherapy without tamoxifen, and in trials examining the addition of LHRH agonists to chemotherapy with tamoxifen.[269]

The ABCTCG overview[279] concluded that the benefit of ovarian suppression/ablation on recurrence-free survival and OS may become apparent only after long-term follow-up. This large trial (n=2144) of tamoxifen in addition to ovarian suppression/ablation compared with tamoxifen alone found no significant benefit with the addition of ovarian suppression/ablation after a mean follow-up period of 5.9 years.

Baum et al.[289] reported data on 2710 women randomised to receive no treatment, tamoxifen alone, goserelin alone, or tamoxifen plus goserelin. Compared with the control group, taking either tamoxifen or goserelin or both had a similar effect, with no advantage seen for the combination of tamoxifen plus goserelin. The effect of chemotherapy-induced menopause may have limited the measurable effect of endocrine therapy.[289]

Ovarian ablation

The EBCTCG (1998) data showed that ovarian ablation by irradiation or surgery significantly increased OS and recurrence-free survival compared with surgery alone after 15 years (OS 52% vs 46%, p=0.001; recurrence-free survival 45% vs 39%, p=0.0007).[113] The benefit was independent of nodal status.

Five of the RCTs included in the BMJ guideline[113] compared ovarian ablation plus chemotherapy with chemotherapy alone. The absolute benefit of ovarian ablation was lower in these studies; chemotherapy may suppress ovarian function itself, making the effect of ovarian ablation more difficult to detect.[113] The EBCTCG (2008) overview findings suggested that the benefit of ovarian ablation on recurrence free survival and OS may become apparent only after long-term follow-up.[268]

Adjuvant chemotherapy

Endocrine therapy alone (with or without tamoxifen) in premenopausal women aged over 35 years with moderate or high risk ER +ve tumours, is as effective as CMF alone and may be superior according to findings reported by Jakesz et al.[290] In women with hormone receptor positive tumours already receiving chemotherapy and tamoxifen, the data was not clear on the benefit of the addition of ovarian suppression. The addition of goserelin and tamoxifen to adjuvant chemotherapy was found to improve disease-free survival (HR 0.74, 95% CI 0.56–0.99, p=0.04).[38]

The GDT noted that it should not be overlooked that only half of the women on CMF experienced premature menopause; the superior efficacy of anthracycline-based regimens over CMF in preventing relapse was also noted, despite the lower rates of amenorrhoea with these regimens. This suggests a direct anticancer effect of chemotherapy not mediated solely by its endocrine effects. Therefore, chemotherapy in premenopausal women may be of some benefit.

Other outcomes

In view of the overall similarity in efficacy between treatments, side-effect profiles are very important to consider.

Ovarian ablation or suppression was associated with an increase in side effects including:[113, 279, 289]

- hot flushes
- sweats and sleep disturbances
- vaginal dryness
- weight gain
- loss of bone mineral density
- cardiovascular risk.

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted that the role of LHRH agonists in adjuvant treatment is not clear. Differences in the method of ovarian function suppression and in the combination of endocrine therapies included in the different studies make comparisons difficult.

In premenopausal women with hormone receptor positive breast cancer, tamoxifen is beneficial, with or without chemotherapy. Ovarian suppression (medical and/or ablation) plus tamoxifen may be more effective than tamoxifen alone but definitive proof is lacking. Ovarian suppression (medical and/or ablation) is beneficial in women who do not receive chemotherapy, but it remains uncertain whether ovarian suppression adds benefit when

given after chemotherapy in women receiving tamoxifen. There is insufficient evidence to currently recommend the use of LHRH agonists in addition to treatment with chemotherapy and tamoxifen, although data suggest there may be a benefit for younger women who remain premenopausal after chemotherapy. This is the subject of ongoing trials.

Recommendations

Description	Grade
Oophorectomy is an acceptable treatment option but is associated with high morbidity and long-term adverse effects	A
A LHRH agonist in addition to tamoxifen should be considered for a woman at high risk of recurrence (age <40 years), who is not postmenopausal (at least 3 months of amenorrhoea) after chemotherapy	B
In a woman considering oophorectomy, a trial of at least one month of a LHRH agonist is recommended to allow an assessment of the tolerability of such treatment before committing to an irreversible procedure	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Ongoing trials are investigating the relative efficacy of different endocrine therapies and the optimal duration of endocrine therapy in premenopausal women. This includes some trials examining the effectiveness of aromatase inhibitors in combination with ovarian suppression, for example, the:

- Suppression of Ovarian Function Trial (SOFT) is a phase III trial evaluating the role of ovarian function suppression and the role of exemestane as adjuvant therapies for premenopausal women with endocrine responsive breast cancer (Krop et al., 2005)
- Tamoxifen and Exemestane Trial (TEXT) is a phase III trial evaluating the role of exemestane plus gnrh analogue as adjuvant therapy for premenopausal women with endocrine responsive breast cancer (International Breast Cancer Study Group IBCSG 25-02 BIG 3-02)
- Austrian Breast Cancer Study Group (ABCSG) Trial 12 is comparing either three years of tamoxifen or anastrozole in combination with goserelin.

Aromatase inhibitors

Background

Third generation AIs anastrozole, exemestane and letrozole are prescribed for treatment in a variety of adjuvant settings in women with early breast cancer and have been compared with standard endocrine therapy with tamoxifen. Comparisons have been made on the basis of:

- upfront or initial therapy with either tamoxifen or an aromatase inhibitor
- sequential regimens involving switching from tamoxifen to an AI or from an AI to tamoxifen after two to three years
- extended or late treatment regimens where an AI is administered after five years of tamoxifen therapy.

Body of evidence

The systematic review undertaken addressed the use of AIs in postmenopausal women as upfront therapy, in sequential regimens, and in extended or late regimens. The following evidence was identified that met the inclusion criteria.

The secondary evidence was primarily based on several key RCTs. The designs of these trials are presented in Table 7.1.

Four guidelines were identified that met the inclusion criteria. The SIGN guideline,[37] the Belgian guideline,[38] the BMJ guideline[113] and the 2008 Cancer Care Ontario guideline (based on the systematic review by Eisen et al., 2007).[291] (The Cancer Care Ontario guideline was given the AGREE tool quality grading: strongly recommended. All of the other guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Four meta-analyses/systematic reviews met the inclusion criteria.[267, 270, 291, 292] (The meta-analyses or systematic reviews were considered to be of high quality, with the systematic review by Eisen et al. considered to be of very high quality.)

Seven additional primary trials were identified that met the inclusion criteria. The ATAC trial[293, 294] was discussed within many of the meta-analyses and systematic reviews. Data is now reported at the 100-month follow-up in 6241 subjects.[293] Rasmussen et al.[295] and Crivellari et al.[296] conducted subgroup analyses of the BIG 1-98 trial, which was also discussed within the secondary studies identified. Two studies reported on the effects of extended endocrine therapy – the National Surgical Adjuvant Breast and Bowel Project NSABP B-33 trial[226] and MA.17 trial.[297, 298] Switch therapy was reviewed by Boccardo et al. (2007).[299] (All of the primary trials were considered to be high quality.)

Summary of findings

Survival

None of the trials of upfront regimens has as yet demonstrated an OS advantage. A pre-planned subgroup analysis of the Intergroup Exemestane Study (IES) study[300] restricted to women with ER +ve or unknown receptor status demonstrates a survival advantage for switching to exemestane after two to three years of relapse-free survival on tamoxifen. A subgroup analysis by Goss et al. (2005) found that the addition of letrozole after five years of tamoxifen also improved OS in women with node-positive disease.[291]

Recent and upcoming data

A recent meta-analysis of the upfront trials and of the switch trials has been carried out.[301] The upfront studies (ATAC and BIG 1 -98) showed no significant OS benefit, though a non-significant trend in favour of breast cancer survival at five years (absolute benefit 1.1%, p=0.1), and a highly significant improvement in distant disease-free survival (HR = 0.82, SE 0.06, p=0.002) was seen for AIs. The switch trial meta-analysis showed that at six years, AIs yielded an absolute reduction in breast cancer mortality of 1.6% (SE 0.8) corresponding to a 22% reduction in breast cancer deaths at six years (p=0.02).

Recurrence

All of the individual large trials of AI use have shown significant reductions in recurrence and improved disease-free survival compared with tamoxifen whether used upfront, in a switch regimen, or as extended therapy (see Table 7.1).

Recent and upcoming data

The recent meta-analysis of AI trials[301] showed that with upfront treatment, AIs reduced breast cancer recurrence by 23%, corresponding to absolute gains of 2.9% at five years (SE 0.7, 2p<0.00001), and by 3.9% at eight years (SE 1.0, 2p<0.00001). The switch trial meta-analysis at the six-year follow-up showed a 3.5% absolute reduction in breast cancer recurrence (29% relative decrease). There appeared to be greater proportional reductions in isolated local recurrence (30–40%) and contralateral breast cancer recurrence (35–41% reduction) than in distant recurrence (16–24%) in both meta-analyses. This study is published in abstract form only, so has not been fully appraised for quality.

Upfront or initial treatment

Letrozole

The BIG 1-98 trial[302, 303] is a four-arm study comparing upfront letrozole with tamoxifen (n=8028), and the sequence of two years of tamoxifen followed by letrozole and two years of letrozole followed by tamoxifen. Upfront letrozole was associated with significant improvements in disease-free survival (HR 0.82, 95% CI 0.71–0.95) compared with tamoxifen, although there was no significant difference in OS.[302, 303] Letrozole was associated with significant benefit in disease specific recurrence (HR 0.72, 95% CI 0.61–0.88) and distant recurrence (HR 0.73, 95% CI 0.60–0.88).

Anastrozole

The ATAC study[293, 294] (n=9366) compared tamoxifen with anastrozole and a combination arm receiving both drugs. When compared with tamoxifen, anastrozole was associated with a significant improvement in disease-free survival (HR 0.90, 95% CI 0.82–0.99). The combination arm was discontinued after interim analyses showed no benefit over tamoxifen.

The ATAC study reported that disease-free survival was significantly improved with the use of anastrozole compared with tamoxifen both in the total population (HR 0.90, 95% CI 0.82–0.99) and for women with hormone receptor positive breast cancer (HR 0.85, 95% CI 0.76–0.94).[293] Time to recurrence was significantly improved with the use of anastrozole at the 100-month follow-up in both the total group (HR 0.81, 95% CI 0.73–0.91) and for women with hormone receptor positive disease (HR 0.76, 95% CI 0.67–0.87).[293]

Switching, sequential and extended therapy

The Belgian guideline stated that for women who started tamoxifen at baseline, switching to an oral AI after two to three years should be considered, especially if they are at high risk.[38] The BMJ guideline[113] cited data from the MA.17 trial reported by Goss (2003). Aromatase inhibitors were found to be superior to tamoxifen administered for five years in postmenopausal women eligible for adjuvant endocrine therapy. Letrozole following five years of tamoxifen improved the estimate of disease-free survival at four years (93% vs 87%).[113] Aromatase inhibitors were consistently associated with an improvement in disease-free survival relative to tamoxifen but with equivocal evidence for OS.[291]

Poole and Paridaens[270] concluded that aromatase inhibitors were more effective than five years of adjuvant treatment with tamoxifen when given either sequentially after two to three years tamoxifen treatment or initially in place of tamoxifen. Concomitant therapy with an AI has not been shown to produce additional benefit. The optimal treatment duration with AIs is yet to be determined.

Exemestane

The IES trial[300, 304, 305] compared two to three years of tamoxifen followed by exemestane for two to three years with tamoxifen alone for five years. The exemestane regimen was associated with significantly improved disease-free survival compared with tamoxifen alone (HR 0.68, 95% CI 0.56–0.82, $p<0.001$). There was no difference in OS, but there was a significant difference in breast cancer-related survival. Time to contralateral breast cancer, time to recurrence and time to distant recurrence were improved in those switching to exemestane. Subgroup analysis excluding ER -ve women showed improvement in OS in the exemestane group (HR 0.83, 95% CI 0.69–1.0).

Anastrozole

The meta-analysis by Jonat et al.[292] concluded that patient groups who switched to anastrozole after two to three years of tamoxifen had fewer recurrences and deaths than those remaining on tamoxifen. Switching to anastrozole also resulted in a significant improvement in disease-free survival and OS and showed significant improvements in event-free and distant recurrence-free survival.[292] The benefit of switching to anastrozole over continued tamoxifen was evident regardless of nodal status, hormone receptor status, previous chemotherapy or tumour size.[292]

The ITA study[299] (n=426) and ABCSG-8 and ARNO-95 studies[290] reported similar results after administering tamoxifen for two or more years, followed by tamoxifen or anastrozole to a total of five years' adjuvant endocrine treatment. Disease-free survival improved in those switching to anastrozole[290, 299] and distant metastases-free survival was significantly longer in the anastrozole group.[290] There was no difference in OS observed between the therapy arms.[290, 299] Although this is so for individual trials, the meta-analysis by Jonat[292] as discussed, did indicate a survival advantage in switching to anastrozole for the completion of a five-year course of endocrine therapy after completing two to three years of tamoxifen.

Letrozole

The MA.17 trial[306, 307] compared letrozole with a placebo after 4.5–6 years of tamoxifen. Extended treatment with letrozole in the MA.17 trial was found to be superior to tamoxifen for five years in terms of recurrence rate.[307] The Belgian guideline[38] reporting on the findings of the MA.17 trial[306] noted that extended treatment with letrozole following five years of tamoxifen treatment significantly reduced recurrence of breast cancer, regardless of nodal status or previous chemotherapy. In the initial analysis at 2.5 years there was no difference in OS; subgroup analysis did indicate a significant increase in OS with letrozole in women with node-positive disease (HR 0.61, 95% CI 0.38–0.98) and in those who had received more than five years of tamoxifen (HR 0.56, 95% CI 0.33–0.97).

Recent and upcoming data

The first randomised assessment of upfront compared with sequential AIs as part of the BIG 1-98 trial was presented at the 2008 San Antonio Breast Cancer Symposium.[308] At the 71 month median follow-up the five-year disease-free survival was 87.9% for five years of letrozole, 87.6% for two years of letrozole followed by three years of tamoxifen, and 86.2% for two years of tamoxifen followed by three years of letrozole. The time to distant recurrence trended in favour of five years of letrozole compared with two years of tamoxifen followed by three years of letrozole (HR 1.22, 95% CI 0.88-1.69). Overall, the sequential treatments: tamoxifen followed by letrozole, and letrozole followed by tamoxifen did not improve the outcome compared with letrozole alone. The results suggest it is better to start treatment with letrozole, rather than tamoxifen, especially for patients at higher risk (eg, node positive). Patients who start with letrozole can be switched to tamoxifen after two years, if required.

This study is published in abstract form only, so has not been fully appraised for quality.

Other outcomes

Adverse effects

Most of the guidelines, reviews and primary studies reported the adverse effects associated with treatment. Tamoxifen is associated with several adverse effects including:

- hot flushes
- vaginal bleeding or discharge (which may lead to an increase in gynaecological interventions and hysterectomy for women on tamoxifen compared with AIs)
- endometrial thickening atypia, and uncommonly cancer
- increased risk of thromboembollic event (about 0.5–1% risk for women aged over 50 years taking a five-year course, and especially a risk if undergoing surgery)
- arthritis (uncommon)
- myalgia (uncommon)
- cataracts (uncommon)
- stroke (very uncommon).

AIs are associated with an increased incidence of:

- hot flushes
- vaginal dryness
- arthralgia and arthritis
- decreased bone mineral density, osteoporosis and increased bone fracture rates (fracture rates increased only during active treatment and did not differ after treatment was completed)[293]
- loss of libido
- diarrhoea
- increased cholesterol levels compared with tamoxifen (which has some cholesterol-lowering effect)
- rarely insomnia and hair thinning.

These agents are generally well tolerated, as evidenced by the ATAC trial, where 88% of women on anastrozole and 87% of women on tamoxifen completed five years of therapy.

Assessment of menopausal status

Measurement of oestrogen and gonadotrophin levels is recommended before initiating treatment with an AI if there is a chance that a woman is still premenopausal (eg, it is less than one year since her last menstrual period). Particular care is required for younger women just post chemotherapy or on tamoxifen, as amenorrhoea can occur when normal premenopausal ovarian oestrogen production is present.

As tamoxifen leads to elevated gonadotrophin levels even in premenopausal women, it is important to be sure that oestrogen levels are postmenopausal, indicating that ovarian oestrogen production is no longer occurring, in order to be sure that use of an AI is appropriate and will be effective at further suppressing oestrogen production. As ovarian function can cease temporarily after chemotherapy, levels should be rechecked probably about three monthly for the first year after completion of chemotherapy if AIs are to be used in this group. Note most trials have excluded this group from AI therapy.

In elderly patients, a patient profile of risk factors for various adverse effects should be considered to decide between different endocrine treatment options. For example, in the presence of comorbidities such as osteoporosis, tamoxifen may be preferred, whereas in the presence of risk for thromboembolic disease, an AI may be preferred.[296]

Quality of life

No significant difference in overall health-related quality of life between standard treatment and either initial or extended adjuvant AI strategies was identified.[267] Quality of life data suggest that exemestane after tamoxifen is well tolerated, with a mild but non-significant increase in symptoms reported in the NSABP 33 trial.[226] In terms of quality of life, women aged 70 years or over in the letrozole group of the MA.17 study reported significantly poorer scores at six months on a scale for vitality. At 12 months, this group reported significantly poorer scores on scales for bodily pain, physical and vasomotor functioning.[298]

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted that five years of aromatase inhibitors is better than five years of tamoxifen with respect to disease-free survival, but not OS. Switching to aromatase inhibitors is better than five years of tamoxifen with regard to disease-free survival, and from a recent meta-analysis, for OS. Extended therapy with AIs is better than five years of tamoxifen but the optimal duration of this treatment has not been determined.

The strategy for use of AIs has been the subject of speculation and some controversy until the recent results of the BIG1-98 trial, which compared two sequential regimens containing tamoxifen and letrozole with upfront letrozole. There were no statistically significant differences in relapse-free survival between five years of letrozole and either of the sequential arms, though there was a trend to more early relapses in the tamoxifen-first sequence.

There are different side-effect profiles with AIs and tamoxifen – more frequent reporting of bone fracture with aromatase inhibitors and greater risk of thromboembolic events, endometrial cancer and other gynaecological conditions with tamoxifen. The GDT noted that these potential harms, as well as the benefits, should be discussed with the individual.

Recommendations

	Grade
Aromatase inhibitors should form at least part of the treatment regimen when adjuvant endocrine therapy is prescribed to postmenopausal women with hormone receptor positive early breast cancer, unless contraindications to their use exist	A
Adjuvant endocrine therapy for postmenopausal women with hormone receptor positive early breast cancer should comprise treatment for 5 years with either an aromatase inhibitor alone or with a sequence of an aromatase inhibitor and tamoxifen. Women already on tamoxifen for 2–3 years should switch to an aromatase inhibitor	A
Adjuvant endocrine therapy should be given for a duration of at least 5 years	A
The use of tamoxifen alone as adjuvant therapy for postmenopausal women is recommended only when an aromatase inhibitor is contraindicated or has been tried and was not tolerated Tamoxifen for 5 years remains the standard of care in premenopausal women with hormone receptor positive breast cancer	A
Premenopausal women who have completed 5 years of tamoxifen and have become menopausal should be given the option of extended therapy with an aromatase inhibitor	A
Extended (or 'late') use of an aromatase inhibitor after 5 years of tamoxifen is recommended only for those women with hormone receptor positive breast cancer who have completed a 5-year course of tamoxifen and become suitable for treatment with an aromatase inhibitor late in that course (eg, having become reliably menopausal after the time when a switch policy would have been considered)	A
Measurement of oestrogen and gonadotrophin levels is recommended before initiating treatment with an aromatase inhibitor where there is a chance that the woman is still premenopausal Note: Particular care is required for younger women just post chemotherapy or on tamoxifen, as amenorrhoea can occur when normal premenopausal ovarian oestrogen production is present. Tamoxifen leads to elevated gonadotrophin levels even in the presence of normal premenopausal ovarian endocrine function	A
Aromatase inhibitors should be prescribed with caution for women in their forties with chemotherapy-induced premature ovarian failure	B
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice points

The side effects of aromatase inhibitors and tamoxifen should be considered against the absolute benefit in breast cancer relapse	✓
For women receiving aromatase inhibitors, baseline assessment of bone density should be completed and ongoing monitoring of bone density planned depending on the initial measurement	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Table 7.1 Summary of key randomised controlled trials comparing tamoxifen and aromatase inhibitors – upfront, switching, sequential and extended therapy regimens

Trial	Treatment arms	Duration	No. of participants	Follow-up (months)	Nodal status	Tumour size	Hormone receptor status
Initial/upfront therapy with tamoxifen or an aromatase inhibitor (AI)							
ATAC[293, 294]	Anastrozole or Tamoxifen or Anastrozole + Tamoxifen	5 years	3125	68–100	61% node -ve	64% ≤2 cm	84% ER+ and/or PR+
		5 years	3116				
		5 years	Terminated early due to a lack of efficacy				
BIG 1-98[302, 303]	Letrozole or tamoxifen	5 years	2463	51	57% node -ve	62% ≤2 cm	ER+ and/or PR+ only
		5 years	2459				
Switching/sequential therapy with tamoxifen followed by AI							
IES[304]	Tamoxifen > Exemestane or Tamoxifen	T 2–3 years > E 2–3 years	2352	55–57	52% node -ve	48% ≤2 cm	ER+/unknown only
		5 years	2372				
ITA[299]	Tamoxifen > Anastrozole or Tamoxifen	T 2 years > A 3 years	225	64	node +ve only	44–49% ≤2 cm	ER+ only
		5 years	223				
ABCSG-8/ ARNO 95[290]	Tamoxifen > Anastrozole Tamoxifen	2 years > A 3 years	1618	28	74% node -ve	70% ≤2 cm	ER+ and/or PR+ only
		5 years	1608				
BIG 1-98[303]	Tamoxifen >Letrozole Letrozole > Tamoxifen	T 2 years > L 3 years	1548	51	Full results not available yet		
		L 2 years > T 3 years	1540				

continued over...

Table 7.1 continued...

Trial	Treatment arms	Duration	No. of participants	Follow-up (months)	Nodal status	Tumour size	Hormone receptor status
Extended therapy with an AI following 5 years of tamoxifen							
MA.17*[306, 307]	Tamoxifen > Letrozole Tamoxifen > placebo	T 5 years > L 5 years	2593	54	50% node -ve	NR	97% ER+ and/or PR+
		T 5 years > P 5 years	2594				
NSABP B33**[226]	Tamoxifen > Exemestane Tamoxifen > placebo	T 5 years > E 5 years	783	30	52% node -ve	T1-3 only	NR
		T 5 years > P 5 years	779				
ABCSG-6a[290]	Tamoxifen > Anastrozole Tamoxifen	T 5 years > A 3 years	387	60	68% node -ve	63% ≤2 cm	ER+ and/or PR+ only
		5 years	469				

* MA.17 was unblinded after 2.4 years because of the significantly better efficacy of the letrozole arm

** Unblinded early when the results from MA.17 were published

Dosages: Tamoxifen 20 mg daily (* ARNO 95 tamoxifen dose 20–30 mg daily); Anastrozole 1 mg daily; Letrozole 2.5 mg daily; Exemestane 25 mg daily

> Followed by: ATAC = Arimidex, Tamoxifen Alone or in Combination Trial; BIG-1 = Breast International Group; IES = Intergroup Exemestane Study; ITA = Italian Tamoxifen Anastrozole trial; ABCSG = Austrian Breast and Colorectal Cancer Study Group Trial; NSABP = National Surgical Adjuvant Breast and Bowel Project

Role of adjuvant bisphosphonates: survival

Background

Bisphosphonates inhibit osteoclastic bone resorption.[309] They are effective in conditions characterised by osteoclast-mediated bone resorption such as Paget's disease and osteoporosis.[310] There is increasing evidence that bisphosphonates may directly affect tumour cells,[311] inducing apoptosis and inhibiting tumour cell growth, in vitro. In malignancy they have become standard treatment for tumour-induced hypercalcaemia.[312] RCTs have shown that in multiple myeloma and metastatic breast cancer (zoledronate and pamidronate at least) and prostate cancer (zoledronate only) bisphosphonates reduce bone pain, improve quality of life, and reduce the number of and time to skeletal events.[312, 313] Although they are often used in metastatic disease, bisphosphonates have also been used in the adjuvant setting in order to prevent treatment-induced osteoporosis and to reduce the risk of developing osseous metastases.

Body of evidence

The systematic review undertaken addressed the question of the effectiveness of adjuvant bisphosphonates for early breast cancer when patient outcomes include disease-free survival, local recurrence, distant recurrence and OS. The following evidence was identified which met the inclusion criteria.

Three clinical guidelines met the inclusion criteria. The SIGN guideline[37] included a practice guideline report[314] and an RCT.[315] The Belgian guideline[38] included a systematic review[316] and practice guideline report.[314] (Both of these guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.) The Practice Guideline (Cancer Care Ontario Guideline)[314] was based on a well-designed Cochrane review that identified three RCTs and included analysis of 1680 women.[315, 317, 318] (This guideline was given the AGREE tool quality grading: strongly recommended.)

One meta-analysis met the inclusion criteria.[319] This included seven studies (n=2156 participants), three of which were relevant to those with early breast cancer. (The meta-analysis was considered to be of high quality.)

Two additional primary studies published in 2006 and 2008 were identified. Powles et al.[320] investigated the addition of clodronate for two years to standard treatment in 1069 premenopausal and postmenopausal women. (The trial was considered to be of very high quality.) Kristensen et al.[321] investigated adding pamidronate to standard treatment over a four-year period in 953 women. (This trial was considered to be of high quality.)

Summary of findings

Osseous metastases

The Cancer Care Ontario Guideline[314] noted data on the development of osseous metastases and metastasis-free survival were controversial, with Diel et al. (2000) reporting significant differences between clodronate and control groups and Saarto et al. (2001) reporting no significant differences.

The SIGN guideline,[37] the Belgian guideline[38] and the meta-analysis by Ha et al.[319] did not identify any significant reduction in incidence of osseous metastases in those with early breast cancer treated with bisphosphonates. Powles et al.[320] concluded that oral clodronate significantly improved the five-year bone relapse-free survival rate when used as a supplementary adjuvant treatment for patients receiving standard treatment for primary operable breast cancer (HR 0.69, p=0.04). Kristensen et al.[321] did not find evidence to support a beneficial effect of oral pamidronate on the occurrence of osseous metastases or fractures in patients with primary breast cancer receiving adjuvant chemotherapy.

Survival

In terms of survival, the Belgian guideline[38] suggested that adjuvant clodronate may improve survival. However, there was significant heterogeneity in outcomes reported by the studies.[38] In sum, there was no evidence that oral bisphosphonates improved OS in those with early breast cancer.[314, 319, 321]

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted the lack of consistent evidence to suggest the effectiveness of oral bisphosphonates in the reduction of osseous metastases or in OS in early breast cancer. At present, bisphosphonates cannot be recommended for use as adjuvant treatment for early breast cancer.

Recommendation

	Grade
Due to the lack of consistent evidence no recommendations were made regarding use of oral bisphosphonates for the reduction of osseous metastases in early breast cancer	I

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Several trials are currently evaluating the role of adjuvant bisphosphonates in patients with early breast cancer, including:

- AZURE (adjuvant zolendronic acid to reduce recurrence)
- GAIN (German Adjuvant Intergroup Node-Positive study)
- ICE (ibandronate with or without capecitabine in elderly patients with early breast cancer)
- S0307, which was designed to assess the efficacy of bisphosphonates in reducing the incidence of osseous metastases (joint SWOG /Intergroup/NSABP trial).

