



CLINICAL PRACTICE GUIDELINES

# Management of advanced breast cancer

# **Clinical practice guidelines for the management of advanced breast cancer**

**Prepared by the iSource National Breast Cancer Centre  
Advanced Breast Cancer Working Group**

**Endorsed January 2001**

**NHMRC**

**National Health and Medical Research Council**

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- providing evidence based advice;
- applying research evidence to health issues thus translating research into better health practice and outcomes; and
- promoting informed debate on health and medical research, health ethics and related issues.

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This document was prepared by the iSource National Breast Cancer Centre Advanced Breast Cancer Working Group.

The current *Clinical practice guidelines for the management of advanced breast cancer* has been endorsed without inclusion of a comparative economic analysis of the costs associated with their implementation. It is the understanding of the NHMRC that an up-to-date economic analysis will be included when the *Clinical practice guidelines of the management of advanced breast cancer* are next updated.

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## CONTENTS

<b>Foreword</b>	<b>v</b>
<b>List of tables</b>	<b>vi</b>
<b>List of figures</b>	<b>vi</b>
<b>List of abbreviations</b>	<b>vii</b>
<b>Introduction</b>	<b>1</b>
<b>Summary of guidelines</b>	<b>5</b>
<b>1 Breast cancer in Australia</b>	<b>13</b>
<b>2 The impact of advanced breast cancer</b>	<b>21</b>
2.1 Quality of life and psychosocial issues	21
2.2 The impact on the family	24
2.3 The impact on children	27
2.4 The impact on health care professionals	27
2.5 Economic impact	28
<b>3 General principles</b>	<b>31</b>
3.1 The goals of management	31
3.2 Assessment	31
3.3 Multidisciplinary care	36
3.4 Telling a woman she has advanced breast cancer	39
3.5 Clinical trials	42
3.6 Alternative and complementary therapies	44
3.7 Palliative care	48
3.8 Bereavement support	51
3.9 Request for an autopsy	54
<b>4 The management of locally advanced disease</b>	<b>57</b>
<b>5 The management of locoregional recurrence</b>	<b>61</b>
<b>6 The management of metastatic breast cancer</b>	<b>67</b>

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<b>7</b>	<b>Special problems of advanced breast cancer</b>	<b>83</b>
<b>8</b>	<b>Interventions to improve quality of life</b>	<b>103</b>
<b>9</b>	<b>Management of symptoms</b>	<b>107</b>
<b>10</b>	<b>Management of pain</b>	<b>113</b>
<b>11</b>	<b>Supportive treatments</b>	<b>119</b>
	11.1 Supportive drug treatments	119
	11.2 Other supportive approaches	122
<b>Appendices</b>		
A	NBCC Advanced Breast Cancer Working Group — Terms of Reference and membership	125
B	Guideline development process	131
C	Quality of life assessment	143
D	Questions you may be asked	147
E	TNM classification system	153
F	Types of clinical trials	155
G	Australian Medical Association Code of Ethics	159
H	Breast cancer support services	165
I	Palliative care resources	169
J	National Breast Cancer Centre publications list	171
	<b>Glossary</b>	<b>175</b>
	<b>References by subject</b>	<b>189</b>
	<b>Reference list</b>	<b>191</b>

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## FOREWORD

Advanced breast cancer includes both locally advanced and metastatic breast cancer.

The *Clinical practice guidelines for the management of advanced breast cancer* have been developed by a multidisciplinary working party, with cooperation from a range of special contributors. The guidelines are primarily intended for use by all health professionals involved in the management of women with advanced breast cancer. The working party has been rigorous in seeking the best available evidence, including research published up to mid-2000. It has also provided material that will be helpful and supportive to those managing the difficult range of problems that may present in advanced breast cancer.

Soon after the project began it was clear that there was a greater range of issues to be considered than had been expected. Typically, breast cancer has a longer history than many other common cancers and often takes the form of a chronic illness. While recognising that there is a clear need for high level professional skills in diagnosis and management, careful attention should also be given to a patient's emotions, psycho-social interrelationships and general wellbeing.

Taking these matters into consideration, in the working party's view, it became important to equate the importance of psychosocial, clinical and quality of life matters. This more encompassing approach is reflected in the arrangement of the material presented here with the aim of facilitating care management. It needs to be emphasised that this approach in no way plays down the clinical needs and directions of care for the patient, but should help to address areas in which patients feel they need a larger measure of understanding and support.

To reiterate, it is clear that the greatest need is to develop a process of caring support when a woman is diagnosed with advanced breast cancer, and to outline the patterns of care available to her in the widest sense in a clear and compassionate manner over an appropriate period of time.

Emeritus Professor Tom Reeve  
Chair  
National Breast Cancer Centre  
Advanced Breast Cancer Working Group

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## LIST OF TABLES

1	Breast cancer incidence and mortality rates for Australian women 1987–92	13
2	Degree of spread of breast cancer at first diagnosis based on figures for NSW 1988–91	15
3	Pattern of first relapse in 438 women treated for early breast cancer at Westmead Hospital and 512 women treated at the Queensland Radium Institute	16
4	Potentially dangerous alternative therapies in women with advanced breast cancer	47
5	Endocrine agents used in therapy of metastatic breast cancer	70
6	Standard chemotherapeutic regimens	77
7	Common chemotherapy drugs and their side effects	80
8	Common symptoms among women with advanced breast cancer	109
9	Common cancer pain treatment options	117
10	Characteristics of a desirable quality of life self-assessment tool	144
11	Cancer-specific quality of life assessment tools	145
12	Classification of clinical trials	156

## LIST OF FIGURES

1	Five-year relative survival (%) from breast cancer by spread of disease at diagnosis in NSW women, 1973–95	17
2	Flow chart of endocrine therapy for women with advanced breast cancer and hormone receptor positive tumours	73

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## LIST OF ABBREVIATIONS

<b>AIHW</b>	<b>Australian Institute of Health and Welfare</b>
<b>AMA</b>	<b>Australian Medical Association</b>
<b>CAT</b>	<b>computerised axial tomography; also referred to as CT</b>
<b>CMF</b>	<b>cyclophosphamide, methotrexate and 5-fluorouracil</b>
<b>CMF(P)</b>	<b>cyclophosphamide, methotrexate, 5-fluorouracil and prednisone</b>
<b>CNS</b>	<b>central nervous system</b>
<b>CSF</b>	<b>colony stimulating factor</b>
<b>CT</b>	<b>computerised tomography</b>
<b>DCIS</b>	<b>ductal carcinoma in situ</b>
<b>ER</b>	<b>oestrogen receptor</b>
<b>FBC</b>	<b>full blood count</b>
<b>FNAB</b>	<b>fine needle aspiration biopsy</b>
<b>GP</b>	<b>general practitioner</b>
<b>HRT</b>	<b>hormone replacement therapy</b>
<b>LASA</b>	<b>linear analogue self-assessment</b>
<b>LFT</b>	<b>liver function test</b>
<b>LHRH</b>	<b>luteinising hormone releasing hormone</b>
<b>MMM</b>	<b>mitozantrone, methotrexate and mitomycin C</b>
<b>MRI</b>	<b>magnetic resonance imaging</b>
<b>NBCC</b>	<b>National Breast Cancer Centre</b>
<b>NHMRC</b>	<b>National Health and Medical Research Council</b>
<b>NSAID</b>	<b>nonsteroidal anti-inflammatory drug</b>
<b>NSW</b>	<b>New South Wales</b>
<b>Prn</b>	<b>as required</b>
<b>PS</b>	<b>performance status</b>

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<b>QCHOC</b>	<b>Quality of Care and Health Outcomes Committee</b>
<b>QOL</b>	<b>quality of life</b>
<b>RCT</b>	<b>randomised controlled trial</b>
<b>SCF</b>	<b>supraclavicular fossa</b>
<b>SNRI</b>	<b>selective noradrenergic re-uptake inhibitors</b>
<b>SSRI</b>	<b>selective serotonin re-uptake inhibitors</b>
<b>TCA</b>	<b>tricyclic antidepressant</b>
<b>TENS</b>	<b>transcutaneous electrical nerve stimulation</b>
<b>UICC</b>	<b>Union Internationale Contre le Cancer (International Union Against Cancer)</b>
<b>WHO</b>	<b>World Health Organization</b>

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## IMPORTANT NOTICE

**This document is a guide to appropriate practice, to be followed subject to the clinician's judgement in each case.**

**The guidelines are designed to provide information to assist decision-making and are based on the evidence available at time of publication. They are not meant to be prescriptive.**

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## INTRODUCTION

In 1996, the NHMRC National Breast Cancer Centre established a multidisciplinary working group to develop clinical practice guidelines for the management of advanced breast cancer.

The working group comprised representatives from breast surgery, radiology, pathology, psychiatry, consumers, medical oncology, radiation oncology, reconstructive surgery, palliative care, counselling and support staff, nursing, general practice, epidemiology, health services management, education and research. The members of the working group are listed in Appendix A.

Although men with advanced breast cancer represent one per cent of those diagnosed with breast cancer, these guidelines specifically relate to advanced breast cancer in women.

The *Clinical practice guidelines for the management of advanced breast cancer* aims to:

- assist the decision-making process by women with advanced breast cancer and their doctors;
- educate all involved in the care of women with advanced breast cancer;
- assess and assure the quality of care;
- improve care and reduce the risk of legal liability; and
- bring the issue of cost-effectiveness into the public arena.

It should be noted that this book refers to **advanced breast cancer**, which includes both locally advanced and metastatic breast cancer. **Locally advanced breast cancer** is defined by the presence of a tumour that has one of the following characteristics: 'peau d'orange', skin ulceration, or fixation to the underlying intercostal or serratus anterior muscles or bones of the chest wall or inflammatory carcinoma. This corresponds to stage III in the International Union Against Cancer (UICC) classification.<sup>1</sup> **Local recurrence** applies to recurrence after previous treatment and is an ill-defined term, usually based on clinical judgement. It relies on features such as the location, size and type of cancer found at follow-up. **Locoregional recurrence** applies where there is recurrence in the axilla following axillary treatment (radiotherapy or surgery), and/or in the internal mammary lymph nodes.

Breast cancer which has spread to distant sites is referred to as **metastatic breast cancer** and corresponds to stage IV in the UICC classification.

This book presents guidelines, and is not intended to be a textbook. Clinicians looking for further information on the biology and natural history of breast cancer should consult the relevant texts.

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The *Clinical practice guidelines for the management of advanced breast cancer* is written in such a way that readers can judge the strength of the evidence on which assertions are based.

The guidelines are based on the best available evidence. Most of the evidence cited in this document pertains to metastatic disease. However, Chapters 3 and 8–11 contain information which is also applicable to locally advanced breast cancer and local recurrence.

The process employed to develop the guidelines is described in Appendix B, including the purpose and scope of the guidelines and its intended audience.

These guidelines are not rigid procedural paths. They are inclusive, not prescriptive. They aim to provide information on which decisions can be made rather than dictating what those decisions should be.

The guidelines use a four-point rating system to identify the evidence base for key decision points. The rating system is recommended by the Quality of Care and Health Outcomes Committee (QCHOC) and has been adapted from the system developed by the US Preventive Services Task Force. The system is recommended by the NHMRC in the publication *Guidelines for the development and implementation of clinical practice guidelines*, AGPS 1995 and is as follows.

- Level I** Evidence is obtained from a systematic review of all relevant randomised controlled trials.
- Level II** Evidence is obtained from at least one properly designed randomised controlled trial.
- Level III** Evidence is obtained from well-designed controlled trials without randomisation; OR from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group; OR from multiple time series with or without the intervention.
- Level IV** This represents the opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.

Level I evidence represents the gold standard.

Level IV recommendations without accompanying references reflect expert opinion.

These guidelines highlight areas of knowledge, but also areas where knowledge is poor. They provide guidance for research. Subsequent to their release, the guidelines will be evaluated to determine their degree of use by practitioners and their effects on patient outcomes.

Clinical practice recommendations are boxed as 'Guidelines' throughout the text and are summarised at the beginning under 'Summary of Guidelines'. These are all evidence-based and the level of evidence is denoted.

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There are also boxed 'Key points' to draw the reader's attention to other issues of importance that may be of interest, but which are not clinical practice recommendations. Although levels of evidence were able to be attributed for some of these, others refer to areas for which there is no 'hard' evidence but which the working group nevertheless considered to be worth consideration by clinicians.

The National Breast Cancer Centre has also developed a consumer booklet for women with advanced breast cancer. This booklet is based on the clinical practice guidelines and is intended for women with advanced breast cancer and their families. The National Breast Cancer Centre recommends that clinicians inform their patients of the availability of this booklet, and that they recommend it as a reference to be used in cooperation with their doctor and other health care professionals with whom they are involved.

## SUMMARY OF GUIDELINES

The following table provides a summary of the guidelines presented in this document. Each of the recommendations should be considered in the care and management of women with advanced breast cancer. To understand the context of this evidence, readers should turn to the appropriate chapter.

Guidelines	Level of evidence	Reference	Chapter
<b>PSYCHOSOCIAL INTERVENTIONS</b>			
1. Psychosocial interventions can improve physical, functional and psychological adjustment and should be considered for introduction into patient care. These include the following:			
a) Appropriate counselling; an offer of referral for further support should be made whenever concern exists.	I	76	2.2
b) Relaxation therapy to ease cancer pain.	I	136	8
c) Education programs to improve pain control.	II	352	8
d) Supportive group counselling to improve 10-year survival.	II	348, 349	8
e) Group therapy to increase self-esteem and reduce anxiety, depression and anger.	II	350	8
f) Education sessions to improve adjustment, knowledge, death awareness and self concept for women newly diagnosed with advanced breast cancer.	III	351	8
g) Antidepressants; most people with cancer who are depressed and are prescribed antidepressants, benefit from them without significant side effects.	IV	341	7
h) Pharmacological agents as an integral part of the care of anxiety and depression.	II	346, 347	7
i) Behavioural techniques, such as muscle relaxation and imagery, to reduce distress in cases of mild anxiety.	III	344	7
j) Encouraging the expression of thoughts and feelings about the diagnosis and its meaning.	II	71	2.2

Guidelines	Level of evidence	Reference	Chapter
<b>PSYCHOSOCIAL INTERVENTIONS</b>			
2. Thorough review of women with advanced breast cancer involves an assessment of mood and coping, and enquiries about how the family is coping.	IV	31	2.2
3. Depression in people with cancer is best evaluated by the severity of the dysphoric mood, loss of interest and pleasure, by the degree of feelings of hopelessness, guilt and worthlessness, and by the presence of suicidal thoughts.	IV	340	7
<b>FAMILIES, PARTNERS AND CHILDREN</b>			
4. The provision of information is important to the partners of women with breast cancer. Clinicians have a role in addressing these needs and in referring partners to appropriate sources of information.	IV	75	2.2
5. Facilitating improved communication, cohesion and conflict resolution in families enhances their support of each other and reduces psychosocial problems.	III	64	2.2
6. It is appropriate for clinicians who diagnose women with advanced breast cancer to: enquire about the family and childrens' adjustment; clarify what assistance the woman may require in discussing her diagnosis and treatment with her family and children; and facilitate referral for information and support as needed.	IV	86	2.3
7. Professional and professionally supported services may reduce the risk of post-bereavement morbidity.	III	178	3.8
8. The consumer version of these guidelines is recommended as a reference to all patients and their families.	IV		2.2
<b>MULTIDISCIPLINARY CARE</b>			
9. Multidisciplinary care improves outcomes for women with breast cancer, and should be considered throughout management and treatment.	III	118	3.3

Guidelines	Level of evidence	Reference	Chapter
<b>CLINICAL TRIALS</b>			
10. There is indirect evidence that women who participate in clinical trials have better outcomes than similar women given similar treatment outside trials. It is appropriate for clinicians to discuss participation in clinical trials with women.	III	130–132	3.5
<b>ASSESSMENT</b>			
11. For women who have been treated for early breast cancer and who continue to feel well, regular scans and tests do not improve the length or quality of life.	II	103	3.2
12. The routine use of tumour markers is not recommended.	III	104, 105	3.2
<b>PALLIATIVE CARE</b>			
13. Specialist palliative care services improve patient outcomes in relation to patient satisfaction, patients being cared for in their place of choice, family satisfaction, and control of pain, symptoms and family anxiety.	I	164	3.7
<b>MANAGEMENT OF LOCALLY ADVANCED DISEASE</b>			
14. Optimal management of locally advanced breast cancer is a combined approach that uses chemotherapy, radiotherapy, surgery and/or endocrine therapy if applicable.	IV	193	4
15. Chemotherapy before local therapy (neoadjuvant chemotherapy) for women with locally advanced disease may substantially reduce the tumour size.	II	196	4
16. Endocrine therapy should also be considered for the treatment of women with locally advanced breast cancer, particularly for those with hormone receptor positive tumours.	I	199, 200	4

Guidelines	Level of evidence	Reference	Chapter
<b>MANAGEMENT OF LOCALLY ADVANCED DISEASE</b>			
Locoregional recurrence following mastectomy			
17. Complete excision of locoregional recurrent macroscopic disease allows more effective radiotherapy and improves local control. Radiotherapy should be administered to the entire chest wall and draining nodal areas if they have not been previously irradiated.	III	205	5
18. If the local recurrence is too extensive for excision with primary closure, radiotherapy should be considered as an alternative to surgery, as high rates of complete response can be achieved with radiotherapy alone.	IV	206	5
Locoregional recurrence following breast conservation			
19. Local recurrence after breast conservation may be a marker for associated systemic disease, although to a lesser degree than local recurrence after mastectomy.	III	215, 216	5
20. Mastectomy is the standard treatment for locoregional recurrence after primary treatment for breast conservation to attain locoregional control.	III	222, 224	5
Systemic therapy after locoregional recurrence			
21. Systemic therapy may improve disease-free survival after local therapy for locoregional recurrence:			
• tamoxifen	II	225	5
• chemotherapy	III	217	5
<b>MANAGEMENT OF METASTATIC DISEASE</b>			
Typically, a combination of anticancer and supportive therapies provide the most effective overall management of metastatic disease.			
<b>Anticancer therapies</b>			
The following recommendations relate to anticancer therapies, endocrine therapy and chemotherapy.			

Guidelines	Level of evidence	Reference	Chapter
<b>MANAGEMENT OF METASTATIC DISEASE</b>			
22. In women with hormone receptor positive breast cancer without rapidly progressing visceral disease, endocrine therapy and chemotherapy are both reasonable options.	I	199, 200 62, 245	6
23. In women with rapidly progressing visceral disease, limited evidence suggests that chemotherapy is better than endocrine therapy.	IV	230	6
24. In choosing endocrine therapy for patients with metastatic disease, it is important to consider the following:			
a) There is no evidence that any one particular endocrine therapy is more effective than others.	I1	22, 198, 199, 200	6
b) Tamoxifen is the endocrine therapy with the fewest side effects.*	I	122, 198	6
c) Within the standard range, higher doses of any given endocrine agent are no more effective than lower doses.	I	199, 200	6
d) Combinations of endocrine agents are no more effective than single endocrine agents used sequentially.**	I	199, 200	6
e) A response, including disease stabilisation, to one form of endocrine therapy often indicates sensitivity to subsequent endocrine manipulations.	III	231	6
* Preliminary results suggest that anastrozole was of equal efficacy with tamoxifen in first line treatment of post menopausal women and had somewhat fewer side effects. <sup>239</sup>			
** A recent randomised controlled trial reported that the combination of tamoxifen and buserelin yielded better results than either drug alone. <sup>244</sup>			
25. In choosing chemotherapy for patients, it is important to consider the following:			
a) Although chemotherapy may have significant side effects, it can improve quality of life and should therefore be considered.	II	27, 229	8

Guidelines	Level of evidence	Reference	Chapter
<b>MANAGEMENT OF METASTATIC DISEASE</b>			
b) Treatment with a greater number of standard dose cycles of chemotherapy is associated with: <ul style="list-style-type: none"> <li>• longer survival; and</li> <li>• better quality of life</li> </ul> than treatment with a fewer number of cycles.	I II	199,200 227	6
c) Within the range of usual doses, there is no evidence that higher doses are of greater benefit than lower doses.	I	122, 198, 199, 200	6
d) Treatment with standard doses of chemotherapy is associated with longer survival and better quality of life than treatment with less than standard doses.	II	229	6
e) Current evidence does not support the use of high dose chemotherapy with stem cell support in advanced breast cancer.	II	246	6
f) Combination therapy confers a modest survival benefit over single drug therapy.	I	122, 198	6
g) There is no evidence of benefit for adding chemotherapy concurrently to endocrine therapy.	I	199, 200	6
<b>SUPPORTIVE TREATMENTS</b>			
26. Anthracyclines, alkylating agents and the platinum drugs remain the most emetogenic. A schedule including a serotonin antagonist and dexamethasone is recommended prior to their usage.	II	370, 371	11
27. When given regularly to women with advanced breast cancer and at least one bony metastasis, bisphosphonates enhance quality of life and reduce bone pain, the need for analgesics, the rate of development of new bony lesions, the incidence of hypercalcaemia and the need for radiotherapy to bony lesions.	I	358	11
28. Steroids play an integral role in most chemotherapy anti-emetic regimens, particularly in the case of metastatic disease.	IV	386	11

Guidelines	Level of evidence	Reference	Chapter
<b>SPECIAL PROBLEMS OF ADVANCED BREAST CANCER</b>			
29. Treatment of spinal cord compression with radiotherapy is considered as equally effective as surgery in achieving symptomatic relief.	III	271	7
30. Radiotherapy is recommended following surgical treatment of spinal cord compression.	III	270	7
31. Patients with spinal cord compression who are ambulatory and retain bladder or bowel function prior to the commencement of radiotherapy, have the most favourable neurological outcome.	III	271, 272	7
32. Intravenous pamidronate lowers serum calcium within one to four days, and may be more effective than intravenous clodronate in severe cases.	II	273	7
33. Maintenance therapy with monthly intravenous pamidronate or daily oral clodronate reduces the number of episodes of malignant hypercalcaemia in women with bony metastases.	II	274	7
34. In treating pleural effusion, talc insufflation is superior to medical pleurodesis using either bleomycin or tetracycline.	III	279	7
35. Pericardiocentesis under echocardiographic control is a safe and initially effective treatment for pericardial effusion.	IV	281	7
36. The instillation of bleomycin as a sclerosing agent is well tolerated and significantly decreases recurrence of pericardial effusion.	IV	281, 282	7
37. Palliative radiotherapy remains the most effective single modality for the treatment of local metastatic bone pain. Various schedules of treatment are used and randomised studies have not shown a marked difference in pain relief from any particular schedule.	IV	296	7
38. Local control of an isolated supraclavicular fossa recurrence improves survival.	III	316, 317	7
39. Treatment of choroidal metastases with radiotherapy should be considered, as it can lead to visual improvement and prevent visual deterioration.	III	319	7

Guidelines	Level of evidence	Reference	Chapter
<b>SPECIAL PROBLEMS OF ADVANCED BREAST CANCER</b>			
40. Treatment of cerebral metastases with radiotherapy should be considered, as it leads to improvement in symptoms.	II	326	7
<b>PSYCHOSOCIAL INTERVENTIONS</b>			
41. Systematic chemotherapy may be an alternative to cerebral radiation therapy, particularly in patients with symptomatic metastases outside the brain.	III	331, 332	7
42. Resection of solitary cerebral metastases followed by radiotherapy potentially results in increased local control and a longer disease-free survival than radiotherapy alone.	II	320, 321	7
<b>ANALGESICS FOR CANCER PAIN</b>			
43. Oral analgesics are the mainstay of pain relief in patients with cancer. Strong opioids are safe and effective for moderate to severe pain.	I	359	10
44. Analgesia should be taken regularly at prescribed times, rather than on an as-needed (prn) basis. Prn analgesics for chronic pain should be reserved for breakthrough pain only.	IV	360	10
45. Radiotherapy plays a major role in the management of acute cancer pain.	I	301	10
46. The regular use of laxatives should be considered in conjunction with the administration of analgesics, preferably before constipation develops.	IV	364	10
47. Bisphosphonates have a role in the treatment and prevention of bone pain in breast cancer.	I	358	10
48. Non-steroidal anti-inflammatory drugs have a role in the treatment of inflammatory or bone pain.	II	369	10
49. Epidural, intrathecal and intracerebroventricular opioids are often effective in treating acute pain that is not controlled with conventional treatment.	I	363	10

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## CHAPTER 1 BREAST CANCER IN AUSTRALIA

### 1.1 BREAST CANCER

About 9,500 women are diagnosed with breast cancer each year in Australia.<sup>2</sup> It is the most common cancer diagnosed, excluding the non-melanocytic skin cancers, and the most common cause of cancer death among adult Australian women, accounting for about 2,600 deaths each year. Based on figures for 1994, it is estimated that 1 in 11 Australian women who live to the age of 75 will develop breast cancer during their lifetime,<sup>2</sup> and 1 in 44 will die from the disease before this age. In national incidence figures from 1982 to 1992, breast cancer incidence increased by an average of 1.5 per cent a year.<sup>3</sup>

The incidence of breast cancer increases with age. Older women are more likely to be diagnosed with breast cancer than younger women. For example, the incidence of breast cancer in women over 70 is 18 times the incidence in women younger than 40 (see Table 1).<sup>3</sup>

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Table 1: Breast cancer incidence and mortality rates for Australian women 1987–92 <sup>3</sup>

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Age group	Incidence (new cases per 100,000 women per year)	Mortality (deaths per 100,000 women per year)
15–39	15	3
40–49	138	30
50–69	207	69
70+	267	125
All ages*	66	21

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\* Age-standardised to the world standard population.

**International variation in breast cancer incidence in 1988–92 was substantial. Rates in the more economically developed western countries, particularly those of North America and Europe (70–90 per 100,000 women), were five times the lowest rates in some African and Asian populations.<sup>4</sup>**

Breast cancer may be classified as primary invasive cancer or as ductal carcinoma in situ (DCIS). These guidelines refer to invasive cancer only.

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## Definitions

Invasive cancer which is confined to the breast and regional lymph nodes is often referred to as early breast cancer. The *NHMRC Clinical practice guidelines for the management of early breast cancer* define **early** breast cancer as ‘tumours of less than 5cm diameter, with either impalpable or palpable but not fixed lymph nodes and with no evidence of distant metastases.’ This is equivalent to stage I and II of the International Union Against Cancer (UICC) staging system (see Appendix E).

**Advanced** breast cancer includes both locally advanced and metastatic breast cancer.

**Locally advanced** breast cancer is a primary diagnosis and is defined by invasion of non-breast tissues adjacent to the breast. In locally advanced breast cancer, the tumour has one or more of the following characteristics: ‘peau d’orange’, skin ulceration, or fixation to underlying intercostal or serratus anterior muscles or bones of the chest wall, or inflammatory carcinoma. The UICC stage III classification applies when one or more of these features is present in the primary cancer, the axillary nodes, or both. Nodal involvement in Stage III disease is characterized by involvement of the ipsilateral axillary nodes, fixed to one another or to other structures, or involvement of the internal mammary nodes.

**Local recurrence** applies to recurrence of the cancer in the scar or breast following breast conservation or recurrence in the scar following mastectomy.

**Locoregional recurrence** applies to local recurrence and/or where there is recurrence in the axilla following axillary treatment (radiotherapy or surgery); and/or in the internal mammary lymph nodes.

Cancer which has spread to distant sites is referred to as **metastatic** breast cancer. This is equivalent to UICC stage IV breast cancer.

## Prevalence of advanced breast cancer

The calculation of the prevalence of advanced breast cancer is not straightforward. Consideration needs to be given to cancers which are advanced at first diagnosis, and to those early breast cancers that have progressed to advanced breast cancer.

## Advanced breast cancer at first diagnosis

In Australia, the main sources of information about the occurrence of advanced breast cancer are published studies on limited series of patients, since population-based cancer registries have not collected information on size and stage of breast cancers until recently.

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#### Advanced breast cancers

The proportions of invasive breast cancer that were classified as advanced in the 1980s and early 1990s were higher (about 25 per cent were stage III or IV cancers) in hospital cases<sup>5,6</sup> than in population-based data for which percentages of around 16–17 per cent were seen.<sup>7,8</sup>

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Table 2: Degree of spread of breast cancer at first diagnosis, based on figures for NSW 1988–91<sup>9</sup>

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Degree of spread of breast cancer at first diagnosis	per cent of all cases	per cent of known cases
Localised to breast	50%	57%
Localised to breast and regional nodes	34%	38%
Distant metastases	4%	5%
Unknown	12%	0

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#### Metastatic breast cancers

In population-based series, metastatic cancers were around 4–5 per cent of invasive breast cancers<sup>8,9</sup> and higher (around 6–8 per cent) in hospital series.<sup>5,6</sup> Estimates from US cancer registries were also around 5 per cent of invasive breast cancer cases in Caucasian women in 1994.<sup>10</sup>

#### Locally advanced breast cancers

Locally advanced breast cancers have been reported as being 16–18 per cent of hospital cases<sup>5,6</sup> and between 7–9 per cent<sup>7,10–13</sup> and 12 per cent<sup>8</sup> of population-based series.

More exact estimates are not possible. Undoubtedly in Australia there have been state-based differences in stage at diagnosis and, in addition, changes in the distribution of stage at diagnosis over time.

#### Recurrence after early breast cancer

Non-population-based data are available about the prevalence of local recurrence and metastases in Australian women treated for breast cancer.

The following estimates are taken from two studies each of about 500 women who had been treated for early breast cancer with breast conservation surgery and radiotherapy, and followed for up to 10 years (median 84 months).<sup>14,15</sup> Six to eight per cent of women had recurrent ipsilateral breast cancer (4–8 per cent were cancers in the breast only), and 14–16 per cent had metastatic disease only as their first relapse (see Table 3). The cancers occurred around the same area in the breast in 56–68 per cent, with 14–31 per cent occurring elsewhere.

Five-year actuarial rates of local recurrence were 4–6 per cent. For women who had an isolated local recurrence, the five-year rate of disease-free survival before a second relapse was 66 per cent.<sup>13,15</sup>

Table 3: Pattern of first relapse in 438 women treated for early breast cancer at Westmead Hospital<sup>16</sup> and 512 women treated at the Queensland Radium Institute<sup>15</sup>

Pattern of first relapse	NSW study		Queensland study	
	Number of patients	per cent	Number of patients	per cent
Disease-free	324	74.0	410	80.0
Distant alone	73	16.0	72*	14.0
Breast alone	30	7.5	22	4.0
Breast + distant	0	0.0	8	2.0
Breast + distant + nodes	2	0.5	-	-
Regional nodes alone	6	1.5	-	-
Nodes + distant	3	0.5	-	-
Total	438	100	512	100

\* Nine patients with distant metastases went on to develop local recurrence.

**Predictors for five-year breast cancer recurrence rates were:**

- age less than 35 (13 per cent recurrence rate compared with 5 per cent for women over 35,  $p=0.04$ );
- involved margins (15 per cent involved v 2 per cent clear,  $p<0.01$ );
- extensive DCIS compared to no DCIS (10 per cent v 2 per cent,  $p<0.01$ ); and
- vessel invasion and higher histological grade.<sup>14,15,17</sup>

Local recurrence after mastectomy tends to occur within the first two years, and associated risk factors are axillary lymph node involvement, lymphatic or vascular invasion by cancer, grade III carcinoma and a tumour larger than 4cm in diameter.<sup>17</sup> Currently, there are insufficient published data to estimate Australian rates for local recurrence and metastases after mastectomy.

Recurrence after advanced breast cancer

Local recurrence in the treated breast or regional lymph nodes occurred in 19 per cent of patients in one series treated by chemotherapy and radiotherapy without routine surgery after a diagnosis of advanced breast cancer and followed for at least two years.<sup>18</sup> There was a significant increase in the recurrence rate with increasing tumour size. Isolated local recurrence occurred as a first relapse

in 12 per cent, and 42 per cent had metastases either with or without local recurrence.

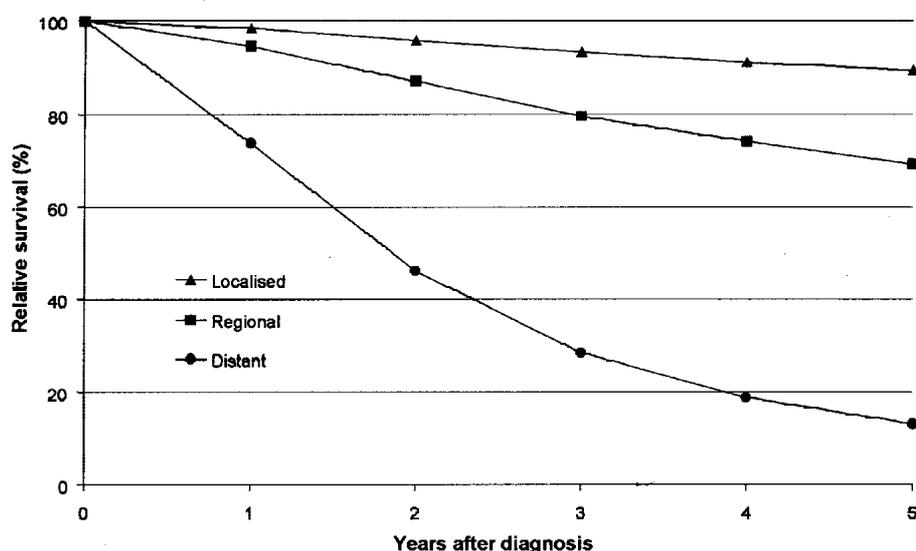
### Survival from breast cancer

Five-year relative survival rates in women diagnosed with breast cancer in the 1980s and early 1990s were 74–77 per cent, with better survival for more localised disease — 90 per cent for localised breast cancer, 70 per cent for regional and 18 per cent for metastatic disease<sup>7,9</sup> and 81–84 per cent for stage I or II breast cancers.<sup>16,15,19</sup> South Australian hospital-based cancer registry data also showed better survival with earlier stages of disease — 90 per cent in women with stage I breast cancer, 80 per cent for stage II, 50 per cent for stage III and 20 per cent for stage IV.<sup>7</sup>

#### Key point

In NSW, the five-year relative survival rate for women diagnosed with breast cancer during 1973 to 1995 was 77 per cent. Women with localised breast cancer at diagnosis had an 89 per cent chance of surviving for five years after diagnosis, those with regional spread 69 per cent and those with metastatic disease 13 per cent (Figure 1).<sup>20</sup>

Figure 1: Five-year relative survival (per cent) from breast cancer by spread of disease at diagnosis in NSW women, 1973–95.



This figure has been adapted with permission from *Breast Cancer Survival in NSW in 1973 to 1995* (July 1998), published by the NSW Cancer Council.<sup>20</sup>

Breast cancer mortality rates in England and Wales declined by about 10 per cent between 1986 and 1993.<sup>21</sup> This decline in mortality is thought to be due mainly to improved treatment — probably systemic treatment of early breast cancers with tamoxifen or cytotoxic chemotherapy.<sup>22</sup>

A retrospective analysis of trends in mortality rates from breast cancer in Australian women found that between 1985–1989 and 1990–1994, breast cancer mortality fell by 3.2 per cent in women 50–69 years of age and by 4.2 per cent in women 25–49 years of age. However, there was almost no change (-0.2 per cent) in breast cancer mortality in older women during this period.<sup>22</sup>

Key point	Level	Reference
Typically, breast cancer has a longer history than many other common cancers. Even in the presence of metastases, it often takes the form of a chronic illness.	IV	23, 24

The risk of breast cancer recurrence is lifelong. The risk of recurrence is highest in the first few years after diagnosis, and while the risk of recurrence in subsequent years is lower, it never disappears completely. Recurrences have been documented even 30–40 years after initial diagnosis and treatment.<sup>25</sup>

#### Outcome of advanced breast cancer

Locally advanced breast cancer resembles recurrent locoregional disease, and the outcome is fundamentally dependent on the result of local tumour control. There is a high incidence of subsequent metastatic disease<sup>7,9</sup> which will reduce survival prospects. There have been cases where women with advanced breast cancer, including with metastases, have lived for several years.

The prognosis is likely to be most unfavourable if the tumour is poorly differentiated on histological examination and has negative hormone receptor status.

Prognosis in the presence of metastatic disease relates powerfully to the disease-free interval following diagnosis and management of the primary tumour. Early relapse is associated with a low median survival rate of less than a year, while a disease-free interval of five years may result in a survival of up to 40 months.<sup>26</sup> Quality of life is also a significant independent prognostic predictor.<sup>27</sup>

The site of metastases is important prognostically, with locoregional recurrence or metastases to bone having a more favourable prognosis than for those patients with metastases in the lung or brain. The number of metastatic sites also has a greater impact on prognosis.

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Oestrogen receptor status may play a role in both treatment and prognosis of locally recurrent and metastatic breast cancer.

