Handbook of Metastatic Breast Cancer
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Contents

List of contributors vii

1. Introduction 1
   Stephen RD Johnston and Charles Swanton

Section I – Systemic Treatments

2. Endocrine therapy for advanced disease 7
   Stephen RD Johnston

3. Chemotherapy and metastatic breast cancer 33
   Charles Swanton

4. Trastuzumab and other novel therapies in breast cancer 61
   Robin L Jones and Ian E Smith

5. Bisphosphonates and their role in metastatic breast cancer 79
   David A Cameron

Section II – Imaging

6. Imaging in the management of metastatic breast cancer 89
   David MacVicar

7. Positron emission tomography/computed tomography in metastatic breast cancer 109
   Bhupinder Sharma

Section III – Local Treatment Options

8. Palliative radiotherapy in the management of metastatic breast cancer 123
   Anthony Chalmers and Richard Simcock

9. Management of neurological complications in metastatic breast cancer 147
   Wim Bouwknecht and Adrian Casey
10. Thoracic complications  
   *George Ladas*  
   163

11. Orthopaedic complications  
   *Kuldeep K Bhangal and Stuart C Evans*  
   181

12. Radiofrequency ablation of hepatic metastases  
   *Andreas Adam*  
   201

**Section IV – Palliative Care**

13. Palliative care  
   *Andrew Davies and Fiona Bailey*  
   211

Index  
   225
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1

Introduction

Stephen RD Johnston and Charles Swanton

EPIDEMIOLOGY OF ADVANCED BREAST CANCER

During the past two decades there have been significant advances in the diagnosis and treatment of early breast cancer, reflected by the significant improvement in mortality from the disease observed both in the USA and Europe since the early 1990s. Reasons for this progress are multifactorial, and have been attributed to the possible impact of screening and detection of earlier-stage disease, better multidisciplinary management of breast cancer by dedicated specialists, together with more widespread use of systemic adjuvant therapies including combination chemotherapy and hormonal treatment with the antioestrogen tamoxifen. Efforts in undertaking large multicentre clinical trials in early breast cancer have been rewarded with continued incremental improvements in overall survival due to incorporation of better cytotoxic drugs (i.e. the taxanes) and schedules, more effective endocrine drugs (i.e. aromatase inhibitors for postmenopausal hormone-sensitive disease) and, most recently, targeted biological therapies (i.e. trastuzumab for women with HER2-positive breast cancer). Consequently, survival rates are expected to further improve in years to come as these more effective systemic therapies become more widely used.

Despite these advances and grounds for realistic optimism, approximately one-third of women diagnosed with breast cancer will develop metastatic disease and subsequently die from their advanced breast cancer. Globally, half a million deaths each year are attributable to metastatic breast cancer. The median survival from the time of diagnosis of metastases is approximately 3 years, although it is recognised that the range is very wide with some patients having more indolent disease, with which they live for many years (10–15 years in some cases). In part this reflects the biological diversity of the disease, with extreme sensitivity to hormonal treatments in some women with endocrine-sensitive breast cancer, together with different patterns of metastatic spread that range from limited bone-alone metastases, which may be relatively asymptomatic, to widespread dissemination with life-threatening involvement of visceral organs such as liver, lung and brain. Risk factors at presentation with early breast cancer for the subsequent development of metastases relate to adverse prognostic factors in the primary tumour, and include large primary size >3 cm, axillary lymph node involvement and/or evidence of lymphovascular invasion, high grade of the tumour (i.e. poorly differentiated grade 3) and adverse biological
tumour phenotype reflected by oestrogen receptor (ER) negative and/or human 
epidermal growth factor receptor 2 (HER2) positive status. Although the advances in 
systemic therapies cited above have improved the outlook for those women at higher 
risk, they are not a cure for all women and the risk for developing metastases has not 
yet diminished to zero.

GLOBAL IMPACT OF ADVANCED DISEASE

The socioeconomic impact of advanced breast cancer and its management is a major 
health problem for a number of reasons. First, the high prevalence of the disease and 
relatively long natural history for many patients means that in the UK approximately 
100,000 women are living with a diagnosis of metastatic disease each year. Secondly, 
the nature of metastatic disease means that some of the associated problems utilise 
significant healthcare resources. For example, management of bone metastases may 
include several courses of radiotherapy, frequent and regular intravenous infusions 
of bisphosphonates, orthopaedic interventions and regular use of analgesics, all of 
which may go on for a number of years. Studies have shown that management of 
advanced breast cancer is a major consumer of healthcare resources. A previous UK 
study over 15 years ago showed that direct care costs over a significant period of time 
were the major components of cost rather than drugs per se. A North American 
study suggested that the average cost per case of metastatic disease was approxi-
mately £17,000. This figure is likely to be substantially higher now due to the wide-
spread use of more effective drugs for advanced disease, many of which – such as the 
new biologicals, endocrine agents and cytotoxics – are deemed high-cost drugs.

AIMS OF TREATMENT WITH METASTATIC DISEASE

At present, metastatic breast cancer cannot be cured, and thus the principal aim of 
treatment is to increase the duration of time free from disease-related symptoms with 
minimal toxicity, thus ensuring the maximum quality of life for the majority of 
patients. As such, choice of treatment options for advanced disease is always influ-
enced by balancing the likelihood of benefit against the associated side effects of any 
given therapeutic manoeuvre. Thus for ER-positive breast cancer, endocrine therapy 
is very important in advanced disease due to its better tolerability than chemotherapy, 
and relatively long time to progression in those patients who respond. Many 
have recognised the importance of stable disease beyond 6 months as a measure of 
clinical benefit from therapy, and with endocrine therapy in particular clinical bene-
fit from such a response is well recognised. However, factors such as the degree 
of hormone sensitivity in the tumour and the extent/location of advanced disease 
together with the presence/absence of disease-related symptoms all influence the 
choice of initial systemic therapy (i.e. endocrine treatment versus chemotherapy).
Quality of life in metastatic breast cancer has been shown to be clearly linked to treatment response, and thus the aim of providing palliative benefit from tumour-related symptoms is integrally linked to ensuring the best chance of treatment response from any given therapy. Decision on the best choice of treatment must therefore look at likelihood of response and duration of benefit in combination with predicted side effects. Whereas objective tumour response rate and time to tumour progression (treatment response) are the gold standard endpoints in assessing efficacy from any given intervention in phase II/III trials, in clinical practice symptom relief and improvement in quality of life are just as important as seeing a 50% shrinkage in tumour size on radiological imaging. A significant number of patients will derive a benefit from treatment, as determined by improvement in disease-related symptoms and net gain in quality of life, and this includes many in whom there is no change in tumour size on objective assessment. These facts are crucially important when discussing the aims of treatment with patients at the outset, and defining the best parameters by which to judge success or otherwise of any treatment intervention in each individual.

It has always been assumed that there is a minimal impact on overall survival through the treatment of advanced disease, although randomised trials of systemic therapies versus best supportive care have never been undertaken to investigate the direct impact on survival. However, several facts suggest that survival can be impacted by treatment options for advanced disease. First, historical comparisons looking at survival from advanced disease have shown an incremental improvement over the decades from the 1970s following the introduction of cytotoxic chemotherapy. Secondly, on an individual basis, it is also clear that patients who present with life-threatening visceral metastases — extensive liver secondaries with deranged liver function and associated symptoms of weight loss, nausea, etc. — may only have a prognosis measured in weeks, yet if they respond well to cytotoxic chemotherapy they clearly derive a significant survival benefit compared to not receiving an anticancer treatment. Finally, the introduction of novel drugs, in particular targeted biological therapies such as trastuzumab for HER2-positive disease, has started to alter the natural history of advanced breast cancer, and an unprecedented significant impact on survival with such treatments has now been seen in randomised trials. As such, it is likely that many patients will now live considerably longer with their metastatic disease under control, although cure in this setting still remains an elusive goal.

TREATMENT OPTIONS FOR METASTATIC BREAST CANCER — A MULTIDISCIPLINARY APPROACH

The principles outlined above govern the choice of treatment options when women present with metastatic breast cancer. Whereas the overall care is supervised by medical or clinical oncologists in the majority of situations, recognising the benefit
of different treatment options requires a good understanding of the natural history of advanced breast cancer. As discussed throughout this book, an integrated approach with several different disciplines will offer the maximum benefit for patients with metastatic breast cancer. Systemic treatments have by far the largest role to play, and comprise four different types: endocrine therapies, cytotoxic chemotherapy, targeted biological therapies and supportive treatments such as the bisphosphonates. There have been significant advances in each of these areas over the last decade, and each chapter discusses the evidence from various clinical trials in more detail. For example, in Chapter 2 the aromatase inhibitors have significantly improved the benefit derived from endocrine therapy for postmenopausal women, while at the same time novel endocrine drugs have been introduced to overcome endocrine resistance seen with tamoxifen. Cytotoxic chemotherapy is discussed in Chapter 3, in particular the taxanes, which have made a significant impact in advanced disease, although as they move into the adjuvant arena there will be a continued need to develop novel cytotoxics that can be effective in recurrent advanced disease. The impact of targeted biological therapies is discussed in Chapter 4 as exemplified by the monoclonal antibody trastuzumab, although advances in cancer therapeutics mean that many more so-called signal transduction inhibitors could become realistic treatment options over the next few years. Finally, as systemic supportive therapies, the role of bisphosphonates in altering the natural history of bone metastases is discussed in Chapter 5.

Alongside the development of better systemic treatment options, there have been advances in imaging that are highly relevant to the assessment of metastatic disease, and in particular determining the objective benefit of various systemic therapies. Chapter 6 outlines the current options for imaging metastatic breast cancer and their role in assessment of treatment response, and also the issues relating to their role in detecting disease in asymptomatic patients. Chapter 7 then highlights recent developments with positron emission tomography (PET), and the future role this could play in assessment of patients with advanced breast cancer.

Palliation of disease-related symptoms is the overarching goal in advanced breast cancer, and radiotherapy continues to play a crucial role for specific local issues in advanced disease. Advances in the techniques used are discussed in Chapter 8, together with future technical developments such as gamma knife therapy for intracranial metastases. The involvement of specialist surgical services is increasingly recognised in the management and effective palliation of specific problems in advanced breast cancer. Several chapters are therefore dedicated to a state-of-the-art review of the various local complications that occur in these patients, and how a multidisciplinary approach integrated with surgical options is used for neurological and spinal complications (Chapter 9), pulmonary complications (Chapter 10), orthopaedic interventions (Chapter 11) and interventional radiological techniques such as radiofrequency ablation (Chapter 12). Close involvement of these services with a metastatic breast cancer clinic will ensure that these treatments can be offered when most appropriate for the specific issues that arise in many patients with advanced breast cancer. Finally, effective palliative care is not to be considered only as an end-stage option. As
discussed in Chapter 13, the involvement of specialist healthcare professionals in pain control and symptom relief should be integrated alongside the use of the systemic and local treatments options described in the preceding chapters.

REFERENCES

Endocrine therapy
for advanced disease

Stephen RD Johnston

INTRODUCTION

In the UK breast cancer affects 1 in 9 women during their lifetime, with an annual incidence that has now reached >41,000, with approximately 13,000 deaths per year.\(^1\) Approximately 5–10% of newly diagnosed breast cancer patients have locally advanced/metastatic disease at the outset, and 20–70% of patients (depending on their tumour biology, initial stage of disease and subsequent therapy) will develop recurrent/metastatic disease in the future. It is estimated that in the UK over 100,000 women are living with advanced/metastatic breast cancer at any one time. Once metastatic disease has been diagnosed it cannot be cured, and the overall median survival from the time metastatic disease is confirmed is between 2 and 3 years.

The optimal management of patients with metastatic disease remains a challenge, with systemic drug treatments such as chemotherapy, endocrine therapy, biological targeted therapy and supportive therapies being the mainstay of care. The decision as to which is the most appropriate treatment option is based on a number of patient and disease-related factors. Approximately two-thirds of human breast carcinomas express oestrogen receptors (ERs) and thus may be dependent on oestrogen for their growth, and for patients in whom their breast cancer (either primary tumour or biopsy of accessible metastatic disease) is positive for ER and/or progesterone receptor (PgR), endocrine therapy is an important treatment option with minimal toxicity. For patients with ER/PgR-positive (ER/PgR+ve) breast cancer and an estimated low risk of rapid progression of their advanced disease – i.e. soft tissue and/or bone metastases as their dominant site, absence of life-threatening visceral involvement, disease-free interval greater than 2 years and limited sites of metastatic involvement – endocrine therapies can be very effective in the treatment of their advanced/metastatic disease (Table 2.1). For example, locally advanced ER+ve disease within the breast of elderly women is often slow growing and extremely hormone sensitive. Excellent clinical responses can be achieved with simple well-tolerated endocrine therapy such as tamoxifen, albeit maximal response and tumour shrinkage may take between 6 and 9 months to occur (Figure 2.1a,b). However, sites of visceral metastases such as the liver may also respond well to endocrine therapy provided appropriate selection of patients is undertaken. For
example, postmenopausal patients with strongly ER/PgR+ve disease, with a long treatment-free interval of many years after completion of adjuvant tamoxifen, may then develop metastatic disease within the liver but with a limited number of tumours and preserved organ function (i.e. normal liver function tests), lack of any symptoms from their advanced disease and good overall performance status. Such patients can have an excellent clinical response to endocrine therapy alone with, for example, aromatase inhibitors, which may last for 18–24 months before their disease progresses and patients require chemotherapy (Figure 2.1c,d). Appropriate selection of patients suitable for initial endocrine therapy is therefore crucially important in order to maximise the benefits from such treatments.

In this chapter the evidence for the current endocrine therapy options that are available for advanced disease is reviewed in more detail, together with the emerging strategies that might be used in future to further enhance their effectiveness.

### ENDOCRINE THERAPY OPTIONS FOR METASTATIC BREAST CANCER

Historically, tamoxifen has been the approved gold standard endocrine therapy for the treatment of metastatic breast cancer, both of pre- and postmenopausal women. Tamoxifen is a non-steroidal ER antagonist which inhibits breast cancer growth by competitive antagonism of oestrogen at the receptor site (Figure 2.2). However its actions are complex due to partial oestrogenic agonist effects which in some tissues (i.e. bone) can be beneficial, but in others may be harmful, increasing the risk of thromboembolism and uterine cancer. Although an effective treatment for advanced breast cancer, the partial agonist effects may account for the development of tamoxifen
resistance after prolonged treatment. Furthermore, the majority of women with ER+ve breast cancer who then develop metastatic disease have already been treated with tamoxifen in the adjuvant setting. In the past, tamoxifen therapy was used again if tamoxifen had been stopped several years previously, although alternative endocrine approaches that deprive tumours of circulating oestrogens are now used in preference.

Within the last 5 years third-generation potent oral aromatase inhibitors (AIs) have become a standard treatment option for postmenopausal patients with ER+ve advanced/metastatic breast cancer. Oral aromatase inhibitors such as anastrozole (Arimidex), letrozole (Femara) and exemestane (Aromasin) all reduce serum oestrogen levels in postmenopausal women by preventing the conversion of adrenal androgens into oestrogens (see Figure 2.2). Whereas oestrogens are normally synthesised in the ovary in premenopausal women, following the menopause mean plasma oestradiol (E2) levels fall from about 400–600 pmol/L to around 25–50 pmol/L. These residual oestrogens come solely from peripheral aromatase conversion, particularly in subcutaneous fat, and plasma E2 levels correlate with body mass index in postmenopausal women.1 As discussed below, in postmenopausal women with advanced breast cancer several clinical trials have demonstrated that aromatase inhibitors are more effective and better tolerated than tamoxifen as first-line management of

Figure 2.1 Locally advanced disease of the breast before (a) and 6 months after (b) therapy with tamoxifen, showing substantial tumour shrinkage. Metastatic disease within the liver with three isolated tumours developing many years after prior adjuvant tamoxifen, before (c) and after (d) 6 months therapy with an aromatase inhibitor.
Figure 2.2  Source of oestrogens in pre- and postmenopausal women, together with endocrine therapy options, to either antagonise oestrogens (tamoxifen), or induce oestrogen deprivation via aromatase inhibition (postmenopausal) or ovarian ablation (premenopausal) via surgical, radiation or medical means.
metastatic breast cancer. Since the late 1990s AIs have become the new gold standard for first-line endocrine treatment in postmenopausal women with advanced breast cancer.

For premenopausal women with ER+ve advanced breast cancer, oestrogen deprivation through ovarian ablation has been the main endocrine approach when tamoxifen has been used previously in the adjuvant setting. This can be achieved either by surgical oophorectomy, radiation of the ovaries or medical ablation with luteinising hormone-releasing hormone (LHRH) agonists such as goserelin (Zoladex) (see Figure 2.2). Such an approach can be effective in premenopausal women with endocrine-sensitive advanced disease, and at the time of further progression the addition of AIs to LHRH agonists has been a successful additional second-line option. As discussed below, for women initially presenting with endocrine-sensitive advanced disease who have not received prior tamoxifen, combined LHRH agonists with tamoxifen appears to be a more effective strategy than tamoxifen alone.

Recently oestrogen suppressive therapies with either AIs or LHRH agonists have started to move into the adjuvant setting for post- and premenopausal women, respectively. This has led to new questions about the optimal sequence of endocrine therapies for subsequent use in advanced disease. The ER down-regulator fulvestrant (Faslodex) is a novel treatment option for women with progressive disease following prior tamoxifen therapy, and current trials are investigating whether fulvestrant is a suitable treatment option for postmenopausal women following progression with an aromatase inhibitor. Research in endocrine therapy has been focusing on understanding the mechanisms of acquired resistance and the molecular pathways which allow ER+ve cells to escape from endocrine therapy. As discussed at the end of this chapter, several new strategies that combine endocrine therapies with various signal transduction inhibitors are now being investigated in ongoing clinical trials in advanced breast cancer. The ultimate goal will be to overcome and/or prevent development of endocrine resistance in ER+ve breast cancer, and thus further enhance the benefits of existing endocrine therapy.

### CLINICAL EFFICACY OF AROMATASE INHIBITORS IN ADVANCED BREAST CANCER

#### Pharmacology

Anastrozole and letrozole are third-generation non-steroidal AIs that have similar pharmacokinetics, with half-lives of approximately 48 hours, allowing a once-daily schedule. Exemestane is a steroidal AI, with a longer half-life of 27 hours (Figure 2.3). All three compounds are orally active, reducing serum oestrogen levels in postmenopausal women by preventing conversion of adrenal androgens (androstenedione and testosterone) into oestradiol (E2) and oestrone (E1) via the cytochrome P450 enzyme aromatase. Based on the clinical trials outlined below, all three AIs are licensed
and approved as endocrine treatment for postmenopausal women with ER+ve advanced breast cancer.

Second-line therapy post tamoxifen

Between 1995 and 2000 the three third-generation aromatase inhibitors established themselves clinically when a series of randomised controlled trials (RCTs) in over 2000 women demonstrated clinical superiority over megestrol acetate as second-line therapy after tamoxifen8–13 (Table 2.2). An analysis of two randomised phase III trials of 764 patients treated with either anastrozole or megestrol acetate as second-line therapy after tamoxifen failure demonstrated equivalent efficacy in terms of objective response rates (10.3% and 7.9%, respectively) and disease stabilisation for 6 months (25.1% and 26.1%, respectively), although better tolerability was shown for anastrozole.8 A subsequent analysis following a median of 31 months follow-up showed a significant improvement in overall survival for anastrozole (hazard ratio 0.78, \( p = 0.02 \)).9 For letrozole, improvements were seen in objective tumour response rate (hazard ratio 1.82, \( p = 0.04 \)) and time to treatment failure compared with megestrol acetate, although no impact on survival was detected.10 In the trial with exemestane, duration of objective response, time to disease progression and overall survival were all significantly better than megestrol acetate.11 A subsequent second trial of letrozole,12 together with a study of the aromatase inhibitor vorozole (no longer in development),13 showed less substantial improvements over megestrol acetate.

This was in contrast to previous trials with the second-generation inhibitors fadrozole and formestane, which had all failed to show any such advantage.14,15 The improvements in clinical endpoints for the third-generation AIs, together with their
consistent superior tolerability profile over megestrol acetate (i.e. reduced weight gain and thromboembolic events), defined the AIs by the late 1990s as the standard endocrine treatment for advanced postmenopausal breast cancer following tamoxifen failure.\textsuperscript{16} In practice, however, developments in first-line endocrine therapy rapidly diminished the clinical relevance of these findings.

First-line therapy versus tamoxifen

Subsequent trials in advanced breast cancer asked whether AIs could challenge tamoxifen as the first-line endocrine agent of choice. Previously, no first- or second-generation AI had proved superior to tamoxifen.\textsuperscript{17–19} In addition to comparing tolerability, the potential of these studies with the new third-generation AIs was to see whether the near-complete oestrogen blockade provided by these drugs could deliver greater control of hormone-sensitive breast cancer than tamoxifen, thus circumventing the problem of acquired resistance due to the partial agonist effects of tamoxifen.\textsuperscript{20}

The first published data came from two parallel multicentre double-blind RCTs in which anastrozole was compared with tamoxifen as first-line therapy in ER+ve breast cancer (Table 2.3). The first study in 353 women showed that anastrozole significantly prolonged the median time to disease progression from 5.6 to 11.1 months ($p=0.005$).\textsuperscript{21} While there was no significant difference in objective tumour response rate (21% anastrozole vs 17% tamoxifen), the clinical benefit rate (defined as the proportion of patients who responded or had stable disease for at least 6 months) was significantly

### Table 2.2  Comparative second-line trials of third-generation aromatase inhibitors versus megestrol acetate

<table>
<thead>
<tr>
<th>Reference</th>
<th>Comparators</th>
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<th>Response (%)</th>
<th>Clinical Benefit (%)\textsuperscript{a}</th>
<th>Median time to progression (months)</th>
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\textsuperscript{a} Defined as total per cent of patients responding or achieving stable disease for at least 6 months.

\textsuperscript{b} Significant difference.
better for anastrozole (59% vs 46%). By contrast, in the larger trial in 668 patients no difference was found between the treatments in terms of median time to progression (8.2 vs 8.3 months), response rate (33% in both arms) or clinical benefit rate (56% in both arms). The explanation for the different results may have involved a higher proportion of patients with unknown ER status in the second trial, and a subsequent combined analysis of women with just ER+ve disease from both trials confirmed a significant improvement in disease-free survival in favour of anastrozole. Short-term side effects such as hot flushes, vaginal dryness and headaches were infrequent and similar in both trials in comparison with tamoxifen.

The largest single trial was conducted with letrozole in comparison with tamoxifen in over 900 women with advanced breast cancer. Patients treated with letrozole had a significantly higher objective tumour response rate (30% vs 20%, \( p < 0.001 \)), clinical benefit rate (49% vs 38%, \( p < 0.001 \)) and prolonged time to disease progression (median time to progression of 9.4 months vs 6.0 months, hazard ratio 0.72, \( p < 0.0001 \)). Of particular note in this trial, nearly 20% of patients had received prior tamoxifen in the adjuvant setting, although this had ceased more than 1 year (median 3 years) prior to development of metastatic disease – in this subgroup, retreatment with tamoxifen had a low response rate of 8% compared with a 32% response rate with letrozole. The improvements in clinical efficacy for letrozole resulted in an early improvement in survival during the first 2 years, with overall 64% of patients treated with letrozole alive at 2 years compared with 58% treated with tamoxifen (\( p = 0.02 \)), although with longer follow-up this difference was lost. The explanation for this result may relate to the high number (>50%) of patients who prospectively crossed over to the alternative treatment at the time of progression, as significantly more patients benefited from second-line letrozole after progression on tamoxifen than to

### Table 2.3 Comparative first-line trials of aromatase inhibitors versus tamoxifen

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<td>9.4&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>et al&lt;sup&gt;24, 25&lt;/sup&gt;</td>
<td>Tamoxifen</td>
<td>454</td>
<td>20&lt;sup&gt;b&lt;/sup&gt;</td>
<td>38</td>
<td>6.0</td>
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<tr>
<td>Paridaens et al&lt;sup&gt;26&lt;/sup&gt;</td>
<td>Exemestane</td>
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<td>46&lt;sup&gt;b&lt;/sup&gt;</td>
<td>66&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>31</td>
<td>49</td>
<td>5.8</td>
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</table>

<sup>a</sup> Defined as total per cent of patients responding or achieving stable disease for at least 6 months.