The results of some of these trials were anticipated in 2008 but were not available when this guideline was prepared.

Role of adjuvant bisphosphonates: bone density

Background

For information on the action of bisphosphonates, see 'Background' in the previous section entitled, 'Role of adjuvant bisphosphonates: survival'.

Bone loss caused by premenopausal women taking tamoxifen does not present a clinical problem requiring bone-protecting medication, and tamoxifen protects against bone loss in postmenopausal women. However, following ovarian suppression with LHRH analogues, the oestrogen agonist action of tamoxifen is insufficient to counteract the rapid bone loss associated with ovarian suppression. Premenopausal women also undergo bone loss with chemotherapy-induced early menopause and postmenopausal women have accelerated bone loss on aromatase inhibitors. Under these circumstances the administration of a bisphosphonate may be efficacious.

Body of evidence

The systematic review undertaken addressed the question of the effectiveness of adjuvant bisphosponates in early breast cancer for the patient outcome of bone density. The following evidence was identified that met the inclusion criteria.

One clinical guideline from a UK expert group[322] met the inclusion criteria. The guideline focused on older women (ie, women aged over 70 years) and postmenopausal women. (The guideline was given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Three additional primary studies[323–325] and an integrated analysis of two RCTs[321] met the inclusion criteria. (Greenspan et al., 2008, and Brufsky et al., 2008, were considered to be of very high quality; the remaining studies were considered to be of high quality.) All studies used bone mineral density (BMD) as an outcome, with or without biochemical markers of bone turnover, and safety data.

Kristensen et al.[321] examined the effectiveness of pamidronate compared with no pamidronate in 953 women, including measurements of skeletal events and survival. Brufsky et al.[324] conducted an integrated analysis of two RCTs, including 1667 postmenopausal women with ER +ve or PR +ve breast cancer. The study compared upfront with delayed administration of zoledronate. Gnant et al.[325] included 401 premenopausal women with ER +ve or PR +ve breast cancer scheduled to receive the LHRH agonist goserelin for three years.

Summary of findings

Pooled analysis by the UK expert group indicated that bisphosphonates effectively and safely prevented loss of BMD (including AI-dependent bone loss) in both premenopausal and postmenopausal women, with or without adjuvant hormone therapy (tamoxifen) or AI therapy.[322] In contrast, Kristensen et al.[321] identified no significant differences in bone metabolism with adjuvant pamidronate compared with no adjuvant pamidronate.

Bisphosphonates in premenopausal women

Gnant et al.[325] reported that treatment with zoledronate effectively and safely prevented loss of BMD in premenopausal women treated with AIs in combination with an LHRH agonist. The addition of the bisphosphonate decreased the proportion of patients with particularly severe bone loss in the lumbar spine (ie, those who met the criteria for overt osteoporosis) from 22% to 1% after three years of therapy.

Bisphosphonates in postmenopausal women

Bisphosphonates are recommended when the BMD as measured by the T-score falls below minus 2, or if the rate of bone loss in women with pre-existing osteopenia exceeds 4% per year.[322] This is also applicable to women with premature menopause. The exception is for women receiving ovarian suppression plus an AI, for whom the recommended T-score threshold is minus 1, due to very rapid losses of bone which occur in this group of women (averaging 16% over three years).[322]

Oral risedronate prevented bone loss or improved bone mass, decreased bone turnover, and was well tolerated in postmenopausal women with chemotherapy-induced menopause, with or without adjuvant hormone therapy or AIs.[323] Upfront administration of zoledronate prevented AI-associated bone loss more effectively than delayed-start in postmenopausal women with early stage breast cancer receiving letrozole. Additionally, disease recurrence appeared to be lower with upfront regimens but further follow-up is needed to confirm interim results.[324]

The UK expert group suggested women aged 75 years and over, with one or more risk factors for osteoporotic fractures, should receive bisphosphonates irrespective of BMD.[322]

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT noted that the reviewed evidence indicated that bisphosphonates effectively and safely prevented loss of BMD (including AI-dependent bone loss) in premenopausal and postmenopausal women, with or without, adjuvant hormone therapy or AI therapy. The GDT also noted that regular BMD measurements and initiation of concomitant bisphosphonate therapy on evidence of bone loss should be considered for patients undergoing endocrine therapy.

Recommendations

	Grade
Women who are osteoporotic and on adjuvant endocrine therapy that enhances loss of bone density or who have undergone premature treatment-induced menopause should receive a bisphosphonate	A
Women who are osteopenic and on adjuvant therapy which enhances loss of bone density, or who have undergone premature treatment-induced menopause should be considered for a bisphosphonate, especially in the presence of other risk factors: prior non-traumatic fracture, aged over 65 years, family history, tobacco use, low body weight	C
Postmenopausal women taking aromatase inhibitors are recommended to commence treatment with bisphosphonates if the T-score is <-2.0, or <-1.0 in the presence of a vertebral fracture. Secondary causes of osteoporosis should be excluded and standard lifestyle advice on smoking and exercise, calcium supplementation and adequacy of vitamin D intake should also be provided	C
Women with premature menopause due to chemotherapy, ovarian function suppression or oophorectomy and postmenopausal women receiving adjuvant therapy with an aromatase inhibitor should have bone density monitored at least every 2 years following a baseline DEXA (dual energy X-ray absorptiometry) scan of the spine and hip	C
Frequency of bone mineral density monitoring should be tailored to the individual. If baseline T-score >-1.0 further monitoring of bone density may not be necessary	C
A woman with early breast cancer at risk of bone mineral loss should be provided with appropriate advice for good bone health. This includes, but is not limited to: • a healthy diet • cessation or continuing abstinence from smoking • maintenance of a healthy body mass index • regular exercise • calcium • adequate vitamin D levels	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

8 Ductal carcinoma in situ

Throughout the development of this guideline the Guideline Development Team (GDT) recognised that the treatment of women with a diagnosis of ductal carcinoma in situ (DCIS) was distinctly different from the management of other early breast cancer. Content in relation to DCIS is presented in this chapter and includes:

- surgical management for DCIS
  - mastectomy compared with breast conserving surgery
  - the margins of excision for breast conserving surgery
  - the management of the axilla
- radiotherapy in addition to breast surgery for DCIS
  - breast conserving surgery ± radiotherapy
  - boost dose radiotherapy
- systemic therapy: endocrine therapy for DCIS.

For the specific clinical questions on these topics, see Chapter 11, *General section: methods*.

Introduction

DCIS or intraductal carcinoma is most commonly diagnosed as a result of detection of microcalcifications on mammography. It is usually not palpable. By definition, it is confined to the duct system of the breast, so is not associated with metastases. DCIS is a heterogeneous disease and pathological grading is similar to invasive cancers, except when based solely on nuclear features (see the section entitled, 'Microscopic reporting of pure ductal carcinoma in situ' in Appendix D).

Surgical management for ductal carcinoma in situ

Mastectomy compared with breast conserving surgery: ductal carcinoma in situ

Background

For a detailed description of surgical interventions available for breast cancer, see the section 'Background' in the section 'Mastectomy compared with breast conserving surgery' in Chapter 4, *Surgery for early invasive breast cancer*.

Body of evidence

For patients with DCIS, the Scottish Intercollegiate Guidelines Network (SIGN) guideline[37] reported that no randomised controlled trials (RCTs) that directly compared patients with DCIS undergoing mastectomy versus breast conserving surgery (BCS) were identified. However, the authors reported a subgroup analysis of an RCT by Fisher et al. (1991)[326] and a meta-analysis of observational studies by Antonini et al. (2007).[168] The Belgian guideline[38] reviewed four previous guidelines.[37, 75, 90, 327] (Both guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

An additional case series study by Boyages et al.[328] was identified by the GDT as relevant.

Summary of findings

Overall survival/recurrence

Boyages et al.[328] reported local recurrence rates of 1% to 2% for mastectomy, approximately 10% for BCS plus radiotherapy, and 20% for BCS alone. The choice of BCS versus total mastectomy, with the option for reconstruction showed similar mortality rates at five years for both procedures.[37, 38]

After BCS approximately 50% of local recurrences are as invasive cancer, the remainder being DCIS.[37] Factors that reduce the risk of local recurrence after BCS for DCIS include:

- radiotherapy
- wider margins of excision
- non-high grade DCIS
- absence of comedo necrosis
- smaller DCIS volume
- increased age.

Complete excision

Multicentricity and residual disease (positive margins) have been reported as contraindications for wide local excision.[75] Complete excision should be achieved as positive or indeterminate resection margins have been associated with an increased risk of loco-regional recurrence.[90]

Development of recommendations

The published evidence identified from the New Zealand Guidelines Group's (NZGG's) systematic review was limited largely to reviews of large case series as there is no RCT evidence. Based on this evidence, the GDT concluded that BCS and radiotherapy results in equivalent outcomes to mastectomy in terms of overall survival (OS), but may be associated with higher rates of local recurrence. The GDT notes the lack of evidence from RCTs of BCS compared with mastectomy for women with DCIS, and given that it has taken the 15-year follow-up on the trials of invasive cancer treatment with and without radiotherapy[106] to show significant survival effects, useful OS data for women with DCIS would not be expected until at least this length of follow-up has occurred.

Recommendation

	Grade
When making the choice between breast conserving surgery and mastectomy the following factors should be considered in discussion with the woman: • ratio of the size of the tumour to the size of the breast and tumour location in terms of acceptable cosmesis • the presence of multifocal/multicentric disease or extensive malignant microcalcification on mammogram which cannot be adequately cleared with an acceptable cosmetic result with breast conserving surgery • potential contraindications to local radiotherapy (eg, previous radiotherapy at this site, connective tissue disease, severe heart and lung disease, pregnancy) • fitness for surgery • patient choice	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Margins of excision for breast conserving surgery: ductal carcinoma in situ

Background

In women undergoing BCS, completeness of excision minimises the risk of local recurrence. However, there is ongoing debate about the actual width of margin that is necessary for complete excision, varying from one cell to greater than 10 mm.[107] Margins are just one factor in the assessment of the risk of local recurrence. Other factors include radiotherapy, the grade of DCIS, the presence or absence of comedo necrosis, DCIS volume and patient age. For a detailed description of pathological requirements for DCIS, see Appendix D.

Body of evidence

A systematic review revealed limited evidence relevant to this question, so the main conclusions are based on the expert evidence supplied by the GDT and some additional evidence from the sources detailed in this section.

The SIGN guideline,[37] National Breast and Ovarian Cancer Centre (NBOCC) 2008 guideline[145] and National Health and Medical Research Council (NHMRC) guideline[48] made some limited reference to margins of excision. (All three guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Four randomised trials, the National Surgical Adjuvant Breast and Bowel Project NSABP B-17,[329] the European Organisation for Research and Treatment of Cancer EORTC 10853,[330] a United Kingdom/Australian and New Zealand (UK/ANZ) study[331] and the Swedish study[332] provided evidence on DCIS. These studies are described in a 2007 review by Morrow and O'Sullivan.[333]

An additional 1999 retrospective study by Silverstein et al.[334] was identified by the GDT as relevant. An additional reference on pleomorphic lobular carcinoma in situ (LCIS)[335] was also identified by the GDT for inclusion.

Summary of findings

One of the difficulties with randomised trials conducted to date evaluating BCS with or without radiotherapy for DCIS, is that accurate assessment of many of the risk factors for local recurrence (eg, margin width, DCIS size, and/or grade) was not prospectively undertaken. The National Breast and Ovarian Cancer Centre (NBOCC) guideline[145] has suggested that the distance from each margin (radial, superficial, and deep) should be recorded in millimetres when less than 10 mm and otherwise given as greater than 10 mm.

The NSABP B-17, European Organisation for Research and Treatment of Cancer (EORTC) 10853 and UK/ANZ trials reported by Morrow and O'Sullivan[333] all required negative margins, defined as tumour-filled ducts not touching an inked surface. In the Swedish study by Emdin et al. (2006)[333] a sector resection extending from Scarpa's fascia to the pectoral fascia with macroscopically clear medial and lateral margins was mandated, but microscopically negative margins were not required.

A retrospective study by Silverstein et al.[334] suggested that excision to a 1 cm margin in all directions and no further therapy resulted in local control equivalent to that seen with excision with lesser margins and radiotherapy, regardless of the DCIS size or grade.

The issue of adequate margins of excision for BCS in women with DCIS is highly controversial because of the lack of evidence from prospective randomised trials. The ability of pathologists to accurately assess surgical clearance of DCIS is complicated by the anatomy of the breast ductal system and contributes to the uncertainty in this area.

Sneige et al.[335] noted that the management of LCIS has not been well described in the literature but that it is suggested that pathology reports state the proximity of pleomorphic LCIS to the margins of excision in order to determine whether additional excision is required within the setting of BCS.

Development of recommendations

The RCTs show that involved microscopic margins result in significantly higher rates of local recurrence, but do not provide good data on the extent of clear margin required. Retrospective series suggest that larger margins of excision are associated with a lower risk of recurrence.

Based primarily on expert opinion the GDT noted that detailed assessment of the distance of the tumour from both the radial or circumferential margins and from the superficial and deep margins should be made. The GDT notes that a circumferential or radial margin of no less than 2 mm should be the standard where possible.

Recommendations

	Grade
Ductal carcinoma in situ (DCIS) extending up to a margin of excision requires further surgery – either wider excision or mastectomy to achieve clear margins in the absence of contraindications	A
Detailed pathological assessment of the distance of the in situ carcinoma from the margins should be made	C

continued over...

Recommendations continued...

	Grade
A circumferential or radial margin of greater than or equal to 2 mm should be achieved where possible	C
For women with margin widths of less than 2 mm several factors should be considered in determining whether re-excision is required. These include: • age • size, grade, and the presence or absence of comedo necrosis • which margin is approximated by DCIS (smaller margins may be acceptable for deep and superficial margins as by definition DCIS does not go into muscle or subcutaneous fat) • extent of DCIS approaching the margin	C

Grades indicate the strength of the supporting evidence rather than the importance of the recommendations

Good practice points

If a clear margin cannot be achieved surgically after either breast conserving surgery or mastectomy, radiotherapy should be considered	✓
Pathology reports should state the proximity of pleomorphic lobular carcinoma in situ (LCIS) to excision margins to allow assessment of whether further excision would be appropriate in the setting of breast conserving surgery	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

Management of the axilla: ductal carcinoma in situ

Background

By definition, DCIS does not involve axillary nodes (or it would be invasive disease). Therefore, in theory, assessment of regional lymph nodes should not be needed for DCIS. The practical problem is that a significant proportion of patients with larger volume and higher grade DCIS diagnosed on imaging and core needle biopsy will be found to have invasive disease on complete excision and final histology. Therefore, these women will need an assessment of regional lymph nodes status.

For further details on management of the axilla in invasive breast cancer see Chapter 4, *Surgery for early invasive breast cancer*.

Body of evidence

The systematic review undertaken identified the Belgian guideline,[38] which reviewed three previous guidelines on this topic.[75, 90, 327] (The guideline was given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Summary of findings

Axillary surgery was considered only for large or grade III DCIS.[38] Axillary clearance is not recommended for DCIS, but sentinel lymph node biopsy (SLNB) can be considered in women with large volume or grade III DCIS where there is a suspicion of invasive disease or for women undergoing mastectomy.[38] A significant proportion of patients with larger volume and higher grade DCIS diagnosed on imaging and core needle biopsy will be found to have invasive disease upon complete excision and final histology. These women will then require axillary staging, and sentinel node biopsy is less accurate when performed after excision of the primary cancer, so should be considered at the time of the initial DCIS excision.

Development of the recommendations

The GDT was informed by the evidence that women with DCIS should not normally undergo axillary surgery. However, SLNB may be a useful option in larger volume and high grade DCIS, because of the risk of invasive cancer being present in these cases.

Recommendations

	Grade
Axillary dissection should not be performed for women with ductal carcinoma in situ	I
In a woman with a larger volume and higher grade ductal carcinoma in situ or where there is suspicion of invasive disease or for women undergoing mastectomy, sentinel lymph node biopsy to stage the axilla may be considered	B

Grades indicate the strength of the supporting evidence rather than the importance of the recommendations

Radiotherapy in addition to breast surgery for ductal carcinoma in situ

Background

Whole breast irradiation following BCS is commonly used in those with DCIS to reduce the risk of recurrence.

Body of evidence

The systematic review undertaken identified the following evidence on radiotherapy in addition to BCS for women with DCIS that met the inclusion criteria.

The SIGN guideline,[37] Belgian guideline[38] and the Cancer Care Ontario 2006 guideline[336] were based on three large RCTs with regards to this topic:

- National Surgical Adjuvant Breast Project NSABP B-17 (n=813)[337]
- European Organisation for Research and Treatment of Cancer EORTC 10853 (n=1010)[330, 338]
- United Kingdom Coordinating Committee on Cancer Research UKCCRC-DCIS trial (n=1030).[331]

(The Cancer Care Ontario guideline was given the AGREE tool quality grading: strongly recommended. The other guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

A 2007 meta-analysis by Viani et al.[339] also included these RCTs, with the addition of the SweDCIS study (n=1046).[332] (This meta-analysis was considered to be of high quality.)

Several case series of DCIS have also been published, with perhaps the best known of these being by Silverstein et al.[334] from the Van Nuys Breast Centre. This publication included reporting of a retrospective study and suggested that excision to a 1 cm margin in all directions with no further therapy resulted in local control equivalent to that seen with excision and radiotherapy, regardless of the DCIS size or grade. Silverstein et al.[334] developed the Van Nuys Prognostic Index based on the series to help classify the risk of recurrence with different local therapies. This prognostic index has been modified to include age as an additional variable.

Summary of findings

Survival

The NSABP B-17, EORTC 10853 and UKCCRC-DCIS trials all showed no difference in survival between women who received radiotherapy and those given surgery alone;[37, 38, 336, 339] but survival differences would not be expected for a pre-cancerous condition such as DCIS, or at least not until after lengthy follow-up. Early data from the NSAB-17 trial showed a cumulative incidence of invasive and non-invasive ipsilateral breast tumour recurrence of 31.7% in lumpectomy alone and 15.7% in the lumpectomy plus radiotherapy arm at the 12-year follow-up. There was no significant difference in OS at 12 years.

Recurrence

The incidence of recurrence was found to be reduced by almost half with the addition of radiotherapy to BCS for women with DCIS.[339] The NSABP B-17 trial identified a significant reduction in ipsilateral recurrence with radiation (16.4% vs 7%, $p<0.001$) at 12 years.[37, 38, 336] Absolute risk reduction for ipsilateral local recurrence was reported as 50% and 47%.

The Belgian guideline[38] reported follow-up data from Bijker et al. (2006) on the EORTC 10853 trial. This showed that the addition of radiotherapy to BCS in women with DCIS measuring less than 5 cm resulted in a 10-year local recurrence-free rate of 85% in women treated with local excision plus radiotherapy, compared with 74% in those treated with local excision alone ($p<0.0001$). A subgroup of women with DCIS who do not benefit from radiotherapy could not be identified in the RCTs, although factors such as complete excision and low nuclear grade were associated with lower risk.[38] The RCTs suffer from a lack of good quality prospective information on DCIS size and margins of excision.

Case series such as that by Silverstein et al.[334] suggest that a low risk group of women who do not benefit from radiotherapy can be identified, and, at the other end of the continuum, that there is a group of women with extensive high grade DCIS requiring mastectomy for local control. Prospective RCTs are needed to validate these findings.

Development of the recommendations

Based on the systematically reviewed published evidence, the GDT concluded that there is a decrease in ipsilateral breast recurrence with radiotherapy following BCS. The GDT noted the importance of discussing the management of women with DCIS within the context of a multidisciplinary meeting, with the appropriate involvement of a radiation oncologist.

Recommendation

For ductal carcinoma in situ only	Grade
A woman who has undergone breast conserving surgery for ductal carcinoma in situ should have their case discussed at a multidisciplinary meeting with a radiation oncologist and/or should be offered consultation with a radiation oncologist	A

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Addition of boost radiotherapy to radiotherapy and breast conserving surgery

Background

Even after whole breast irradiation following BCS a significant risk of loco-regional recurrence remains. An additional boost dose of radiotherapy to the tumour bed may reduce recurrence. Boost dose radiotherapy may also be associated with an increased risk of adverse effects.

Body of evidence

The systematic review undertaken did not identify any randomised trials that compared radiotherapy plus boost radiotherapy to radiotherapy alone following BCS in women with DCIS.

Summary of findings

No RCTs were identified that examined the use of a boost dose of radiotherapy in addition to BCS and radiotherapy in women with DCIS.

Development of recommendations

The GDT noted the lack of evidence in this area for women diagnosed with DCIS.

Recommendation

	Grade
Due to lack of evidence no recommendations were made for the routine use of a boost dose of radiotherapy in women with ductal carcinoma in situ	I

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Systemic therapy: endocrine therapy

Background

Endocrine therapy eliminates the influence of oestrogen on breast cancer cells, preventing their growth and spread. Only tamoxifen has been tested in randomised trials for women with DCIS.

Body of evidence

The systematic review undertaken on the topic of endocrine therapy for women with DCIS identified the following evidence that met the inclusion criteria.

Four clinical guidelines met the inclusion criteria and made recommendations on this topic. The SIGN guideline,[37] Belgian guideline[38] and BMJ guideline[113] all included the 1998 Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis.[206] The SIGN guideline[37] and BMJ guideline[113] also both included the UKCCRC-DCIS trial.[331] The SIGN[37] and Belgian[38] guidelines were both partly based on a previous guidelines. The NICE guideline (2006) was based on a 2006 systematic review by Hind et al.[267] and focused on the use of endocrine therapies in ER +ve early breast cancer. (All guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Summary of findings

For the management of DCIS, tamoxifen was associated with lower disease recurrence, particularly in women aged under 50 years or with receptor positive disease.[37] No significant advantage was found in preventing recurrence of DCIS or development of invasive cancer with tamoxifen in the UKCCR-DCIS trial[37] but this study has not been analysed according to hormone receptor status. The Belgian guideline[38] reported a lower disease recurrence rate at seven years with ER +ve DCIS treated with adjuvant tamoxifen (11% vs 17%, p=0.0004).

Other outcomes

Tamoxifen was associated with a higher rate of endometrial cancer and gynaecological problems, such as endometrial thickening.[37, 113]

Development of recommendations

Based on the systematically reviewed published evidence, the GDT noted that in women with hormone receptor positive DCIS, there is evidence of benefit for use of tamoxifen, particularly in women aged under 50 years. There are also a number of adverse effects and toxicities associated with endocrine therapy that should be considered alongside the financial costs of prolonged treatment.

Good practice point

For DCIS only	
For women with hormone receptor positive ductal carcinoma in situ, the benefits and risks of endocrine therapy should be discussed and treatment decisions made based on individual circumstances	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

9 Follow-up

This chapter presents content in relation to follow-up for women with early breast cancer and includes:

- radiological follow-up
- clinical follow-up.

Appropriate follow-up of women with early breast cancer incorporates both regular imaging and clinical assessment. The primary goal of radiological follow-up is to detect recurrence on the ipsilateral (treated) breast or a new contralateral breast cancer by methods such as mammography. Clinical follow-up involves ongoing patient support, the continued monitoring of ongoing adjuvant treatment and associated adverse effects, and clinical examination for detection of recurrent or new breast cancer. Clinical follow-up may be carried out through a hospital outpatient service or in the community through a general practitioner or private specialist.

Two clinical questions were developed to assess the role of radiological and clinical follow-up in women with early breast cancer (see Chapter 11, *General section: methods*).

Radiological follow-up

Background

Mammography is a specific type of imaging that uses a low-dose X-ray system to examine breasts. Two recent enhancements to traditional mammography include digital mammography and computer-aided detection. Mammography is widely used in surveillance programmes to detect recurrence or new primary tumours either in the treated or contralateral breast.

Body of evidence

The systematic review undertaken identified the following evidence that met the inclusion criteria.

Four clinical guidelines were identified.[37, 38, 48, 340] Two earlier guidelines[49, 75] were included in the development of the Belgian guidelines.[38] The National Health and Medical Research Council (NHMRC) (2001) guideline[48] was also based on a previous guideline[341] and two randomised controlled trials (RCTs).[342, 343–344, 345] The American Society of Clinical Oncology (ASCO) guideline[340] was based on a systematic review.[344] (All the guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Three systematic reviews were identified.[345–347] Barnsley et al.[345] identified studies specifically addressing the issue of surveillance mammography among women with breast reconstruction following treatment for primary breast cancer. No meta-analysis was conducted due to heterogeneity.[345] (This study was considered to be of low quality.) Rojas et al.[346] conducted a Cochrane systematic review to assess the effectiveness of different policies of follow-up for distant metastases on mortality, morbidity and quality of life in women treated for

stage I, II or III breast cancer. (This review was considered to be of very high quality.) Lu et al.[347] conducted a meta-analysis of 13 retrospective studies to assess the impact of early detection of loco-regional or contralateral breast cancer recurrence on survival. (The study was considered to be of high quality.)

One additional case-series study conducted by Paszat et al.[348] was identified that aimed to ascertain outcomes of surveillance mammography following treatment of early stage breast cancer.

Summary of findings

Loco-regional recurrence and survival

Rojas (2000) concluded that follow-up programmes based on regular physical examinations and yearly mammography alone are as effective as more intensive approaches based on regular performance of laboratory and instrumental tests in terms of timeliness of recurrence detection, overall survival and quality of life.[346] Detection of loco-regional or contralateral recurrence in asymptomatic patients during routine follow-up or assessed by mammography improves survival compared with late symptomatic detection.[347] Cases of local recurrence could be detected by surveillance mammography in women with breast reconstruction following mastectomy.[345] The systematic review by Barnsley et al.[345] also highlighted the need for further research to evaluate this issue.

Optimal frequency of mammography

The SIGN guideline[37] and Belgian guideline[38] concluded that mammography was the gold standard method of imaging for breast cancer detection, although there was a lack of evidence regarding the optimal frequency of this procedure. Mammography was recommended annually in the Belgian guideline and once to twice yearly within the first five years in the SIGN guideline as follow-up. Annual mammography and regular physical examinations were recommended by Rojas et al.[346] The NHMRC guideline[31] suggested mammography every one to two years commencing at six to 12 months after radiotherapy for the conserved breast; then annually from three years.

The systematic review by Grunfeld (2002), on which the ASCO guideline[340] was based, documented the lack of high-level evidence supporting current practice in mammography surveillance. The review concluded that women treated with breast conserving therapy should have their first post-treatment mammogram no earlier than six months after definitive radiation therapy. Subsequent mammograms should be obtained every six to 12 months for surveillance of abnormalities. Mammography should be performed annually if stability of mammographic findings is achieved after completion of loco-regional therapy.[340]

Development of recommendations

Based on the New Zealand Guidelines Group's (NZGG's) systematic review of the published evidence, the Guideline Development Team (GDT) noted its support for routine mammographic follow-up after surgery for early breast cancer. Two of the reviewed guidelines, the NHMRC guideline[31] and ASCO guideline,[340] recommended that the first follow-up mammogram should be performed at six months after initial treatment with annual mammograms thereafter. The recommendation on surveillance mammography frequency reflects this view.

The GDT also noted that both local recurrence and new breast cancers could be detected by surveillance mammography and that there was no advantage either for local or distant recurrence in the use of more intensive approaches (ie, regular laboratory and instrumental tests). The reviews also identified a lack of evidence in this area and suggested further research was required. A good practice point was formulated by the GDT to reflect the importance of mammographic surveillance for women at high risk of contralateral disease following initial diagnosis and treatment for early breast cancer (eg, BRCA1 and BRCA2 gene carriers).