A retrospective study has identified several factors which significantly affect post-metastasis survival: metastasis-free interval, site of metastasis, and previous type of therapy (for example, hormone or chemotherapy).<sup>28</sup>

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## CHAPTER 2 THE IMPACT OF ADVANCED BREAST CANCER

### 2.1 QUALITY OF LIFE AND PSYCHOSOCIAL ISSUES

Quality of life is a multidimensional construct that is generally accepted to include several important areas or domains of a person's life: physical functioning, psychological functioning, social functioning, sexual functioning and spiritual and existential matters (Level IV).<sup>29,30</sup> A body of literature supports the concept that cancer has a significant impact on all these major life domains (Level III, IV).<sup>31,32</sup> (Please refer to the NHMRC NBCC *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer*, 2000).

The focus of management should be the minimisation of the physical and psychosocial impact of the cancer and its treatment. This is especially important in the case of metastatic disease. Clinicians need to be aware of the potential impact of the disease on women's quality of life, and have in place strategies for monitoring this so that appropriate interventions can be implemented. Quality of life has been shown to be a significant, independent prognostic predictor of survival in clinical trials (Level III).<sup>27,33</sup> Quality of life assessment is also important because changes in sequential assessments may influence the choice of continued observation or the introduction of active treatment.

Identification of those at risk of adverse psychosocial outcome and its early detection and treatment is a crucial step in enhancing the quality of life of women with advanced breast cancer.

A major issue is the assessment of women's needs for information and support in each of these major life domains, and the extent to which these needs are being met by existing clinical or other services.

The effect of advanced breast cancer on quality of life

Physical issues

With breast cancer having a longer history than many other common cancers, it can often take the form of a chronic illness with a range of implications for a woman's quality of life.

In the physical domain, quality of life is affected by symptoms, loss of function, and curtailment of activity due to the disease process and the physical effects of treatment (Level IV).<sup>34</sup>

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Symptoms may be related to the cancer, its treatment or other medical conditions. Symptoms which affect quality of life include nausea, pain, dyspnoea, tiredness, anorexia, vomiting, constipation, abdominal bloating and lymphoedema.

Loss of function may relate to the performance of (or capacity to perform) a variety of activities that are normal for most people. Such activities may include self-care activities (feeding, dressing, bathing), mobility (ability to move indoors/outdoors), physical activities (walking, lifting, bending) and role activities (work, school, household activities).

When women with advanced breast cancer are asked to rank quality of life issues in terms of importance, general health items such as self-care, mobility, physical activity, appetite and sleep are ranked in the upper quartile of importance (Level IV).<sup>35</sup>

As women with advanced breast cancer enter the phase of palliative care, pain and a variety of other symptoms need active treatment. When pain and fatigue are less well controlled, psychological distress increases and physical and social functioning decrease (Level IV).<sup>36-40</sup> Compared with women in remission, women with metastatic disease have significantly more unmet needs in the area of help with physical aspects of daily living (Level IV).<sup>41</sup>

For further information, see Chapters 6 and 7.

#### Psychological issues

A number of studies have indicated that 25–50 per cent of women show clinically significant levels of anxiety and depression when a diagnosis of recurrence of breast cancer is made (Level III).<sup>37,38,42,43</sup> One study indicated that 21 per cent of women with advanced breast cancer attending a clinic had significant levels of anxiety (as measured by the Hospital Anxiety and Depression Scale), compared with 14 per cent of women without breast cancer in a matched control group.<sup>44</sup>

Studies also indicate that 50–75 per cent of women rate the diagnosis of recurrence as more devastating than the original diagnosis. The diagnosis of recurrence challenges women to confront their mortality more than any other stage of the cancer illness (Level III).<sup>42,43,45</sup>

For many women, distress increases as the cancer progresses.<sup>42</sup> Compared with patients in remission, patients with metastatic disease have significantly more unmet needs in the area of psychological support (Level IV).<sup>41</sup>

#### Social issues

The effect of illness on the quality of relationships with family and friends is consistently ranked as a major concern for women with advanced disease. The diagnosis of recurrence of disease has been shown to impact negatively on marital and other relationships (Level IV).<sup>46</sup> Women may feel that their partner fails to appreciate the devastating impact of disease progression, thus failing to

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meet their needs (Level IV).<sup>47</sup> Yet family members may be even more distressed by the diagnosis than the woman (Level IV).<sup>48</sup> Families play a major role in a woman's ability to cope — more open communication styles and expression of feelings are generally helpful in adjustment (Level IV).<sup>49</sup>

There are a number of ways in which cancer and cancer treatment can disrupt social relationships. Functional problems due to pain or fatigue may restrict the individual's ability to pursue normal social activities. Similarly, the demands of treatment regimens may seriously limit the ability to maintain social contacts, and psychological reactions may lead to restricted social interactions. Friends and family may also restrict the level of contact because of fear of inadequacy.

#### Sexual issues

The impact of advanced breast cancer on the sexual functioning of couples has not been extensively researched, and there are few descriptions in the literature. It is clear that a diagnosis of breast cancer brings fear of death or disfigurement, loss of a partner, and perhaps a fear of becoming a burden to one's loved ones. These and other concerns must inevitably influence sexuality in ways which have not yet been clarified.<sup>50</sup> In the early phase, treatment may have a profound impact on sexual functioning. Even twelve months after mastectomy, 33 per cent of women have moderate to severe sexual difficulties, compared with 8 per cent of controls.<sup>51</sup> For the woman who has advanced breast cancer, there may be a significant impact on sexual functioning because of the side effects of systemic treatment. In addition to hair loss, nausea and vomiting, and potential weight gain, other side effects such as ovarian failure related to chemotherapy must, inevitably, affect sexual function.<sup>52</sup> As the disease progresses, fatigue will inevitably affect a woman's sense of wellbeing and, thus her sexual functioning.

For younger women with early stage breast cancer, some research indicates that psychosexual adjustment depends, to a large extent, on the good functioning of the woman's relationship.<sup>53</sup> The development of a depressive illness will, inevitably, also have a negative impact on a woman's libido. While it is important for clinicians to recognise that the issue of sexual functioning may be of considerable concern to couples, it is an issue which couples may find difficult to discuss. There is currently no agreed approach to the use of HRT and the contraceptive pill in women with breast cancer (please refer to the NHMRC *Clinical practice guidelines on the management of early breast cancer*).

#### Other issues

Many people who are seriously ill report that existential issues have acquired greater importance since they became ill.<sup>54-56</sup> These include concerns regarding death, freedom, isolation and the question of meaning (Level IV).<sup>57</sup> In a group of patients with advanced cancer, Cohen et al. found that the existential domain was at least as important as the physical, psychological and social support domains in determining quality of life (Level IV).<sup>58</sup>

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In the spiritual domain, the basic human need for transcendence — ‘to step back and move beyond what is’ — manifests itself in a search for meaning in illness and for resources to endure present discomforts and, if need be, to face death with courage and dignity (Level IV).<sup>59,61</sup> There is evidence that as physical condition deteriorates, spiritual issues gain importance as determinants of quality of life (Level IV).<sup>61</sup>

Key points	Level	Reference
Many, if not most, women rate the diagnosis of recurrence as more devastating than the original diagnosis.	IV	47
Quality of life is a significant, independent, prognostic predictor of survival in clinical trials.	III	27, 33
Advanced breast cancer and its treatment can both have a significant impact on quality of life.	II	62

## 2.2 THE IMPACT ON THE FAMILY

The development of breast cancer in one family member has an impact on the whole family. Family studies where members have advanced cancer reveal that there may be significant anxiety, mood disturbance and poor mental health.<sup>63</sup> Also, psychiatric illness is reported in up to one-third of spouses and one-quarter of the offspring of men and women with advanced cancer.<sup>64</sup> Husbands of women with breast cancer perceive that they receive less support than the patients themselves.<sup>65</sup> Distress may even be more marked in family members than in the woman herself.<sup>48</sup> The type of family communication pattern may affect coping, with more open and expressive families doing better.<sup>49,66</sup>

Although partners may feel highly anxious, only a small proportion actively seek out professional assistance.<sup>67</sup> Partners may also feel frustrated that they are unable to do anything about the disease, and be distressed by the possibility of the woman dying.<sup>68</sup>

Many partners may experience levels of distress which make it difficult for them to support their partner fully. The common and automatic assumption that the partner will act as a support person for the woman may be false.

Inevitably, the development of advanced breast cancer will affect marital relationships, although there is little direct research in this area. The perception of the demands of the illness seems to be an important predictor of depressed mood in the woman, and this in turn predicts levels of marital adjustment.<sup>69</sup> Over a period of time, depression in the woman has been shown to affect the marital

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relationship.<sup>70</sup> However, the possibility that the diagnosis of advanced breast cancer may draw couples closer together has not been addressed in the literature.

### Discussing dying

Many couples report that talking about dying is difficult.<sup>46</sup> In part, this may relate to the common belief that talking about dying will undermine the woman's capacity to maintain a fighting spirit, which will in turn shorten life. Family members may also avoid discussion about dying because they feel uncertain about what to say. There is no evidence that being upset will worsen the prognosis. In fact, there is evidence that expression of feelings may improve adjustment.<sup>71</sup>

The approach to death depends upon many factors, including culture, socioeconomic status and the personality of the individuals involved. For example, an Australian study which examined the experience of cancer patients in their final year of life<sup>72</sup> identified key features of a good death as: the social life of the dying person; the creation of open awareness; the social adjustment to and personal preparation for death; the public preparation such as arrangements relating to work; and the final farewells. Given the opportunity, clinicians should ask the patient about their expectations of dying and death, and discuss related matters with them.

### Practical issues

The many practical issues involved in planning care for women with advanced breast cancer include how to manage distressing events; how death occurs; and what to do around the time of death and afterwards.<sup>72</sup>

Patients, family and carers have a continuing need for information that is appropriately given on request and backed up with support relating to:

- the likely course of the disease;
- specific measures available to relieve symptoms; and
- knowledge of services available and how to use them (Level IV).<sup>73</sup>

Patients, family and carers also have practical needs — domestic help, financial, transport — and emotional/spiritual needs. These latter needs may be more pronounced if the patient has non-adult children and/or living parents.<sup>74</sup>

Specific arrangements for counselling/support/information may be required by partners and parents, as well as by young children, teenagers and their school community.

Other practical issues may pose major difficulties for couples. These include the financial impact of the cancer, disruption to the routine of family life, the need for renegotiation of previous roles, and the functioning of other family members.<sup>73</sup>

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## What do partners want?

It is recognised that women with breast cancer may have male or female partners. In general, the partners of women with breast cancer consider the following issues to be important:<sup>75</sup>

- **Information on the emotional consequences of a breast cancer diagnosis. Although many partners feel that this is critically important, there is no information available.**
- **Information about how women feel about their breasts.**
- **Coping strategies — both for themselves and the woman.**
- **Ways of assisting the woman who has breast cancer.**
- **Access to other partners in a similar situation.**
- **Information about alternative therapies (see section 3.6).**
- **Difficulty coping with the needs of younger children, as partners are focused on the needs of the woman with breast cancer.**
- **Coping with breast cancer in a rural setting. This raises a number of issues related to geographic isolation.**

Guidelines	Level	Reference
Appropriate counselling has the potential to improve quality of life; an offer of referral for further support should be made whenever concern exists.	I	76
Encouraging the expression of thoughts and feelings about the diagnosis and its meaning enhances overall adjustment.	II	71
Facilitating improved communication, cohesion and conflict resolution in families enhances their support of each other and reduces psychosocial problems.	III	64
The provision of information is important to the partners of women with breast cancer. Clinicians have a role in addressing these needs and in referring partners to appropriate sources of information.	IV	75
Thorough review of women with advanced breast cancer involves an assessment of mood and coping, and enquiries about how the family is coping.	IV	31
The consumer version of these guidelines is recommended as a reference to all patients and their families.	IV	

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## 2.3 THE IMPACT ON CHILDREN<sup>†</sup>

The adjustment of children whose mothers have advanced breast cancer has not been extensively studied in the literature. Evidence comes mainly from general studies of children with a parent with cancer.

A major factor affecting adjustment is the developmental age of the child. Younger children are often concerned about the disintegration of the family, and are worried about the vulnerability of the well parent.<sup>77</sup> Guilt about their own possible contribution to parental illness is common.<sup>78</sup> For adolescents, disruption to social networks and leisure activities and increased domestic responsibilities are prominent issues.<sup>79,80</sup> Adolescent daughters of women with breast cancer have been the subject of some detailed research, which has revealed that they are particularly emotionally vulnerable.<sup>81-84</sup> This vulnerability may relate in part to identification with their mother, and changes in role expectation.

Parents coping with cancer may fail to recognise emotional distress in their children,<sup>84</sup> and some reports suggest that children perceive their families offer them little support.<sup>85</sup>

Guideline	Level	Reference
It is appropriate for clinicians who diagnose women with advanced breast cancer to: enquire about the family and childrens' adjustment; clarify what assistance the woman may require in discussing her diagnosis and treatment with her family and children; and facilitate referral for information and support as needed. <sup>†</sup>	IV	86

## 2.4 THE IMPACT ON HEALTH CARE PROFESSIONALS

Although dealing with patients with cancer has been acknowledged as a source of stress for many clinicians, it is only recently that the origins of this stress have been examined in the literature.

Clinicians may experience frustration and a sense of professional failure in their dealings with oncology patients,<sup>87</sup> many of whom have a poor prognosis. Major areas of concern for oncologists include dealing with the patient's suffering, and being involved with decisions about treatments which are increasingly complex and potentially toxic. These issues occur against a background of organisational responsibilities which may conflict with clinical demands, and worry about the impact of overwork on home life.<sup>88</sup> The ethical and legal issues which arise in patient care add a further dimension of complexity to clinical work.

<sup>†</sup> More information is available from Turner J, McGrath P. *Needs of Children of Mothers with Advanced Breast Cancer* (1998), available from the NHMRC National Breast Cancer Centre. It is recommended that this document be treated as a companion to these guidelines.

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Exposure to dying patients may pose conflicts between curative roles, which underpin much of medical education in particular, and the need to adopt the palliative or supportive roles of cancer care. The same training often provides little preparation for the intensity of grief, anger, frustration and resentment displayed by patients and their families.<sup>89</sup> Many medical schools provide little time for students to discuss the emotional impact of distressing experiences, and this is compounded by the tendency for students to compare themselves unfavourably with their peers whose coping they perceive to be superior to their own.<sup>90</sup> In addition, many clinicians may have unrealistic expectations about their role and how they will cope. Coping is also inevitably affected by past experiences of loss. Thus, in understanding clinicians' distress, it is important to acknowledge the contribution of their personality style and their capacity to develop priorities in their personal and professional lives.<sup>91</sup>

Clinicians may be reluctant to acknowledge emotional matters, and often find it difficult to seek assistance in coping.<sup>92</sup> Interventions such as debriefing were originally developed in the field of trauma, and have gained wide popularity. Debriefing has frequently been applied within the health care setting, but there is a paucity of methodologically sound evaluation and outcome studies which support its efficacy.<sup>93</sup> Common elements to interventions which have been described include the provision of peer support, education, opportunities to share difficult workplace experiences in a supportive group framework, identification of key stressor experiences, and discussion of the demands of care.<sup>89</sup> It is also important for those working in oncology to recognise and utilise the skills and expertise of members of multidisciplinary teams when dealing with complex clinical problems.<sup>94</sup> One avenue for reduction of stress is enhancement of communication skills, as there is evidence that those who feel insufficiently trained in communication and management skills have experience significantly higher levels of stress.<sup>88</sup>

Inherent in any intervention is the responsibility of clinicians to optimise their professional skills, to recognise their personal responsibilities to care for themselves physically, emotionally and spiritually and to maintain ongoing monitoring of their own coping.<sup>95</sup>

## 2.5 ECONOMIC IMPACT

Advanced breast cancer has a substantial economic impact on women and their families, and on agencies which fund health and community care services. These costs comprise both the direct costs of treatment (medical and hospital services, drugs and so on) and the indirect costs associated with work and leisure time lost due to illness. Clinicians should be aware that worries about having to relinquish employment and subsequent financial burdens, including medical costs, may affect the coping ability of both the woman and her family. The available evidence on the costs associated with advanced breast cancer is confined to estimates of the direct costs; these are poorly understood but appear to be several orders of magnitude greater than those of early breast cancer.

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In one Australian study, the direct costs of treatment for women with breast cancer detected at a late stage (stage IV on the TNM staging system) and who subsequently died were predicted to be in excess of AU\$20,000 (1987–88 prices).<sup>5,96</sup> These costs were about five times higher than the treatment costs for women with breast cancer detected at an early stage (stage 0 or stage I).

Another Australian study of the costs of treatment of recurrent breast cancer found the predicted cost of a fatal recurrence of breast cancer of median duration (15.7 months) to be AU\$10,575 (1988 prices).<sup>97</sup> This includes only the cost of treatment of the recurrent disease and hence excludes the cost of surgical and other treatment for primary disease. This compares with an estimate of the cost of treatment of breast cancer from the onset of advanced disease until death of AU\$14,415 (1991 prices).<sup>98</sup>

These Australian estimates are comparable with those from a similar study in the UK.<sup>99</sup> However, in the United States the cost of breast cancer treatment from diagnosis to death in a group of women aged 65 or over at diagnosis has been found to be in excess of US\$50,000 (1990 prices).<sup>100</sup>

These estimates of treatment costs do not include any allowance for the costs of any home care. Home care can be provided by professionals or can take the form of informal care by relatives, friends, neighbours and volunteers. The costs of home care can be substantial. One study of the cost of home care for women with advanced breast cancer in the Netherlands estimated the average cost of such care to be about \$4,700 (1987 prices), with more than half these costs incurred in the month before death.<sup>101</sup>

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## CHAPTER 3 GENERAL PRINCIPLES

### 3.1 THE GOALS OF MANAGEMENT

The primary goals of the management of advanced breast cancer are to improve the length and quality of life.

Once metastasis to distant sites occurs, the disease may not be curable. Nevertheless, it is amenable to treatment, and this is an important distinction to make.

Treatment choices should focus on the balance between the potential benefits of the therapeutic options and their side effects. Decisions will vary in individual cases, and should be the result of informed discussions between doctor and patient.

### 3.2 ASSESSMENT

#### Initial assessment

The diagnosis of advanced breast cancer may occur in widely differing circumstances. Most women who present with advanced breast cancer will have already been diagnosed with and treated for early breast cancer, although this will be the first presentation for some.

Assessment of women with advanced breast cancer is performed for a variety of reasons, including to ascertain the extent of disease (for example, locally advanced, locally recurrent or metastatic disease) and to consider the extent of complications of the disease that have developed.

Most women with advanced breast cancer are diagnosed either because a sign or symptom has developed, or because recurrence has been detected during a routine clinical examination or at mammography.<sup>102</sup>

Most women present with slowly progressive symptoms or signs which develop over weeks to months. These may be non-specific and difficult to distinguish from less sinister problems. An important minority of women present acutely unwell, with life-threatening but treatable complications of previously unsuspected advanced disease. It is therefore important that women with recently diagnosed advanced breast cancer are assessed carefully before treatment decisions are discussed. The presence of impending serious complications (such as spinal cord compression or long bone fracture) should be ascertained, since these require urgent treatment. However, a number of matters will not require that degree of investigation and will depend on the clinician's assessment.

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### Key points

The initial assessment of advanced breast cancer may include confirmation of the clinical diagnosis which may include biopsy, as well as tests to determine the extent and nature of any metastases.

Investigations should be appropriate to the patient's presenting problem, history and physical examination, so both the clinician and the woman know the extent of the problem and suitable options are discussed.

CT or MRI scanning of the whole body is rarely appropriate.

**Anti-cancer treatment is important but rarely urgent, so women should be given as much time as they need to discuss and consider available options. Symptoms and physical signs should be recorded carefully, so that progress can be monitored.**

### Key points

The initial approach will generally involve consideration and discussion of surgery, radiotherapy, endocrine therapy, chemotherapy or supportive treatment options. Some, all or none of these might be appropriate, and the precise direction taken will depend on patient preference, general state of health, the pattern of metastatic spread and other considerations. For example, a woman living in a remote rural area will have to think of the travel consequences of having chemotherapy, while a woman with no symptoms might elect not to start any treatment at all for a time.

Guidelines	Level	Reference
For women who have been treated for early breast cancer and who continue to feel well, regular scans and tests do not improve the length or quality of life.	II	103
The routine use of tumour markers is not recommended.	III	104, 105

### Continuing assessment

**Following the diagnosis of advanced breast cancer, all symptoms and signs should be assessed, measured and recorded at each clinic visit. Given that cancer-related symptoms often improve before tumour shrinkage is evident using conventional measures of response, failure to see a change in the size of metastatic deposits, particularly early in a course of treatment, does not mean that the treatment is not effective. However, unequivocal disease progression, manifested either by the growth of existing metastases or the development of new ones, is a clear sign of treatment failure which necessitates a reassessment of the options.**

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As a part of continuing assessment, the following should be considered:

- Frequently, response to treatment can be determined quickly and simply with a focused history and careful physical examination. Simple tests, such as chest X-rays, liver function tests and serum calcium results, are also often helpful.
- Before proceeding to further investigations, clinicians should evaluate whether or not the information possibly obtained would change their management of the patient. For example, radioisotope bone scans are useful in documenting the initial extent of disease, but are rarely helpful in gauging response to therapy.<sup>106</sup> Other tests, such as computerised axial tomography (CAT) and magnetic resonance imaging (MRI), should be reserved for situations where the disease is not amenable to simpler forms of assessment, and where such information will make a difference to management.
- Assessment of response to treatment is based on serial assessments; longer intervals between assessments allow for clearer appraisals of response.
- A plan should be made at the outset of treatment as to when and how response will be assessed; this judgement will be influenced by the severity of symptoms and the progress of the disease.
- There needs to be a clear idea in the minds of both patient and doctor of what the specific goals of treatment are, so that the context of the treatment is borne in mind.

If, for instance, there is stabilisation of disease as measured on a chest X-ray, but the woman herself feels worse after a few months of treatment, then little is likely to be achieved by continuing with the same treatment.

Conversely, if treatment has been associated with a clear improvement in cancer-related symptoms, then treatment should probably be continued despite the presence of a stable chest X-ray rather than an improving one.

- Lastly, the toxicity of any treatments should be monitored carefully, as troublesome side effects may mar an otherwise effective treatment.

Some side effects are acute and short-lived, such as nausea and vomiting with some chemotherapy drugs. These problems can often be alleviated with the use of measures such as anti-nausea drugs, or by reducing the dose of chemotherapy. Other side effects, such as hot flushes associated with tamoxifen, may gradually disappear over time.

Finally, some side effects may only develop over time and, if anticipated, should be discussed before treatment begins. Examples include fluid retention and peripheral neuropathy seen after prolonged treatment with some chemotherapy drugs.

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## Assessing quality of life

There is recognition that quality of life data should be obtained, although only a minority of clinicians currently incorporate this into their routine practice (Level IV).<sup>107,108</sup>

## Asking the patient

The simplest method to obtain information on the woman's quality of life and unmet needs is to ask her. This can best be done by asking her regularly and monitoring her responses over a period of time. The strategy of looking for factors in the person and their environment that place them at increased risk of morbid concern is well established in medicine.<sup>109</sup> Studies from other areas have shown that creating a non-threatening environment by using open-ended questions at the beginning of a consultation, displaying empathy and clarifying verbal cues given by the patient results in a more accurate assessment of patients' emotional and social state (Level II).<sup>110</sup>

The woman's physical symptoms regarding pain, discomfort, nausea, tiredness, dyspnoea, anorexia, vomiting, constipation, abdominal bloating and lymphoedema should be discussed, as should the effects of those symptoms on her life.

The woman's perceptions of her support network, her relationships and family, and any degree of social alienation all need consideration. Any significant life events in her recent past need to be reviewed, and women should be asked about current worries.<sup>109</sup> While major psychiatric illnesses are recognised, clinicians are often unaware of more minor episodes that may inform coping capacities and adjustment (Level IV).<sup>109</sup> Charting risk factors and psychosocial issues assists recognition and future management, but is invariably neglected (Level IV).<sup>111</sup> (For further information refer to the NHMRC NBCC *Psychosocial clinical practice guidelines: providing information, support and counselling to women with breast cancer*, 2000).

## Self-completed questionnaires

A wide range of instruments has been developed that reliably and validly measure quality of life in people with cancer. A description of the psychometric properties of currently available questionnaires is given in Appendix C, and these are summarised in Table 11 (Appendix C). Generally these instruments have been developed to measure outcomes in clinical trials. Quality of life as an outcome is vitally important in trials of treatment for advanced breast cancer, where therapies are targeted at morbidity reduction.

There is growing interest in using these validated measures for individual patient application in clinical practice to monitor a person's quality of life, thereby detecting changes that are amenable to intervention. It has been argued that

these instruments allow information to be collected in a standard fashion so that response to treatment and disease progression can be monitored over time.<sup>112,113</sup> Trials are currently under way to examine the effect of routine administration of validated questionnaires on communication between doctors and patients, and the ability of the health care practitioner to detect and effectively manage issues to improve quality of life for patients.

A touch-screen computer survey has been found to be an acceptable method to collect information on quality of life issues and unmet needs from medical oncology patients, including women with advanced breast cancer (Level IV).<sup>114</sup> This study also showed that patients are willing to have oncologists receive copies of their survey results at each visit so that clinicians are kept up to date about their unmet needs and quality of life issues (Level IV).<sup>114</sup> The effectiveness of this approach for improving psychosocial outcomes is currently being examined in a randomised controlled trial.

Key point	Level	Reference
Information on quality of life should be obtained as part of routine practice	IV	107, 108

#### Quality of Life assessment in everyday clinical practice

So far, quality of life measures have been developed and used for group level applications in clinical trials. The routine use of cancer-specific quality of life assessments in the general clinical setting has been less well described, although studies have been performed in Australia,<sup>107,115</sup> the UK,<sup>108</sup> and New Zealand and Hong Kong.<sup>107</sup>

There is growing interest in applying quantitative measures of quality of life in daily clinical practice. Theoretically, the incorporation of quality of life measures in clinical practice could serve a number of purposes, including:

- aiding doctor/patient/caregiver communication;
- being useful for screening and for monitoring individuals over time; and
- eliciting preferences from patients and family caregivers that can assist clinical decision-making.<sup>113,116</sup>

When surveyed, most oncologists believe an assessment of quality of life should be made in most circumstances, whether treatment is curative or palliative.<sup>107</sup> However, at present fewer than 50 per cent formally assess and record quality of life information in everyday clinical practice.

It remains to be seen whether obtaining quantitative quality of life information in everyday clinical practice translates into better outcomes for patients. This is a testable hypothesis and is currently being examined in a randomised clinical trial.

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## Social assessment

The clinician should enquire about the woman's social situation. There is evidence that women who experience adverse social circumstances and life events or who feel that they have poor social support are at risk of experiencing increased emotional distress (Level III).<sup>117</sup> In such cases consideration may be given to referral for further assessment or counselling. (Refer to NHMRC NBCC *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer*, 2000).

## 3.3 MULTIDISCIPLINARY CARE

Advanced breast cancer is a highly variable disease which passes through many different stages, usually over a reasonably long period of time. Given that a woman may be treated by many different health professionals during the treatment process, effective coordination of care will improve the outcome for women.<sup>118</sup> Continuity of care is also important to both the health outcomes and wellbeing of women.

Multidisciplinary treatment is coordinated treatment by a range of individuals using a range of modalities of treatment. The team as a whole is responsible for the diagnosis, continuing management (including regular assessment of the needs of the woman) and palliative care. To help maintain continuity of care, it is suggested there be a designated lead clinician, who may change with time, who bears overall responsibility for the relationship with the patient. The woman should be part of the decision-making process which determines the composition of the team and the lead clinician.

The team should include, at various times, clinicians with specialist knowledge of aspects of diagnosis and treatment such as surgeons, pathologists, medical oncologists, radiation oncologists, breast care nurses, counsellors and other therapists as needed. For example, physiotherapists may be required to deal with problems such as lymphoedema, family counsellors may deal with genetic testing and counselling, and the palliative care team has special expertise and practical services to offer as the disease progresses. All of these people may provide patient support. The woman's general practitioner (GP) should also be regarded as an integral part of the team and may provide the long-term continuity of care.

There is evidence that multidisciplinary care improves outcomes for women with breast cancer.<sup>119-122</sup> It is difficult to determine whether or not this evidence applies to Australian conditions. But as a UK National Health Service (NHS) report points out,<sup>121</sup> it is unlikely that there will be randomised controlled trials on matters such as management approaches, so weaker scientific evidence and strong consumer support may provide the appropriate level of evidence in this case.

In general, consumers are in favour of ‘multidisciplinary teams, good teamwork and communication between professionals.’<sup>123</sup> Continuity of care is considered important — frequent staff changes are disruptive and counter-productive, both for the woman and from the professional point of view. Continuity of care is best assured by identifying a principal caregiver who has overall responsibility for the management of a woman at each stage of her treatment.<sup>124</sup>

Wherever the woman is located at a particular time, the practical issues of care which need to be addressed for her and her family/carers as the illness progresses include:

- access to assistance 24 hours per day, every day;
- regular review of pain and other symptom control measures;
- access to necessary aids and equipment;
- understanding the role of the various professionals within the team;
- information about the possible developments in the disease and its complications as well as the dying process;
- discussion about the preferred site of care and death; and
- family awareness of what to do when death occurs and after the death.

Guideline	Level	Reference
Multidisciplinary care improves outcomes for women with breast cancer, and should be considered throughout management and treatment.	III	118

### Coordination of care - the role of the general practitioner

Whether or not the ideal of multidisciplinary care is attained, breast cancer is a multisystem disease. A woman with breast cancer is likely to see many different specialists, often over a period of years. Coordinated care and continuity of care ensure high quality treatment for women, and the general practitioner (GP) has an important role to play in coordinating care.

In Australia, the GP is established as the doctor of first contact, and referrals to specialists are required for patients to receive benefits from Medicare.<sup>125</sup> In many cases, the GP will provide the initial diagnosis of breast cancer, and may also diagnose a recurrence signifying advanced breast cancer. For these reasons, women who do not currently have established contact with a GP should be encouraged to do so.

GPs usually have knowledge of patients essential to treating specialists, including family and social circumstances, the patient’s preferred communication style, usual responses to illness and treatment, drug allergies, history and so on. The patient may forget some of this information in a crisis.

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Many women find the range of specialists to which they are referred confusing and need a practitioner who knows and understands her needs to act as the coordinator of her care. A GP frequently fulfils this role. The choice of the coordinator of care should be made by the woman in consultation with both her GP and her specialists.

A woman with advanced breast cancer may have quite long periods of time when she is well and hence have minimal contact with her specialists. At these times, the GP has a key role to play in the continuity of care and in identifying changes in the woman's condition which may indicate a new phase in the course of the disease.

The GP can play an important role in the management of a woman's condition. It is therefore essential that the GP be kept informed and up to date about the patient's management, and that his/her input be sought when appropriate. Equally, the GP should maintain an effective relationship with specialists so that he or she can refer the women to the most appropriate specialist, given the nature of the woman's disease.<sup>126</sup> For relevant information on the Australian Medical Association's Code of Ethics, see Appendix G.

Those women who have no preferred GP should be advised to get one.

Optimal management would involve the following:

- Ideally, the woman should have a GP with whom she feels comfortable, as the GP is in a prime position to keep track of the patient's clinical progress.
- All health professionals caring for the patient should be aware of the patient's preferred GP.
- The woman is responsible for deciding whether or not she sees her GP as the long-term coordinator of her care, and what role she sees for her GP. The woman's wishes should be respected.
- GPs should be informed of, and where appropriate involved in, team decisions about management.
- The GP should be notified promptly after each patient visit to a specialist, and when there are any changes in treatment. Options include a phone call, a fax, or a letter carried by the patient if she is to see the GP soon.
- Interspecialist referrals should preferably occur with the involvement of the GP. A phone call or fax message may be sufficient (or even preferable), rather than sending the patient back to the GP for a separate referral.
- All treating health professionals should indicate clearly to the patient that the GP will be given all relevant health information. This should not preclude the patient from directly contacting another health professional directly with relevant problems or questions. Instead, it should help the patient to know the GP can be contacted when it is unclear whom to contact about a particular problem.
- All health professionals should communicate clearly with one another.<sup>127</sup>

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### 3.4 TELLING A WOMAN SHE HAS ADVANCED BREAST CANCER<sup>††</sup>

The woman who is diagnosed with advanced breast cancer will, in most cases, have been diagnosed with and previously treated for early breast cancer. When the woman presents with new symptoms suggestive of disease progression or this is suspected because of clinical findings, it is essential that the possibility of bad news be discussed when organising further tests or arranging referrals.

If several tests are being performed, it is vital that the woman is informed at the outset that an accurate picture can be obtained only if all the test results are interpreted at the same time. For this reason, she will not be able to gain results of individual tests as they are being performed, even if she asks the person performing the tests for feedback.

One person should be responsible for breaking the bad news. Ideally, this is the clinician who knows the woman, and the one who will be actively involved in her ongoing management. From a practical point of view, however, it is often the case that the diagnosis of advanced disease necessitates referral for further treatment, hence the clinician who has given the news may not be involved actively in the woman's ongoing management. In these circumstances, it is important for clinicians to recognise that this transfer of clinical care may make the woman feel anxious and uncertain, and to discuss with her any distress she may feel.

What should women be told?

1. The doctor has a duty to disclose information fully about the diagnosis and prognosis according to a woman's wishes. There are also legal issues related to disclosure of information about management plans.<sup>128</sup>
2. The primary responsibility of the clinician is to the individual woman. It is her wishes regarding disclosure of information that are most important, not the wishes of her family or other health professionals.
3. Different people have different coping styles. Some people cope by desiring a lot of information, while others prefer minimal information. However, since the process of assimilating information such as this is a dynamic process, it is likely that a woman's informational needs will change over time. Therefore, it is important not only to assess how much information a woman wants initially, but also to check whether this initial reaction changes with time.

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<sup>††</sup> This chapter is adapted from the NSW Cancer Council's booklet *Breaking Bad News* (1997). Further detailed discussion of this issue is also available in NHMRC *NBCC Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer* (2000)

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Women also need a framework to be able to give an opinion on how much information they want to be given. It is difficult for women to say how much information they desire, if they do not know how much information is available. At the consultation where the bad news is given, it may be desirable to 'set the agenda' by specifying the range of information that can be given, before asking how much information people want.

4. Following from this, it is important to tell the patient that no major decisions about future management need be made at the initial consultation.
5. Wherever possible, an attempt should be made to set aside time to allow people to digest information and react to this. If there has been a long waiting time or if there is an unavoidable time limit on the consultation when the news of recurrence is to be given, the woman needs to be informed of this and the reasons for it. In any event, another appointment should be offered as soon as possible, so that the issues can be discussed in greater depth. At the time of the further appointment, the woman should be offered the option of a taped interview and other suggested reading matter which can be taken home. This helps the woman to understand the context in which decisions are being made about her case.
6. It is important that women are allowed to express their feelings, and that these expressions receive an empathetic response.  
*'This is obviously very bad news, and it is understandable that you are very upset about it. Many of my patients feel upset and even angry when they receive this kind of news. Just take your time.'*
7. The news about recurrence, and the prognosis, should be given in simple language but not bluntly. Technical jargon or euphemisms that obscure the truth should be avoided.  
*'The tests show that the cancer has come back, and has spread to ... It is certain as all the tests indicate the same result.'*
8. A prognosis with a definite time frame should be avoided, and if possible, a broad, realistic time should be given.  
*'This obviously comes as a shock, but it is important not to jump to the wrong conclusions. It does not mean that you are going to die in the next few days or months. No-one can tell exactly what will happen, but many women in your situation have survived for ... to ... (realistic time frame).'*
9. The news should contain some element of hope.  
*'Although the disease can't be cured, there is much that we can do to help.'*

Avoid the notion that nothing further can be done. Even if the disease is too far advanced for curative treatment, it is possible to emphasise hopeful aspects, such as the existence of long-term survivors, and the uncertainty of the disease course for any one individual. Reassure the patient that support will be provided for as long as needed to make the patient's remaining life as comfortable as possible.<sup>129</sup>

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Where should the news be given?

10. The person needs to be assured of privacy when the news is given. Interruptions from beepers and telephone calls should not occur.