<sup>b</sup> Significant difference vs tamoxifen.
second-line tamoxifen after letrozole. Again, there were no significant differences in toxicity between the two treatments.

Finally, a large European study in 383 patients has compared the efficacy and tolerability of the steroidal AI exemestane with tamoxifen as first-line therapy. After a median follow-up of 29 months, there was an improvement in progression-free survival from 5.8 months for tamoxifen to 9.9 months for exemestane (hazard rate 0.84, \( p = 0.028 \) by Wilcoxon sensitivity test). There was a significantly higher objective response rate (ORR) with exemestane than tamoxifen (46% vs 31%, ORR 1.85, \( p = 0.005 \)). Likewise, the clinical benefit rate was significantly higher (66% vs 49%). Both treatments were well tolerated, with more grade 1 myalgia in the exemestane-treated group, and more grade 2 oedema, grade 1 hot flushes, vaginal bleeding and sweating in the tamoxifen group.

Thus, the available data from the four RCTs of the inhibitors in advanced disease suggest consistent improved efficacy over tamoxifen; therefore, they are all approved as first-line endocrine therapy for postmenopausal women with ER+ve advanced breast cancer, especially where prior adjuvant endocrine therapy was with tamoxifen. Since 2001, the third-generation AIs have become the standard of care as first-line endocrine therapy in this setting.

**Tolerability in advanced disease**

All the third-generation AIs are in general very well tolerated, with a remarkably low incidence of serious short-term side effects, reflecting the extreme specificity of their action. The commonest side effects include hot flushes, vaginal dryness, musculoskeletal stiffness/pain and headache, but are usually mild. In general, comparative trials show these side effects to be very similar in nature and frequency to those of tamoxifen, and less troublesome than with the progestins. A better indication of the drug-specific side effects, particularly the long-term effects of AIs on bone and cognition over many years, has come from the large-scale adjuvant trials. Furthermore, unlike the advanced breast cancer studies, these adjuvant trials are not confounded by tumour-related symptoms and have reported that patients treated with AIs had a significantly lower incidence of hot flushes, vaginal bleeding, vaginal discharge, weight gain and venous thromboembolism than patients treated with tamoxifen. However, musculoskeletal symptoms and fractures were more common than with tamoxifen.

**Comparisons between different third-generation aromatase inhibitors in advanced disease**

Letrozole achieved greater aromatase inhibition than anastrozole in a cross-over pharmacodynamic trial, and the clinical data for its superiority over tamoxifen in advanced disease are more solid. Preliminary data from a comparative trial of these two inhibitors in advanced breast cancer after tamoxifen are confusing, with letrozole achieving significantly more regressions overall than anastrozole, but not in the
key subgroup with known ER+ve tumours. Overall, current clinical evidence suggests that there are unlikely to be major direct clinical differences between the different AIs in advanced disease. There are no comparative data for exemestane with anastrozole or letrozole, although (as discussed below) further responses have been reported for this drug and the second-generation inhibitor formestane in patients relapsing after anastrozole, letrozole or the other non-steroidal inhibitors, suggesting partial non-cross resistance.

**POSTMENOPAUSAL SECOND-LINE TREATMENT OPTIONS POST AROMATASE INHIBITORS**

It has become important to develop effective endocrine therapies that will work following non-steroidal AIs, and to date clinical options have included treatment with tamoxifen (especially if this had not been used prior to the AI), use of the steroidal AI exemestane, based on phase II data suggesting non-cross-resistance), or the ER down-regulator fulvestrant, based on its novel endocrine mechanism of action.

**Tamoxifen following prior non-steroidal aromatase inhibitors**

There are few prospective data to show the true efficacy of tamoxifen in those who had progressed on a non-steroidal AI (i.e. anastrozole or letrozole). The largest available data come from the letrozole vs tamoxifen study, where over 50% of the patients prospectively crossed over to the alternative treatment at the time of progression. Median overall survival from the data of cross-over was 19 months for patients who crossed to second-line tamoxifen, compared with 31 months for patients who crossed to second-line letrozole. The only other data come from retrospective questionnaire data from the combined analysis of the two international phase III anastrozole vs tamoxifen TARGET trials. This analysis suggested that of 119 patients who went on to receive tamoxifen following progression on anastrozole, 58 patients (49%) derived clinical benefit and 12 patients (10%) had an objective response. A subsequent double-blind cross-over study by the Swiss centres in the TARGET Trial (SAKK 21/95 subtrial) further investigated the clinical impact of the sequence anastrozole followed by tamoxifen, and reported that 8/16 (50%) derived clinical benefit from tamoxifen. Thus, tamoxifen may have some efficacy as second-line therapy after an AI. However, data are sparse to confidently determine the optimal sequence. Furthermore, preclinical studies (discussed below) suggest that tamoxifen may be an agonist in cells’ resistance to long-term oestrogen deprivation, and that more effective endocrine/signalling strategies may exist for use following failure of first-line AI therapy.

Whereas the clinical data with the third-generation AIs suggest they are more effective if given as first-line therapy for advanced breast cancer, they are more expensive and in some healthcare systems will only gain greater acceptance if they can also
demonstrate cost-effectiveness. Life table analyses have been used to compare the costs and benefits of treating postmenopausal women with advanced breast cancer with the first-line AI letrozole with the option of second-line tamoxifen, compared with first-line use with tamoxifen with the option of second-line letrozole. The results of a UK-based analysis showed that the mean cost of providing first- and second-line hormonal therapy was £4765 if letrozole was first-line therapy, compared with £3418 if tamoxifen is provided first (a difference of £1347).33 However, patients who received letrozole as first-line therapy gained an additional 0.228 life years, or 0.158 quality-adjusted life years (QALYs). In public healthcare terms, these values were highly cost-effective compared with many other generally accepted medical treatments.

**Exemestane following prior non-steroidal aromatase inhibitor**

Steroidal AIs such as exemestane have an androgen structure and compete with the aromatase substrate androstenedione. They inactivate aromatase by irreversibly binding to its catalytic site, and additional aromatase must be produced before oestrogen biosynthesis can resume. This is in contrast to non-steroidal AIs that reversibly interact with the cytochrome P450 moiety of aromatase and the interference with oestrogen biosynthesis is dependent on the continued presence of the non-steroidal agent.34 Preliminary data suggest that there may be a lack of cross-resistance between steroidal AIs and non-steroidal AIs, and that steroidal AIs may be an option in non-steroidal AI-resistant disease.35–38

In a phase II, open-label, multinational trial, 24% of patients overall achieved clinical benefit with exemestane following either aminogluthethimide (n=136) or non-steroidal AI treatment (n=105).37 The objective response and clinical benefit rates were 8% and 27%, respectively, for patients who received prior aminogluthethimide. The corresponding rates were 5% and 20%, respectively, for those patients who had previously received non-steroidal AIs. A separate retrospective analysis of 96 patients receiving exemestane, 89 of whom had received prior non-steroidal AIs, reported that 37 (39%) patients experienced clinical benefit with exemestane.38

**Fulvestrant – an antioestrogen with a novel mechanism of action**

Fulvestrant (Faslodex) is a novel type of ER antagonist that, unlike tamoxifen, has no known agonist effects.39,40 Fulvestrant binds to the ER, but due to its steroidal structure and long side-chain, induces a different conformational shape with the receptor to that achieved by the non-steroidal antioestrogen tamoxifen. Consequently, fulvestrant prevents ER dimerisation and leads to the rapid degradation of the fulvestrant–ER complex, producing the loss of cellular ER. Thus, fulvestrant, unlike tamoxifen, inhibits ER binding with DNA and produces abrogation of oestrogen-sensitive gene transcription41 (Figure 2.4). It has been shown that due to its unique
mechanism of action, fulvestrant delays the emergence of acquired resistance compared with tamoxifen in an MCF-7 hormone-sensitive xenograft model. The lack of agonist effects means that fulvestrant did not support the growth of tumours that became resistant to, and subsequently stimulated by, tamoxifen.

Fulvestrant entered clinical trials after preclinical studies had suggested it was active in tamoxifen-resistant cancer. An initial phase II study analysing the pharmacokinetic, pharmacological and antitumour effects of fulvestrant demonstrated that fulvestrant was not cross-resistant with tamoxifen in the clinical setting and was well tolerated. Subsequent phase III trials compared fulvestrant with anastrozole in postmenopausal women with locally advanced or metastatic breast carcinoma who had progressed after prior endocrine therapy (~97% with tamoxifen; 56% of these as adjuvant therapy). These trials were prospectively designed to allow combined analysis of data. The intent-to-treat population for the combined analysis comprised 851 patients: 428 patients received fulvestrant 250 mg monthly and 423 patients received anastrozole 1 mg daily. At a median follow-up of 15.1 months, fulvestrant was at least as effective as anastrozole in terms of median time to progression (5.5 months vs 4.1 months, respectively (Figure 2.5)) and objective response (19% vs 17%, respectively). At an extended follow-up (median follow-up 22.1 months), the median duration of response in patients who responded to treatment was 16.7 months in patients receiving fulvestrant and 13.7 months in patients receiving anastrozole. A subsequent survival analysis after a median follow-up of 27 months has shown there was no

**Figure 2.4** Mechanism of action of oestradiol, tamoxifen and fulvestrant on oestrogen receptor dimerisation and transcription of oestrogen-regulated genes.
A significant difference in the median time to death between fulvestrant and anastrozole (27.4 months vs 27.7 months, respectively). Fulvestrant is therefore unique among ER antagonists as it is effective in tamoxifen-resistant disease. Moreover, a retrospective questionnaire-based follow-up analysis showed that progression on or after fulvestrant does not appear to preclude response to subsequent endocrine treatments, including anastrozole, letrozole, tamoxifen and megestrol acetate. The integration of fulvestrant into the treatment sequence may therefore extend the opportunity for endocrine therapy to be used before less well-tolerated treatments need to be considered.

**Efficacy of fulvestrant following aromatase inhibitors**

Clinical data with fulvestrant in advanced breast cancer following resistance to AIs are limited, but preliminary results from five phase II studies have shown that fulvestrant produced clinical benefit (CB) – complete response (CR) + partial response (PR) + stable disease (SD) ≥ 24 weeks – in between 20% and 52% of patients who had received, and had progressed on, prior treatment with tamoxifen and a non-steroidal AI. These results suggest that in addition to producing responses after prior tamoxifen, disease progression after non-steroidal AIs may not preclude subsequent treatment with fulvestrant.
Recent preclinical data have suggested that the efficacy of fulvestrant, especially in the setting of endocrine resistance (i.e. post tamoxifen or aromatase inhibitors) where activated ER signalling may be dominant, may critically depend on the background oestrogen environment in which the cells exist. Recent experiments with tamoxifen-stimulated breast cancer xenografts demonstrated paradoxical effects on tumour growth dependent on whether fulvestrant was administered in the presence or absence of oestrogen.55 Whereas wild-type MCF-7 xenografts were growth stimulated by oestrogen and inhibited both by tamoxifen and fulvestrant, long-term tamoxifen-treated (MCF-7TAML T) tumours which became resistant and growth stimulated by tamoxifen were inhibited by oestradiol. The addition of fulvestrant to oestradiol-treated tumours reversed these effects and actually stimulated growth of MCF-7TAML T tumours. However, when fulvestrant was given to these tumours on its own in a low oestradiol environment, tumours did not grow. Similar results have been reported in LTED-R cells in vitro where maximal growth inhibition of cells was observed with a dose of $10^{-8} \text{ mol/L}$ fulvestrant, yet the titration back of increasing amounts of oestradiol resulted in regrowth of cells which fulvestrant was no longer able to effectively antagonize.56

On the basis of these findings, several phase II and III clinical trials of fulvestrant are currently in progress that will investigate additional roles for fulvestrant in breast cancer.
cancer therapy either following prior non-steroidal AI treatment, or in combination with AIs (to maintain low oestradiol levels) as first-line therapy (Figure 2.6). The comparator for several of these studies is the steroidal AI exemestane which in phase II studies has shown some efficacy following progression on non-steroidal AIs.\textsuperscript{35,37,38} At present there are two randomised, controlled phase III trials comparing the efficacy and tolerability of fulvestrant vs exemestane in postmenopausal women progressing after long-term oestrogen deprivation resulting from prior AI therapy. The primary aim of the Study of Faslodex vs Exemestane with/without Arimidex (SoFEA) trial is to compare progression-free survival in patients who have progressed on a non-steroidal AI, and who are subsequently treated with either fulvestrant + continued anastrozole, or with fulvestrant alone, or with exemestane. At the same time the Evaluation of Faslodex vs Exemestane Clinical Trial (EFECT) has completed recruitment and will assess the efficacy of fulvestrant vs exemestane in patients who have progressed on treatment with non-steroidal AIs. In addition, two trials (FACT and SWOG 226) will compare the efficacy of a combination of fulvestrant plus anastrozole with anastrozole alone in the first-line setting. As AIs move forward into the adjuvant setting, the results of these trials will help define optimal sequencing of endocrine therapies, and in particular whether fulvestrant used alone or in combination with AIs is the most effective strategy.\textsuperscript{57}

**ENDOCRINE THERAPY FOR PREMENOPAUSAL WOMEN WITH ADVANCED BREAST CANCER**

For women with ER+ metastatic breast cancer who are still premenopausal when they develop advanced disease, the available endocrine therapy options include ovarian ablation (via surgery, radiotherapy or LHRH analogues (LHRHa)), tamoxifen or a combination of ovarian ablation with tamoxifen or with an AI (see Figure 2.2). Whereas oophorectomy and ovarian irradiation induce permanent ovarian ablation, the most widely used method involves using an LHRHa to induce a potentially reversible medical ovarian ablation. Goserelin (Zoladex) is the most widely used LHRHa in ER+ advanced disease, and is administered as a 3.6 mg subcutaneous monthly depot injection. The most common side effects are those of oestrogen suppression, including hot flushes and less frequently reduced libido, vaginal dryness, headache; the local injection is well tolerated. A pooled analysis of several phase II studies, which included 228 pre- and perimenopausal women with advanced breast cancer, showed that 36% had an objective response to goserelin, with an additional 50% showing stabilisation of their disease.\textsuperscript{58} The median duration of response was 10 months, with an overall survival of 26 months. These results were comparable to previously published data with either tamoxifen or surgical oophorectomy in this group of premenopausal patients with advanced disease.\textsuperscript{59}

Combined therapy of goserelin plus tamoxifen has been compared with goserelin alone as first-line endocrine therapy in 318 pre- and perimenopausal women
**EFECT: Evaluation of Faslodex and Exemestane Clinical Trial**

**Eligibility**
- Histological confirmation
- Postmenopausal status
- Progression/recurrence on a non-steroidal AI
- ER +ve and/or PgR +ve
- Measurable disease
- Performance status 0–2

**Endpoints**
- **Primary**
  - Time to progression (TTP)
- **Secondary**
  - Objective response rate (ORR)
  - Duration of response (DoR)
  - Clinical benefit (CB)
  - Overall survival (OS)
  - Quality of life (QoL)
  - Pharmacokinetics
  - Safety

**Endpoints: progression-free survival (PFS), OR, CB, duration of CB, TTP, OS, tolerability, (ER expression/activation, EGFR/HER2 expression, MAPK/ERK/IGFR/AKT activation)**

**SoFEA Trial – Study of Faslodex, Exemestane and Arimidex**

ER+ve postmenopausal patients with locally advanced/metastatic breast cancer who have recurred/progressed on treatment with non-steroidal AIs

**Randomisation 1:1:1 (n = 750)**

- Fulvestrant (LD) (n = 250)
- Fulvestrant (LD) + Anastrozole (n = 250)
- Exemestane (n = 250)

**Endpoints:** progression-free survival (PFS), OR, CB, duration of CB, TTP, OS, tolerability, (ER expression/activation, EGFR/HER2 expression, MAPK/ERK/IGFR/AKT activation)

LD = Fulvestrant 500 mg (IM) day 1, 250 mg (IM) days 14 and 28, 250 mg (IM)/month, thereafter
Progression

Registration/randomisation
First-line hormone receptor-positive (HR+ve) advanced breast cancer (ABC) postmenopausal patients ($n = 690$)

Anastrozole
Fulvestrant (LD) + Anastrozole

Progression
Off-treatment

LD = Fulvestrant 500 mg (IM) day 1, 250 mg (IM) days 14 and 28, 250 mg (IM)/month, thereafter

**FACT: Faslodex and Arimidex Clinical Trial**
Postmenopausal women with HR+ve breast cancer in first relapse after primary treatment of localised tumour

Randomisation 1:1 ($n = 580$)

Anastrozole (1 mg daily) + Fulvestrant LD
Anastrozole (1 mg daily)

LD = Fulvestrant 500 mg (IM) day 1, 250 mg (IM) days 14 and 28, 250 mg (IM)/month, thereafter

**Figure 2.6** Four phase III randomised clinical trials of fulvestrant in advanced breast cancer either following prior aromatase inhibitors (a and b), and/or in combination with aromatase inhibitors (b, c and d).
with advanced breast cancer. In this study ORRs were statistically similar (38% for goserelin + tamoxifen, 31% for goserelin), but there was a significant improvement in median time to disease progression (6.5 months vs 5.3 months). Overall survival was similar (32 vs 29 months), and there was no difference in tolerability for the combination. In another trial 161 premenopausal patients with advanced breast cancer were randomly assigned to treatment with the LHRHa buserelin, tamoxifen, or both. Combined treatment with buserelin and tamoxifen was superior to treatment with buserelin or tamoxifen alone by ORR (48% vs 34% and 28%, respectively), median progression-free survival (9.7 months vs 6.3 months and 5.6 months, respectively, \( p = 0.03 \)), and overall survival (3.7 years vs 2.5 years and 2.9 years, respectively, \( p = 0.01 \)). Subsequently there was a meta-analysis of four randomised trials of LHRHa + tamoxifen vs LHRHa alone, and significant benefits were found for the combination in terms of improved ORR (39% vs 30%, \( p = 0.03 \)), median progression-free survival (8.7 months vs 5.4 months, hazard ratio 1.31, \( p < 0.001 \)) and, most importantly, overall survival (34.8 months vs 30.0 months, \( p = 0.02 \)). As such, standard practice is now to recommend LHRHa + tamoxifen as first-line endocrine therapy in hormone-sensitive advanced breast cancer.

Several unanswered questions remain in the endocrine therapy of premenopausal patients. In particular, it is unclear whether complete oestrogen suppression using LHRHa and an aromatase inhibitor will be superior to using LHRHa + tamoxifen as first-line endocrine therapy for advanced disease. Given the superiority of AI over tamoxifen in postmenopausal women, it is not unreasonable to suppose that LHRHa + AI could further enhance endocrine responsiveness over LHRHa + tamoxifen; however, there are no randomised data yet to answer this, and there are concerns that the hormonal toxicities of maximal oestrogen blockade might outweigh the benefits. Likewise, it is unclear whether sequential oestrogen suppression might not be a better long-term strategy compared with maximal oestrogen suppression upfront. In the past, further clinical benefit has been reported for premenopausal women with advanced breast cancer initially treated with goserelin, and then at progression given an AI combined with goserelin. New randomised trials will be required to see if a sequential approach of LHRHa alone or LHRHa + tamoxifen followed by a switch at progression to LHRHa + AI would produce overall greater disease control and improved survival than using LHRHa + AI upfront. Unfortunately the relatively small number of suitable patients for such trials makes them difficult to undertake, and answers to these clinical questions are unlikely to occur quickly.

**FUTURE ENDOCRINE THERAPY STRATEGIES IN ADVANCED DISEASE**

Whereas there have been significant improvements in the efficacy of endocrine therapy for breast cancer, especially following the introduction of AIs, a major clinical issue with all endocrine therapies including oestrogen deprivation is either primary
lack of endocrine response in the tumour (de-novo resistance) or the subsequent failure of therapy following an initial endocrine response in the tumour (acquired resistance). Understanding the basis for this resistance in advanced breast cancer is an important issue in helping determine what will be the most effective therapy options for the clinic. In the past much research has concentrated on mechanisms of resistance to tamoxifen. However, recent progress has been made in elucidating the basis for acquired resistance to long-term oestrogen deprivation which may provide helpful clues as to prevention of resistance to AIs.

Understanding resistance to aromatase inhibitors

Laboratory research with ER+ve breast cancer cells into the mechanisms of resistance to long-term oestrogen deprivation (LTED) has demonstrated that various growth factor pathways and oncogenes involved in the signal transduction cascade become activated and utilised by breast cancer cells to bypass normal endocrine responsiveness. Preclinical data indicate that exposure to LTED (analogous to that caused by AIs), and subsequent development of acquired resistance, may be accompanied by adaptive increases in ER gene expression and intercellular signalling, resulting in hypersensitivity to low oestradiol levels. There is evidence for increased ‘cross-talk’ between various growth factor receptor signalling pathways and ER at the time of relapse on LTED (Figure 2.7), with ER becoming activated and supersensitised by a number of different intracellular kinases, including mitogen-activated protein kinases (MAPKs), epidermal growth factor receptor (EGFR) and HER2/HER3 signalling, and the insulin-like growth factor (IGF)/AKT pathway. In cells resistant to long-term oestrogen deprivation (LTED-R), ER-mediated gene transcription is enhanced 10-fold in these cells, but can be abrogated by a number of different approaches to interrupt upstream signalling, including the EGFR tyrosine kinase inhibitor (TKI) gefitinib (Iressa), MEK inhibitors, and the ER down-regulator fulvestrant (Faslodex) which degrades ER protein.

Thus, it would appear that the ER remains an integral part of signalling even following failure of AIs, and that a possible successful approach could involve the use of fulvestrant or various signal transduction inhibitors (STIs) to remove ER and/or activation of ER signalling (see Figure 2.7). As discussed below, evidence is now emerging that such drugs may be more effective when given in combination with endocrine therapy in an attempt to delay or prevent resistance occurring.

Aromatase inhibitors in combination with targeted therapies to overcome endocrine resistance

For hormone-resistant breast cancer, in particular ER+ve cells that overexpress HER2, the strategy of combined STIs and endocrine therapy may be more effective than using STIs alone in this setting. Most of the experimental data in support of this concept have come from HER-2+ve tamoxifen-resistant models rather than
LTED-resistant scenarios, but similar principles may apply. It has been shown that in hormone-resistant MCF-7 cells with up-regulated HER2 signalling combined therapy of gefitinib and tamoxifen provided maximal growth inhibition and significantly delayed the time to progression of the disease.\textsuperscript{76} Similar effects were seen with gefitinib combined with oestrogen deprivation, which provided greater inhibition of growth and substantially delayed acquired resistance compared with oestrogen deprivation alone.\textsuperscript{77}

Based on the evidence outlined above, a number of phase II trials were initiated with either trastuzumab, TKIs, farnesyltransferase inhibitors or mTOR antagonists in combination with endocrine therapy. However, the ultimate clinical test for the hypothesis that STIs may enhance the efficacy of endocrine therapy is the randomised phase III controlled clinical trial. Some of these trials have now started in the first-line hormone-sensitive setting in combination with an aromatase inhibitor.\textsuperscript{75} The primary endpoint for many of these trials is to investigate whether time to disease progression
can be significantly prolonged by the addition of an STI to endocrine therapy, thus delaying the emergence of resistance as demonstrated in various preclinical models described above. Table 2.5 lists some of the current randomised, controlled clinical trials of endocrine therapy with or without STIs in advanced breast cancer. The majority are placebo-controlled, double-blind studies in the first-line ER+ve setting, asking whether the combination can provide greater antitumour activity and clinical benefit than endocrine therapy alone. If positive, these studies could lead to improved endocrine strategies that ultimately will be tested in the adjuvant setting with the aim of further enhancing survival.

### Table 2.5 Current randomised phase II/III clinical trials of endocrine therapy ± signal transduction inhibitors in advanced/metastatic breast cancer

<table>
<thead>
<tr>
<th>Trial no.</th>
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<th>Primary endpoint</th>
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* Open-label study. TTP, time to disease progression; PFS, progression-free survival; ORR, objective response rate; CBR, clinical benefit rate.