Recommendations

	Grade
Regular mammography should be used in order to detect recurrence or new breast cancers at an early stage in patients who have undergone previous treatment for breast cancer	A
A woman should have her first post-treatment mammogram one year after her first diagnostic mammogram or 6 months after radiotherapy, and annually thereafter	A
Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations	

Good practice point

For a woman at high risk of contralateral breast cancer (eg, BRCA1 or BRCA2 gene carriers) mammography of the contralateral breast should be performed no later than 12 months after the post-diagnostic mammogram and other imaging modalities may also be considered	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Clinical follow-up: hospital-based versus general practice

Background

Follow-up (care after primary treatment) of women with breast cancer should have several aims, which include the provision of physical and psychosocial rehabilitation, monitoring of treatment effectiveness, and detection of recurrence or new cancers.[346] Detection of local recurrence or new cancers at an early stage is important, as these are potentially curable events if treated early. However, follow-up care is sometimes offered with the main objective of detecting distant recurrence at an early stage, so that treatment for any relapse can be started.

In this context, terms such as 'routine testing' or 'surveillance' indicate the regular use of laboratory or other investigations in otherwise asymptomatic patients to detect distant metastases earlier. Despite the lack of convincing proof that this improves outcomes in these patients, intensive follow-up is quite common in clinical practice and represents a significant workload. Follow-up has been provided in the primary care setting and this may be preferable to some women.

Body of evidence

The systematic review undertaken to answer this question identified the following evidence that met the inclusion criteria.

Three clinical guidelines met the inclusion criteria. One systematic review and two RCTs were included in the SIGN guideline.[37] The Belgian guideline[38] and the ASCO guideline[340] were based on an RCT by Grunfeld et al. (1996), which was one of the RCTs included in the SIGN guideline.[37] The ASCO guideline[340] also included an additional RCT by Grunfeld and colleagues (2006). (All the guidelines were given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

Two systematic reviews were identified that met the inclusion criteria.[346, 349] Rojas et al.[346] conducted a Cochrane systematic review that identified four RCTs, assessing the effectiveness of different policies on follow-up for distant metastases in terms of mortality, morbidity and quality of life for women treated for stage I, II or III breast cancer. (The study was considered to be of very high quality.) The review by Montgomery et al.[349] aimed to identify any alternative methods of follow-up and obtain any evidence to suggest an ideal length or schedule of follow-up. Seven RCTs were identified. (The study was considered to be of high quality.)

One primary study by Nissen et al.[350] used a survey sent to primary care providers that focused on the care of breast and colorectal cancer survivors. (The study was considered to be of low quality.)

Summary of findings

The SIGN guideline[37] reported limited evidence to suggest the effectiveness of long-term follow-up, or to indicate optimal follow-up. The systematic review by Rojas et al.[346] suggested that regular hospital-based review has no survival benefit over general practice follow-up for women treated with early breast cancer. Rojas et al.[346] identified one small RCT (n=296) conducted by Grunfeld and colleagues (1996) that found no significant differences between hospital-based and general practice care in the time to detection of recurrence and patients' quality of life. It should be noted that the results of this trial, and the subsequent 2006 study by Grunfeld and others, may not be generalisable because participants were limited to those women who had self-selected to either general practitioner or hospital specialist follow-up.

In some parts of Australia, the follow-up of women with cancer is the responsibility of the general practitioner. Under such circumstances, it is essential that the general practitioner is aware of an appropriate schedule of follow-up. The NHMRC guideline[31] considered that the 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 to five years, then an annual review thereafter. If follow-up is undertaken by specialists, it is essential that the woman's current general practitioner is kept informed of the outcome of visits and of any investigations undertaken.

The ASCO guideline[340] concluded that continuity of care for breast cancer patients should be encouraged and should be performed by a physician experienced in the surveillance of cancer patients and in breast examination, including the examination of irradiated breasts. Rojas et al.[346] suggested that decentralised follow-up (ie, general practitioner surveillance) had the same effect on detection of recurrence as centralised (specialist) follow-up. This was the result of special training given to general practitioner and this should be taken into consideration when planning to transfer this experience or further investigate this topic.

The systematic review by Montgomery et al.[349] concluded that all RCTs in the review were of inadequate power or duration to establish ideal frequency of clinic visits, or the safety of alternative follow-up methods, such as general practitioner-led and/or breast care nurse-led follow-up. Those studies that were conducted did not suggest that alternative methods were any less safe than routine specialist-based follow-up. Alternative follow-up methods were acceptable to patients, were associated with no reduction in quality of life or increase in anxiety, and may offer significant savings in time and costs. More high quality RCTs are required in this area.

Nissan et al.[350] identified from their survey that primary care providers' levels of comfort, confidence and satisfaction in providing follow-up care for breast and colorectal cancer survivors was generally low. However, follow-up care provided with adequate guidelines could support better care for survivors' non-cancer concerns without sacrificing appropriate cancer care.[350]

Development of recommendations

Based on NZGG's systematic review of the published evidence the GDT noted that in highly specified circumstances, including fully subsidised access to general practitioners with specific training in breast cancer follow-up, ready and rapid access to specialist clinics, and in women who were comfortable with general practitioner follow-up, hospital-based follow-up had no survival benefit over general practitioner follow-up. General practitioner follow-up of women with early breast cancer was not associated with an increase in time to diagnosis, an increase in anxiety, or a deterioration in health-related quality of life in these studies. However, adequacy of therapy for treatment-related side effects was not investigated. In addition, more recent evidence has raised the need for consideration of changes to adjuvant therapy some years after initial treatment, and the GDT noted that this is not an area in which primary care providers have expertise.

Alternative follow-up methods, including care provided by nurse practitioners, were acceptable to patients, associated with no reduction in the quality of life or increase in anxiety, and were considered more economical and less time-consuming. This is an option that may be considered in New Zealand in the future.

In the countries where general practitioner-based follow-up was examined, this service comes without general practitioner fees. In New Zealand, most patients pay at least a proportion of the cost of primary care. This additional financial burden may dissuade some women with early breast cancer from seeking follow-up in the primary care sector. There is a risk that those with lower socioeconomic status would be more likely to stop follow-up and/or treatment in this setting, aggravating those inequities of outcome that already exist across ethnic and socioeconomic groups.

In other countries as in New Zealand, there has been professional role development to allow specialist breast nurse practitioner-led or breast physician-led clinics. This may be an option within New Zealand for follow-up care. With the increased complexity of adjuvant hormone therapy and the acknowledgement of the importance of addressing survivorship issues after chemotherapy (such as the management of premature menopause and fertility issues), the development of a nurse practitioner or breast physician workforce is felt to be desirable in order to address the ongoing and increasing demand in this area.

The GDT notes that it is important for women to be informed of who is responsible for providing or ensuring appropriate follow-up, so that they know who to approach, if necessary, to instigate follow-up appointments or care.

Recommendations

	Grade
Continuity of care for those with breast cancer is encouraged and should be undertaken by a clinician (eg, breast specialist, breast physician, nurse practitioner) experienced in the surveillance of breast cancer and in breast examination, including the examination of irradiated breasts	B
Continuity of care may be shared with a general practitioner in appropriate circumstances (ie, ready access to specialist support)	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Good practice points

Where patients are discharged to follow-up in primary care, guidance to general practitioners on appropriate management and referral back to secondary care should be provided	✓
Provision of follow-up care should endeavour to avoid known barriers to patient care and follow-up such as financial, geographic and linguistic barriers	✓

Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available

10 Special issues

In the development of the guideline several issues arose that the Guideline Development Team (GDT) felt were important in the discussion of early breast cancer, including:

- genetic testing
- prophylactic treatment
- pregnancy
- clinical trials
- complementary therapies
- other specific issues.

Introduction

Two clinical questions were developed to assess prophylactic treatment and genetic testing in women with early breast cancer. The remaining issues were identified after the formal systematic searches had been conducted. A non-systematic literature search was used alongside the expert opinion of the GDT to inform the discussion of pregnancy, participation in clinical trials, the use of complementary therapies and other issues.

Genetic testing

Background

Approximately 5% of all breast cancer cases are currently thought to be hereditary, and mainly caused by mutations in the highly penetrant BRCA1 gene (found on chromosome 17) or the BRCA2 gene (found on chromosome 13). Mutations in these genes predispose an individual to breast and ovarian cancer, and to a lesser extent, prostate, melanoma, bile duct and pancreatic cancers. The BRCA genes are considered tumour suppressor genes, and follow an autosomal dominant pattern of inheritance, so mutations are inherited equally by males and females.[351, 352] Rarer hereditary breast cancer syndromes, contributing less than 1% of all breast cancer cases, include Li Fraumeni syndrome (TP53 gene), Peutz-Jeghers syndrome (STK11/LKB1 genes), Cowden syndrome (PTEN gene), Hereditary Diffuse Gastric Cancer (HDGC; CDH-1 gene) and Ataxia Telangectasia (ATM gene).

BRCA1 and BRCA2 are very large genes, with hundreds of different mutations identified to date. Some mutations are more common in certain populations, for example, the two so-called 'Dutch Founder mutations' in BRCA1[353] and the four Ashkenazi Jewish mutations in BRCA1 and BRCA2, with as many as 1 in 40 Ashkenazi having one of these founder mutations.[354] The BRCA1 and BRCA2 genes also contain more than 1500 distinct sequence variants that are currently reported as having unknown clinical significance.[355] These variants pose significant problems when identified, because patients and physicians do not know whether these subtle changes predispose an individual to breast and ovarian cancer or are neutral. As a result, carriers of these unclassified variants and their at-risk family members cannot take advantage of predictive testing, prevention and therapeutic measures available to carriers of known pathogenic BRCA mutations.

Body of evidence

As this area was not prioritised for a full systematic review, a non-systematic review was undertaken in conjunction with the expert opinion of the GDT. The question addressed concerned who should undergo genetic testing and the timing of this testing. One clinical guideline[38] and a monograph were identified.[356]

Summary of findings

Genetic testing is currently recommended for high-risk families only. Important risk factors to define high-risk families include multiple affected family members, early onset breast cancer, male breast cancer, bilateral breast cancer, ovarian cancer, Ashkenazi Jewish ancestry, or a known BRCA1 or BRCA2 mutation in the family. There is consensus that molecular testing for BRCA1 or BRCA2 mutations should be arranged through referral to tertiary genetic services, as evaluation by health care practitioners experienced in cancer genetics is required in determining the appropriateness of testing.

Screening for BRCA1 or BRCA2 mutations involves sequencing the genes, and Multiplex Ligation-dependent Probe Amplification (MLPA) analysis to detect large deletions or duplications in DNA from an affected family member. Technically, it is still only possible to screen about 90% of these genes for mutations, and a mutation cannot always be identified in high-risk families despite extensive laboratory testing. This is not a negative result, as the possibility that a mutation may be present cannot be excluded (unless the mutation has been previously identified in the family), so is considered an uninformative result.

Several risk estimation models have been developed to aid the clinician or genetic counsellor in predicting the probability (prior to testing) of an individual carrying a BRCA1 or BRCA2 mutation. These include the BRCAPRO model,[357] the Manchester Scoring System[358] and BOADICEA.[359] These are useful tools when providing genetic counselling to individuals with a family history of breast cancer to help answer the question: What are her/his chances of carrying a mutation in the BRCA1 or BRCA2 gene?

The National Institute of Clinical Excellence (NICE) guidelines[30] recommend a threshold for mutation screening at 20% or greater probability of a mutation being present in the affected individual having testing. Risk-prediction models allow an objective assessment of the family history,[360] supported by the genetic counsellor or clinical geneticist's own judgment of risk based on experience, and they are not appropriate for use by practitioners without specialised training and experience.

Given the complexity of genetic testing, genetic counselling services and testing should be provided by health practitioners with specific training and who are familiar with the problems associated with BRCA mutation testing.[361] Genetic counselling in the context of BRCA1 or BRCA2 genetic susceptibility testing needs to include discussion of the aim of testing, inheritance, the accuracy of the test (sensitivity and specificity), the uncertainty of cancer risk estimates with a mutation, possible test results (positive, negative, uninformative or variant of unknown clinical significance), implications for the individual and family, clinical management options, the psychosocial impact of testing, the potential risks of discrimination (eg, by life and health insurers) and alternative options to testing.

Interpretation of test results and estimation of cancer risks for the family need to take into account the pedigree information, the analytical and clinical validity of the test methodology, and the penetrance and nature of the detected mutation.

Identifying a mutation in a family is most likely to be informative if mutation screening occurs in an individual who has already had breast and/or ovarian cancer. Where there is more than one family member who meets these criteria, it is best to test the individual who is most likely to have a BRCA1 or BRCA2 mutation (ideally with youngest age of onset and in the centre of the cluster of cancers within a family), and who is less likely to have developed sporadic breast or ovarian cancer.

Once a deleterious mutation has been identified within a family, adult at-risk relatives may then be tested for the same family-specific mutation with great accuracy.

For unaffected relatives who are found not to carry the family mutation, the risk of breast or ovarian cancer drops to that of the general population. This risk clarification has a major impact on clinical management for an individual and her offspring. Unaffected relatives in whom a mutation is identified have a substantially higher risk of breast and ovarian cancer than the general population, and require targeted surveillance, prevention or prophylactic measures. Individuals with breast or ovarian cancer in whom a BRCA1 or BRCA2 mutation is identified are at increased risk of developing a second cancer (another breast primary or ovarian cancer).

Development of recommendations

Based on the New Zealand Guidelines Group's (NZGG's) review of the published evidence and expert opinion, the GDT concluded that genetic testing for a deleterious mutation in the BRCA1 or BRCA2 genes should be available and considered in high-risk families. Testing primarily benefits families in which a BRCA1 or BRCA2 mutation is identified, and means that the risk and clinical management for adult at-risk family members can be clarified. Most women referred for testing will not be found to be carrying a BRAC1 or BRCA2 mutation and it is important that these women are aware that this negative finding does not exclude the possibility of another breast cancer gene mutation being carried in the family.

Recommendations

	Grade
All women from high risk families* should be offered referral to their regional genetics centre for information on genetic testing * Important risk factors include: early onset breast cancer, multiple affected family members, male breast cancer, bilateral breast cancer, ovarian cancer, Ashkenazi Jewish ancestry, or a known BRCA1 or BRCA2 mutation in the family	C
Genetic counselling should be undertaken by a health practitioner with appropriate training (a certified genetic counsellor or medical geneticist)	C
Pre-test genetic counselling should include discussion of the following: • aim of testing, inheritance, accuracy of the test (sensitivity and specificity) • timeframe for providing results • uncertainty of cancer risk estimates with a mutation • possible test results (positive, negative, uninformative or variant of unknown clinical significance) • implications for the individual and family including clinical management options, psychosocial impact of testing, potential risks of discrimination (eg, by life and health insurers) • alternative options to testing	C
Genetic testing aimed at identifying a mutation in a family should be offered to an affected family member. If a mutation is identified, predictive testing can then be offered to adult at-risk family members	C
Women or men with an estimated probability of 20% or greater of carrying a BRCA1 or BRCA2 mutation (probability estimated by use of models such as BRCAPRO or BOADICEA, and clinical judgment) should have access to genetic testing	C
Interpretation of test results and estimation of cancer risks for the family should take into account pedigree information, the analytical and clinical validity of the test methodology, and the penetrance and nature of the detected mutation	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Prophylactic treatment

Background

Three prophylactic strategies exist for women with a high genetic or familial risk for breast cancer: prophylactic mastectomy; prophylactic salpingo-oophorectomy; and chemoprevention with tamoxifen, raloxifene, or fenretinide. Women carrying a BRCA1 or BRCA2 gene mutation have an estimated 45% to 87% lifetime risk of developing breast cancer, while the risk of ovarian cancer is estimated at 11% to 66%.[38] BRCA1-related breast tumours are generally grade 3, infiltrating ductal carcinomas which are usually oestrogen receptor and progesterone receptor negative. BRCA2-related breast tumours are usually grade 2 or grade 3, and can be estrogen receptor positive or negative.[362] Ovarian cancers are usually serous, occasionally clear-cell or endometrioid, while borderline mucinous ovarian cancer is not associated with BRCA mutations.[363] The risk of contralateral breast cancer in BRCA-mutation carriers is up to 40%.

Body of evidence

The systematic review undertaken to answer this question identified one clinical guideline[38] and one cohort study.[364]

The Belgian guideline[38] summarised evidence for:

- prophylactic mastectomy[365, 366]
- prophylactic salpingo-oophorectomy[365, 367]
- chemoprevention with tamoxifen,[368, 369] and other drugs, including raloxifene[370] and fenretinide.[371]

(The guideline was given the AGREE tool quality grading: recommended for use in practice with provisos or alterations.)

One primary study was identified.[364] (The study was considered to be of low quality.)

Summary of findings

Domchek et al.[364] reported significant reductions in mortality in the primary analysis and some secondary analyses, suggesting that risk-reducing surgery (mastectomy, salpingo-oophorectomy) is associated with mortality reduction.

Prophylactic mastectomy

Overall findings show that risk-reducing skin sparing/total mastectomy significantly reduces the risk of breast cancer in women with a significant family history of breast cancer, or with BRCA1 and BRCA2 gene mutations (overall magnitude 85–90% reduction).[38] Several of the studies suggest that the provision of pre-surgical multidisciplinary support is likely to assist women with difficult decisions and coping with subsequent surgery.[38] However, a minority of women do express regrets and experience adverse psychosocial events following their surgery. There is no clear evidence on the optimal surgical technique (from a risk-reduction perspective) for risk-reducing mastectomy (ie, skin sparing or total mastectomy). With good surveillance methods for early detection of breast cancer in BRCA mutation carriers,

in particular the use of magnetic resonance imaging (MRI) and mammography, many women prefer this option, at least until after childbearing to enable breastfeeding and/or may prefer the option long term. Women considering risk-reducing surgery should seek genetic counselling (see the section entitled 'Genetic testing' in this chapter.

Prophylactic salpingo-oophorectomy

Findings demonstrate that risk-reducing salpingo-oophorectomy has a beneficial effect in terms of significantly reducing the risk of breast cancer by up to 50%, and in reducing the risk of ovarian cancer in women with BRCA1 or BRCA2 gene mutations (80–90% reduction).[38] Salpingo-oophorectomy is also a useful treatment for premenopausal women with hormone receptor positive breast cancer.[372]

A salpingo-oophorectomy is recommended because fallopian tube carcinoma appears relatively common in women carrying a BRCA1 or BRCA2 gene mutation.[38] Postoperative complications following prophylactic salpingo-oophorectectomy were reported in a minority of women in one of the observational studies, and some women experienced adverse effects from the surgery.[38] The NICE guideline (2004) advised that information about bilateral salpingo-oophorectomy as a potential risk-reducing strategy should be made available to women at high risk of breast cancer.[38] These women should also be informed about negative consequences associated with this surgery including early menopause, a possible impact on sexuality, and a small residual risk of developing peritoneal cancer. Unlike the situation with breast management, good surveillance methods for early detection of ovarian cancer do not currently exist.[373] Ovarian cancer in BRCA mutation carriers tends to have later age of onset – uncommonly under age 40 and most commonly over age 50. This may influence decisions on the timing of prophylactic surgery.

Recent and upcoming data

A recent study combining data from 10 European centres[374] found that risk-reducing surgery (mastectomy, salpingo-oophorectomy) was highly effective.

Chemoprevention

For women with hormone receptor positive breast cancer, endocrine therapies should be given. These therapies have been shown to reduce the risk of new cancers in the contralateral breast and to prevent breast cancer in women at high risk.[38]

Development of recommendations

Based on NZGG's systematic review of the published evidence, the GDT concluded that prophylactic mastectomy and prophylactic salpingo-oophorectomy do have risk-reducing benefits in women with a significant family history of breast cancer, or with BRCA1 and BRCA2 mutations. The results of prophylactic treatment with tamoxifen for BRCA1 and BRCA2 mutation carriers are not as clear, though tamoxifen clearly prevents some breast cancers in women at moderate to high risk in general, but at the cost of some side effects. Prophylactic surgery is recommended only for women at very high risk (ie, BRCA mutation carriers) or in families with a very significant history of breast and/or ovarian cancer. For further details, see the section 'Genetic testing' in this chapter.

The GDT notes the psychological impact of prophylactic surgery and possible impact on sexuality. Side effects of chemoprevention should also be taken into account and discussed with the woman.

Recommendations

	Grade
A woman with a significant family history of breast cancer or who is known to carry a BRCA1 or BRCA2 gene mutation should be offered the option of prophylactic mastectomy. Prophylactic salpingo-oophorectomy should also be discussed	C
A woman with a significant family history of breast cancer or who is known to carry a BRCA1 or BRCA2 gene mutation should have genetic counselling in a specialist cancer genetics clinic	C
For premenopausal women with a significant family history of breast cancer or who are known to carry a BRCA1 or BRCA2 mutation, information about bilateral salpingo-oophorectomy as a potential risk-reducing strategy for breast cancer should be made available	C
In women considering risk-reducing bilateral salpingo-oophorectomy, the lack of efficacy of screening should be discussed	C

Grades indicate the strength of the supporting evidence, rather than the importance of the recommendations

Pregnancy

The topic of pregnancy in early breast cancer was raised for general discussion by the GDT during the development of the guideline. As this area was not prioritised for a full systematic review, a non-systematic review and the opinion of the GDT were used to develop content on this topic. Breast cancer is one of the most commonly diagnosed cancers during pregnancy and women who have been treated for breast cancer often have concerns about subsequent pregnancies and their ability to breastfeed their infant.

One review by Navrozologlou et al.[375] and three guidelines[31, 376, 377] were identified addressing this issue. The source of data and searches were not explicit in the review by Navrozologlou et al. 2008.[375] The data identified was primarily from case-control or retrospective case series studies.

Two main issues in relation to pregnancy and breast cancer were identified from the evidence. The first issue arises in women who are diagnosed while pregnant or who become pregnant during treatment; the second issue concerns premenopausal women who may wish to become pregnant later.

During treatment

Pregnancy-associated breast cancer is defined in this guideline as any breast carcinoma diagnosed during pregnancy or during the first post-partum year. Women who are pregnant when diagnosed or who become pregnant during treatment need to be aware of potential risks to themselves and the unborn child.

Diagnostic and staging imaging in pregnant women should be carefully considered and balanced against risk of disease. Some imaging techniques (eg, CT scan or bone scintigraphy) may expose mother and foetus to ionising radiation, which could be dangerous to the foetus. Ultrasound and mammography are not contraindicated during pregnancy.[376, 377]

Treatment

Decisions regarding surgery and adjuvant therapy may be based on the gestational age of the foetus and the woman's requirements for fertility and ovarian function. Women in early pregnancy may wish to consider termination of the pregnancy. Women in a later stage may be offered early delivery. For women who wish to continue their pregnancy the following points need consideration.

Surgery

The woman should be informed of the risks associated with surgery during pregnancy, including premature delivery, though this is very uncommon, especially after the first trimester.[375]

Radiotherapy

Exposure of the foetus to ionising radiation is not considered a safe option for treatment.[376] Radiation doses of 0.1 Gy to 0.9 Gy in the first trimester are associated with an increased risk of mental retardation. Radiotherapy should be delayed where possible until after delivery.[377]

Systemic therapy: chemotherapy

Physiological changes in pregnancy may affect the pharmacokinetic and pharmacodynamic action of chemotherapeutic agents. First trimester chemotherapy is not advised[375, 376] whereas adjuvant or neoadjuvant regimens in later pregnancy are noted to have reduced risks of spontaneous abortion and teratogenesis.[375, 376] Women should be informed of the high risk of congenital malformations, in particular in the first trimester, associated with taxane and methotrexate regimens.[375, 377] The anthracyclines have been reported to be less teratogenic, so may be more acceptable.[375, 377] Chemotherapy during the second and third trimester carries an inherent risk that delivery will occur at a time of neutropenia and/or thrombocytopenia, increasing the risk of birth complications. Discussions regarding chemotherapy in this situation should include these points and treatment decided on an individual basis.

Systemic therapy: endocrine therapy

For pregnant women with oestrogen receptor positive or progesterone receptor positive breast cancer, where endocrine therapy may be considered, it should be noted that tamoxifen is associated with foetal abnormalities.[375, 377]

Termination of pregnancy or early delivery

Termination of pregnancy or early delivery should be discussed as an option to allow treatment, if carrying the pregnancy to full term is potentially harmful. Later in pregnancy early delivery allows drug or radiation treatment to be delivered without exposing the baby to these and may be preferable when delivery can be achieved safely from the infant's perspective (eg, after 28 weeks' gestation), and should be discussed as an option to allow treatment.[375, 376]

After treatment

Future pregnancy

Pregnancy is possible after breast cancer although most of the available evidence on the safety, risk of recurrence and future prognosis is based on low quality studies and women should be informed of this limited evidence when making decisions about pregnancy after a diagnosis of breast cancer. One of the most important issues to discuss with the woman considering pregnancy after a diagnosis of breast cancer is whether a future pregnancy will adversely affect her prognosis. No evidence was found to support this.[375]

Fertility in women over the age of 30 years is reduced following chemotherapy as a result of reduced ovarian reserve leading to premature ovarian failure.[375, 376] Fertility issues and options for fertility preservation need to be discussed with premenopausal women prior to commencing chemotherapy, preferably well in advance, so that chemotherapy is not unduly delayed if women wish to undergo fertility preservation treatment.

The GDT notes that recommendations for or against planned pregnancy have to consider many issues. The main consideration is whether a relapse during pregnancy would impose significant risk to the woman or her unborn child. Early relapse within the first two years portends an aggressive clinical course and relapse in this timeframe during pregnancy. Therefore, it poses a significant risk to one or other, if not both. An analysis of the risk of relapse is useful when considering recommendations of this nature; a woman with a very small risk of breast cancer relapse poses little problem, whereas a young woman whose cancer has aggressive features might receive strong recommendations against early pregnancy.

There is no evidence that pregnancy increases relapse risk, so there is no medical reason to terminate an unplanned pregnancy in a mother in the absence of evidence of relapse.

Breastfeeding

Women should also be informed that surgical interventions and radiotherapy may result in a reduced milk flow to the infant and radiotherapy may affect the elasticity of the nipple, making it more difficult for the infant to latch and suckle efficiently.[376] Breastfeeding may be undertaken from the contralateral unaffected breast alone if necessary. The GDT highlighted safety issues relating to breastfeeding while receiving chemotherapy or endocrine treatments and advised against it.

Participation in clinical trials

The topic of participation in clinical trials in early breast cancer was raised for general discussion by the GDT during the development of the guideline. As this area was not prioritised for a full systematic review, a non-systematic review and the opinion of the GDT were used to develop the discussion around this topic.

It is generally accepted that clinical trials are an essential component of the process of finding better treatments for breast cancer and that there is indirect evidence that women who participate in clinical trials have better outcomes than women given similar treatments outside trials.[31] There are large-scale national and international collaborations for clinical trials such as the Australian New Zealand Breast Cancer Trials Group available

to New Zealand specialists and women. In New Zealand there are rigorous standards for the provision of complete and appropriate information regarding clinical trials and for written informed consent. These include the requirement to make clear that entry into a trial remains voluntary and subsequent access to treatment should not be affected by the decision to participate or not.

A high participation rate in clinical trials will enable questions of scientific importance to be answered more rapidly. Well-conducted clinical trials set high standards of practice for participating centres, with very careful audit and review of many aspects of the treatment process. This process helps ensure optimal breast cancer management in individual centres.

The websites of the following groups provide information and/or links and some protocols of ongoing trials:

- Australian New Zealand Breast Cancer Trials Group (www.anzbctg.org)
- National Breast and Ovarian Cancer Centre, Australia (www.nbocc.org.au)
- New Zealand Cancer Society (www.cancernz.org.nz)
- Cancer Trials New Zealand (www.fmhs.auckland.ac.nz/sms/oncology/ctnz)
- International Breast Cancer Study Group (www.ibcsg.org)
- National Ethics Advisory Committee (www.neac.health.govt.nz)
- Cancer Research UK (www.cancerresearchuk.org).