Involving others

11. The person should be given the choice of having other family members or significant others present during the consultation.  
*'There are people who will want to know what is happening to you. Are there people that you would like me to tell specifically? Are there people you would wish not to have this information? I would be happy to talk with anyone, either on the phone or in general discussion with your family or other friends.'*
12. It is often helpful to have another health professional, such as a nurse, present during the consultation to help assess how women are reacting to the information. The woman needs to be asked whether she minds having the second health professional present in the consultation. The woman can be expected to be upset.  
*'There are a number of different people and support groups with whom you and your family might find it useful to talk. Talking about your situation with others who have been through a similar experience may help you cope with it.'*
13. The person's GP and other treating clinicians should be informed of the recurrence as soon as practicable after the consultation. The woman needs to be told that the clinicians will receive this information.

Other issues

14. It is important that all treating clinicians are aware of and informed about the role that a woman's culture, religious beliefs, and social background may play in her reaction to the news.
15. A trained interpreter should be employed if language difficulties exist.
16. It is important for clinicians to be aware of their own competencies when telling a woman she has advanced cancer, and to seek ongoing training to supplement these skills throughout their career.
17. Suggest a return appointment for a consultation.

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### 3.5 CLINICAL TRIALS

Improvements in the management of women with advanced breast cancer come from evidence gained from clinical trials. As far as possible, these guidelines are based on such evidence, but many questions remain unanswered. It is important that women with advanced breast cancer be offered the chance to participate in clinical trials suitable to their particular situation. It is estimated that less than five per cent of women with breast cancer participate in clinical trials.<sup>12</sup>

Clinical trials usually involve the testing of new treatments, or of new indications for treatments established for other indications. The development of a new treatment involves progression through three phases of clinical trials:

- Phase I trials are designed to evaluate the relationship between dose and toxicity, and aim to establish a tolerable schedule of administration. They usually include only small numbers of patients who have already received the standard treatments for their condition.
- Phase II trials are designed to screen new treatments for their antitumour effects, in order to identify those worthy of further evaluation. In phase II trials, a series of patients with particular types of cancer receive the new treatment to determine the proportion in whom the tumours shrink. If this proportion of patients responding compares favourably with other available treatments, then the usefulness of the treatment in patient management is assessed in a phase III trial.
- In phase III studies, patients are randomly allocated to receive either the new treatment or the best available standard treatment. Ideally the two arms of treatment should be indistinguishable, so if possible an inactive placebo is used to mask the standard treatment arm. This is rarely possible in trials of chemotherapy drugs, because of their side effects. Phase III trials often include large numbers of patients from many hospitals. They may be conducted through national and international collaborations, for example under the auspices of the Australia and New Zealand Breast Cancer Trials Group or the International Breast Cancer Study Group. For more information on the different types of clinical trials, see Appendix E.

In Australia clinical trials must be approved by an Institutional Ethics Committee (which might be known as an Institutional Review Board or a Research and Ethics Committee). Women must be provided with relevant and complete information about the trial protocol and provide their written consent before they take part. Entry into a trial must be entirely voluntary and refusal to enter a trial or a decision to withdraw later without giving a reason must not affect the woman's relationship with her treating practitioner.

At all times, medical practitioners must treat the woman in her best interests. This means that she should only be offered participation in a clinical trial if the best available evidence suggests that the treatments being tested are likely to be at least as effective as the best standard treatment. It also means that if during a trial

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the treatment appears to be detrimental, she must be withdrawn from the trial and offered alternative treatment appropriate to her condition at the time.

An individual woman may benefit from taking part in a clinical trial. Indirect evidence suggests that patients who participate in clinical trials have better outcomes than similar patients given similar treatment outside the context of a trial (Level III).<sup>130-132</sup> This may be due to patient selection, closer monitoring and supervision, earlier identification and treatment of complications or better compliance.

Participation in clinical trials gives the woman access to new treatments before they become generally available. Many women are pleased with the prospect of improving knowledge about their disease and treatment.

Many oncologists participate in clinical trials. Information about trials currently being conducted in Australia may also be found on the National Breast Cancer Centre's home page (<http://www.nbcc.org.au>).

There are a number of issues relevant to women participating in clinical trials, that may need to be addressed at the time that requests for participation are made. Women need to know:

- that the trial will be conducted properly;
- that the trial will give useful results;
- that their refusal to participate in a trial will not compromise their treatment;
- that their doctor is not putting his or her own research interests before patient care;
- enough information to be able to give informed consent to participate or refuse to participate;
- how to decide whether or not to participate at a time when they are adjusting to the diagnosis or new development and considering treatment options;
- the costs and benefits to themselves of taking part in a trial; and
- what will happen during the course of the trial.<sup>133</sup>

Guideline	Level	Reference
There is indirect evidence that women who participate in clinical trials have better outcomes than similar women given similar treatment outside trials. It is appropriate for clinicians to discuss participation in clinical trials with women.	III	130-132

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### 3.6 ALTERNATIVE AND COMPLEMENTARY THERAPIES

The term 'alternative therapies' is 'used loosely to describe anything outside the orthodox circle of surgery, radiation and chemotherapy'.<sup>134</sup> It includes different approaches which operate in the 'hope that we can boost the immune system through a mind-body connection. ... these range from visualisation to diet and prayer...'.<sup>135</sup> There are hundreds of different therapies which have very different effects on the body.

Some alternative therapies have been acknowledged by the medical profession as useful — these are usually known as complementary therapies. The effect of other alternative therapies is unknown and may be harmful. The majority of alternative therapies have not been tested in randomised clinical trials and proven to be effective. Whereas complementary therapies can work alongside conventional therapies, alternative therapies may involve some tension or interference with conventional therapies.

Complementary therapies such as relaxation (Level I) and meditation have been shown to be effective, or at least not harmful, by western medical standards (see Chapter 8 on psychosocial interventions).<sup>136</sup> Both relaxation and meditation are frequently and effectively used by GPs and palliative care teams.

Alternative therapies, as they are referred to for the rest of this chapter, are used by many Australians. In a random sample of 3004 South Australians, 48.5 per cent of respondents (reflecting the general population) had used at least one non-physician-prescribed alternative medicine during the past year, while 20.3 per cent had visited at least one alternative practitioner.<sup>137</sup> Women were significantly more likely to use alternative products than men, especially vitamin and mineral supplements, evening primrose oil, aromatherapy oils and homoeopathic medicines.

Looking specifically at people with cancer, one study found that 21.9 per cent of people attending one of three NSW oncology clinics said they were using alternative therapies.<sup>138</sup> Other studies (both overseas and Australian) have found that 9–54 per cent of adults with cancer<sup>139-143</sup> and 46 per cent of children with cancer<sup>144</sup> use alternative therapies.

In 1993, Australians spent an estimated AU\$309 million per year on alternative therapists and AU\$621 million per year on alternative therapies, which far exceeds the patient contribution of AU\$360 million to standard pharmaceuticals for 1992/93.<sup>137</sup>

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The main reasons for using alternative therapies given in the Begbie et al. study<sup>138</sup> were:

- new source of hope (49 per cent of users of alternative therapies);
- preference for natural therapy (40 per cent);
- impression that it is a non-toxic therapy (37 per cent);
- supportive alternative practitioner (29 per cent);
- desire to try something different (23 per cent); and
- a sense of greater personal involvement (14 per cent).

The main therapies used were:

- relaxation/meditation (59 per cent of users of alternative therapies);
- diet therapy (57 per cent);
- megavitamins (43 per cent);
- positive imagery (44 per cent);
- faith/spiritual healing (30 per cent);
- naturopathy (27 per cent);
- immune therapy (17 per cent);
- homeopathy (16 per cent); and
- acupuncture (11 per cent).

Seventy-five per cent of people using alternative therapies used more than one (median 3, range 1–8).<sup>138</sup>

Even though there are no data specifically examining the use of alternative therapies by women with advanced breast cancer, there is no obvious reason why usage would not be similar to that of other people with cancer.

The three important issues to consider in the use of alternative therapies are effectiveness, safety and cost — just as with mainstream therapies.

### Effectiveness

There is little evidence that alternative therapies are effective. Most have not been examined rigorously, and some of those that have been examined have not been found effective.<sup>145-147</sup>

In the USA, the National Institutes of Health have set up an Office of Alternative Medicine which aims to explore the merits of alternative therapies. Complementary therapies which concentrate on strengthening the mind-body relationship have been tested, and shown to be effective. For example, prayer is

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being tested in controlled clinical trials and thus far has been shown to be effective.<sup>148</sup> Laughter has also been effective for some individuals.<sup>149</sup> Relaxation and meditation have been tested and shown to be valuable.<sup>150</sup>

In a recent initiative, the Australian Federal Government has established a new unit to consider and evaluate complementary treatments: Office of Complementary Medicines, Therapeutic Goods Administration, Department of Health and Aged Care, PO Box 100, WODEN ACT 2606. Tel: 02 6232 8634. Fax: 02 6232 8577.

### Safety

Many alternative therapies requiring changes in diet should be safe, although diets promoting substantial weight loss should be avoided.<sup>139</sup> Meditation and spiritual approaches appear to do no harm.

Most alternative therapies involving the consumption of substances have not been assessed for safety. Their content is uncontrolled and may be quite variable.<sup>151</sup> They may be adulterated with corticosteroids or other active compounds.<sup>152</sup> They may be intrinsically toxic.<sup>153</sup> There have been reports of deaths from royal jelly,<sup>154</sup> and of hepatitis from chaparral tea,<sup>155</sup> which is a herbal remedy for cancer used by Native Americans.

The safety of megavitamins, particularly the fat-soluble vitamins, has also been questioned.<sup>156</sup> There is potential for high doses of vitamin A to cause headaches due to raised intracranial pressure.<sup>157</sup> The safety of many other compounds is unknown, as is their potential for cross-reactivity with standard therapies. One problem that is known, however, is the potential for women taking large doses of vitamin D or its derivatives to develop hypercalcaemia.<sup>158</sup>

In addition, the knowledge base of alternative therapists may be inadequate. Although some are well trained in their craft, others are not. Most alternative therapists are not yet under state regulatory control.

Many leguminous plants and some Chinese herbs, including dang quai, contain substances capable of binding oestrogen receptors. These have complex actions and the balance of background hormones will determine whether they have stimulatory or inhibitory effects on receptor binding. Until more is known of their safety these substances should be used with care by women with receptor-positive tumours.<sup>159</sup>

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Table 4: Potentially dangerous alternative therapies in women with advanced breast cancer

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- 1 Taking calcium (with or without vitamin D) for bone disease may exacerbate hypercalcaemia.
  - 2 Anaemic women receiving blood transfusions who take iron and vitamin C may develop iron overload. Anaemia in women with advanced breast cancer is usually due to the 'anaemia of chronic disease', to infiltration of the bone marrow by cancer cells or as a side effect of chemotherapy. It is almost never caused by iron deficiency. Iron overload damages cardiac muscle, as well as liver and pancreatic function.
  - 3 Vitamin C may exacerbate the toxicity of methotrexate.
  - 4 Some diets recommended for treatment of cancer, such as the beetroot diet, the grape diet and the Gerson diet, may be nutritionally inadequate.<sup>160,161</sup>
  - 5 The frequent use of enemas (such as coffee enemas or high colonic washouts) can cause electrolyte imbalances.<sup>162</sup>
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## Cost

It seems that many alternative therapies are inexpensive. In the study by Begbie et al., the median annual cost was AU\$530.<sup>138</sup> Almost two-thirds of women using alternative therapies thought they were getting value for money. In the South Australian study, mean monthly expenditure on alternative therapies ranged from AU\$1–\$500, with a median expenditure of \$10. Expenditure on alternative therapists was similar.

However, some therapies are remarkably expensive, with one woman spending AU\$20,000 per year on alternative treatments.<sup>138</sup> Since conventional therapies are effectively subsidised by governments, most patients do not pay the full cost of treatments. With alternative therapies, however, they are required to pay the full cost. Women using alternative therapies should therefore be advised to enquire about costs before embarking on a course of alternative therapies, just as is advisable for standard therapies.

## Discussing alternative therapies

These three issues need to be explored with all women with breast cancer who use alternative therapies. However, they can only be explored if the doctor is aware of the woman's use of such therapies. Begbie et al. found that 40 per cent of women with cancer using alternative therapies did not tell their doctors about them.<sup>138</sup> Presumably, those people were either not asked, or chose not to tell their doctors. It can be assumed that a negative attitude emanating from medical practitioners about alternative therapies would inhibit frank discussion. Such inhibition would mean that women would not learn of the medical practitioner's support of, or concerns for, the way in which the alternative or complementary therapies may affect the conventional treatment patterns.

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For many women, feeling they can assume some control of the treatment of their disease is psychologically empowering. The physical problems which may arise from interference with conventional therapies may be attenuated by the strong psychological value of the alternative therapy. Given that conventional therapies often hold little hope of cure for women, it is understandable that women will seek other solutions. Clinicians should also be aware that decisions to use alternative therapies may not be based on the same philosophical approach as that used by doctors.

It is to everyone's advantage if women are able to discuss alternative therapies openly, secure in the knowledge that they will continue to receive support and understanding from their doctors, whether or not those doctors agree with the therapy being used.

### 3.7 PALLIATIVE CARE

The palliative approach is the application of good symptom control in association with particular attention to the psychological, social and spiritual wellbeing of the person and her family/carers.<sup>163</sup>

It is expected that all women with advanced breast cancer will be offered the palliative approach, and that some will take up the offer of palliative care.

Palliative care may be provided in a variety of ways. Most palliative care is provided by the existing network of carers, coordinated by either the GP or the treating oncologist. The person coordinating care draws on the expertise of others already caring for the woman and may, where possible, draw on other health professionals as their particular expertise is needed. The palliative care team should be encouraged to communicate with those clinicians who have ongoing contact with the woman.

In some cases, particularly the more complex ones, palliative care is provided by specialist palliative care teams. Specialist palliative care teams should be particularly considered when the woman with advanced breast cancer has many and complex needs. A systematic review of the evidence for palliative care found that specialist palliative care services had improved patient outcomes in relation to patient satisfaction; the proportion of patients being cared for in their place of choice; family satisfaction; control of pain; symptoms and family anxiety (Level I).<sup>164</sup>

Guideline	Level	Reference
Specialist palliative care services improve patient outcomes in relation to patient satisfaction, patients being cared for in their place of choice, family satisfaction, and control of pain, symptoms and family anxiety.	I	164

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Although no data are available specifically for women with breast cancer, nor for all types of palliative care services, an idea of the scope of services in Australia can be gleaned from a paper reporting that 56 per cent of people who died of cancer during 1990 received care from a hospice service.<sup>165</sup>

#### Timing of referral

The precise time at which the services of a palliative care specialist and/or multidisciplinary team are introduced depends on the disease stage and a person's wishes and needs. Relevant considerations include the course of the individual illness and its varied symptom complexes, the psychosocial factors involved, and the proximity of the cancer centre or palliative care service to the person's home.<sup>166</sup> Early referral to a palliative care service will often be helpful. The transition, when it occurs, is facilitated if the palliative care health professionals are already an integral part of the multidisciplinary treatment team at the breast cancer centre or treating hospital.<sup>167,168</sup>

There are benefits to the woman in establishing contact with a palliative care team, even if she is relatively well, at a time when it is becoming clear that her treatment options are limited. This allows the establishment of access and contacts, with exploration of options for future care without the need for immediate decisions. Palliative care emphasises advanced planning rather than crisis intervention.

The concept of parallel care is important. Parallel care suggests a close and continuing cooperation between oncological and palliative services throughout the often prolonged course of advanced breast cancer. Parallel care may mitigate the threat of being abandoned that some women feel when referred to a palliative care service in the final stages of illness.

The involvement of palliative care professionals should not preclude the continuation or commencement of chemotherapy or hormonal treatment programs, courses of radiotherapy, or other surgical or procedural interventions aimed at reducing tumour burden or relieving symptoms.

Services and expertise should be available and offered to all women with advanced breast cancer so they can make informed choices about their care and have the opportunity of professional assistance at home.

#### Site of palliative care

As the disease progresses, care can be provided in the person's own place of residence — be it their home or another's, a nursing home, a hostel, an acute hospital or an inpatient hospice.

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### Own residence

At this time, the GP will be the local health care provider, working with the palliative care team and will visit the woman at home, if that assistance has been accepted. Depending on the particular community, the palliative care team will consist of specialist palliative care nurses or generalist community nurses with specialist nurses consulting, and a specialist palliative care physician available to advise the GP. These people are usually available 24 hours a day. Counsellors and pastoral care workers, as well as volunteer help, are also available. Links with other community services mean also that other help can be accessed as required, including physiotherapy, dietary advice, occupational therapy, home help and so on.

Although home care programs are generally assessed favourably,<sup>169-171</sup> families undertaking home care experience higher levels of stress and social disruption than those whose relatives are cared for in institutions.<sup>172</sup>

### Acute hospital

Even when the person is not expecting to receive any additional anticancer treatment, situations can arise which will be best treated in the acute hospital. These include the surgical pinning of a pathological fracture, radiotherapy for a painful bone metastasis, thoracocentesis, treatment of hypercalcaemia, pain and symptom control, and respite care.

When the patient's strength and time are limited, hospital outpatient visits for review may be burdensome and should be minimised. Patients and their families often speak of having been distressed and exhausted by tiring ambulance journeys and long waits on uncomfortable furniture, only to have been seen for a few minutes with no change in the recommended care.

Where the palliative care team works closely with the cancer team at the acute hospital, information about the patient can be exchanged without the necessity for frequent visits.

On the other hand, some patients do not wish to sever their direct links with the treatment team and continue to make what some would consider unreasonable efforts to keep appointments. An effective level of contact should be achieved, with priority based on need and anxiety. On occasions a weaning process may be required.

### Inpatient hospice

Admission for short periods may be required for symptom assessment and review of medication if new problems have arisen. Also, admission to provide respite for family/carers may be arranged and, if it is the person's wish, for terminal care.

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Women with breast cancer occasionally require long-term admission to a hospice if extensive skeletal metastases or neurological damage from spinal cord compression or brain metastases create heavy nursing requirements, mobility difficulties, and other needs which cannot be indefinitely provided in the community.

Some women with advanced breast cancer will move between home, hospital and hospice in any direction, more than once, often many times. It is important that it is clear to the woman who bears the primary responsibility for her care at various points in these events. Continuity of care can be promoted by conveying detailed and accurate information about all aspects of the woman's condition, her wishes, her needs, her treatment plan and medications.

For further information, contact state-based palliative care organisations (see Appendix I).

### Outcomes of palliative care

The outcomes of palliative care have not been assessed as rigorously as outcomes in other areas of management. Patient satisfaction, an important outcome, is one area where attempts have been made. One psychometrically sound instrument<sup>173</sup> used to measure family satisfaction with advanced cancer care is the FAMCARE Scale.<sup>174</sup> This has been modified by the Silver Chain Nursing Association in Perth to a set of 19 responses followed by two open-ended comments.

However, Hohl argues that patient satisfaction ratings are usually uniformly high, regardless of the model of care being examined, and do not give useful information leading to change.<sup>169</sup> There is no doubt that it is difficult to measure patient satisfaction with quality of care. Face-to-face interviewing and qualitative analysis may be the only way to elicit the 'subjective reality' of consumer satisfaction.<sup>175</sup>

In general, research has identified few measurable differences in different models of palliative care.<sup>171</sup> Patient satisfaction may be independent from the model of care used, whether or not agreed goals have been met. Hohl suggests that these goals should be developed jointly by the patient and the health care team.<sup>169</sup>

## 3.8 BEREAVEMENT SUPPORT

Historically, grieving has been facilitated through families, church, funeral rituals and other social customs. In many western cultures, however, there has been a move away from such formalities and rituals, and death may be a taboo subject. Thus, although grieving and response to loss is a normal task, for some people, the feelings and thoughts involved are very distressing. People in this situation will often accept an offer of help, especially when they are having difficulty resolving the loss on their own.<sup>176</sup> The woman diagnosed with breast cancer may experience grief either due to losses related to her diagnosis or treatment, or in anticipation of her death.

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There has been some research about the effectiveness of professional and professionally supported services and self-help groups in reducing the risk of post-bereavement morbidity.<sup>177</sup> In one study, patients offered support received significantly fewer prescriptions of drugs and reported fewer consultations with physicians and less of a general feeling of ill-health (Level III).<sup>178</sup> Self-help intervention has been shown to lessen the degree of morbid outcome.<sup>179</sup>

Raphael (1984) described a therapeutic assessment process for identifying people at risk of poor resolution:<sup>180</sup>

- Can you tell me a little about the death? What happened that day?
- Can you tell me about her, about your relationship from the beginning?
- What has been happening since the death? How have things been with you and your family and friends?
- Have you been through any other bad times like this recently or when you were young?

With regard to breast cancer, two specific situations are common:

- grief after the death of a wife or partner from breast cancer; and
- grief complicating a long and debilitating illness.

#### Grief after death

A study comparing the sex differences in health risks of the widowed by Stroebe and Stroebe (1983)<sup>181</sup> found that men suffer after bereavement more than women, both physically and psychologically, and are most vulnerable shortly thereafter. Men have described their experience as a dismemberment,<sup>182</sup> were more likely to be uncomfortable with the direct, emotional expression of grief and seemed to require more rational justification for their thoughts and feelings; however, they appeared to make more rapid social recovery. After the death, men required more assistance in coping with the resulting practical problems — such as obtaining help with the housework and children.

Specific recommendations for working with bereaved spouses and partners include:

- Help the griever identify functions and roles previously assumed by their partner.
- Be aware of any consequent loss of social connection that the death of the patient may bring about. Determine whether the survivor can manage independently, particularly if elderly.
- Assist the survivor in maintaining appropriate relationships with and role expectations for children. Children, especially when living at home, may have unrealistic expectations placed upon them.

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- Provide the surviving parent with appropriate information about family dynamics and grief in children.
  - Work towards an appropriate redefinition of identity.
  - Be aware of sex differences with regard to perception of loss, expressions of grief, social versus emotional recovery and differing focus of needs.
  - Refer to self-help group or professional counselling if needed.<sup>183</sup>

Grief following a long and debilitating illness

Grief after a long and debilitating illness can predispose survivors to poorer outcomes.<sup>184</sup> This is due to:

- coping with remissions and relapses, and the demands of debilitating illness;
- managing anticipatory grief, uncertainty, anxiety and the consequences of chronic and unremitting stress;
- confusion resulting from the uncertain course of the illness;
- handling increased financial, social, physical, time and emotional demands;
- surviving long-term family disruption and disorganisation;
- coping with consequences commonly observed in the families of the very ill person—psychological conflicts, emotional exhaustion, physical debilitation, social isolation and family discord as well as the typical emotional reactions of guilt, anxiety, sorrow, depression, anger and hostility;
- managing intensive treatment regimens and their side effects; and
- confronting dilemmas about decision-making and treatment choices.

The grief of children

Most of what is true for adults in grief also holds true, in age appropriate ways, for children.<sup>183</sup> Children display a variety of reactions to the death of someone they love. Understanding children's experience of bereavement requires knowledge of their relationships, concepts of death and bereavement and responses across several age groups. Raphael (1984) provides a useful framework for understanding these concepts.<sup>180</sup>

There are three needs of children described by Furman (1970) which are easily overlooked:<sup>185</sup>

- their life;
- that children grow up with the loss — important events in the child's life will remind them of the lost relationship; and

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- that young children need both a significant male and female to relate to — it is important to have the opportunity to identify and interact with adults of both sexes.

Below are some simple and useful interventions for meeting the need of bereaved children:<sup>176</sup>

- children need information that is clear and comprehensible, taking into consideration their age and affective understanding. Children do not talk sufficiently about the circumstances of the death;
- children need to feel involved and important in ritual and other family occasions;
- children need reassurance about adult grief — especially if it is intense;
- children need their own thoughts and feelings — they should be allowed to grieve in their own, individual way as their relationship with the person who has died was different from that of any adult;
- they are still children, and need to be able to maintain appropriate interests and activities;
- children need to be able to memorialise, retaining the connection with the person who has died; and
- children need a functioning parent.

The grief of parents of adult children

Older parents of adult children who die may be in a uniquely vulnerable situation, as much of the support will be given to the surviving partner and children. A basic function of a parent is to preserve the family and protect their child, and there is an implicit expectation that the parent will die before the child. No matter what the age of their child, parents experience the loss of hopes, dreams and expectations for that child — they have lost parts of themselves and their future.<sup>183</sup>

Guideline	Level	Reference
Professional and professionally supported services may reduce the risk of post-bereavement morbidity.	III	178

### 3.9 REQUEST FOR AN AUTOPSY

Autopsies may prove of considerable value in addressing unanswered questions that existed clinically. However, clinicians need to be aware that any request they make for an autopsy comes at a time of intense grief, distress and uncertainty for families. While some families may find that the results of an autopsy are helpful in

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understanding the course of the disease, it is important that families are given a realistic time frame for final results of an autopsy to become available.

Even though the mental state of the relatives is likely to make the request difficult, there is evidence that this task is often delegated to junior staff (Level IV)<sup>186</sup> who are offered little training (Level IV).<sup>187</sup> Such practices not only undervalue the traumatic impact of this work on junior staff, but are a failed opportunity for preventing psychological distress among the patient's family and among staff (Level IV).<sup>188</sup>

Clinicians should recognise that attitudes towards autopsy are shaped by personal and cultural attitudes toward death and medical science, and also by the context in which the request is made. Many of the techniques detailed in the section on telling a woman she has advanced cancer (see section 3.4) can be adapted to requesting an autopsy. It is essential that the request for autopsy be followed with clear communication of the results, as this feedback is crucial for families. The senior clinician should arrange a time — usually a few weeks after the death — to meet with the surviving family members to explore any concerns that may persist or may have emerged since the woman's death.

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## CHAPTER 4 THE MANAGEMENT OF LOCALLY ADVANCED BREAST CANCER

This chapter discusses the management of locally advanced disease. However, the user of this guideline should be aware that sections of subsequent chapters (Chapters 7–11) may also have relevant information pertaining to the management of this condition.

Locally advanced breast cancer represents 10–20 per cent of all cases of breast cancer at presentation.<sup>189</sup> It is less common than it used to be,<sup>190</sup> presumably because of greater awareness of breast cancer.

Surprisingly, most women with locally advanced disease do not have evident systemic disease, although it is often suspected. Despite common belief, the prognosis is not inevitably poor. With multimodality therapy (discussed below), five-year survival rates for stage IIIA disease (T0–2, N2, M0 and T3, N1–2, M0) of 84 per cent and for stage IIIB disease (T4, N1–3, M0, and T1–4, N3, M0) of 44 per cent have been reported in one study (Level IV).<sup>191</sup> Likewise, four-year disease-free and overall survival rates for inflammatory cancer — often erroneously considered to have a uniformly dire prognosis — have been reported as 54 per cent and 74 per cent respectively (Level IV).<sup>192</sup>

The prognosis may be such that even if mastectomy is required, women could be informed that a form of reconstruction may be possible, and this should be discussed with the woman if she wishes.

Key point	Level	Reference
In one study, five-year survival for women with locally advanced stage IIIA breast cancer is 84 per cent, and for locally advanced stage IIIB cancer is 44 per cent.	IV	191

### Diagnosis

The initial assessment of locally advanced breast cancer is the same as for any woman presenting with advanced breast cancer. It must include confirmation of the clinical diagnosis by biopsy, as well as tests to determine the extent and nature of any metastases. See section 3.2 for details.

### Treatment

The best outlook for patients with stage III breast cancer is obtained by using combined modality therapy with surgery, radiotherapy and systemic therapy (chemotherapy and/or hormone therapy). Treatment of local disease in women

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with locally advanced breast cancer must be more intensive than in women with early breast cancer, because the tumour is larger or involves tissue other than breast soft tissue.

Due to the potential complexity of the treatment program, patients with stage III breast cancer need to be seen by the various specialists, so the order of treatments can be agreed upon, ideally in a multidisciplinary clinic. As a consequence of the paucity of randomised controlled trials involving women with locally advanced disease, there is considerable uncertainty as to the optimum order of these treatments and whether all four treatments are required for the best results. There is some evidence<sup>193-195</sup> and reasonable agreement that if multimodality treatment is considered the best option, then the optimal program could entail:

- chemotherapy (known as neoadjuvant chemotherapy if given before radiotherapy or surgery);
- local therapy (either surgery or radiotherapy);
- then more chemotherapy;
- then consideration of further local therapy - whichever was not used previously; and
- endocrine therapy (for example, tamoxifen if the tumour is oestrogen receptive, for at least five years (Level IV)).<sup>193-195</sup>

Regular clinical follow-up is recommended because of the relatively high risk of local relapse.

### Chemotherapy

Even though there is no evidence that any particular combination is superior in locally advanced breast cancer, it is common practice to use a combination which includes an anthracycline. Anthracyclines should be avoided if chemotherapy is to be given at the same time as radiotherapy, because of the risk of potentiating the radiation reaction.

Neoadjuvant chemotherapy, preceding local therapy may reduce the tumour to such an extent that an operation, even breast conserving surgery (particularly for T3 lesions) is feasible in women whose lesion would not initially have allowed this option (Level II).<sup>196</sup> Appropriate local therapy — radiotherapy, or surgery followed by radiotherapy — is often followed by further adjuvant chemotherapy.

Endocrine therapy should also be considered for women with locally advanced breast cancer, particularly for those with hormone receptor positive tumours (either oestrogen receptor or progesterone receptor positive). Tamoxifen 20mg daily for five years is suitable for pre- or post-menopausal women; ovarian ablation should also be considered for pre-menopausal women. This recommendation is based on the efficacy of ovarian ablation and tamoxifen in reducing the risks of recurrence and death in women with early breast cancer (Level I),<sup>197</sup> and on their

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efficacy in women with advanced breast cancer (Level I),<sup>122,198-200</sup> rather than on evidence in women with locally advanced breast cancer.

See Chapter 6 for more details on chemotherapy.

Guidelines	Level	Reference
Optimal management of locally advanced breast cancer is a combined approach that uses chemotherapy, radiotherapy, surgery and/or endocrine therapy if applicable.	IV	193
Chemotherapy before local therapy (neoadjuvant chemotherapy) for women with locally advanced disease may substantially reduce the tumour size.	II	196
Endocrine therapy should also be considered for women with locally advanced breast cancer, particularly for those with hormone receptor positive tumours.	I	199, 200

### Surgery

In most cases involving surgery, mastectomy is required. If surgery is chosen as the form of treatment for the axilla, a level III (full) dissection should be performed to decrease risk of regional relapse. Breast reconstruction techniques may be applicable in selected patients. Breast conserving surgery may be feasible after neoadjuvant chemotherapy.

If radiotherapy is given first, surgery for known or anticipated residual disease should be delayed until the radiation reaction has settled down. This may take six to eight weeks.

### Radiotherapy

Radiation therapy needs to be given in appropriately high doses to the entire breast tissue and nodal areas. However, due to the implications for lymphoedema, irradiation of the axilla should only be conducted if the completeness of surgery is in doubt. If there is doubt about axillary clearance or there is residual macroscopic disease after surgery, the axilla should be irradiated. Consultation with a radiation oncologist is appropriate in the planning of treatment.

In addition, areas of palpable disease will require further radiation, either with external beam or possibly a brachytherapy implant.

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For most locally advanced carcinomas, conventional fractionation of two Gray per fraction is considered adequate, but this can be modified if the history is that of a rapidly growing tumour.

Tissue equivalent build-up material to bring up the radiation dose to the skin surface may be required for local control in the presence of peau d'orange, ulceration or any skin involvement. This will make the skin reaction more florid and is likely to cause temporary desquamation.

#### Exceptions

There are exceptions to the intensive multimodal approach. One such example is the elderly and frail woman with a receptor-positive tumour, in whom tamoxifen alone (20 mg/day) is likely to reduce substantially tumour size and morbidity with few or no side effects. Response rates of 45-68 per cent to tamoxifen alone have been reported (Level III;<sup>201</sup> Level II<sup>202</sup>). Of course, in such situations the patient must be reviewed at regular intervals and additional treatment applied should the disease progress. Alternatively, if the disease remains static, continued hormone therapy may be considered.<sup>202</sup>

#### Inflammatory carcinoma

Inflammatory carcinoma presents clinically with involvement of the whole breast with redness and oedema and is characterised pathologically by infiltration of dermal lymphatics with tumour cells. Neoadjuvant pre-operative chemotherapy produces high clinical response rates, particularly if anthracycline-based regimens are used and favourable responses are associated with improved survival (Level IV).<sup>203</sup>

Mastectomy and radiotherapy are also recommended, followed by endocrine therapy if the tumour is receptor positive.<sup>193,200</sup> Sequential high dose chemotherapy with stem cell transplantation is being explored in this setting in a large phase II trial (PEGASE 02), with high pathological complete response rates reported (32 per cent).<sup>204</sup> Mature results are awaited and a randomised trial will be required to compare this approach with standard dose therapy.

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## CHAPTER 5 THE MANAGEMENT OF LOCOREGIONAL RECURRENCE

Although this chapter specifically focuses on the management of locoregional recurrence, the reader is also directed to subsequent chapters which contain information that is also relevant to the management of this condition (Chapters 7–11).

The development of a locoregional recurrence after breast cancer is a psychologically traumatic event for the woman concerned. It may be even more traumatic than the initial diagnosis, with the woman's confidence that she might have beaten the disease being destroyed (Level III).<sup>65</sup> The attending practitioner must therefore consider the psychosocial impact of recurrences as well as the physical aspects of diagnosis and treatment.

### Locoregional recurrence following mastectomy

Following mastectomy, locoregional recurrence is defined as recurrent disease in the chest wall, the skin, subcutaneous tissue, muscle or contents of the axilla and internal mammary chain. About five per cent of women with breast cancer treated by modified radical mastectomy will present with locoregional recurrence. Although later recurrences can be observed, 80–90 per cent of locoregional failures after mastectomy occur within five years of therapy (Level III).<sup>205</sup>

### Diagnosis

It is desirable that biopsy evidence of local recurrence be obtained before any consideration of therapy. In instances of unresectable or diffuse chest wall involvement, fine needle biopsy or core biopsy should be performed to establish the diagnosis. The initial assessment should also include tests to determine the nature and location of any metastases, given that a considerable proportion of such women will have associated metastatic disease (see 'Prognosis' below).

### Treatment

Complete excision of gross disease reduces tumour burden, which allows more effective radiotherapy. When determining the optimal surgical treatment for extensive local disease, the woman's medical condition is an important factor to consider. If the local recurrence is too extensive for excision with primary closure, radiotherapy should be used as an alternative to surgery. There is no benefit in partial excision and radiation to clear the remainder. High rates of complete response can be achieved with radiotherapy alone.<sup>206</sup> Extensive local recurrence after previous radiotherapy may require excision and skin graft or flap repair.

The addition of radiotherapy after complete excision of tumour recurrence significantly improves local control (Level I).<sup>207</sup> Radiotherapy should be administered to the entire chest wall and draining nodal areas if they have not been previously irradiated.

The potential benefits of combining irradiation and systemic therapy on local control and subsequent survival are uncertain, although a number of uncontrolled trials have suggested improved survival for the combined approach (Level IV).<sup>208,209</sup>

### Prognosis

Local recurrence after mastectomy is often a marker of progression of systemic disease (Level II),<sup>210</sup> and is associated with a worse prognosis than local recurrence after breast conservation surgery. Five-year survival rates range from 34–64 per cent in patients with locoregional recurrence after mastectomy (Level IV).<sup>211</sup> Poor prognostic factors include a disease-free interval of less than two years,<sup>206</sup> positive nodal status, large tumour size and negative hormone receptor status and the omission of radiotherapy (see section on ‘treatment’ above). Other poor prognostic factors include multiple versus single nodule recurrence and unresectable versus completely excised recurrences. (Level I;<sup>207</sup> Level III;<sup>212</sup> Level III;<sup>213</sup>).

Key point	Level	Reference
Five-year survival for women with locoregional recurrence after mastectomy is 34–64 per cent	IV	211

Guidelines	Level	Reference
Complete excision of locoregional recurrent macroscopic disease allows more effective radiotherapy and improves local control. Radiotherapy should be administered to the entire chest wall and draining nodal areas if they have not been previously irradiated.	III	205
If the local recurrence is too extensive for excision with primary closure, radiotherapy should be used as an alternative to surgery, as high rates of complete response can be achieved with radiotherapy alone.	IV	206

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## Locoregional recurrence following breast conservation

Following breast conservation, locoregional recurrence is defined as recurrent cancer in the ipsilateral breast or in local soft tissues, the ipsilateral axillary, infraclavicular or internal mammary nodes. Women with locoregional recurrence after breast conserving surgery are at increased risk of developing distant metastases (Level III).<sup>214-218</sup> After conservative surgery and radiotherapy, local recurrence occurs at the rate of about one per cent per year for the first decade.<sup>14,219,220</sup> When all modalities are taken into account about 70–80 per cent of breast cancer recurrence occurs within five years of initial diagnosis and therapy (Level III).<sup>221,222</sup>

### Diagnosis

Local recurrence after breast conservation is detected by either the clinical presence of an abnormality or at regular mammographic follow-up. Changes at mammography may be difficult to interpret due to the presence of scar tissue at the operation site. Following radiotherapy to the breast, pathological diagnosis may be difficult and atypia is commonly reported. Stereotactic core biopsy is thus preferable to fine needle biopsy (Level IV).<sup>223</sup> MRI has been advocated but is less sensitive.<sup>214</sup> The initial assessment should also include tests to determine whether any distant metastases are present.