CONCLUSION – NEW OPPORTUNITIES FOR ENDOCRINE THERAPY IN ADVANCED DISEASE

Endocrine therapy is an important part of the systemic treatment for women with hormone-sensitive advanced/metastatic breast cancer. Appropriate selection of patients for this approach is crucial, and it is well recognised that substantial clinical benefit in both pre- and postmenopausal women can be achieved by use of such therapies ahead of the need for chemotherapy. Aromatase inhibitors have had a major impact on the treatment of breast cancer over the last decade, and shown substantial
improvements over the previous standard of care, amoxifen. As these treatments now move into the adjuvant scenario, there is an urgent need to establish which endocrine strategies are still effective following disease progression on oestrogen-deprivation approaches. Progress in this area critically depends on understanding mechanisms of resistance to AIs, and may involve utilising novel approaches such as fulvestrant or various signal transduction inhibitors to combat resistance pathways and block cross-talk. Many studies in advanced disease have started recently, and over the next few years we should learn whether such an approach will produce significant further gains in clinical benefit from endocrine therapy.

REFERENCES


INTRODUCTION

As patients with metastatic breast cancer cannot be cured, the role of any treatment including cytotoxic chemotherapy is to maximise the duration of time without disease-related symptoms. This should be achieved with minimal toxicity from therapy in order that quality of life can be maintained. It has been shown that quality of life in advanced breast cancer is clearly linked to treatment response\textsuperscript{1-3} and that chemotherapy can have a significant benefit for patients due to anticancer effects that can reduce or prevent tumour-related symptoms. It has been questionable whether chemotherapy for metastatic breast cancer has any significant benefit in terms of overall survival, and the clinical trials of chemotherapy versus best supportive care have not been undertaken in this setting. However, historical comparisons have shown that the introduction of combination cytotoxic chemotherapy in the late 1970s has produced a modest 9–12 month gain in survival compared with untreated patients.\textsuperscript{4,5} Likewise, individual patients with life-threatening visceral disease who have a good clinical response to chemotherapy will clearly have a survival benefit compared to not having therapy. With the recent introduction of effective cytotoxic drugs and combinations, including those with biological agents, significant impacts on survival are now being observed in individual trials compared with previous standard chemotherapy drugs. It is likely therefore that patients with metastatic breast cancer will derive significant clinical benefit from modern-day chemotherapy. Finally, the plethora of drugs with non-cross-resistant mechanisms of action has given the oncologist several lines of therapy to offer patients.

This chapter reviews some of the underlying principles in the use of chemotherapy to treat metastatic breast cancer, outlines the major classes of cytotoxic drugs and highlights some of the recent developments in schedules and new agents available.

PRINCIPLES OF TREATMENT

Patients who relapse with metastatic breast cancer may often present with a single site of disease (i.e. bone or visceral organs). The decision to start chemotherapy is
often complex and involves a careful assessment of the patient’s treatment history, biological characteristics of the tumour (oestrogen and progesterone receptor status and her2/neu expression), disease-free interval, site and extent of metastatic relapse, tumour-related symptoms, the effect of visceral or bone metastases upon organ function and performance status (Table 3.1).

Chemotherapy is usually reserved for patients with disease unresponsive to endocrine agents or patients with rapidly progressive or life-threatening disease. Patients who have relapsed with oestrogen/progesterone receptor positive (ER/PgR +ve) disease with a long treatment-free interval, soft tissue or bone as the dominant site of metastasis and good performance status are usually treated with endocrine therapy first (see Chapter 2). Equally, ER/PgR +ve patients with low volume visceral disease and normal organ function assessed biochemically may also be treated with a trial of endocrine therapy. Symptomatic or radiological progression of metastatic disease after a trial of endocrine therapy inevitably leads to the decision to initiate chemotherapy.

Many patients with metastatic breast cancer are over the age of 65 and may present with life-threatening disease requiring chemotherapy.

Elderly patients may be at increased risk of myelosuppression induced by cytotoxic agents, and co-morbidity as well as drug history should be considered when choosing the appropriate regimen. Thus, agents with lower toxicity may often be considered as preferable for this patient group.

**INFLUENCE OF PRIOR THERAPIES**

Use of prior adjuvant chemotherapy is not an impediment to the benefit of chemotherapy for metastatic breast cancer. However, a disease-free interval of less than 12 months prior to adjuvant treatment implies a degree of resistance to the previous regimen and will influence the choice of first-line chemotherapy for metastatic breast cancer.

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**Table 3.1  ECOG performance status (www.ecog.org)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all pre-disease performance without restriction.</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light and sedentary nature, light house work, office work.</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.</td>
</tr>
</tbody>
</table>
The goals of chemotherapy treatment continue to remain the same for all patients with metastatic breast cancer: namely, minimising toxicity of treatment and hospital admissions while maximising symptom improvement, quality of life and survival. Following use of first-line chemotherapy for metastatic breast cancer, at subsequent disease progression, different cytotoxic drugs or combinations may be used. However, further use of sequential chemotherapy needs careful consideration in relation to likelihood of benefit versus risk of toxicity and deteriorating performance status. The extent of prior treatment is one factor that should be considered in estimating the likelihood of clinical benefit derived from further chemotherapy. Tumour response rates are greatest if patients have previously received one or no prior therapy (40–60% depending on study and drug combination) but sadly decline as treatment progresses (20–30% in the third- and fourth-line setting). Likewise, prior lack of response to first-line chemotherapy with or without a short treatment and/or progression-free period is associated with a much lower likelihood of subsequent response to second- or third-line chemotherapy. This needs to be borne in mind when discussing further lines of chemotherapy with patients.

**RESPONSE ASSESSMENT**

Tumour response assessment usually occurs 8–12 weeks after the start of chemotherapy and comprises a summary of radiological and clinical response, symptomatic benefit (including any improvement in performance status) balanced against toxicities of treatment. Radiological response (determined by RECIST criteria; Table 3.2) is an important guide to the clinician in the decision to continue or change therapies. Whereas objective tumour responses (i.e. tumour shrinkage by more than 30%; see Table 3.2) set the standard used in clinical trials to judge the efficacy of chemotherapy, stabilisation of disease by RECIST criteria with a symptomatic benefit is an equally important endpoint. In patients with non-measurable disease (e.g. bone-only disease), treated with chemotherapy, serial tumour markers together with symptomatic benefit are important indicators of response to treatment.

Measuring symptomatic benefit from treatment should include an assessment of the patient’s main tumour-related complaints and overall functional status as measured by ECOG performance status (see Table 3.1). This should be carried out prior to starting chemotherapy, followed by repeat assessments during treatment that are balanced by treatment-related toxicities (graded according to the ECOG common toxicity criteria scale: www.ecog.org/general/ctc.pdf).

**CHOICE AND DURATION OF CHEMOTHERAPY REGIMEN (SEQUENTIAL OR COMBINATION THERAPY)**

There is considerable debate in the management of metastatic breast cancer as to whether combination or sequential monotherapy strategies should be pursued.
In general, response rates tend to be higher with combination regimens when used as first-line therapy, but often at the expense of greater toxicity and short-term deterioration in quality of life. Furthermore, the majority of clinical trials assessing new combination strategies have not been adequately structured to address whether long-term outcomes (especially survival) are equivalent or superior to using the same agents administered sequentially.

Several clinical trials comparing a sequential versus a combined regimen in a randomised fashion support this concept (Table 3.3). Combination doxorubicin (A) and paclitaxel (T) therapy leads to improved response rates with no survival benefit over sequential treatment. Similarly, equivalent survival and response rates were observed in a trial comparing single agent mitoxantrone with combination 5-fluorouracil, epirubicin and cyclophosphamide (FEC), with less toxicity and improved quality of life in the monotherapy arm. Joensuu and colleagues demonstrated that there was no survival difference when FEC followed by mitomycin C and vinblastine was compared to monotherapy with epirubicin followed by mitomycin C on disease progression. An overview of 106 randomised trials in metastatic breast cancer involving over 17,000 patients suggested only a small, but significant benefit for combination chemotherapy vs single-agent chemotherapy. This was before the widespread introduction of taxanes as first-line chemotherapy.

Despite the lack of impact on long-term outcome, combination strategies may be advisable for patients of good performance status (0/1) with rapidly progressing visceral disease and evidence of organ dysfunction, particularly in the first-line setting. In general, monotherapy is considered best for second- or third-line chemotherapy options when toxicity considerations become paramount, often on the background of worsening performance status in relation to progressive disease. In addition, single-agent treatment is often preferable for women with extensive life-threatening visceral involvement of the liver or bone marrow. In this situation, dose reductions of a single agent are more readily controllable and titrated to organ function. If organ function improves following successful reduction in tumour burden, the chemotherapy dose can be increased.

One course of chemotherapy encompasses a period of approximately 4–6 months given a satisfactory response at interval assessments. Maintenance chemotherapy has not demonstrated a clear advantage. In certain cases, chemotherapy regimens may be
extended beyond 6 months (taking into account cumulative toxicity of drugs such as the anthracyclines) if patients are continuing to derive benefit from treatment and have symptoms that can be effectively palliated by prolonged chemotherapy.

**Anthracyclines**

Doxorubicin (Figure 3.1) is an anthracycline antibiotic synthesised by the fungus *Streptomyces peucetius*. Anthracycline cytotoxicity is mediated through DNA intercalation and inhibition of DNA and protein synthesis, topoisomerase II inhibition and free radical generation. Side effects of this class of drug include the risk of cardiac toxicity above a cumulative dose threshold, alopecia, gastrointestinal disturbances (nausea, vomiting, diarrhoea and stomatitis) and complications of neutropenia. Patients should also be aware of the risk associated with treatment-related leukaemia. In studies of epirubicin therapy in the adjuvant setting, the cumulative risk of secondary acute myelogenous leukaemia was 0.2% at 2 years and 0.8% at 5 years. Premenopausal patients should also be warned of the risks of irreversible amenorrhoea and premature menopause.
In women with metastatic breast cancer who have not received prior adjuvant anthracycline-based chemotherapy, meta-analyses support the view that anthracycline chemotherapy regimens improve response rates, time to disease progression and survival over non-anthracycline-containing regimens.10,11

In patients who have relapsed with no prior anthracycline exposure, first-line treatment options include doxorubicin or epirubicin with cyclophosphamide (AC or EC), or with cyclophosphamide and 5-fluorouracil (FAC or FEC) or single-agent epirubicin or doxorubicin. The anthracenediones such as mitoxantrone are less toxic than anthracyclines, but have been deemed less effective.

In recent years, however, most patients who relapse with metastatic breast cancer have received anthracycline chemotherapy as part of an adjuvant treatment protocol. Cumulative exposure and cardiac risk have made retreatment with anthracycline difficult. The cumulative dose of anthracycline should not exceed 450–550 mg/m² for doxorubicin or 700–900 mg/m² for epirubicin (Table 3.4). Retrospective studies demonstrated an incidence of symptomatic cardiac failure of 6–10% of adults who had received cumulative bolus doses above 550 mg/m² of doxorubicin, with elderly patients at increased risk.

Therefore factors such as age (>70 years old) and co-morbidity such as diabetes, hypertension, ischaemic, valvular or myocardial heart disease should be taken into

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**Figure 3.1** Anthracyline structures.

- **Doxorubicin**: 
  - R₁: OCH₃
  - R₂: H
  - R₃: OH
  - R₄: OH

- **Daunorubicin**: 
  - R₁: OCH₃
  - R₂: H
  - R₃: OH
  - R₄: H

- **Epirubicin**: 
  - R₁: OCH₃
  - R₂: OH
  - R₃: H
  - R₄: OH

- **Idarubicin**: 
  - R₁: H
  - R₂: H
  - R₃: OH
  - R₄: H
account prior to the use of these agents. In particular, previous chest wall radiotherapy has been shown to increase the risk of cardiac damage. Furthermore, doxorubicin is considered unsafe in combination with trastuzumab due to the higher risk of cardiotoxicity.\textsuperscript{12}

A baseline electrocardiogram (ECG) is recommended for all patients prior to initiation of anthracycline therapy. Left ventricular ejection fraction (LVEF) should be assessed by multigated radionuclide angiography (MUGA) or by echocardiography. Repeat assessment of LVEF is recommended for patients treated with higher cumulative doses of anthracycline. In patients with a high-risk cardiac profile or patients with a prior history of chest wall radiotherapy in need of anthracycline therapy, consideration may be given to the use of liposomal anthracyclines or anthracyclines with less cardiotoxicity such as epirubicin. The pegylated liposomal formulation of doxorubicin (Caelyx/Doxil) has been shown to have comparable efficacy with reduced cardiotoxicity, myelosuppression, vomiting and alopecia in comparison to standard doxorubicin in the first-line treatment of metastatic breast cancer.\textsuperscript{13} Dexrazoxane (Cardioxane) is a cardioprotective agent used in patients requiring anthracycline therapy. Its active metabolite is thought to act through iron chelation, thereby reducing doxorubicin-induced free-radical generation. Several studies have demonstrated the cardioprotective role of dexrazoxane in anthracycline-treated patients. A study of patients randomised to doxorubicin (as part of an FAC regimen) and placebo versus doxorubicin and dexrazoxane after a total dose of 300 mg/m\textsuperscript{2} revealed a 3\% incidence of congestive cardiac failure in the dexrazoxane-treated patients compared with 22\% in the placebo arm.\textsuperscript{14} 26\% of patients treated with dexrazoxane were able to receive 15 courses of therapy vs only 5\% of the placebo group. Furthermore, median survival for those receiving doxorubicin and placebo was 460 days as opposed to 882 days in those receiving both doxorubicin and dexrazoxane. Therefore, dexrazoxane may limit the cardiotoxic side effects of anthracyclines, allowing potentially effective treatment to continue beyond the maximum tolerated dose limit. The American Society of Clinical Oncology has issued guidelines regarding the use of this agent: Cardioxane/dexrazoxane is not routinely recommended for patients with metastatic breast cancer who receive doxorubicin-based chemotherapy but may be considered in those who have received a cumulative dose of more than 300 mg/m\textsuperscript{2} who may benefit from the continued use of doxorubicin.

There are some practical considerations in the use of anthracyclines. Anthracyclines should not be given to patients with a baseline neutrophil count <1500 cells/mm\textsuperscript{3},

<table>
<thead>
<tr>
<th>Cumulative dose</th>
<th>Incidence</th>
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<tbody>
<tr>
<td>550 mg/m\textsuperscript{2}</td>
<td>0.9%</td>
</tr>
<tr>
<td>700 mg/m\textsuperscript{2}</td>
<td>1.6%</td>
</tr>
<tr>
<td>900 mg/m\textsuperscript{2}</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

Chemotherapy and metastatic breast cancer
recent myocardial infarction or history of cardiac failure, severe arrhythmias or significant hepatic dysfunction. Previous anthracycline exposure up to the maximum cumulative dose is a contraindication to further use. Lower starting doses should be considered in patients with pre-existing bone marrow depression (and malignancy-related marrow infiltration).

Patients with a bilirubin concentration of 1.2–3 mg/dl (20–51 µmol/dl) or an aspartate transaminase (AST) 2–4 times the upper limit of normal should receive a 50% dose reduction of epirubicin. Patients with bilirubin level > 3 mg/dl (>51 µmol/dl) or AST > 4 times the upper limit of normal should receive a 75% dose reduction of epirubicin. There is evidence that epirubicin toxicity correlates better with AST values than with bilirubin levels. The schedule with the most extensive data in patients with liver metastases and organ dysfunction is weekly epirubicin (25 mg/m²), with further dose reductions made according to liver function tests.¹⁵¹⁶

Dose adjustments should also be made if doxorubicin is to be considered in patients with liver dysfunction. The risk of haematological and mucosal toxicity is increased with significant liver dysfunction. The manufacturers suggest a 50% dose reduction of doxorubicin with a bilirubin level of 1.2–3 mg/dl (20–51 µmol/dl) with no clear recommendation according to AST rise. A 75% dose reduction is advisable if the bilirubin level rises above 3 mg/dl (51 µmol/dl). Lower doses should also be considered for patients with severe renal impairment.

**Taxanes**

Taxanes stabilise the microtubule through interaction with β-tubulin, thereby preventing normal chromosomal segregation at mitosis (Figure 3.2). An intricate molecular process activates the spindle checkpoint, leading to cellular proliferation arrest at the metaphase/anaphase transition. Following cell cycle arrest, sensitive cancer cells may activate a conserved death pathway (apoptosis) or die by necrosis. Alternatively, cells may remain in a permanent state of arrest, failing to segregate chromosomes faithfully. There is in-vitro evidence that cells with a defective spindle checkpoint are more resistant to microtubule inhibitors.

Taxanes are now considered one of the most active compounds in clinical use for metastatic breast cancer. A recent Cochrane meta-analysis confirmed a statistically significant overall survival benefit in favour of taxane-containing regimens (hazard ratio for survival 0.90).¹⁷ The two most commonly used taxanes in clinical practice are paclitaxel and docetaxel (Figure 3.3).

Side effects associated with paclitaxel given in a 3-weekly schedule are neutropenia, alopecia, myalgia and neurosensory impairment. Weekly schedules of paclitaxel cause significantly less myelosuppression and hair loss, but may still be associated with neurosensory side effects associated with cumulative long-term exposure. Weekly schedules of docetaxel are also associated with less myelosuppression, but a greater incidence of mycutaneous toxicity, fatigue and asthenia.

Docetaxel side effects are otherwise similar to paclitaxel, with neutropenia usually occurring slightly earlier (days 5–7 as opposed to day 11 with paclitaxel). Asthenia
and stomatitis are also common adverse events. In addition, early studies of the drug encountered problems with fluid retention, oedema and pleural effusions. This side effect has been largely overcome with the 3-day dexamethasone course (8 mg bd) starting the day before chemotherapy. Other side effects include nail changes, nausea and diarrhoea.

**Figure 3.2** Normal cell division (a–d) and treatment with paclitaxel (e and f). (a) Prometaphase: nuclear envelope breaks down and chromosomes condense. (b) Metaphase: chromosomes align on equator forming metaphase plate. (c) Anaphase: sister chromatids move towards spindle poles once spindle checkpoint satisfied. (d) Telophase: separated chromatids have reached spindle poles and cells can now divide into two daughter cells (cytokinesis). (e and f) Cell morphology after paclitaxel treatment: chromosomes are disorganised at the spindle pole and metaphase plate. Mitosis is blocked at the metaphase/anaphase transition.
Docetaxel should not be given to patients with bilirubin higher than the upper limit of normal (ULN) or alkaline phosphatase >2.5×ULN or AST/ALT >1.5×ULN. Patients with neutrophil counts <1500 cells/mm³ should not receive docetaxel or paclitaxel. Patients with a history of hypersensitivity to docetaxel or other drugs formulated in Polysorbate 80 should not receive docetaxel.

Dose adjustments of paclitaxel should be considered in patients with moderate to severe hepatic impairment. Concerning paclitaxel administered every 3 weeks in a 3-hour infusion at the standard dose of 175 mg/m², the manufacturer recommends a dose reduction to 135 mg/m² for patients, with baseline bilirubin levels of 1.26–2 mg/dl (21–34 µmol/dl) and to 90 mg/m² for patients with bilirubin levels of 2.0–5.0 mg/dl (34–85 µmol/dl). Modified doses of weekly paclitaxel may be appropriate for patients with liver dysfunction due to its reduced myelosuppressive effects compared to the 3-weekly schedule (which can be exacerbated by liver function impairment).

Paclitaxel is contraindicated in patients who have a history of hypersensitivity to paclitaxel or other drugs formulated in Cremophor EL.

**Anthracycline-naive patients**

*First-line monotherapy*

Response rates to paclitaxel monotherapy in the first-line setting range from 15% to 60% depending on the study and dosing schedule. The two most commonly used dosing schedules are weekly paclitaxel (80–90 mg/m²) and paclitaxel 175 mg/m² every 3-weeks. Doses higher than 175 mg/m² have failed to consistently demonstrate improved response rates or overall survival. Weekly paclitaxel is often the treatment of choice for elderly patients or those with poor performance status owing to the
reduced myelosuppression associated with this schedule. However, weekly paclitaxel is associated with more neurotoxicity than the 3-weekly schedule. Recent data have demonstrated the superiority of a weekly paclitaxel to the traditional 3-weekly schedule. The drug is commonly administered at a dose of 80–90 mg/m²/week continuously, although treatment for 3 weeks followed by a 1 week break may reduce the incidence of neurotoxicity. The CALGB 9840 study confirmed higher treatment response rates and longer time to progression for weekly paclitaxel, as opposed to the 3-weekly schedule in patients treated with 0 or 1 chemotherapy regimens. Further studies are required to answer whether weekly paclitaxel is equivalent to 3 weekly docetaxel.

The usual docetaxel dose used in the advanced disease setting is between 75 and 100 mg/m². A randomised phase III trial demonstrated higher toxicity with no survival benefit for 100 mg/m² vs 75 mg/m² docetaxel in the second-line setting. In this study, however, there was a dose–response relationship, with superior response rates with 100 mg/m² than the lower two doses (29.8% vs 22.3% vs 19.9% \( p = 0.026 \)). Therefore, 100 mg/m² is still recommended for patients of performance status 0 or 1 with aggressive visceral disease, in whom immediate disease control is a priority, with or without granulocyte colony-stimulating factor (G-CSF) support and/or prophylactic antibiotics. A dose of 75 mg/m² is recommended for heavily pretreated patients, patients of poorer performance status or with mild impairment of liver function.

Reported response rates to first-line 3-weekly docetaxel monotherapy appear superior to 3-weekly paclitaxel. Studies with docetaxel (dose 100 mg/m²) have demonstrated response rates of 54–68%, and of 40–52% with the lower dose of 75 mg/m². Previous indirect evidence has suggested superiority for docetaxel over paclitaxel monotherapy in studies comparing docetaxel or paclitaxel to doxorubicin. A phase III study revealed superior response rates for 100 mg/m² docetaxel over 75 mg/m² doxorubicin (47.8% vs 33.3%; \( p = 0.008 \)) in patients who had received prior alkylating-based treatment, although overall survival was equivalent in the two groups. In addition, a recently reported phase III trial reported higher response rates for 60 mg/m² docetaxel vs doxorubicin and cyclophosphamide (41% vs 30%) in the first-line setting. In contrast, a trial of 3-weekly paclitaxel vs doxorubicin showed no difference in disease and symptom control in the first-line treatment of metastatic disease. Likewise, an intergroup phase III study that compared single-agent doxorubicin or paclitaxel vs the combination of doxorubicin and paclitaxel with growth factor support in the first-line setting revealed equivalent response rates for patients receiving doxorubicin or paclitaxel. A recent randomised trial confirmed that 100 mg/m² docetaxel was superior to 175 mg/m² paclitaxel, with superior response rates (32% vs 25%), prolonged time to progression (5.7 months vs 3.6 months, hazard ratio 1.64) and overall survival (15.4 vs 12.7 months, hazard ratio 1.41). In this study, there were 4 treatment-related deaths in the docetaxel group (1.8%) and none in the paclitaxel-treated patients.

In clinical practice, therefore, docetaxel monotherapy (75–100 mg/m²) may lead to improved response rates when compared with doxorubicin in anthracycline-naive patients. This is the standard taxane schedule of choice for patients of good performance
status. In addition, previous trials have shown it to be superior to other cytotoxic regimens in anthracycline pretreated patients, in particular those with anthracycline-resistant disease. These studies demonstrated the superiority of docetaxel to either mitomycin with vinblastine or methotrexate with 5-fluorouracil in patients who have previously received anthracycline therapy. Nabholtz and colleagues provided data demonstrating higher response rates with docetaxel in patients previously resistant to anthracycline-containing regimens. Weekly paclitaxel (80–90 mg/m²) is the most effective schedule for delivering paclitaxel and is an important alternative taxane option for patients of poorer performance status, extensive visceral disease or heavy pretreatment.

First-line taxane combinations

For chemotherapy-naive patients, trials were initiated to see whether combined anthracycline/taxane chemotherapy would be superior to taxane monotherapy. Nabholtz and colleagues demonstrated the superiority of docetaxel/doxorubicin combination vs doxorubicin/cyclophosphamide in the first-line treatment of metastatic breast cancer with improved overall response rates (59% vs 47%) and time to progression in the taxane combination arm. There was no overall survival difference in the taxane arm, although there was a higher rate of grade 3/4 neutropenia (33% vs 10%) and febrile neutropenia (8% vs 2%). Likewise, docetaxel/anthracycline/cyclophosphamide (TAC) combinations may also lead to higher response rates than 5-fluorouracil/anthracycline/cyclophosphamide (FAC) combinations but with greater toxicity. Combination strategies encompassing an anthracycline (doxorubicin) with paclitaxel produced higher response rates than with either drug alone but with no difference in quality of life observed between the treatment arms (response rate 36% anthracycline vs 34% paclitaxel vs 47% doxorubicin combined with paclitaxel). Response rates were superior with combination therapy; however, this study failed to demonstrate a survival benefit. Although one study demonstrated an overall survival superiority of doxorubicin/paclitaxel to FAC, there was no difference in terms of response rate, progression-free survival and overall survival in an EORTC phase III study comparing doxorubicin/paclitaxel with doxorubicin/cyclophosphamide. A further phase III study investigating paclitaxel/epirubicin combinations failed to show superiority over epirubicin/cyclophosphamide.