Development of recommendations

The GDT formulated a good practice point in relation to participation in clinical trials.

Good practice point

Patients should be given the opportunity to participate in clinical trials, where eligible and available	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Use of complementary therapies

The topic of the use of complementary therapies in early breast cancer was raised for general discussion by the GDT during the development of the guideline. As this area was not prioritised for a full systematic review, a non-systematic review and the opinion of the GDT were used to develop the discussion around this topic.

Some complementary therapies may be beneficial, others harmful. Few alternative or complementary therapies have been tested in rigorous randomised clinical trials. Despite this, many individuals will turn to such sources. The Cancer Society of New Zealand website indicates that more than 60% of New Zealanders use complementary therapies at least once a year (www.cancernz.org.nz). The website lists sources of information and links to other websites regarding the use of complementary and alternative therapies. (Note: The evidence base for the information on these websites has not been assessed

by NZGG.) Some complementary therapies may interact detrimentally with particular treatment medications. How complementary therapy interacts with conventional treatment is largely unknown, so care should be exercised when using both concurrently.

Other specific issues

Several other specific issues in early breast cancer were raised for general discussion by the GDT during the development of the guideline. As these areas were not prioritised for a full systematic review, a non-systematic review and the opinion of the GDT were used to develop the discussion around these topics.

Obesity

The GDT noted that obesity is an increasing concern and that a body mass index of more than 30 results in a decrease in survival from breast cancer, even with appropriate treatment. Increased complication rates from some treatments, including infection and lymphoedema after surgery, have been noted in association with obesity.

Disposal of tissue

The disposal of tissue may be of particular significance to Māori, so health practitioners should approach this issue with sensitivity and awareness. Culturally appropriate disposal of tissue following surgery or investigations should be available, if requested. Health practitioners should also be aware that Pacific people may wish to be buried as a whole person if they are to die. This has implications for whether a Pacific woman will opt for mastectomy. If a mastectomy is chosen, it may have implications for whether the woman chooses to retain the tissue postoperatively. Women should be given this option. Provision needs to be made during surgery and following pathological evaluation of tissue for its return to the individual. Considerations for Māori and Pacific peoples are discussed further in Chapter 2, *General principles of care*. Recommended practice in relation to determining the preference of Māori and Pacific women for disposal of tissue is included in a good practice point in that section of the guideline. The good practice point is repeated below for ease of reference.

Good practice point

Practitioners should consult with Māori and Pacific women with early breast cancer about preferences for care, including final disposal of tissue or body parts surgically removed	✓
Opinion of the Guideline Development Team, or feedback from consultation within New Zealand where no evidence is available	

Tissue banking

The use of tissue banking may present a particular cultural issue for Māori and Pacific women. If tissue banking is planned for research purposes, especially if testing for heritable genetic traits is planned, clinicians should follow the national guidance on this issue.[378]

11 General section: methods

Methods

This section overviews the research methodology utilised during the development of this guideline. It describes how the clinical questions were developed, the literature review that was undertaken, and the process by which the reviewed evidence was developed into recommendations and good practice points. For further details, see the NZGG *Handbook for the preparation of explicit evidenced-based guidelines*.[4]

Clinical questions

The scope for this guideline was developed prior to the first guideline meeting and specified the focus was *treatment for early breast cancer*. At the first Guideline Development Team (GDT) meeting (see Chapter 12, *Contributors*, for GDT members) an extensive list was compiled of potential areas for consideration for the guideline. These areas were based on important patient outcomes, areas of knowledge that were controversial or uncertain, and current practice gaps based on GDT experience. Further discussion limited the areas of interest to those within scope and of major importance for patients. The remaining questions were prioritised at the second GDT meeting based on the main treatment modalities, those areas that were known to be controversial or uncertain, and where there was identifiable practice variation.

The 44 clinical questions focused on the following outcomes:

- overall survival
- disease-free survival
- relapse-free survival
- distant disease-free survival
- breast cancer–specific survival
- time to recurrence
- quality of life
- local recurrence
- contralateral breast cancer
- loco-regional recurrence
- adverse effects.

The questions are listed below.

1. In patients with early breast cancer what advice, communication and information methods are most effective?
2. What is the effectiveness of psychosocial support for breast cancer patients and their families?
3. What is the effectiveness of a multidisciplinary team/coordinator of care in patients with early breast cancer?

4. What is the effectiveness of routine staging investigations (ie, bone scanning, liver imaging, chest X-ray, CT, and CA 15-3) to stage breast cancer?
5. What is the effectiveness of preoperative breast MRI in women with early breast cancer?
6. In patients (including BRCA gene carriers and high familial risk) with early breast cancer what is the effectiveness of breast conserving surgery (BCS) versus mastectomy in invasive breast cancer?
7. When performing BCS, what are adequate margins of excision in early invasive breast cancer?
8. In patients with early breast cancer what is the effectiveness of lumpectomy versus quadrantectomy?
9. In patients with early breast cancer what is the effectiveness of excising the axillary, supraclavicular and internal mammary nodes versus no excision?
    - In patients with early breast cancer what is the effectiveness of axillary sampling versus no axillary sampling?
    - In patients with early breast cancer what is the effectiveness of axillary dissection versus no axillary dissection?
10. What is the diagnostic accuracy of sentinel lymph node biopsy (SLNB) compared to axillary dissection to detect metastases?
11. What is the effectiveness of SLNB compared to axillary dissection?
12. When should axillary clearance be performed following SLNB?
13. Is there any evidence that carrying out breast reconstruction immediately is more or less effective than delayed reconstruction?
14. In patients with early breast cancer does venous access to the arm on the side of axillary surgery increase the risk of lymphoedema on that side when compared with venous access on the opposite side?
15. In patients with early breast cancer what is the effectiveness of BCS plus radiotherapy versus BCS alone?
16. In patients with early breast cancer what is the effectiveness of mastectomy plus radiotherapy versus mastectomy alone?
17. In patients with early breast cancer what is the effectiveness of BCS plus radiotherapy plus a boost dose of radiotherapy versus BCS plus radiotherapy without a boost dose of radiotherapy?
18. In patients with early breast cancer what is the effectiveness of mastectomy plus radiotherapy plus a boost dose of radiotherapy versus mastectomy plus radiotherapy without a boost dose of radiotherapy?
19. In patients with early breast cancer what is the effectiveness of BCS plus partial or accelerated breast radiotherapy versus BCS plus whole breast radiotherapy?
20. In patients with early breast cancer what is the effectiveness of BCS plus hypofractionated radiotherapy (with or without a boost) versus BCS plus full radiotherapy?
21. In patients with early breast cancer following mastectomy and chest wall radiotherapy or BCS and breast radiotherapy what is the effectiveness of additional regional nodal radiotherapy compared with no regional nodal radiotherapy? Regional nodes to include, supraclavicular, axillary or internal mammary nodes.

22. In patients with early breast cancer, does the use of fluorouracil, anthracycline (doxyrubicin or epirubicin) and cyclophosphomide improve patient outcome when compared with cyclophosphomide methotrexate and fluorouracil (CMF)?
23. In patients with early breast cancer does the use of paclitaxel or docetaxel in addition to chemotherapy improve patient outcome when compared with chemotherapy alone?
24. In patients with early breast cancer does the use of trastuzumab in addition to chemotherapy improve patient outcome when compared with chemotherapy alone?
25. In patients with early breast cancer what is the effectiveness of chemotherapy provided before surgery ± radiotherapy compared with chemotherapy provided after surgery ± radiotherapy?
26. In patients with early breast cancer what is the diagnostic accuracy and reproducibility of scoring systems for oestrogen and progesterone receptors?
27. In women with early breast cancer does the use of endocrine therapy (tamoxifen, ovarian suppression, ovarian ablation) alone or in addition to chemotherapy improve patient outcome when compared with no treatment or chemotherapy alone?
28. In patients with early breast cancer what is the effectiveness of endocrine therapy + chemotherapy ± radiotherapy ± surgery versus endocrine therapy ± radiotherapy ± surgery?
29. In premenopausal patients with early breast cancer what is the effectiveness of one endocrine therapy versus other forms of endocrine therapy?
30. In postmenopausal patients with early breast cancer what is the effectiveness of aromatase inhibitors (AI) versus tamoxifen?
    - In postmenopausal patients with early breast cancer what is the effectiveness of switching to an AI after two years of tamoxifen versus tamoxifen for five years?
    - In postmenopausal patients with early breast cancer what is the effectiveness of switching to an AI after five years of tamoxifen versus continued tamoxifen therapy?
31. What is the effectiveness of adjuvant therapy with bisphosphonates compared with adjuvant therapy without bisphosphonates in patients with early breast cancer when outcomes are disease free survival or local recurrence, or distant recurrence, or overall survival?
32. What is the effectiveness of adjuvant therapy with bisphosphonates compared with adjuvant therapy without bisphosphonates in patients with early breast cancer in terms of bone density as an outcome measure?
33. In patients (including BRCA gene carriers and high familial risk) with ductal carcinoma in situ (DCIS) what is the effectiveness of BCS versus mastectomy?
34. When performing BCS, what are adequate margins of excision in DCIS?
35. In patients with DCIS, what is the effectiveness of excising the axillary nodes versus no excision?
    - In patients with DCIS, what is the effectiveness of axillary sampling versus no axillary sampling?
    - In patients with DCIS, what is the effectiveness of axillary dissection versus no axillary dissection?

36. In patients with early breast cancer what is the effectiveness of breast conserving surgery (BCS) plus radiotherapy versus BCS alone for DCIS?
37. In patients with DCIS, what is the effectiveness of BCS plus radiotherapy (RT) plus a boost dose of RT versus BCS plus RT without a boost dose of RT?
38. In patients with DCIS does the use of endocrine therapy (tamoxifen, ovarian suppression, ovarian ablation) alone or in addition to chemotherapy improve patient outcome when compared with no treatment or chemotherapy alone?
39. In patients with early breast cancer, what is the effectiveness of endocrine therapy + chemotherapy ± radiotherapy ± surgery versus endocrine therapy ± radiotherapy ± surgery for DCIS?
40. In pre-menopausal patients with DCIS, what is the effectiveness of one endocrine therapy versus other forms of endocrine therapy?
41. In patients who have completed therapy for early breast cancer what is the effectiveness of mammography versus follow-up without mammography?
42. In patients who have completed therapy for early breast cancer what is the effectiveness of follow-up in hospital-based care compared to GP care?
43. When should genetic testing be offered and in whom?
44. In patients with early breast cancer (including BRCA gene carriers and/or high familial risk) what is the effectiveness of:
    a. prophylactic mastectomy, and/or
    b. salpingo-oophorectomy?

Reviewing the literature and developing recommendations

Following final agreement on the clinical questions to be included, the research team prepared the questions in the Patient Exposure Comparison Outcome (PECO) format to ensure effective and focused searches and reviews could be undertaken.

The New Zealand Guidelines Group (NZGG) research team then sought existing guidelines in the topic area. In line with international guideline best practice, where an existing guideline of high quality has systematically reviewed a body of evidence, NZGG works to conserve resourcing and reduce replication in the guideline-development process by choosing not to reappraise these studies. The exception to this approach is where the guideline of interest is assessed as being of poor quality, where there is considerable controversy, or where there are additional research and outcomes of interest not covered by the existing guideline.

At the time of the initial search, when the NZGG guideline was initiated, two relevant guidelines were identified. These were the:

- Belgian Health Care Knowledge Centre (KCE) guideline: Scientific support of the College of Oncology: a national clinical practice guideline for breast cancer. 2007.[38]
- Scottish Intercollegiate Guidelines Network (SIGN): Management of breast cancer in women. A national clinical guideline. 2005.[37]

These guidelines were appraised for quality using the Appraisal of Guidelines for Research and Evaluation (AGREE) instrument.[379] The two guidelines were assessed as being well-developed, evidence-based guidelines with relevant sections that were suitable for updating. The GDT and the NZGG research team agreed to use them as a basis for the NZGG guideline. The evidence from these guidelines would be considered in conjunction with, and in places an extended, evidence search.

The NZGG research team in consultation with the GDT set the inclusion and exclusion criteria for the updated searches. Systematic literature searches relating to each PECO question were designed in consultation with an information specialist. The search for each question was limited to:

- English-language systematic reviews, guidelines and health technology assessments published since the SIGN guideline (ie, from 2006)
- any relevant English-language randomised controlled trials published after the latest systematic review, guideline and health technology assessment (from 2006) for each review question
- in addition, where the GDT identified earlier studies that it felt were of particular relevance to the New Zealand practice environment (and that the existing international guidelines or systematic reviews had not included) these were appraised and included for discussion by the GDT.

Studies investigating cost effectiveness were not included. The full searches and inclusion criteria for studies are available on the NZGG website (www.nzgg.org.nz).

Systematic searches of relevant electronic databases were undertaken and the retrieved studies meeting the inclusion criteria for each question were appraised using the SIGN tools for appraising study quality. The characteristics and results of studies selected for inclusion were summarised in evidence tables, available on the NZGG website (www.nzgg.org.nz). A Considered Judgment Form[4] was then prepared, taking into account the quality volume, consistency, applicability and clinical impact of the evidence available.

Systematic reviews of the literature were not conducted for four topic areas of the guideline: axillary clearance following sentinel lymph node biopsy; genetic testing; considerations for Māori and other ethnic groups; and information provision. These areas were based on non-systematic reviews of the literature and the expert opinion of the GDT.

Before each meeting of the GDT evidence tables for the relevant set of clinical questions were circulated to the GDT with the Considered Judgment Form. The GDT then developed consensus recommendations following a review and discussion of this evidence. Recommendations were graded based on the level to which they were supported by the evidence (described in the following sections). Toward the completion of the guideline process additional searches were undertaken for very relevant data published since the completion of the original literature searches.

The draft guideline was written by the NZGG research team in partnership with the GDT.

Special issue: trastuzumab

While this guideline did restrict its searches to published evidence due to both methodological and resource concerns, unpublished studies were included in the review of the literature regarding the role of trastuzumab-based regimens. This was because that discussion in the current scientific literature focuses heavily on unpublished data. Including this unpublished data was necessary in this case to be as inclusive as possible.

Further information

For further general information on the NZGG guideline development process and details of the consultation process for this guideline, see the 'About the guideline' section.

Evidence and recommendation grading system

The relevant evidence identified was assessed and graded, and recommendations were developed using the three-step process described in the NZGG *Handbook for the preparation of explicit evidence-based clinical practice guidelines*.[4]

Step 1: Study appraisal

Study appraisal was conducted as follows:

- for study designs where formal quantitative appraisal is not possible (eg, case-series) a brief narrative overview was prepared
- relevant guidelines were assessed using the AGREE instrument,[379] and the individual relevant sections of each guideline were appraised as for a systematic review (see below)
- diagnostic accuracy studies were appraised for quality using the QUADAS tool,[380] which was designed for this purpose. QUADAS consists of 14 questions. The number of items (out of 14) that were judged as valid on the QUADAS scoring list are given for each study
- all other studies (eg, meta-analyses, systematic reviews and randomised controlled trials) that met the inclusion criteria for each clinical question were appraised and graded for quality, using relevant checklists developed by SIGN.[381] These were modified to incorporate summary levels of evidence for the validity, magnitude or precision of effect, and applicability of each study.

An overall summary level of evidence was assigned to each study, as follows:

Very high quality ++	assigned when all or most validity criteria met
High quality +	assigned when some criteria met and where unmet criteria are not likely to affect the validity, magnitude or precision, or applicability of the results markedly
Low quality –	assigned when few or none of the criteria met.

Intermediate grades (+$\pm$, $\pm$) were assigned when the overall study quality fell between the three categories listed above.

For every study included in the evidence review, the level of evidence assigned is listed alongside the citation in the reference list at the end of the guideline.

Step 2: Weighing the evidence

Evidence tables were prepared for each clinical question and summarised on Considered Judgment Forms.[4] The GDT considered the body of evidence and made recommendations, based on the validity, quantity, consistency and clinical impact of the whole body of evidence.

Step 3: Developing recommendations

The grading of the recommendations was based on the quality of the evidence, which does not equate to the importance of the recommendation. When there was no evidence to answer a specific question, recommendations were based on the consensus of the GDT and were classified as 'good practice points'. The NZGG grading system is outlined in the section 'Grading of recommendations'.

Grading of recommendations

The NZGG grades of recommendation are as follows:

Recommendations

Description	Grade
The recommendation is supported by good evidence (based on a number of studies that are valid, consistent, applicable and clinically relevant)	A
The recommendation is supported by fair evidence (based on studies that are valid, but there are some concerns about the volume, consistency, applicability and clinical relevance of the evidence that may cause some uncertainty but are not likely to be overturned by other evidence)	B
The recommendation is supported by international expert opinion	C
The evidence is insufficient, evidence is lacking, of poor quality or opinions conflicting, the balance of benefits and harms cannot be determined	I
Grades indicate the strength of the supporting evidence rather than the importance of the evidence	

Good practice points

General section: methods	
Where no evidence is available, best practice recommendations are made based on the experience of the Guideline Development Team, or feedback from consultation within New Zealand	✓

Consultation

A draft of this guideline was circulated to 317 individuals and organisations for comment between 31 October and 10 December 2008 as part of the peer-review process. Comments were received from:

- AstraZeneca Limited
- Breast Cancer Network (NZ) Inc
- Breast Cancer Special Interest group
- BreastScreen Aotearoa Clinical Directors' Unidisciplinary Group
- BreastScreen Aotearoa Pathologists' Unidisciplinary Group
- BreastScreen Aotearoa Surgeons' Unidisciplinary Group
- BreastScreen Counties Manukau
- Cancer Society of New Zealand
- Cancer Trials New Zealand
- Daniel Hind
- Federation of Women's Health Councils Aotearoa/NZ
- Hauora Taranaki Primary Health Organisation
- New Zealand Society of Physiotherapists Inc
- Northern Regional Genetic Service
- Pasifika Medical Association
- Pharmac
- Richard Egan – PhD candidate
- Roche Products Ltd
- Royal Australasian College of Surgeons

12 Contributors

Guideline Development Team

The New Zealand Guidelines Group (NZGG) convened the multidisciplinary Guideline Development Team. Team members were nominated by a diverse range of stakeholder groups, including the Royal Australasian College of Surgeons, the Royal Australian and New Zealand College of Radiologists, the New Zealand Association of Cancer Specialists, Pasifika Medical Association, Te Ohu Rata o Aotearoa (Te ORA) and consumers. Team members are listed below.

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Declarations of competing interests

Elisabeth Burgess received financial support to attend the Advancing Breast Cancer Advocacy meeting in Italy in 2006, which Novartis sponsored.

Ian Campbell received financial support from AstraZeneca to attend as guest speaker at the St Vincents Biennial Breast Cancer meeting in February 2009; from Pfizer to attend the San Antonio Breast Cancer Convention 2009; from Roche to attend the St Gallen International Breast Cancer Consensus Conference and International Breast Cancer Study Group meeting in 2007, and the San Antonio Breast Cancer Convention in 2006; from Novartis to attend the San Antonio Breast Cancer Convention in 2005 and fourth European Breast Cancer Conference Zofast and International Steering Group meeting in Hamburg in 2004.

Ian Campbell is the clinical director of the Waikato Hospital Breast Care Unit, is a member of the ANZ Breast Cancer Trials Group Board of Directors and Scientific Advisory Committee, is the chair of the SNAC2 clinical trial and Australian New Zealand Breast Cancer Trials Group IBCSG 23-01 trial, and has shares in Novartis and AstraZeneca.

Anita Frew received sponsorship from Roche Pharmaceuticals to attend the Society of Hospital Pharmacists of Australia/New Zealand Healthcare Pharmacists' Association conference in 2006.

Gavin Harris received sponsorship to attend the New Zealand Pathologists Conference in 2005.

Lyndell Kelly received financial support from Novartis to attend the Breast Cancer meeting in Cairns and from Schering Plough to attend a New Zealand Association of Cancer Specialists conference.

Cheryl MacDonald received financial support from Roche to attend the ninth National Breast Care Nurses meeting in Australia.

Mary Obele received financial support from Ely Lily to attend the Women's Mental Health Conference 2007.

David Porter received sponsorship from Roche to attend the Lymphoma Conference Lugano 2005, and American Society of Clinical Oncology conference in 2007; from Novartis for the GIST Global Opinion Leaders Summit in 2006 and 2008, and the Australasian Gastro-Intestinal Trials Group Annual Meeting in 2007; from Schering Plough, Bristol-Myers Squibb, and Sanoti-Aventis to attend scientific meetings; and from AstraZeneca for dinner meetings with visiting speakers. David is on the Pfizer Advisory Board – Sunitinib and Novartis Advisory Board – GIST and received fees from Pfizer for consulting on the matter of Sunitinib in renal cancer and GIST; and fees from Novartis for a video presentation on the management of gastrointestinal stromal tumours. David is a member of the Breast Special Interest Group of the New Zealand Association of Cancer Specialists.

Andrew Simpson received sponsorship from Roche, Novartis, Eli Lily, Sanoti-Aventis and Pfizer to attend conferences and educational meetings, including the American Society Clinical Oncology Annual Meeting, San Antonio Breast Cancer Symposium, and World Lung Cancer Congress.

Appendices

A. TNM classification

B. Verbal prompts to assist when raising specific concerns with people with cancer

C. Websites providing information on breast cancer and treatment

D. Pathology guidance for early management of breast cancer

E. Prognostic tools

F. Endocrine responsiveness and risk of relapse categories

Appendix A:
TNM classification

The most widely used classification for breast carcinomas is the TNM classification. The T, N and M categories (tumour, nodes and metastases, respectively) are assessed by the combination of physical examination and imaging such as mammography.[1]

T	Primary tumour categories
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma in situ: intraductal carcinoma, or lobular carcinoma in situ, or Paget disease of the nipple with no tumour Note: Paget disease associated with a tumour is classified according to the size of the tumour.
T1	Tumour 2 cm or less in greatest dimension
T1mic	Microinvasion 0.1 cm or less in greatest dimension
T1a	Tumour more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b	Tumour more than 0.5 cm but not more than 1 cm in greatest dimension
T1c	Tumour more than 1 cm but not more than 2 cm in greatest dimension
T2	Tumour more than 2 cm but not more than 5 cm in greatest dimension
T3	Tumour more than 5 cm in greatest dimension
T4	Tumour of any size with direct extension to (a) chest wall or (b) skin Note: Chest wall includes ribs, intercostal muscles and serratus anterior muscle but not pectoral muscle.
T4a	Extension to chest wall, not including pectoralis muscle
T4b	Oedema (including peau d'orange), or ulceration of the skin, of the breast, or satellite skin nodules confined to the same breast
T4c	Both T4a and T4b above
T4d	Inflammatory carcinoma

N Node categories

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

* Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.

pN Pathologic classification†

pNX	Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)
pN0	No regional lymph node metastasis histologically; no additional examination for isolated tumour cells (ITC) Note: ITCs are defined as single tumour cells or small cell clusters not larger than 0.2 mm, usually detected only by immunohistochemical (IHC) or molecular methods but that may be verified on hematoloxylin and eosin (H&E) stains. ITCs do not usually show evidence of malignant activity (eg, proliferation or stromal reaction).
pN0(I-)	No regional lymph node metastasis histologically, negative IHC
pN0(I+)	No regional lymph node metastasis histologically, positive IHC, and no IHC cluster larger than 0.2 mm
pN0(mol-)	No regional lymph node metastasis histologically, and negative molecular findings (RT-PCR)[a]
pN0(mol+)	No regionally lymph node metastasis histologically, and positive molecular findings (RT-PCR)[a]

continued over...

pN	continued...
pN1	Metastasis in one to three axillary lymph nodes, and/or in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent‡
pN1mi	Micrometastasis (larger than 0.2 mm but not larger than 2.0 mm)
pN1a	Metastasis in 1 to 3 axillary lymph nodes
pN1b	Metastasis in internal mammary nodes with microscopic disease detected by SLN dissection but not clinically apparent‡
pN1c	Metastasis in 1 to 3 axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by SLN dissection but not clinically apparent‡ (If associated with more than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumour burden.)
pN2	Metastasis in four to nine axillary lymph nodes, or in clinically apparent§ internal mammary lymph nodes in the *absence* of axillary lymph node metastasis to ipsilateral axillary lymph node/s fixed to each other or to other structures
pN2a	Metastasis in four to nine axillary lymph nodes (at least one tumour deposit larger than 2.0 mm)
pN2b	Metastasis in clinically apparent§ internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN3	Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent§ ipsilateral internal mammary lymph node/s in the *presence* of one or more positive axillary lymph node/s; or, in more than three axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or, in ipsilateral supraclavicular lymph nodes
pN3a	Metastasis in 10 or more axillary lymph nodes (at least one tumour deposit larger than 2.0 mm); or, metastasis to the infraclavicular lymph nodes
pN3b	Metastasis in clinically apparent§ ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph node/s; or, in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent‡
pN3c	Metastasis in ipsilateral supraclavicular lymph nodes

† Classification is based on axillary lymph node dissection with or without sentinel lymph node (SLN) dissection. Classification based solely on SLN dissection without subsequent axillary lymph node dissection is designated (sn) for 'sentinel node', eg, pN0(I+) (sn)

‡ Not clinically apparent is defined as not detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination

§ Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination

ª RT-PCR = reverse transcriptase-polymerase chain reaction

M	Metastases categories
MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastases (includes metastasis to supraclavicular lymph nodes)

Stage grouping for breast cancer

Table A.1 Stage grouping for breast cancer

Stage	T classification	N classification	M classification
Stage 0	Tis	N0	M0
Stage I	T1[b]	N0	M0
Stage IIA	T0	N1	M0
	T1[b]	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1[b]	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

[b] T1 includes T1mic

Note: Stage designation may be changed if post-surgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

Source: The TNM classification is used with the permission of the International Union against Cancer, Geneva, Switzerland. The original source for this material is LH Sobin, C Wittekind, editors. TNM classification of malignant tumours, 6th ed. John Wiley & Sons; 2002. The seventh edition is planned for late 2009.

Additional notes from the Guideline Development Team:

The prognosis of patients with pN1a is similar to that of patients with pN0.

Note that these are clinical categories. It is also possible to use the pTNM system of classification based on pathological examination of the tumour and axillary lymph nodes.

Stage IIIC breast cancer includes patients with any T stage who have pN3 disease. Patients with pN3a and pN3b disease are considered operable and are managed as described in the section on Stage I, II, IIIA, and operable IIIC breast cancer. Patients with pN3c disease are considered inoperable and are managed as described in the section on Inoperable stage IIIB or IIIC or inflammatory breast cancer.

References

1. American Joint Committee in Cancer. AJCC cancer staging handbook: from the AJCC cancer staging manual. 6th ed. New York: Springer 2002.

Appendix B:
Verbal prompts to assist when raising specific concerns with people with cancer

Body image concerns

'Cancer certainly changes how we feel about ourselves, and I would like to hear if you have particular concerns about the way the cancer and treatments might affect your body – how you look and how you feel?'

Sexual difficulties

'Cancer affects so many aspects of life including our body image and sexuality. Can you tell me a little about the way cancer has affected those issues for you?'

Interpersonal problems

'The diagnosis and treatment of cancer affects everyone in the family.' 'I was wondering how things have been going for your family… How do you feel your partner and family are handling things?'

Physical symptoms or difficulties

'Having pain or other symptoms certainly makes a big difference to the way we feel emotionally as well. It is important to have a sense of how troublesome these symptoms are for you, and how much they are affecting your life.'