### Treatment

Most women with locoregional recurrence after breast conservation present with a cancer that is operable. In some women, surgery is inappropriate either because of simultaneous distant metastases, or because locoregional recurrence is too extensive. However, further conservative excision may be feasible in some patients, especially if the breast has not previously been irradiated (Level III).<sup>222</sup>

Mastectomy is recognised as the standard treatment for breast relapses after primary treatment with breast conservation, although local excision may be considered for a small recurrence. There is only limited clinical information on the efficacy and safety of less radical surgery. Locoregional control after such surgery is reported in 36–92 per cent of cases (Level III).<sup>222,224</sup> If a further breast conserving approach is used and the woman has not had previous radiotherapy, then radiotherapy to the residual breast is appropriate.

Isolated regional lymph node recurrence after axillary dissection associated with breast conservation is uncommon and if radiotherapy has not been given to the axilla previously, is best treated with surgery and radiotherapy. Treatment may lead to lymphoedema. This should be discussed with the woman before treatment commences, and suitable physiotherapy should be arranged.

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## Prognosis

As with local recurrence after mastectomy, local recurrence after breast conservation may be a marker for associated systemic disease, although to a lesser degree than local recurrence after mastectomy. This is particularly the case with local recurrence occurring within the first year (Level III).<sup>215,216</sup>

Key point	Level	Reference
After conservative surgery and radiotherapy, local recurrence occurs at the rate of about one per cent per year for the first decade.	II	14, 219, 220

Guidelines	Level	Reference
Local recurrence after breast conservation may be a marker for associated systemic disease, although to a lesser degree than local recurrence after mastectomy.	III	215, 216
Mastectomy is the standard treatment for locoregional recurrence after primary treatment for breast conservation to attain locoregional control.	III	222, 224

## Systemic therapy after locoregional recurrence

As locoregional recurrence may occur in association with distant metastases, investigation with bone and CT scans will be appropriate for accurate staging and prognostication. If distant disease is found, treatment should proceed as described in Chapters 6–11, with local disease being treated if symptomatic.

In women with localised disease, systemic therapy may be considered after local treatment with surgery or radiotherapy, in an effort to prevent later distant relapse. In patients with oestrogen receptor (ER) positive tumours, or ER unknown tumours with a disease-free interval of greater than 12 months and minimal tumour burden, tamoxifen improves disease-free and overall survival compared with observation (Level II).<sup>225</sup> In receptor negative patients or those progressing despite adjuvant tamoxifen, chemotherapy may be indicated. A single study demonstrated improved disease-free survival with a 24-month program of chemoimmunotherapy (5FU, adriamycin, cyclophosphamide and BCG) compared with historical controls (Level III).<sup>217</sup> Retreatment with the same chemotherapy given in the adjuvant setting (CMF) also induced responses in patients with soft tissue locoregional recurrences, provided at least 12 months had elapsed from original therapy.<sup>218,226</sup>

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Guideline	Level	Reference
Systemic therapy may improve disease-free survival after local therapy for locoregional recurrence:		
• tamoxifen	II	225
• chemotherapy	III	217

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## CHAPTER 6 THE MANAGEMENT OF METASTATIC BREAST CANCER

This chapter deals with anticancer therapies for metastatic disease, and with chemotherapy and endocrine therapy in particular. In most cases, a combination of anticancer and supportive therapies will provide the most effective overall management of metastatic disease. The extent to which these different approaches are used and combined will vary according to each woman's unique circumstances.

Before initiating treatment, it is desirable to obtain histological or cytological confirmation of metastatic disease.

Systemic anticancer therapies are drugs given orally or parenterally that treat tumour cells in all parts of the body. This differs from local therapies, such as surgery and radiotherapy, which affect only those parts of the body at which they are directed.

Anticancer therapies work by either killing cancer cells or inhibiting their growth. By reducing the number of cancer cells in the body, they may improve the symptoms and other consequences of the cancer. Although such therapy is often helpful, once breast cancer spread to multiple distant sites is apparent, it is unable to completely rid the body of cancer. Anticancer therapy for metastatic breast cancer is therefore best regarded as a controlling rather than a curative treatment.

Supportive therapies which reduce the detrimental effects of the cancer without affecting its growth are also important, and are described in Chapter 11.

Evidence for efficacy of systemic anticancer therapies

The evidence and recommendations on chemotherapy and endocrine therapy presented here are principally based on the findings of two separate systematic reviews of published randomised controlled trials, other studies and expert opinion. One set of systematic reviews was prepared for the British National Health Service in 1996,<sup>122,198</sup> and the other was specifically conducted for the National Breast Cancer Centre in 1997.<sup>199,200</sup> The goals of treatment are to improve both the quality and duration of survival, and although these reviews found limited data regarding quality of life, such evidence is crucial, given that the effects of treatment on overall survival are modest.

Does systemic therapy prolong survival in metastatic breast cancer?

Ideally this question would be answered by trials comparing best supportive care with and without systemic anticancer therapy. However, no randomised trials directly comparing these approaches in metastatic breast cancer have been published. Neither are such trials likely to be carried out in the future, because

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endocrine therapy and chemotherapy have become standard treatments for women with advanced breast cancer on the basis of evidence that they kill cancer cells in test tubes, that they shrink tumours in women with advanced breast cancer, and that women so treated report improved quality of life (Level II).<sup>227</sup>

Indirect support for the use of anticancer therapies in metastatic breast cancer comes from two sources. Firstly, there is overwhelming evidence that both endocrine therapy and chemotherapy prolong survival in women with early breast cancer (Level I).<sup>228</sup> It would be surprising if these treatments had no effect on survival in metastatic disease. Secondly, randomised trials of endocrine therapy and chemotherapy in advanced breast cancer also provide indirect evidence of efficacy. This evidence is further discussed below, but can be summarised in this way:

- treatment with a greater number of cycles of chemotherapy is associated with longer survival (Level I)<sup>199,200</sup> and better quality of life (Level II)<sup>227</sup> than treatment with a fewer number of cycles; and
- treatment with standard doses of chemotherapy is associated with longer survival and better quality of life than treatment with less than standard doses (Level II).<sup>229</sup>

When should treatment start?

There are no randomised trials that have assessed the effects of delaying treatment on survival or quality of life. The question of when to start treatment, particularly in asymptomatic women, remains unanswered and is a matter of judgement for the woman and her doctor. Factors to be taken into consideration include the woman's disease-related symptoms, the toxicity of possible treatments, and the anticipated effects of disease and treatment on her life expectancy.

Should initial treatment be endocrine therapy, cytotoxic therapy or both?

Only two trials have addressed this issue, and they do not support the superiority of either treatment over the other (Level I).<sup>199,200</sup> It is widely believed that chemotherapy is preferable to endocrine therapy in the presence of rapidly progressing visceral disease (ie liver, brain or lung) (Level IV).<sup>230</sup>

However, a large randomised trial of the Australian New Zealand Breast Cancer Trials Group compared three policies for initial therapy of metastatic breast cancer — tamoxifen alone, chemotherapy alone (using a combination of doxorubicin and cyclophosphamide) and combined chemotherapy and tamoxifen. Groups assigned to either treatment modality alone were to cross to the other on disease progression. There was no significant difference in survival between these three approaches.<sup>62</sup> Subgroup analysis showed that there was no survival deficit for initial tamoxifen, even among patients with poor prognostic

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features such as negative oestrogen receptor or liver metastases; it should be stressed that patients were switched to cytotoxic therapy promptly on disease progression. Quality of life was not measured in this trial, but the lesser toxicity and equivalent outcome support a policy of initial endocrine therapy with tamoxifen.

The patient's preferences, views, physical status and emotional status also influence the selection of the treatment.

### Endocrine therapy

Many endocrine therapies are effective in producing antitumour responses in metastatic breast cancer (see Table 5). They include:

- measures to reduce normal hormone levels (ablative therapies and agents which inhibit hormone synthesis);
- the use of pharmacological doses of hormones (oestrogens, progestins or androgens); and
- the use of agents aimed at interfering with the effect of hormones on tumour cells (antioestrogens).

Several factors are associated with an increased chance of response to endocrine therapy. These include the ability to detect hormone receptors in the primary tumour, a long interval between initial treatment and subsequent progression, greater age of the patient, and malignant disease restricted to soft tissue and/or bone (Level IV).<sup>230</sup> However, while these features are helpful, they are not definitive, as responses are seen in women without any of these characteristics.

A response to one form of endocrine therapy often indicates sensitivity to subsequent endocrine manipulations (Level III).<sup>231</sup> Women with advanced disease may thus be treated over time with a series of endocrine therapies. Both objective tumour response and prolonged maintenance of stable disease (for example, greater than six months) are associated with a greater likelihood of response to subsequent endocrine therapy (Level III).<sup>223,233</sup> Progressive disease in the first six months on first line endocrine therapy predicts for poorer survival on second line endocrine therapy (Level III).<sup>232</sup>

The value of continuing endocrine therapy in women with stable disease but without major tumour shrinkage is highlighted by a study of first and second line endocrine therapy where patients with disease stabilisation had comparable survival to women with substantial tumour shrinkage.<sup>232</sup>

### Which endocrine therapy?

Using overall survival as the endpoint of efficacy, there is no evidence that any one particular agent is superior to all others (Level I).<sup>122,198-200</sup> The choice among endocrine therapies is therefore based on other factors, particularly differences in toxicity.

Ablative endocrine therapies date from the demonstration by Beatson that surgical oophorectomy-induced tumour shrinkage.<sup>234</sup> Suppression of ovarian function by radiation therapy or LHRH (luteinising hormone releasing hormone analogues) has similar effects. This approach remains valuable, though only in premenopausal women.

Surgical ablation of the adrenal or pituitary has been replaced by pharmacological endocrine suppression.

Aromatase inhibitors reduce circulating oestrogen levels in post-menopausal women. Aminoglutethimide is the oldest drug of this class, but it also affects other adrenal steroids. It produces rash and somnolence in some patients. Newer selective aromatase inhibitors include anastrozole and letrozole. While their place in routine therapy is evolving, recent trials suggest at least equivalent efficacy and less toxicity than megestrol acetate or aminoglutethimide as second line endocrine therapy.<sup>235-238</sup> Comparison with tamoxifen as first line therapy for advanced disease is ongoing.\*

The side effects of endocrine therapies are usually mild and these drugs are generally well tolerated. Table 5 lists the most commonly used agents, together with their potential side effects.

Table 5: Endocrine agents used in therapy of metastatic breast cancer\*

GROUP	EXAMPLES	NOTES	POSSIBLE SIDE EFFECTS
Ovarian ablation	Surgical oophorectomy	May be laparoscopic	Menopause permanent
	Ovarian irradiation	Delayed effect	Menopause permanent
	LHRH analogues	Requires injections every 1–3 months	Menopause potentially reversible
Antioestrogens	Tamoxifen 20mg/day	Established first line drug	Generally well tolerated. Common and mild side effects include hot flushes, irregular periods and vaginal discharge
	Toremifene 240 mg/day	Tamoxifen analogue, more selective ER modulator	Rare and severe side effects include thromboembolism and endometrial carcinoma
Aromatase inhibitors	Anastrozole, letrozole	Preferred second line treatments for post-menopausal women	For use in post-menopausal patients, generally mild (including hot flushes)
Progestins	Medroxyprogesterone acetate 500 mg/day	Second or third line treatment	Weight gain, fluid retention, vaginal bleeding, venous thromboembolism
	Megestrol acetate 160 mg/day	As above	As above

\* Preliminary results suggest that anastrozole was of equal efficacy with tamoxifen in first line treatment of post-menopausal women and had somewhat fewer side effects.<sup>239</sup>

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Based on the systematic reviews,\* combinations of endocrine agents used together appear no more effective than single endocrine agents used sequentially (Level I).<sup>199,200</sup> Higher doses of any given agent are not superior to lower doses (Level I),<sup>228,199,200</sup> and a single trial examining the use of different doses of megestrol acetate showed that doses above 160 mg per day were associated with reduced quality of life (Level II).<sup>240</sup> Meta-analysis of randomised controlled trials raises the possibility that the addition of endocrine therapy to chemotherapy may be beneficial (Level I).<sup>199,200</sup> This question warrants further clinical trials.

In summary, endocrine therapy should be recommended for all women with hormone-receptor positive metastatic disease. The likelihood of response to endocrine therapy is small in women with hormone-receptor negative breast cancer. The following recommendations about endocrine therapy apply to women with hormone-receptor positive disease.

Tamoxifen and progestins are effective in both pre-menopausal and post-menopausal women. In pre-menopausal women ovarian ablation is also effective. Aromatase inhibitors are effective in post-menopausal women. Pre-menopausal women should be rendered post-menopausal with some form of ovarian ablation before aromatase inhibitors are used. The optimal sequence of endocrine agents depends mainly on side effects and convenience.

Tamoxifen 20mg daily is appropriate first line endocrine therapy for all women with hormone receptor positive breast cancer based on its effectiveness and limited toxicity (Level I).<sup>122,198-200</sup> Ovarian ablation is also suitable first line therapy in pre-menopausal women (Level II).<sup>199,200,241</sup> Aromatase inhibitors and progestins are effective following progression on tamoxifen or intolerance to it (Level I).<sup>199,200</sup>

The newer aromatase inhibitors (eg anastrozole and letrozole) may be preferable to progestins as second line endocrine therapy because of their better toxicity profile and possibly greater effectiveness (Level II).<sup>242,243</sup> Aminoglutethimide is no longer recommended. Figure 2 is a flow chart of endocrine therapy for women with hormone receptor positive breast cancer.

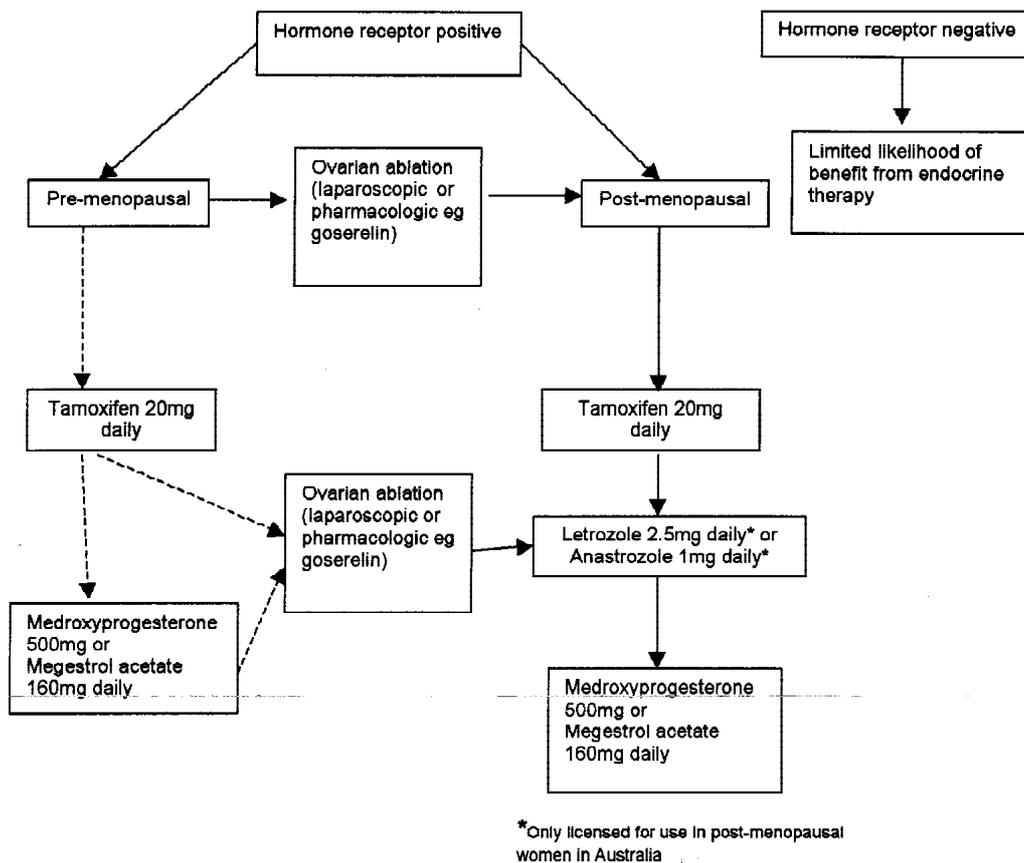
\* A recent trial reported that the combination of tamoxifen and buserelin yielded better results than either drug alone.<sup>244</sup>

Guidelines	Level	Reference
In women with hormone receptor positive breast cancer without rapidly progressing visceral disease, endocrine therapy and chemotherapy are both reasonable options.	I	200, 199, 62, 245
In women with rapidly progressing visceral disease, limited evidence suggests that chemotherapy is better than endocrine therapy.	IV	230
There is no evidence that any one particular endocrine therapy is more effective than others.	I	122, 198, 199, 200
Tamoxifen is the endocrine therapy with the fewest side effects.*	I	122, 198
Within the standard range, higher doses of any given endocrine agent are no more effective than lower doses.	I	200, 199
Combinations of endocrine agents are no more effective than single endocrine agents used sequentially.**	I	199, 200
A response, including disease stabilisation, to one form of endocrine therapy often indicates sensitivity to subsequent endocrine manipulations.	III	231

\* Preliminary results suggest that anastrozole was of equal efficacy with tamoxifen in first line treatment of post-menopausal women and had somewhat fewer side effects.<sup>239</sup>

\*\* A recent trial reported that the combination of tamoxifen and buserelin yielded better results than either drug alone.<sup>244</sup>

Figure 2: Flow chart of endocrine therapy for women with advanced breast cancer and hormone receptor positive tumours



## Chemotherapy

Strictly speaking, chemotherapy means treatment with chemicals (ie drugs) for any purpose, but the term is generally applied to cytotoxic drugs used in the treatment of cancer. Chemotherapy drugs act in numerous ways to interfere with cell function. They are designed to have a more damaging effect on cancer cells than on normal cells. The desired result is the death of cancer cells, but normal cells are inevitably damaged to some extent. This is the cause of treatment toxicity.

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### Combinations versus single agents

There is evidence that the use of combination chemotherapy rather than single agent chemotherapy is associated with a modest survival benefit (Level I).<sup>122,198</sup> However, these trials were designed in the 1970s and 1980s and do not include comparisons with newer single agents such as the taxanes, vinorelbine or capecitabine.

### Number of cycles

Chemotherapy given for a greater number of cycles rather than a fewer number (for instance six or more versus four or fewer) is likewise associated with a modest prolongation of overall survival (Level I).<sup>199,200</sup> This evidence of a survival benefit is enhanced by data from the largest of these randomised trials, which demonstrated that the use of a greater number of cycles of chemotherapy was also associated with better quality of life (Level II).<sup>227</sup>

### Dose

There is no evidence that, within the range of usual doses, there is any benefit in higher as opposed to lower doses of chemotherapy (Level I).<sup>122,198-200</sup> There is, however, evidence that lower than standard doses of chemotherapy are associated with reduced overall survival and quality of life (Level II).<sup>229</sup>

### High doses with stem cell support ('bone marrow transplantation')

Current evidence does not support the use of high dose chemotherapy with stem cell support in advanced breast cancer (Level II).<sup>246</sup> A single trial reported a substantial survival benefit (doubling of median survival) associated with the use of high dose chemotherapy with stem cell support in women with advanced breast cancer.<sup>247</sup> The trial was small and the chemotherapy used in the control arm is not a recognised standard. This trial received wide attention. However, its results are now in serious doubt following an independent review of another trial of high dose chemotherapy conducted by the same principal investigator and his subsequent admission of scientific fraud.<sup>248,249</sup> A larger randomised trial reported subsequently has shown no benefit associated with high dose chemotherapy with stem cell support.<sup>246</sup>

### Drug selection

In early breast cancer, systematic review of randomised trials suggests a modest benefit associated with the use of anthracycline containing chemotherapy over non-anthracycline containing chemotherapy. Randomised trials in advanced breast cancer have not shown a survival benefit with anthracycline containing over non-anthracycline containing chemotherapy (Level I).<sup>122,198</sup> Evidence does not support adding chemotherapy to endocrine therapy (Level I) — that is, it

does not suggest that concurrent chemotherapy and endocrine therapy is superior to endocrine therapy followed by chemotherapy.<sup>199,200</sup>

Modest benefits in survival due to chemotherapy must be weighed against possible increases in side effects. Randomised controlled trials (RCTs) of chemotherapy assessing quality of life would best address this problem, but such trials are disappointingly rare. The few trials that have assessed quality of life indicate that more effective anticancer therapy improves quality of life.<sup>227 229,245,250</sup> This suggests that on average, improvements in cancer related symptoms due to more effective chemotherapy outweigh extra side effects. Overall, the policy of giving standard doses of combination chemotherapy over several cycles (perhaps six cycles or more) is the best supported option for maximising both overall survival and quality of life.

Guidelines	Level	Reference
Treatment with a greater number of standard cycles of chemotherapy is associated with: • longer survival; and • better quality of life than treatment with a fewer number of cycles.	I II	200, 199 227
Within the range of usual doses, there is no evidence that higher doses are of greater benefit than lower doses.	I	122, 198 199, 200
There is no evidence of benefit for adding chemotherapy concurrently to endocrine therapy.	I	199, 200
Treatment with standard doses of chemotherapy is associated with longer survival and better quality of life than treatment with less than standard doses.	II	229
Current evidence does not support the use of high dose chemotherapy with stem cell support in advanced breast cancer.	II	246
Combination chemotherapy confers a modest survival benefit over single drug therapy.	I	122, 198

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Which chemotherapy drugs?

Response rates to single agents are highly variable with greater responses in previously untreated women. The highest rates are reported for anthracyclines, taxanes and vinorelbine. Other commonly used drugs with lower single agent response rates include cyclophosphamide, 5-fluorouracil, methotrexate, mitoxantrone, mitomycin, and cisplatin (Level III).<sup>251</sup>

Evidence to support the choice of a particular combination is limited. Of nearly 500 randomised trials identified by a systematic review, 170 were identified as studying chemotherapy.<sup>199,200</sup> Most of these trials compared different combinations of chemotherapy drugs. The difficulty is in establishing a fixed point for comparison. As noted above, the indirect evidence supporting the value of chemotherapy rests on trials of standard versus lower doses, and of more versus fewer cycles of chemotherapy. It seems logical to accept the actual regimens used in these trials as standard therapies, to remove any that are subsequently shown to be inferior and to add regimens that have been adequately tested against one of the resulting standard regimens. The standard therapies identified by this approach are listed in Table 6 below. Small comparative trials which merely fail to show a difference between a standard regimen and an alternate regimen provide only weak evidence of equivalence.

Table 6: Standard chemotherapeutic regimens

Regimen	Doses	Comment/References
ACT	Doxorubicin 50mg/m <sup>2</sup> plus Cyclophosphamide 750mg/m <sup>2</sup> each 3 weeks*	227
CMF(P)	Cyclophosphamide 100mg/m <sup>2</sup> orally days 1–14  Methotrexate 40mg/m <sup>2</sup> days 1,8  5-Fluorouracil 600mg/m <sup>2</sup> days 1,8  (Prednisone 40mg/m <sup>2</sup> orally days 1–14 may also be given) <sup>252,253</sup>  (Standard or oral CMF)	Level II evidence that intravenous CMF q21d is inferior <sup>254</sup>
Taxane <sup>†</sup>	Paclitaxel 175–200 mg/m <sup>2</sup> 3 hours each 3 weeks or  Docetaxel 75–100 mg/m <sup>2</sup> 1 hour each 3 weeks	255  256
Vinorelbine <sup>†</sup>	30mg/m <sup>2</sup> /D1 and D8 of a 3-week cycle	257
Capecitabine**	2500mg/m <sup>2</sup> /days 1-14/q 21 days	258

\* 5-Fluorouracil is sometimes added, forming regimens known as CAF, FAC in varying schedules.

† Currently approved for authority prescription only after failure of anthracycline.

\*\* Currently approved for advanced or metastatic breast cancer after failure of standard therapy which includes a taxane and an anthracycline, or where those agents are clinically contraindicated (PBS).

Note: Other regimens are also being used in Australia, but have not been subjected to the same level of scrutiny.

**Although a modified CMF regimen with all drugs given intravenously each three weeks was better than the same regimen in half dosage,<sup>229</sup> there is direct evidence (Level II) that this regimen is inferior to the ‘classical’ CMF regimen using oral cyclophosphamide.<sup>254</sup> This intravenous CMF regimen cannot therefore be regarded as a standard therapy.**

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The combination known as MMM (mitozantrone, methotrexate and mitomycin C) is popular, but evidence that it is as effective as CMF is limited (Level II).<sup>259</sup>

The taxanes (paclitaxel and docetaxel) and vinorelbine are active agents in metastatic breast cancer.

Four randomised trials have compared single agent taxanes to standard chemotherapy with either doxorubicin or oral CMF as first line therapy. The first compared paclitaxel 200mg/m<sup>2</sup> in a three-hour infusion with standard CMF(P) in 209 patients. There was no significant difference in response rate or time to progression, but there was a trend in survival favouring paclitaxel.<sup>255</sup> Another trial in 331 patients found that paclitaxel in the same dosage yielded inferior response rate and time to progression when compared to single agent doxorubicin 75mg/m<sup>2</sup>,<sup>260</sup> while a third trial with 326 patients found that taxotere 100mg/m<sup>2</sup> yielded better response rate and time to progression than doxorubicin 75mg/m<sup>2</sup>.<sup>256</sup>

The fourth study compared paclitaxel as a 24-hour infusion versus doxorubicin versus the combination of both agents. The combination yielded better response rate and time to progression than either single agent, but with increased toxicity. Survival results were not presented.<sup>261</sup> Other combinations of a taxane with an anthracycline, or with cyclophosphamide, 5-fluorouracil, cisplatin, carboplatin or capecitabine are being explored.

Thus we can conclude that both paclitaxel and docetaxel are active agents and that the combination of a taxane with an anthracycline appears promising, but the optimal regimen involving these agents remains to be defined.

Until the mature results of further studies are available, proven combinations should be preferred for first line cytotoxic therapy of metastatic breast cancer outside of clinical trials. Second line chemotherapy after failure of an anthracycline containing regimen, or where anthracyclines were included in adjuvant therapy, may include taxanes or vinorelbine. Subsequent therapy requires careful consideration of the relatively low probability of benefits in survival and symptom control, against the higher probability of side effects.

It is worth noting that numerous studies of other combinations are currently under way and that findings in this area are rapidly evolving.

#### Side effects

Chemotherapeutic agents are best administered under the close supervision of experienced physicians and nurses, as their safe use requires careful monitoring. Patients must be warned to seek medical attention should they develop any severe side effects.

All these drugs, either individually or in combination, can cause serious side effects including nausea, vomiting, hair loss, diarrhoea, neutropenia and thrombocytopenia.

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Haematological side effects usually commence within 7–10 days of therapy, but typically last only a few days, unless bone marrow involvement is present.

Patients should be instructed to report fever, which takes on a special significance either alone, or with other symptoms suggesting infection. Fever must be assessed urgently, since an infection at a time of chemotherapy-induced neutropaenia (usually 1–2 weeks after each dose) can be fatal unless treated promptly with the appropriate broad spectrum antibiotics.

Less commonly, thrombocytopenia may cause a risk of bleeding, including fatal or disabling stroke. Patients should be instructed to report any unusual bruising or bleeding so that platelet transfusion can be administered if required.

Alopecia is universal with anthracyclines and taxanes, while less than half of all women exposed to CMF lose sufficient hair to require a wig. Alopecia is reversible within weeks or months of ceasing therapy.

Nausea and vomiting are subjectively and objectively less severe with CMF than with anthracyclines (Level II),<sup>227</sup> but prolonged low grade nausea is experienced by some patients during oral cyclophosphamide therapy. Vomiting, although still a problem for some, is less common than it was previously due to improvements in anti-emetic therapy, including the use of steroids and serotonin antagonists such as ondansetron, tropisetron and dolasetron (Level III).<sup>262</sup> Metoclopramide and steroids have been shown to be effective with an oral CMF regime,<sup>263</sup> while serotonin (5HT<sub>3</sub>) antagonists and steroids are effective with anthracycline-based chemotherapy (Level II).<sup>264</sup> Anti-emetics are given routinely at the time of chemotherapy treatment and for a few days afterwards.

Table 7: Common chemotherapy drugs and their side effects

Class of drug	Possible side effects	Approximate time from therapy to onset of symptom
Anthracyclines - doxorubicin - epirubicin	hair loss nausea, vomiting fatigue lowered blood counts mouth ulcers cardiac toxicity	2–3 weeks days days 7–14 days 7–10 days months to years
Alkylating agents - cyclophosphamide	hair loss nausea, vomiting lowered blood counts fatigue bladder irritation	2 weeks 1–3 days 7–14 days days days
Taxanes - paclitaxel - docetaxel	fatigue hair loss lowered blood counts muscle aches neurological damage allergic reactions (paclitaxel)	days 2 weeks 10–14 days days months minutes–hours
Vinorelbine	fatigue injection site pain hair loss (moderate) lowered blood counts neuropathy	days minutes–hours weeks–months 10–14 days days
Capecitabine	fatigue diarrhoea hand-foot syndrome nausea stomatitis	days weeks months days weeks

Cardiac toxicity can be a problem with anthracyclines, particularly with cumulative doses of greater than 400mg/m<sup>2</sup> of doxorubicin or 1000mg/m<sup>2</sup> of epirubicin. Individual patients may experience cardiac toxicity at lower cumulative doses, especially after irradiation to the heart or in the presence of existing heart disease, hypertension or other cardiac risk factors.

Cyclophosphamide may cause haemorrhagic cystitis, and a fluid intake of 2–3 litres per day is recommended during cyclophosphamide therapy to lessen this risk.

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Taxanes can cause severe hypersensitivity reactions mandating pretreatment with steroids (for docetaxel and paclitaxel) and histamine receptor 1 and 2 blockers such as promethazine and cimetidine (for paclitaxel). These hypersensitivity reactions may be caused by the diluents used to dissolve the taxanes (polysorbates and cremophor) rather than the taxanes themselves. Docetaxel may also cause peripheral oedema due to vascular leak; this is also ameliorated by steroid premedication.

Vinorelbine is generally well tolerated but it is a potent vesicant and may cause injection site reactions. It should be given over 6–30 minutes by slow bolus or short infusion intravenously with additional fluids. Cumulative peripheral neuropathy may also occur with vinorelbine, particularly in patients pretreated with taxanes.<sup>265</sup>

Capecitabine is generally well tolerated, but can cause the hand-and-foot syndrome (palmar-plantar erythrodysesthesia). This is characterised by varying combinations of abnormal sensation, swelling, erythema, rash, desquamation, pain, or blistering involving the hands and/or feet. It resolves with interruption of treatment and subsequent dose reduction.<sup>258</sup>

Chemotherapy may induce or worsen menopausal symptoms such as hot flushes, vaginal dryness and sexual dysfunction. Endocrine therapies may also compound these symptoms (Level IV).<sup>266</sup>

The effects of standard chemotherapy on cognitive function are currently being studied.

### Radiotherapy

Radiotherapy is an effective, local palliative treatment in women with metastatic breast cancer. It is discussed in more detail under Chapter 7.

### Surgery of the primary tumour in metastatic breast cancer

Occasionally, women present with metastatic cancer and are found to have a primary tumour in the breast. Biopsy is indicated to assess hormone receptor status and exclude other histologies such as lymphoma. In general, removing the primary is not necessary, because it is likely to respond to systemic treatment and provides a useful measure of its effect. Some women have difficulty with this approach, being constantly reminded of their disease by the presence of a breast lump. Local excision, without axillary dissection or radiotherapy, may be considered in such cases. If the primary site continues to enlarge despite systemic therapy, surgery to control the local disease before it becomes inoperable may be considered.

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## CHAPTER 7 SPECIAL PROBLEMS OF ADVANCED BREAST CANCER

This chapter deals with the main problems of advanced breast cancer, with emphasis on metastatic disease. However, some of the problems addressed in this chapter, for example those addressing depression and anxiety, may be applicable to women with locally advanced breast cancer or local recurrence.

Advanced breast cancer can give rise to a broad range of problems which need to be addressed, some of which are medical emergencies. However, while clinical problems may be more immediately demanding, psychological problems may become apparent before physical problems. Particularly when making treatment decisions for women with metastatic disease, it is important to consider quality of life issues, to assess mood and coping and to treat depression and anxiety as part of the clinical care of women with advanced breast cancer.

### Spinal cord compression

This is a medical emergency and urgent multidisciplinary management is advisable.

Patients who are known to have bony metastatic disease and their carers should be warned about the possibility of, and educated regarding the early symptoms of spinal cord compression. Patients should be encouraged to notify their doctor of such symptoms as soon as possible. Primary medical carers should also be aware of the risks of spinal cord compression and paraplegia and the importance of prompt action. Symptoms suspicious of spinal cord compression should be investigated in the absence of signs.

If spinal cord compression is suspected, whether on symptomatic or clinical grounds, the investigation of choice is MRI scan.<sup>267</sup> This is non-invasive and the precise level or levels of cord compression can be ascertained. If this is not available, then plain X-rays and CT myelogram should be used (Level IV).<sup>268</sup>

Dexamethasone should be started on suspicion of spinal cord compression and while awaiting assessment.<sup>269</sup>

Patients presenting with suspected spinal cord compression should be reviewed as early as possible by a radiation oncologist and considered for review by an orthopaedic surgeon or neurosurgeon with an interest and expertise in spinal problems. Radiotherapy is the treatment of choice in most patients.

Surgical intervention should be considered in the following situations:

- solitary vertebral compression in a patient without previous diagnosis of malignancy;
- solitary vertebral compression in a patient with a long disease-free interval;
- pathological fracture or dislocation causing compression;

- progressive disease while on radiotherapy or in previously irradiated site.

The surgical approach should be dictated by the position of the tumour within the vertebra, so that for a disease involving the vertebral body, a lateral or anterior approach is recommended rather than a laminectomy. Following surgery, radiotherapy is indicated (Level III).<sup>270</sup>

When surgery is not considered appropriate, radiotherapy should be started immediately. Radiotherapy is considered as equally effective as surgery in achieving symptomatic relief (Level III).<sup>271</sup> Patients who are ambulatory and retain bladder or bowel function before the commencement of radiotherapy have the most favourable neurological outcome (Level III).<sup>271,272</sup>

#### Key point

Spinal cord compression is a medical emergency and urgent multidisciplinary management is advisable.

Guidelines	Level	Reference
Treatment of spinal cord compression with radiotherapy is considered as equally effective as surgery in achieving symptomatic relief.	III	271
Radiotherapy is recommended following surgical treatment of spinal cord compression.	III	270
Patients with spinal cord compression who are ambulatory and retain bladder or bowel function prior to the commencement of radiotherapy, have the most favourable neurological outcome.	III	271, 272

## Hypercalcaemia

Severe hypercalcaemia is a medical emergency.

Hypercalcaemia is a well recognised complication in women with bony metastases. However, it is also a paraneoplastic phenomenon and as such may occur in the absence of bone metastases. Among its many symptoms are polyuria, polydipsia, vomiting, constipation, muscle weakness, thirst, dehydration, confusion and obtundation. Mild cases may be difficult to recognise. In severe cases it can lead to death through renal failure, cardiac arrest or coma.

Treatment of severe hypercalcaemia involves rehydration (with up to six litres per day of normal saline) plus a drug to stabilise bony calcium. Currently, the best such drugs belong to the bisphosphonate group (see Chapter 11) which includes pamidronate and clodronate. Pamidronate is given intravenously over 2–4 hours in a dose of 30–90 mg, depending on the level of serum calcium. It leads to a

lowering of serum calcium within 24–96 hours. In severe cases, it may be more effective than intravenous clodronate (Level II).<sup>273</sup> Since the advent of the bisphosphonates, other calcium-lowering agents are not so commonly used, but in certain circumstances one may need to consider frusemide (which causes calciuresis), calcitonin, corticosteroids, mitomycin C, mithramycin or cytotoxic drug therapy such as intravenous cyclophosphamide.