Taxane combinations with other cytotoxics

As other active cytotoxic drugs have been developed, trials have assessed whether these can be added safely to taxanes in order to further enhance their efficacy. An overall survival benefit (Table 3.5) was recently reported for the combination of gemcitabine and paclitaxel (compared with paclitaxel alone) in patients with metastatic breast cancer, pretreated with an anthracycline in the adjuvant setting. Median overall survival was 18.5 months in the combination arm vs 15.8 months for paclitaxel alone. Early quality of life parameters were not adversely affected by the combination strategy. Likewise, the capecitabine/taxane combination has attracted much interest.
In the first-line setting, treatment with capecitabine (850 mg/m$^2$ bd days 1–14) and paclitaxel (175 mg/m$^2$ q 3 weekly) achieved response rates of 51%. A similar response rate was seen with this combination (higher dose of capecitabine 1000 mg/m$^2$ bd) in anthracycline pretreated patients. Docetaxel in combination with capecitabine (docetaxel 75 mg/m$^2$ and capecitabine 1250 mg/m$^2$ days 1–14 q 3 weekly) leads to improved survival and response rates (overall survival 14.5 months vs 11.5 months and response rate 42% vs 30%) when compared with docetaxel alone (100 mg/m$^2$) (see Table 3.5). However, in this study, following failure of docetaxel monotherapy, 35% of patients did not receive further chemotherapy. Interestingly, in an updated analysis of the patients who were randomised to docetaxel monotherapy, those patients who received post-study capecitabine experienced a significantly improved survival over other cytotoxic agents. Thus, the question of whether combined taxane/capecitabine treatment is superior overall to sequential use of both drugs has not been answered. A prospective phase III clinical trial is required to address whether sequential docetaxel with capecitabine monotherapy at subsequent progression is equivalent to the upfront combination in terms of survival, toxicity and quality of life.

**Novel therapeutics in combination with taxane-based therapy**

Trastuzumab is a monoclonal antibody targeting the epidermal growth factor receptor Her2 that is overexpressed in 20% of breast carcinomas. Combinations of either paclitaxel and trastuzumab, or docetaxel and trastuzumab, are significantly superior to the use of taxane chemotherapy alone in these patients. The rationale and clinical data for use of trastuzumab are discussed in greater detail in Chapter 4.

Recent trial results indicate that the combination of the vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (Avastin) with paclitaxel improves progression-free interval and response rates in metastatic breast cancer. A total of 700 women were randomised to receive either paclitaxel alone or paclitaxel with bevacizumab. The majority of patients (65%) had received prior chemotherapy, were Her2 negative and had hormone receptor-positive disease (64%). The response rates in the bevacizumab arm were 28% compared with 14% in the paclitaxel alone. Average progression-free survival was 10.9 months vs 6.11 months in those receiving only paclitaxel.

**Novel antitubulin agents**

Preclinical data suggest that the epothilones may overcome taxane-drug resistance associated with p-glycoprotein expression and tubulin mutations. Ixabepilone is a semisynthetic analogue of epothilone B. A phase II study of ixabepilone in patients previously treated with a taxane in either the adjuvant or metastatic setting demonstrated tumour control (PR, CR and SD) in over 50% of patients treated, supporting in-vitro data. Phase III studies are in progress with ixabepilone and capecitabine in pretreated metastatic breast cancer. Toxicities experienced with epothilones are neurotoxicity, diarrhoea and febrile neutropenia.
Preclinical data have established that ABI-007 (Abraxane), a derivative of paclitaxel complexed with albumin, may be preferentially transported to tumour tissue over traditional paclitaxel. Furthermore, ABI-007 does not require Cremophor as the drug vehicle which has been implicated in some of the toxic effects seen with paclitaxel (including myelosuppression and neuropathy). A phase III trial of ABI-007 and paclitaxel revealed superior response rates and less myelosuppression with ABI-007 and the drug is approved in the USA for treatment of metastatic breast cancer.

### Treatment options following prior anthracycline and taxane-based chemotherapy

Inevitably, patients with metastatic breast cancer will develop resistance to both anthracyclines and taxanes. Common therapeutic options in the third-line setting are single-agent treatment with capecitabine, vinorelbine or gemcitabine. Combination therapy with platinum-based therapies may also be an effective third-line option. There are few data comparing the relative efficacy of these agents with either other, and therefore treatment should be selected for patients balanced on knowledge of the

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>Number of patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nabholtz et al25</td>
<td>D vs M + V</td>
<td>392</td>
<td>OS 11.4 months D vs 8.7 months M + V</td>
</tr>
<tr>
<td>O’Shaughnessy et al29</td>
<td>D + C vs D</td>
<td>511</td>
<td>RR 42% D + C vs 30% D</td>
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<tr>
<td>Jones et al24</td>
<td>D (100 mg/m²) vs P (175 mg/m²)</td>
<td>449</td>
<td>RR 32% D vs 25% P (p = 0.1)</td>
</tr>
<tr>
<td>Albin et al32</td>
<td>G + P vs P</td>
<td>529</td>
<td>RR 40.8% G + P vs 22.1% P</td>
</tr>
<tr>
<td>Slamon et al32</td>
<td>Anthracycline naive: Dox + Cyc vs Dox + Cyc + T Anthracycline pre-treated: P vs P + T</td>
<td>469</td>
<td>OS 25.1 months vs 20.3 months</td>
</tr>
<tr>
<td>Marty et al37</td>
<td>D + T vs D</td>
<td>186</td>
<td>RR 61% D + T vs 34% D</td>
</tr>
</tbody>
</table>

D, docetaxel; M, mitomycin; V, vinblastine; C, capecitabine; P, paclitaxel; T, trastuzumab; G, gemcitabine; Dox, doxorubicin; Cyc, cyclophosphamide; RR, response rate; OS, overall survival.
risks in terms of side-effect profile and potential quality of life benefits offered by chemotherapy.

**Capecitabine**

Capecitabine (Figure 3.4) is an oral fluoropyrimidine carbamate that is converted to 5-fluorouracil by the enzyme thymidine phosphorylase, which is overexpressed in tumour tissue.

The main toxicities associated with oral capecitabine administration are mucositis, hand-foot syndrome (plantar palmar erythema), nausea, vomiting and diarrhoea. Patients should be instructed to stop treatment and seek medical advice in the event of grade 2 diarrhoea (an increase of 4–6 stools/day or stools at night), nausea and vomiting (2–5 episodes in 24 hours), hand and foot syndrome (painful erythema), stomatitis (painful erythema, oedema or ulcers of the mouth or tongue). Patients should also stop treatment and seek medical support in the event of a fever >38°C.

**Contraindications for capecitabine use and dose adjustments.** The most commonly used dose is 1000–1250 mg/m² bd swallowed with water 30 minutes after a meal for 14 days followed by 7 days rest. Patients should be aware that capecitabine is supplied as 150 mg and 500 mg tablets. Capecitabine and its metabolic products are predominantly excreted in the urine and it is therefore contraindicated in patients with severe renal impairment (creatinine clearance <30 ml/min). Patients with a creatinine clearance of 30–50 ml/min should receive a 25% dose reduction. The drug is also contraindicated in patients with known dihydropyrimidine dehydrogenase deficiency (DPD) and in patients with a known hypersensitivity to 5-fluorouracil. Capecitabine may induce myocardial ischaemia/infarction, angina, cardiac arrest, arrhythmias, cardiomyopathy and sudden death. Patients with a history of coronary artery disease or cardiac failure should not receive capecitabine. Capecitabine may cause severe diarrhoea, necessitating urgent intravenous rehydration and careful fluid balance. If grade 2, 3 or 4 diarrhoea develops, treatment should be stopped immediately and the drug not reintroduced until symptoms have subsided, when a dose reduction should be considered (Table 3.6). Capecitabine may provoke hyperbilirubinaemia (7–15% grade 3 1.5–3×ULN and 2–3.9% >3×ULN) and is more likely to occur in those patients...
with hepatic metastases. If the serum bilirubin increases to >1.5 × ULN, treatment should be interrupted immediately until the episode resolves and dose reduction initiated. The manufacturers do not recommend a dose adjustment for mild to moderate hepatic dysfunction at baseline. Neutropenia is a rare event with capecitabine monotherapy but may occur in approximately 3% of patients. Thrombocytopenia and anaemia have been reported in 1.7% and 2.4% of patients, respectively. Capecitabine decreases the clearance of warfarin and the international normalised ratio (INR) should be more frequently monitored and warfarin dose adjusted appropriately while on treatment. Some oncologists would recommend switching to low-molecular-weight heparin during the course of treatment. The dose of phenytoin may also need to be reduced in patients treated with capecitabine.

Capecitabine is active in taxane and anthracycline refractory patients and generally well tolerated with the benefits of causing minimal hair loss and limited bone marrow suppression. Therefore, its use should also be considered in elderly patients or patients of poorer performance status. A 20% response rate was reported in a phase II study with 163 patients, all of whom had received prior paclitaxel: 91% had received an anthracycline and 82% had received prior bolus 5-fluorouracil treatment. Importantly for this patient group, capecitabine was well tolerated, with diarrhoea (14%) and hand and foot syndrome (10%) as the only grade 3 and 4 events reported in more than 10% of patients. Both these events were managed successfully with dose adjustment or dose interruption. A further phase II study confirmed that capecitabine is active and well tolerated in patients who have disease resistant to taxane therapy, with response rates of 26% reported. Fumoleau and colleagues reported a 28% response rate in patients with anthracycline and taxane pretreated disease, with an improvement of the mean Global Health quality of life score.

Table 3.6 Dose adjustment of capecitabine monotherapy (manufacturer’s advice)

<table>
<thead>
<tr>
<th>NCIC toxicity</th>
<th>During treatment</th>
<th>Dose adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Maintain dose level</td>
<td>Maintain dose</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1st event: Interrupt until grade 0–1</td>
<td>100%</td>
</tr>
<tr>
<td>2nd event</td>
<td>Interrupt until grade 0–1</td>
<td>75%</td>
</tr>
<tr>
<td>3rd event</td>
<td>Interrupt until grade 0–1</td>
<td>50%</td>
</tr>
<tr>
<td>4th event</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>1st event: Interrupt until grade 0–1</td>
<td>75%</td>
</tr>
<tr>
<td>2nd event</td>
<td>Interrupt until grade 0–1</td>
<td>50%</td>
</tr>
<tr>
<td>3rd event</td>
<td>Discontinue</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>1st event: Discontinue at physician’s discretion Interrupt until grade 0–1 and 50% dose adjustment</td>
<td></td>
</tr>
</tbody>
</table>

NCIC, National Cancer Institute of Canada.
Clinical trials are ongoing, studying the combination of capecitabine with trastuzumab. Currently there are no phase III clinical trial data supporting the use of capecitabine in combination with trastuzumab. However, bevacizumab (a monoclonal antibody targeting the VEGF receptor) in combination with capecitabine improves response rates (with no overall survival difference) in comparison to capecitabine monotherapy in patients with anthracycline and taxane pretreated disease.\textsuperscript{45}

Vinorelbine

Vinorelbine (Figure 3.5) is a vinca alkaloid that interferes with microtubule assembly. Reminiscent of the taxanes, vinorelbine also induces a cell cycle arrest at mitosis due to its microtubule targeting activity. Vinorelbine may induce neutropenia as its dose-limiting side effect, and patients should be warned in advance of the complications and management of febrile neutropenia. Severe constipation, paralytic ileus and intestinal obstruction and perforation have also been reported. Diarrhoea is a recognised complication of therapy. Rarely, cases of interstitial pulmonary changes and acute respiratory distress have been reported with single-agent vinorelbine use. Patients with recent-onset dyspnoea, cough or hypoxia following vinorelbine use should be evaluated immediately. Use of vinorelbine in patients who have received prior radiotherapy may result in radiation recall reactions. Patients with a history of neuropathy should be monitored for an exacerbation during treatment (severe neuropathy <1% of patients). Women of childbearing potential should be advised against becoming pregnant during treatment due to its genotoxic potential. Vinorelbine is a moderate vesicant and pain at the injection site is common. Vinorelbine is not a potent emetogenic drug and therefore prophylaxis with serotonin antagonists is not required. Fatigue is a common side effect and increases with cumulative dosing.

The common dose range of vinorelbine is 25–30 mg/m\textsuperscript{2} administered on day 1 and day 8 of a 3-week cycle. Neutrophil nadirs usually occur at 7–10 days. Vinorelbine
undergoes hepatic metabolism mediated by the CYP3A cytochrome complex. Although data are limited regarding vinorelbine use in patients with hepatic dysfunction, patients with deranged liver function should undergo dose modification (Table 3.7). A careful drug history should be taken to avoid concurrent use of cytochrome enzyme inhibitors.

No dose modification is suggested for renal impairment. Vinorelbine should be discontinued if neurotoxicity occurs at grade 2 or above. There are no established guidelines for vinorelbine extravasation events, and local policies should be followed.

Vinorelbine is an attractive agent due to its limited toxicity profile, with minimal alopecia and low emetogenic potential. Although vinorelbine is active in patients with previously untreated metastatic breast cancer in practice, its use tends to be reserved for anthracycline-resistant disease in the second- or third-line setting with pooled response rates from phase II trials of 19% (CI 14–24%). One study demonstrated a survival benefit for vinorelbine (over melphalan) in patients who had failed to respond to an anthracycline regimen, with no difference in quality of life scores between the two treatment arms.

An exception to this practice is in the Her2 3+ or 2+/FISH+ patient group who may warrant treatment with vinorelbine and trastuzumab in the first-line setting due to the impressive response rates in phase II studies with this combination. Vinorelbine/trastuzumab combination approaches are effective as first-line treatment of metastatic breast cancer, with response rates of 61–78% reported. It remains unclear how to manage patients who have relapsed on trastuzumab or taxane/trastuzumab combination. A small phase II study reported impressive response rates of 42% with vinorelbine/trastuzumab in the second- or third-line setting following

---

**Table 3.7 Dose modification for Vinorelbine**

<table>
<thead>
<tr>
<th>Granulocytes on day of treatment (cells/mm³)</th>
<th>Percentage of starting dose of Vinorelbine</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1 500</td>
<td>100%</td>
</tr>
<tr>
<td>1000–1499</td>
<td>50%</td>
</tr>
<tr>
<td>&lt;1 000</td>
<td>Do not administer Repeat granulocyte count in 1 week. If 3 consecutive weekly doses are held because granulocyte count is &lt;1000 cells/mm³, discontinue Vinorelbine</td>
</tr>
</tbody>
</table>

Note: For patients who, during treatment with Vinorelbine, experienced fever and/or sepsis while granulocytopenic or had 2 consecutive weekly doses held due to granulocytopenia, subsequent doses of Vinorelbine should be:

| ≥1 500                                     | 75%                                      |
| 1000–1499                                  | 37.5%                                     |
| <1 000                                     | See above                                 |

Table from prescribing information GSK/Pierre Fabre.
relapse after trastuzumab or trastuzumab/taxane therapy. Larger trials are required to answer this important question.

Vinorelbine has been combined with other active drugs in metastatic breast cancer. A phase III randomised study in patients who have not received prior chemotherapy reported the comparable activity of the combination of vinorelbine and doxorubicin (75% response rate) to FAC (74% response rate), with no survival difference and similar toxicities in each arm. A separate phase III randomised study demonstrated no survival benefit and similar efficacy of the combination of 5-fluorouracil and vinorelbine compared with docetaxel monotherapy (100 mg/m²) in patients who had received prior anthracycline therapy. Docetaxel monotherapy appeared to be less toxic than the vinorelbine combination, with 5 possible treatment-related deaths in the combination arm and 1 with docetaxel. Finally, a phase III study revealed the combination of doxorubicin and vinorelbine does not appear to offer a survival benefit over doxorubicin alone in vinca alkaloid and anthracycline-naïve patients. Therefore the combination of vinorelbine with either doxorubicin or docetaxel does not offer any significant advantage over anthracycline or taxane monotherapy. Thus, the utility of this drug is likely to be in combination with trastuzumab or as monotherapy in patients with anthracycline-resistant disease. However, oral derivatives of vinorelbine are in development which may be attractive in combination with other active oral agents such as capecitabine.

**Platinum combinations**

Mitomycin C, vinblastine and cisplatin (MVP) is an active combination regimen in pretreated patients with metastatic breast cancer. In a recently reported phase II study, the response rates associated with this regimen were approximately 30%, with no statistically significant difference in response rates when MVP was given as the first, second or subsequent line of treatment. The toxicity profile is also mild with this regimen, with minimal hair loss. MVP may therefore be appropriate for use in the third-line setting after anthracycline and taxane relapse.

The combination of cisplatin or carboplatin with 5-fluorouracil may be well suited to the treatment of patients with significant liver dysfunction but normal renal function with response rates of 40–60% in the first-line setting.

Synergy between trastuzumab, platinum salts and taxanes has been demonstrated in preclinical studies. Two multicentre phase II studies have recently reported activity of this combination in metastatic breast cancer in patients with Her2 overexpressing disease. Response rates were impressive, ranging between 58% and 79%.

**Gemcitabine**

Gemcitabine is a nucleoside analogue that is metabolised within the cell by nucleoside kinases to the active diphosphate and triphosphate nucleosides. The cytotoxic effects of this drug are thought to be due to these two products of nucleoside phosphorylation by inhibiting ribonucleotide reductase and competing with dCTP for incorporation into DNA, leading to inhibition of further DNA synthesis.
The most frequent adverse events associated with gemcitabine are bone marrow suppression, with neutropenia occurring more frequently than thrombocytopenia and anaemia. Nausea, vomiting and fatigue are also recognised side effects. A macular or maculopapular rash is common with gemcitabine (30% of patients). Reversible elevation of liver transaminases may also occur with serious hepatotoxicity reported rarely either alone or in combination with other hepatotoxic drugs. Mild proteinuria and haematuria were commonly reported in clinical trials. Haemolytic uraemic syndrome (HUS) (0.25%) and renal failure have been reported in patients treated with one or more doses of gemcitabine. HUS should be suspected if a patient develops evidence of microangiopathic haemolysis, a raised bilirubin or lactate dehydrogenase (LDH), severe thrombocytopenia, anaemia or renal failure. Pulmonary toxicity has also been observed, and discontinuation of therapy should proceed immediately. Anaphylaxis and bronchospasm may also occur. Supraventricular arrhythmias, congestive heart failure and myocardial infarction have been reported rarely with gemcitabine. Hair loss is usually minimal.

Gemcitabine is contraindicated in patients with a known hypersensitivity to the drug. Clearance of the drug is reduced in women and the elderly. There are few data for the treatment of patients with severe hepatic or renal impairment, and gemcitabine should be used cautiously in patients with hepatic and renal insufficiency. A starting dose of 800 mg/m² is recommended for patients with hyperbilirubinaemia (with normal renal function). Routine evaluation of hepatic and renal function should be obtained prior to initiating therapy and during therapy. There are reports of fatal cholestatic liver failure associated with gemcitabine.

Gemcitabine dose adjustments are indicated for haematological toxicity and a full blood count and differential should be taken prior to each cycle of therapy (Table 3.8).

Gemcitabine is active as a single agent in metastatic breast cancer, with response rates of between 14 and 37%. Phase II studies in anthracycline and taxane refractory patients have documented response rates of 22–30%. Several phase II trials have studied the combination of docetaxel with gemcitabine. One small second-line phase II trial revealed response rates of 79% with this combination. However, grade 4 neutropenia occurred in over 90% of patients, with febrile neutropenia occurring in 3 of 39 patients. Grade 3 or 4 thrombocytopenia may be less frequent than with gemcitabine alone, indicating a possible platelet sparing affect with the taxane combination. Similar activity has also been reported for paclitaxel/gemcitabine combination strategies with toxicity of myelosuppression, neuropathy and nausea and vomiting.

### Table 3.8 Gemcitabine monotherapy dose adjustments: haematological toxicity

<table>
<thead>
<tr>
<th>Absolute granulocyte count ×10⁶/L</th>
<th>Platelet count ×10⁶/L</th>
<th>Percent of full dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1000 and ≥100 000</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>500–999 or 50 000–99 000</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>&lt;500 or &lt;50 000</td>
<td>Hold</td>
<td></td>
</tr>
</tbody>
</table>
Table 3.9  Day 8 dose adjustments for gemcitabine in combination with paclitaxel

<table>
<thead>
<tr>
<th>Absolute granulocyte count ×10^6/L</th>
<th>Platelet count ×10^6/L</th>
<th>Percent of full dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1200 and &gt;75,000</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>1000–1199 or 50,000–75,000</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>700–999 and ≥50,000</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>&lt;700 or &lt;50,000</td>
<td>Hold</td>
<td></td>
</tr>
</tbody>
</table>

(paclitaxel 175 mg/m^2 every 3 weeks and gemcitabine 1250 mg/m^2 days 1 and 8 of a 3-weekly cycle) (Table 3.9). In December 2004 the MHRA (Medicines and Healthcare Products Regulatory Agency) awarded a licence for the combination of paclitaxel and gemcitabine for the treatment of metastatic breast cancer in patients who have been treated with an anthracycline. Interim phase III trial data for gemcitabine/paclitaxel vs paclitaxel alone have shown a 41% response rate for the doublet compared with 22% for single-agent paclitaxel. Time to progression was also improved with the combination (5.2 months vs 2.9) and interim median survival analysis was also superior in the combination arm (18.5 months vs 15.8 months). As expected in the combination arm, the incidence of febrile neutropenia was higher (5% vs 1%). Nevertheless the important question as to whether combination therapy is superior to sequential (paclitaxel–gemcitabine) treatment remains to be answered before this regimen becomes a new standard of care.

Phase I clinical trials

Once all treatment lines have been exhausted in patients with metastatic breast cancer, patients with good performance status and organ function may want to consider phase I clinical trial options. A recent review of National Cancer Institute sponsored phase I studies in the United States in the period 1991–2002 documented an overall response rate of 10.6%, with an overall death rate due to toxic events of 0.49%.

SPECIAL TREATMENT CONSIDERATIONS

Elderly patients

Elderly patients generally tolerate chemotherapy that does not seem to be at the expense of a deterioration in quality of life. Therefore, chronological age should not influence the decision to commence palliative chemotherapy. Physiological age, with attention to co-morbidity, pharmacological, nutritional and psychosocial issues, should have more influence over the choice of chemotherapy regimen. Unfortunately, as the majority of clinical studies preclude entry to patients >75 years old, there is little evidence base on which to make the appropriate decisions. Furthermore, as most studies have strict entry criteria, results with regards to toxicity and quality of life benefit may not necessarily translate to the management of metastatic breast cancer in the elderly.
Patients >70 years old may suffer from increased chemotherapy-related myelosuppression, and growth factor support should be considered in this high-risk group. Capecitabine monotherapy in the elderly population (>80 years old) can cause significant morbidity, with over half of patients experiencing a grade 3 or 4 adverse event. Grade 3 and 4 thrombocytopenia is more common in elderly patients treated with gemcitabine.

Caution should be taken with trastuzumab combinations in elderly patients at risk of cardiac toxicity, and liposomal anthracycline formulations should be considered in those at risk of cardiomyopathy. Declining renal function with age necessitates appropriate chemotherapy dose adjustments with reference to the patient’s glomerular filtration rate (GFR).