Psychological problems

'How do you think the cancer has affected you emotionally?'

Anxiety

'Anxiety is understandably common in people who have been treated for cancer. Would you say that anxiety is an issue for you?'

Depression

'Coping with cancer isn't just about physical issues, the emotional impact is important too.' This prompt could be followed with open-ended questions, such as:

- 'Could you tell me about what the cancer has meant emotionally?'
- 'Would you say that you had ever felt really sad or depressed?'

Suicidal thoughts

'Sometimes people feel so overwhelmed by things that they feel everything is 'just too much'. Would you say you have ever felt like that?' 'Have you ever felt that you can't keep going?' 'Do you feel that things will ever get better?'

Traumatic symptoms

'How much do you feel that thoughts about the cancer intrude on your life?'

'Have you found that you are feeling jumpy and easily upset?

Source: National Breast Cancer Centre. Clinical practice guideline for the psychosocial care of adults with cancer. Campertown, NSW: 2005.

Appendix C:
Websites providing information on breast cancer and treatment

Organisations with websites providing information on breast cancer and treatment include:

- Australian New Zealand Breast Cancer Trials Group – www.anzbctg.org
- Breast Cancer Aotearoa Coalition – www.breastcancer.org.nz
- Breast Cancer Network – www.breastcancernetwork.org.nz
- Breast Cancer Foundation – www.nzbcf.org.nz
- Cancer Society of New Zealand – www.cancernz.org.nz
- National Breast and Ovarian Cancer Centre – www.nbcc.org.au
- American National Cancer Institute – www.cancer.gov
- American Cancer Society – www.cancer.org
- Cancerbackup – www.cancerbackup.org.uk
- Cancer Learning – www.cancerlearning.gov.au/mdc.htm

Note: This list is not exclusive and many other sites are available. Those suggested offer credible and responsible information, but we cannot guarantee that the information on the websites is correct, up to date or evidence based. We advise you to discuss any information you find with your health care practitioner.

Appendix D:
Pathology guidance for early management of breast cancer

The following guidance has been provided by the Guideline Development Team to offer further details on the pathological requirements and management of early breast cancer. The content is based on the unpublished BreastScreen Aotearoa treatment standards.

Macroscopic handling of the specimen: general comments

General points

Various comprehensive international guidelines for pathology cut-up and reporting exist and are a useful reference.[1, 2, 3] The following are only general points which are covered in detail in the guidelines referenced.

Frozen section

Frozen section examination of breast tissue has a limited role in management of patients with palpable breast lesions and is rarely indicated in the management of clinically impalpable lesions. Frozen sections should not be performed in cases where the subsequent pathological examination is likely to be compromised.

Surgical specimen

The surgical team should provide information regarding the source of the specimen (ie, which breast and which quadrant – a diagram and a standardised form are often useful); appropriate clinical and imaging findings such as calcification, stellate or cystic lesions; the results of previous biopsy procedures and significant operative findings.

The surgeon taking the specimen should ensure that the specimen/s are orientated using radio-opaque markers (where the specimen will be X-rayed) or sutures to enable the pathologist and radiologist to orientate the specimen correctly. If further tissue is removed after the main specimen, further clips/sutures should be placed to indicate the new margin or any area of concern.

Fixation

On receipt in the laboratory, the tumour should be incised as quickly as possible to allow timely fixation. Suboptimal fixation can impact on tumour grading and the results of receptor testing.

Margins of excision

For local excision specimens the tissue should be measured in three dimensions and weighed. Any lesion present within the specimen should be described and its maximum dimensions recorded in millimetres. The distance to the nearest radial, superficial and deep margins should be measured.

For mastectomy specimens, the distance from the nipple and the quadrant where the lesion is located should also be mentioned. Where multiple lesions are present, the distance between the two or more lesions should be recorded in millimetres.

Local excision specimens should have their margins painted to mark the various excision margins prior to incision. A variety of pigments are available.

Radiographs and ultrasound

Specimen radiographs should be received by the pathologist for all cases of impalpable mammographically detected lesions and where specimen X-ray is considered to facilitate pathological examination (eg, for a palpable invasive carcinoma with an extensive ductal carcinoma in situ [DCIS] component). These should be accompanied by a verbal or written report from the radiologist.

Occasionally an impalpable lesion may not be visible on mammography or specimen radiography. If ultrasound was used for preoperative localisation, ultrasound of the specimen may be necessary to confirm removal of the lesion.

It is essential to correlate the radiological/histological appearances. Blocks should be selected from the area of the radiological abnormality, which can be identified either by slicing and re-radiographing the slices or by using a localisation device in which a grid reference is used to locate the area of interest. A sample radiograph may also be of assistance in some instances for palpable lesions.

Wide local excision specimens

For wide local excision specimens containing impalpable/palpable lesions, blocks should be taken to show the size of the lesion, the relationship to the nearest margin or margins and associated disease processes. Detailed assessment of the distance of in situ or invasive carcinoma from the radial margins in particular should be made. There is evidence that detailed margin assessment may have an impact on local recurrence rates.[4]

Smaller specimens

For smaller specimens all the tissue should be blocked and processed.

Mastectomy specimens

For mastectomy specimens some laboratories in addition to blocks assessing lesion size and proximity to margins may also favour sampling from quadrants and the nipple. Sections of skin are also important, particularly in the setting of inflammatory breast carcinoma.

Axillary dissection specimens

For axillary dissection specimens all lymph nodes should be submitted. Large lymph nodes should be sliced at 2 mm to 3 mm thickness, perpendicular to the long axis. Smaller lymph nodes (up to 5 mm) may be submitted in their entirety. Only a sample needs to be blocked from grossly involved nodes.

Sentinel node biopsy

For sentinel node biopsy the recommendations of the Australian National Breast and Ovarian Cancer Centre[1] are suggested. Briefly, where intraoperative assessment is required cytological imprints and/or frozen section assessment may be undertaken. For definitive assessment, if the initial haematoxylin and eosin-stained section is negative, four sections at 500 microns are cut through a 2 mm sliced node, three stained with haematoxylin and eosin and one randomly chosen section submitted for cytokeratin immunohistochemistry.

Microscopic reporting of invasive breast carcinoma

The histology report should follow a synoptic format as illustrated in international guidelines.[1, 2, 3] The following histological parameters should be included.

Size: This should be recorded in millimetres. The invasive carcinoma should be measured between the furthest points of extension of the tumour cells. Where DCIS is present with an invasive component, the whole tumour size (ie, the size of the DCIS and the invasive carcinoma) should be recorded as well. Various illustrations for the different combinations of in situ and invasive disease are provided in the UK NHSBSP Pathology Reporting of Breast Disease[2] and the pathology reporting of breast cancer-a guide for pathologists, surgeons, radiologists and oncologists.[1] The size of the carcinoma, particularly DCIS, may need to be estimated by the number of sections in which the lesion occurs and multiplying by the average section thickness. When multiple discrete tumour foci are present, each focus should be measured separately and described in the report. Microinvasion should be applied as per the definition of the World Health Organization (WHO)[5] (ie, 1 mm or less in maximum diameter).

Where the invasive and/or in situ carcinoma are in multiple excisions, a final comment regarding overall size should be made.

Grading: Histological grading should use the modified Bloom Richardson/Nottingham/ Elston Ellis grading system. This assesses tubule formation, nuclear pleomorphism and mitotic rate. This should be applied to all invasive carcinomas including invasive lobular carcinomas and medullary carcinomas. This grading system requires calibration of field areas for mitotic counts.[2]

Typing: Histological typing should follow a recognised classification system (eg, WHO).[2, 5]

Margins of excision: For margins of excision, the distance of the invasive carcinoma and DCIS should be recorded to each radial and superficial/deep margins in millimetres. This will have been recorded in the macroscopic description of the specimen and will be verified by microscopic examination.

Lymphovascular invasion: This should be assessed at the periphery of the tumour and surrounding tissue as stromal retraction is more prominent within the tumour mass. If dermal vessels are involved this should be specified as it may be significant in terms of assessing prognosis. The identification of lymphatic invasion may be assisted by using immunohistochemistry (D240 antibody).

Adjacent breast tissue: The presence of DCIS and lobular neoplasia including pleomorphic lobular carcinoma in situ, in tissue adjacent to the invasive carcinoma should be assessed by taking blocks from areas around the carcinoma. The cytonuclear grade of the DCIS, the architecture and necrosis should be recorded. Some datasets still require the percentage of DCIS within the invasive carcinoma and the presence or absence of an extensive intraductal component to be recorded.

Lymph nodes: The lymph node status in the pathology report should include the total number of lymph nodes identified and the number involved by metastatic carcinoma. Extranodal spread of carcinoma into axillary adipose tissue should also be recorded. Further information including the extent of extranodal invasion and adequacy of excision may be required. The presence of extranodal deposits should also be noted.

The size of the deposit should be classified as isolated tumour cells (not greater than 0.2 mm), micrometastases (greater than 0.2 mm but not greater than 2 mm) and macrometastases (greater than 2 mm) as per American Joint Committee on Cancer guidelines.[6]

Oestrogen/progesterone receptor testing: For oestrogen receptor (ER) and progesterone receptor (PR) testing the average intensity of nuclear staining and the percentage of tumour that is positive should be recorded. A variety of scoring systems are available (eg, H-score, Quick/Allred score), which can be applied. A more comprehensive discussion is made in the section entitled, 'Accuracy of oestrogen and progesterone receptor scores' in Chapter 7: *Systemic therapy: endocrine therapies*.

A high level of quality assurance is required for oestrogen/progesterone receptor staining to ensure the accurate identification of patients who may benefit from adjuvant treatment. Participation in external quality assurance programmes as supplied by the The Royal College of Pathologists of Australasia (RCPA) and United Kingdom National External Quality Assessment Scheme (UK NEQAS) is strongly advised.

A recent article from the results of the RCPA quality improvement programme emphasises the critical need for a high level of quality assurance in oestrogen/progesterone receptor testing.[7]

HER2 testing: HER2 expression can be tested with immunohistochemistry, fluorescent in situ hybridisation (FISH) and bright field in situ hybridisation (which includes chromogenic in situ hybridisation and the recently introduced silver in situ hybridisation).

Fluorescent in situ hybridisation (FISH) and immunohistochemistry are the predominant techniques used currently in New Zealand. Using the standard testing algorithm immunohistochemistry is performed initially. A score of 0/1 is regarded as negative, 2+ is regarded as equivocal requiring further testing, (currently FISH), and 3+ is regarded as positive.

FISH testing is scored as a ratio of the number of copies of the HER2 gene identified to the number of copies of centromere 17 present. Less than 1.8 is regarded as negative, 1.8 to 2.2 equivocal and greater than 2.2 is regarded as positive.

FISH appears more accurate and reproducible than immunohistochemistry. Bright field in situ hybridisation shows correlation with FISH scoring but is still an evolving field which should be kept under review.

The recent American Society of Clinical Oncology (ASCO) guidelines[8] provides details of testing and scoring criteria for immunohistochemistry and FISH. The guidelines also emphasise the need for test validation and a high level of quality assurance. It should be noted that the threshold for the percentage of tumour cells showing complete intense membrane staining for HER2-positive cases (score 3+) has been changed from 10% to 30% in the pathology reporting of breast cancer-a guide for pathologists, surgeons, radiologists and oncologists, as per ASCO guidelines.[1]

Participation in external quality-assurance programmes as supplied by the RCPA and/or UK NEQAS is strongly encouraged. A recent article from the results of the RCPA QAP programme emphasises the critical need for a high level of quality assurance in HER2 testing.[7]

Stage: A final pathological TNM stage and/or Nottingham Prognostic Index may be recorded.

Microscopic reporting of pure ductal carcinoma in situ

Reporting should follow a synoptic format described in international guidelines.[1, 2, 3] The following parameters should be recorded.

Size: The maximum size of the DCIS identified histologically should be recorded and correlated with imaging. Given the limits of histology, uninvolved tissue may be identified between involved ducts. For practical purposes, the largest distance between involved ducts should be recorded including the uninvolved intervening areas.

Margins: The distance from radial, superficial and deep margins should be recorded in millimetres. As suggested by the Australian National Breast and Ovarian Cancer Centre guidance[1] the distance from each margin should be recorded in millimetres when less than 10 mm and otherwise given as greater than 10 mm. The wording, 'Excision is complete' is not recommended as uninvolved margins do not necessarily indicate complete excision. Some clinicians may require a record of the extent of involvement by the DCIS if present at margins.

The management of pleomorphic lobular carcinoma in situ has not been comprehensively described but it is suggested that pathology reports should state the proximity of pleomorphic lobular carcinoma in situ to excision margins to allow assessment of whether further excision would be appropriate in the setting of breast conserving surgery.[9]

Grading/morphology: DCIS is graded on nuclear features, giving rise to low, intermediate and high grade DCIS.[1, 5] Description of the various architectures present, the presence of necrosis, microcalcifications and cancerisation of lobules should also be stated.

Lymph nodes: Lymph node stage should be recorded if nodes have been submitted for histological examination.

An explicit comment confirming the absence of invasion should be made.

References

1. National Breast and Ovarian Cancer Centre. The pathology reporting of breast cancer – a guide for pathologists, surgeons, radiologists and oncologists. Surrey Hills, NSW: National Breast and Ovarian Cancer Centre 2008.
2. National Health Service (British Society of Pathologists). Pathology reporting of breast disease; 2005.
3. College of American Pathologists. College of American Pathologist Reporting Guidelines; 2005.
4. Pass H, Vicini FA, Kestin LL, et al. Changes in management techniques and patterns of disease recurrence over time in patients with breast carcinoma treated with breast-conserving therapy at a single institution. Cancer. 2004 Aug 15;101(4):713–20.
5. World Health Organization. Pathology and genetics of tumours of the breast and female genital organs. Oxford: Oxford University Press; 2003.
6. American Joint Committee in Cancer. AJCC cancer staging handbook: from the AJCC cancer staging manual. 6th ed. New York: Springer 2002.
7. Francis GD, Dimech MK, Giles L, et al. Frequency and reliability of oestrogen receptor, progesterone receptor and HER2 in breast carcinoma determined by immunohistochemistry in Australasia: results of the RCPA Quality Assurance Program. J Clin Pathol. 2007;60:1277–83.
8. Wolff AC, Hammond MEH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007 01;25(1):118–45.
9. Sneige N, Wang J, Baker BA, et al. Clinical histopathologic, and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in-situ of the breast: a report of 24 cases. Mod Pathol. 2002;15:1044–50.

Appendix E:
Prognostic tools

Two widely used prognostic tools are Adjuvant! Online and the Nottingham Prognostic Index (NPI). These are discussed below.

Adjuvant! Online

Adjuvant! Online (www.adjuvantonline.com) is a validated tool to assist health practitioners and patients with early stage breast cancer discuss the risks and benefits of adjuvant therapy after surgery. It presents estimates of the risk of cancer-related mortality or relapse occurring within 10 years when receiving specific treatment.

The estimate is based on well-validated factors such as age, menopausal status, oestrogen receptor status, and number of involved axillary nodes.

It should be noted that Adjuvant! Online is a decision aid and does not replace clinical judgment in deciding on treatment options.

The tool is widely used by breast specialists internationally.

Nottingham Prognostic Index

The NPI[1] is a well-established, validated and widely used method of predicting survival for operable primary breast cancer. The NPI is calculated thus: lymph node (LN) stage (1–3) + grade (1–3) + maximum diameter (cm 0.2), giving an observed range of NPI from 2.08 (LN negative, grade 1, 0.4 cm) to 6.8 (LN stage 3, grade 3, size 4.9 cm).

The NPI:

- separates patients into groups with significantly differing survival chances
- achieves wide separation (ie, to recognise a 'cured' group and a group with poor survival)
- places a sufficient percentage of cases into each group
- is applicable to all operable breast cancers (ie, small, screen detected as well as symptomatic) and those in patients of young age
- has been prospectively validated intra-centre in a new tumour set from that on which it was derived, and intercentre and internationally
- is capable of measurement in all units and is inexpensive.

Reference

1. Haybittle JL, Blamey RW, Elston CW, et al. A prognostic index in primary breast cancer. Br J Cancer. 1982 Mar;45(3):361–366.

Appendix F:
Endocrine responsiveness and risk of relapse categories

This content is included to complement Tables 7.1 and 7.2, which provide summary guidance from the St Gallen Consensus[1] on appropriate adjuvant treatment for women with early breast cancer according to endocrine responsiveness and risk of relapse.

Endocrine responsiveness

The degree of endocrine responsiveness varies quantitatively, and will contribute, together with an assessment of the level of risk of relapse, to a decision about whether endocrine therapy alone may be sufficient.[1]

An expert panel at the 10th St Gallen (Switzerland) expert consensus meeting in March 2007 reaffirmed the primary importance of determining endocrine responsiveness of the cancer as a first approach to selecting systemic therapy. [1]

Three disease responsiveness categories were defined:

- **Highly endocrine responsive:** tumours express high levels of both steroid hormone receptors in a majority of cells (identified with proper immunohistological methods)
- **Incompletely endocrine responsive:** some expression of steroid hormone receptors but at lower levels or lacking either oestrogen receptor (ER) or progesterone receptor (PR)
- **Endocrine non-responsive:** tumours have no detectable expression of steroid hormone receptors. While this group is clearly defined in terms of lack of responsiveness to endocrine therapies, it includes tumours of diverse phenotype

Definition of risk categories for patients with operated breast cancer

One of the specific outcomes of the 10th St Gallen (Switzerland) expert consensus meeting in March 2007 was the endorsement of a definition of risk categories[1] (see Box F.1).

Box F.1 Definition of risk categories

Risk category	
Low risk[a]	**Node negative** and **all** of the following features: pT* ≥2 cm, and Grade 1,** and Absence of extensive peritumoral vascular invasion,[b] and ER and/or PR*** expressed,[c] and HER2/*neu* gene neither overexpressed nor amplified,[d] and Age ≥35 years
Intermediate risk[e]	**Node negative** and **at least one** of the following features: pT* >2 cm, or Grade 2–3,** or Presence of extensive peritumoral vascular invasion,[b] or ER and PR absent,[c] or HER2/*neu* gene overexpressed or amplified,[d] or Age <35 years **Node positive (1–3 involved nodes)** and ER and/or PR expressed, and HER2/*neu* gene neither overexpressed nor amplified[d]
High risk	**Node positive (1–3 involved nodes)** and ER and PR absent, or HER2/*neu* gene overexpressed or amplified[d] **Node positive (4 or more involved nodes)**

a Some panel members view pT1a and pT1b (ie, pT <1 cm) tumours with node-negative disease as representing low risk even if higher grade and/or younger age.

b Extensive peritumoral vascular invasion (ie, neoplastic emboli seen in two or more blocks of the tumour) was recognised as a discriminatory feature of increased risk; its presence defined intermediate risk for node-negative disease, but did not influence risk category for node-positive disease.

c Some cases such as medullary carcinoma and apocrine carcinoma may be regarded as low risk despite the absence of steroid hormone receptor expression.

d HER2/*neu* gene overexpression or amplification must be determined by quality-controlled assays using immunohistochemistry or fluorescent in situ hybridisation (FISH) analysis.

e Note that the intermediate risk category includes both node-negative and node-positive 1–3 disease.

* pT, pathological tumour size (ie, size of the invasive component)

** histologic and/or nuclear grade

*** ER, estrogen receptor; PR, progesterone receptor.

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References

1. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol. 2007 Jul;18(7):1133–1144.

Abbreviations

AC	doxorubicin/epirubicin plus cyclophosamide
AGREE	Appraisal of Guidelines for Research and Evaluation
AI	aromatase inhibitor
ALND	axillary lymph node dissection
APBI	accelerated partial breast irradiation
ASCO	American Society of Clinical Oncology
BCS	breast conserving surgery
BMD	bone mineral density
BMJ	British Medical Journal
BRCA	breast cancer gene mutation
BRCA1	breast cancer gene 1
BRCA2	breast cancer gene 2
CEA	carcinoembryonic antigen
CEF	cyclophosphamide, epirubicin and fluorouracil
CMF	cyclophosamide, methotrexate and fluorouracil (5-FU)
CT	computerised tomography
DCIS	ductal carcinoma in situ
DEXA	dual energy X-ray absorptiometry
EBCOG	Early Breast Cancer Overview Group
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EIC	extensive in situ component
EIC+	extensive in situ component present
EIC-	extensive in situ component absent
EORTC	European Organisation for Research and Treatment of Cancer
ER	oestrogen receptor
ER +ve	oestrogen receptor positive
ER -ve	oestrogen receptor negative
FAC	fluorouracil, doxorubicin or epirubicin, cyclophosphamide
FEC	fluorouracil, epirubicin, cyclophosphamide
FDG	fluorodeoxyglucose
FISH	fluorescent in situ hybridisation
GDT	Guideline Development Team
Gy	gray
HER2	human epidermal growth factor receptor 2

HR	hazard ratio
IBTR	ipsilateral breast tumour recurrence
IHC	immunohistochemical
IMC	internal mammary chain
LHRH	luteinising hormone releasing hormone
LVEF	left ventricular ejection fraction
MCA	mucin-like cancer-associated antigen
MRI	magnetic resonance imaging
NBCC	National Breast Cancer Centre (named changed in February 2008 to National Breast and Ovarian Cancer Centre)
NBOCC	National Breast and Ovarian Cancer Centre (prior to February 2008, known as the National Breast Cancer Centre)
NICE	National Institute of Clinical Excellence
NHMRC	National Health and Medical Research Council
NLR	negative likelihood ratio
NPV	negative predictive value
NZGG	New Zealand Guidelines Group
OS	overall survival
PBI	partial breast irradiation
PET	positron emission tomography
PLR	positive likelihood ratio
PPV	positive predictive value
PR	progesterone receptor
QOL	quality of life
QUALYS	quality of life years gained
RCPA	Royal College of Pathologists of Australasia
RCT	randomised controlled trial
RR	relative risk
RT	radiotherapy
SE	standard error
sHER2	serum human epidermal growth factor receptor 2
SIGN	Scottish Intercollegiate Guidelines Network
SLNB	sentinel lymph node biopsy
TAC	docetaxel, doxorubicin or epirubicin, cyclophosphamide
TPA	tissue polypeptide antigen
TPS	tissue polypeptide specific antigen
WBI	whole breast irradiation

Glossary

Adjuvant therapy	Treatment following surgery designed to remove any microscopic traces of tumour that may have been left behind
Alopecia	Hair loss
Amenorrhoea	The absence of a menstrual period in a woman of reproductive age
Aromatase inhibitors	Drugs that reduce the blood levels of oestrogen in postmenopausal women by blocking aromatase, a key enzyme that helps to form oestrogen from other steroids
Arthralgia	Joint pain. It is a symptom of injury, infection, drug reaction, illnesses or an allergic reaction
Asthenia	Weakness. Lack of energy and strength. Loss of strength
Axial plane	The long axis of the body
Axilla	Armpit
Axillary lymph node dissection/ axillary node sampling	Surgical removal of fat and lymph nodes from the armpit. It can be done at the same time as a mastectomy or as a separate operation, and it can be partial or complete
Bilateral	Relating to both sides
Biomarkers	A substance used as an indicator of a biologic state. It is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes or pharmacologic responses to a therapeutic intervention
Biopsy	Removal of a sample of tissue from the body to assist in the diagnosis of a disease
Bisphosphonates	Drugs used to treat or prevent osteoporosis and to treat the bone pain caused by some types of cancer
Bone mineral density	The amount of calcium present in bone. It can be used to identify people at risk of osteoporosis, fracture and treatment-related illness
Boost dose	An additional dose of radiotherapy (boost) given to just the part of the body where the cancer was
Breast care nurse/ breast nurse specialist	A nurse with specialist knowledge of breast cancer and skills in communication
Breast conserving surgery	Surgery in which only the cancer is removed, together with a margin of normal breast tissue
Cancerisation	Extension of ductal carcinoma in situ into lobules
Breast physician	A specialisation within general practice medicine

Breast reconstruction	The formation of a breast shape after a total mastectomy, using a synthetic implant or tissue from the woman's body
Carcinoma	Most common type of cancer; malignant neoplasm (tumour) derived from epithelial cells, chiefly glandular (adenocarcinoma) or squamous (squamous cell carcinoma)
Cardiotoxicity	Having a harmful effect on the tissues of the heart
Chemotherapy	The use of medication (drugs) that is toxic to cancer cells. The drugs kill the cells, or prevent or slow their growth
Chest wall radiotherapy	Radiotherapy to the chest wall after mastectomy
Cognitive behavioural therapy	Type of psychological intervention used in the treatment of depression, anxiety and other mental disorders
Computerised tomography	A diagnostic imaging technique that uses X-rays and a computer to produce a detailed picture of a cross-section of the body
Concurrent	Occurring at the same time
Contralateral breast cancer	Cancer in the opposite breast
Comedonecrosis	A type of necrosis (localised death of tissue) occurring within milk ducts involved with ductal carcinoma in situ of the breast
Coronal plane	Also known as the frontal plane. Any vertical plane that divides the body into ventral and dorsal (belly and back) sections
Cosmesis	Retaining or restoring normal appearance or body image
Counselling	Encompasses supportive care delivered by a variety of health practitioners. Techniques are diverse and may include supportive listening, the provision of practical information and education, instruction in relaxation therapies, assistance with communication and relationship problems, training in assertiveness and advice on problem-solving
Cytotoxic	Toxic (harmful) to cells of the body
Dual energy X-ray absorptiometry (DEXA)	An imaging technique for quantifying bone mineral density
Ductal carcinoma in situ	A malignant tumour that is confined to the duct of the breast from which it arose and that has not yet become an invasive cancer. A form of pre-invasive cancer
Endocrine	Having to do with glandular tissues that secrete hormones directly into the blood stream
Endocrine therapy/treatment	The treatment of cancer by removing and/or blocking the effects of hormones that stimulate the growth of cancer cells
***erb*B-2**	Membrane receptor of HER2/*neu* oncogene
Excision	The act of surgically removing or 'cutting out' tissue from the body
Fibrosis	Hardening or thickening of the breast tissue
Fraction	The radiation dose delivered in each treatment

Gene mutation	A permanent change in the DNA sequence that makes up a gene
Grading	The degree of malignancy of a tumour, judged by its appearance under a microscope
HER2/*neu*	A gene that is over-amplified in some breast cancers predicting response to antibodies to its receptor (eg, Herceptin)
Heterogeneous	Having a large number of variants
Histology	An examination of the cellular characteristics of a tissue
Holistic care	Care that provides for the psychological as well as the physical requirements of the individual
Hormone receptors	Proteins in the cancer cell that bind to specific hormones
Hormone replacement therapy	Supplements to replace the female hormone oestrogen and/or progesterone
Human epidermal growth factor receptor 2 (HER2)	A gene that encodes a growth-promoting protein that helps to control how cells divide and repair themselves
Hypofractionated schedules	Radiotherapy given with fewer, larger doses
Immediate reconstruction	The reconstruction of the breast at the time of mastectomy
Immunohistochemistry	A technique that uses antibodies to identify specific proteins in tissues under a microscope
In situ component	A cancer that has not metastasised (spread to distant body sites) or invaded neighbouring tissue
Intensity modulated radiotherapy	A specialised form of conformal radiotherapy where the radiation can be adjusted to vary the dose given to different parts of an organ
Invasive breast cancer	Breast cancer where the cancerous cells have broken through the lining layer and begun to damage the tissue surrounding the breast ducts
Invasive lobular carcinoma	Breast cancer where the cancer cells originate from the lining of the lobules of the breast and that is of an invasive nature
Ipsilateral	On, or affecting, the same side
Irradiation/radiation	Treatment with, or exposure to, any form of radiation
Leukopenia	A decrease in the number of circulating white blood cells
Local recurrence	Return of the cancer in the affected breast
Loco-regional recurrence	Recurrence of the tumour at or near the original site of the cancer
Lumpectomy	The surgical removal of a lump from the breast without an attempt to achieve a wide excision
Luteinising hormone-releasing hormone agonists	Hormonal drugs that inhibit the production of the hormones that control the production of sex hormones, such as oestrogen
Lymph nodes	Small organs that act as filters in the lymphatic system. Lymph nodes close to the primary tumour are often the first sites to which cancer spreads
Lymphoedema	Swelling in the arm or breast because of a collection of lymphatic fluid