With one exception, the development of hypercalcaemia is a clear indication that the woman's bony metastatic disease is not controlled, and that a change is needed in the patient's systemic anticancer therapy. Maintenance therapy needs to be given with monthly intravenous pamidronate or with continuous oral clodronate (1600–3200 mg per day) if women have recurrent episodes, although some women have only one. This treatment reduces the number of episodes of malignant hypercalcaemia (Level II).<sup>274</sup>

The exception to the statement that hypercalcaemia signifies failed control of bony metastases is the situation where a woman has recently started taking endocrine therapy, particularly tamoxifen. Occasionally, this causes transient hypercalcaemia within 2–4 weeks. This phenomenon is known as a 'flare'. If it occurs, an effective anticancer response can be expected within a few weeks. The usual treatments for hypercalcaemia may be required in the meantime.

Not all episodes of hypercalcaemia soon after tamoxifen are tamoxifen flares, and thorough assessment of the cause of hypercalcaemia is still required.

Guidelines	Level	Reference
Intravenous pamidronate lowers serum calcium within one to four days, and may be more effective than intravenous clodronate in severe cases.	II	273
Maintenance therapy with monthly intravenous pamidronate or daily oral clodronate reduces the number of episodes of malignant hypercalcaemia in women with bony metastases.	II	274

### Pleural effusion

The development of a malignant pleural effusion is a common complication of advanced breast cancer. The usual mechanism is through infiltration of the pleura by neoplastic cells, but occasionally an effusion may be secondary to impaired pleural lymphatic drainage from mediastinal tumour. In the latter case, the effusion may not contain malignant cells, even though it is due to the patient's cancer.

Pleural effusions in patients with breast cancer may have many causes other than cancer, such as pulmonary embolism, cardiac failure and infection. It is essential

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that appropriate diagnostic procedures, including a pleural tap, be performed before starting any treatment. For optimum cytological examination, 250–500 mL of fluid should be sent to the laboratory for preparation of a cell block from the spun sediment.

Pleural effusions may be diagnosed unexpectedly when a chest X-ray or CT scan is performed for routine follow-up. Small asymptomatic effusions do not require specific treatment, but their presence must be taken into account in the total evaluation of the patient's clinical state. For example, the development of an effusion may be the first indication of a relapse and of the need for a change of systemic therapy. Like all complications in advanced breast cancer, it should not necessarily be regarded as indicating a poor prognosis. With effective local and systemic treatment, some patients may live for years.

Symptomatic pleural effusions cause a dry cough, dyspnoea, fatigue and localised or pleuritic chest pain. Pleural drainage (therapeutic thoracentesis) will relieve the symptoms, but there is a high recurrence rate, with most recurring within one month.<sup>275</sup> If indicated, systemic therapy or a change in systemic therapy may control the problem. If not, further local treatment will be required.

In cases where there is a recurrence despite initiation of or a change in systemic therapy, or where systemic therapy is inappropriate, tube thoracostomy should be performed and the tube left in place until drainage falls to 50–100 mL/day, followed by chemical instillation. Many drugs and chemical agents have some degree of effectiveness against recurrence when instilled into the pleural space, but there have been few controlled trials comparing one with another. The most widely used agents are doxycycline (a tetracycline) and bleomycin. One study showed that medical instillation was just as effective as surgical installation of tetracycline (Level III).<sup>276</sup> Two studies have shown bleomycin to have advantages over tetracycline (Level II).<sup>277,278</sup>

In cases where medical treatment is ineffective, a variety of surgical procedures are available, but there have been few controlled evaluations. They include thoracoscopy and talc insufflation, surgical pleurectomy and pleuro-peritoneal shunting. Pleurectomy has a high morbidity (pain) and should be avoided unless there is clearly no alternative. In one study, talc insufflation was superior to medical pleurodesis using either bleomycin or tetracycline (Level III).<sup>279</sup>

Guideline	Level	Reference
In treating pleural effusion, talc insufflation is superior to medical pleurodesis using either bleomycin or tetracycline.	III	279

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## Pericardial effusion

The most common features of malignant pericardial effusion are dyspnoea, chest pain, cough, fever and oedema.<sup>280</sup> The apex beat may be impalpable, and the heart sounds muffled. Tachycardia with pulsus paradoxus, and elevation of the jugular venous pressure with a prominent x descent, suggest tamponade.

The diagnosis of pericardial effusion is confirmed with echocardiography. Management of malignant effusions must be individualised. If tamponade is present, then an initial pericardiocentesis under echocardiographic control is usually indicated. This procedure is a safe and initially effective treatment (Level IV),<sup>281</sup> and has the advantage of confirming a malignant aetiology. Instillation of bleomycin as a sclerosing agent has been shown to be well tolerated, and to decrease significantly the recurrence of effusion (Level IV).<sup>281,282</sup> This should be considered as part of initial therapy. Surgical creation of a pericardial window can be considered, either thoracoscopically or via a subxiphoid approach. Percutaneous formation of a window can be performed with a balloon catheter, and appears very effective where available.<sup>281,283</sup> Radiotherapy and chemotherapy can both be used as adjuncts to mechanical interventions, or alone in the absence of tamponade.

Guidelines	Level	Reference
Pericardiocentesis under echocardiographic control is a safe and initially effective treatment for pericardial effusion.	IV	281
The instillation of bleomycin as a sclerosing agent is well tolerated and significantly decreases recurrence of pericardial effusion.	IV	281, 282

## Bony metastases

The majority of patients with metastatic breast cancer will have bony metastases (approximately 60 per cent).<sup>284</sup> Many will be painful and some will lead to pathological fracture (approximately 9 per cent). The incidence of bone metastases is significantly higher in steroid positive receptor tumours and those that are well differentiated.<sup>285</sup>

A recent review of women with breast cancer and bone metastases showed that clinical review by an orthopaedic surgeon was not always sought when appropriate.<sup>286</sup>

Unfortunately, routine follow-up and screening for metastases, based on symptoms alone has been shown, thus far, to be ineffective.<sup>287</sup> Bony metastases show a bi-phasic rate of development (based on serial radionuclide bone images),

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averaging only 0.5 per cent per month during the first year after diagnosis, rapidly increasing to two per cent per month after 15 months.<sup>288</sup> Roselli and co-workers recommended against routine follow-up with chest X-rays and bone scans as a routine policy. Their clinically followed-up group had a significantly higher five-year relapse-free survival rate.<sup>289</sup> The GIVIO investigators also concluded that frequent laboratory tests and roentgenography after primary treatment did not improve survival or influence health-related quality of life.<sup>290</sup>

Symptoms suggestive of bone metastasis such as persistent, severe or unexplained bone pain (particularly if worse at night and interfering with sleep) warrant investigation, initially with a plain X-ray. A radioisotope bone scan may help determine the extent and number of metastasis. CT or MRI scans may be useful if doubt remains about the diagnosis.

#### Solitary bone lesion

It is important to ensure that a solitary lesion is a metastasis before treatment. In such cases bone biopsy should be considered.

#### Solitary vertebral lesion

If X-ray and bone scan suggest a solitary metastasis, MRI should be performed. This may reveal that the lesion is not solitary or that it has characteristics of a metastasis. Management should not be changed without histological evidence.<sup>291</sup>

#### The pathological fracture

This may be the first presentation of a bony metastasis. It is most common in the proximal femur.

#### Staging

All patients should undergo:

- FBC, creatinine, electrolytes estimations, liver function tests and serum calcium;
- imaging of chest, pelvis and liver; and
- plain films of bones that show marked isotope uptake on bone scan, especially weight-bearing bones.

Orthopaedic referral is required if:

- fifty per cent of bone cortex is lost in a long bone;
- or there is pain with over 50 per cent of vertebral body destruction and/or pedicle destruction without collapse;
- and there is moderate deformity and collapse.<sup>292</sup>

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## Treatment of bony metastases

The treatment of bony metastases has two aims: to reduce the risk of fracture, particularly in long bones; and to reduce pain.

The available treatments are:

- systemic treatment (endocrine therapy and chemotherapy—see Chapter 6);
- radiotherapy (see below);
- internal fixation/replacement (see below); and
- bisphosphonates (see Chapter 11).

All are effective and improve quality of life.<sup>293,294</sup>

## Radiotherapy

Palliative radiotherapy remains the most effective single modality for the treatment of local metastatic bone pain.<sup>295</sup> Response rates are in the order of 80 per cent and two-thirds of patients experience complete pain relief.<sup>296</sup> Various schedules of treatment are used, and randomised studies have not shown a marked difference in pain relief from any particular schedule (Level II).<sup>296</sup>

The pathophysiology of bone pain from metastases and the mechanism of pain relief from radiotherapy is unclear (Level IV).<sup>297</sup> Recent trials have shown that 8 Gray single fraction is as efficacious for pain relief as other schedules (Level I).<sup>298-300,301</sup> Further trials may define those patients who would benefit from fractionated radiotherapy.<sup>296</sup> The optimum schedule following elective pinning of lytic lesions has not been determined.

Lesions in long bones should be assessed in conjunction with an orthopaedic surgeon. If the risk of fracture is considered high enough, elective internal fixation is indicated and should always be followed by radiation treatment. The aim of the radiation is not only to relieve the pain but also to cause tumour regression and subsequent healing.

In patients who have widespread bony lesions which do not respond to endocrine therapy or chemotherapy, consideration can be given to single fraction hemibody radiation treatment (Level III). Doses of eight Gray to the lower hemibody and six Gray to the upper hemibody are well tolerated with modern anti-emetics, and are able to give considerable relief with little morbidity provided that blood counts are satisfactory.<sup>302-304</sup>

Systemic radiation therapy with bone seeking radioisotopes may be helpful when there is a preponderance of sclerotic lesions (Level III).<sup>305,306</sup>

Guidelines	Level	Reference
Palliative radiotherapy remains the most effective single modality for the treatment of local metastatic bone pain.	IV	295
Various schedules of treatment are used and randomised studies have not shown a marked difference in pain relief from any particular schedule.	II	296

### Orthopaedic management

While radiotherapy can relieve bone pain when no significant mechanical failure has occurred, it is quite ineffective in circumstances in which a fracture in a weight-bearing bone has occurred or is inevitable.

Orthopaedic management falls into three categories:

- prophylactic fixation of long bone deposits, where there is a risk of fracture;
- stabilisation or reconstruction following pathological fracture; and
- decompression of the spinal cord and nerve roots, followed by stabilisation of the affected vertebrae.

### Mechanisms of fracture and risk assessment

As a general rule, fracture is likely when 50 per cent of a cortex in a long bone has been destroyed.<sup>307</sup> Prophylactic fixation should be performed prior to radiotherapy. Avulsion of the lesser tuberosity is an indication of imminent hip fracture. Any erosion of the femoral neck is an indication for prophylactic fixation.

Non-weight bearing bones, such as ribs, fibula and much of the pelvis, can be safely treated with radiotherapy alone in most cases.

### General principles

- the procedure should provide immediate stability;
- the surgeon must assume that the fracture will not unite; and
- the fixation should aim to last the lifetime of the patient.

Whatever implant is used should restore sufficient strength to allow immediate unsupported use. In the lower limb, this includes weight bearing. If the implant alone cannot satisfy these criteria, it might need supplementation by other material such as cement, bone substitutes or endoprostheses.<sup>293</sup>

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Intramedullary nailing is indicated in fractures of the shaft of the femur, tibia or humerus. Osteosynthesis with a plate has only limited indications and should never be used in the lower limb. Cement, ceramic rings or one of the newer bone substitutes should be added to achieve immediate axial stability.<sup>308</sup>

Endoprosthetic replacement (joint replacement with cement) is better than osteosynthesis (fracture fixation with or without cement) in the proximal femur. This should also be considered in the distal femur and proximal humerus.

Intramedullary nailing of femoral lesions is associated with a significant risk of intraoperative embolism and death. Barwood and co-workers have reported a 24.4 per cent rate of acute oxygen desaturation during surgery.<sup>309</sup> Such procedures need adequate monitoring and preventative measures.

The whole of the bone which has a metastasis should be imaged to ensure that the most appropriate fixation is used. Patients with multiple deposits should have all lesions at risk treated, if possible. This aids nursing care and the provision of radiotherapy. If the patient is terminally ill, the limb should be splinted and the limb made comfortable.

#### Axial skeleton

If a patient has a metastasis compressing the spinal cord or cauda equina, any treatment should be preceded by MRI where available or otherwise CT myelography and multidisciplinary assessment. With modern imaging and implants it is possible to decompress and stabilise the vertebral column either anteriorly or posteriorly, followed by radiotherapy. It is probable that the outcomes of modern treatment are superior to earlier assessments (largely retrospective and unrandomised) which concluded that spinal surgery had little role to play.<sup>310-312</sup>

#### The future

Orthopaedic surgery is on the verge of a revolution in the techniques of replacing and repairing bone. A new skeletal repair system (SRS) offers an off-the-shelf bone replacement which is close to hydroxyapatite.<sup>313</sup> The availability of bone morphogenic protein (BMP), which means that one can theoretically produce new bone at any site in the body, is very promising in this area of management.<sup>314</sup> Both substances are still under investigation.

#### Bisphosphonates

See Chapter 11.

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### Lymphangitis carcinomatosa

This refers to a diffuse pattern of lung involvement due to the infiltration of pulmonary lymphatics. Patients may present with breathlessness or a cough, or without symptoms. Physical examination may reveal inspiratory crackles or may be normal. The chest X-ray typically shows diffuse reticulonodular opacification, sometimes with a batswing configuration. Blood gases may reveal hypoxaemia. The differential diagnosis includes pneumonia, radiation pneumonitis, adult respiratory distress syndrome and pulmonary oedema. The main feature distinguishing lymphangitis carcinomatosa is its slower rate of development — review of previous chest X-rays will often show gradual progression over a period of months. Treatment comprises symptomatic management of cough and dyspnoea with opioids, oxygen and anticancer treatment with endocrine therapy or cytotoxic chemotherapy.

### Liver metastases

Liver involvement is common in advanced breast cancer. The most frequent pattern of involvement is with multiple spheroidal parenchymal lesions, although diffuse infiltration can also occur. Presenting symptoms include pain in the right upper quadrant or epigastrium, nausea, vomiting, anorexia, fatigue, asthenia or weight loss. Jaundice is infrequent with parenchymal disease alone and usually signifies biliary tract obstruction, often at the porta hepatis or more distally. Serum levels of liver enzymes commonly have a mixed pattern with moderate elevations of transaminases (eg ALT and AST), alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT). Ultrasound and CT scan are similarly effective and often complementary for diagnosing parenchymal liver metastases. CT is preferable for following response of liver metastases to therapy. Treatment comprises both symptomatic management of pain, nausea and anorexia or other symptoms and anticancer treatment with endocrine therapy or chemotherapy. The presence of bulky or rapidly progressing liver metastases is a relative indication for chemotherapy (rather than endocrine therapy) as the initial anticancer therapy.<sup>241</sup> The presence of jaundice should prompt consideration of investigation for biliary tree obstruction and decompression with a stent placed either percutaneously or endoscopically.

### Isolated ipsilateral supraclavicular fossa recurrence

Recurrence in the ipsilateral supraclavicular fossa (SCF) is considered metastatic, ie UICC stage IV. SCF disease is also metastatic at first presentation, ie stage IV, although the prognosis for survival is better than that for metastatic disease in distant organs while being worse than that for stage III at presentation.<sup>315</sup> It may be postulated, therefore, that an isolated ipsilateral SCF recurrence carries a better prognosis than other stage IV recurrences provided that treatment is adequate.

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## Investigation

The suspected recurrence should be confirmed by fine needle biopsy cytology or excisional biopsy. There is no place for block dissection in diagnosis or treatment because of the proximity of the brachial plexus. Thereafter, distant metastases should be searched for by imaging of the chest, bone scan, liver function tests (LFTs) and haematology. Altered LFTs would indicate a need for imaging of the liver.

## Treatment

As control of local recurrence is associated with improved survival prognosis (Level III),<sup>316,317</sup> it is recommended that treatment should aim to eradicate an isolated SCF recurrence.

If other metastases are present apart from the SCF recurrence, local treatment may not be warranted unless the SCF disease is symptomatic and does not respond to appropriate systemic treatment.

Local treatment with radiation is the single modality that may eradicate the disease in the area (Level IV). Surgery is not recommended because of the high risk of damage to the brachial plexus.

Late morbidity such as radiation-induced brachial plexopathy is unlikely if due regard is given to the dose per fraction (generally 2 Gray/fraction), avoidance of overlaps with previous or concurrent fields of treatment, dose and depth of penetration of boost doses. The risk of brachial plexopathy with conventional radiotherapy to the axilla and supraclavicular fossa is 0–1.8 per cent.<sup>318</sup> It is unlikely to be higher when the SCF is treated for recurrence.

The place of systemic therapy is less clear. Due to the significant potential for stage IV (SCF) disease to progress to widespread dissemination, it seems logical that systemic chemotherapy or hormonal therapy should be considered. However, studies addressing the role of systemic therapy after any locoregional failure are few, and none have shown an improvement in overall survival. In one randomised trial, tamoxifen produced an improvement in disease-free survival after local treatment (surgery and radiotherapy), but not in overall survival.<sup>225</sup>

Systemic therapy after radiotherapy for isolated supraclavicular recurrence may include tamoxifen or chemotherapy, as discussed under 'Systemic therapy after locoregional recurrence' (Level II;<sup>225</sup> Level III<sup>217</sup>). It may also be considered if there is a need to reduce bulky disease before radiotherapy (Level IV).

If the investigations outlined above find distant metastases, the woman should receive treatment appropriate for her overall condition.

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## Prognosis

The two-year and five-year survival rates after isolated SCF recurrence are 56 per cent and 28 per cent respectively,<sup>316</sup> while those for SCF recurrence combined with any other form of locoregional recurrence are 20 per cent and 7 per cent.<sup>316</sup> Comparable survival figures for recurrence on the chest wall alone are 79 per cent and 52 per cent at two and five years, and for axillary recurrence alone are 75 per cent and 50 per cent.<sup>316</sup>

Guidelines	Level	Reference
Local control of an isolated supraclavicular fossa recurrence improves survival.	III	316, 317

## Choroidal and orbital metastases

Choroidal and orbital metastases are rare, but breast cancer is the commonest cause. Although the main symptom is blurred vision, which may be associated with retinal detachment, choroidal metastases may not cause symptoms.

The diagnosis of choroidal metastases is made by ophthalmoscopy. Sometimes, other diagnostic methods are employed, including fluorescein angiography and ultrasound. CT scanning will exclude orbital or intracranial metastatic disease and should be considered.

Treatment with radiotherapy leads to visual improvement in 70–80 per cent of patients.<sup>319</sup> Radiotherapy may help to prevent further deterioration in vision in some patients, and is a relatively safe and effective treatment. Not all choroidal metastases, however, need immediate treatment and in some cases may be monitored, especially in patients undergoing simultaneous chemotherapy.

Radiation doses in the order of 20–30 Gray in five to ten fractions over one to two weeks delivered to the orbit and globe are sufficient. Soft tissue metastases within the orbit can also cause proptosis and can be treated with similar techniques.

Guideline	Level	Reference
Treatment of choroidal metastases with radiotherapy should be considered, as it can lead to visual improvement and prevent visual deterioration.	III	319

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## Cerebral metastases

Cerebral metastases are common in breast cancer. The most common symptoms are focal neurological signs, headache, confusion and personality changes, and nausea and vomiting.

Diagnosis is made by history, physical examination and CT and/or MRI scan. It is important to distinguish true cerebral metastatic disease from bony disease of the skull impinging on the brain or base of the skull causing cranial nerve damage or meningeal disease, as radiotherapy fields will differ.

In women with preserved neurological function, a long disease-free interval, an apparently solitary brain metastasis and no extracranial metastasis, neurosurgical removal should always be considered to confirm the diagnosis of a brain metastasis. There is also evidence that resection of a solitary metastases followed by radiotherapy potentially results in increased local control and a longer disease-free survival than radiotherapy alone (Level II).<sup>320,321</sup> Stereotactic radiosurgery may be an alternative to surgical resection of a solitary brain metastasis.<sup>322</sup>

Metastases involving the cerebellum may require early intervention owing to their tendency to cause obstructive hydrocephalus and raise intracranial pressure. Insertion of a cerebrospinal fluid shunt may be useful.

Cerebral metastatic disease is rarely a medical emergency but does require early diagnosis and evaluation. Radiotherapy to the whole brain has been an accepted standard of care for patients with brain metastases (Level II).<sup>323–325</sup> At least four randomised trials carried out by the Radiotherapy Oncology Group (RTOG) in America, the Royal College of Radiologists (RCR) in Britain and a French group comparing different whole brain radiotherapy doses ranging from 10 Gray in a single fraction to 40 Gray in 20 fractions, show no differences in symptom response rates or times to disease progression according to dose/fractionation schedule (Level II).<sup>325–328</sup> The overall response rate of symptoms of cerebral metastases to radiotherapy is around 75–100 per cent, depending upon symptom type (Level II).<sup>326</sup> The main side effect of radiotherapy to the whole brain is inevitable complete alopecia. Hair will usually regrow after a 2–3 month period although it may be less dense than previously. Other acute side effects include lethargy, nausea, vomiting, headaches and ataxia, which altogether occur in around 10 per cent of patients (Level II).<sup>326</sup>

Dexamethasone is particularly useful in reducing cerebral oedema.<sup>329</sup> The overall survival for breast cancer patients with brain metastases is generally longer than for patients with brain metastases from other primary tumour sites, at around 10 months.<sup>326</sup> Progressive brain metastases are the cause of death for only around one quarter of patients with cerebral metastases.<sup>330</sup> As the brain is rarely the only site of metastases, chemotherapy should also be considered. Systematic chemotherapy may be an alternative to cerebral radiation therapy, particularly in patients with symptomatic metastases outside the brain (Level III).<sup>331,332</sup>

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**Re-irradiation for progressive brain metastases may be considered in selected patients without progressive disease at other sites (Level IV).<sup>333</sup>**

Guidelines	Level	Reference
Treatment of cerebral metastases with radiotherapy should be considered, as it leads to improvement in symptoms.	II	326
Systematic chemotherapy may be an alternative to cerebral radiation therapy, particularly in patients with symptomatic metastases outside the brain.	III	331, 332
Resection of solitary cerebral metastases followed by radiotherapy potentially results in increased local control and a longer disease-free survival than radiotherapy alone.	II	320, 321

#### Meningeal carcinomatosis

**Meningeal carcinomatosis is most commonly diagnosed because of the development of cranial or spinal nerve signs or symptoms. It can occur at any level of the meninges. Patients with extensive leptomeningeal disease rarely survive more than a few weeks.**

**Diagnosis may be difficult, even with cerebrospinal fluid cytology. It is usually made by CT or MRI scan.**

**Treatment of meningeal carcinomatosis involves intrathecal chemotherapy, and may be supplemented with whole-brain or spinal irradiation, depending on the location of focal abnormalities (Level IV).<sup>268</sup> The optimum combination of intrathecal chemotherapy and irradiation has not been defined.**

#### Base of skull metastases

**Metastases to the base of the skull usually manifest with headaches and cranial nerve palsy. Diagnosis is usually made by CT or MRI scan, and bone scans may be complementary.**

**Unlike cerebral metastases or leptomeningeal disease, base of skull metastases can be associated with comparatively longer survival as they are essentially a 'special case' of bone metastases.**

**Treatment involves irradiation of the base of skull only (Level IV).<sup>268</sup>**

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## Delirium

For patients who have advanced cancer, delirium and other organic mental disorders are common. Delirium is a reversible process (as opposed to dementia), even in patients with advanced illness.<sup>334</sup>

Delirium has been described as an aetiologically non-specific, global cerebral dysfunction, characterised by disturbance in any of a number of different functions. These include level of consciousness, attention, thinking, perception, emotion, memory, psychomotor behaviour and sleep/wake cycles. Critical features of a delirium are disorientation, fluctuation in symptoms, and the acute or abrupt onset of such disturbances.

Organic mental disorders such as delirium may be due either to the direct effects of cancer on the central nervous system (CNS), or to indirect CNS effects of the disease or treatments (medication, electrolyte imbalance, dehydration, failure of a vital organ or system, infection or pre-existing cognitive impairment or dementia).

Urgent investigation and treatment of the cause of delirium is crucial and may be life-saving, for example in the case of hypercalcaemia. The clinician should consider checking electrolytes, calcium levels, liver function, temperature, and chest sounds and order a mid-stream urine specimen and treat the underlying cause of delirium accordingly.

Studies of terminally ill cancer patients reveal cognitive impairment in more than 40 per cent of patients.<sup>335,336</sup> Just prior to death, cognitive impairment approaches 70 per cent.<sup>336</sup> Patients who are cognitively abnormal on admission to a palliative care facility may have improvement of cognitive state; highlighting that delirium, even in terminally ill patients, is worthy of investigation and treatment of reversible causes.

The diagnosis of an organic mental disorder should be considered in any medically ill patient who demonstrates an acute onset of agitation, behavioural disturbance, impaired cognitive function, change in attention and concentration, or fluctuating level of consciousness.

Management of delirium also involves providing support, communication with the family, manipulation of the environment to provide a re-orientating and safe milieu, and the appropriate use of drug therapy.<sup>334</sup> Consultation with palliative care, hospice staff or consultation-liaison psychiatrists should be considered for patients whose agitation is marked or sustained.

## Depression

It is commonly acknowledged in the literature that almost half of patients with malignancy suffer from psychiatric disorders, with adjustment disorders being the most common.<sup>337</sup>

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Assessment of mood and coping is therefore essential in the clinical care of women with advanced breast cancer. The presence of depression or anxiety mandates treatment in their own right to reduce suffering for the woman. There is also evidence that depression in the woman is a powerful factor influencing family coping.<sup>70</sup> A further concern is the potential for depression or anxiety to impair the woman's ability to cope with her physical disease burden, particularly pain, or even to influence adversely her acceptance or tolerance of treatments such as chemotherapy.

Although depression and anxiety are common in virtually all patients with cancer, they are frequently underdiagnosed and undertreated (Level IV).<sup>338</sup> It may be that clinicians see depressed and anxious mood as a 'normal' response to the cancer, and many women may themselves be reluctant to mention their distress to their doctor, feeling that depression or anxiety are signs of weakness. Depression and anxiety may occur as responses to the impact of diagnosis and the implications of the cancer, but can also be triggered by neurologic, metabolic and nutritional and endocrine changes, as well as by medication (Level IV).<sup>339</sup>

The diagnosis of depression in physically healthy patients relies heavily on symptoms such as anorexia, insomnia, anergia, fatigue, weight loss and reduced interest in sex. However, in patients with cancer, these may be related to the disease process. Thus, depression in cancer patients is best evaluated by the severity of dysphoric mood, loss of interest and pleasure, the degree of feelings of hopelessness, guilt and worthlessness, and the presence of suicidal thoughts (Level IV).<sup>340</sup>

Ideally, the management of depression in women with breast cancer should incorporate a combination of supportive psychotherapy, cognitive and behavioural techniques, and pharmacotherapy. The concern that antidepressant therapy poses a further side effect burden on patients is not supported by research. In one study, about 80 per cent of people with cancer receiving antidepressants showed good clinical response, and the majority did not have significant adverse effects (Level IV).<sup>341</sup>

Clinicians choosing which antidepressant medication to use should consider the specific symptoms which are distressing the patient, the potential for side effects, the risk of exacerbating current medical problems and the potential for drug interactions. It is generally appropriate to commence with a low dose, and to increase this slowly.

#### Tricyclic antidepressants

The tricyclic antidepressants have been used for many years for the treatment of depression. Their sedating properties are particularly useful for management of the agitated, depressed cancer patient with insomnia.<sup>334</sup> They are also useful in their role of potentiation and enhancement of opioid analgesia for those with pain.<sup>173</sup>

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Anticholinergic side effects may aggravate stomatitis secondary to chemotherapy, and exacerbate constipation. These drugs also have the potential to affect cardiac rhythm.

Depressed cancer patients may respond to tricyclic antidepressants at a lower dose than physically healthy psychiatric patients.

(see Commonwealth Department of Health and Aged Care and AIHW (1999) National Health Priority Areas: Mental Health 1998).

Selective serotonin re-uptake inhibitors

Unlike the tricyclic antidepressants, the selective serotonin re-uptake inhibitors (SSRIs) are a newer class of drugs, and there have been fewer studies of their effectiveness in the cancer population. One study of 115 cancer patients (Level II)<sup>342</sup> has shown some benefit for the use of fluoxetine. However, the half-life of fluoxetine is long, and in patients with hepatic or renal dysfunction, short-acting drugs such as sertralene and paroxetine are preferable.

The SSRIs have fewer anticholinergic or cardiovascular side effects and are less sedating than the tricyclic antidepressants, but may be associated with some exacerbation of anxiety or insomnia. Nausea may be a limiting side effect in the cancer population.

Selective noradrenergic re-uptake inhibitors

Selective noradrenergic re-uptake inhibitors (SNRIs) are new agents which provide both selective noradrenergic and serotonergic re-uptake inhibition. They have fewer anticholinergic, histaminic and adrenergic side effects than SSRIs and no monoamine oxidase inhibition. They are likely to have a helpful role in cancer care.

Psychostimulants

Limited research suggests that patients with advanced cancer may experience some improvement in depressed mood, appetite and wellbeing when treated with low dose psychostimulants (Level IV).<sup>343</sup> Side effects include nervousness, overstimulation, mild increases in blood pressure and pulse rate, and tremor (Level IV).<sup>334</sup>

Long-term use of these drugs is associated with tolerance and dependence. Methylphenidate and dextroamphetamine are two examples.

Anxiety

Anxiety in women with breast cancer may be related to a number of different factors. These include:

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- reaction to the stress of the diagnosis and treatment;
  - response to medical problems related to the cancer such as uncontrolled pain;
  - response to drug treatment such as steroids;
  - response to investigations such as CT and MRI scans;
  - specific fears and phobias which existed before the cancer diagnosis, but which are exacerbated by it (Level IV);<sup>334</sup> and
  - specific fears for the future of their partner and children, including who should care for their children if they die.

Anxiety may also be a symptom of other medical conditions such as thyroid disease, and is commonly associated with alcohol or benzodiazepine withdrawal.

In cases of relatively mild anxiety, behavioural techniques such as muscle relaxation and imagery can be useful in reducing levels of distress (Level III).<sup>344</sup>

Benzodiazepines are the mainstay of pharmacological treatment of anxiety. Shorter acting benzodiazepines such as alprazolam are safest, but patients may experience breakthrough anxiety necessitating substitution with a longer acting benzodiazepine such as diazepam. For those with hepatic disease, drugs such as oxazepam are safest (Level IV).<sup>334</sup> Benzodiazepines should never be ceased abruptly because of the risk of withdrawal symptoms, which may include seizures.

Other drugs used to treat anxiety include antipsychotics, antihistamines and antidepressants. The choice of a particular agent depends on the acuteness or chronicity of the anxiety state, the drug's absorption rate, the available route for administration, and concurrent medical problems and drug side effects (Level IV).<sup>345</sup>

Antipsychotics such as thioridazine or haloperidol are generally used only in low doses in cases of extreme agitation, bearing in mind the risk of extra-pyramidal side effects.<sup>334</sup>

When anxiety or panic impede or complicate treatment, prompt psychiatric consultation is recommended (Level IV).<sup>334</sup>

Key point	Level	Reference
Depression and anxiety are common in people with cancer, although they are frequently underdiagnosed and undertreated.	IV	338

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Guidelines	Level	Reference
Most people with cancer who are depressed and are prescribed antidepressants benefit from them without significant side effects.	IV	341
Pharmacological agents are an integral part of the care of anxiety and depression.	II	346, 347
Behavioural techniques such as muscle relaxation and imagery can reduce distress in cases of mild anxiety.	III	344
Depression in people with cancer is best evaluated by the severity of the dysphoric mood, loss of interest and pleasure, by the degree of feelings of hopelessness, guilt and worthlessness, and by the presence of suicidal thoughts.	IV	340

(See also Chapter 8 and NHMRC NBCC *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer*, 2000).

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## CHAPTER 8 INTERVENTIONS TO IMPROVE QUALITY OF LIFE

Although much of the material presented in this chapter is based on studies of women with metastatic breast cancer, some of the interventions described may be considered in the clinical care of women with locally advanced and local recurrence of breast cancer. These matters are also substantially addressed in the recently released NHMRC NBCC *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer*, 2000.

### Physical interventions

Anything that reduces distress from symptoms has the potential to improve quality of life, as long as the benefits outweigh the side effects. Over the past 20 years, a small number of phase III clinical trials (see section 3.5) in metastatic breast cancer have included self-reporting assessments of quality of life as a major outcome.

Two major trials have shown significant benefit.<sup>227,229</sup> An Australian – New Zealand trial compared continuous and intermittent chemotherapy in metastatic breast cancer, and quality of life was measured using five linear analogue self-assessment (LASA) scales for physical wellbeing, mood, pain, appetite and nausea and vomiting, as well a separate scale representing overall quality of life ('uniscale').<sup>227</sup> Although chemotherapy led to nausea and vomiting, there was evidence of improvement in each of the other quality of life scales (when all patients received treatment). Overall quality of life was better in patients who continued to receive chemotherapy continuously than in those who received it intermittently.

A Canadian study compared two dose levels of chemotherapy — standard cyclophosphamide/methotrexate/5 fluorouracil (CMF) versus half doses.<sup>229</sup> The trial demonstrated a higher tumour response rate with higher-dose chemotherapy. Toxic side effects were also more prevalent. Assessment of quality of life utilised a series of 31 LASA scales related to general health, as well as scales related to the effects of disease and its treatment. A uniscale rating overall quality of life was also included. As expected, scores after treatment were lower (reflecting more symptoms) for scales relating to nausea and vomiting. However, patients receiving full dose chemotherapy reported fewer symptoms that related to effects of the disease. The uniscale rating was higher for women receiving full dose chemotherapy than for those receiving half dose chemotherapy.

These two trials establish the appropriate role of quality of life as a major endpoint in clinical trials with a goal of palliation. The trials indicate that chemotherapy can palliate symptoms, in spite of side effects, and that continuous chemotherapy at standard dose is superior to intermittent or half dose chemotherapy in terms of quality and duration of life.

Information from validated quality of life instruments used in these trials has also been shown to have independent, prognostic significance. One study found that in a group of women with metastatic breast cancer receiving chemotherapy, baseline and serial quality of life scores predicted survival independently of other prognostic factors, including performance status.<sup>27</sup> In another study, baseline quality of life assessment also predicted survival in women with advanced breast cancer receiving paclitaxel chemotherapy.<sup>33</sup> This association between survival and patient self-assessment of quality of life provides a powerful argument for including such measures in future clinical trials, and also in the routine clinical practice of oncology.

Key point	Level	Reference
Baseline and serial quality of life measures independently predict survival.	III	27, 33

Guideline	Level	Reference
Although chemotherapy may have significant side effects, it can improve quality of life and should therefore be considered.	II	27, 229

### Psychosocial interventions

There is level II evidence that psychosocial interventions with women with advanced disease are associated with improved outcomes in a number of domains of quality of life (Level II),<sup>49,348</sup> including mood, self-esteem, coping and a sense of personal control.

‘Psychosocial interventions’ is a broad term which covers a number of treatment modalities. These include pharmacotherapy, relaxation, insight-orientated psychotherapy, cognitive-behavioural therapy, and supportive psychotherapy. Although psychosocial support thus underpins many of these treatments, they are not interchangeable terms. Psychosocial support is defined as the culturally sensitive provision of psychological, social and spiritual care.

Psychosocial interventions can be undertaken by members of the treatment team or by specialist providers of psychological care. Providing psychosocial support to patients with advanced cancer requires a multidisciplinary approach, as patients pass through many different phases of the disease and require varied treatment from a range of specialists.<sup>346,347</sup> In addition to medical specialists and nursing staff, the team may variously include liaison psychiatrists, social workers, psychologists and physiotherapists. An important role is also often played by music and art therapists, volunteers and pastoral care workers.

One study has shown that women with metastatic breast cancer randomised to receive one year of supportive group counselling, where feelings, fears and worries were shared, had improved 10-year survival compared with controls. At initial 12-month follow-up, 34 women in the intervention group had significantly reduced phobic response, tension, fatigue, confusion, pain and maladaptive coping responses compared with controls (Level II).<sup>348,349</sup>

An Australian study of women with metastatic breast cancer has shown that a group therapy strategy that incorporates teaching coping skills, goal setting and problem solving resulted in reduced anxiety, depression, anger and increased self-esteem (Level II).<sup>350</sup>

Another study reported that compared with controls, newly diagnosed patients with advanced cancer who took part in educational sessions had improved adjustment, knowledge about disease, death awareness and self concept (Level III).<sup>351</sup>

These studies provide strong evidence for the benefits of supportive care in enhancing quality of life in women with metastatic breast cancer. This conclusion is supported by meta-analyses of trials including patients with early breast cancer, which show the benefits of psychosocial support for alleviating anxiety and depression, and for improving coping and physical and functional adjustment (Level I).<sup>76,136</sup>

Cancer pain can be significantly improved by relaxation therapy, either alone or with guided imagery and music (Level I).<sup>136</sup> Educational programs conducted by nurses and aimed at enhancing pain control result in better adherence to treatment and improved pain control (Level II).<sup>352</sup> Many patients also draw spiritual support by actively practising meditative and other complementary therapies (see section 3.6).<sup>346,347</sup>

It is recommended that psychosocial interventions should be used as an integral part of comprehensive patient care.