Renal impairment

Special consideration should be given to patients with renal impairment, and cytotoxic dose adjustments should be made appropriately. For example, capecitabine is contraindicated in patients with a creatinine clearance <30 ml/min. A 25% dose reduction is indicated for patients with a creatinine clearance (CrCl) of 30–50 ml/min as grade 3 and 4 toxicities are increased. Cisplatin is nephrotoxic and it is contraindicated in patients with renal impairment (GFR <40 ml/min) and dose reductions should be considered with a GFR of 40–60 ml/min. Carboplatin use is preferable in patients with a GFR <60 ml/min. There are no recommended dose adjustments for docetaxel or paclitaxel in renal impairment. Mitoxantrone dose adjustments are not necessary in patients with renal impairment. Epirubicin and doxorubicin should be given at a reduced dose in patients with severe renal impairment. Vinorelbine dose modifications in renal impairment are recommended.

The diabetic patient

Glucocorticoid-induced hyperglycaemia is common in diabetic patients treated with chemotherapy where steroids form part of the antiemetic regimen, and patients should be advised to monitor blood glucose levels more frequently. Diabetic neuropathy can be exacerbated by treatment with taxane or vinca alkaloid-based chemotherapy. Patients with diabetic cardiomyopathy may be more sensitive to the cardiac toxicity of anthracyclines.

Cutaneous metastasis and topical miltefosine

A small patient group may present with isolated cutaneous metastatic disease with no organ involvement. A trial of topical miltefosine may be considered in this group prior to initiating systemic chemotherapy. A randomised double-blind placebo-controlled trial using a topical 6% solution demonstrated an increased time to treatment failure with the use of miltefosine over placebo.
Central nervous system disease and intrathecal chemotherapy

The management of cerebral metastatic disease requires a multidisciplinary approach. For some patients of good performance status with disease well controlled at other sites and a solitary cerebral metastasis, neurosurgical intervention may be appropriate (see Chapter 9). For patients with multifocal disease, palliative whole brain radiotherapy (see Chapter 8) or stereotactic approaches may improve quality of life. There is limited randomised prospectively collected data for the management of cerebral metastasis. Meningeal disease may be managed with intrathecal chemotherapy. In a retrospective analysis, high-dose intrathecal methotrexate may improve neurological function over conventional-dose methotrexate. However, treatment with intrathecal chemotherapy is controversial, with other studies demonstrating no improvement in relief from clinical symptoms associated with leptomeningeal metastasis. Indeed, a recent small randomised trial demonstrated no survival benefit and increased risk of neurotoxicity associated with the addition of intraventricular therapy.

Liver dysfunction

Patients with liver metastases with deranged liver function tests are frequently encountered in the management of metastatic breast cancer. Dose reductions are required according to the bilirubin and aspartate transaminase (AST) levels with anthracyclines, taxanes, the vinca alkaloids and gemcitabine (Table 3.10). Even in patients treated with these agents with appropriate dose reductions, unexpected toxicities may occur. Particular care should be taken with the elderly, patients with poor performance status, patients on warfarin or other drugs metabolised by the liver and those with limited bone marrow reserve. Consideration should be given to the use of drugs with predominant renal excretion such as platinum agents or capecitabine. In patients with normal renal function, no dose reductions are required for platinum agents and, as noted previously, the combination of cisplatin or carboplatin with 5-fluorouracil may be appropriate in the first-line setting.

CONCLUSIONS

Progress in the field of metastatic breast cancer has been rapid over the last 5 years. Improved therapy in the adjuvant setting has led to fewer relapses with metastatic disease and improved survival. Ultimately, the greatest advance in metastatic breast cancer will derive from optimising adjuvant therapy to prevent relapse. The targeted agent Herceptin (trastuzumab) has had a major impact on response rates and survival in the metastatic breast cancer population. Other targeted therapies are showing promise such as the dual egfr/her2 small molecule inhibitor Lapatinib and the anti-angiogenic monoclonal antibody bevacizumab. The challenge over the next decade...
will be to establish how to integrate these agents with commonly used chemotherapeutic agents and how to predict a subpopulation of patients most likely to benefit from treatment.

### REFERENCES


### Table 3.10  Suggested dose modifications according to liver function

<table>
<thead>
<tr>
<th>Drug</th>
<th>Bilirubin (µmol/dl)</th>
<th>Alkaline phosphatase (or 2–4 × ULN)</th>
<th>AST (%) or AST or dose</th>
<th>Suggested DR (%) or dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epirubicin</td>
<td>20–51</td>
<td>or 2–4 × ULN</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;51</td>
<td>or 4 × ULN</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>20–51</td>
<td>&gt;AST</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;51</td>
<td>&gt;AST</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>21–34</td>
<td>&lt;10 × ULN</td>
<td>135 mg/m²</td>
<td></td>
</tr>
<tr>
<td>(175 mg/m² q3w)</td>
<td>34–85</td>
<td>&gt;10 × ULN</td>
<td>90 mg/m² Not recommended</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;85</td>
<td>&gt;10 × ULN</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>&gt;ULN</td>
<td>or &gt;2.5 × ULN</td>
<td>Not recommended</td>
<td></td>
</tr>
<tr>
<td>100 mg/m²</td>
<td></td>
<td>or &gt;1.5 × ULN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>36–51</td>
<td>50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt;51</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AST, asparate aminotransferase; ULN, upper limit of normal; DR, dose reduction.

See Mano et al for review.


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Trastuzumab and other novel therapies in breast cancer

Robin L Jones and Ian E Smith

INTRODUCTION

With increasing knowledge of the molecular pathways responsible for carcinogenesis, the possibility has arisen for effective antineoplastic drugs directed against specific targets within the cancer. Such agents have the potential for improved efficacy with fewer adverse effects than with conventional chemotherapy. Central to the development of so-called ‘targeted therapy’ is identification that the target is involved in the pathogenesis of the cancer, and that inhibition of the target either inhibits the growth of a malignant cell, or enhances the effectiveness of conventional anticancer agents. Both monoclonal antibodies and small molecules have been developed against key components of signal transduction pathways, and several are in advanced stages of clinical development. The best example is the development of the monoclonal antibody trastuzumab (Herceptin) targeted against HER2, and this chapter highlights the key stages in its development. The clinical improvements that trastuzumab has brought gives much encouragement for the development of several other novel therapies, including signal transduction inhibitors (STIs) and vascular targeted agents.

HER2

HER2 (Human Epidermal Growth Factor Receptor 2) is a member of the erbB epidermal growth factor receptor tyrosine kinase family and is overexpressed in 15–20% of human breast cancers. The HER family consists of four receptors (HER1, 2, 3 and 4) which play an essential role in cell proliferation, survival and differentiation. These receptors have three main domains: an extracellular ligand-binding domain, a transmembrane section, and an intracellular tyrosine kinase domain, flanked by autophosphorylation sites. As monomers these receptors are inactive, but binding of a ligand to the extracellular domain induces receptor homodimer and heterodimer formation. Consequently, the tyrosine kinase is phosphorylated (activated), and thus a complex and interlinked network of signalling pathways is activated. Activation of HER2 results in downstream effects on cell growth, division, differentiation, migration
and adhesion. Targeted therapy directed against this receptor has been developed in the form of a humanised monoclonal antibody, trastuzumab.

**The development of trastuzumab (Herceptin)**

HER2 amplification is observed early in the development of breast cancer and in ductal carcinoma in situ. Experimental work has confirmed that HER2 overexpression is correlated with a number of adverse pathological prognostic factors, including high tumour grade, tumour size, aneuploidy and a high percentage of S-phase cells. Analysis of 86 node-positive tumour specimens first suggested that overamplification of the HER2 gene was a robust independent adverse prognostic indicator.

The discovery of HER2 overexpression in a significant proportion of breast cancer patients and its negative prognostic significance led to the development of murine monoclonal antibodies to the extracellular domain of HER2. It was demonstrated that some of these antibodies were capable of inhibiting the growth of cell lines that overexpressed the HER2 receptor. Pietras and colleagues found that the antibody had synergistic effects with chemotherapeutic drugs such as cisplatin in human breast xenografts. Researchers at Genetech Inc. developed a panel of murine monoclonal antibodies capable of inhibiting HER2+ cell lines. A chimeric antibody (95% human and 5% murine) called trastuzumab was subsequently developed.

**Techniques for assessing HER2 status**

There are a number of methods available for HER2 testing, the most widely used being immunohistochemistry (IHC) and fluorescence in-situ hybridisation (FISH); see Figure 4.1. Clinically the most frequently used technique is IHC; this involves staining paraffin-embedded tissue with an antibody specific for HER2. The advantages of this method are that it is well established, relatively inexpensive and widely available. Commercially available tests include Pathway HER2 (Ventana, Tucson, Arizona, USA) and HerCep Test (Dako, Carpinteria, California, USA), with staining graded on a semiquantitative scale from 0 (no expression) to 3+ (high-level overexpression). However, because of different antibodies, possible differences in tissue fixation and alternative scoring systems, this technique lacks full objectivity, which explains contradictory results in the earlier literature.

FISH analysis measures quantitatively the amount of HER2 gene amplification, and studies have shown it to be more specific and sensitive than IHC. Thus, this method may eliminate variability and subjectivity between different institutions.

Dybdal et al have evaluated the concordance between IHC and FISH in 529 breast cancer patients. The results are displayed in Table 4.1.

It is apparent from the trial by Vogel and colleagues that FISH analysis offers the best correlation with response to trastuzumab, and in our view this is currently the optimal methodology. Because of cost restraints, however, many centres use IHC 3+ as a basis for treatment and restrict FISH analysis to patients whose tumours are IHC 2+. The results are displayed in Table 4.1.
With regard to prognostic significance of HER2, a retrospective study by Sun and colleagues investigated the clinical relevance of HER2 overexpression in combination with the St Gallen classification in 906 women with lymph node negative early breast cancer. Fifty-three per cent of these patients received some form of systemic treatment: 34% chemotherapy only, 11% hormone therapy only and 8% both. HER2 was determined using IHC and the risk groups based on the St Gallen classification categorised as average or minimal risk. The overall 7-year disease-free survival (DFS) was 87.5%. For those with HER2-positive disease the 7-year DFS was 77.9%, compared with 91.2% in the HER2-negative group, \( p = 0.002 \). The 7-year DFS for the average St Gallen group was 85% and for the minimal group 97.9%, \( p < 0.001 \). HER2 overexpression significantly predicted the risk of distant recurrence, odds ratio 3.03 (95% CI 1.63–5.63). Combining HER2 status and the St Gallen classification, there was a significant difference between DFS rate in the HER2-positive/average group (73.3%) and the HER2-negative/average group (88.4%), \( p = 0.007 \).

A further technique called chromogenic in-situ hybridisation (CISH) is also available for HER2 detection. Studies have suggested that CISH has several advantages over FISH: it is more economical, requires an ordinary microscope and the signal intensity is permanent.
Clinical trials of single-agent trastuzumab in metastatic breast cancer

A multicentre study of 222 patients with HER2-overexpressing metastatic breast cancer investigated the use of trastuzumab in patients who had progressive disease following one or two chemotherapy regimens. In total, 213 women received trastuzumab and 9 patients were excluded. Outcome details for this study are displayed in Table 4.2. In the intent-to-treat population, there were 8 (4%) complete responses (CRs) and 26 (11%) partial responses (PRs), translating into an overall objective response rate (ORR) of 15%. An important observation was that women with tumours that over-expressed HER2 at the 3+ level had higher response rates than those with 2+ overexpression (18% v 6%; \( p = 0.06 \)). Multivariate proportional hazards analysis revealed that, number of metastatic sites at trial entry, level of HER2 overexpression and months to first relapse significantly affected time to tumour progression (TTP) (\( p < 0.05 \)).

Another trial evaluated the efficacy and safety of trastuzumab as first-line therapy in 114 patients with HER2-overexpressing metastatic breast cancer. Patients were randomised to receive either a loading dose of 4 mg/kg followed by 2 mg/kg weekly or a loading dose of 8 mg/kg followed by 4 mg/kg weekly. Seven complete and 23 partial responses were documented, corresponding to an objective response rate of 26% (95% CI 18.2–34.4%). Further details of this trial are displayed in Table 4.2. Similar response rates were reported in both dosage groups of trastuzumab. Only those with HER2 3+ overexpressing tumours demonstrated responses. In 108 cases, retrospective pathology slide analysis of tumour HER2 gene amplification was possible. The response rate in women whose tumour amplified HER2 was 34% (95% CI, 23.9–45.7%) compared with 7% (95% CI 0.8–22.8%) in those whose tumours did not. The median TTP in patients with tumours that amplified HER2 was 4.9 months (95% CI 3.4–8.0 months) compared with 1.7 months in those whose tumours did not amplify HER2.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Response rate</th>
<th>MR +SD</th>
<th>TTP (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>30 (26%)</td>
<td>13 (11%)</td>
<td>3.8 + 3.5</td>
<td>25.8 + 22.9</td>
</tr>
<tr>
<td>HER2 3+</td>
<td>30 (26%)</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>HER2 2+</td>
<td>0</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>Second-line therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>34 (15%)</td>
<td>74 (35%)</td>
<td>3.1 (0–28)</td>
<td>13 (0.5–30)</td>
</tr>
<tr>
<td>HER2 3+</td>
<td>18%</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
<tr>
<td>HER2 2+</td>
<td>6%</td>
<td>Not available</td>
<td>Not available</td>
<td>Not available</td>
</tr>
</tbody>
</table>

MR, minimal response; SD, stable disease; TTP, time to progression; OS, overall survival.
Randomised trials of trastuzumab in combination with chemotherapy as first-line therapy for metastatic breast cancer

Preclinical data have suggested synergy between trastuzumab and chemotherapy.22–24 A pivotal trial by Slamon and colleagues evaluated the use of trastuzumab in combination with chemotherapy in 469 women with HER2-overexpressing metastatic breast cancer.25 Patients were randomised between chemotherapy + trastuzumab or chemotherapy alone. For those patients who had not received adjuvant anthracycline treatment, the chemotherapy regimen consisted of an anthracycline (doxorubicin 60 mg/m² or epirubicin 75 mg/m²) in combination with cyclophosphamide 600 mg/m² once every 3 weeks for 6 cycles. The patients who had been treated with adjuvant anthracycline therapy were treated with paclitaxel 175 mg/m² once every 3 weeks for 6 cycles. Trastuzumab was administered as a standard loading dose of 4 mg/kg, followed by 2 mg/kg weekly until disease progression.

At a median follow-up of 30 months there was a significantly improved survival in the trastuzumab + chemotherapy group (25.1 months) compared with the chemotherapy-only group (20.3 months). Such a treatment-related survival difference has previously been unusual in metastatic breast cancer. The trastuzumab + chemotherapy-treated group had statistically significantly longer TTP, duration of response, time to treatment failure (TTF) and higher overall response rate; details are given in Table 4.3. Statistically significant differences in overall response rate, duration of response and TTF were also observed in the subgroups treated with anthracycline and trastuzumab compared with anthracycline-based therapy alone, and likewise for the paclitaxel + trastuzumab group compared with the paclitaxel alone group.

Marty and colleagues have confirmed the results of the pivotal trial described above, with a randomised trial comparing docetaxel alone or in combination with trastuzumab in patients with HER2-positive (IHC 3+ or FISH positive) metastatic breast cancer.26 In both groups, women received docetaxel 100 mg/m² every 3 weeks with or without trastuzumab (loading dose of 4 mg/kg followed by 2 mg/kg weekly) until disease progression. Overall survival was 31.2 months in the combination arm, which was significantly better than 22.7 months in the docetaxel group (p = 0.0001). Again, statistically significant improvements in response rate and median TTP were observed in the combination group; see Table 4.3. Of note, fewer women in the docetaxel and trastuzumab group discontinued treatment due to toxicity than those treated with docetaxel alone.

Phase II studies of trastuzumab with cytotoxics

There have been numerous phase II trials published using different chemotherapy drugs in combination with trastuzumab, and these are reviewed in detail elsewhere.27 Some of the more important recent studies are summarised here.

In a study by Esteva et al a weekly regimen of docetaxel 35 mg/m² and trastuzumab 2 mg/kg, given for 3 weeks with 1 week off, was administered to 30 patients with
A phase II study investigating the combination of vinorelbine and trastuzumab has demonstrated a good safety profile and efficacy. Eligible patients had HER2 overexpression by IHC at the 2+ or 3+ level. Forty women who had received one, two or no prior chemotherapy regimens for metastatic breast cancer were included in the study. Trastuzumab was given at 4 mg/kg for the first dose and then 2 mg/kg. Vinorelbine was given weekly at 25 mg/m² on the same day but after the trastuzumab infusion. Prior chemotherapy, either as adjuvant or metastatic therapy, had been given to 83% of patients. The overall response rate in the intent-to-treat population was 75%, with 3 complete responders and 27 partial responders. Two women had stable disease in excess of 6 months. For the group of women with overexpression at the 3+ level, the response rate was 80%, and for the others the response rate was 60%. Twenty-seven women developed progressive disease and were withdrawn from the study; 4 of these had CNS (central nervous system) metastases.

The results of two open-label phase II studies using a combination of docetaxel, trastuzumab and either cisplatin or carboplatin, conducted by the University of California at Los Angeles – Oncology Research Network (UCLA-ORN) and the Breast Cancer International Research Group (BCIRG) have been published. Docetaxel was given at 75 mg/m², cisplatin 75 mg/m² or carboplatin AUC 6 mg/mL min every 3 weeks. Trastuzumab was given as a 4mg/kg loading dose and subsequently 2 mg/kg weekly for 1 year or disease progression. In the BCIRG study, there were 49 responses out of 62 (overall response rate =79%, 95% CI 66–89%). In the other study

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Median OS (months)</th>
<th>ORR (%)</th>
<th>Median TTP (months)</th>
<th>Median duration of response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slamon et al²⁵</td>
<td>Trastuzumab+ chemotherapy</td>
<td>235</td>
<td>25.1</td>
<td>50</td>
<td>7.4</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy alone</td>
<td>234</td>
<td>20.3</td>
<td>32</td>
<td>4.6</td>
</tr>
<tr>
<td>Marty et al²⁶</td>
<td>Trastuzumab+ chemotherapy</td>
<td>94</td>
<td>31.2</td>
<td>61</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy alone</td>
<td>94</td>
<td>22.7</td>
<td>34</td>
<td>6.1</td>
</tr>
</tbody>
</table>

OS, overall survival; ORR, overall response rate; TTP, time to tumour progression.

<table>
<thead>
<tr>
<th>Median duration of response (months)</th>
<th>Median duration of response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>p = 0.046</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>p = 0.0002</td>
<td>p = 0.0001</td>
</tr>
<tr>
<td>p = 0.009</td>
<td>p = 0.009</td>
</tr>
</tbody>
</table>

metastatic breast cancer who had received up to 3 previous regimens of chemotherapy. The overall response rate was 63%. Together with those who had a minimal response and stable disease, the clinical benefit rate was 83%.

Table 4.3 Randomised trials of trastuzumab with or without chemotherapy in metastatic breast cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>Median OS (months)</th>
<th>ORR (%)</th>
<th>Median TTP (months)</th>
<th>Median duration of response (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slamon et al²⁵</td>
<td>Trastuzumab+ chemotherapy</td>
<td>235</td>
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<td>50</td>
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<td>234</td>
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<td>32</td>
<td>4.6</td>
</tr>
<tr>
<td>Marty et al²⁶</td>
<td>Trastuzumab+ chemotherapy</td>
<td>94</td>
<td>31.2</td>
<td>61</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>Chemotherapy alone</td>
<td>94</td>
<td>22.7</td>
<td>34</td>
<td>6.1</td>
</tr>
</tbody>
</table>

OS, overall survival; ORR, overall response rate; TTP, time to tumour progression.
there were 34 responses in the 59 evaluable patients (overall response rate 58%, 95% CI 44–70%). The median TTP was 9.9 months (95% CI 8.3–13.1 months) in the BCIRG study and 12.7 months (95% CI 8.6–15.5 months) in the UCLA-ORN study.

**Other clinical issues with trastuzumab in metastatic breast cancer**

Several retrospective studies have investigated the incidence of CNS metastases in metastatic breast cancer patients treated with trastuzumab. Clayton and colleagues studied 93 patients diagnosed with cerebral metastases following treatment with trastuzumab; of these patients, 23 (25%) developed symptomatic brain metastases, of which 18 (78%) had stable disease or a response at other disease sites outside the CNS. In total, 16 patients (70%) developed cerebral metastases during therapy with trastuzumab. In the series described by Bendell and colleagues, of 122 patients treated with trastuzumab (either alone or in combination with chemotherapy), 42 patients (34%) developed CNS metastases. The high incidence of CNS metastases may result from an alteration in the natural history of breast cancer associated with prolonged survival, predilection of HER2-overexpressing tumours to develop CNS disease or the pharmacology of trastuzumab.

An extension study of the pivotal randomised trial conducted by Slamon and colleagues investigated the use of trastuzumab following disease progression. Patients were divided into two groups: 154 (66%) of 234 patients treated with chemotherapy alone (group 1) and 93 (40%) of 235 treated with trastuzumab and chemotherapy (group 2). Responses were observed when trastuzumab was used as a single agent and in combination with various chemotherapy agents. Fourteen percent of patients in group 1 experienced an objective response compared with 11% in group 2. Clinical benefit rates for both groups were 32% and 22%, respectively. A retrospective study addressing the same issue in 80 women documented response rates of 24%, 14% and 19% with second-, third- and fourth-line trastuzumab, respectively. Another retrospective analysis assessed the use of trastuzumab beyond disease progression in 105 patients previously treated with up to 6 chemotherapy regimens. The overall response rate to trastuzumab alone or with a taxane as first regimen was 39%. This compared with 36% and 39% when trastuzumab was administered as a second regimen either alone or in combination with chemotherapy (paclitaxel or vinorelbine), respectively.

These data suggest that trastuzumab does have activity beyond disease progression and the use of this agent with a different chemotherapy regimen can prove effective. Currently, a randomised trial is evaluating this question in 438 women who have progressed on trastuzumab in combination with a taxane. Patients are randomised to receive capecitabine with or without trastuzumab, the combination administered until disease progression.

Meng et al demonstrated that 9 out 24 patients with HER2-negative primary tumours acquired HER2 gene amplification in circulating tumour cells on disease
recurrence. This has implications regarding the reassessment of HER2 status on development of recurrent disease.

**Trastuzumab in the adjuvant and neoadjuvant setting**

This clinical topic is beyond the scope of this chapter but it is worth noting that first results of 3 large adjuvant trials have recently shown remarkably large disease-free survival benefit in favour of trastuzumab, either with or after adjuvant chemotherapy. In addition, trastuzumab has demonstrated considerable activity as neoadjuvant therapy for breast cancer. The challenge that this will give for metastatic breast cancer is that many patients will have already received trastuzumab; therefore there will be a need to explore ways of overcoming resistance to this agent.

**Adverse effects, including cardiotoxicity**

In general, adverse effects with trastuzumab are rare, and mainly transient and self-limiting, usually occurring only with the first course of treatment if at all. These include fever, asthenia and rigors. An important exception was the unexpected finding of cardiotoxicity in the two single-agent trials and the combination trial with chemotherapy. Consequently, an independent Cardiac Review and Evaluation Committee (CREC) was established, to obtain independent and unbiased estimates of cardiotoxic risk for patients receiving trastuzumab. The CREC analysed 1219 patient records, and 202 cases were identified for detailed review. Of these, 112 patients experienced cardiac dysfunction, 83 had clinical presentations with explanations other than cardiotoxicity and 7 were not assessable. The patients treated with concurrent trastuzumab and anthracycline, in the pivotal phase III trial, had a 27% rate of cardiotoxicity compared with 8% in the anthracycline-alone group. An increased incidence of cardiotoxicity was also observed in the trastuzumab and paclitaxel group compared with paclitaxel alone (13% compared with 1%, respectively). In the trials with trastuzumab as monotherapy, cardiotoxicity was observed in 3% of patients in the first-line setting and 5% in the trial of trastuzumab as second- or third-line therapy. Most of the patients with cardiotoxicity presented with symptoms (83 of 110 had their symptoms noted), and 82 of these 83 received treatment for cardiac failure. The CREC concluded that the majority of these patients (79%) improved with therapy. Trastuzumab-containing regimens resulted in improved time to treatment failure (defined as time to progressive disease or cardiotoxicity) compared with regimens that did not contain trastuzumab. Similarly, for cardiac dysfunction-free survival, defined as time to symptomatic congestive heart failure (New York Heart Association class III or IV) or death, longer survival was observed in the trastuzumab-treated groups.