Lymphovascular invasion	Microscopic vascular (blood vessel) or lymphatic involvement by cancer cells
Magnetic resonance imaging	A diagnostic imaging technique that uses powerful electromagnets, radio waves and a computer to produce well-defined images of the body's internal structures
Mammography	The process of taking a mammogram – a soft tissue X-ray of the breast that may be used to evaluate a lump or as a screening test in women with no signs or symptoms of breast cancer
Mana	Power, respect, status
Margins	The edge of the tissue removed
Markers	Substances found in increased amounts in the blood, other body fluids or tissues that suggest that a certain type of cancer may be in the body
Mastectomy	The surgical removal of the breast
Medical oncologist	A doctor who specialises in the treatment of cancer patients, using drugs as the main modality of treatment
Medical oophorectomy	Endocrine therapy to stop the functioning of the ovaries (see ovarian ablation)
Menopause	The end of ovulation and ovarian hormone production
Metastases	The spread of cancer away from the primary site (origin) to somewhere else via the bloodstream or the lymphatic system
Microcalcifications	Specks of calcium that may be found in an area of rapidly dividing cells. When many are seen in a cluster, they may indicate a small cancer. About half of the breast cancers detected appear as these clusters on mammography
Micrometastases	Metastases (cancer spread) that are too small to be seen without a microscope
Morbidity	A diseased condition or state
Mortality	Death
Mucositis	Any inflammation of a mucous membrane, such as the lining of the mouth and throat
Multidisciplinary team	A team with members from different health care professions (eg, surgery, oncology, pathology, radiology and nursing)
Multifocal disease	Having two or more foci or arising from two or more places
Myalgia	Muscle pain
Myelodysplasia	Bone marrow abnormalities
Myelosuppression	The reduction in the ability of the bone marrow to produce blood cells
Neoadjuvant	Refers to drug treatment given to people with cancer prior to surgery
Neoplasia	The abnormal proliferation of cells, resulting in a structure known as a neoplasm (tumour)

Neurotoxicity	Occurs when the exposure to natural or artificial toxic substances, which are called neurotoxins, alters the normal activity of the nervous system in such a way as to cause damage to nervous tissue
Neutropenia	An abnormally low number of neutrophils (type of white blood cells)
Neutropenic sepsis/ febrile neutropenia	The development of fever, often with other signs of infection, in a patient with neutropenia
Noa	Ordinary, safe
Node negative	The absence of cancer in a lymph node or nodes
Node positive	The presence of cancer in a lymph node or nodes
Nomogram	A graphical calculating device, a two-dimensional diagram designed to allow the approximate graphical computation of a function
Oedema	Swelling
Oestrogen	A female sex hormone
Oestrogen receptor positive	A protein on breast cancer cells that binds to oestrogens. It indicates that the tumour may respond to endocrine therapies. Tumours rich in oestrogen receptors have a better prognosis than those that are not
Oncologist	A doctor who specialises in treating cancer
Oophorectomy	The surgical removal of an ovary
Osteopenia	Decreased bone mineral density
Osteoporosis	The loss of bony tissue resulting in bones that are brittle and liable to fracture
Ovarian ablation/ ovarian suppression	Surgery, radiation therapy or drug treatment that stops the functioning of the ovaries and significantly reduces oestrogen levels in the blood
Overexpression	An increase in expression (activity), for example of a gene or growth factor receptor
Paresthesia	A sensation of tingling, pricking or numbness of the skin
Pathologist	A doctor who examines and identifies cells. A pathologist can tell where a cell comes from in the body and whether it is normal or a cancer cell
Pathology	A branch of medicine concerned with disease, especially its structure and functional effects on the body
Pedicled flaps	A surgical flap sustained by a blood-carrying stem from the donor site during transfer
Peripheral neuropathy	Any disorder of the peripheral nervous system. Symptoms may include numbness and/or tingling in the fingers or toes. Neuropathy occurs as a side effect of some chemotherapy drugs
Pleomorphic	Tumours expressing variable appearance
Predictive values/markers	Something that produces a readily recognisable identification of disease (eg, a gene or protein)

Primary care	Services provided in community settings with which patients usually have first contact (eg, general practice)
Primary systemic therapy	Systemic therapy given before surgery or radiotherapy
Positron emission tomography (PET)	An imaging technique that produces a three-dimensional image or map of functional processes in the body
Progesterone receptor	A protein on breast cancer cells that binds to progesterones
Prognosis	A prediction of the likely outcome or course of a disease; the chance of recovery or recurrence
Prognostic factors	Patient or disease characteristics (eg, age and disease stage) that influence the course of the disease under study
Prophylactic	A medication or treatment designed and used to prevent a disease
Prosthesis	An artificial extension that replaces a missing body part
Psychotherapy	An interaction between a therapist and a patient that aims to decrease distress and increase morale, self-esteem and the ability to cope by increasing the patient's sense of mastery over the situation and helping them to overcome the practical challenges
Quadrantectomy	When a whole quadrant of breast is surgically removed
Radiation oncologist	A doctor who specialises in the treatment of cancer patients, using radiation as the main modality of treatment
Radioisotopes	Are extensively used in nuclear medicine to allow physicians to explore bodily structures and functions *in vivo* (in the living body) with a minimum of invasion to the patient
Radionecrotic	Necrosis (death of living cells) caused by exposure to ionising radiation
Radiotherapy	A treatment for cancer to prevent cell growth that uses high energy ionising radiation
Recurrence	Relapse of the cancer in the same place or elsewhere in the body
Regimen	A plan or regulated course of treatment
Resection margins	Margins of tissue removed from the body by surgery
Sagittal plane	An imaginary line from the top to the bottom of the body, dividing it into left and right portions
Salpingo-oophorectomy	The surgical removal of the ovaries and fallopian tubes
Scintigraphy	A diagnostic method in which a radioactive tracer is injected into the body. The radiation it sends out produces flashes of light on a scintillator (instrument used to detect radioactivity), and these are recorded
Scleroderma	An autoimmune disease that affects the blood vessels and connective tissue; a chronic disease characterised by excessive deposits of collagen in the skin or other organs
Segmentectomy	A segmental excision or sector resection is similar to a wide local excision, but the excision incorporates tissue from the nipple out to the periphery of the breast in a segmental shape

Sentinel lymph node	The first lymph node that filters fluid from the breast
Sentinel lymph node biopsy/ sentinel lymph node dissection	A less invasive procedure with a lower risk of complications than axillary clearance/dissection
Sequential	One treatment following another
Seroma	A pocket of clear serous fluid that sometimes develops in the body after surgery
Spiculated	A lump of tissue with spikes or points on the surface
Staging	The clinical description of the size and extent of a patient's tumour, by allocation into internationally agreed categories
Stomatitis	An inflammation of the mucous lining of any of the structures in the mouth, which may involve the cheeks, gums, tongue, lips and throat
Stroma	The supportive framework of an organ (or gland or other structure)
Supraclavicular fossa	The indentation immediately above the clavicle (collar bone)
Systemic therapy/treatment	Treatment, usually given by mouth or injection, that reaches and affects tumour cells throughout the body rather than targeting one specific area
T-score	Compares bone density to the optimal peak for gender. A T-score of greater than -1 is considered normal; -1 to -2.5 is defined as osteopenia and a risk for developing osteoporosis; less than -2.5 is diagnosed as osteoporosis
Tapu	Sacred, forbidden, special
Telangiectasia	The permanent dilation of groups of superficial capillaries and venules (small veins)
Telemedicine	The use of telecommunications and information technologies for the provision of health care at a distance
Thromboembolic disease/ thromboembolism	The obstruction of a blood vessel with a blood clot carried by the bloodstream from the site of origin to plug another blood vessel
Toxicity	The ability of a drug or radiation to cause harmful effects
Triple negative breast cancer	A specific subtype of breast cancer that does not express receptors or gene over-amplification for ER, PR or HER2/*neu*
Tumour bed	Where the cancer was before surgical removal
Ultrasound	An imaging method in which high-frequency sound waves are used to outline a part of the body
Vasomotor flushes	Hot flushes and sweats
Wide local excision	The complete removal of a tumour with a surrounding margin of normal breast tissue
Whānau	Family, community

References

1. Cancer Control Taskforce. The New Zealand cancer control strategy: action plan 2005–2010. Wellington: Ministry of Health; 2005.
2. Ministry of Health. Cancer: new registrations and deaths 2005. Wellington: Ministry of Health; 2008.
3. Althuis MD, Dozier JM, Anderson WF, et al. Global trends in breast cancer incidence and mortality 1973–1997. Int J Epidemiol. 2005;34(2):405–412.
4. New Zealand Guidelines Group. Handbook for the preparation of explicit evidence-based clinical practice guidelines. Wellington: New Zealand Guidelines Group; 2003.
5. New Zealand Health Information Service. Cancer: new registrations and deaths 2003. Wellington: Ministry of Health; 2007.
6. Blue J. Breast cancer screening in New Zealand. N Z Med J. 2005;118(1221):U1626.
7. Ajwani S, Blakely T, Robson B. Decades of disparity: ethnic mortality trends in New Zealand 1980–1999. Wellington: Ministry of Health and University of Otago; 2003.
8. Ministry of Health. Cancer in New Zealand: trends and projections. Wellington: Ministry of Health; 2002.
9. Cormack D, Robson B, Purdie G, et al. Access to cancer services for Māori. Wellington: Ministry of Health; 2005.
10. Bramley D, Hebert P, Jackson R, et al. Indigenous disparities in disease-specific mortality, a cross-country comparison: New Zealand, Australia, Canada, and the United States. N Z Med J. 2004;117(1207):U1215.
11. Curtis E, Wright C, Wall M. The epidemiology of breast cancer in Māori women in Aotearoa New Zealand: implications for screening and treatment. N Z Med J. 2005;118(1209):U1297.
12. Robson B, Purdie G, Cormack D. Unequal impact: Māori and non-Māori cancer statistics 1996–2001. Wellington: Ministry of Health; 2005.
13. Blakely T, Ajwani S, Robson B, et al. Decades of disparity: widening ethnic mortality gaps from 1980 to 1999. N Z Med J. 2004;117(1199):U995.
14. Sarfati D, Blakely T, Shaw C, et al. Patterns of disparity: ethnic and socio-economic trends in breast cancer mortality in New Zealand. Cancer Causes Control. 2006;17(5):671–678.
15. Ministry of Health. Asian health chart book 2006. Wellington: Ministry of Health 2006.
16. Ministry of Health. The New Zealand cancer control strategy. Wellington: Ministry of Health and the New Zealand Cancer Control Trust; 2003.
17. Weir R, Day P, Ali W. Risk factors for breast cancer in women. NZHTA Report 2007;10(2).
18. National Institute for Clinical Excellence (NICE). Referral guidelines for suspected cancer. NICE clinical guideline 27. London: National Institute for Health and Clinical Excellence 2005.
19. National Breast Cancer Centre. The investigation of a new breast symptom: a guide for general practitioners. Camperdown, NSW: National Breast Cancer Centre 2006.
20. Ni Mhurchu C, Turley M, Stefanogiannis N, et al. Mortality attributable to higher-than-optimal body mass index in New Zealand. Public Health Nutr. 2005;8(4):402–408.
21. Firth H, Gray A, Carpenter LM, et al. Cancer mortality by occupation among New Zealand women: 1988–1997. N Z Med J. 2007;120(1266):U2833.
22. Emery J, Lucassen A, Murphy M. Common hereditary cancers and implications for primary care. Lancet. 2001;358:56–63.
23. McIntosh A, Shaw C, Evans G, et al. Clinical guidelines and evidence review for the classification and care of women at risk of familial breast cancer. London: National Collaborating Centre for Primary Care / University of Sheffield 2004.

24. Ford D, Easton D, Peto J. Estimates of the gene frequency of BRCA1 and its contribution to breast and ovarian cancer incidence. Am J Hum Genet. 1995;57(6):1457–1462.
25. National Collaborating Centre for Primary Care. Referral guidelines for suspected cancer in adults and children. Part 1. London: National Collaborating Centre for Primary Care 2005.
26. Bennett H, Marshall R, Campbell I, et al. Women with breast cancer in Aotearoa New Zealand: the effect of urban versus rural residence on stage at diagnosis and survival. N Z Med J. 2007;120(1266):U2831.
27. Armstrong W, Borman B. Breast cancer in New Zealand: trends, patterns, and data quality. N Z Med J. 1996;109(1024):221–224.
28. Kinnersley P, Edwards A, Hood K. Interventions before consultations to help patients address their information needs by encouraging question asking: systematic review. Br Med J. 2008;337.
29. National Breast Cancer Centre and National Cancer Control Initiative. Clinical practice guideline for the psychosocial care of adults with cancer. Camperdown, NSW: National Breast Cancer Centre; 2005.
30. National Institute for Clinical Excellence (NICE). Guidance on supportive and palliative care. London: National Institute for Clinical Excellence (NICE) 2004; Available from www.nice.org.uk/Guidance/CSGSP
31. National Breast Cancer Centre. Clinical practice guidelines for the management of early breast cancer. 2nd ed. Camperdown, NSW: National Health and Medical Research Council (NHMRC) 2001.
32. Cancer Society of New Zealand. National stocktake and review of a selection of consumer cancer information resources. Auckland: Cancer Society of New Zealand 2006.
33. Bleiker EM, Pouwer F, van der Ploeg HM, et al. Psychological distress 2 years after diagnosis of breast cancer: frequency and prediction. Patient Education and Counselling 2000;40:209–217.
34. Glanz K, Lerman C. Psychological impact of breast cancer: a critical review. Annals of Behavioural Medicine 1992;14(3):204–212.
35. Irvine D, Brown B, Crooks D, et al. Psychosocial adjustment in women with breast cancer. Cancer. 1991;67:1097–1117.
36. Maguire P. Psychological aspects. In: Dixon M, ed. *ABC of Breast Diseases*. London: BMJ Books 2000:85–89.
37. Scottish Intercollegiate Guidelines Network (SIGN). Management of breast cancer in women: a national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN); 2005. **Overall quality: +**
38. Christiaens M, Vlayen J, Gailly J, et al. Scientific support of the College of Oncology: a national clinical practice guideline for breast cancer. KCE Report 63A. Brussels: Belgian Health Care Knowledge Centre (KCE) 2007. **Overall quality: +**
39. Bantum E, Donovan K, Owen J. A systematic review of outcomes associated with psychological interventions for women with breast cancer. J Clin Outcomes Manag. 2007;14(6):341–352. **Overall quality: +**
40. Chow E, Tsao M, Harth T. Does psychosocial intervention improve survival in cancer? A meta-analysis. Palliat Med. 2004;18:25–31. **Overall quality: +**
41. Smedslund G, Ringdal GI. Meta-analysis of the effects of psychosocial interventions on survival time in cancer patients. J Psychosom Res. 2004;57(2):123–131. **Overall quality: +**
42. Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. Int J Psychiatry Med. 2006;36(1):13–34. **Overall quality: + +**
43. Girgis A, Johnson C, Aoun S, et al. Challenges experienced by informal caregivers in cancer. Cancer Forum. 2006;30(1):21–25.
44. Kirsten L, Wain G, Butow P, et al. Diversity and availability of support groups. Cancer Forum. 2006;30(1):35–38.
45. Allen S, Shah A, Nezu A. A problem solving approach to stress reduction among younger women with breast carcinoma: a randomized controlled trial. Cancer. 2002;94:3089–3100.

46. Meyer T, Mark M. Effects of psychosocial interventions with adult cancer patients: a meta-analysis of randomized experiments. Health Psychol. 1995;14:101–108.
47. Greer S, Moorey S, Baruch J, et al. Adjuvant psychological therapy for patients with cancer a prospective randomised trial. Br Med J. 1992;304:675–680.
48. National Breast Cancer Centre. Clinical practice guidelines. Management of early breast cancer. Canberra: National Health and Medical Research Council 2001. **Overall quality: +**
49. Scottish Intercollegiate Guidelines Network (SIGN). Management of breast cancer in women: a national clinical guideline. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN) 2003. **Overall quality: +**
50. Cruickshank S, Kennedy C, Lockhart K, et al. Specialist breast care nurses for supportive care of women with breast cancer. Cochrane Database Syst Rev. 2008(2):CD005634. **Overall quality: +**
51. Houssami N, Sainsbury R. Breast cancer: multidisciplinary care and clinical outcomes. Eur J Cancer. 2006;42(15):2480–2491. **Overall quality: +**
52. Morris E, Haward RA, Gilthorpe MS, et al. The impact of the Calman-Hine report on the processes and outcomes of care for Yorkshire's breast cancer patients. Ann Oncol. 2008;19(2):284–291. **Overall quality: +**
53. Chang J, Vines E, Bertch H, et al. The impact of a multidisciplinary breast cancer center on recommendations for patient management. Cancer. 2001;91(7):1231–1237. **Overall quality: +/-**
54. Chan WF, Cheung PSY, Epstein RJ, et al. Multidisciplinary approach to the management of breast cancer in Hong Kong. World J Surg. 2006;30(12):2095–2100. **Overall quality: +/-**
55. National Breast Cancer Centre. Multidisciplinary meetings for cancer care: a guide for health service providers. Camperdown, NSW: National Breast Cancer Centre; 2005.
56. Ministry of Health. Ethnicity data protocols for the health and disability sector. Wellington: Ministry of Health; 2004.
57. Weston MK, Moss DP, Stuart J, et al. Differences in breast cancer biological characteristics between ethnic groups in New Zealand. Breast Cancer Res Treat. 2008;111(3):555–558.
58. Li C, Malone K, Darling J. Differences in breast cancer stage, treatment, and survival by race and ethnicity. Arch Intern Med. 2003;163(1):49–56.
59. New Zealand Guidelines Group. Suspected cancer in primary care. Wellington: New Zealand Guidelines Group 2009.
60. Jansen P, K. S. Māori experiences of primary health care: breaking down the barriers. N Z Fam Physician. 2006;33:298–300.
61. Huakau G. Negotiating health: perspectives from Pacific women in Dunedin [Master of Arts]: University of Otago; 2001.
62. Huakau G, Bray A. 'Talking Disabilities' from a Pacific perspective. Dunedin: Donald Beasley Institute; 2000.
63. Davis P, Suaalii-Sauni T, Lay-Yee R, et al. Pacific patterns in primary health care: a comparison of Pacific and all patient visits to doctors. Wellington: Ministry of Health; 2005.
64. Flores G. The impact of medical interpreter services on the quality of health care: a systematic review. Med Care Res Rev. 2005;62(3):255–299.
65. Goel M, Burns R, Phillips R, et al. Trends in breast conserving surgery among Asian Americans and Pacific Islanders, 1992–2000. J Gen Intern Med. 2005;20:604–611.
66. Ministry of Health. Towards a cancer control strategy for New Zealand Marihi Tauporo discussion document: submission analysis. Wellington: Ministry of Health; 2004.
67. Bassett SF, Holt AL. New Zealand resident Tongan peoples' health and illness beliefs and utilisation of the health care system. Pacific Health Dialogue. 2002;9(1):40–47.
68. Finau S, Tipene-Leach D, Finau E. Traditional healing and Pacificans: a manual for community workers. Auckland: Masilamea Press 2004.

69. Tamaki Healthcare PHO, Te Kupenga o Hoturoa PHO. Cancer control strategy: review of community-based service for Māori in ADHB and CMDHB. Auckland: Tamaki Health Care Primary Health Organisation 2006.
70. Walker T, Signal L, Russell M, et al. The road we travel: Māori experience of cancer. N Z Med J. 2008;121(1279):27–35.
71. Ratima MM, Brown R, Garrett N, et al. Strengthening Māori participation in the New Zealand health and disability workforce. Med J Aust. 2007;186:541–543.
72. Bramley D, Latimer S. The accuracy of ethnicity data in primary care. N Z Med J. 2007;120(1262):U2779.
73. American Joint Committee in Cancer. AJCC cancer staging handbook: from the AJCC cancer staging manual. 6th ed. New York: Springer 2002.
74. Myers RE, Johnston M, Pritchard K, et al. Baseline staging tests in primary breast cancer: a practice guideline. CMAJ. 2001;164(10):1439–1444.
75. Zuiden V. Richtlijn Behandeling van het mammacarcinoom. In: Zuiden V, ed. *Kwaliteitsinstituut voor de Gezondheidszorg (CBO) en Vereniging van Integrale Kankercentra (VIKC)*: Alphen aan den Rijn 2005.
76. Shie P, Cardarelli R, Brandon D, et al. Meta-analysis: comparison of F-18 fluorodeoxyglucose-positron emission tomography and bone scintigraphy in the detection of bone metastases in patients with breast cancer. Clin Nucl Med. 2008;33(2):97–101. **Overall quality: + +/-**
77. Hwa H, Kuo W, Chang L, et al. Prediction of breast cancer and lymph node metastatic status with tumour markers using logistic regression models. Journal of Evaluation in Clinical Practice. 2008;14:275–280. **Overall quality: QUADAS score 9/14**
78. Silowska I, Kopczynski Z, Grodeska-Gazdecka S. Diagnostic value of measuring serum CA 15-3, TPA, and TPS in women with breast cancer. Postepy Higieny i Medycyny Doswiadczalnej. 2006;60:295–299. **Overall quality: QUADAS score 7/14**
79. Baskic D, Ristic P, Matic S, et al. Clinical evaluation of the simultaneous determination of CA 15-3, CA 125 and sHER2 in breast cancer. Biomarkers. 2007;12(6):657–667. **Overall quality: QUADAS score 7/14**
80. Aslan S, Cetin B, Akinci M, et al. Computed tomography in detecting bone metastases of breast carcinoma: is it better than plain X-ray? Saudi Medical Journal. 2006;27(9):1326–1328. **Overall quality: QUADAS score 9/14**
81. Goldhirsch A, Wood WC, Gelber RD, et al. Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol. 2007;18(7):1133–1144.
82. Drotman MB, Machnicki SC, Schwartz LH, et al. Breast cancer: assessing the use of routine pelvic CT in patient evaluation. AJR Am J Roentgenol. 2000;176(6):1433–1436.
83. Puglisi F, Follador A, Minisini A, et al. Baseline staging tests after a new diagnosis of breast cancer: further evidence of their limited indications. Ann Oncol. 2005;16(2):263–266.
84. Mann R, Hoogeveen Y, Blickman J, et al. MRI compared to conventional diagnostic work-up in the detection and evaluation of invasive lobular carcinoma of the breast: a review of existing literature. Breast Cancer Res Treat. 2008;107:1–14. **Overall quality: +**
85. Houssami N, Ciatto S, Macaskill P, et al. Accuracy and surgical impact of magnetic resonance imaging in breast cancer staging: systematic review and meta-analysis in detection of multifocal and multicentric cancer. J Clin Oncol. 2008;29(16):3248–3257. **Overall quality: + +/-**
86. Deurloo EE, Klein Zeggelink WFA, Teertstra HJ, et al. Contrast-enhanced MRI in breast cancer patients eligible for breast-conserving therapy: complementary value for subgroups of patients. Eur Radiol. 2006;16(3):692–701. **Overall quality: QUADAS score 10/14**
87. van Goethem M, Schelfout K, Dijckmans L, et al. MR mammography in the pre-operative staging of breast cancer in patients with dense breast tissue: comparison with mammography and ultrasound. Eur Radiol. 2004;14(5):809–816. **Overall quality: QUADAS score 11/14**

88. Solin LJ, Orel SG, Hwang WT, et al. Relationship of breast magnetic resonance imaging to outcome after breast-conservation treatment with radiation for women with early-stage invasive breast carcinoma or ductal carcinoma in situ. J Clin Oncol. 2008;26(3):386–391. **Overall quality: +**

89. Drew PJ, Harvey I, Handy A, et al. The UK NIHR multicentre randomised COMICE trial of MRI planning for breast conserving treatment for breast cancer. *31st Annual San Antonio Breast Cancer Symposium*. San Antonio (TX) 2008:Abstract 51.

90. Wright JR, Whelan TJ, McCready DR, et al. Management of ductal carcinoma in situ of the breast. Toronto, ON: Cancer Care Ontario; 2003.

91. McCready D, Holloway C, Shelley W, et al. Surgical management of early stage invasive breast cancer: a practice guideline. Can J Surg. 2005;48(3):185–194.

92. Jatoi I, Proschan MA. Randomized trials of breast-conserving therapy versus mastectomy for primary breast cancer: a pooled analysis of updated results. Am J Clin Oncol. 2005;28(3):289–294.

93. Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and surgery in early breast cancer: an overview of the randomized trials. N Engl J Med. 1995;333(22):1444–1455.

94. Veronesi U, Banfi A, Salvadori B, et al. Breast conservation is the treatment of choice in small breast cancer: long-term results of a randomized trial. Eur J Cancer. 1990;26(6):668–670.

95. Blichert-Toft M, Rose C, Andersen JA, et al. Danish randomized trial comparing breast conservation therapy with mastectomy: six years of life-table analysis. Danish Breast Cancer Cooperative Group. J Natl Cancer Inst Monogr. 1992(11):19–25.

96. Fisher B. Lumpectomy versus quadrantectomy for breast conservation: a critical appraisal. Eur J Cancer. 1995;31A(10):1567–1569.

97. Fallowfield LJ, Hall A, Maguire GP, et al. Psychological outcomes of different treatment policies in women with early breast cancer outside a clinical trial. Br Med J. 1990;301:575–580.

98. Turner J, Wooding S, Neil C. Psychosocial impact of breast cancer: a summary of the literature 1986–1996. Woolloomooloo, NSW: NHMRC National Breast Cancer Centre; 1998.

99. Moyer A. Psychosocial outcomes of breast-conserving surgery versus mastectomy: a meta-analytic review. Health Psychol. 1997;16(3):284–298.

100. Rodger A, Stebbing J, Thompson AJ,. Clinical evidence: breast cancer: non-metastatic. Br Med J. 2006;February. **Overall quality: +**

101. Poggi MM, Danforth DN, Sciuto LC, et al. Eighteen-year results in the treatment of early breast carcinoma with mastectomy versus breast conservation therapy: the National Cancer Institute Randomized Trial. Cancer. 2003;98(4):697–702.

102. Sacchini V, Luini A, Tana S, et al. Quantitative and qualitative cosmetic evaluation after conservative treatment for breast cancer. Eur J Cancer. 1991;27(11):1395–1400.

103. Arriagada R, Lê MG, Rochard F, et al. Conservative treatment versus mastectomy in early breast cancer: patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. J Clin Oncol. 1996;14(5):1558–1564.

104. Jacobson JA, Danforth DN, Cowan KH, et al. Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. N Engl J Med. 1995;332(14):907–911.

105. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. J Natl Cancer Inst. 2000;92(14):1143–1150.

106. Early Breast Cancer Trialists' Collaborative Group, Clarke M, Collins R. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;366 (9503):2087–2106.

107. Taghian A, Mohiuddin M, Jagsi R, et al. Current perceptions regarding surgical margin status after breast-conserving therapy: results of a survey. Ann Surg. 2005;241(4):629–639.