Key point	Level	Reference
Psychosocial interventions in women with advanced breast cancer improve quality of life.	II	49, 348

Guidelines	Level	Reference
Psychosocial support alleviates anxiety and depression, improves coping, and improves physical and functional adjustment.	I	76, 136
Relaxation therapy eases cancer pain.	I	136
Education programs improve pain control.	II	352
Supportive group counselling improves 10-year survival.	II	348, 349
Group therapy increases self-esteem and reduces anxiety, depression and anger.	II	350
Education sessions for women newly diagnosed with advanced breast cancer improve adjustment, knowledge, death awareness and self concept.	III	351

### Counselling referral processes

**There is a range of referral sources for the clinician who is concerned about the emotional wellbeing of the woman and/or members of her family. Most oncology units have a social worker who has expertise in counselling patients with cancer as well as practical knowledge which may be of value to women and their families. Most large metropolitan hospitals also have a psychiatric consultation-liaison service, staffed by psychiatrists, psychologists and sometimes occupational therapists and registered nurses who are qualified in counselling. These services exist not only to assess medically ill patients with mental illness, but also to provide assessment, and advice about interventions for those coping with debilitating or life-threatening illness. In many cases, these services can arrange appropriate longer-term follow-up, if that is indicated.**

**For those who work within the private health sector, the lack of ready access to an existing multidisciplinary team may mean that provision of psychosocial support for women poses some difficulty. Given the significant contribution of psychosocial factors to overall quality of life, it is crucial that clinicians in this situation are sensitive to the psychosocial needs of their patients and develop their own referral network of counsellors (for example psychiatrists, psychologists, or social workers) who have expertise in the area of breast cancer.**

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## CHAPTER 9 MANAGEMENT OF SYMPTOMS

Symptoms in women with advanced breast cancer are multifactorial, caused directly or indirectly by the underlying tumour, its complications or treatment. Non-cancer related causes should not be forgotten. In an Australian sample of cancer patients receiving chemotherapy in 1993 (45 per cent for breast cancer) an average of 20 symptoms were reported, 13 of which were physical and seven psychosocial.<sup>262</sup> More than 50 per cent reported experiencing nausea, tiredness, hair loss, concern about family members, depression, anxiety and dread of treatment.

The World Health Organization (WHO) Cancer and Palliative Care Unit evaluated the prevalence of symptoms in patients attending 40 palliative care centres across the world, including Australia. The most commonly reported symptoms in the 186 women with advanced breast cancer were pain (60 per cent), weakness (57 per cent), anorexia (26 per cent), dyspnoea (24 per cent) and nausea (23 per cent).<sup>353</sup>

The general principles applied to optimise comfort and the ability to function are:

1. identify and modify the underlying cause of the symptoms if possible, and/or
2. alter the patient's perception of the symptom.

Chapter 10 contains the principles of good pain control, which should be available to all who need it.

Various modalities of treatment can be considered, depending on the clinical situation and severity of symptoms (see Table 8). In each case, an assessment of the potential benefits and toxicity of treatment is essential as is the prognosis of the patient.

The appropriate use of anticancer therapy is sometimes the most effective means of controlling symptoms in women with advanced metastatic disease, as it is a specific measure directed at the underlying cause and thereby provides symptom control. Active interventions, such as radiotherapy for pain or spinal cord compression, surgery for fractures or visceral obstruction, and paracenteses for pleural effusions and ascites, are integral components of the care of women with metastatic breast cancer.

Symptom control needs show a wide variability between individuals and at different times in each individual's illness trajectory. As one symptom or site of symptoms is controlled, others may develop.

It is important to consider which patients may benefit from a period of formal rehabilitation after a period of more severe illness, or as debilitating symptoms resolve.

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Key point	Level	Reference
People with cancer receiving chemotherapy report an average of 20 symptoms, with the most common being pain, weakness, anorexia, dyspnoea and nausea.	III	262, 353

Table 8: Common symptoms among women with advanced breast cancer

Symptom	Possible causes	Management	Special issues
Pain	<p>Disease-related</p> <ul style="list-style-type: none"> <li>• Bone metastases +/- fracture</li> <li>• Soft tissue infiltration by tumour</li> </ul> <p>Treatment related</p> <ul style="list-style-type: none"> <li>• Neuropathy</li> <li>• Mucositis</li> </ul>	<p>Aspirin, NSAIDs, opioids, co-analgesics</p> <p>Treat underlying cause</p> <p>Psychosocial support — see Chapter 8</p>	<p>Back pain — spinal cord compression (oncological emergency)</p> <p>Bisphosphonates for bone pain (Level II)</p> <p>Meningeal carcinomatosis</p>
Nausea	<p>Disease-related</p> <ul style="list-style-type: none"> <li>• Metabolic disturbances eg hypercalcaemia, liver failure</li> <li>• Raised intracranial pressure — cerebral metastases</li> <li>• Bowel obstruction</li> <li>• Liver metastases</li> </ul> <p>Treatment related</p> <ul style="list-style-type: none"> <li>• Cytotoxic drugs</li> <li>• Radiation therapy</li> <li>• Other drugs, opioids</li> </ul>	<p>Treat underlying cause</p> <p>Anti-emetics — antidopaminergic, antihistamine agents, corticosteroids</p> <p>Bisphosphonates for hypercalcaemia (Level II)</p> <p>Anti-emetics including 5HT3 antagonists (Level II)</p>	
Dyspnoea	<p>Disease-related</p> <ul style="list-style-type: none"> <li>• Pleural/pericardial effusion</li> <li>• Parenchymal/lymphangitis</li> <li>• Bronchial obstruction (extrinsic or intrinsic)</li> <li>• Anaemia</li> <li>• Infection</li> </ul> <p>Treatment related</p> <ul style="list-style-type: none"> <li>• Radiation therapy</li> <li>• Pneumonitis from cytotoxic drugs or radiotherapy</li> <li>• Cardiac failure due to cytotoxic drugs</li> </ul>	<p>Treat underlying cause</p> <p>Drainage of fluid +/- instillation of sclerosant</p> <p>Steroids and/or opioids for parenchymal metastases</p> <p>Bronchial obstruction: radiation therapy, laser therapy, bronchial stenting</p> <p>Oxygen</p>	<p>Pericardial tamponade (oncological emergency)</p> <p>Paracentesis</p>

Symptom	Possible causes	Management	Special issues
Fatigue	Systemic effects of disease and/or treatment	Treat underlying cause Corticosteroids	Anaemia - transfusion
Anorexia	Systemic effects of disease and/or treatment	Treat underlying cause Progestational agents (Level II), corticosteroids, dietary advice	
Anxiety	Disease-related <ul style="list-style-type: none"> <li>● impact of diagnosis and treatment</li> <li>● uncontrolled pain</li> </ul> Treatment related <ul style="list-style-type: none"> <li>● drugs eg steroids</li> </ul> Other <ul style="list-style-type: none"> <li>● pre-existing medical disease eg thyroid disease</li> <li>● as part of a depressive illness</li> </ul>	Treat underlying cause, offering support and education  Behavioural techniques, including muscle relaxation  Benzodiazepines	Benzodiazepine and alcohol withdrawal may present with anxiety  Oxazepam safest in hepatic disease
Depression	Disease-related <ul style="list-style-type: none"> <li>● emotional response to the diagnosis, treatment and effects of illness</li> <li>● cerebral metastases</li> <li>● electrolyte disturbance</li> <li>● nutritional deficiency</li> <li>● endocrine disturbance</li> </ul> Treatment related <ul style="list-style-type: none"> <li>● chemotherapy</li> <li>● steroids</li> </ul>	Tricyclic antidepressants, SSRIs, SNRIs	TCAs useful in the potentiation of analgesia
Constipation	<ul style="list-style-type: none"> <li>● Low fibre intake</li> <li>● Low fluid intake</li> <li>● Immobility</li> <li>● Weakness</li> <li>● Medications, especially analgesics</li> </ul>	Encourage intake of fluids and fibre  Laxatives  Enemas if required	

Symptom	Possible causes	Management	Special issues
Abdominal distension	<ul style="list-style-type: none"> <li>• Ascites</li> <li>• Hepatomegaly from metastases</li> <li>• Constipation</li> </ul>	Treat underlying cause Paracentesis of ascites Appropriate treatment of constipation	Enterocolitis secondary to effect of chemotherapy +/- radiation therapy Subacute bowel obstruction
Lymphoedema	Obstruction of lymphatic drainage  Disease-related <ul style="list-style-type: none"> <li>• Node involvement by tumour</li> <li>• Thrombosis</li> </ul> Treatment related <ul style="list-style-type: none"> <li>• Fibrosis from previous therapy</li> </ul>	Elastic garments  Pneumatic compression and massage  Prevention of infection, skin care  Analgesics	
Immobility	<ul style="list-style-type: none"> <li>• Neurological deficits</li> <li>• Muscle weakness or wasting</li> <li>• Pain, especially from skeletal deposits</li> </ul>	Treat underlying cause where appropriate  Passive movement where appropriate  Splinting Physiotherapy Pressure care Sphincter care  Analgesics before procedures involving movement (according to the WHO ladder)	Paraplegia from spinal cord compression
Dysphagia	Disease-related <ul style="list-style-type: none"> <li>• Mediastinal nodes</li> <li>• Candidiasis</li> </ul> Treatment related <ul style="list-style-type: none"> <li>• Oesophageal infiltration</li> <li>• Chemotherapy-induced mucositis</li> </ul>	Radiotherapy Anti-fungals	

Symptom	Possible causes	Management	Special issues
Delirium	<ul style="list-style-type: none"> <li>• CNS effect of cancer</li> <li>• Electrolyte imbalance</li> <li>• Hypercalcaemia</li> <li>• Organ dysfunction eg liver, kidney</li> <li>• Infection</li> <li>• Medication</li> </ul>	<p>Management of cause</p> <p>Safe, supportive, orientating environment</p> <p>Explanation to family members</p> <p>Appropriate use of medication</p>	<p>Up to 70 per cent of terminally ill people show cognitive impairment close to death. Consideration of the patient's clinical situation, quality of life and prognosis should underpin any attempts to establish the aetiology.</p>

More information is available from:

- **D Doyle, GW Hanks, N MacDonald eds. Oxford Textbook of Palliative Medicine. Oxford: Oxford University Press, 1993.**
- **Ipswich & West Moreton Division of General Practice. The Blue Book of Palliative Care: A Handbook for General Practitioners. Ipswich: Ipswich & West Moreton Division of General Practice, 1995.**
- **Regional Palliative Care Service, Barwon South-Western Region. Palliative Care: The Nitty Gritty Handbook—a Guide for General Practitioners. Royal Australian College of General Practitioners Service Division, 1995.**

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## CHAPTER 10 MANAGEMENT OF PAIN

According to WHO guidelines,<sup>354</sup> more than 70 per cent of people with terminal cancer experience pain. Except in rare cases, cancer pain should be controllable.

### General principles

Prompt recognition of the presence of pain is required. This involves:

- direct questioning of patient and family; and
- indirect observation of facial expression, movement and gait.

Health professionals need to acknowledge the psychosocial, cultural and spiritual influences on pain perception, including fears that the pain may be uncontrollable, that it is inevitable, that it will continue, and that it will get worse. Fear of analgesics, particularly opioids, may contribute to a patient's reluctance to report cancer pain.<sup>355</sup>

Pain needs to be accurately assessed and diagnosed, as not all pains are due to cancer. While acknowledging the subjective nature of the pain experience, measurement of pain with a visual analogue scale or a numerical rating scale (0–10) assists in objectifying the intensity of pain.

Comprehensive pain assessment involves:

- a detailed history, including pain intensity, location, quality, time course;
- physical examination;
- a psychosocial assessment;
- investigations to confirm the diagnosis, although these will vary according to the woman's condition; and
- contribution from various members of the multidisciplinary team, according to their perspective and skills.<sup>356,357</sup>

Pain may be the presenting symptom of an oncological emergency such as:

- fracture;
- spinal cord compression;
- brain metastases;
- infection;
- venous thromboembolism; and
- bowel obstruction.

These specific diagnoses need to be considered and appropriately treated.<sup>357</sup> Treatment of the cancer with radiotherapy (Level I),<sup>301</sup> chemotherapy, hormonal therapy or bisphosphonates (Level I)<sup>358</sup> will often provide the best long-term pain relief, but analgesia will be required in the interim even where such options are available.

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Assessment and diagnosis need to be repeated at each new form of pain, and at an escalation in previously diagnosed pain. Awareness of the woman's cultural background and any language difficulties is important in assessment, as is recognition of prior drug dependency problems. Ongoing pain is a potent risk factor for the development of depression (Level IV).<sup>334</sup> Clinicians need to be vigilant for the emergence of depression, as untreated depression may further undermine the woman's ability to cope with physical symptoms.

The management plan should aim to achieve pain relief at night and by day, and both at rest and on movement. It may include pharmacological and non-pharmacological methods, and both local and systemic approaches. Some patients will benefit from non-pharmacological methods of pain relief such as relaxation (Level I)<sup>136</sup> or acupuncture. Psychosocial and spiritual concerns may also need to be addressed. Practitioners are commonly told by patients and families that pain improved significantly once the doctor listened to their story and explained the likely cause of the pain.

The woman and her family should be offered as much information as possible about the aetiology of the pain, and all attempts should be made to ensure that they understand the recommended management plan. The recommended plan should also be known to all members of the multidisciplinary team — GP, specialists, community services and others — to give consistency in approach.

A mechanism for continued assessment and follow-up should be available to, and known by, all patients and their families.

#### Analgesics for cancer pain

Analgesics are the mainstays of treatment of cancer pain.<sup>359</sup> The appropriate analgesic should be given, in accordance with the cause of the pain and its severity (see Table 9). If mild analgesics are ineffective or only partly effective when given optimally, prompt change to stronger analgesics should be made, with the addition of suitable adjuvant therapies. This follows the 'analgesic ladder' approach advocated by the World Health Organization.<sup>354</sup> Strong opioids (eg morphine) will be required at the outset if pain is severe at its initial presentation.<sup>356</sup> Strong opioids are safe and effective for moderate to severe pain.<sup>359</sup>

Cancer pain is usually chronic and unremitting. Constant pain requires regular doses of analgesic at time intervals which will maintain a steady blood level of the active agent. Women with cancer and their families should be encouraged to take analgesia at regular prescribed times, rather than on an as needed basis (prn) (Level IV).<sup>360</sup> Prn analgesics for chronic pain should be reserved only for breakthrough pain (Level IV).<sup>360</sup>

In general, the correct dose of an analgesic is that which achieves pain control. The exceptions to this principle are those agents, such as aspirin, which have

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upper limits placed on dosage because of unacceptable side effects or risks. In particular, the dose of morphine is not limited. Dose should be influenced only by the severity of the woman's pain and not by her prognosis. Cancer pain can be well controlled in the majority of patients<sup>361,362</sup> providing that prescribing is appropriate. Women with uncontrolled pain should be referred to a palliative care or specialist pain service to consider the use of coanalgesics, nerve blocks or epidural delivery of analgesics (Level I).<sup>363</sup>

The oral route is preferable at all times, provided that there is no impediment to swallowing or absorption. If oral administration is not possible, subcutaneous or rectal administration is preferable to intravenous or intramuscular.

The management plan given to women and their families should include instructions for dealing with an unexpected exacerbation of pain or for breakthrough pain between doses.

Many people with cancer have some degree of constipation. Most taking analgesics require laxatives (both softener and stimulant types) to be administered regularly (Level IV)<sup>364</sup> preferably before constipation develops.

#### Morphine for cancer pain

Morphine is the drug of choice for moderate to severe pain. Initial stabilisation should be undertaken only with immediate release preparations of morphine, such as morphine mixture or parenteral (eg subcutaneous) morphine if oral intake is difficult. These should be prescribed at least four-hourly in the initial stages, with additional breakthrough doses if needed. Once pain is controlled and the total 24-hour dose requirements are established, women can be transferred to a slow release preparation which provides the same 24-hour dose. These preparations are not suitable for initial titration. Immediate release preparations should be on hand for ongoing breakthrough pain, with a dose equal to one-sixth of the daily requirements being appropriate (Level IV).<sup>365</sup> If frequent breakthrough doses are being used, the regular prescribed dose needs to be reviewed.

Concerns about the risk of addiction and tolerance, and the occurrence of unpleasant side effects such as nausea and drowsiness, often inhibit the prescription and use of morphine. The concerns about addiction to morphine are misplaced.<sup>366,367</sup> In most instances, the increasing dose requirement of morphine over the course of a long illness is attributable to a worsening of the disease process, resulting in more pain rather than true tolerance. Where a course of radiotherapy or other treatment has reduced the pain, the person's morphine dose can be reduced. In practice, this is done gradually to titrate their new requirements for any residual pain. The concern is not for physiological withdrawal symptoms but for the emergence of nausea and drowsiness (for which they had developed tolerance) if the dose is not decreased to that needed to meet present analgesic needs.

Nausea and drowsiness often occur when morphine is started or when the dose is increased. These effects usually ease within 48 hours as tolerance develops.<sup>366,367</sup> They can be minimised by giving a small initial dose such as 5mg orally q4h, then increasing it by 50 per cent every 24–48 hours until pain control is achieved. Anti-emetics should be provided. Constipation represents an ongoing problem, and aperients will usually be required.

In the elderly and in patients with renal or hepatic dysfunction, additional care is needed to prevent side effects. Milder analgesics or smaller doses of morphine may be effective, and a steady state may be achieved by six-hourly rather than four-hourly doses of morphine. Increases in dosage should be made more cautiously, perhaps no more than every three to four days.

### Coanalgesics

Patients with neuropathic pain frequently benefit from supplementation of opioids with tricyclic anti-depressants and anticonvulsants.<sup>368</sup> Severe neuropathic pain not controlled by analgesics and coanalgesics is an indication for referral for specialised pain assessment (see Table 9).

Non-steroidal anti-inflammatory agents may be of benefit in pain associated with inflammation or bone pain (Level II).<sup>369</sup>

Bisphosphonates also have a role in the treatment and prevention of bone pain (Level I)<sup>363</sup> (see Chapter 11).

Guidelines	Level	Reference
Oral analgesics are the mainstay of pain relief in patients with cancer. Strong opioids are safe and effective for moderate to severe pain.	I	359
Analgesia should be taken regularly at prescribed times, rather than on an as-needed (prn) basis. Prn analgesics for chronic pain should be reserved for breakthrough pain only.	IV	360
Radiotherapy plays a major role in the management of acute cancer pain.	I	301
The regular use of laxatives should be considered in conjunction with the administration of analgesics, preferably before constipation develops.	IV	364
Bisphosphonates have a role in the treatment and prevention of bone pain in breast cancer.	I	358
Non-steroidal anti-inflammatory drugs (NSAIDs) have a role in the treatment of inflammatory or bone pain.	II	369
Epidural, intrathecal and intracerebroventricular opioids are often effective in treating acute pain that is not controlled with conventional treatment.	I	363

Table 9: Common cancer pain treatment options

Type of pain	First line analgesics	Second line analgesics	Other modalities apart from analgesics
Oral ulceration, mucositis	<ul style="list-style-type: none"> <li>● aspirin</li> <li>● paracetamol</li> <li>● topical or local anaesthetic</li> </ul>	<ul style="list-style-type: none"> <li>● opioids</li> </ul>	<ul style="list-style-type: none"> <li>● treat thrush or other infections</li> </ul>
Ulcerating skin or tumours	<ul style="list-style-type: none"> <li>● aspirin</li> <li>● paracetamol</li> <li>● opioids</li> <li>● NSAIDs</li> </ul>	<ul style="list-style-type: none"> <li>● corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>● palliative</li> <li>● palliative surgery</li> <li>● chemotherapy</li> <li>● topical metronidazole</li> <li>● treat infections</li> <li>● debridement, dressings</li> <li>● irrigation</li> </ul>
Bony metastases	<ul style="list-style-type: none"> <li>● aspirin</li> <li>● paracetamol</li> <li>● NSAIDs</li> </ul>	<ul style="list-style-type: none"> <li>● opioids</li> <li>● corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>● radiotherapy</li> <li>● chemotherapy</li> <li>● hormonal manipulation</li> <li>● orthopaedic surgery</li> <li>● bisphosphonates</li> <li>● strontium 89</li> </ul>
Liver capsule distension	<ul style="list-style-type: none"> <li>● NSAIDs</li> <li>● corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>● opioids</li> </ul>	<ul style="list-style-type: none"> <li>● radiotherapy</li> <li>● chemotherapy</li> </ul>
Raised intracranial pressure	<ul style="list-style-type: none"> <li>● corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>● opioids</li> <li>● paracetamol</li> </ul>	<ul style="list-style-type: none"> <li>● radiotherapy</li> <li>● neurosurgery for isolated metastases</li> </ul>
Visceral malignancy	<ul style="list-style-type: none"> <li>● opioids</li> </ul>	<ul style="list-style-type: none"> <li>● corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>● radiotherapy</li> <li>● surgery</li> <li>● spinal opioids and local anaesthetic</li> </ul>
Upper abdominal malignancy	<ul style="list-style-type: none"> <li>● opioids</li> </ul>	<ul style="list-style-type: none"> <li>● corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>● coeliac plexus block</li> </ul>

Type of pain	First line analgesics	Second line analgesics	Other modalities apart from analgesics
Bowel obstruction	<ul style="list-style-type: none"> <li>• opioids</li> </ul>	<ul style="list-style-type: none"> <li>• antispasmodics</li> <li>• corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>• palliative surgery</li> </ul>
Nerve compression	<ul style="list-style-type: none"> <li>• corticosteroids</li> <li>• NSAIDs</li> <li>• anti-convulsants</li> <li>• tricyclic anti-depressants</li> </ul>	<ul style="list-style-type: none"> <li>• opioids</li> <li>• paracetamol</li> <li>• ketamine</li> </ul>	<ul style="list-style-type: none"> <li>• radiotherapy</li> <li>• neurosurgery - rhizotomy or cordotomy</li> </ul>
Spinal cord compression	<ul style="list-style-type: none"> <li>• corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>• opioids</li> </ul>	<ul style="list-style-type: none"> <li>• urgent radiotherapy</li> <li>• urgent surgical decompression</li> </ul>
Mixed nociceptive/neuropathic pain	<ul style="list-style-type: none"> <li>• opioids + tricyclic antidepressants</li> <li>• anticonvulsants</li> <li>• antiarrhythmics</li> </ul>	<ul style="list-style-type: none"> <li>• ketamine</li> </ul>	<ul style="list-style-type: none"> <li>• transcutaneous electrical nerve stimulation (TENS)</li> <li>• spinal morphine + local anaesthetic</li> <li>• cordotomy</li> <li>• rhizotomy</li> </ul>

This table has been adapted with permission from *Therapeutic Guidelines: Analgesics* (third edition, March 1997), published by Therapeutic Guidelines Ltd.

Further information on pain management can be obtained from the National Health and Medical Research Council. *Acute pain management: scientific evidence*. Canberra: AusInfo, 1999.

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## CHAPTER 11 SUPPORTIVE TREATMENTS

### 11.1 SUPPORTIVE DRUG TREATMENTS

#### Anti-emetics

The use of anti-emetics is now standard practice with the majority of chemotherapy regimes, with the choice of agents being tailored to the emetogenic potential of the cytotoxics and the prior experience of the patient. Anthracyclines, alkylating agents and the platinumums remain the most emetogenic, and a schedule including a serotonin antagonist and dexamethasone is recommended before their usage (Level II)<sup>370,371</sup> with additional medication afterwards. Serotonin antagonists used in this way have been shown to improve the patient's quality of life during the period of chemotherapy (Level II).<sup>372</sup>

There is little difference in the efficacy or side effect profile between the serotonin antagonists available on the market today, with the main difference being in the frequency of administration (Level II).<sup>373,374</sup> All have good bioavailability for oral administration, which has proved to be as effective as intravenous administration (Level II).<sup>375</sup> Although the serotonin antagonists have fewer side effects than older anti-emetics, headache occurs in about 20 per cent of patients and either constipation or diarrhoea occurs in about 15 per cent of patients (Level III).<sup>376</sup>

Cost effectiveness studies have shown that ondansetron used on the recommended schedule is as cost-effective as other individually cheaper drugs available. This is also effective in radiation-induced nausea.

The serotonin antagonists have also been combined with other agents (in addition to steroids), such as dopamine-selective D2 antagonists, with resultant improvement in efficacy (Level II).<sup>377</sup> In certain patients, a more complex combination of drugs is required to relieve the symptoms of nausea and vomiting, for example, lorazepam, prochlorperazine, and scopolamine (Level II).<sup>378</sup> Metoclopramide is a dopamine antagonist at standard doses, and blocks the 5-HT<sub>3</sub> pathway at higher doses. Given in high doses it is at least as effective as serotonin antagonists in preventing delayed emesis (Level I).<sup>379</sup> However, at high doses there is an increased incidence of dystonic reactions.

The newer chemotherapy drugs now becoming available as second and third line treatments, including the taxanes, navelbine and gemcitabine, have the advantage of producing less nausea and vomiting. In general, only simple anti-emetic regimes are required before their administration, although this depends on the needs of individual patient. Often these patients have been heavily pre-treated or have metastatic disease that causes significant nausea and vomiting in its own right.

Anti-emetics also play an important role in the palliative management of patients with symptomatic nausea and vomiting from their metastatic disease, in particular with liver and cerebral metastases. In general, the use of endocrine therapy is not associated with symptomatic nausea and vomiting requiring medical intervention.

Guideline	Level	Reference
Anthracyclines, alkylating agents and the platinum remain the most emetogenic. A schedule including a serotonin antagonist and dexamethasone is recommended prior to their usage.	II	370, 371

### Bisphosphonates

Bisphosphonates are analogues of pyrophosphate and inhibit osteoclast activity, which means they inhibit bone resorption. When given regularly to women with advanced breast cancer and at least one bony metastasis, the bisphosphonates pamidronate (intravenously) or clodronate (orally) reduce bone pain and the need for analgesics, the rate of development of new bony lesions, the incidence of hypercalcaemia and the need for radiotherapy to bony lesions (Level I).<sup>358</sup>

Pamidronate and clodronate have not been demonstrated to reduce mortality in these trials, as other causes of mortality in these patients compete, but they do benefit quality of life. The cost-effectiveness of their routine use is currently under evaluation.

Bisphosphonates are also an important component of the treatment of hypercalcaemia in patients with advanced breast cancer, along with intravascular volume repletion with saline. Hypercalcaemia causes nausea, vomiting, constipation, polyuria, dehydration, confusion, obtundation and even coma.<sup>380</sup>

Hypercalcaemia should therefore be treated vigorously unless it is clearly a terminal event, and the decision to forego treatment is a planned and considered one. Even in the terminal situation, however, relief of hypercalcaemia may be justified to reduce distress unless impairment of consciousness dominates.

Bisphosphonates are generally well tolerated. The most frequent side effects of pamidronate are fever, flare of bone pain and myalgia in the 24 hours after infusion. Neutropaenia, uveitis and scleritis have been reported.<sup>381</sup> Oral bisphosphonates may also cause oesophageal discomfort and irritation.<sup>382</sup> The risk of serious side effects is low and, in particular, there is a very low rate of symptomatic hypocalcaemia even when bisphosphonates are given to normocalcaemic patients (Level II).<sup>274,383-385</sup>

Guideline	Level	Reference
When given regularly to women with advanced breast cancer and at least one bony metastasis, bisphosphonates enhance quality of life and reduce bone pain, the need for analgesics, the rate of development of new bony lesions, the incidence of hypercalcaemia and the need for radiotherapy to bony lesions.	I	358

### Colony stimulating factors

Colony stimulating factors (CSFs) are glycoproteins which act on certain haematopoietic stem cells to stimulate the proliferation and differentiation commitment. The granulocyte CSFs (GCSF) are specific for the neutrophil lineage and are the most commonly used agents in oncology.

There are no standard guidelines for the use of CSFs in the management of patients with metastatic breast cancer.

CSFs are being investigated in clinical trials, namely with myelosuppressive and myeloablative chemotherapy and trials that involve dose escalations. There is no current evidence of improved survival with higher than standard chemotherapy dosing.<sup>199, 200</sup> In patients who have a febrile neutropenic episode after standard doses of non-trial chemotherapy, the subsequent cycles should be dose reduced, dependent on the degree and extent of the nadir, rather than adding GCSF. Similarly patients who are neutropenic before, or on the day of their scheduled treatment should have their course delayed, and again a decision regarding the dose reduction should depend on the degree and duration of the nadir.

### The use of corticosteroids in advanced breast cancer

Steroids have a varied role in the management of patients with advanced breast cancer. They play an integral role in most chemotherapy anti-emetic regimens, more so in the metastatic setting where patients have a tendency to become nauseous due to either extensive prior treatment or the nature of their metastatic disease (Level IV).<sup>386</sup>

Steroids may induce psychiatric problems in some patients; symptoms include hallucination, delusions and affective disorders. The severity of these symptoms is dose related.<sup>387</sup>

Dexamethasone is the best studied steroid and is often used intravenously prior to chemotherapy and orally afterwards to prevent delayed emesis.

Certain cytotoxic regimens require steroid pre-medication, in particular the taxanes. Hormonal treatment of breast cancer with standard doses of aminoglutethimide (1g daily) requires corticosteroid replacement.

Steroids are also frequently employed in the treatment of symptomatic metastatic cerebral lesions. Dexamethasone is most commonly used, at a starting dose of 16 mg/day (Level II).<sup>388,389</sup> Steroids are usually started prior to cerebral irradiation, continued throughout, and then tapered. Steroids are used similarly in the management of patients with spinal metastases, particularly those causing spinal cord compression or nerve root compression.

The other role for steroid use is in the management of late stage patients where it is started with the intent of improving quality of life, general wellbeing, appetite and energy (Level II).<sup>390,391</sup>

As they reduce peritumour oedema, corticosteroids have an important role in the management of various pains, especially those caused by nerve compression, and organ capsule distension (Level IV).<sup>392</sup> Unfortunately, the long-term use of steroids is limited by their side-effect profile, among the most debilitating of which are proximal myopathy, cushingoid features, skin fragility, gastrointestinal tract bleeding and blood serum level disturbance.

Guideline	Level	Reference
Steroids play an integral role in most chemotherapy anti-emetic regimes, particularly in the case of metastatic disease.	IV	386

## 11.2 OTHER SUPPORTIVE APPROACHES

### Diet

Women with breast cancer, like those with any chronic illness, need to pay attention to their nutrition. It is most important to ensure adequate energy (calorie/kilojoule) intake.

Advice from a qualified dietitian or nutritionist may be invaluable. Consideration should be given to prescribing a nutritional supplement. Where food intake is particularly poor, and especially when the patient is unable to eat sufficient quantities of fruit or vegetables, a vitamin supplement may be of assistance.

Impediments to adequate intake must be addressed. For example, sore mouth and throat may require topical therapy for chemotherapy-induced ulcers, or anti-viral therapy for herpes simplex lesions. Nausea and vomiting may require improved anti-nausea medication; hypercalcaemia should be considered.

Contrary to much popular belief, there is no one 'special' food or group of foods for the treatment of cancer. Nor are there any foods that must be avoided at all costs. Rather, the need is for a good mixed diet that includes plenty of fruit and vegetables plus a source of protein such as meat, cheese, eggs or soy beans.

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Patients with cancer should not deny themselves gastronomic pleasures such as sauces, mushrooms, puddings, cakes, or alcohol in moderation. These may themselves stimulate the appetite.<sup>156</sup>

### Exercise

Within the limits imposed by the disease and its treatment, women with breast cancer should continue their normal activities. Exercise in moderation is an important means of maintaining fitness. It also encourages blood circulation which reduces the risk of venous thrombosis, and pulmonary ventilation which reduces the risk of hypostatic pneumonia.

There is preliminary evidence to suggest that exercise improves psychological wellbeing and reduces fatigue in cancer patients undergoing chemotherapy (Level III).<sup>393,394</sup> However, research studies to date have methodological limitations and further work is required on this topic.

It is not known whether exercise is of any direct anticancer benefit in women with advanced breast cancer, but it is unlikely to be harmful.

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## APPENDIX A: NBCC ADVANCED BREAST CANCER WORKING GROUP - TERMS OF REFERENCE AND MEMBERSHIP

### Terms of reference

- To undertake the development and subsequent implementation of evidence-based Clinical Practice Guidelines for the Management of Advanced Breast Cancer.
- To develop these guidelines following the procedures outlined in the First Edition of the NHMRC's Guidelines for the development and implementation of clinical practice guidelines (1995).
- To ensure that the clinical practice guidelines can be understood and applied (with modifications when necessary) in the treatment of women with advanced breast cancer.
- To produce and provide publications which can be readily used by providers and consumers.
- To act as a clearing house for the information developed in the clinical practice guidelines.

### Membership of the NBCC Advanced Breast Cancer Working Group

Emeritus Professor Tom Reeve (Chair)	Surgeon Executive Director Australian Cancer Network
Dr Roger Allison	Radiation Oncologist Director Queensland Radium Institute
Mrs Pam Baber	Breast Cancer Action Group NSW (Deceased 2000)
Dr Jim Butler	Health Economist Senior Fellow National Centre for Epidemiology and Population Health Australian National University
Ms Hilary Clarke	Coordinator of Family Services Karuna Hospice

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<b>Professor Alan Coates</b>	<b>Medical Oncologist Chief Executive Officer Australian Cancer Society</b>
<b>Dr Jill Cockburn</b>	<b>Behavioural Scientist Head, Discipline of Behavioural Science in Relation to Medicine University of Newcastle</b>
<b>Professor Ian Gough</b>	<b>General Surgeon Clinical Professor, University of Queensland Wesley Medical Centre</b>
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<b>Associate Professor David Ingram</b>	<b>Breast Surgeon Mount Hospital Medical Centre</b>
<b>Dr Barbara Jones</b>	<b>Medical Educator RACGP Training Program, Queensland. Royal Australian College of General Practitioners</b>
<b>Professor John Kearsley</b>	<b>Radiation Oncologist Director St George Cancer Care Centre St George Hospital</b>
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<b>Dr Sue-Anne McLachlan</b>	<b>Medical Oncologist Department of Medical Oncology Street Vincent's Hospital, Victoria.</b>
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<b>Dr Angela Rutherford</b>	<b>General Practitioner, Victoria.</b>
<b>Dr Rob Simons</b>	<b>Manager Professional Education and Training NSW Cancer Council</b>
<b>Dr Martin Stockler</b>	<b>Medical Oncologist Schlink Education Centre Royal Prince Alfred Hospital</b>
<b>Associate Professor Robin Stuart-Harris</b>	<b>Medical Oncologist Senior Staff Specialist Canberra Hospital</b>
<b>Dr Jane Turner</b>	<b>Psychiatrist Department of Psychiatry University of Queensland Royal Brisbane Hospital</b>
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<b>Dr Mark Ragg</b>	<b>Consultant writer and editor</b>

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<b>Dr Anne Kricker</b>	<b>Epidemiologist National Breast Cancer Centre</b>
<b>Dr Pam McGrath</b>	<b>Research Fellow Centre for Public Health Research Queensland University of Technology</b>
<b>Ms Pat Neely</b>	<b>Consumer Queensland Cancer Foundation</b>
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## APPENDIX B: GUIDELINE DEVELOPMENT PROCESS

The *Clinical practice guidelines for the management of advanced breast cancer* have been prepared by the National Breast Cancer Centre (NBCC) in accordance with the NHMRC's *Guidelines for the Development and Implementation of Clinical Practice Guidelines* (1995). The NBCC Advanced Breast Cancer Working Group has coordinated the development of the guidelines.

Membership of the Working Group reflected the multi-disciplinary nature of breast cancer treatment. It comprised representatives from all aspects of clinical practice including breast surgery, radiology, pathology, psychiatry, medical oncology, radiation oncology, reconstructive surgery, orthopaedics, neurosurgery, ophthalmology, palliative care, general practice and nurses as well as consumers and breast cancer support groups, counsellors, and other related experts such as epidemiologists, health economists and medical educators.

The Working Group's terms of reference and membership details are provided in Appendix A. The Working Group also maintained close links with other groups currently working in this area such as the Australian Cancer Society, the Australian Cancer Network, and the Clinical Oncologist Society of Australia. Additional contributions received are also listed in Appendix A.