**Endocrine therapy, HER2 overexpression and trastuzumab**

Both preclinical and clinical work have suggested that HER2 overexpression may be associated with resistance to endocrine treatment, and in particular tamoxifen.
This may occur through ‘cross-talk’ between the ER (oestrogen receptor) and HER2 signalling pathways. Randomised neoadjuvant trials have likewise demonstrated that ER+/HER2+ breast cancer is more likely to respond to an aromatase inhibitor than tamoxifen. Osborne and colleagues have explored the role of the ER coactivator AIB1 (SRC-3) and HER2 expression in early breast cancer. In their study, high AIB1 expression in patients not receiving adjuvant tamoxifen was associated with better prognosis and longer disease-free survival. However, in patients who were treated with tamoxifen high AIB1 expression was associated with a worse disease-free survival. When expression of AIB1 and HER2 were considered together, patients with high levels of both had worse outcomes with tamoxifen than all other patients. These data have stimulated trials of trastuzumab, and other agents targeted against the HER family of growth factor receptors, in conjunction with either aromatase inhibitors or tamoxifen. This is discussed in Chapter 2.

### SMALL MOLECULE INHIBITORS OF THE HER FAMILY

**Lapatinib**

Burris and colleagues have reported initial results of a phase I dose-escalation study of GW572016 (lapatinib), a reversible, orally active, dual inhibitor of HER1 and HER2 tyrosine kinases (see Figure 4.2), in patients with solid tumours. The drug was administered on a once-daily schedule (escalating from 175 to 1800 mg/day) with the exception of one cohort that was given 900 mg twice a day. Thirty-nine patients were enrolled (3 in each of the 175 and 375 mg/day cohorts; 4 in the 675, 900 and 1600 mg/day cohorts; 6 in the 1200 mg/day and 9 in the 1800 mg/day). In addition, 6 patients received 900 mg twice a day to compare safety with once per day administration. Grade 3 toxicity was not observed in any of the patients administered the once-daily schedule. However, grade 3 diarrhoea was observed in 2 of the 6 patients treated with the twice-daily schedule, requiring dose reductions. Eight patients remained on study with stable disease for 4 months or greater. Recently, the results of a study investigating the biological effects of 5 dose levels of lapatinib in heavily pretreated cancer patients with various malignancies have been published. The effects of lapatinib on survival pathways and tumour growth were assessed by obtaining biopsies before and following 21 days of treatment. Forty-two percent of those enrolled had metastatic breast cancer. Four partial responses were observed in these patients, all having previously progressed on various chemotherapy regimens, most in combination with trastuzumab. Some of these patients had progressed on hormone therapy. Disease stabilisation was observed in 11 others. This study reports a striking response in a patient with inflammatory breast cancer and we have had a similar response in this subtype in our institution.

The results of these initial studies have prompted the initiation of a number of trials of lapatinib in advanced breast cancer. An open-label, multicentre, single-arm phase II
study (EGF20002/EGF20008) will explore the use of lapatinib as a single agent in patients with advanced breast cancer who have progressed on trastuzumab-containing regimens. Results available on the first 81 patients have recorded an objective response in 7 and a further 19 women progression-free at 16 weeks.52

Initial results of a randomised phase II trial of lapatinib in patients not previously treated with any prior therapy for metastatic disease have been reported. Of the first 13 women enrolled, 5 (38%) have obtained a partial response and a further 6 stable disease.53

EGF100151 is a phase III randomised, open-label, multicentre trial comparing capecitabine with or without lapatinib in women with advanced breast cancer. EGF30001 compares paclitaxel with or without lapatinib in patients with previously untreated advanced or metastatic breast cancer.

EGF30008 is a randomised, double-blind placebo-controlled trial comparing lapatinib plus letrozole to letrozole alone in women with oestrogen- and progesterone-positive advanced breast cancer.

**EGFR Tyrosine kinase inhibitors**

EGFR Tyrosine kinase inhibitors bind to the ATP-binding site of the epidermal growth factor receptor (EGFR) thus preventing activation of and signal transduction
from the receptor (see Figure 4.2). Two reversible, oral tyrosine kinase inhibitors have been investigated in breast cancer: gefitinib (Iressa) and erlotinib (Tarceva). Results of 4 phase II trials of these agents in metastatic breast cancer are displayed in Table 4.4.54–57

Albain and colleagues have reported the initial findings of a phase II trial of gefitinib (500 mg once daily) in patients with metastatic breast cancer, previously treated with either endocrine therapy or chemotherapy.54 Of 63 women enrolled in the trial, 31 had received more than three prior chemotherapy regimens. Treatment was well tolerated but 28 (44%) developed a reversible grade 3–4 acneiform rash. One patient obtained a partial response and 2 achieved stable disease. Overall, 12 women had symptomatic bone pain, of whom 5 had decreased analgesic requirements on gefitinib. The median progression-free survival was 57 days (95% CI 56–58 days), and median survival time was 144 days (95% CI 110–242 days).

A phase II muticentre study conducted by Winer and colleagues evaluated the efficacy and safety of erlotinib in women with previously treated locally advanced and metastatic breast cancer.55 Patients were treated with a starting dose of 150 mg/day. The first cohort of patients had disease progression on or after previous therapy with an anthracycline, a taxane and capecitabine. Patients in the second cohort had disease progression on or after at least one prior regimen for locally advanced or metastatic breast cancer. Forty-seven women were recruited to cohort 1 and 1 partial response was observed, translating to an objective response rate of 2.1% (95% CI 0–11%). A further 2 patients had stable disease for 12 and 16 weeks. Twenty-two patients were recruited to cohort 2, with 1 patient achieving disease stabilisation for greater than 28 weeks but no responses were observed. Therapy was generally well tolerated with mild adverse events including acneiform rash, diarrhoea, asthenia, nausea and vomiting.

The trials of tyrosine kinase inhibitors as monotherapy in advanced disease have shown limited activity, possibly a result of patients having numerous previous lines of therapy and the possible need to select appropriate patients for treatment with these

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of patients</th>
<th>ORR (%)</th>
<th>CBR (%)</th>
<th>TTP (weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Robertson et al56</td>
<td>33</td>
<td>7</td>
<td>30</td>
<td>–</td>
</tr>
<tr>
<td>Baselga et al57</td>
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<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Albain et al54</td>
<td>63</td>
<td>2</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Erortinib</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Winer et al55</td>
<td>69</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
</tbody>
</table>

ORR, overall response rate; CBR, clinical benefit rate; TTP, time to tumour progression.

Table 4.4  Phase II trials of small molecule tyrosine kinase inhibitors in metastatic breast cancer
agents. There are current studies investigating the use of these agents in combination with cytotoxics and endocrine therapy.

FARNESYL TRANSFERASE INHIBITORS

There are numerous proteins involved in the process of malignant transformation downstream from growth factors and cell membrane receptor tyrosine kinases. These include the 21 kDa guanine nucleotide-binding proteins encoded by the \textit{ras} proto-oncogene. Processed ras proteins localise to the inner plasma membrane, and have a crucial role in transmission of extracellular signals from the cell surface, including from growth factors that activate cell surface receptors.\textsuperscript{58} Mutations of \textit{ras} are found in <2% of human breast carcinomas,\textsuperscript{59} but aberrant function of the ras signal transduction pathway may be common because of enhanced upstream growth factor receptor activity.\textsuperscript{60} A step in post-translational ras processing is catalysed by the farnesylprotein-transferase enzyme and several non-peptide inhibitors have been developed to target this enzyme.\textsuperscript{61} One such orally active inhibitor of farnesyl transferase is R115777 (tipifarnib).

A phase II study of 76 women with locally advanced or metastatic breast cancer evaluated R115777 either given as a continuing dosing schedule (41 patients) or an intermittent schedule (35 women).\textsuperscript{62} Patients in the intermittent schedule received 300 mg bd for 21 days followed by 7 days off treatment. In the continuing dose group, 4 of 41 patients (10%) had a PR, with a median duration of objective response of 6.1 months (range 4.5–11.9 months). Six women also had stable disease (SD) that lasted for more than 24 weeks. In terms of secondary endpoints, median TTP for the continuing dose group was 3.2 months (95% CI 2.8–4.5 months) and overall survival was 15.1 months (95% CI 10.3–21.1 months).

For the intermittent dosage group, 5 of 35 patients (14%) had a PR and 3 (9%) had SD greater than 24 weeks. The median duration of objective response was 9.6 months (range 8.0–13.3 months). The median TTP was similar to the continuing dose group (2.9 months, 95% CI 2.0–4.0 months) and median overall survival was 10.4 months (95% CI 7.9–16.6 months) in the intermittent dosing group.

The first 6 patients in the continuous schedule of 400 mg bd all developed grade 3 or 4 neutropenia; consequently, the subsequent 35 women were treated at 300 mg bd. There was a statistically significantly lower incidence of haematological toxicity in the intermittent compared with the continuous schedule. Likewise, there was a significant difference in the incidence of neurotoxicity between the two groups: 1 patient developed this adverse effect in the intermittent group compared with 15 patients in the continuing dosage group.

Following results that farnesyl transferase inhibitors may enhance the response of endocrine therapy, a clinical trial of tipifarnib and letrozole versus letrozole alone has been completed.\textsuperscript{63} Preliminary results suggest no improvement in response rate for the combination of tipifarnib and letrozole. The trial was not powered to detect any impact on time to disease progression.
INHIBITORS OF MAMMALIAN TARGET OF RAPAMYCIN

The Akt/mammalian target of rapamycin (mTOR) pathway has been suggested as a central regulator of protein synthesis, playing a role in cell proliferation, differentiation and survival.64,65 Research has demonstrated that rapamycin, a specific inhibitor of mTOR, and its analogues (including CCI-779, RAD001 and AP23573) have exhibited growth-inhibitory effects against a wide range of malignancies in experimental systems.65–67

A phase II randomised trial has assessed the efficacy and safety of 2 dose levels (75 and 250 mg) of intravenous CCI-779 (temsirolimus) given weekly in 109 patients with stage III/IV breast cancer who had failed prior taxane- or anthracycline-based therapy in the metastatic or adjuvant setting.68 An objective response rate of 9.2% (10 partial responses) was observed and median TTP was 12 weeks. Efficacy was similar for both dose levels, but adverse effects were observed more frequently in the higher-dose group. The most frequently encountered grade 3 or 4 adverse effects were mucositis, leucopenia, hyperglycaemia, somnolence, thrombocytopenia and depression.

Another randomised phase II study has evaluated letrozole alone or in combination with CCI-779, either daily or daily for 5 days every 2 weeks.69 In the first instance, 6 patients were enrolled on each of the high-dose schedules, 25 mg for daily CCI-779 and 75 mg for the intermittent dose. Three women in each arm developed toxicity that resulted in dose reduction, delay or discontinuation. As a result, the protocol was amended and doses were adjusted to the low-dose schedule, 10 mg CCI-779 daily and 30 mg for the intermittent dose. Initial results for 13 patients treated with CCI-779 have revealed 1 complete response and 3 partial responses, all on the high-dose schedule. Nine patients have also achieved stable disease, 6 on the high-dose schedule and 3 on the low. Of the 6 treated with letrozole alone, there were 2 partial responses and 4 patients with stable disease. This has now spurred a large phase III trial of over 1200 patients.

ANTIANGIOGENIC AGENTS

Bevacizumab (Avastin) is a recombinant humanised monoclonal antibody to vascular endothelial growth factor (VEGF) that has displayed clinical activity and safety in phase I trials.70,71 A phase I/II open-label dose-escalation study of bevacizumab in women with metastatic breast cancer who had relapsed after at least one conventional chemotherapy regimen for metastatic disease has been reported.71 Based on the results of the phase I studies,72 a starting dose of 3 mg/kg every other week was chosen, and dose escalation to 10 mg/kg was to occur if no objective responses were observed among the first 15 patients. If objective responses were observed, then additional cohorts of 15 were enrolled. In total, 75 patients were enrolled: 18 at 3 mg/kg; 41 at 10 mg/kg; and 16 at 20 mg/kg. In 7 patients out of 75, an objective response was observed.
(9.3%, 6.7% confirmed); 1 patient treated at the 3 mg/kg dose achieved a partial response. In the 10 mg/kg dose group, 5 patients achieved an objective response, 1 CR and 4 PRs including 2 unconfirmed PRs. In the group treated with the 20 mg/kg dose, there was 1 PR. The median duration of response was 5.5 months. Overall median TTP was 2.4 months, being similar in all 3 groups, and median survival was 10.2 months. Twelve of 75 (17%) patients at the date of last tumour assessment, day 154, had stable disease or an ongoing objective response. Bevacizumab was discontinued due to an adverse event in 4 patients. In 17 patients (22%), hypertension was reported as an adverse event, necessitating antihypertensive therapy in 14 cases.

Miller and colleagues have recently reported on a randomised phase III trial of 462 metastatic breast cancer patients who were assigned to capecitabine (2500 mg/m²/day twice daily from day 1 to 14) alone or in combination with bevacizumab (15 mg/kg on day 1) every 3 weeks. Women were eligible if they had previously received both an anthracycline and a taxane, and at least 1 (but no more than 2) prior chemotherapy regimens for metastatic disease. Radiology and clinical information were reviewed by an independent review facility (IRF). The objective response rate was significantly higher in the combination arm, as evaluated by the IRF and investigators: 19.8% (95% CI 14.7–25.0%) vs 9.1% (95% CI 5.4–12.9%) and 30.2% (95% CI 24.3–36.1%) vs 19.1% (95% CI 14.1–24.2%), respectively, but no improvement in progression-free survival for the combination arm was seen. Median overall survival was similar in both treatment arms. The combination group did not experience an increase in capecitabine-associated toxicities. Four women discontinued bevacizumab due to hypertension, but no cases of grade 4 hypertension were reported. Proteinuria was more common in the combination arm, but was rarely clinically significant. However, more minor mucosal bleeding was observed in those treated with combination therapy.

Because of positive results in colorectal carcinoma, bevacizumab is being further studied in breast cancer. The first interim analysis of a phase III trial randomising patients to receive paclitaxel with or without bevacizumab has demonstrated a significantly higher objective response rate in the combination group (28.2%) compared with 14.2% in the paclitaxel-alone group, \( p < 0.0001 \). In addition, the combination group had longer progression-free survival: 6.11 months in the paclitaxel group and 10.97 in the combination group (\( p < 0.001 \)). Early evaluation of overall survival also suggests a benefit for combination treatment (hazard ratio 0.674, \( p = 0.01 \)). Thirteen per cent of patients treated with bevacizumab required treatment for hypertension and approximately 1.5% developed proteinuria of greater than 2 g/day. Chemotherapy-related neuropathy occurred in 13.6% of patients in the paclitaxel-alone group and 19.9% in the combination group.

CONCLUSIONS

Several novel agents have been developed over the last few years as targeted therapy for breast cancer. The monoclonal antibody trastuzumab targeted against HER2 growth factor receptor has shown significant clinical activity, in patients with HER2-overexpressing metastatic breast cancer, both as a single agent and in combination with
Chemotherapy. This agent is generally well tolerated, with mild adverse effects such as fevers, chills, asthenia and pain, particularly with first administration. The only important adverse effect is cardiotoxicity, particularly in combination with anthracycline. It is currently being investigated in four large adjuvant trials. Other novel agents, including lapatinib, targeted against both EGFR and HER2 receptors, gefitinib and erlotinib, targeted against the internal domain of the epidermal growth factor receptor tyrosine kinase, bevacizumab, an anti-VEGF antibody, mTOR and farnesyl transferase inhibitors are all in development with clinical activity in breast cancer already demonstrated. The results of ongoing, and future, trials will give greater understanding of these therapies and their precise role in combination regimens. It is likely that new targets in addition to ER and HER2 will become increasingly important in guiding oncologists to make more informed decisions regarding optimal targeted treatment for an individual patient.

REFERENCES


Bisphosphonates and their role in metastatic breast cancer

David A Cameron

Metastatic breast cancer remains a challenge for the patient and her clinician. The advent of new therapies that successfully target cancer cells has led to a welcome improvement in survival.\(^1\) Patients live longer with metastatic disease, but do not necessarily avoid the morbidity it causes. This chapter will address the role of bisphosphonates in treating and preventing the skeletal morbidity, including pain, which patients have to face when they develop bone metastases.

INTRODUCTION

Quite why breast cancer has such a propensity to spread to bone is not fully established, but almost certainly it is a dynamic dependent on the microenvironment of bone and the biological characteristics of breast cancer cells. Bone is a dynamic organ, actively maintained in a healthy state to permit a good quality life. Traditionally, bone metastases are seen as less important than visceral disease, with a low-key palliative approach often being taken in terms of endocrine therapy and occasional radiotherapy. However, the degree of dysfunction, pain and loss of motility that can be consequent upon bone metastases is considerable. It remains a common site of disease, occurring in up to 75% of all patients with advanced breast cancer, and eventually appearing in around one-third of all patients presenting with early, operable, breast cancer. It might be considered less important as rapid progression is less common than in visceral disease; however, the recent improvements in survival from metastatic disease may be greater in those with hormone-sensitive disease, a group which includes the majority of patients with bone metastases. Therefore as our systemic treatments get better, more patients live longer with bone metastases, so that to an extent they can become the major source of morbidity and resource utilisation of patients with metastatic breast cancer.

PATHOPHYSIOLOGY OF BONE METASTASES

Normal bone is in a constant state of turnover, with osteoclasts resorbing old bone and osteoblasts synthesising down new bone. By finely balancing these two opposing
processes of bone destruction and synthesis, bone health is maintained. However in many disease states this balance is altered, for example, as a normal consequence of fracture repair, in benign conditions such as Paget’s disease and of course in bone metastases from any primary. Under normal circumstances, there is a cross-talk between the osteoclasts and osteoblasts that contributes to the maintenance of bone homeostasis. In addition, the bone matrix acts as a repository for many growth-regulating factors, of which one of the most abundant is transforming growth factor β (TGFβ).

The relevance of the normal bone turnover in metastatic bone disease becomes clear when one considers the potential for metastatic cancer cells to disrupt the cross-talk between osteoclasts and osteoblasts. Micrometastatic disease leads to local bone destruction by the stimulation of osteoclasts through the production of factors such as PTHrP (parathyroid hormone-related peptide), and the increased bone resorption can release factors from the bone matrix that in turn can encourage further tumour growth. It has been clearly shown, for example, that TGFβ, released from the resorbed bone matrix, can increase production of PTHrP by tumour cells in the vicinity, leading to a vicious cycle of increased bone resorption that results in yet more PTHrP and subsequent osteolysis.

Both the loss of normal bone through increased osteolysis and the presence of soft-tissue metastases lead to weakened bone and neural compression. This gives rise to the clinical manifestations of bone metastases such as pathological fractures, pain and nerve compression syndromes such as spinal cord compression. The increased release of calcium from the inorganic bone matrix may exceed clearance mechanisms and give rise to hypercalcemia, although the relative contributions to this process of local and systemically produced PTHrP remains unclear.

**BISPHOSPHONATES**

The bisphosphonates are a family of compounds based on the structure of pyrophosphate that have a high affinity for trabecular bone. They have a basic P–C–P structure, which promotes their binding to mineralized bone matrix, and the remainder of the molecule determines potency, side effects, etc. It appears that their main mechanism of action is the inhibition of osteoclast activity, and thus they can significantly reduce bone resorption by interrupting the vicious cycle of increased bone destruction discussed above.

However, not all bisphosphonates are the same, as can be seen from their molecular structures (Table 5.1). The main distinction lies in whether or not they contain nitrogen, as this relates to their mechanism of action. Nitrogen-containing amino-bisphosphonates such as pamidronate, ibandronate and zoledronate are capable of interfering with mevalonate metabolism, acting as farnesyl transferase inhibitors, downstream of the Ras protein. There is good evidence that their efficacy as farnesyl transferase inhibitors directly correlates with their potency in inhibiting osteoclasts. In contrast, the non-aminobisphosphonate clodronate induces cell death after it has been incorporated into a non-hydrolysable ATP analogue, adenosine 5-triphosphate.
There is increasing experimental evidence that these agents have direct effects on tumour cells as well as osteoclasts. They appear to be able to induce tumour cell apoptosis both on their own, but possibly more importantly, in synergy with both cytotoxics and tamoxifen. Whether these experimental observations are relevant to their clinical benefits, remains unclear.

### CLINICAL EXPERIENCE OF BISPHOSPHONATES IN ADVANCED DISEASE

Bisphosphonates have been effectively used for many years to treat hypercalcaemia of malignancy. Early studies with the intravenous compound pamidronate showed an efficacy of around 90%, and thus, in the UK as well as the USA, this drug became the most widely used agent, although other drugs such as intravenous clodronate are also active. It was in this setting therefore that the first studies with the new, more potent aminobisphosphonates ibandronate and zoledronate were conducted. For example, 4 mg of zoledronate has been shown in a randomised trial to restore calcium levels faster and more effectively than the current standard dose of 90 mg of pamidronate.
Once the pathophysiology of bone metastases was understood, the potent anti-oстеoclast activity of bisphosphonates made a preventative approach in patients with bone metastases a logical development. Early studies suggested efficacy, but the most convincing data came from two large randomised trials of the intravenous bisphosphonate pamidronate given in conjunction with systemic therapy for patients with osteolytic bone metastases. Table 5.2 gives a summary of the benefits, and it is clear from the more recent updates that this effect lasts at least for the 2 years of therapy. Similar studies were conducted with the more potent compound ibandronate, including both oral and intravenous formulations. It is clear that this agent is also active, as compared with placebo. In contrast, studies have also been reported with the oral bisphosphonates clodronate, etidronate and pamidronate. Although benefits were clearly seen, in general it is clear from the data that less activity has been observed.

Whether this is due to variable oral bioavailability, or a difference in activity is not clear, but based on indirect comparisons, the oral agent with the most convincing efficacy data is ibandronate at a dose of 50 mg daily. Only one bisphosphonate has to date shown superiority over another in a head-to-head comparison, and that is 4 mg of zoledronate given over 15 minutes as compared to 90 mg of pamidronate given over 90–120 minutes. This large phase III trial included patients with both multiple myeloma and breast cancer, and demonstrated a 20% further reduction in skeletal morbidity, based on a multiple-event analysis. However, retrospective subgroup analysis suggests that the benefit is confined largely to patients with breast cancer, by virtue of their higher baseline rates of bone resorption.

In addition to the ability of bisphosphonates to prevent skeletal complications, there are good data on their efficacy in reducing bone pain in patients with skeletal metastases, and therefore one area of debate lies in whether all patients with bone metastases should receive these drugs in a prophylactic manner, or just those patients with symptoms. A detailed cost–benefit analysis for the UK has not been published – that from the USA is not relevant because the base cost of pamidronate is much higher. Treatment was given for 24 months in the two pivotal pamidronate studies, and the data suggest that the benefit, if anything, increased with longer duration of therapy. Therefore, many clinicians would recommend bisphosphonates for up to 2 years in patients with symptomatic, or previously symptomatic, bone disease who have a reasonable life expectancy. The data suggest that bisphosphonates are associated with excellent long-term tolerability. Furthermore, there are good data that the risk of skeletal events, and even death, is directly proportional to the level of bone resorption. A useful scoring system for prioritising patients was developed in Sheffield, and was included as an appendix in the previously published British Association of Surgical Oncology (BASO) guidelines on the management of metastatic bone disease from breast cancer. The difficulty in healthcare management lies in choosing a cut-off score for denying patients a drug with proven prophylactic efficacy, while at the same time recognising that there will be patients who get no benefit but for whom there remains a cost, in both financial and toxicity terms.

Similarly, there is the dilemma as to whether patients should receive bisphosphonates intravenously at the hospital, or receive an oral preparation in the community.
Table 5.2  Benefit from bisphosphonates in advanced breast cancer (in combination with systemic therapy).