108. Bleicher RJ, Morrow M. Management of close margins in invasive breast cancer. Breast Cancer Online. 2007;10(2)(e4).

109. Smitt MC, Nowels KW, Zdeblick MJ, et al. The importance of the lumpectomy surgical margin status in long-term results of breast conservation. Cancer. 1995;76(2):259–267.

110. Mariani L, Salvadori B, Marubini E, et al. Ten year results of a randomised trial comparing two conservative treatment strategies for small size breast cancer. Eur J Cancer. 1998;34:1156–1162.

111. CBO (Dutch Institute for Healthcare Improvement). Richtlijn Behandeling van het mammacarcinoom. Utrecht: CBO; 2005.

112. Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005;23(30):7703–7720.

113. Stebbing J, Delaney G, Thompson A. Breast cancer: non-metastatic. Clin Evid (Online). 2007;12(102):1–47. **Overall quality: +**

114. Browning CJ, Redman S. Lymphoedema: prevalence, risk factors and management: a review of the research. Kings Cross, NSW: NHMRC National Breast Cancer Centre 1998.

115. Chetty U, Jack W, Prescott RJ, et al. Management of the axilla in operable breast cancer treated by breast conservation: a randomized clinical trial. Edinburgh Breast Unit. Br J Surg. 2000;87(2):163–169.

116. Wildiers H, Kunkler I, Biganzoli L, et al. Management of breast cancer in elderly individuals: recommendations of the International Society of Geriatric Oncology. Lancet Oncol. 2007;8(12):1101–1115. **Overall quality: +**

117. International Breast Cancer Study Group. Randomised trial comparing axillary clearance versus no axillary clearance in older patients with breast cancer: first results of IBCSG trial 10–93. J Clin Oncol. 2006;24(3):337–344. **Overall quality: +**

118. Forrest AP, Everington D, McDonald CC, et al. The Edinburgh randomized trial of axillary sampling or clearance after mastectomy. Br J Surg. 1995;82(11):1504–1508. **Overall quality: +**

119. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347(16):1233–1241.

120. Louis-Sylvestre C, Clough K, Asselain B, et al. Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. J Clin Oncol. 2004;22(1):97–101.

121. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival: a Bayesian meta-analysis. Ann Surg Oncol. 1999;6(1):109–116.

122. National Breast and Ovarian Cancer Centre. Recommendations for the use of sentinel node biopsy in early (operable) breast cancer. Surrey Hills, NSW: National Breast and Ovarian Cancer Centre 2008.

123. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Lancet. 2000;355(9217):1757–1770.

124. Veronesi U, Paganelli G, Viale G, et al. A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med. 2003(6):546–553. **Overall quality: +**

125. Veronesi U, Paganelli G, Viale G, et al. Sentinel-lymph-node biopsy as a staging procedure in breast cancer: update of a randomised controlled study. Lancet Oncol. 2006;7(12):983–990. **Overall quality: +**

126. Fleissig A, Fallowfield LJ, Langridge CI, et al. Post-operative arm morbidity and quality of life: results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. Breast Cancer Res Treat. 2006;95(3):279–293.

127. Weitzig N, Gill P, Ung O. Participation in the RACS sentinel node biopsy versus axillary clearance trial. ANZ J Surg. 2005;75(3):98–100.

128. Gill P, Gebski V, Weizig N. Sentinel node (SN) based management causes less arm swelling and better quality of life than routine axillary clearance (AC): 1 year outcomes of the SNAC trial. *29th Annual San Antonio Breast Cancer Symposium*. San Antonio (TX) 2006:Abstract 27.

129. Ung OA. Australasian experience and trials in sentinel lymph node biopsy: the RACS SNAC trial. Asian J Surg. 2004;27(4):284–290.

130. Julian T, Krag D, Brown A. Preliminary technical results of NSABP B-32, a randomized phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer patients. *27th Annual San Antonio Breast Cancer Symposium*. San Antonio (TX) 2004:Abstract 14.

131. Harlow SP, Krag DN, Julian TB, et al. Prerandomization surgical training for the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial: a randomized phase III clinical trial to compare sentinel node resection to conventional axillary dissection in clinically node-negative breast cancer. Ann Surg. 2005(1):48–54.

132. Krag DN, Anderson SJ, Julian TB, et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. Lancet Oncol. 2007;8(10):881–888. **Overall quality: + +**

133. Purushotham AD, Upponi S, Klevesath MB, et al. Morbidity after sentinel lymph node biopsy in primary breast cancer: results from a randomized controlled trial. J Clin Oncol. 2005;23(19):4312–4321.

134. Del Bianco P, Zavagno G, Burelli P, et al. Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial. Eur J Surg Oncol. 2008;34(5):508–513.

135. Zavagno G, De Salvo GL, Scalco G, et al. A randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the sentinella/GIVOM trial. Ann Surg. 2008;247(2):207–213.

136. Cox CE, Bass SS, McCann CR, et al. Lymphatic mapping and sentinel lymph node biopsy in patients with breast cancer. Annu Rev Med. 2000;51:525–542. **Overall quality: x**

137. Fraile M, Rull M, Julian FJ, et al. Sentinel node biopsy as a practical alternative to axillary lymph node dissection in breast cancer patients: an approach to its validity. Ann Oncol. 2000;11(6):701–705. **Overall quality: +**

138. Miltenburg DM, Miller C, Karamlou TB, et al. Meta-analysis of sentinel lymph node biopsy in breast cancer. J Surg Res. 1999;84:138–142. **Overall quality: x**

139. Kim KJ, Huh SJ, Yang JH, et al. Treatment results and prognostic factors of early breast cancer treated with a breast conserving operation and radiotherapy. Jpn J Clin Oncol. 2005;35(3):126–133. **Overall quality: + +**

140. Martin IRCG, Chagpar A, Scoggins CR, et al. Clinicopathologic factors associated with false-negative sentinel lymph-node biopsy in breast cancer. Ann Surg. 2005;241(6):1005–1015. **Overall quality: +**

141. Tafra L, Lannin D, Swanson M, et al. Multicenter trial of sentinel node biopsy for breast cancer using both technetium sulfur colloid and isosulfan blue dye. Ann Surg. 2001;233(1):51–59. **Overall quality: +**

142. Bergkvist L, Frisell J, Lijergen G, et al. Multicentre study of detection and false-negative rates in sentinel node biopsy for breast cancer. Br J Surg. 2001;88:1644–1648. **Overall quality: +**

143. McMasters K, Tuttle T, Carlson D, et al. Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. J Clin Oncol. 2000;18(13):2560–2566. **Overall quality: +**

144. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst. 2006(9):599–609.

145. National Breast and Ovarian Cancer Centre. The pathology reporting of breast cancer: a guide for pathologists, surgeons, radiologists and oncologists. Surrey Hills, NSW: National Breast and Ovarian Cancer Centre 2008.

146. Martelli G, Miceli R, De Palo G, et al. Is axillary lymph node dissection necessary in elderly patients with breast carcinoma who have a clinically uninvolved axilla? Cancer. 2003;97:1369–1375.

147. Martelli G, Boracchi P, De Palo M, et al. A randomized trial comparing axillary dissection to no axillary dissection in older patients with T1N0 breast cancer: results after 5 years of follow-up. Ann Surg. 2005;242(1):1–6.

148. Holmberg SB, Crivellari D, Zahrieh D, et al. A randomised trial comparing axillary clearance versus no axillary clearance in older patients (=60 years) with breast cancer: first results of IBCSG Trial 10-93. Proc Am Soc Clin Oncol,; 2004; 2004. p. abstr 505.

149. Truong P, Bernstein V, Wai E, et al. Age-related variations in the use of axillary dissection: a survival analysis of 8038 women with T1-ST2 breast cancer. Int J Radiat Oncol Biol Phys. 2002;54(3):637–639.

150. Naik A, Fey J, Gemignani M, et al. The risk of axillary relapse after sentinel lymph node biopsy for breast cancer is comparable with that of axillary lymph node dissection: a follow-up study of 4008 procedures. Ann Surg. 2004;240(3):462–468. **Overall quality: +**

151. Grube B, Giuliano AE. Observation of the breast cancer patient with a tumor-positive sentinel node: implications of the ACOSOG Z0011 trial. Semin Surg Oncol. 2001;20(3):230–237.

152. Degnim AC, Griffith KA, Sabel MS, et al. Clinicopathologic features of metastasis in nonsentinel lymph nodes of breast carcinoma patients. Cancer. 2003;98(11):2307–2315.

153. Viale G, Maiorano E, Pruneri G, et al. Predicting the risk for additional axillary metastases in patients with breast carcinoma and positive sentinel lymph node biopsy. Ann Surg. 2005;241(2):319–325.

154. Schrenk P, Woelfl S, Bogner S, et al. The use of sentinel node biopsy in breast cancer patients undergoing skin sparing mastectomy and immediate autologous reconstruction. Plast Reconstr Surg. 2005;116(5):1278–1286.

155. van der Loo EM, Hop WCJ, Tervoort MA, et al. Very slight chance of other metastases in axillary nodes of breast cancer patients with a small sentinel node metastasis without extranodal tumour growth. Ned Tijdschr Geneeskd. 2004;148(19):938–943.

156. Joseph KA, El-Tamer M, Komenaka I, et al. Predictors of nonsentinel node metastasis in patients with breast cancer after sentinel node metastasis. Arch Surg. 2004;139(6):648–651.

157. Leidenius M, Salmenkivi K, Von Smitten K, et al. Tumour-positive sentinel node findings in patients with ductal carcinoma in situ. J Surg Oncol. 2006;94(5):380–384.

158. Clark B, Sitzia J, Harlow W. Incidence and risk of arm oedema following treatment for breast cancer: a three-year follow-up study. Q J Med. 2005;98:343–348. **Overall quality: +**

159. Cole T. Risks and benefits of needle use in patients after axillary node surgery. Br J Nurs. 2006;15(18):969–974. **Overall quality: Expert opinion**

160. Pötter R, Gnant M, Kwasny W, et al. Lumpectomy plus tamoxifen or anastrozole with or without whole breast irradiation in women with favorable early breast cancer. Int J Radiat Oncol Biol Phys. 2007;68(2):334–340. **Overall quality: +**

161. Schnaper LA, Hughes KS. The use of radiation in the elderly. Breast Cancer Online. 2007;10(1):e1. **Overall quality: +**

162. Prescott RJ, Hunkler IH, Williams LJ, et al. A randomised controlled trial of postoperative radiotherapy following breast-conserving surgery in a minimum-risk older population. The PRIME trial. Health Technology Assessment. 2007;11(31):1–149. **Overall quality: +**

163. Ministry of Health. Health targets: shorter waiting times for cancer treatment. [n.d.] [cited 2009 July 1]; Available from: http://www.moh.govt.nz/moh.nsf/indexmh/healthtargets-targets-cancerwaitingtimes

164. Killander F, Anderson H, Ryden S, et al. Radiotherapy and tamoxifen after mastectomy in postmenopausal women: 20 year follow-up of the South Sweden Breast Cancer Group randomised trial SSBCG II:I. Eur J Cancer. 2007;43(14):2100–2108. **Overall quality: +**

165. Nielsen HM, Overgaard M, Grau C, et al. Study of failure pattern among high-risk breast cancer patients with or without postmastectomy radiotherapy in addition to adjuvant systemic therapy: long-term results from the Danish Breast Cancer Cooperative Group DBCG 82 b and c randomized studies. J Clin Oncol. 2006;24(15):2268–2275. **Overall quality: +**

166. Overgaard M, Nielsen HM, Overgaard J. Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol. 2007;82(3):247–253. **Overall quality: +**

167. Karlsson P, Cole BF, Price KN, et al. The role of the number of uninvolved lymph nodes in predicting locoregional recurrence in breast cancer. J Clin Oncol. 2007;25:2019–2026.

168. Antonini N, Jones H, Horiot JC, et al. Effect of age and radiation dose on local control after breast conserving treatment: EORTC trial 22881-10882. Radiother Oncol. 2007;82(3):265–271. **Overall quality: +**

169. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. J Clin Oncol. 2007;25(22):3259–3265. **Overall quality: +**

170. Arthur D, Vicini F, Kuske R, et al. Accelerated partial breast irradiation: an updated report from the American Brachytherapy Society. Brachytherapy. 2002;1(4):184–190.

171. Magee B, Swindell R, Harris M, et al. Prognostic factors for breast recurrence after conservative breast surgery and radiotherapy: results from a randomised trial. Radiother Oncol. 1996;39(3):223–227.

172. Dodwell DJ, Dyker K, Brown J, et al. A randomised study of whole-breast vs tumour-bed irradiation after local excision and axillary dissection for early breast cancer. Clin Oncol. 2005;17(8):618–622.

173. Rothenberg BM, Aronson N, Ziegler KM, et al. Accelerated partial breast irradiation as sole radiotherapy after breast-conserving surgery for early stage breast cancer. Technol Eval Cent Asses Program. 2007;22(4):1–34. **Overall quality: +**

174. Polgar C, Fodor J, Major T, et al. Breast-conserving treatment with partial or whole breast irradiation for low-risk invasive breast carcinoma-5-year results of a randomized trial. Int J Radiat Oncol Biol Phys. 2007;69(3):694–702. **Overall quality: +**

175. Polgar C, Fodor J, Orosz Z, et al. Electron and high-dose-rate brachytherapy boost in the conservative treatment of stage I–II breast cancer: first results of the randomized Budapest boost trial. Strahlentherapie und Onkologie. 2002;178(11):615–623.

176. Vicini F, Baglan K, Kestin L, et al. The emerging role of brachytherapy in the management of patients with breast cancer. Semin Radiat Oncol. 2002;12(1):31–39.

177. Polgar C, Major T, Fodor J, et al. High-dose-rate brachytherapy alone versus whole breast radiotherapy with or without tumor bed boost after breast-conserving surgery: seven-year results of a comparative study. Int J Radiat Oncol Biol Phys. 2004;60(4):1173–1181.

178. King TA, Bolton JS, Kuske RR, et al. Long-term results of wide-field brachytherapy as the sole method of radiation therapy after segmental mastectomy for T(is,1,2) breast cancer. Am J Surg. 2000;180(4):299–304.

179. Fentiman IS, Poole C, Tong D. Inadequacy of irridium implant as sole radiation treatment for operable breast cancer. Eur J Cancer. 1996;32A(4):608–611.

180. Fentiman IS, C P, Tong D. Irridium implant treatment without external radiotherapy for operable breast cancer: a pilot study. Eur J Cancer. 1991;27(4):477–450.

181. Ott OJ, Schulz-Wendtland R, Uter W, et al. Fat necrosis after conserving surgery and interstitial brachytherapy and/or external-beam irradiation in women with breast cancer. Stahlenther Onkol. 2005;181:638–644.

182. Hall EJ. Radiobiology for the radiologist. 4th ed. Philadelphia: JB Lippincott 1994.

183. Yamada Y, Ackerman I, Franssen E, et al. Does the dose fractionation schedule influence local control of adjuvant radiotherapy for early stage breast cancer? Int J Radiat Oncol Biol Phys. 1999;44(1):99–104.

184. Whelan T, MacKenzie R, Julian J, et al. Randomized trial of breast irradiation schedules after lumpectomy for women with lymph node-negative breast cancer. J Natl Cancer Inst. 2002;94(15):1143–1150.

185. Owen JR, Ashton A, Bliss JM, et al. Effect of radiotherapy fraction size on tumour control in patients with early-stage breast cancer after local tumour excision: long-term results of a randomised trial. Lancet Oncol. 2006;7(6):467–471. **Overall quality: +**

186. START Trialists Group. The UK standardisation of breast radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet. 2008;371(9618):1098–1107. **Overall quality: +**

187. Whelan T, Pignol J, Julian J, et al. Long-term results of a randomized trial of accelerated hypofractionated whole breast irradiation following breast conserving surgery in women with node-negative breast cancer. Int J Radiat Oncol Biol Phys. 2008;72(1):S28.

188. START Trialists Group. The UK standardisation of breast radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. Lancet Oncol. 2008;9:331–341. **Overall quality: +**

189. Powell S, Taghian A, Kachnic L, et al. Risk of lymphoedema after regional node irradiation with breast conservation therapy. Int J Radiat Oncol Biol Phys. 2003;55(5):1209–1215.

190. Whelan T. Treatment of the internal mammary nodes in early breast cancer: back to the future. Clin Oncol. 2003;15(1):14–16.

191. Recht A. Selecting patients for breast-conserving therapy. Semin Breast Dis. 2001;4(4):198–206.

192. Ragaz J, Olivotto I, Spinelli J, et al. Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst. 2005;Jan 19;97(2):116–126.

193. McArdle CS, Crawford D, Dykes EH, et al. Adjuvant radiotherapy and chemotherapy in breast cancer. Br J Surg. 1986;73(4):264–266.

194. Kuske RR, Hayden D, Bischoff R, et al. The impact of extracapsular axillary nodal extension (ECE) with and without irradiation on patterns of failure and survival from breast cancer. Int J Radiat Oncol Biol Phys. 1996;36(Suppl1):272.

195. Ewers S, Attewell R, Baldetorp B, et al. Flow cytometry DNA analysis and prediction of local regional recurrences after mastectomy in breast cancer. Acta Oncologica. 1992;31(7):733–740.

196. Lacour J, Le MG, Caceres E, et al. Radical mastectomy versus radical mastectomy plus internal mammary dissection: ten year results of an international cooperative trial in breast cancer. Cancer. 1983;51(10):1941–1943.

197. Veronesi U, Marubini E, Mariani G, et al. The dissection of the internal mammary nodes does not improve the survival of breast cancer patients: 30 year results of a randomised trial. Eur J Cancer. 1999;35(9):1320–1325. **Overall quality: +**

198. Yamashita T, Hurukawa M, Sekiguchi K. Efficacy of loco-regional lymph nodes irradiation after mastectomy for breast cancer with biopsy proven lymph node metastases. A randomised controlled trial. Int J Radiat Oncol Biol Phys. 1996;36(Suppl 1):277.

199. Freedman GM, Fowble BL, Nicolaou N, et al. Should internal mammary lymph nodes in breast cancer be a target for the radiation oncologist? Int J Radiat Oncol Biol Phys. 2000;46(4):805–814.

200. Veronesi U, Orecchia R, Zurrida S, et al. Avoiding axillary dissection in breast cancer surgery: a randomized trial to assess the role of axillary radiotherapy. Ann Oncol. 2005;16(3):383–388.

201. Musat E, Poortmans P, Van den Bogaert W, et al. Quality assurance in breast cancer: EORTC experiences in the phase III trial on irradiation of the internal mammary nodes. Eur J Cancer. 2007;43(4):718–724.

202. Arriagada R, Lê MG, Mouriesse H, et al. Long-term effect of internal mammary chain treatment: results of a multivariate analysis of 1195 patients with operable breast cancer and positive axillary nodes. Radiother Oncol. 1988(3):213–222.

203. Veronesi U, Arnone P, Veronesi P, et al. The value of radiotherapy on metastatic internal mammary nodes in breast cancer: results on a large series. Ann Oncol. 2008;19(9):1553–1560.

204. Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;365:1687–1717.

205. Levine MN, et al. Randomized trial comparing cyclophosphamide, epirubicin, and fluorouracil with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer: update of National Cancer Institute of Canada Clinical Trials Group Trial MA5. J Clin Oncol. 2005;23(22):5166–5170.

206. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet. 1998;352(9132):930–942.

207. Ejlertsen B, Mouridsen HT, Jensen MB, et al. Improved outcome from substituting methotrexate with epirubicin: results from a randomised comparison of CMF versus CEF in patients with primary breast cancer. Eur J Cancer. 2007;43:877–884. **Overall quality: +**

208. De Laurentiis M, Cancello G, D'Agostino D, et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: a meta-analysis of randomized trials. J Clin Oncol. 2008;26:44–53. **Overall quality: +**

209. Henderson I, Berry D, Demetri G. Improved outcomes from adding sequential paclitaxel but not from escalating doxorubicin dose in an adjuvant chemotherapy regimen for patients with node-positive primary breast cancer. J Clin Oncol. 2003;21(6):976–983.

210. National Institute for Clinical Excellence (NICE). Docetaxel for the adjuvant treatment of early node-positive breast cancer: NICE technology appraisal guidance 109. London: National Institute for Clinical Excellence; 2006. **Overall quality: +**

211. Martin M, Pienkowski T, Mackey J. Adjuvant docetaxel for node positive breast cancer. N Engl J Med. 2005;352(22):2302–2313.

212. Trudeau M, Eisen A, Messersmith H, et al. Adjuvant taxane therapy for women with early-stage invasive breast cancer: a clinical practice guideline. Toronto, ON: Cancer Care Ontario; 2007. **Overall quality: +**

213. Ferguson T, Wilcken N, Vagg R, et al. Taxanes for adjuvant treatment of early breast cancer. Cochrane Database Syst Rev. 2007(4):CD004421. **Overall quality: +**

214. Bria E, Nistico C, Cuppone F, et al. Benefit of taxanes as adjuvant chemotherapy for early breast cancer: pooled analysis of 15,500 patients. Cancer. 2006;106(11):2337–2344. **Overall quality: +**

215. Estevez LG, Munoz M, Alvarez I, et al. Evidence-based use of taxanes in the adjuvant setting of breast cancer: a review of randomized phase III trials. Cancer Treat Rev. 2007;33(5):474–483. **Overall quality: +**

216. Ward S, Simpson E, Davis S, et al. Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation. Health Technology Assessment. 2007;11(40):1–144. **Overall quality: +**

217. Ward SE, Pilgrim H, Hind D. Trastuzumab for the treatment of primary breast cancer in HER2 positive women: a single technology appraisal. Sheffield: University of Sheffield School of Health and Related Research; 2006. **Overall quality: +**

218. Goldstein L, O'Neill A, Sparano J. E2197: phase III AT vs AC in the adjuvant treatment of node positive and high risk node negative breast cancer. Proc Annu Meet Am Assoc Cancer Res. 2005;23(16 Suppl):Abstract 512.

219. Martin M, Lluch A, Segui MA, et al. Toxicity and health related quality of life (HRQoL) in node negative breast cancer (BC) patients (pts) receiving adjuvant treatment with TAC (docetaxel, doxorubicin, cyclophosphomide) or FAC (5-fluorouracil, doxorubicin, cyclophosphomide): impact of adding prophylactic growth factors (GF) to TAC. GEICAM study 9805. J Clin Oncol. 2005;23(16 Suppl):A604.

220. Gianni L, Baselga J, Eiermann W, et al. European Cooperative Trial in Operable Breast Cancer (ECTO): improved freedom from progression from adding paclitaxel to doxorubicin followed by cyclophospamide methotrexate and fluoroucil. Proc Annu Meet Am Assoc Cancer Res. 2005;23(16S):Abstract 513.

221. Kümmel S, Krocker J, Kohls A, et al. Randomised trial: survival benefit and safety of adjuvant dose-dense chemotherapy for node positive breast cancer. Br J Cancer. 2006;94:1237–1244.

222. Roche H, Fumoleau P, Spielmann M, et al. Sequential adjuvant epirubicin-based and docetaxel chemotherapy for node-positive breast cancer patients: the FNCLCC PACS 01 Trial. J Clin Oncol. 2006;24(36):5664–5671.

223. Jones SE, Savin MA, Holmes FA, et al. Phase III trial comparing doxorubicin plus cyclophosphamide with docetaxel plus cyclophosphamide as adjuvant therapy for operable breast cancer. J Clin Oncol. 2006;24(34):5381–5387.

224. Crown J, Francis P, DiLeo A. Docetaxel given concurrently with or sequentially to anthracycline-based adjuvant therapy for patients with node positive breast cancer, in comparison with non-taxane combination chemotherapy: first results of the BIG 2-98 trial at 5 years median follow-up. J Clin Oncol. 2006;24(18S):LBA519.

225. Bianco AR, De Matteis A, Manzione Aea. Sequential epirubicin-docetaxel-CMF as adjuvant therapy of early breast cancer: results of the Taxit 216 multicenter phase III trial. J Clin Oncol. 2006;24(18S):LBA520.

226. Mamounas E, Bryant J, Lembersky B, et al. Paclitaxel after doxorubicin plus cyclophosphamide as adjuvant chemotherapy for node-positive breast cancer: results from NSABP B-28. J Clin Oncol. 2005;23(16):3686–3696.

227. Fountzilas G, Skarlos D, Dafni U. Postoperative dose-dense sequential chemotherapy with epirubicin, followed by CMF with or without paclitaxel, in patients with high risk operable breast cancer. Oncology. 2005;16:1762–1771.

228. Martin M, Rodriguez-Lescure A, Ruiz A. Multicentre, randomized phase III study of adjuvant chemotherapy for node positive breast cancer comparing 6 cycles of FEC(90) versus 4 cycles of FEC(90) followed by 8 weekly paclitaxel administrations: interim efficacy variables of Geicam 9906 Trial. *28th Annual San Antonio Breast Cancer Symposium*. San Antonio (TX) 2005:Abstract 39.

229. Buzdar AU, Singleton SE, Valero V, et al. Evaluation of paclitaxel in adjuvant chemotherapy for patients with operable breast cancer: preliminary data of a prospective randomised trial. Clin Cancer Res. 2002;8(5):1073–1079.

230. Yeon CH, Pegram MD. Anti-erbB-2 antibody trastuzumab in the treatment of HER2-amplified breast cancer. Invest New Drugs. 2005;23(5):391–409.

231. Dybdal N, Leiberman G, Anderson S, McCune B, Bajamonde A, Cohen RL et al. Determination of HER2 gene amplification by fluorescence in situ hybridization and concordance with the clinical trials immunohistochemical assay in women with metastatic breast cancer evaluated for treatment with trastuzumab. Breast Cancer Res Treat. 2005;93(1):3–11.

232. Wolff AC, Hammond MEH, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. J Clin Oncol. 2007;25(1):118–145.

233. Francis GD, Dimech MK, Giles L, et al. Frequency and reliability of oestrogen receptor, progesterone receptor and HER2 in breast carcinoma determined by immunohistochemistry in Australasia: results of the RCPA Quality Assurance Program. J Clin Pathol. 2007;60:1277–1283.

234. National Institute for Clinical Excellence (NICE). Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer. NICE technology appraisal guidance 107. London: National Institute for Clinical Excellence; 2006.

235. Trudeau M, Madarnas Y, McCready D, et al. The role of trastuzumab in adjuvant and neoadjuvant therapy in women with HER2/*neu*-overexpressing breast cancer: a clinical practice guideline. Toronto, ON: Cancer Care Ontario; 2007. **Overall quality: + +**

236. National Breast Cancer Centre. Trastuzumab for HER2-positive breast cancer: a systematic review. Camperdown, NSW: National Breast Cancer Centre; 2007.

237. Huybrechts M, Hulstaert F, Neyt M, et al. Trastuzumab in early stage breast cancer. Brussels: Belgian Health Care Knowledge Centre (KCE); 2006. **Overall quality: +**

238. Romond E, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. N Engl J Med. 2005;353(16):1673–1684.

239. Piccart-Gebhart M, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med. 2005 353(16):1659–1672.

240. Smith I, Procter M, D Gelber R, et al. 2-year follow-up of trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer: a randomised controlled trial. Lancet. 2007;369(9555):29–36. **Overall quality: +**

241. Joensuu H, Kellokumpu-Lehtinen P, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. N Engl J Med. 2006;354(8):809–820.