The clinical practice guidelines document covers best practice for the management of advanced breast cancer from the point of diagnosis. Using the guidelines as a basis, the NBCC has also developed a consumer booklet for women with advanced breast cancer. The consumer booklet is intended to assist women and their families in the process of making informed decisions regarding advanced breast cancer.

### Purpose and scope of the guidelines

In order to maintain achievable terms of reference, the Working Group confined its scope to the management of advanced breast cancer, which includes both locally advanced, locoregional recurrence and metastatic breast cancer.

There is variation in the way in which patients with breast cancer are treated across Australia.<sup>395</sup> However, evidence has shown that guidelines can improve the consistency of care and patient outcomes.<sup>396,397</sup>

The guidelines aim to:

- assist the decision-making process regarding the management of advanced breast cancer;
- provide further education to all involved in the care of women with advanced breast cancer;
- assess and assure the quality of care;

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- improve care and reduce the risk of legal litigation; and
  - bring the issue of cost-effectiveness into the public arena.

The guidelines provide a framework within which to apply clinical judgement and consider individual women's needs. As such, the guidelines are not rigid procedural paths; rather their objective is to ensure that clinicians and women are well informed about the risks and benefits of the recommended interventions. It is acknowledged that some variations in clinical practice may reflect reasonable differences in clinical judgement, clinical situations and patient preferences and needs.

The guidelines are based on the following key principles, which form the basis of the NHMRC's recommendations for guideline development:

- a focus on the improvement of patient outcomes;
- a basis in the best available scientific evidence;
- inclusion of statements concerning the strength of the recommendations; and
- the adoption of a multi-disciplinary approach which involves all stakeholders, including consumers.

#### Processes employed

The Working Group approached the development of the guidelines by setting itself five key tasks.

- Task 1: Identification of the known clinical problems and areas of uncertainty in each of the disciplines involved in advanced breast cancer treatment.
- Task 2: Collection and review of scientific evidence, including meta-analyses, to identify best and most appropriate practice for the various interventions in advanced breast cancer treatment.
- Task 3: Collaboration of appropriate subgroups, to review and present special issues for the consideration of the full working group.
- Task 4: Development of a glossary of technical terms in the breast cancer area, for incorporation in both the practice guidelines and the consumer document.
- Task 5: A review and revision process following the NHMRC first and second stage public consultation, initiated in August 1999.

Most of the work of the Working Group was conducted out of session, with meetings used primarily to identify the scope of the guidelines and to review out-of-session activity. A medical writer was then contracted to prepare the document and draw all the information together in consultation with the Working Group.

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### Task 1

At initial Working Group meetings, various individuals and groups identified known clinical problems or issues in their respective fields. A specialists' subgroup was then formed to advance the clinical group's input to the guidelines in the medical oncology, psychosocial, palliative care and radiation oncology areas.

It was established that the guidelines should focus on recommendations that would improve the outcomes of patients with advanced breast cancer. Broadly, these were:

- for patients with locally advanced breast cancer, to improve relapse free survival and overall survival; and
- for women with metastatic breast cancer to maintain the highest quality of life and to relieve symptoms.

The Working Group considered it vitally important for the management of advanced breast cancer to consult widely with clinicians and consumers to ensure that the resultant guidelines gained broad acceptance.

### Task 2

Evidence was obtained through various avenues, including Medline and Cancer Link, and then systematically evaluated by the Working Group. Analysis of the literature elicited a number of principles, that were incorporated in the guidelines, to ensure that the guidelines reflect the needs of women. Where necessary the Working Group contracted reviews of the evidence.

As far as possible, the guideline recommendations are evidence-based. A systematic review of randomised controlled trials and a review of the literature were conducted in the following areas:

- *The management of advanced breast cancer: systematic reviews of randomised controlled trials regarding the use of cytotoxic chemotherapy and endocrine therapy* by Drs Martin Stockler and Nicholas Wilcken, Ms Davina Gherzi and Associate Professor John Simes; and
- *The needs of children of mothers with advanced breast cancer* by Drs Jane Turner and Pam McGrath.

The psychosocial recommendations were based on the document NHMRC NBCC *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer, 2000*. This document is based on comprehensive reviews of the published and unpublished literature with regard to psychosocial aspects of breast cancer, which were commissioned by the NBCC.

The findings from these reviews were incorporated into the guidelines. The amount and strength of supporting evidence available for some topics varies, partly reflecting the fact that research has tended to focus on some issues more

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than others. Since decisions must often be made in the absence of published evidence, a number of recommendations are based on level IV evidence. For those recommendations for which level I or II evidence was lacking, conclusions were drawn from the considered opinion of clinical experts. The processes used in developing these guidelines were designed to ensure that, as far as possible, the recommendations reflect a consensus of those concerned with advanced breast cancer treatment in Australia.

The Working Group decided that it was important to give a clear indication in the guidelines as to the strength of the evidence for guidelines and key statements, and to provide references where appropriate.

The levels of evidence and associated guidelines are presented in tabular form throughout the text. The evidence cited in the guidelines has been classified as accurately as possibly into four levels, as follows:

- |           |  |
|-----------|--|
| Level I   | Evidence is obtained from a systematic review of all relevant randomised controlled trials.  |
| Level II  | Evidence is obtained from at least one properly designed randomised controlled trial.  |
| Level III | Evidence is obtained from well-designed controlled trials without randomisation; or from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group; or from multiple time series with or without the intervention. |
| Level IV  | This represents the opinions of respected authorities based on clinical experience, descriptive studies or reports of expert committees.   |

This rating system is recommended by the Quality of Care and Health Outcomes Committee (QCHOC) and has been adapted from the system developed by the US Preventive Services Task Force.<sup>398</sup>

### Task 3

Significant issues relating to advanced breast cancer treatment were identified by Working Group members, individually, in consultation with others working in the field, by interaction with the Working Group and in small groups that considered a woman's perspective. This range of consultation, which incorporated the members' wide knowledge of the literature, expertise as users and providers of breast cancer services, and professional and community experience led to the identification of issues which shaped the development of the guidelines. These included:

- quality of life issues;
- needs of partners, families and children;
- economic issues;
- information needs;
- choice and control;

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- counselling and support;
  - communication between women and health care providers;
  - treatment process;
  - alternative therapies;
  - clinical trials;
  - access issues;
  - pain management; and
  - palliative care and bereavement support issues.

One area of the advanced breast cancer guidelines that received particular attention by the Working Group is palliative care. Upon implementation, the palliative care component of the guidelines has the potential to have a much broader impact than the initially intended area of advanced breast cancer alone.

The two contracted review documents listed above also provide further valuable information of wider interest, in the form of a supplementary report on the effects of treatment on quality of life<sup>199,200</sup> and an appendix list and commentary on available resources, to assist with the needs of children with mothers with advanced breast cancer.<sup>86</sup>

#### Task 4

All members of the Working Group contributed to the compilation of a glossary of breast cancer terms, which forms an appendix to both the clinical guidelines and the consumer document.

#### Task 5

The guidelines were sent out to relevant experts, representatives of professional colleges and consumer representatives. Submissions were also received from others who responded to the NHMRC call for submissions. Comments received were considered by a subgroup of the Working Party (comprising nine members), and modifications were made if deemed appropriate by this subgroup. Decisions to include or exclude comments were based on expert clinical judgement and whether the comments reasonably reflected best practice and the available evidence. After revision the final drafts were approved by the subgroup to forward to the NHMRC.

Consumers have been involved in all stages of guideline development. Consumers are permanent members of the Advanced Breast Cancer Working Group which have overseen the development of the guidelines. Consumers unconnected to the NBCC were able to respond to the NHMRC call for submissions on the guidelines at the first and second stage rounds of public consultations.

A consensus-building process, involving discussion among members of the subgroup until consensus was achieved, was used to resolve difficult issues.

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## Target audience

The guidelines were developed to equip the treatment team with recommendations for the optimal care of women with locally advanced, locoregional recurrence and metastatic breast cancer, taking into account the individual needs of patients with advanced breast cancer.

## Costing issues

A review of the existing literature on the economic evaluation of advanced breast cancer treatment was undertaken and a section on economic impact incorporated into the body of the guidelines. The available evidence on the costs of advanced breast cancer is confined to estimates of the direct costs of treatment, and does not include indirect costs such as loss of work and leisure time due to illness. However, the estimates of direct costs of treatment, do not include home care components, which can be a significant part of the total cost of advanced breast cancer treatment.

Nevertheless, while the results cannot be generalised to the whole costs incurred to women, the information gives some indication as to where further research in the Australian setting may be worthwhile and is therefore included. Comparisons are also drawn with studies of economic impact issues arising from other countries.

## Implementation and dissemination

The NBCC will be responsible for disseminating, implementing, evaluating and updating the guidelines. The implementation strategy prepared by the NBCC will draw on the Centre's experience with the early breast cancer guidelines. Evaluation and updating processes will be in accordance with NHMRC guidelines.

The implementation plan includes the following strategies:

### Endorsement

The guidelines have been submitted to the NHMRC for endorsement and will be circulated to relevant stakeholders as a critical first step to aid dissemination and implementation.

### Dissemination

An initial print run of 10,000 copies of the guidelines will be disseminated to relevant professional groups free of charge. Copies will also be made available to allied health organisations, state and territory health authorities, breast cancer treatment centres, consumer and patient groups, patient support groups,

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professional colleges and associations, public policy makers, health economists and professional journals.

To assist electronic dissemination, the NBCC will also include the Clinical practice guidelines for the management of advanced breast cancer on the NBCC webpage, enabling Internet access. The availability of the guidelines will also be advertised through the NBCC's newsletters, which are published frequently throughout the year, and distributed through professional colleges nationally.

Lastly, the guidelines will be promoted through national seminar series, presentations at relevant professional meetings and conferences and submissions to professional journals.

#### Consultation/feedback

Since acceptability of the guidelines by relevant stakeholders is a critical first step towards their implementation, consultation is an integral part of the implementation process.

The guidelines were submitted to the NHMRC, who oversaw the consultation process.

#### Consideration of local conditional and resource constraints

Implementation of the guidelines will, in some cases, depend on the availability of expertise and resources. Unfortunately, little evidence is available that specifically concerns the range of local treatment options available for remote or rural women with advanced breast cancer, although services are known to often be limited. Nonetheless, where best care is available in the patient's region, the patient should be given the option of being treated near home.

To assist with such issues, the NBCC has been involved in the preparation of guideline implementation kits to help address issues of local variability and in establishing pilot projects to electronically link remotely located clinicians and create a network of expertise. Such a network is ideally multidisciplinary in nature, offering a range of expertise and assistance as well as continuity of care for management of the disease. Clinicians and other carers from non-urban areas are also encouraged to interact with multidisciplinary teams in the larger cities. Other projects aimed at alleviating rural and remote isolation have included the establishment of a Rural Surgeons Fellowship Scheme.

The guidelines have been framed in a manner that is flexible and mindful of the variation in local conditions and resource considerations. Some of the psychosocial recommendations, in particular, may be difficult to implement. For instance, the provision of interventions which require a psychiatrist or clinical psychologist. The NBCC has initiated a number of projects to explore what is required by specific treatment centres to meet needs and develop resources, such as specialist breast nurses, in diverse settings.

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## Evaluation and updating

An essential part of the guideline development and implementation process is an evaluation of their effectiveness. An evaluation strategy will be drafted at the implementation stage and will include the collection of data to determine the impact of the guidelines on clinician behaviour and patient health outcomes.

The NBCC has already undertaken key steps to facilitate this process. Baseline data has already been collected on women's perceptions of care through the NBCC National Consumer Survey (NCS). The NCS was based on a representative national sample of women treated for breast cancer in the preceding 12 months. This information will assist the development of an implementation strategy.

The guidelines reflect the best available knowledge at the time of their publication. However, as new evidence emerges from systematic reviews, they will require regular revision in order to maintain validity. The NBCC proposes to investigate the most cost-effective way of doing this. Collaboration between the NBCC's treatment team and the Advanced Breast Cancer Working Group (which meets quarterly) provides an established mechanism to review advances in the field and implications for revising the guidelines.

In addition, the NBCC's experience with the evaluation and revision of the early breast cancer guidelines, and with the Cochrane Breast Cancer Group, will assist with the guideline review process. The NBCC will continue to foster close links with the Australasian Cochrane Centre and relevant international guideline bodies in order to facilitate the updating of the guidelines.

## Further research

Areas that the Working Group believes require significant further research in the management of advanced breast cancer include:

- quality of life issues;
- drugs;
- radiation oncology;
- pathways of palliative care;
- family dynamics; and
- continuing research into current methods

The Working Group also believes that there should be significant encouragement of clinical trials for the improvement of management processes.

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### List of submissions received for the First Stage Consultation

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No	Name(s)	Address
1	Diane Walsh	Walshdp@onaustralia.com.au
2	Professor RC Bennett AM	Executive Director for Surgical Affairs Royal Australasian College of Surgeons College of Surgeon's Gardens Spring Street Melbourne Victoria 3000
3	Dr Peter Willsher	Department of General Surgery Royal Perth Hospital Box X2213 GPO Perth WA 6001
4	Dr Arlene Chan	Department of Medical Oncology Royal Perth Hospital Wellington Street Campus Box X2213 GPO Perth WA 6001
5	Mr Peter Malycha	Chairman, Section of Breast Surgery Royal Australasian College of Surgeons 333 South Terrace Adelaide SA 5000
6	Ms Lyn Swinburne	National Coordinator Breast Cancer Network Australia PO Box 4082 Auburn South Victoria 3122
7	Dr MJ Turner	Senior Lecturer in Psychiatry The University of Queensland Mental Health Centre, K Floor Royal Brisbane Hospital Herston Queensland 4029
8	Linda Purves	Plunkett Centre for Ethics in Health Care Street Vincent's Hospital Darlinghurst NSW 2010
9	Ms Ena Vanthoff	395 Beenleigh-Beaudesert Road Bannockburn Queensland 4207 Diane-ena@powerup.com.au
10	Dr Fran Boyle	Chair Breast Cancer Advisory Committee Medical Oncology Group of Australia
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12	Dr Verity Ahern	Radiation Oncologist Skill@radonc.wsahs.nsw.gov.au
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14	Mr S Krul	Registrar The Royal Australia College of Medical Administrators 35 Drummond Street Carlton Victoria 3053
15	Dr Graeme Dickie Melinda Hunt	Secretary College of Radiologists Dickie@health.qld.gov.au Faculty@racr.edu.au
16	Dr Martin Borg	Senior Staff Specialist Department of Radiation Oncology Royal Adelaide Hospital North Terrace Adelaide SA 5000
17	Dr RM Lowenthal	Director of Medical Oncology Royal Hobart Hospital GPO Box 1061 Hobart Tasmania 7001
18	Dr Liz Kenny	Radiation Oncologist Queensland Radium Institute Royal Brisbane Hospital Herston Road Brisbane Queensland 4092
19	Ms Roslyn Mors	Program Coordinator Primary and Secondary Prevention Program Hornsby Ku-ring-gai Division of General Practice PO Box 784 Wahroonga NSW 2076
20	Dr Colin MacLeod	Honorary Secretary The Royal College of Pathologists of Australasia Durham Hall 207 Albion Street Surrey Hills NSW 2010

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No	Name(s)	Address
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#### List of submissions received for the Second Stage Consultation

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1	Ms. Dianne Walsh	3/51-53 Victoria Road Nth Malvern Victoria 3144
2	Dr Jane Turner	Department of Psychiatry Royal Brisbane Hospital Herston Queensland 4029
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4	Ms Marilyn Beaumont	Executive Director Women's Health Victoria GPO Box 1160K Melbourne Victoria 3001
5	Ms Gillian Rothwell	abbott@comcen.co.au
6	Ms Kim Pearce	Acting Coordinator Cancer Information Service P O Box 572 Kings Cross NSW 1340
7	Dr Debra Graves	Chief Executive Officer Royal College of Pathologists of Australasia 207 Albion Street Surry Hills NSW 2010
8	Ms Joyce Balnaves	Convenor Catholic Women's League Australia Bioethics Working Party 50 Mortlock Circuit Kaleen ACT 2617

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No	Name(s)	Address
9	Dr Michael Copeman	Specialist Medical Adviser - Oncology Novartis Pharmaceuticals 54 Waterloo Road North Ryde NSW 1670
10	Dr Verity Ahern	Department of Radiation Oncology Westmead Hospital Westmead NSW 2145
11	Ms Kathryn White	Senior Lecturer and Clinical Research Fellow Faculty of Health Sciences Australian Catholic University Sydney NSW
12	Dr Martin Borg	Senior Consultant Department of Radiation Oncology Royal Adelaide Hospital North Terrace Adelaide SA 5000

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## APPENDIX C: QUALITY OF LIFE ASSESSMENT

Metastatic breast cancer is incurable with currently available treatments, and therapy is usually administered with the aim of producing improvement in duration and/or quality of survival. In recent years, it has been recognised that the evaluation of outcomes in clinical trials must move beyond traditional biomedical endpoints, such as tumour shrinkage, to include assessments of the impact of disease and its treatment on the patients' quality of life.<sup>227,229,399</sup>

What is meant by quality of life?

Since there is no universally accepted definition of quality of life, it is difficult to reach consensus on the full range of issues that may be relevant. What has emerged for the purpose of evaluation in clinical trials in oncology is a pragmatic construct which can be applied in different settings and cultures. The concept 'quality of life' has been limited to components that are health-related, leading to the term 'health-related quality of life'.<sup>400</sup>

While the terminology may differ between investigators, there is emerging consensus that quality of life can be represented by a multidimensional construct composed minimally of four domains; emotional, social and functional status, disease and treatment-related physical symptoms.<sup>30,401</sup> It is desirable to assess a broad range of quality of life issues, because of the complexity of the quality of life construct and the varied ways in which cancer and its treatment can affect the life of a patient.

How to measure quality of life

Many well constructed and valid instruments now exist to evaluate quality of life in cancer patients. However, no instrument is satisfactory for all purposes. Ultimately, the combination of quality of life dimensions assessed in a given situation is a function of the patient population under consideration, the nature of the treatments being applied and the specific question of interest.

Clinicians often focus on health-related quality of life, although when a patient is ill almost all aspects of life can become health-related. Economic, political, cultural and spiritual issues are likely to influence an individual's assessment of their overall quality of life.

Measures of quality of life developed specifically for cancer patients are predominantly self-reporting, because empirical evidence strongly suggests that a valid assessment of quality of life must be based on the opinions of patients and may not be reflected in the opinion of the attending health professional or other surrogates.<sup>402,403</sup> Like all scientific tests, quantitative indices of quality of life should meet basic measurement properties, as listed in Table 10.

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Table 10: Characteristics of a desirable QOL self-assessment tool

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1. **Multidimensional: usually including physical (symptoms and function), social, and emotional domains at a minimum.**
  2. **Brief (takes less than 15 minutes to complete).**
  3. **Measures what it is purported to (validity) in a consistent way (reliability).**
  4. **Sensitive to clinically important change (can be administered repeatedly over time).**
  5. **Demonstrates a clear and potentially significant contribution to patient care.**
  6. **Acceptable to patients.**
  7. **Interpretable by clinicians and those measuring QOL.**
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Two basic approaches characterise the measurement of health-related QOL: generic and specific.<sup>404</sup> Generic health status indices assess concepts broadly applicable across types and severities of disease, across different medical treatments or health interventions and across demographic and social subgroups.<sup>405</sup> Specific health status indices assess concepts which may be specific to the disease, to the treatment for the disease, or to the study in question.

Investigators in oncology have preferred cancer-specific measures because the specific approach focuses on aspects of quality of life relevant to the area of interest, and have the potential for improved responsiveness. A modular approach is favoured by several investigators as this allows the combination of a general measure applicable across broad groups of cancer patients, with treatment or disease specific modules. See Table 11 for examples.

Abbreviations used in Table 11.

Phy - physical concerns (eg symptoms, pain, nausea, hair loss)

Fnc - functional ability (eg mobility, household duties)

Emo - emotional wellbeing

Tre - treatment satisfaction (includes financial worries)

Soc - social functioning (includes family wellbeing)

Sex - sexuality/intimacy (includes body image, femininity)

Occ - occupational functioning

Fut - future orientation (planning, hope)

Tot - total score (when items are summed or a global rating is made).

**Table 11: Cancer-specific Quality of Life assessment tools**

Scale name	Dimensions	No items/ format	Measurement properties
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer 30 item Quality of Life Questionnaire	Phy, Fnc, Soc, Emo, Occ, Tre, Tot	7 yes/no, 23 Likert	Distinguishes patients on the basis of stage, performance status (PS), toxicity and treatment status. Converges with independent measures of symptoms, psychosocial function and aspects of QOL. Responsive to changes in PS, neurological status and acute toxicity from chemotherapy. Satisfactory test/retest reliability in outpatients. Cross-cultural validity in North American and European subjects.
EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Breast Cancer Module	Sex, Fut, Symp	23 Likert	Distinguishes patients on the basis of disease stage, previous surgery, PS and treatment modality. Sensitive to changes in PS. Cross-cultural validity in North American and European subjects.
FACT-G: Functional Assessment of Cancer Therapy Scale: General measure	Phy, Fnc, Soc, Emo, Symp, Sex, Tre, Fut, Tot	33 Likert	Distinguishes patients on the basis of stage of disease, PS, hospitalisation status. Converges with independent measures of psychosocial function and aspects of QOL. Sensitive to change in PS. Satisfactory test/retest reliability.
FACT-B: Functional Assessment of Cancer Therapy Scale: Breast Cancer Module	Symp, Sex, Soc	9 Likert	Distinguishes patients on the basis of PS. Sensitive to change in PS and QOL. Converges with independent measures of similar concepts. Satisfactory test/retest reliability.
Spitzer QLI: Quality of Life Index (Physician or patient reported)	Fnc, Soc, Fut, Occ Uniscale	5 ordinal scales 1 LASA	Distinguishes between healthy and ill. Converges with independent measures of physical and psychological function. Inter-rater reliability satisfactory.
GLQ-8: General Questionnaire	Emo, Symp, Sex, GQL-8 Uniscale	8 LASA 1 LASA	Discriminates patients on the basis of continuous versus interrupted chemotherapy. Converges with independent measures of psychosocial function and QOL. Responsive to change in PS and side effects of chemotherapy.

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## APPENDIX D: QUESTIONS YOU MAY BE ASKED

Being diagnosed with advanced breast cancer is a great shock for many women. Most women know little about breast cancer and its treatment. In many cases, they don't even know where to start asking questions.

Following is a list of questions which women may ask about their cancer, treatment and prognosis. These are included to prepare practitioners for questions that women may ask. This list will appear in the consumer guide for women with advanced breast cancer. Further assistance may be obtained from the NHMRC NBCC *Psychosocial clinical practice guidelines: providing information, support and counselling for women with breast cancer, 2000*.

### General questions

- Do you mind if I tape record this consultation?
- Do you mind if my friend/relative comes in with me?
- Why did I get breast cancer?
- Why has it recurred?
- What type of breast cancer have I got? Where exactly is it? Where has it spread to?
- How could it have spread in this way?
- Why wasn't the spread of the disease picked up earlier?
- How could I have advanced disease when I have felt quite well until recently?
- Where else could the disease spread to?
- How will I know when and if the disease has spread?
- What will cause the cancer to spread?
- What will happen from here?
- Does this mean I am going to die?
- How long do you think I will live?
- Am I hormone receptor-positive or receptor-negative? What does this mean?
- Do I need more tests? What sort of tests? Why do I need them? What do you expect them to show?
- With any tests, what happens? What are the risks? The benefits? Is the test conventional or experimental? Who will do it? What other options exist?
- When will the results be available?
- How certain are you that the results of these tests will be accurate?
- Are there any specialist centres for the treatment of breast cancer?

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- How can I find a doctor/surgeon/oncologist/counsellor I feel comfortable with?
  - In everything you tell me about tests and treatment, how much uncertainty is there?
  - How will the cancer affect my personal and sexual relationships?
  - What emotions might I experience?
  - Are there any books I can read which may help me understand this disease?

#### Chemotherapy

- Why do you think I should (or should not) have chemotherapy?
- If I do have chemotherapy, should I start it now? Or later?
- If I have chemotherapy, how will it be given? For how long?
- Will the drugs make me sick? Will it make my hair fall out?
- What other side effects might it give me? How can I deal with them? How long will I take to recover from them?
- Will I still be able to work?
- If chemotherapy doesn't work, are there any other treatments that might help?

#### Hormone therapy

- Why do you think I should (or should not) have hormone therapy?
- If I have hormone therapy, what type of hormone therapy will it be?
- Can I have a form of hormone therapy that does not induce permanent menopause?

#### Radiotherapy

- Why do you think I should (or should not) have radiotherapy?
- If I have radiotherapy, what type of radiotherapy will I have?
- Who will do it? When? Where?
- How long will it take?
- What side effects might it give me? How can I deal with them? How long will I take to recover from them?

#### Surgery

- Can surgery remove the cancer?
- What benefits might I gain from surgery?
- If you do recommend surgery, exactly what is involved? Exactly how much will you remove?
- How will I feel after surgery? How long will I take to recover?

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## Deciding

- What treatment do you recommend? Why?
- What happens if I choose a different treatment? Or no treatment?
- For all these treatments, what benefits would you expect for the average woman? Am I the average woman?
- For all these treatments, what are the risks?
- How successful are these treatments for my type of breast cancer?
- Would any treatment cure me?
- Will this treatment make any difference to the length of my life?
- Will this treatment make any difference to the quality of my life?
- Is there a chance that I can get very sick from the treatment, and that it will shorten my life?
- Will it just control the cancer? In what way will it control the cancer? Will it mean I live longer? Will it reduce any problems that the cancer is giving me? What will my life be like during and after treatment?
- Will there be any permanent damage? Will I still be able to have children? Will I be able to breast-feed? Will I get my menopause early? Will my sex life be affected?
- I would like a couple of weeks to make a decision - will that make any difference?
- What would you do in my situation?
- Are there any treatment centres around the world that may be able to help me ,or can I obtain the same treatments and care here?
- Are there alternative treatments that might help me?
- Can I undertake alternative/complementary and mainstream treatments concurrently?
- What will happen if I decide against any further treatment?
- Do I need a special diet to help me fight the disease?
- Does stress cause cancer?
- Will a positive attitude help me to live longer?
- Could I have another medical opinion?

## During treatment

- How much time will all this take? Will I have to stay in hospital?
- How long will I be away from work?
- How much will it all cost?
- Do I need to use contraception during my treatment? Will I have to wait for a while after my treatment before I can become pregnant?

- 
- Is there anything I need to be particularly careful about during my treatment?
  - Is there anything I can do to help during my treatment? Should I eat special foods? How can I reduce stress?
  - If I need a wig or breast prosthesis, how will I get one? Will I need special clothing?
  - Am I entitled to any benefits and services, such as subsidies for travel or prostheses?
  - What side effects can I expect? What can I do about them?
  - Are there any side effects or problems I should tell you about immediately? How do I get in touch with you to do this? How about if the problem occurs out of hours?
  - How will you know if the treatment is working? What sort of tests will you do? How often will you do them? How long will they take to do? When will you have the results?

#### After treatment

- What long-term effects — physical, mental, emotional, social, sexual or anything else — may occur?
- Is there anything I should be particularly careful about after my treatment ends? Will I need to come back for a check-up? When should I come back?
- Should I have regular mammograms? If so, how often?
- Is the cancer likely to spread? If it does spread, where will it spread to? Will I get it in the other breast? What signs should I look out for? What can I ignore?

#### Dying

- Will I die in pain?
- Will I be able to have control of my life until I die?
- How will I know when I am dying?
- How will I die?
- Are there doctors trained in the management of advanced breast cancer?
- What does hospice/palliative care mean?
- Will I need this type of care?
- Who can my family and I talk to about hospice/palliative care?
- What supports would be available for me and my family to allow me to be cared for at home if I become very sick?
- What if my family and I can't cope with my being at home?
- Is it possible to die at home?

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- What supports would be available for me and my family to allow me to die at home?
  - Do you believe in euthanasia?
  - Where is euthanasia legal?

### Support

- Will you look after me until I die?
- How can I and my family be helped to live one day at a time?
- How can I help myself?
- What should I say to my family?
- Would it be useful to record my consultations with the doctors to play back to them?
- How will this alter my relationship with my loved ones?
- How can I prepare my family for my death?
- How much should I tell my children?
- What sort of things should I tell my children?
- Who can give me assistance in doing this?
- How can I find a counsellor?
- Would my family benefit from seeing a counsellor?
- Will I be able to continue to work?
- What financial benefits are available to me if I cannot work?
- How can I find out about:
  - making a will?
  - power of attorney?
  - arranging a funeral?
- Will you always be honest with me?
- Will you discuss treatments, prognosis and so on with me before you discuss them with the family?
- Who will look after my children after my death?
- Are there support groups for people with advanced breast cancer?
- Are there agencies that will help my family after my death?
- Should my daughters undertake regular screening?
- Is breast cancer genetic?

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## APPENDIX E: TNM CLASSIFICATION SYSTEM

The most widely used classification for breast carcinomas is the TNM classification.<sup>1</sup> T, N and M categories (tumour, nodes and metastases respectively) are assessed by the combination of physical examination and imaging such as mammography.

### T - Primary tumour

- TX** Primary tumour cannot be assessed
- TO** 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** - More than 0.1 cm but not more than 0.5 cm in greatest dimension
  - T1b** - More than 0.5 cm but not more than 1 cm in greatest dimension
  - T1c** - 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 chest wall or skin  
Note: Chest wall includes ribs, intercostal muscles and serratus anterior muscle but not pectoral muscle.
- T4a** - Extension to chest wall
  - 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 categories

- NX** Regional lymph nodes cannot be assessed (eg 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 one another or to other structures
- N3** Metastasis to ipsilateral internal mammary lymph node(s)

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## M categories

**MX** Distant metastasis cannot be assessed

**M0** No distant metastasis

**M1** Distant metastases (includes metastasis to supraclavicular lymph nodes)

## Stage grouping

Stage	T classn	N classn	M classn
Stage 0	Tis	N0	M0
Stage I	T1 <sup>1</sup>	N0	M0
Stage IIA	T0	N1	M0
	T1 <sup>1</sup>	N1 <sup>2</sup>	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1 <sup>1</sup>	N2	M0
	T2	N2	M0
	T3	N1, N2	M0
Stage IIIB	T4	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note: 1. T1 includes T1mic

2. 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.

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## APPENDIX F: TYPES OF CLINICAL TRIALS

The purpose of a clinical trial is to answer specific questions about the effects of a treatment. Different types of questions require different types of trial. Schwartz and Lellouch (1980) emphasised the distinction between explanatory trials which are designed to evaluate the biological effects of treatment, and pragmatic trials which are designed to evaluate the practical effects of treatments.<sup>406</sup> This distinction is crucial, because treatments which have desirable biological effects (eg the ability to kill cancer cells and cause tumour shrinkage) may not have desirable effects in practice (ie may not lead to improvement in duration or quality of life). For example, many drugs with strong antitumour effects are so toxic that patients are unable to tolerate and derive benefit from them. The major differences between explanatory and pragmatic trials is listed in Table 12.

The evaluation of new cancer treatments usually involves progression through a series of clinical trials. Phase I trials are designed to evaluate the relationship between dose and toxicity, and aim to establish a tolerable schedule of administration. Phase II trials are designed to screen treatments for their antitumour effects in order to identify those worthy of further evaluation. Phase III trials are designed to determine the usefulness of treatments in the management of patients. The designation of phase IV is used for trials which are designed to monitor the effects of treatments which have been incorporated into clinical practice.

Phase I and II trials are explanatory — they assess the biological effects of treatment on host and tumour in small numbers of subjects, to guide decisions about further research.

Phase I trials are designed to identify the maximum tolerable dose of a new drug. The focus is on the relationship between dosage and toxicity. Small numbers of patients are treated at successively higher doses until the maximum acceptable degree of toxicity is reached. The maximum tolerable dose is defined as the maximum dose at which dose-limiting toxicity occurs in less than one-third of patients tested. This design is based on experience rather than data, and is predicated on the assumption that the maximum tolerable dose is also the most effective anticancer dose.

Phase II trials are designed to determine whether a new treatment has sufficient activity to justify further evaluation. They usually include highly selected patients, excluding those with 'non-evaluable' disease, and use tumour response rate as the primary measure of outcome. Their sample size is calculated to distinguish active from inactive drugs according to whether the response rate is greater or less than some arbitrary level, often 20 per cent. The resulting sample size is inadequate to provide a precise estimate of activity. For example, a phase II trial with 24 patients and an observed response rate of 33 per cent has a 95 per cent

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confidence interval of 16–55 per cent. While tumour response rate is a reasonable endpoint for assessing the anticancer activity of a drug, it is not an adequate surrogate for patient benefit.

Phase II trials are suitable for guiding decisions about further research, but are not suitable for making or guiding decisions about patient management. However, the literature is often confusing, because phase II trials are often reported and interpreted as if they do provide answers to questions about patient management.<sup>229</sup>

Phase III trials are pragmatic since they are designed to answer questions about the usefulness of treatments in patient management. Questions about patient management tend to be comparative since they involve choices between alternatives, ie an experimental versus the current standard management. The current standard may include other anticancer treatments, or may be the best supportive care without specific anticancer therapy.

The aim of a phase III trial is to estimate the difference in outcomes associated with a difference in treatments, sometimes referred to as the treatment effect. Ideally, alternative treatments are compared by administering them to groups of patients which are equivalent in all other respects. Randomised controlled phase III trials are the best, and often only reliable, means of determining the usefulness of treatments in patient management.

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Table 12: Classification of clinical trials

Characteristic	Explanatory	Pragmatic
Purpose	To guide research and provide information about mechanisms and specific effects of treatment	To guide patient management and provide information about net effects and patient benefit
Primary focus	The treatment	The patient
Conditions	Idealised	Real
Treatment	Chosen to accentuate the phenomenon under study	Chosen with tolerance of the target population in mind
Controls	Chosen to isolate the phenomenon of interest	Chosen according to standard practice
Assessment criteria	Direct measures of biological activity, such as tumour response and host toxicity	Direct measures of patient benefit, such as survival, quality of life and functional capacity
Choice of patients	Those most likely to demonstrate an effect	Those most typical of patients to whom the results will be applied

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## Clinical trials in palliative care

Palliative care is an area which has only fairly recently tried to evaluate the outcomes of care, and in particular the outcomes of different models of care. These evaluations have not always been successful.

Based on a review of 13 representative papers on palliative care<sup>407</sup> of which only a few focused on women with breast cancer, the following approach could be taken to trials on palliative care:

- Further trials are needed, as the existing number of trials yielding useful information is low.
- Trials should be structured carefully so the variables of site of care, cost/benefit, patient satisfaction and family satisfaction can be measured independently.
- The biases (usually towards the positive) inherent in recalling a stressful event need to be taken into account.
- Satisfaction measures which can be administered to frail and sometimes confused patients need to be developed.
- Study designs need to be robust enough to survive the death of some of their participants.
- The conflict between the investigators' desire for randomisation and the patients' and/or families' desire that wishes be met needs to be handled with care.

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## APPENDIX G: AMA CODE OF ETHICS

Because of their special knowledge and expertise, doctors have a responsibility to improve and maintain the health of their patients who, either in a vulnerable state of illness or for the maintenance of their health, entrust themselves to medical care.

Over the centuries, doctors have held to a body of ethical principles developed to guide their behaviour towards patients, their professional peers and society. The Hippocratic Oath was an early expression of such a code. These codes of ethics encourage doctors to promote the health and wellbeing of their patients and prohibit doctors from behaving in their own self-interest.

The Australian Medical Association accepts the responsibility for setting the standard of ethical behaviour expected of doctors. The AMA Code of Ethics provides a set of fundamental principles which should guide doctors in their professional conduct.

Advancing knowledge and technology create new and challenging ethical problems. The Ethics, Science and Social Issues Committee of the AMA will address these issues from time to time.

### 1 The Doctor and the Patient

#### 1.1 Standards of Care

- 1.1.1 Practise the science and art of medicine to the best of your ability and within the limits of your expertise.
- 1.1.2 Continue self-education to improve your standard of medical care.
- 1.1.3 Evaluate your patient completely and thoroughly.
- 1.1.4 Maintain accurate contemporaneous clinical records.
- 1.1.5 Ensure that doctors and other health professionals who assist in the care of your patient are qualified and competent to carry out that care.

#### 1.2 Respect for Patients

- 1.2.1 Ensure that your professional conduct is above reproach.
- 1.2.2 Do not exploit your patient for sexual, emotional or financial reasons.
- 1.2.3 Treat your patients with compassion and with respect for their human dignity.