<table>
<thead>
<tr>
<th></th>
<th>Chemotherapy</th>
<th>Hormonal therapy</th>
<th>Zoledronate vs pamidronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>Significant reduction</td>
<td>Significant reduction</td>
<td>No data</td>
</tr>
<tr>
<td>Radiation to bone</td>
<td>45% reduction</td>
<td>30% reduction</td>
<td>No significant differences were seen in these individual endpoints, but multiple event analysis showed a significant 20% further improvement for zoledronate over pamidronate</td>
</tr>
<tr>
<td>Hypercalcaemia</td>
<td>55% reduction</td>
<td>60% reduction</td>
<td></td>
</tr>
<tr>
<td>Cord compression</td>
<td>N/A</td>
<td>(50% reduction n.s.)</td>
<td></td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>65% reduction</td>
<td>(35% reduction n.s.)</td>
<td></td>
</tr>
</tbody>
</table>

50 mg/day oral ibandronate vs placebo

<table>
<thead>
<tr>
<th></th>
<th>6 mg iv ibandronate vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>Significant reduction</td>
</tr>
<tr>
<td>Radiation to bone</td>
<td>26% reduction</td>
</tr>
<tr>
<td>Vertebral fractures</td>
<td>8% reduction</td>
</tr>
<tr>
<td>Surgery to bone</td>
<td>11% reduction</td>
</tr>
<tr>
<td>Overall event rate</td>
<td>38% reduction</td>
</tr>
</tbody>
</table>

Endpoint definitions are different for the ibandronate studies as compared to the pamidronate studies, so cross-agent comparisons are not meaningful from these data.
Some clinicians compromise by giving the bisphosphonates intravenously while the patient is on chemotherapy (since the patients are already attending the hospital regularly), and then switching to oral therapy once there is no need for 3- or 4-weekly visits to hospital. However, it must be borne in mind that zoledronate, at present the one drug that has been shown to be superior to other bisphosphonates, is only available intravenously: direct comparisons with oral ibandronate have been conducted in terms of bone marker effects, but not yet in terms of skeletal events.

UNANSWERED QUESTIONS

Although the data are clear that bisphosphonates reduce the skeletal morbidity for patients with bone metastases, important questions remain unanswered.

Do all patients need to be treated?

The clinical trials only included patients with lytic disease: yet the pathophysiology suggests that any bone metastasis is associated with increased bone resorption, which can be reversed by administration of bisphosphonates. Defining a group of patients with bone metastases who do not benefit from their use is not therefore possible at the present time.

Which is the best drug?

Current data suggest that zoledronate is the most effective drug, being the only one to be shown to be superior to another agent. However, important randomised trials comparing it with the other third-generation aminobisphosphonate, ibandronate, have yet to complete and/or report. Therefore, precisely defining the group who can be equally well treated with a less-potent agent is not possible. Recent data suggest that the actual level of bone resorption may be important, such that those with persisting high levels of resorption, despite the use of a bisphosphonate, do worse.27

Which is the best schedule?

Also, the optimal schedule has not been defined. For patients with persisting osteolysis despite standard dosing, we do not know if a more intense schedule might help: similarly, for those whose bone resorption is well controlled, less-frequent administration might well be as effective. The latter question will be addressed in the BISMARK trial (cost-effective use of BISphosphonates in metastatic bone disease—a comparison of bone MARKer directed zoledronic acid therapy to a standard schedule) which will be run as a multicentre academic study within the UK over the next couple of years. This is a randomised trial which compares bone marker directed zoledronic acid therapy to standard 3–4-weekly bisphosphonate treatment in 1400 women with advanced breast cancer.
Finally, newer agents that inhibit bone resorption are being developed. Their clinical role has not been defined: we do not know if they will replace bisphosphonates or complement them, giving added efficacy. For the time being therefore, bisphosphonates remain a key component of the treatment of bone metastases, alongside systemic anticancer treatment, and other radiotherapeutic or operative interventions as required.

**TOXICITY**

Bisphosphonates are in general well tolerated. There are toxicities common to all those used in clinical practice, but there is considerable variation between them. All are capable of causing gastrointestinal side effects, although they appear to be worse with the oral route of administration, especially with oral clodronate. An acute-phase response, consisting of chills or flu-like symptoms, is seen in a proportion of patients treated with intravenous bisphosphonates, although tachyphylaxis does occur with repeated administrations.

Two important toxicities deserve a more detailed discussion, as there are suggestions that there may be key differences between agents.

**Renal dysfunction**

There is evidence, particularly with the intravenous drugs pamidronate and zoledronate, that chronic administration can cause a deterioration in renal function. More recent data from the USA have reported that this can in rare cases give rise to acute renal failure, leading in some cases to death. An important paper related this to the use of zoledronate in the USA, particularly in patients with multiple myeloma. However, it has to be acknowledged that the actual manner in which the drug was given, including degree of monitoring of renal function, is not clear. It must be recognised that the rate of infusion may be important in determining renal toxicity, such that giving a drug more slowly may reduce renal toxicity. The early data with zoledronate point to this, in that during the trial which compared zoledronate with pamidronate in breast cancer and multiple myeloma, two substantial protocol modifications had to be made, due to an initial higher rate of renal toxicity with zoledronate. First, the higher dose, 8 mg given over 5 minutes, was discontinued, and then the 4 mg dose was given over 15 rather than 5 minutes. As a result of these changes, in the final analysis, the renal toxicity with 4 mg of zoledronate was not significantly worse than with the comparator of pamidronate given over 2 hours. Preclinical data are consistent with this. Therefore, apparent differences in renal toxicity when using 6 mg of ibandronate given over 1 hour could result not from fundamental differences in pharmacology, but just from the rate of infusion.

In practice, if there is any suggestion of deterioration in renal function with an intravenous bisphosphonate, the first action taken is to reduce the rate of infusion.
Recent guidance data from the manufacturer of zoledronate have suggested lower doses (to be given over the same time) could be given to patients with lower initial creatinine clearance, although they have not been confirmed in phase III trials to be either safer or as efficacious. Nonetheless, caution and regularly monitoring of renal function are needed with bisphosphonates and with zoledronate in particular.

Osteonecrosis of the jaw

Osteonecrosis of the jaw is another rare side effect which has only recently been recognised. It appears to be a class effect, but has been most commonly reported with zoledronate. This painful condition may have been previously underreported, being mistaken as mandibular bone metastases. The incidence appears higher in patients with dental problems, recent dental history, and those with cancer, receiving chemotherapy, radiotherapy and/or steroids.

Optimal management or prevention strategies have not been defined, but clinicians need to be aware of this condition, particularly in patients who develop jaw pain.

CONCLUSIONS

For patients with advanced breast cancer, regular bisphosphonate therapy, whether administered orally or intravenously, is well tolerated and has been shown to reduce skeletal morbidity, including bone pain, hypercalcaemia and the need for other therapeutic interventions. Although one cannot mandate which patient should get a particular drug or schedule, the extensive phase III data clearly show the efficacy of bisphosphonates, and therefore the use of a bisphosphonate should be considered for any patient with breast cancer that has metastasised to bones.

REFERENCES


Imaging in the management of metastatic breast cancer

David MacVicar

INTRODUCTION

Over the past 50 years there have been major shifts in practice regarding the diagnosis and treatment of breast cancer, with trends away from radical surgical procedures to breast-conserving treatment. The national screening programme in the UK has been active for almost 20 years, targeted at patients between the ages of 50 and 64 years old, but available to patients outside this age range under certain circumstances. Mammography, ultrasound (US) and fine needle aspiration cytology (FNAC) have facilitated the diagnosis of small tumours, and US, FNAC and sentinel node imaging can detect nodal disease prior to or at the time of primary surgery. Imaging assessment and clinical examination now guide the decision to treat with neoadjuvant chemotherapy, which has been shown to reduce the need for mastectomy. The role of imaging is crucial and well-defined in the diagnosis of locoregional disease and nodal metastasis, but how it should be deployed in the staging of breast cancer and search for metastatic disease at the time of diagnosis has been less clear-cut.

STAGING OF BREAST CANCER AT DIAGNOSIS

The questions to ask in this clinical setting are:

1. Which patients are likely to have distant metastatic disease at the time of diagnosis?
2. Is it justified to use imaging investigations to diagnose asymptomatic metastases?

Schneider et al. described 488 consecutive patients with primary operable breast cancer who underwent surgery and a work-up for distant metastases, including chest radiograph (CXR), liver US and isotope bone scan. Distant metastases were found in 3.9% (19 patients). Bone metastases were detected in 2.7%, liver metastases in 1% and pulmonary metastases in 0.4%. Among patients with breast tumours < 1 cm at pathological examination, none had metastatic deposits. In patients with pathological T4 tumours (e.g. extension to chest wall, skin oedema and satellite nodules, and inflammatory...
carcinomas), the incidence of metastasis was 18%. This reflects other contributions to the literature, which found that patients with T1 and T2 tumours (lesions <5 cm in diameter) had positive isotope bone scans in only 2%. The message here is unsurprising – locally advanced tumours are more likely to have metastasised at the time of diagnosis – and Schneider et al conclude that imaging work-up can be omitted in patients with small breast tumours presenting with symptoms of local disease only.

The question of whether it is worthwhile detecting metastatic disease which is asymptomatic at presentation was addressed by two multicentre randomised trials conducted in Italy. Rosselli del Turco et al randomised a group of 1243 consecutive patients with no symptoms of metastases at the time of diagnosis of breast cancer into two groups. One group had physical examination and mammography at 6-monthly intervals, whereas patients in the ‘intensive follow-up’ group had, in addition, CXR and bone scan every 6 months. Vital status at 5 years was the main outcome measure. A total of 393 recurrences (104 local and 289 distant) were observed. Increased detection of isolated lung and bone deposits was evident in the intensive follow-up group compared with the clinical follow-up group. No difference in incidence was observed for metastasis at other sites or for local or regional recurrences. There was no difference in 5-year overall mortality, but the relapse-free survival rate was significantly higher in the group subjected to clinical follow-up only, with patients in the intensive follow-up group showing earlier detection of recurrence. This group followed up with 10-year statistics and, once again, no difference in survival was detectable.

In a similar study, the GIVIO investigators randomised 1320 women into two groups, one group being assessed with clinical examination and an annual mammogram, the other being assessed with isotope bone scan and liver US at yearly intervals, CXR twice yearly and laboratory blood tests every 3 months. Median follow-up was 71 months, and there was no overall difference in survival. The study also measured health-related quality of life, including quality of life perception, emotional well-being, body image, social functioning, satisfaction with care and symptoms. No difference was found, so symptom relief cannot be used as a justification for attempts to detect metastatic disease early. Both trials came to the firm conclusion that routine use of imaging investigations for patients with no symptoms of metastasis should be discouraged.

The Faculty of Clinical Oncology of the Royal College of Radiologists issued a document entitled *Imaging for Oncologists*, which recommended that CXR should be performed on women undergoing conservation surgery for T1 and T2 breast carcinomas, and CXR, isotope bone scan and cross-sectional imaging of the liver should be performed on women undergoing mastectomy. This provoked a brisk response from diagnostic radiologists involved in the care of breast cancer patients. It was pointed out that it is illogical to use the type of surgery proposed as a prognostic indicator, as a patient with a small low-grade invasive tumour with extensive surrounding ductal carcinoma in situ (DCIS) needs a mastectomy, but is at low risk of developing metastases. However, a patient undergoing conservation surgery for a small high-grade invasive cancer may well have micrometastases which declare in future years. It was reiterated that there is no survival benefit in early detection of metastases, and attention was
drawn to the likelihood of false-positive results generating anxiety and consuming resources unnecessarily. The decision to administer adjuvant therapy to patients with a poor prognosis is based on adverse pathological features. The Royal College of Radiologists subsequently amended the advice to the effect that, prior to mastectomy, if there is any suspicion that patients may have metastatic disease, isotope bone scan and cross-sectional imaging of the liver should be employed. In the response, attention was drawn to the problem faced by oncologists treating patients that there is no reliable way of identifying patients with early metastasis, and therefore it is difficult to assess the effect on the natural history of metastatic disease of expensive modern cytotoxic drugs, bisphosphonates and emerging novel biological agents such as Herceptin (trastuzumab).

Since diagnosis of metastatic disease renders a patient 'incurable', the diagnosis should be made with due circumspection and only when it is unequivocal. Modern imaging techniques are capable of throwing up a multitude of false-positive findings. Even in a patient with an established diagnosis of cancer, the majority of radiological findings will prove to be benign entities such as lung granulomas and liver cysts. There is no place for imaging studies done with the intention of reassuring the patient, as they will frequently do the opposite. The time to image a patient is when there are symptoms which need investigation and for which systemic or local treatment may be beneficial.

**IMAGING INVESTIGATIONS FOR SYMPTOMATIC METASTATIC DISEASE**

Autopsy studies demonstrate that breast cancer is capable of metastasising to any organ. Lung, bone, liver and lymph nodes are the most frequent sites of metastatic disease. Lee summarised the results of seven autopsy studies conducted between 1950 and 1982, and the more frequent sites of metastatic disease are listed in Table 6.1. There are some surprising statistics, notably that central nervous system (CNS) metastases seem under-represented by today's standards. It does seem that the pattern of metastatic disease is somewhat different in patients <50 years old and in patients who have received prolonged cytotoxic chemotherapy in that these patients tend to have more sites of metastatic disease discovered at autopsy. Given that multiple sites of metastatic disease are frequently found, once metastatic disease has been diagnosed it is a more reasonable proposition to trawl through various organs using cross-sectional imaging. The most versatile readily available investigation is computed tomography (CT), but magnetic resonance imaging (MRI), US, isotope bone scanning and positron emission tomography with 18-fluorodeoxyglucose (18FDG-PET) may also be used. Such imaging techniques may be helpful in guiding the decision to change or abandon systemic treatment, and tumour assessment (including volume measurement) forms a part of many clinical trials. In the first instance, however, a symptom must be investigated with the intention of diagnosing and palliating metastatic disease, and each set of symptoms will require a tailored approach to investigations. A careful
clinical history and physical examination are of inestimable value in providing clinical details which will guide appropriate investigation and enable the radiologist to interpret imaging findings. Without such information, discrepancies of interpretation may occur, which is of detriment to the patient.

**Nodal metastatic disease**

In the current version of the TNM staging system metastatic disease in the supravclavicular fossa nodes is categorised as N3, although it has previously been staged M1. Cervical nodal disease is considered metastatic. Most nodal metastases to the neck and axilla can be diagnosed by clinical examination, but CT and US (Figure 6.1) may be used for confirmation in clinically equivocal cases and CT is useful for demonstrating mediastinal or retroperitoneal nodal metastasis.

**Intrathoracic metastatic disease**

Dyspnoea is the commonest symptom that raises the suspicion of pulmonary metastatic disease, and should be initially investigated by CXR. A baseline CXR is frequently available, although regular follow-up is not indicated\(^{13}\) and any change in the appearance is relevant. CT may be helpful in discriminating metastases from other pathology such as intercurrent infection, but CXR is frequently the only investigation necessary. Metastatic disease to the lungs typically takes the form of nodules, which are usually slightly irregular and of different sizes throughout the lungs (Figure 6.2).

Lymphangitis carcinomatosa is a common manifestation of metastatic breast cancer which presents with marked dyspnoea that is disproportionate to the often minimal radiographic change. The classic appearance on CXR is of basal septal lines and peripheral reticulonodular shadowing, sometimes associated with small pleural effusions in

<table>
<thead>
<tr>
<th><strong>Site of metastasis</strong></th>
<th><strong>Percentage of patients affected</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>71</td>
</tr>
<tr>
<td>Bone</td>
<td>71</td>
</tr>
<tr>
<td>Nodes</td>
<td>67</td>
</tr>
<tr>
<td>Liver</td>
<td>62</td>
</tr>
<tr>
<td>Pleura</td>
<td>41</td>
</tr>
<tr>
<td>Adrenal</td>
<td>26</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>21</td>
</tr>
<tr>
<td>Ovary</td>
<td>20</td>
</tr>
<tr>
<td>Dura</td>
<td>18</td>
</tr>
<tr>
<td>Leptomeninges</td>
<td>16</td>
</tr>
<tr>
<td>Pituitary</td>
<td>9</td>
</tr>
<tr>
<td>Spinal cord</td>
<td>8</td>
</tr>
</tbody>
</table>

Adapted from Lee."
the presence of a normal-sized heart (Figure 6.3). When CXR is normal or borderline abnormal, high-resolution CT can demonstrate limited degrees of lymphangitis.

Pulmonary involvement is frequently associated with intrathoracic nodal metastasis. This is best demonstrated by CT, and involved nodes may be discrete soft-tissue masses, or as an infiltrative poorly defined process distorting the anatomy of

**Figure 6.1** Ultrasound examination of right infraclavicular region showing a solid lymph node (N) in close proximity to the subclavian artery (A) and vein (V). There is no fat in the hilum of the node and it is of rounded rather than ovoid shape. It was also of increased vascularity on Doppler studies, and the size and characteristics are typical of a tumour-involved node, which was not clinically palpable.

**Figure 6.2** CT scan of pulmonary metastases from breast cancer. Irregularity of outline and variation in size are typical features.
the mediastinum (Figure 6.4). This form of the disease is sometimes associated with venous obstruction and symptoms of vague chest pain and dysphagia.

Pleural disease is common and the majority of patients present with pleural effusion that can be diagnosed by clinical examination and CXR; occasionally, US is helpful if there is difficulty discriminating consolidation from effusion.

**Bone metastases**

In oncological practice, the clinical context of musculoskeletal pain is of paramount importance. Back pain in a patient with a previous diagnosis of breast cancer is a good example of how the clinical background fundamentally influences the selection of imaging tests and their subsequent interpretation. For example, a patient who had a 1 cm grade 1 carcinoma of breast, with no nodes involved, 15 years previously, and
reaches the age of 70 only to complain of low back pain while gardening, is likely to have degenerative disc disease. The chances of metastatic breast cancer being the cause of these symptoms is low, and a period of observation with no imaging tests would be appropriate. A plain radiograph of the lumbar spine may confirm degenerative change. An entirely different approach would be in order for a patient aged 40 years old presenting with back pain 3 years after resection of a 5 cm grade 3 carcinoma with multiple involved nodes. In such a patient the likelihood of bony metastases is sufficiently high that plain film imaging, with its inherent lack of sensitivity, is scarcely worthwhile. An isotope bone scan is an appropriate initial study and is able to identify multiple sites of disease, thus confirming metastases. Full clinical details afford the investigating radiologist a far greater chance of interpreting the imaging findings appropriately. There is a small but important false-negative rate attached to isotope bone scanning, which is probably attributable to deposits which are confined to the bone marrow or which fail to excite any osteoblastic activity. If the clinical background is highly suggestive of metastatic disease, MRI is a suitable method of further evaluation of painful areas. T1-weighted spin-echo sequences yield good contrast between metastatic deposits and normal fatty bone marrow (Figure 6.3). Further sequences, such as T2-weighted spin-echo and gradient-echo techniques and short tau inversion recovery (STIR), may be used at the discretion of the investigating radiologist. Approximately 7% of patients who have a normal isotope bone scan can be demonstrated to have spinal metastases using MRI.14,15

In patients with high risk of metastatic disease, a whole body technique is appropriate. However, many patients will fall into a grey area where clinical suspicion is intermediate. Under these circumstances, it is appropriate to image the symptomatic area with plain radiography. Where typical features are observed, a diagnosis of metastatic disease may be made (Figure 6.6). Bearing in mind the relative insensitivity of plain radiography, follow-up imaging may be necessary to confirm the diagnosis of metastatic disease.

Liver deposits

Statistically, liver deposits are slightly less common than bone and pulmonary deposits. Hepatomegaly or disturbance of liver biochemistry are the usual precipitants of a radiological search for liver metastases. It remains a moot point whether deranged liver function tests constitute a symptom. Initially, investigation with US will usually make the diagnosis, breast deposits are typically hypoechoic and sometimes demonstrate a ‘target’ lesion appearance (Figure 6.7). If CT is being undertaken to investigate intra-thoracic disease, extension of the CT study should demonstrate breast metastases as rim-enhancing poorly defined lesions. Small metastases may become confluent and diffuse, resulting in an appearance which can be confused with cirrhosis (Figure 6.8).16,17 Magnetic resonance imaging is not routinely used in the evaluation of hepatic metastatic disease, but it has a useful problem-solving role, particularly in the evaluation of indeterminate focal lesions.
NEUROLOGICAL PRESENTATIONS IN PATIENTS WITH BREAST CANCER

In Lee’s review of autopsy findings between 1950 and 1982, CNS metastases were found in 26% of patients. If a large number of autopsy studies were performed on patients with breast cancer today, it is difficult to imagine that the incidence would be as low as this figure. With modern chemotherapy, it seems that the CNS acts as a sanctuary site, possibly as a result of incomplete penetration of systemic chemotherapy beyond the blood–brain barrier, or alternatively because the natural history of the disease is altered in other ways. Intra-axial brain deposits are common, but there are several important ways in which metastatic breast cancer can affect the nervous system.

Figure 6.5  (a) Isotope bone scan of whole body is within normal limits, with no focal increased uptake of isotope in the spine. (b) Owing to high clinical suspicion of metastatic breast cancer, MRI was performed. A sagittal T1-weighted sequence shows high signal (white) return in normal marrow cavities. However, many vertebral bodies return a lower (darker) signal, and these are tumour-involved areas. An upper thoracic vertebra is threatening mechanical cord compression (arrow). The MRI study was performed 4 days after the isotope bone scan.
Neurological presentations can be complex, and it is extremely important to ensure that careful clinical assessment is undertaken. For example, a symptom such as inability to walk can result from a parafalcine brain deposit, cord compression, steroid myopathy or general debility. It is unreasonable to image the entire neuraxis and carry out electrophysiological studies when a patient may simply need some rehydration, and the referring physician must try to localise the lesion clinically, even if only to place it above or below the foramen magnum.

Figure 6.6 Pelvic radiograph in a patient with a past history of breast cancer complaining of left hip pain. There is a diffuse lytic lesion (arrows) in the iliac bone extending to the roof of the acetabulum. Typical features such as the loss of bony trabeculae and the wide zone of transition between normal and abnormal bone allow a confident diagnosis of a metastatic deposit to be made.

Figure 6.7 Liver ultrasound showing two predominantly hypoechoic lesions in the hepatic parenchyma (arrows). The diagnosis of hepatic metastatic disease is sometimes less straightforward than in this example.
Spinal cord compression

Epidural spinal cord compression (SCC) is a not-infrequent complication in patients with bony metastatic disease to the spine. The investigation of choice is MRI of the whole spine. It should be noted that pain is an almost invariable feature of true spinal cord compression, and loss of motor power is the most reliable physical sign. Sphincter disturbance, abnormalities of muscle tone, extensor plantar reflexes and sensory signs are subjective and often unreliable.

In the presence of a convincing clinical picture, epidural cord compression may be diagnosed without a major degree of mechanical compression. The vascular supply of the cord is predominantly via the anterior spinal artery, which forms an anastomotic chain running the length of the cord from T12 to C1. It is supplied by anterior radicular arteries which take origin from the aorta, the proximal posterior intercostal artery or vertebral arteries. Interruption of this blood supply can have a catastrophic clinical effect, as penetrating branches from the anterior spinal artery run into the anterior parts of the cord, which carry the major descending motor functions.
pathways and the anterior horn cells. Infarction of the cord leads to power loss that is unlikely to recover, rendering the patient paraplegic. Metastases in the vertebral body, especially if associated with a soft-tissue mass, can put the blood supply of the cord at risk (Figure 6.9).

On some occasions compression of the spinal cord may result from expansion of the posterior elements of the vertebral body, particularly the pedicles. Pain will be the predominant clinical symptom, and power loss may be less marked than compression from deposits in the vertebral body. The imaging findings can be subtle, but trained radiographic staff will be able to perform supplementary sequences to confirm the diagnosis (Figure 6.10). When investigating SCC, the entire spine should be imaged. Multiple levels of cord compression occur frequently. In early SCC, the sensory level is usually several segments below the true level of compression, and as the syndrome develops the sensory level rises cranially.

When MRI is contraindicated, myelography and CT myelography may be used, but this investigation carries increased risk to the patient as some cord compression syndromes worsen as a result of the lumbar puncture procedure.