242. Slamon D, Eiermann W, Pienkowski T, et al. Phase III randomized trial comparing doxorubicin and cyclophosphamide followed by docetaxell (AC->T) with doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab (AC->TH) with docetaxel, carboplatin and trastuzumab (TCH) in HER2 positive early breast cancer patients (BCIRG 006 study). 2006 1 June 2009 [cited 1 June 2009]; Available from: http://www.bcirg.org/

243. Viani GA, Afonso SL, Stefano EJ, et al. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. BMC Cancer. 2007;7(153). **Overall quality: +**

244. Bria E, Cuppone F, Fornier M, et al. Cardiotoxicity and incidence of brain metastases after adjuvant trastuzumab for early breast cancer: the dark side of the moon? A meta-analysis of the randomized trials. Breast Cancer Res Treat. 2008;109(231–239).

245. Perez E, Romond EH, Suman VJ, et al. Updated results of the combined analysis of NCCTG N9831 and NSABP B-31 adjuvant chemotherapy with/without trastuzumab in patients with HER2 positive breast cancer. Proc Annu Meet Am Assoc Cancer Res. 2007;25(18S):Abstract 512.

246. Buzdar AU, Valero V, Ibrahim NK, et al. Neoadjuvant therapy with paclitaxel followed by 5-fluorouracil, epirubicin, and cyclophosphamide chemotherapy and concurrent trastuzumab in human epidermal growth factor receptor 2-positive operable breast cancer: an update of the initial randomized study population and data of additional patients treated with the same regimen. Clin Cancer Res. 2007;13(1):228–233. **Overall quality: -**

247. Sledge G, O'Neill A, Thor A, et al. Adjuvant trastuzumab: long term results of E2198. *29th Annual San Antonio Breast Cancer Symposium*. San Antonio (TX) 2006:Abstract 2075.

248. Spielmann M, Roche H, Humblet Y, et al. 3-year follow-up of trastuzumab following adjuvant chemotherapy in node positive breast cancer patients: results of the PACS-04 trial. Breast Cancer Res Treat. 2007;106(Suppl 1):S19, A-72.

249. Madarnas Y, Trudeau M, Franek J, et al. Adjuvant/neoadjuvant trastuzumab therapy in women with HER-2/neu- overexpressing breast cancer: a systematic review. Cancer Treat Rev. 2008;34:539–557.

250. Bird B, Swain S. Cardiac toxicity in breast cancer survivors: review of potential cardiac problems. Clin Cancer Res. 2008;14:14–24.

251. Joensuu H, Isola J, Lundin M, et al. Amplification of erbB2 and erbB2 expression are superior to estrogen receptor status as risk factors for distant recurrence in pT1N0M0 breast cancer: a nationwide population-based study. Clin Cancer Res. 2003; 9:923–930.

252. Spielmann M, Roché H, Humblet Y. 3-year follow-up of trastuzumab following adjuvant chemotherapy in node positive HER-2-positive breast cancer patients: results of the PACS-04 trial. 30th Annual San Antonio Breast Cancer Symposium; 2007 December 13–16; San Antonio (TX); 2007.

253. Spielmann M, Roché H, Humblet Y. Trastuzumab following adjuvant chemotherapy in node positive, HER-2-positive breast cancer patients: 4-year follow-up results of the PACS-04 trial. *30th Annual San Antonio Breast Cancer Symposium*. San Antonio (TX) 2007.

254. Mieog J, van der Hage J, van der Velde C. Preoperative chemotherapy for women with operable breast cancer. Cochrane Database Syst Rev. 2007(2):CD005002. **Overall quality: +**

255. Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of national surgical adjuvant breast and bowel project protocols B-18 and B-27. J Clin Oncol. 2008;26(5):778–785. **Overall quality: +**

256. van Nes JG, Putter H, Julien JP, et al. Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up: clinical and translational results from the EORTC trial 10902. Breast Cancer Res Treat. 2008;115(1):101–113. **Overall quality: +**

257. Boughey JC, Peintinger F, Meric-Bernstam F, et al. Impact of preoperative versus postoperative chemotherapy on the extent and number of surgical procedures in patients treated in randomized clinical trials for breast cancer. Ann Surg. 2006;244(3):464–469. **Overall quality: +**

258. Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001(30):96–102.

259. Allred DC, Clark GM, Elledge R, et al. Association of p53 protein expression with tumor cell proliferation rate and clinical outcome in node-negative breast cancer. J Natl Cancer Inst. 1993;85(3):200–206.

260. Harvey JM, G.M. C, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol. 1999 17:1474–1481.

261. Gown A. Current Issues in ER and HER2 testing by IHC in breast cancer. Mod Pathol. 2008;21:S8–S15.

262. Kurosumi M. Immunohistochemical assessment of hormone receptor status using a new scoring system (J-Score) in breast cancer. Breast Cancer. 2007;14(2):189–193. **Overall quality: -**

263. Dowsett M, Allred C, Knox J, et al. Relationship between quantitative estrogen and progesterone receptor expression and human epidermal growth factor receptor 2 (HER-2) status with recurrence in the arimidex, tamoxifen, alone or in combination trial. J Clin Oncol. 2008;26(7):1059–1065. **Overall quality: +**

264. National Health Service Breast Screening Programme. NHSBSP guidelines for pathology reporting in breast disease. London: Cancer Screening Programme; 2005.

265. Fisher ER, Anderson S, Dean S, et al. Solving the dilemma of the immunohistochemical and other methods used for scoring estrogen receptor and progesterone receptor in patients with invasive breast carcinoma. Cancer 2004;103(1):164–173.

266. National Institute for Clinical Excellence (NICE). Hormonal therapies for the adjuvant treatment of early oestrogen receptor positive breast cancer. London: National Institute for Clinical Excellence; 2006.

267. Hind D, Wyld L, Beverley CB, et al. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). Cochrane Database Syst Rev. 2006(1):CD004272.

268. Early Breast Cancer Trialists' Collaborative Group, Clarke M, Coates AS, et al. Adjuvant chemotherapy in oestrogen-receptor-poor breast cancer: patient-level meta-analysis of randomised trials. Lancet. 2008;371(9606):29–40. **Overall quality: +**

269. Early Breast Cancer Overview Group. Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials. Lancet. 2007;369:1711–1723. **Overall quality: +**

270. Poole R, Paridaens R. The use of third-generation aromatase inhibitors and tamoxifen in the adjuvant treatment of postmenopausal patients with hormone-dependent breast cancer: evidence based review. Curr Opin Oncol. 2007;19(6):564–572. **Overall quality: +**

271. Morales L, Canney P, Dyczka J, et al. Postoperative adjuvant chemotherapy followed by adjuvant tamoxifen versus nil for patients with operable breast cancer: a randomised phase III trial of the European Organisation for Research and Treatment of Cancer Breast Group. Eur J Cancer. 2007;43(2):331–340. **Overall quality: +**

272. Gordon NH, Silverman P, Lasheen W, et al. Thirty-year follow-up of chemo/hormonal therapy in node-positive breast cancer. Breast Cancer Res Treat. 2007;102(3):301–312. **Overall quality: +**

273. Bernhard J, Zahrieh D, Castiglione-Gertsch M, et al. Adjuvant chemotherapy followed by goserelin compared with either modality alone: the impact on amenorrhea, hot flashes, and quality of life in premenopausal patients: the International Breast Cancer Study Group trial VIII. J Clin Oncol. 2007;25(3):263–270. **Overall quality: +**

274. Kaufmann M, Graf E, Jonat W, et al. A randomised trial of goserelin versus control after adjuvant, risk-adapted chemotherapy in premenopausal patients with primary breast cancer: GABG-IV B-93. Eur J Cancer. 2007;43(16):2351–2358. **Overall quality: +**

275. Goldhirsch A, Gelber RD, Yothers G, et al. Adjuvant therapy for very young women with breast cancer: need for tailored treatment. JNCI Monographs. 2001;30:44–51.

276. Love RR, Duc NB, Allred DC, et al. Oophorectomy and tamoxifen adjuvant therapy in premenopausal Vietnemese and Chinese women with operable breast cancer. J Clin Oncol. 2002;20:2559–2566.

277. Krop I, Winer E. Ovarian suppression for breast cancer: an effective treatment in search of a home. J Clin Oncol. 2005;23:5869–5872.

278. Gelber RD, Cole BF. Adjuvant chemotherapy plus tamoxifen compared with tamoxifen alone for post-menopausal breast cancer: meta-analysis of quality adjusted survival. Lancet. 1996;347(9008):1066–1071.

279. Adjuvant Breast Cancer Trials Collaborative Group. Ovarian ablation or suppression in premenopausal early breast cancer: results from the international adjuvant breast cancer ovarian ablation or suppression randomized trial. J Natl Cancer Inst. 2007;99(7):516–525.

280. Thurlimann B, Price KN, Gelber RD, et al. Is chemotherapy necessary for premenopausal women with lower-risk node-positive, endocrine responsive breast cancer? 10-year update of International Breast Cancer Study Group Trial 11-93. Breast Cancer Res Treat. 2008;113(1137–44). **Overall quality: -**

281. Namer M, Fargeot P, Roche H, et al. Improved disease-free survival with epirubicin-based chemoendocrine adjuvant therapy compared with tamoxifen alone in one to three node-positive, estrogen-receptor-positive, postmenopausal breast cancer patients: results of French Adjuvant Study Group 02 and 07 trials. Ann Oncol. 2006;17(1):65–73. **Overall quality: +**

282. Viale G, Regan MM, Maiorano E, et al. Chemoendocrine compared with endocrine adjuvant therapies for node-negative breast cancer: predictive value of centrally reviewed expression of estrogen and progesterone receptors – International Breast Cancer Study Group. J Clin Oncol. 2008;26(9):1404–1410. **Overall quality: +**

283. Albain K, Barlow W, O'Malley F, et al. Concurrent versus sequential chemohormonal therapy versus T alone for postmenopausal, node – positive, estrogen and/or progesterone receptor-positive breast cancer: mature outcomes and new biological correlates on Phase III intergroup trial 0100. *San Antonio Breast Cancer Symposium*. San Antonio (TX) 2004 Dec 8–11:Abstract 37.

284. Aebi S. Chemotherapy: overview and future perspectives. Breast. 2006;15(Suppl. 2):S11–S14. **Overall quality: +**

285. Cancer Care Ontario. Adjuvant systemic therapy for node negative breast cancer. Toronto, ON: Cancer Care Ontario; 2002.

286. Kaufmann M, Jonat W, Blamey R, et al. Survival analyses from the ZEBRA study: goserelin (zoladex) versus CMF in premenopausal women with node negative breast cancer. Eur J Cancer. 2003;39(12):1711–1717.

287. Sharma R, Beith J, Hamilton A. Systematic review of LHRH agonists for the adjuvant treatment of early breast cancer. Breast. 2005;14(3):181–191.

288. Davidson NE, O'Neill A, Vukov A, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). J Clin Oncol. 2005;23(25):5973–5982.

289. Baum M, Hackshaw A, Houghton J, et al. Adjuvant goserelin in pre-menopausal patients with early breast cancer: results from the ZIPP study. Eur J Cancer. 2006;42(7):895–904. **Overall quality: +**

290. Jakesz R, Samonigg H, Greil R, et al. Extended adjuvant treatment with anastrozole: results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). J Clin Oncol. 2005; 23(16S):527.

291. Eisen A, Trudeau M, Shelley W, et al. Aromatase inhibitors in adjuvant therapy for hormone receptor positive breast cancer: a systematic review. Cancer Treat Rev. 2007;34(2):157–174. **Overall quality: + +**

292. Jonat W, Gnant M, Boccardo F, et al. Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis. Lancet Oncol. 2006;7(12):991–996. **Overall quality: +**

293. Forbes J, Cuzick J, Buzdar AU, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100 month analysis of the ATAC trial. Lancet Oncol. 2008;9(1):45–53.

294. Howell A, Cuzick J, Baum M, et al. Results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet. 2005;365(9453):60–62. **Overall quality: +**

295. Rasmussen BB, Regan MM, Lykkesfeldt AE, et al. Adjuvant letrozole versus tamoxifen according to centrally-assessed ERBB2 status for postmenopausal women with endocrine-responsive early breast cancer: supplementary results from the BIG 1-98 randomised trial. Lancet Oncol. 2008;9(1):23–28. **Overall quality: +**

296. Crivellari D, Sun Z, Coates AS, et al. Letrozole compared with tamoxifen for elderly patients with endocrine-responsive early breast cancer: the BIG 1-98 Trial. J Clin Oncol. 2008. **Overall quality: +**

297. Ingle JN, Tu D, Pater JL, et al. Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17 Ann Oncol. 2008;19(5):877–882. **Overall quality: +**

298. Muss HB, Tu D, Ingle JN, et al. Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG Intergroup Trial MA.17. J Clin Oncol. 2008;26(12):1956–1964. **Overall quality: +**

299. Boccardo F, Rubagotti A, Aldrighetti D, et al. Switching to an aromatase inhibitor provides mortality benefit in early breast carcinoma: pooled analysis of 2 consecutive trials. Cancer. 2007;109(6):1060–1067. **Overall quality: +**

300. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. Lancet. 2007;369(9561):559–570.

301. Ingle J, Dowsett M, Cuzick J, et al. Aromatase inhibitors versus tamoxifen as adjuvant therapy for postmenopausal women with estrogen receptor positive breast cancer: meta-analysis of randomized trials of monotherapy and switching strategies. *31st Annual San Antonio Breast Cancer Symposium*. San Antonio (TX) 2008:Abstract 12.

302. Coates AS, Keshaviah A, Thurlimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine responsive early breast cancer: update of study BIG 1-98. J Clin Oncol. 2007;25(5):486–492.

303. Thurlimann B. Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer: first results of IBCSG 18-98/ BIG 1-98. Early Breast Cancer 9th International Conference; 2005 26th–29th January; St Gallen, Switzerland; 2005.

304. Coombes R, Hall E, Gibson L, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081–1092.

305. Coleman RE, Banks LM, Girgis SI, et al. Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study. Lancet Oncol. 2007;8(2):119–127.

306. Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. N Engl J Med. 2003;349(19):1793–1802.

307. Goss PE, Ingle JN, Martino S, et al. Randomised trial of letrozole following tamoxifen as extended adjuvant therapy in receptor positive breast cancer: updated findings from NCIC CTG MA.17. J Natl Cancer Inst. 2005;97(17):1262–1271.

308. Mouridsen H, Giobbie-Hurder A, Mauriac L, et al. Big 1-98 Collaborative and the International Breast Cancer Study Group. *31st Annual San Antonio Breast Cancer Symposium*. San Antonio (TX) 2008:Abstract 13.

309. Rogers M, Watts D, Russell R. Overview of bisphosphonates. Cancer. 1997;80(8):1652–1660.

310. Russell R, Rogers MJ. Bisphosphonates: from the laboratory to the clinic and back again. Bone. 1999;25(1):97–106.

311. Woodward J, Coleman R, Holen I. Preclinical evidence for the effect of bisphosphonates and cytotoxic drugs on tumour cell invasion. Anticancer Drugs. 2005;16:11–19.

312. Body JJ, Bartl R, Burkhardt P, et al. Current use of bisphosphonates in oncology. J Clin Oncol. 1998;16(12):3890–3899.

313. Bloomfield DJ. Should bisphosphonates be part of the standard therapy of patients with multiple myeloma or bone metastases from other cancers? An evidence-based review. J Clin Oncol. 1998;16(3):1218–1225.

314. Warr D, Johnston M, Breast Cancer Disease Site Group. Use of bisphosphonates in women with breast cancer. (Practice guideline report No. 1–11. Version 2.2002). Toronto, ON: Cancer Care Ontario; 2004. **Overall quality: + +/-**

315. Powles T, Paterson S, Kanis J, et al. Randomized, placebo-controlled trial of clodronate in patients with primary operable breast cancer. J Clin Oncol. 2002;20:3219–3224.

316. Pavlakis N, Schmidt R, Stockler M. Bisphosphonates for breast cancer. Cochrane Database Syst Rev. 2005(3):CD003474.

317. Saarto T, Blomqvist C, Virkkunen P, et al. Adjuvant clodronate treatment does not reduce the frequency of skeletal metastases in node-positive breast cancer patients: 5-year results of a randomised controlled trial. J Clin Oncol. 2001;19(1):10–17.

318. Diel I, Solomayer E, Gollan C, et al. Bisphosphonates in the reduction of breast cancer: results of the extended follow-up of the first study population. Proceedings of the American Society of Clinical Oncology. 2000;19:82a.

319. Ha T, Li H. Meta-analysis of clodronate and breast cancer survival. Br J Cancer. 2007;96(12):1796–1801. **Overall quality: + +/-**

320. Powles TJ. Prevention of breast cancer using selective oestrogen receptor modulators (SERMs). Breast Cancer Res. 2006;8(5)(111). **Overall quality: + +**

321. Kristensen B, Ejlerrtsen B, Mouridsen H, et al. Bisphosphonate treatment in primary breast cancer: results from a randomised comparison of oral pamidronate versus no pamidronate in patients with primary breast cancer. Acta Oncologica. 2008;47:740–746. **Overall quality: +**

322. Reid D, Doughty J, Eastell R, et al. Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. Cancer Treat Rev. 2008;34:S3–S18. **Overall quality: +**

323. Greenspan S, Brufsky A, Lembersky B, et al. Risedronate prevents bone loss in breast cancer survivors: a 2-year, randomized, double-blind, placebo-controlled clinical trial. J Clin Oncol. 2008;26(16):2644–2652. **Overall quality: + +**

324. Brufsky A, Bundred N, Coleman R, et al. Integrated analysis of zoledronic acid for prevention of aromatase inhibitor-associated bone loss in postmenopausal women with early breast cancer receiving adjuvant letrozole. The Oncologist. 2008;13:503–514. **Overall quality: + +**

325. Gnant MF, Mlineritsch B, Luschin-Ebengreuth G, et al. Zoledronic acid prevents cancer treatment-induced bone loss in premenopausal women receiving adjuvant endocrine therapy for hormone-responsive breast cancer: a report from the Austrian Breast and Colorectal Cancer Study Group. J Clin Oncol. 2007;25(7):820–828. **Overall quality: +**

326. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet. 1991;338(8763):327–331.

327. FNCLCC. Standards, options and recommendations for the management of ductal carcinoma in situ of the breast (DCIS): update 2004. Paris: Federation of French Cancer Centres (FNCLCC) 2004.

328. Boyages J, Recht A, Connolly J, et al. Early breast cancer: predictors of breast recurrence for patients treated with conservative surgery and radiation therapy. Radiother Oncol. 1990;19(1):29–41.

329. Fisher E, Anderson S, Tan-Chiu E. Fifteen-year prognostic discriminants for invasive breast carcinoma: National Surgical Adjuvant Breast and Bowel Project Protocol-06. Cancer. 2001; Apr 15;91(8 Suppl):1679–1687.

330. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853: a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol. 2006;24(21):3381–3387.

331. Houghton J, George WD, Cuzick J, et al. Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: randomised controlled trial. Lancet. 2003;362(9378):95–102.

332. Emdin SO, Granstrand B, Ringberg A, et al. SweDCIS: radiotherapy after sector resection for ductal carcinoma in situ of the breast. Results of a randomised trial in a population offered mammography screening. Acta Oncologica. 2006;45(5):536–543.

333. Morrow M, O'Sullivan MJ. The dilemma of DCIS. Breast. 2007;16(2 Suppl):59–62.

334. Silverstein M, Lagios M, Groshen S. The influence of margin width on local control of ductal carcinoma in situ of the breast. N Engl J Med. 1999;340(19):1455–1461.

335. Sneige N, Wang J, Baker BA, et al. Clinical histopathologic, and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in-situ of the breast: a report of 24 cases. Mod Pathol. 2002;15:1044–1050.

336. Shelley W, McCready D, Holloway C. Management of ductal carcinoma in situ of the breast: a clinical practice guideline. Toronto, ON: Cancer Care Ontario; 2006. **Overall quality: +**

337. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol. 1998;16(2):441–452.

338. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. Lancet. 2000;355(9203):528–533.

339. Viani GA, Stefano EJ, Afonso SL, et al. Breast-conserving surgery with or without radiotherapy in women with ductal carcinoma in situ: a meta-analysis of randomized trials. Radiat Oncol. 2007;2:28. **Overall quality: +**

340. Khatcheressian J, Wolff A, Smith T, et al. American Society of Clinical Oncology 2006: update of the breast cancer follow-up and management in the adjuvant setting. J Clin Oncol. 2006;24(31):5091–5097. **Overall quality: +**

341. Kricker A, Hunt J, Smith C. Second primary breast cancer. Woolloomooloo (NSW): NHMRC National Breast Cancer Centre; 1997.

342. Palli D, Russo A, Saieva C, et al. Intensive vs clinical follow-up after treatment of primary breast cancer: 10-year update of a randomized trial. National Research Council Project on Breast Cancer Follow-up. JAMA. 1999;281(17):1586.

343. GIVIO Investigators. Impact of follow-up testing on survival and health related quality of life in breast cancer patients: a multicenter randomized controlled trial. JAMA. 1994;271:1587–1592.

344. Grunfeld E, Noorani H, McGahan L, et al. Surveillance mammography after treatment of primary breast cancer: a systematic review. Breast 2002;11(3):228–235.

345. Barnsley GP, Grunfeld E, Coyle D, et al. Surveillance mammography following the treatment of primary breast cancer with breast reconstruction: a systematic review. Plast Reconstr Surg. 2006;120(5):1125–1132. **Overall quality: +/-**

346. Rojas M, Telaro E, Russo A, et al. Follow-up strategies for women treated for early breast cancer. Cochrane Database Syst Rev. 2000(4):CD001768. **Overall quality: + +**

347. Lu WL, Jansen L, Post WJ, et al. Impact on survival of early detection of isolated breast recurrences after the primary treatment for breast cancer: a meta-analysis. Breast Cancer Res Treat. 2008. **Overall quality: + +/-**

348. Paszat L, Sutradhar R, Grunfeld E, et al. Outcomes of surveillance mammography after treatment of primary breast cancer: a population-based case series. Breast Cancer Res Treat. 2008. **Overall quality: +/-**

349. Montgomery DA, Krupa K, Cooke TG. Alternative methods of follow up in breast cancer: a systematic review of the literature. Br J Cancer. 2007;96(11):1625–1632. **Overall quality: + +/-**

350. Nissen MJ, Beran MS, Lee MW, et al. Views of primary care providers on follow-up care of cancer patients. Fam Med. 2007;39(7):477–482. **Overall quality: +/-**

351. Miki Y, Swenson J, Shattuck-Eidens D, et al. A strong candidate for the breast and ovarian cancer susceptibility gene, BRCA1. Science 1994;378:66–71.

352. Wooster R, Bignell G, Lancaster J. Identification of the breast cancer gene BRCA2. Nature. 1995;378:789–791.

353. Petrij-Bosch A, Peelen T, van Vliet M, et al. BRCA1 genomic deletions are major founder mutations in Dutch breast cancer patients. Nat Genet. 1997;17(3):341–345.

354. Roa B, Boyd AA, Volcik K, et al. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. Nat Genet. 1996;14(2):185–187.

355. Easton DF, Deffenbaugh AM, Pruss D, et al. A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the BRCA1 and BRCA2 breast cancer-predisposition genes. Am J Hum Genet. 2007;81(5):873–883.

356. Tranchemontagne J, Boothroyd L, Blancquaert I. Contribution of BRCA1/2 mutation testing to risk assessment for susceptibility to breast and ovarian cancer. Montreal: Agence d'évaluation des technologies et des modes d'intervention en santé (AETMIS) 2006.

357. Parmigiani G, Berry D, Aguilar O. Determining carrier probabilities for breast cancer-susceptibility genes BRCA1 and BRCA2. Am J Hum Genet. 1998;62(1):145–158.

358. Domchek SM, Eisen A, Calzone K, et al. Application of breast cancer risk prediction models in clinical practice. J Clin Oncol. 2003;21(4):593–601.

359. Antoniou AC, Hardy R, Walker L. Predicting the likelihood of carrying a BRCA1 or BRCA2 mutation: validation of BOADICEA, BRCAPRO, IBIS, Myriad and the Manchester scoring system using data from UK clinics. J Med Genet. 2008;45(7):425–431.

360. Hopper JL, Dowty JG, Apicella C, et al. Towards more effective and equitable genetic testing for BRCA1 and BRCA2 mutation carriers. J Med Genet. 2008;45(7):409–410.

361. Stopfer JE. Genetic counseling and clinical cancer genetics services. Semin Surg Oncol. 2000;18(4):347–357.

362. Honrado E, Benitez J, Palacios J. Histopathology of BRCA1- and BRCA2-associated breast cancer. Crit Rev Oncol Hematol. 2006;59(1):27–39.

363. Hogg R, Friedlander M. Biology of epithelial ovarian cancer: implications for screening women at high genetic risk. J Clin Oncol. 2004;22(7):1315–1327.

364. Domchek S, Friebel TM, Neuhausen SL, et al. Mortality after bilateral salpingo-oophorectomy in BRCA1 and BRCA2 mutation carriers: a prospective cohort study. Lancet Oncol. 2006;7(3):223–229. **Overall quality: +/~**

365. Calderon-Margalit R, Paltiel O. Prevention of breast cancer in women who carry BRCA1 or BRCA2 mutations: a critical review of the literature. Int J Cancer. 2004;112(3):357–364.

366. Lostumbo L, Carbine N, Wallace J, et al. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst Rev. 2004(4):CD002748.

367. Bermejo-Perez MJ, Marquez-Calderon S, Llanos-Mendez A. Effectiveness of preventive interventions in BRCA1/2 gene mutation carriers: a systematic review. Int J Cancer. 2007;121(2):225–231.

368. Narod SA, Brunet JS, Ghadirian P, et al. Tamoxifen and risk of contralateral breast cancer in BRCA1 and BRCA2 mutation carriers: a case-control study. Lancet. 2000;356(9245):1876–1881.

369. Cuzick J, et al,. Overview of the main outcomes in breast-cancer prevention trials. Lancet. 2003;361(9354):296–300.

370. Vogel VG, Costantino JP, Wickerham DL, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. JAMA. 2006;295(23):2727–2741.

371. Guerrieri-Gonzaga A, Robertson C, Bonanni B, et al. Preliminary results on safety and activity of a randomized, double-blind, 2 x 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in premenopausal women. J Clin Oncol. 2006;24(1):129–135.
372. Kauff ND, Domchek SM, Friebel TM, et al. Risk-reducing salpingo-oophorectomy for the prevention of BRCA1- and BRCA2-associated breast and gynecologic cancer: a multicenter, prospective study. J Clin Oncol. 2008;26(8):1331–1337.
373. van der Velde NM, Mourits MJ, Arts HJ, et al. Time to stop ovarian cancer screening in BRCA1/2 mutation carriers? Int J Cancer. 2009;124(4):919–923.
374. Evans DG, Baildam AD, Anderson E, et al. Risk reducing mastectomy: outcomes in 10 European centres. J Med Genet. 2009;46(4):254–258.
375. Navrozoglou I, Vrekoussis T, Kontostolis E, et al. Breast cancer during pregnancy: a mini-review. Eur J Surg Oncol. 2008;34(8):837–843.
376. Society of Obstetricians and Gynaecologists of Canada. Breast cancer, pregnancy and breastfeeding. J Obstet Gynaecol Can. 2002;111:1–8.
377. Loibl S, von Minckwitz G, Gwyn K, et al. Breast carcinoma during pregnancy: international recommendations from an expert meeting. Cancer. 2005;106(2):237–246.
378. Ministry of Health. Guidelines for the use of human tissue for future unspecified research purposes. Wellington: Ministry of Health 2007.
379. AGREE Collaboration. The appraisal of guidelines for research and evaluation (AGREE) instrument. London: The AGREE Research Trust 2001.
380. Whiting P, Rutjes A, Reitsma J, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;Nov 10(3):25.
381. Scottish Intercollegiate Guidelines Network (SIGN). SIGN 50. A guideline developer's handbook. Edinburgh: Scottish Intercollegiate Guidelines Network (SIGN) 2008.

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