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- 1.3 Responsibilities to Patients
- 1.3.1 Do not deny treatment to any patient on the basis of their culture, ethnicity, religion, political beliefs, sex, sexual orientation or the nature of their illness.
  - 1.3.2 Respect your patient's right to choose their doctor freely, to accept or reject advice and to make their own decisions about treatment or procedures.
  - 1.3.3 To help with these decisions, inform and advise your patient about the nature of their illness and its possible consequences, the probable cause and the available treatments, together with their likely benefits and risks.
  - 1.3.4 Keep in confidence information derived from your patient, or from a colleague regarding your patient, and divulge it only with the patient's permission. Exceptions may arise where the health of others is at risk or you are required by order of a court to breach patient confidentiality.
  - 1.3.5 Recommend only those diagnostic procedures necessary to assist in the care of your patients and only that therapy necessary for their wellbeing.
  - 1.3.6 Protect the right of doctors to prescribe, and any patient to receive, any new treatment, the demonstrated safety and efficacy of which offer hope of saving life, re-establishing health or alleviating suffering. In all such cases, fully inform the patient about the treatment, including the new or unorthodox nature of the treatment, where applicable.
  - 1.3.7 Upon request by your patient, make available to another doctor a report of your findings and treatment.
  - 1.3.8 Continue to provide services for an acutely ill patient until your services are no longer required, or until the services of another suitably qualified doctor have been obtained.
  - 1.3.9 When a personal moral judgement or religious belief alone prevents you from recommending some form of therapy, inform your patient so that they may seek care elsewhere.
  - 1.3.10 Recognise that an established relationship between doctor and patient has a value, which you should not undermine.
  - 1.3.11 In non-emergency situations, where you lack the necessary knowledge, skill, or facilities to provide care for a patient, you have an ethical obligation to refer that patient on to a professional colleague.
  - 1.3.12 Be responsible when placing an appropriate value on your services, and consider the time, skill, experience and any special circumstances involved in the performance of that service, when determining any fee.

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- 1.3.13 Where possible, ensure that your patient is aware of your fees. Be prepared to discuss fees with your patient.
  - 1.3.14 Do not refer patients to institutions or services in which you have a financial interest, without full disclosure of such interest.
- 1.4 Clinical Research
- 1.4.1 Where possible, accept a responsibility to advance medical progress by participating in properly developed research involving human subjects.
  - 1.4.2 Before participating in such research, ensure that responsible independent committees appraise the scientific merit and the ethical implications of the research.
  - 1.4.3 Recognise that the wellbeing of the subjects takes precedence over the interests of science or society.
  - 1.4.4 Ensure that all research subjects or their agents have been fully informed and have consented to participate in the study.
  - 1.4.5 Inform treating doctors of the involvement of their patients in any research project, the nature of the project and its ethical basis.
  - 1.4.6 Recognise that the subjects have a right to withdraw from a study at any time.
  - 1.4.7 Do not allow a patient's refusal, at any stage, to participate in a study, to interfere with the doctor-patient relationship or to compromise appropriate treatment and care.
  - 1.4.8 Ensure that research results are first communicated to appropriate peer groups so that a balanced view can be obtained before communication to the public.
- 1.5 Clinical Teaching
- 1.5.1 Pass on your professional knowledge and skills to colleagues and students.
  - 1.5.2 Before embarking on any clinical teaching involving patients, explain the nature of the teaching methods and obtain the patients' consent.
  - 1.5.3 Do not allow a refusal to participate in teaching to interfere with the patient relationship.
  - 1.5.4 In any teaching exercise, ensure that your patient is managed according to the best proven diagnostic and therapeutic methods and that your patient's comfort and dignity are maintained at all times.
  - 1.5.5 Do not sexually or emotionally exploit students or colleagues under your supervision.

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## 1.6 The Dying Patient

**Remember the obligation to preserve life, but, where death is deemed to be imminent and where curative or life-prolonging treatment appears to be futile, try to ensure that death occurs with dignity and comfort.**

## 1.7 Transplantation

- 1.7.1 **If you are caring for a donor, you must provide to the donor, or their relatives where appropriate, a full disclosure of the intent to transplant organs, the purpose of the procedure and, in the case of a living donor, the risks of the procedure.**
- 1.7.2 **Accept that when brain death has occurred, bodily functions may be supported if some parts of the body may be used to prolong life or to improve the health of other people.**
- 1.7.3 **Ensure that the determination of the death of any donor is made by doctors who are not involved with the transplant procedure nor caring for the proposed recipient.**
- 1.7.4 **Donor families have made an important contribution to the health of others in very difficult circumstances. They must be offered ongoing counselling and appropriate support.**

## 2 The Doctor and the Profession

### 2.1 Professional Conduct

- 2.1.1 **Build a professional reputation based on integrity and ability. Be aware that your personal conduct may affect your reputation and that of your profession.**
- 2.1.2 **Refrain from making comments which may needlessly damage the reputation of a colleague or cause a patient anxiety.**
- 2.1.3 **Report to the appropriate body of peers any unethical or unprofessional conduct by a colleague.**
- 2.1.4 **Where a patient alleges sexual or other misconduct by another doctor ensure that the patient is fully informed about the appropriate steps to take to have that complaint investigated.**
- 2.1.5 **Accept responsibility for your personal health, both mental and physical, because it affects your professional conduct and patient care.**

### 2.2 Contracts

**Do not enter into any contract with a colleague or organisation which may diminish the maintenance of your patient's autonomy, or your own, or your colleagues' professional integrity.**

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- 2.3 Advertising
    - 2.3.1 Do not advertise professional services or make professional announcements unless the chief purpose of the notice is to present information reasonably needed by any patient or colleague to make an informed decision about the appropriateness and availability of your medical services.
    - 2.3.2 Ensure that any announcement or advertisement directed towards patients or colleagues is demonstrably true in all respects, does not contain any testimonial or endorsement of your clinical skills and is not likely to bring the profession into disrepute.
    - 2.3.3 Avoid public endorsement of any particular commercial product or service.
    - 2.3.4 Ensure that any therapeutic or diagnostic advance is described and examined through professional channels, and, if proven beneficial, is made available to the profession at large.
  - 2.4 Referral to Colleagues
    - 2.4.1 Obtain the opinion of an appropriate colleague acceptable to your patient if diagnosis or treatment is difficult or obscure, or in response to a reasonable request by your patient.
    - 2.4.2 When referring patients, make available to your colleagues all relevant information and indicate whether or not they are to assume the continuing care of your patients during their illness.
    - 2.4.3 When an opinion has been requested by a colleague, report in detail your findings and recommendations to that doctor.
    - 2.4.4 Should a consultant or specialist find a condition which requires referral of the patient to a specialist or consultant in another field, the referral should, where possible, be made following discussion with the patient's general practitioner.
  - 3 The Doctor and Society
    - 3.1 Strive to improve the standards and quality of medical services in the community.
    - 3.2 Accept a share of the profession's responsibility to society in matters relating to the health and safety of the public, health education and legislation affecting the health or wellbeing of the community.
    - 3.3 Use your special knowledge and skills to consider issues of resource allocation, but remember that your primary duty is to provide your patient with the best available care.

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- 3.4 The only facts contained in a medical certificate should be those which you can personally verify.
  - 3.5 When giving evidence, recognise your responsibility to assist the court in arriving at a just decision.
  - 3.6 When providing scientific information to the public, recognise a responsibility to give the generally held opinions of the profession in a form that is readily understood. When presenting any personal opinion which is contrary to the generally held opinion of the profession, indicate that this is the case.
  - 3.7 Regardless of society's attitudes, do not countenance, condone or participate in the practice of torture or other forms of cruel, inhuman, or degrading procedures, whatever the offence of which the victim of such procedures is suspected, accused or convicted.

**1 February 1996**

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## APPENDIX H: BREAST CANCER SUPPORT SERVICES

To find out about breast cancer support groups and other local services, state or territory cancer organisations and the Cancer Information Service should be contacted. The Cancer Information Service can be contacted in any state/territory by telephone on 13 11 20.

**Australian Capital Territory Cancer Society**  
159 Maribyrnong Avenue  
Kaleen ACT 2617  
Tel: 06 6262 2222  
Fax: 06 6262 2223  
Email: [actcancer@cancer.org.au](mailto:actcancer@cancer.org.au)  
Website: [www.cancer.org.au/act](http://www.cancer.org.au/act)

**Anti-Cancer Council of Victoria**  
1 Rathdowne Street  
Carlton South Victoria 3053  
Tel: 03 9635 5000  
Fax: 03 9635 5270  
Email: [enquiries@accv.org.au](mailto:enquiries@accv.org.au)  
Website: [www.accv.org.au](http://www.accv.org.au)

**Can-Help: 13 11 20**

**Anticancer Foundation of South Australia**  
202 Greenhill Road  
Eastwood SA 5063  
Tel: 08 8291 4111  
Fax: 08 8291 4122  
Email: [cancersa@cancersa.org.au](mailto:cancersa@cancersa.org.au)  
Website: [www.cancersa.org.au](http://www.cancersa.org.au)

**Cancer Council of Tasmania**  
140 Bathurst Street  
Hobart Tasmania 7000  
Tel: 03 6233 2030  
Fax: 093 6233 2123  
Email: [Iride@courier.tas.gov.au](mailto:Iride@courier.tas.gov.au)  
Website: [www.cancer.org.au/tas](http://www.cancer.org.au/tas)

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**Cancer Foundation of Western Australia**  
46 Ventnor Avenue  
West Perth WA 6005  
Tel: 089212 4333  
Fax: 08 9212 4334  
Email: [cancerwa@cancerwa.asn.au](mailto:cancerwa@cancerwa.asn.au)  
Website: [www.cancerwa.asn.au](http://www.cancerwa.asn.au)

**Cancer Council of the Northern Territory**  
Shop3, Casi House  
23 Vanderlin Drive  
Casuarina NT 0810  
Tel: 08 8927 4888  
Fax: 08 8972 4990  
Email: [uvstop@cancernt.org.au](mailto:uvstop@cancernt.org.au)  
Website: [www.cancercouncilnt.citysearch.com.au](http://www.cancercouncilnt.citysearch.com.au)

**NSW Cancer Council**  
153 Dowling Street  
Woolloomooloo NSW 2011  
Tel: 02 9334 1900  
Fax: 02 9358 1452  
Email: [feedback@nswcc.org.au](mailto:feedback@nswcc.org.au)  
Website: [www.nswcc.org.au](http://www.nswcc.org.au)

**Queensland Cancer Fund**  
553 Gregory Terrace  
Fortitude Valley Queensland 4006  
Tel: 07 3258 2200  
Fax: 07 3257 1306  
Email: [qldcf@qldcancer.com.au](mailto:qldcf@qldcancer.com.au)  
Website: [www.qldcancer.com.au](http://www.qldcancer.com.au)

Other breast cancer services for women

**Breast Cancer Network of Australia (BCNA)**  
P O Box 4082  
Auburn South Vic 3122  
(03) 9805 2500  
(03) 9805 2599 (fax)  
[www.bcna.org.au](http://www.bcna.org.au)  
[beacon@bcna.org.au](mailto:beacon@bcna.org.au)

The BCNA produces The Beacon - a newsletter for women with breast cancer

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**Bosom Buddies (ACT)**  
Tel: 041 969 8188 (mobile)  
**Breast Cancer Action Group (VIC)**  
c/o: PO Box 281  
Fairfield Victoria 3078  
Fax: 03 9457 6318

**Breast Cancer Action Group (NSW)**  
c/o: Sally Crossing  
Tel: 02 9436 1755

**Action for Breast Cancer South Australia**  
c/o: Denise Wehnert  
Tel: 08 8294 6435

**NT Breast Cancer Voice**  
GPO Box 4822  
Darwin NT 0801  
c/o Karen Finch  
Tel: 08 8945 6582

#### Lymphoedema Associations & Support Groups

**These groups provide information on lymphoedema, local services and resources and support to women with lymphoedema.**

**The Australian Lymphology Association**  
8 Kergo Place  
Wantirna South Victoria 3152

**ACT Lymphoedema Support Group**  
66 Bindaga Street  
Aranda ACT 2614  
Tel: 02 6251 1294

**Darwin Lymphoedema Support Group**  
PO Box 4127  
Casuarina NT 0811  
Tel: 08 8927 4888  
Fax: 08 8927 4990

**Lymphoedema Support Group of NSW**  
79 Beechworth Road  
Pymble NSW 2073  
Tel: 02 9402 5625

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**Lymphoedema Support Group of SA**  
**PO Box 1006**  
**Kent Town SA 5071**  
**Tel: 08 8204 4711**  
**Tasmanian Lymphoedema Support Group**  
**42 Stanley Street**  
**Bellerive Hobart Tasmania 7018**  
**Tel: 03 62444634**

**Lymphoedema Association of Victoria**  
**Murray Drive**  
**Point Leo Victoria 3916**  
**Tel: 03 9801 7547**

**Lymphoedema Association of Western Australia**  
**PO Box 2037**  
**Claremont North WA 6010**  
**Tel: 0500 576 000**

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## APPENDIX I: PALLIATIVE CARE RESOURCES

For more information about palliative care in your state or territory contact your local association.

ACT Hospice Palliative Care Society Inc.  
PO Box 88  
Civic Square ACT 2608  
Tel: 02 6247 4511  
Fax: 02 6247 5422

Palliative Care Association of New South Wales  
PO Box 55  
Allawah NSW 2217  
Tel: 02 9546 2603  
Fax: 02 9546 3482

Northern Territory Hospice and Palliative Care Association  
PO Box 42255  
Casuarina NT 0811  
Tel: 08 8927 4888  
Fax: 08 8927 4990

Palliative Care Association of Queensland Inc.  
PO Box 338  
Red Hill Queensland 4059  
Tel: 07 3258 2281  
Fax: 07 3258 2281  
Email: [pcaq@pallcare.org.au](mailto:pcaq@pallcare.org.au)  
Website: <http://www.pallcare.org.au/qld>

Palliative Care Council of South Australia Inc.  
202 Greenhill Road  
Eastwood SA 5063  
Tel: 08 8291 4137  
Fax: 08 8290 4122  
Email: [pcare@pallcare.asn.au](mailto:pcare@pallcare.asn.au)  
Website: <http://www.pallcare.asn.au>

Tasmania Association for Hospice & Palliative Care  
PO Box 517  
North Hobart Tasmania 7002  
Tel: 03 6224 3808  
Fax: 03 6223 5042

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**Palliative Care Victoria Inc.**  
2nd Floor  
182 Victoria Parade  
East Melbourne Victoria 3002  
Tel: 03 9662 9644  
Fax: 03 9662 9722  
Email: [info@pallcarevic.asn.au](mailto:info@pallcarevic.asn.au)  
Website: <http://www.pallcarevic.asn.au>

**WA Hospice Palliative Care Association**  
Lotteries House  
79 Stirling Street  
Perth WA 6000  
Tel: 08 9228 4084  
Fax: 08 9228 4084

**Palliative Care Australia**  
PO Box 55  
Yarralumla ACT 2600  
Tel: 02 6232 4433  
Fax: 02 6232 4434  
Email: [pcainc@pallcare.org.au](mailto:pcainc@pallcare.org.au)  
Website: <http://www.pallcare.org.au>

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## APPENDIX J: NBCC PUBLICATIONS LIST

### WEBSITE

Breast cancer information on the internet. The Centre's website is a "one-stop shop" for information about breast health and breast cancer in Australia. Updated regularly, the website features information about the Centre's projects and resources, breast cancer news, personal stories and viewpoints and publications. Visit the Centre's website at [www.nbcc.org.au](http://www.nbcc.org.au)

### NEWSLETTERS

**Clinical Update**  
For surgeons, medical oncologists and radiation oncologists. A quarterly newsletter which reviews recent research articles with immediate significance to clinical practice.

**Breast News**  
Quarterly newsletter of the National Breast Cancer Centre, featuring information about the Centre's projects and resources, new policy and program developments, recent key research papers, and current issues and debates, as well as upcoming breast cancer meetings in Australia and overseas.

**Breast Fax**  
Monthly newsletter of the National Breast Cancer Centre, with the latest in the Centre's activities and projects. This one-page update includes information about the Centre's launches and new projects. Sent either as a fax or can be sent as an email and viewed with Acrobat Reader.

### PUBLICATIONS ORDER FORM

#### How to order

 iSource National Breast Cancer Centre,  
PO Box 572,  
Kings Cross NSW 1340

 National publications Line:  
(voicemail) on 1800 624 973  
OR (02) 9334 1882

National Publications Line:  
(facsimile) on (02) 9326 9329

#### Online order form at:

[www.nbcc.org.au/pages/info/resource/nbccpubs/nbccpubs.htm](http://www.nbcc.org.au/pages/info/resource/nbccpubs/nbccpubs.htm)

**NB:** The Centre's written materials are available for preview or downloading from [www.nbcc.org.au](http://www.nbcc.org.au)

#### Costs

Free of charge unless otherwise stated.

#### Order Limits

Limits are shown beside the title eg  
To discuss orders which exceed the stated limits call (02) 9334 1700

#### Delivery

Orders will be processed within 2 weeks.

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## GLOSSARY

### **adjuvant therapy**

A treatment which aids or assists another. The term is especially used to describe the use of chemotherapy or hormone treatment given with or after primary surgery, the aim being to eradicate hidden cancer cells which were not removed at the operation.

### **advanced disease**

For breast cancer, the disease when it has advanced beyond the stage of being confined to the breast tissue alone, or the breast tissue plus armpit (axillary) lymph nodes. See also 'locally advanced', 'locally recurrent', and metastatic (or secondary) cancer.

### **anti-oncogene**

A gene (part of a cell's DNA) that causes the production of a protein that, in turn, antagonises actions of oncogenes. Also called a tumour suppressor gene.

### **anxiety**

A diffuse, highly unpleasant, often vague feeling of apprehension, accompanied by bodily sensations such as pounding heart or sweating. There is an associated anticipation of future misfortune or danger, external or internal.

### **ascites**

The presence of fluid in the abdominal cavity. Its presence is often a sign of either liver disease or intra-abdominal malignancy.

### **autologous bone marrow transplantation**

The procedure of collecting a cancer patient's own bone marrow, storing it (by freezing), giving treatment with high doses of anticancer medication, then returning the stored marrow to the patient.

### **axillary dissection**

An operation in which the lymph glands in the axilla (armpit) are identified and removed; it is usually performed with either mastectomy or lumpectomy as part of the surgical treatment of breast cancer.

### **benign**

Not malignant; that is, not cancerous.

### **biopsy**

The removal of a small piece of tissue for examination in the laboratory, under the microscope. It is usually obtained by a minor operation.

---

**blood cell separator**

An instrument into which blood is run and then spun in a centrifuge so that the heaviest components (the cells) go to the outside and the plasma (the liquid component) remains in the centre; its principle is the same as that of a milk and cream separator. It is used to collect certain blood components, for example platelets or stem cells.

**body image**

The individual's conception of and feelings about their body - its overall integrity, its physical characteristics such as form, size and shape, and its conformity to societal values and norms. Self-esteem, psychosocial functioning and sexuality are intimately linked with body image.

**bone marrow**

The soft, spongy, central portion of bones, where the blood cells are made. Once the cells (red blood cells, white blood cells and platelets) have reached the right stage of their development, they are released into the bloodstream.

**bone marrow aspiration**

A procedure, performed under a local anaesthetic, in which a small quantity of liquid bone marrow material is sucked out of the marrow cavity and sent to the laboratory for examination.

**bone marrow biopsy**

A procedure (slightly more involved than bone marrow aspiration, above), performed under a local anaesthetic, in which a small piece of bone including its contained marrow is removed for examination in the laboratory.

**bone marrow transplantation**

A procedure in which bone marrow collected from another person (allogeneic transplantation), or from the patient herself (autologous transplantation) is transplanted or returned to the patient after her bone marrow has been eradicated, for example by large doses of anticancer medication.

**bone scan**

An investigation in which a radioactive tracer is injected and its distribution in the bones is detected by a scanning instrument. The tracer goes to areas of abnormal bone activity (such as may be caused by cancer) and shows up as a 'hot spot' on the scan. However, not all hot spots are caused by cancer, and bone scans need to be interpreted with X-rays and in clinical context.

**brachial plexus**

A complex group of nerves which extends from the lower part of the side of the neck to just above the armpit.

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**brachytherapy**

The temporary placement of a source of radioactivity into one of the body's internal cavities for treatment of cancer.

**cancer genes**

See 'oncogenes'.

**carcinogen**

A cancer-causing substance.

**carcinogenic**

Cancer-causing.

**chemotherapy**

The use of drugs that are toxic to cancer cells. These drugs kill the cells or prevent or slow their growth. They may be taken in the form of tablets or intravenous injections.

**clinical practice guidelines**

Published guidelines issued by a central authority such as the National Breast Cancer Centre, which are aimed at informing medical practitioners of treatment and investigation methods preferred by experts and/or proven by research.

**colony stimulating factors**

Natural substances that stimulate the growth and differentiation (diversification) of white blood cells in the body.

**combination chemotherapy**

The use of two or more anticancer drugs together.

**complete remission ('complete response')**

This is the term used when, following treatment, there is no sign of any remaining disease. It is not necessarily the same as 'cure', as some cancer cells may remain hidden and undetectable.

**computerised tomography ('CT scan')**

A widely used X-ray technique that is especially valuable for looking at the brain and internal organs. A series of X-rays which provides a series of images of cross-sections of the body part.

**consensus document**

A publication that contains the distillation of the deliberations of a 'consensus meeting' attended by a wide range of experts in the disease, at which an attempt has been made to reach agreement on controversial or contentious aspects of the disease in question.

---

**coping strategies**

Mental strategies or behaviours employed to maximise functioning and reduce or eliminate psychological distress in response to stressful situations. Coping strategies may be influenced by personality style and the specific situation, and may change over time.

**cosmesis**

The appearance of the breast following conservative treatment. It is generally accepted that one goal of conservative treatment is to retain a breast with an appearance as close to normal as is compatible with effective treatment.

**CSFs**

Abbreviation for colony-stimulating factors.

**CT**

Abbreviation for computerised tomography.

**cytokines**

Natural body substances released by cells which influence the behaviour of other cells.

**delirium**

A global non-specific cerebral dysfunction characterised by disturbances in some or all of the following: level of consciousness, attention, thinking, perception, emotion, memory, psychomotor behaviour and sleep/wake cycles.

**denial**

Failure to acknowledge some aspect of external reality that would be apparent to others.

**depression**

A pervasive and sustained lowering of mood, often associated with tearfulness, guilt or irritability. Other features include loss of interest or pleasure in activities, lowered energy levels, impaired concentration and disturbance of sleep and appetite.

**differentiation**

The degree of similarity to normal cells. Cells which resemble normal cells closely are described as well differentiated, while those which do not resemble normal cells are described as poorly differentiated. The degree of differentiation is a feature of pathological systems for grading cancer cells.

---

**dose-intensity**

The term used to describe the relationship between drug dose and frequency of administration; in other words the amount of drug given over a particular time period.

**early breast cancer**

Breast cancer confined to the breast, or breast plus axillary lymph node tissue.

**ECOG performance status**

See 'performance status'.

**endocrine therapy**

The use of medical or surgical therapies that interfere with the body's endocrine balance.

**EORTC core quality of life questionnaire (QLQ)**

Developed by the European Organisation for Research and Treatment of Cancer (EORTC) study group for quality of life, QLQ-C30 is a generic 'core questionnaire' relevant to any cancer, to be used with modules specific to a particular cancer. It has undergone extensive translation and testing for interpretation and is available in most European languages. A 23-item breast cancer module (QLQ-B23) has been developed.

**fear**

Anxiety due to consciously recognised external threat or danger.

**fine needle aspiration biopsy (FNAB)**

The sampling of cells for examination by a pathologist by the use of a fine needle. Also known as fine needle aspiration (FNA).

**fraction**

Radiotherapy is usually given over several weeks. The dose delivered each day is known as a fraction.

**gene**

A large molecule, part of a cell's DNA, that controls the production of a protein molecule and through it, some action or function of the cell.

**general anaesthetic**

The technique of putting someone 'to sleep', so that an operation can be performed; it contrasts with a local anaesthetic

**GLQ-8**

An eight-item LASA instrument measuring specific side effects of cancer and cancer treatment.

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**grading**

The degree of similarity of the cancer cells to normal cells. If they closely resemble normal cells, they are said to be well differentiated. Grading is assessed by a pathologist observing a microscopic section.

A grade one carcinoma is well differentiated and associated with a good prognosis.

A grade two carcinoma is moderately differentiated and associated with an intermediate prognosis.

A grade three carcinoma is poorly differentiated and associated with a poor prognosis.

**grief**

The normal emotional responses to loss which may include a complex range of painful feelings such as sadness, anger, helplessness, guilt and despair.

**growth factor**

Natural substances that control the growth of certain body tissues; for example, growth factors have been discovered that control the growth of particular white blood cells or of nerve tissue.

**Halsted mastectomy**

Total mastectomy, removal of all the lymph nodes from the armpit and removal of the muscles of the chest. Formerly common, this operation is now rarely performed.

**Health-related Quality of Life (HRQL)**

A pragmatic representation of patients' physical, psychological, and social response to disease and its treatment. See also 'quality of life'.

**histology**

Assessment of cellular features by light microscopy of sections from paraffin embedded tissue.

**hormones**

Natural chemical substances that are produced by one body organ and travel through the bloodstream to other organs, where they exert their effects. Insulin, which controls the blood sugar level, is a well-known example.

**hormone treatment**

See 'endocrine therapy'.

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**hospice**

The service providing support and comfort to someone who is terminally ill or dying. Alternatively, a building or part of a building where this service is provided.

**hypercalcaemia**

Excessive levels of calcium in the blood. Its presence in a woman with advanced breast cancer often signifies bony metastases.

**ipsilateral**

On the same side.

**Likert scale**

A subjective numerical rating scale used in questionnaires.

**Linear Analogue Self-Assessment (LASA) scale**

A horizontal line of fixed length, usually 10 cm, with descriptors anchoring the extreme ends. Respondents are required to place a mark on the line corresponding to their perceived state.

**liver biopsy**

A minor procedure, performed under a local anaesthetic, in which a piece of liver tissue is removed for examination by a pathologist.

**locally advanced**

Locally advanced breast cancer is defined by invasion of non-breast tissues adjacent to the breast, such as the overlying skin or the underlying muscle or bones of the chest wall.

**local anaesthetic**

The technique of making a small part of the body numb, so that minor operations can be performed without pain, while allowing the patient to remain awake; it contrasts with a general anaesthetic.

**locally recurrent**

Cancer that has recurred (come back) after treatment, but which is confined to the breast area or nearby tissues only. It includes recurrences in the skin over the breast or breast area, in a previous surgical scar, and in axillary lymph nodes and nodes above the collar bone (supraclavicular lymph nodes) on the same side as the original cancer. Compare with 'advanced breast cancer'.

**locoregional**

In advanced breast cancer, locoregional refers to the breast and/or nearby tissues and structures, including the axilla and ribs.

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**lumpectomy**

An operation to remove a lump. The term is most commonly used to describe the small operation of removal of breast lump together with some surrounding normal tissue, as opposed to total removal of the breast.

**lymph glands**

Lymph nodes.

**lymph nodes**

Small, generally pea-sized pieces of tissue found all over the body but easier to feel in the neck, armpits, groins and the back of the abdomen. They act as filters for foreign substances and commonly become inflamed if there is an infection nearby. They can also harbour cancer cells that have spread from elsewhere, such as the breast.

**lymphangitis**

Inflammation of lymphatic vessels; in the context of breast cancer, it also refers to a particular type of secondary cancer to the lungs, in which the cells spread by filling up the lung's lymphatic vessels. It has a recognisable X-ray appearance.

**malignant**

Cancerous.

**mammography**

That process whereby X-rays of the soft tissue of the breast are obtained.

**mastectomy**

Surgical removal of the breast. A radical mastectomy is an operation where the breast is removed together with its overlying skin and underlying muscle; it is not often performed today. It compares with a simple mastectomy (also called total mastectomy) which describes the operation to remove the breast and overlying skin, leaving the muscles intact.

**meningeal carcinomatosis**

Carcinoma of the meninges, the membranes that cover the brain and spinal cord. It is often spread widely at the time of detection.

**metastasis**

The secondary or distant spread of cancer, away from its primary or initial site in the body.

**metastatic**

Pertaining to secondary cancer.

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**monitoring**

The process whereby patients are followed up after initial diagnosis and treatment. It may include clinical examination and/or the regular performance of tests.

**neoadjuvant**

Refers to chemotherapy if given before radiotherapy or surgery.

**neutropenia**

That condition which exists when the numbers of circulating neutrophil leucocytes are reduced. If the numbers fall to very low levels, there is the risk of supervening infection and the syndrome is then known as febrile neutropenia or neutropenic sepsis.

**nodal status**

Indicates the histological presence or not of metastases in the axillary nodes. Node +ve = one or more nodes involved. Node -ve = no nodes involved.

**oestrogen receptor (ER)**

A protein on breast cancer cells that binds oestrogen. It indicates that the tumour may respond to hormonal therapy. Tumours with plenty of ER have a better prognosis than those that do not. Tumours may be described as 'ER +ve' if they contain detectable oestrogen receptors, and as 'ER -ve' if they do not. (See also 'progesterone receptors').

**oncogenes ('cancer genes')**

Pieces of molecular information which are variations of normal genes and are found within the DNA of the cell; their normal counterparts ('proto-oncogenes') are responsible for the growth and multiplication of cells. The presence of cancer genes, some of which may be inherited, can increase the risk that the person will develop cancer, but usually does not necessarily lead to cancer unless they are stimulated or otherwise made active.

**ovarian ablation**

A procedure that removes or destroys the function of the ovaries. It may be achieved by surgical removal, chemotherapy, or radiation or hormonal therapy. Surgical removal of the ovaries is also known as oophorectomy.

**oophorectomy**

Surgical removal of the ovaries.

**opiates**

Natural substances derived from the opium poppy.

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**opioids**

Purified, opiate-like chemicals derived from opiates or manufactured in a laboratory.

**palliative care**

The active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social and spiritual problems is paramount. The goal of palliative care is to achieve the best possible quality of life for patients and their families. (From: World Health Organization 2000)

**palliative treatment**

Treatment directed at the cancer to reduce its effects, without the intention of curing it or prolonging survival. Such treatment may include surgery, radiotherapy or chemotherapy. Investigative procedures are kept to a minimum.

**paracentesis**

The removal of ascitic fluid from the abdomen using a fine needle or trocar and cannula, sometimes under ultrasound control.

**partial remission (or response)**

The situation when, following treatment, signs of the disease process have partially resolved but have not disappeared completely.

**performance status**

An assessment of the patient's level of function and self care. The ECOG scale is one of the most widely used scales. It is comprised of five ordered levels of impairment ranging from zero (no impairment) to four (bedridden).

**PET scan**

'Positron emission tomography', a new type of scanning technique.

**Pharmaceutical Benefits Schedule (PBS)**

The Australian Government's scheme of making available a restricted range of medical drugs at subsidised cost to the Australian populace.

**primary**

The original site where the cancer developed.

**prn**

Refers to taking drugs, usually painkillers, as needed, rather than at set times.

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**progesterone receptors (PR)**

The intracellular receptor which binds progestins and antiprogestins. It is an oestrogen-induced protein and can therefore be used as a marker of functional oestrogen receptor status. High expression of progesterone receptors is associated with a good prognosis. Tumours may be described as 'PR +ve' if they contain progesterone receptors, and as 'PR -ve' if they do not.

**protocol**

A well defined program for treatment.

**psychosocial**

Referring to the psychological, social and spiritual needs of cancer patients.

**quality of life (QOL)**

More accurately health-related quality of life. The individual's overall appraisal of their situation and their subjective sense of wellbeing.

Quality of life encompasses symptoms of disease and side effects of treatment, functional capacity, social interactions and relationships, and occupational functioning. Key psychological aspects include subjective distress, satisfaction with treatment, existential issues, and the impact of illness and treatment on sexuality and body image.

There is general acceptance of the operational definition in terms of a patient's ability to function physically, mentally, spiritually and socially, and the extent of the symptoms of both the disease and its treatment.

There are a number of standardised measures of quality of life, ranging in sophistication from the simple visual scale through to comprehensive self-administered questionnaires. Some questionnaires have been designed for specific diseases or conditions, including several directed specifically at cancer. It is important that standardised measures have demonstrated validity and reliability.

**radioisotope**

A radioactive variant of an element, commonly used as a tracer in scanning tests; for example, a radioisotope of iodine can be used to identify thyroid tissue, since normal iodine has a natural affinity for the thyroid gland. See also 'strontium'.

**radiotherapy**

The use of radiation in X-rays or gamma rays to kill tumour cells.

**reliability (of a test)**

The ability to measure something in a reproducible and consistent fashion. Measurements of individuals on different occasions, or by different observers, or by similar or parallel tests produce the same results.

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**resectable**

Removable with a satisfactory margin as part of a cancer surgery operation.

**responsiveness (of a test)**

The ability to detect clinically important changes over time.

**recurrence**

The re-occurrence of cancer some time after it was first treated.

**response**

Measurement of the effect of treatment on the disease. For cancer, usually recorded as one of four categories: 'complete response', 'partial response', 'stable disease' and 'progressive disease' (or 'no response').

**secondary tumour**

Spread of cancer from its source (or 'primary' site) to another part of the body. For breast cancer, common sites of secondary spread include the bones, liver and lungs. The secondary cancerous growths are known as metastases or 'secondaries'.

**single-agent chemotherapy**

Use of one anticancer drug on its own (see 'combination chemotherapy').

**staging**

The process of determining the extent of the disease. There are two main approaches to staging - pathological and clinical (see Appendix E).

**stem cells**

Cells which are normally present mainly in the bone marrow. By dividing and differentiating (diversifying), they act as the source of blood cells, including red blood cells, white blood cells and platelets. They can be induced to enter the circulation in large numbers, from where they may be collected on a blood cell separator, as part of the process of autologous stem cell rescue.

**strontium**

An element which has a predilection to mimic calcium and go to the bones. This property can be exploited by using a radioactive isotope of strontium to act as a tracer for calcium in performing a bone scan; or in larger concentrations as a form of treatment, so that it concentrates at sites of damaged bone and attacks cancer cells in the vicinity.

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**support**

The existence or availability of people on whom an individual can rely for the provision of emotional caring and concern, and for reinforcement of a sense of personal worth and value. Other components of support may include the provision of practical or material aid, information, guidance, feedback and validation of the individual's stressful experiences and coping choices.

**support persons**

The persons giving support to the cancer patient.

**symptoms**

Anything physical, psychological or social that causes noticeable concern to a patient.

**syndrome**

A collection of symptoms and signs.

**systemic**

Pertaining to the whole body.

**tamoxifen**

An anti-oestrogen medication, given in the form of tablets. It is most commonly used in post-menopausal women to inhibit the growth of hormone responsive breast cancer cells.

**tumour**

Any swelling. In the context of cancer, the word usually refers to malignant (cancerous) lumps.

**tumour suppressor genes**

Pieces of molecular information which are found within the DNA of the cell, and which are normally responsible for restricting the rate of cell growth and multiplication. If they are altered (mutated) and unable to perform this normal function, there may be excessive proliferation of cells and thus cancer. They are also called anti-oncogenes.

**tumour type**

The overall histological pattern of the tumour.

**ultrasound**

High frequency sound waves above 20,000 Hz. Ultrasonic waves are reflected by deep structures in the body, allowing the visualisation of internal organs.

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**validity (of a test)**

A process of determining what is being measured by a scale. An index is valid if it is measuring what it is intended to measure.

**X-rays**

Electromagnetic radiations with wave lengths in the range of 0.1 to 100 angstroms. X-rays are absorbed exponentially by the irradiated tissue.

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## REFERENCES BY SUBJECT

### **Breast care: incidence, mortality and prevalence rates**

references 1–11

### **Recurrence rates**

references 12–15

### **Survival and prognosis**

references 16–26

### **Quality of life and psychosocial impact on patient and family**

references 25–87

### **Impact on health professionals**

references 88–95

### **Economic impact**

references 96–101

### **Assessment**

References 102–106

### **Assessing quality of life**

107–117

### **Multidisciplinary care and co-ordination of care**

references 118–127

### **Communicating with the woman**

References 128–129

### **Clinical trials**

references 130–133

### **Alternative and complementary medicine**

references 134–162

### **Palliative care**

references 163–75

### **Bereavement support**

references 176–185

### **Request for autopsy**

references 186–188

---

**Management of locally advanced breast cancer**  
references 189–204

**Management of locoregional recurrence**  
references 205–226

**Management of metastatic breast cancer**  
references 227–266

**Special problems of advanced breast cancer**  
references 267–345

**Interventions to improve quality of life**  
references 346–353

**Management of pain**  
references 354–369

**Supportive treatments**  
references 370–394

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