**Figure 6.9** (a) Sagittal T2-weighted MRI showing metastatic disease at several levels, with vertebral collapse at D6 causing cord compression (arrow). Although the degree of mechanical compression is less than is sometimes seen, the patient was paraplegic. (b) Axial T2-weighted image which shows retropulsion of the metastasis in the vertebral body extending towards the site of the anterior spinal artery (arrow). Infarction of the cord at this level may be responsible for the clinical syndrome of cord compression.
Spinal meningeal metastases

In a patient with metastatic breast cancer and definite neurological abnormality, meningeal metastatic disease should be considered. Poorly defined vague back pain and headache are usually present, and the neurological symptoms and signs cannot be correlated to a single anatomical site as should be the case with SCC. If clinical suspicion is high, MRI remains the investigation of choice but the technique will include gadolinium-enhanced T1-weighted imaging. The presence of meningeal metastatic disease gives typical nodular enhancement of the meninges (Figure 6.11). MRI is relatively insensitive in detection of meningeal metastatic disease; therefore, if clinical suspicion remains high, lumbar puncture and cerebrospinal fluid (CSF) cytology may be positive for tumour cells in the presence of a normal MRI study.\textsuperscript{18,19} Meningeal disease as the first manifestation of metastatic disease is extremely rare. Intra-axial spinal cord deposits present with similar clinical findings to meningeal metastases. They are usually associated with brain deposits and have a tendency to affect the conus (Figure 6.12).
Figure 6.11 Gadolinium-enhanced T1-weighted images of lumbar spine show enhancing nodules (arrows), typical of meningeal metastases from breast cancer. Gd DTPA, gadolinium diethylenetriamine pentaacetic acid.

Figure 6.12 Gadolinium-enhanced T1-weighted sagittal MRI images showing an enhancing metastasis in the conus (arrow).
Brain metastases in breast cancer most frequently present with headache or convulsions. Localising signs such as hemiplegia or ataxia may be found. MRI is the most sensitive method of detecting small metastases, but CT is often adequate for diagnostic purposes. Breast metastases to the brain tend to be peripheral, and an association between primary breast cancer and development of meningioma has been described. If a solitary cerebral deposit is identified, it is tempting to suggest a diagnosis of meningioma. However, in the author’s experience, a solitary brain deposit is much more frequent than an incidental meningioma and a pragmatic approach favours early follow-up investigation rather than immediate craniotomy. As with neurological presentations below the foramen magnum, meningeal metastatic disease may result in a syndrome of diverse clinical signs, often affecting cranial nerves. Contrast enhancement is routinely performed for MRI investigation of brain metastases, but different imaging planes may be used if cranial nerve palsies are observed, either as a result of meningeal metastatic disease or skull base deposits (Figures 6.13 and 6.14).
Breast cancer also has a predilection for metastasising to the orbit. Solid deposits may be found on the ocular muscles, on the choroid or sclera, and it may also infiltrate the retro-orbital fat. Once again, clinical examination should direct the MR technique, so that the orbits are studied in more detail. A tailored approach to demonstration of neuroanatomy on MRI can give exquisite detail, and the technique is at its best when used to answer specific questions (Figures 6.15 and 6.16).

**Brachial plexopathy**

Following treatment for breast cancer, symptoms of pain down the arm raise the possibility of brachial plexopathy as a result of metastatic disease. True brachial plexopathy is characterised by power loss as well as sensory symptoms. The brachial plexus originates with the nerve roots of C5–T1, which exit the neural foramen and run between the anterior and middle scalene muscles. Upper, middle and lower trunks are formed, which give anterior and posterior divisions to reform as the cords of the brachial plexus which lie posterior to the subclavian vessels in the infraclavicular or retroclavicular region. Metastatic breast cancer can involve the brachial plexus at spinal level, cervical nodes may involve the plexus at the lateral border of the scalene muscles, but most frequently the point of involvement is where the cords lie behind the subclavian vessels. Detailed investigation of the symptoms should include the spine, and MRI has been demonstrated to be highly accurate in diagnosis of tumour...
recurrence. As with nodal disease in the mediastinum, recurrence can take the form of infiltrative plaques rather than discrete lumps. However, a mass or plaque of tumour tissue around the brachial plexus is usually sufficient to confirm the diagnosis. In equivocal cases, US may be useful, as FNAC can be performed for disease confirmation (Figure 6.17). The main clinical differential diagnosis is with

**Figure 6.15** Fat-suppressed gadolinium-enhanced MRI of the orbits shows a diffuse high signal mass lesion infiltrating the retro-orbital fat on the right (arrows). Using this sequence, the retro-orbital fat on the normal left side returns a low signal. This type of MRI sequence is not routinely used unless orbital pathology is suspected.

**Figure 6.16** Fat-suppressed gadolinium-enhanced parasagittal T1-weighted images through the orbit demonstrating choroidal and retinal deposits (arrows).
radiation plexopathy. This results in thickening in the elements of the brachial plexus within the radiation field. PET–CT is likely to be useful in this clinical context when there is no obvious mass lesion demonstrable by MRI, although there is little documented evidence in the literature as yet.

**Intra-abdominal metastases**

CT is an established and available method for investigating the abdomen in a patient with metastatic breast cancer. CT experience reflects the autopsy studies in that virtually any organ may be involved, including adrenals, spleen, pancreas and
ovaries. The serosa and mucosa of the gut may be involved, but peritoneal metastatic disease is notoriously difficult to diagnose on imaging. Infiltration of the retroperitoneum by small-volume nodes is also an occasional manifestation of breast cancer metastases, and the disease can miss out the thoracic cavity completely and show up first in the abdomen. Peritoneal deposits in the abdomen are from lobular carcinoma in a disproportionate number of patients.21,22

WHOLE-BODY IMAGING TECHNIQUES

Once a diagnosis of metastatic breast cancer has been made, there is some justification in imaging the whole body, as follow-up studies will be required to assess response to various lines of systemic treatment. CT is the most versatile technique, and is capable of demonstrating metastases to lymph nodes, lungs, liver, pleura, peritoneum, intra-abdominal organs and bone. Assessment of lesion size is the mainstay of response assessment, but in this approach there are many pitfalls. Bony deposits may become sclerotic and appear larger, but this may be a result of a healing response. Some assessments are beyond certain techniques: for example, CT cannot assess the meninges, and PET, owing to the high uptake of glucose in the brain, cannot detect brain metastases. Whole-body MRI using the STIR sequence has been advocated for identifying metastases in all organs.21 However, the bony extremities, skull and brain are not well imaged using this technique and MRI undoubtedly works better when targeted to a clinical problem. For the time being, diagnosis of symptoms is best achieved with a tailored approach using the single most appropriate imaging technique. In the assessment of response, CT will carry out most of the donkey-work at the present time, owing to speed and availability of the technology.

CONCLUSION

With the increasing complexity of available technological investigations, the fundamental message remains that to get the best out of these techniques requires careful history-taking and clinical examination. A sound knowledge of patterns of metastatic spread of breast cancer will allow appropriate use of imaging investigations, and discussion of management at multidisciplinary team meetings involving imaging consultants will enhance patient care.

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INTRODUCTION

The morbidity and mortality related to metastatic breast cancer remains high, a contributing factor to this being difficulty in accurate cancer detection and staging. Functional imaging approaches are now being increasingly used in oncological management, the principal advantage relative to anatomical imaging being that sites of active disease are accurately assessed. A particularly exciting development in recent years has been that of the advent of positron emission tomography/computed tomography (PET/CT) scanners that provide functional information regarding disease status (defining sites of active/inactive disease) combined with the anatomical definition of CT.

The principal tracer used in clinical PET to date is 2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG). The extent of 18F-FDG uptake in tumours is directly related to the number of viable tumour cells. In addition, the number of viable tumour cells expressing the cell surface transporter GLUT-1 best correlates with the extent of 18F-FDG uptake in a given tumour, GLUT-1 being overexpressed in breast cancer. Once it is taken up by the cell, 18F-FDG undergoes a single phosphorylation step in the glycolytic pathway and is then retained.

This chapter will outline the role of PET/CT in breast cancer patients. The assessment of primary/axillary nodal disease will be briefly reviewed prior to the role of PET/CT in defining metastatic disease, treatment response assessment and disease recurrence. Probable future applications of PET in breast cancer will also be briefly addressed.

PRIMARY STAGING

A number of studies have demonstrated that PET is not sufficiently accurate compared to conventional work-up for primary staging, a routine staging role therefore not being recommended. Avril et al demonstrated a sensitivity range of 64–80% and a specificity range of 75–94% for detection of breast malignancy by 18F-FDG PET.
in 144 patients with known or suspected malignant breast masses, depending on whether conventional image reading (CIR) or sensitive image reading (SIR), respectively, was used. For CIR, only focal areas of markedly increased 18F-FDG uptake were considered to represent malignancy; for SIR, diffuse or focal areas of moderately increased tracer accumulation were also interpreted as representing malignancy. The same authors also demonstrated that the accuracy of whole-body 18F-FDG PET in the detection of primary breast cancer depends on lesion size: 0/4 stage pT1a tumours (≤0.5 cm) and 1/8 pT1b tumours were detected by PET; 81% (CIR) and 92% (SIR) of pT2 tumours (2–5 cm) were demonstrated (Figure 7.1).

Figure 7.1 Primary disease. PET/CT performed to assess recurrent laryngeal carcinoma (recurrence shown as ‘golden glow’ of 18F-FDG in laryngeal bed on coronal half-body fused PET/CT images 3–5). An occult left breast primary tumour and involved left axillary adenopathy were also detected however, shown as focal tracer uptake in lower outer quadrant (LOQ) of breast (2–3 upper row images) and nodal axillary uptake (5–6 lower row images) – proven on ultrasound and biopsy subsequent to PET/CT findings (2 cm primary breast tumour).

False-negative findings are also observed with slow-growing or well-differentiated tumours, non-invasive, tubular, ductal carcinoma in situ (DCIS) and lobular tumours. It should also be recognised that 18F-FDG is a glucose ligand, not a truly tumour-specific agent. False-positive uptake is therefore observed with inflammatory or infectious lesions and for a short-interval post biopsy/surgery.

Whereas there is some interest in the potential use of 18F-FDG PET for axillary nodal staging, it seems that current whole-body PET/CT scanners do not allow sufficient accuracy to be of practical use. Wahl et al3 conducted a prospective multi-centre trial in 360 women with newly diagnosed invasive breast cancer, assessing 308 axillae with a gold standard of nodal pathology. With 3 highly experienced independent readers a sensitivity range of 54–67%, specificity of 79–81%, positive predictive value (PPV) of 62% and negative predictive value (NPV) of 79% were observed.
Therefore, the technique appears moderately accurate but often fails to detect small and/or few nodal metastases.

**DISTANT METASTATIC DISEASE**

Contrary to the assessment of primary disease, a number of studies clearly demonstrate that PET/CT is the most accurate imaging modality now available to stage metastatic disease, often revealing unsuspected metastases in up to 30% of patients, with resultant management change.

The strengths of PET/CT are the fact that it is a *whole-body* scanning modality, accurately assessing the soft tissues, viscera and skeleton with one test; functional imaging also defines sites of *active* tumour (Figure 7.2). The technique is particularly effective in demonstrating small (<5–10 mm) metastatic nodal sites of involvement and bony disease, conventional imaging having limitations. With anatomical CT imaging, the significance of small (<1 cm) sites of change (adenopathy) is difficult to assess. Technetium-99m methylene diphosphonate ($^{99m}$Tc MDP) bone scintigraphy is conventionally used to assess the skeleton but is not a specific technique: an osteoblastic
response is imaged and therefore false-positive uptake is seen, with degenerative change, trauma, inflammation and infection. In addition, bone scan is not sensitive in the context of lytic metastatic disease, when a significant osteoblastic response may not occur as areas of photopenia are difficult to define. CT bony window assessment is insufficiently sensitive for staging. Magnetic resonance imaging (MRI), although a sensitive technique, is targeted at certain parts of the skeleton and is not currently a whole-skeleton scanning modality in clinical practice.

18F-FDG PET demonstrates sites of viable tumour cells in the bony skeleton, and is therefore a more specific modality than a bone scan. The other significant benefit of PET over a bone scan is the improved accuracy in detection of lytic metastatic disease. Cook et al assessed 23 patients with known bone metastatic disease with 18F-FDG PET and 99mTc MDP bone scintigraphy. Overall, PET detected more sites of disease than bone scan (mean 14.1 vs 7.8 lesions, respectively); this difference is greatest with osteolytic disease. Since lytic disease is associated with more aggressive breast cancer and a worse prognosis, earlier and accurate detection by FDG PET may be beneficial.

The entity of the bone scan-negative PET-positive patient with bony metastatic disease is now clearly recognised; these patients usually have lytic lesions (Figure 7.3). If a negative bone scan is observed in a patient where the clinical index for suspicion of bony disease is high – in the context of bone pain or a raised alkaline phosphatase – then an 18F-FDG PET scan should be considered.

It should also be recognised that, as PET/CT is more accurate in defining small volume metastatic disease than other imaging modalities, metastatic disease may be detected earlier in a number of patients than hitherto has been the case. For example, <5 mm chest nodal sites of disease may be demonstrated; conventionally, these patients were thought to be disease-free (by CT criteria, for example). Clinicians need to recognise that disease is being defined by this new more sensitive imaging modality at an earlier stage of evolution in such patients; clearly, treatment strategy and prognosis also need to be considered accordingly.

Given that PET/CT is the most sensitive current imaging modality to define metastatic disease, there is clearly an argument that it should be used as the first-line investigation in patients with metastatic breast cancer, rather than potentially performing a number of serial investigations which may include plain films, bone scintigraphy, CT and MRI, perhaps culminating with a PET/CT scan. Disease status is accurately defined early in the patient’s work-up; the patient pathway is thus simpler and more efficient, with healthcare provision being more cost-effective. PET/CT is currently a very limited clinical resource; when scanners are widely available patient investigation pathways are likely to change.

**ASSESSING RESPONSE TO TREATMENT**

18F-FDG PET is very useful in assessing response to a number of different types of treatment, particularly hormone therapy, chemotherapy and radiofrequency/laser ablation.
Early treatment response assessment

The early assessment of treatment response is a particularly exciting use of functional imaging; metabolic changes in tumours/metastases clearly occur before morphological (anatomical) changes occur. The early differentiation of responding from non-responding patients would allow for alteration/discontinuation of ineffective treatment, improving patient morbidity and mortality and also leading to public healthcare savings.

Data indicate that PET may be of clinical value in predicting response to chemotherapy in patients with metastatic breast cancer earlier than any other method used.\textsuperscript{5,6} Gennari et al\textsuperscript{6} evaluated the treatment response to an epirubicin/paclitaxel chemotherapy regimen in 13 patients with metastatic breast cancer. Response was evaluated in a conventional manner, clinically and radiographically after every 2 cycles; baseline PET (within a week before treatment initiation), day 8 PET (after the first chemotherapy
course) and end of chemotherapy PET studies were performed. Qualitative (visual) and semiquantitative (standard uptake value, SUV) analysis of the PET data were performed – the SUV is a numerical value indicating the degree of tracer uptake. In the 6 patients who achieved a response to treatment (by clinical and conventional imaging criteria), 18F-FDG uptake diminished substantially: median SUV at baseline 7.65 (range 3.4–12.3); 5.7 (range 2.8–7.6) at day 8; and 1.2 (range 0.99–1.3) at the end of the planned 6 cycles of chemotherapy. Three patients who achieved stable disease as best response had no significant qualitative or semiquantitative reduction in FDG uptake. Non-responding patients also had no significant modification at day 8 from baseline FDG levels. These studies therefore indicate that FDG PET scanning of metastatic breast cancer shows a rapid and significant reduction in glucose metabolism in responding patients, whereas no significant reduction is seen in non-responding patients or patients with stable disease.

Radiofrequency ablation/laser therapy

Early assessment of complete tumour destruction following radiofrequency (RF) ablation and subsequent follow-up of RF ablation sites is difficult with conventional imaging; ultrasound, CT and MRI all have limitations with regard to sensitivity and specificity. PET is a modality which is particularly useful in this regard, enabling both early assessment of complete or incomplete tumour destruction and also being a sensitive and accurate modality in subsequent follow-up.7–9

Carditello et al8 assessed treatment response of liver metastases from a number of different primaries (including breast), while Donckier et al9 carried out a larger series (colorectal hepatic metastases being assessed). In this series, 28 lesions were assessed in 17 patients, CT and FDG PET being performed preoperatively, at 1 week, 1 month and 3 months post RFA. In 24/28 lesions, PET and CT were negative post RFA, and none of these patients subsequently developed local recurrence. In 4 patients, PET at 1 week and 1 month showed recurrence, CT being negative. Recurrence was confirmed in 3 out of these 4 patients by biopsy, recurrence in the 4th patient being confirmed by follow-up. One of the key points of this paper is that PET seems to be a useful modality for the early detection of incomplete tumour destruction; this is a difficult distinction with anatomical CT/MRI imaging.

Bone response assessment

Response assessment of bony metastatic disease is a difficult area with conventional imaging. Whereas assessment of disease progression with CT, MRI or bone scan for example is straightforward, determination of response or evaluation of the presence of active disease (as opposed to inactive disease) is problematic. This is because once a lesion is present on CT (bony windows) or MRI, the bony texture/destruction will clearly not return to normal, often remaining relatively abnormal (and static). 99mTc MDP bone scintigraphy is also relatively non-sensitive as visualisation of lesions
depends on an osteoblastic response, which often lags behind changes in the tumour component itself.

FDG PET is an excellent modality to assess bony response\textsuperscript{10} (Figure 7.4). Viable tumour cells only show significant FDG uptake and thus response assessment of bony lesions can be performed early and accurately. Bony windows of the CT correlate (of the PET/CT), demonstrating the underlying anatomical bony change (lysis, sclerosis, cortical expansion/disruption, vertebral body collapse, soft-tissue change or pathological fracture).

**Response to radiotherapy**

The evaluation of residual/active metastatic disease following radiotherapy treatment, for example in the brachial plexus, is difficult with conventional imaging in a proportion of patients. PET/CT can be useful in this regard but there are limitations with this modality. Some FDG uptake is observed at the radiotherapy site for a short-term period (of the order of a few weeks at least) after treatment as a result of (benign) granulation tissue uptake and macrophage activity. Fortunately, however, immediate post-radiotherapy imaging is usually not clinically required.

**RECURRENT DISEASE**

PET/CT is an extremely useful modality in defining and restaging disease recurrence. It is not highly accurate in defining local recurrence in the breast, because of the limitations as described for primary breast cancer, but it is currently the most accurate modality available to define metastatic disease recurrence and to restage metastatic disease extent. PET/CT is particularly effective relative to other modalities in the context of bony disease, difficult-to-image sites, post-surgery and post-radiotherapy\textsuperscript{11–14} (Figure 7.5).

Although MRI is clearly an accurate modality in the assessment of bony disease, PET has the advantage of being a whole-body technique, and is effective in the evaluation of indeterminate bony lesions. This also applies to soft-tissue sites such as the brachial plexus. The differentiation of disease recurrence as opposed to radiation damage causing unilateral upper limb oedema is a not uncommon clinical problem in the follow-up of patients with breast cancer. Although MRI will usually accurately define recurrent disease in this setting, it is well recognised that a small number of MRIs will be indeterminate: in these cases, diffuse altered signal change is usually observed in the brachial plexus, as opposed to discrete ‘measurable’ masses, which would indicate disease recurrence. Hathaway et al\textsuperscript{15} assessed 10 patients with suspected locoregional disease involving the supraclavicular fossa/brachial plexus with MRI and PET. MRI was diagnostic for tumour in 5 patients and indeterminate in 4 patients. PET positively identified tumour in all 9 patients, being particularly helpful just outside the region of the axilla and in the chest wall. In the case of
an equivocal or ‘negative’ MRI with a high index of clinical suspicion, PET is nearly always an extremely useful test for the brachial plexus, absolutely and accurately defining as to whether recurrent disease is present or not (Figure 7.6). If equivocal conventional imaging findings are obtained, as opposed to repeating MRI or other imaging at an interval (3–6 months for example), a PET/CT will usually provide a categorical answer regarding disease status.

Rising tumour markers, unknown cause

PET/CT is recognised as being an indicated investigation in the evaluation of patients with a tumour of unknown primary and for patients with the paraneoplastic syndrome. It is also useful specifically in breast cancer in the context of patients with...
Figure 7.5  Recurrence, restaging and assessment of treatment response. A 69-year-old female with known (biopsy-proven) anterior chest wall recurrence of breast cancer. Restaging PET/CT shows of the order of 12 focal sites of FDG uptake in the anterior chest wall (cutaneous/subcutaneous and related to chest wall musculature), together with FDG uptake in left axillary adenopathy, indicative of sites of disease recurrence (a and b). However, no visceral (pulmonary, hepatic) or bony sites of recurrence are defined. (c) A subsequent follow-up PET/CT (c) performed after letrozole therapy (ER+ve tumour) shows an excellent metabolic response, no metabolically active disease being defined on this study (confirming a very good clinical response). This study also demonstrates the utility of PET in ‘difficult-to-image sites’. Contrast-enhanced breast MRI is the only other imaging test that would reliably depict disease at this site. Breast MRI does not stage the remainder of the body and treatment response is also categorically shown on PET, ‘complete response’ being a more difficult judgement on MRI.
Figure 7.6  Disease recurrence. A patient with a 19-year ‘disease-free interval’ after treatment (including radiotherapy) for a left-sided lobular breast cancer. Increasing left upper limb lymphoedema. Clinical evaluation, ultrasound, CT, MRI brachial plexus and percutaneous biopsy negative/equivocal; recurrent breast cancer. PET/CT shows focal sites of intense FDG uptake in the left axilla/neck, indicative of sites of active tumour. (Image a showing sagittal, coronal and axial fused PET/CT images and image b showing axial CT and fused PET/CT images.) Note the superficial (anterior) skin breakdown and ulceration shown in the left superior chest wall in addition (particularly well shown on the axial, images a and b). The question of ‘disease recurrence or treatment/radiotherapy-related lymphoedema’ usually occurs of the order of years after radiotherapy. PET is therefore an effective modality; some radiotherapy-related FDG uptake is observed for at least a few weeks after radiotherapy, but intense (benign) uptake is certainly not usually observed >6 months after radiotherapy.
elevated CA 15-3 and/or CEA tumour markers in otherwise apparent remission.\textsuperscript{16–18} Suarez et al\textsuperscript{16} performed PET in 45 women in apparent clinical and imaging remission from histologically proven breast cancer, in whom CA 15-3 and/or CEA were elevated. PET results were validated by histological sampling wherever possible, otherwise by other imaging (X-ray, ultrasound, CT, MRI) and/or by clinical follow-up of at least 12 months. A total of 54 sites of focal intense FDG uptake were shown in 27 patients (19 skeleton, 18 lymph node sites, 5 liver, 5 pelvic, 1 lung, 1 pericardium, 1 pleura, 1 contralateral breast, 2 peritoneum and 1 thyroid bed), with 48 of these lesions subsequently being proven to be metastases. In 11 further patients, 9 true-negative and 2 false-negative results were obtained. The sensitivity in this series was 92\%, specificity 75\%, PPV 89\%, NPV 82\% and accuracy 87\%; Liu et al\textsuperscript{17} retrospectively evaluating 30 patients in a similar series, found a sensitivity of 96\% and an accuracy of 90\%. PET/CT is therefore a useful technique for detecting recurrent disease in patients with elevated tumour marker levels of unknown cause, and may have an important clinical impact on the management of these patients.

\textbf{CURRENT/FUTURE CLINICAL PRACTICE}

Given the current resource limitations of PET/CT in the UK and a number of other countries, conventional work-up/assessment, bone scan and CT will remain the workhorse modalities to define metastatic/recurrent disease and assess treatment response. Clearly, CT is a suitable modality in the vast majority of patients (\textgreater 99\%) in this regard. We currently recommend that PET/CT should be performed in the very small percentage of patients where there is true clinical or imaging uncertainty regarding recurrent or metastatic disease status or where treatment response cannot be assessed by other means, and where clinical management will be affected by the result.

A further important development which may occur is the development of more tumour-specific radiotracers suitable for clinical practice: \textit{18F-FDG} is not truly tumour specific; exciting ligands (which are currently under research development) for breast cancer are tracers used to target ER, HER-2 and EGFR, for example. As PET/CT becomes more widely available – which is now likely to occur over the next few years in the UK and a number of other countries – then, clearly, patient management pathways will change and PET/CT is likely to be used early and extensively in the management of patients with metastatic breast cancer. Functional (anatomolmolecular) imaging will have an increasing role to play in patient management in years to come.

\textbf{CONCLUSIONS}

PET/CT, a relatively new imaging modality, is fundamental for the appropriate and optimal management of selected oncology patients. With current clinical radiotracers and technology, it is not accurate enough to be used routinely in the context of
primary breast disease or axillary nodal assessment; the converse is true regarding the assessment of recurrent or metastatic disease and treatment response. It is currently the most accurate imaging modality available for defining recurrent or metastatic disease, a key advantage being a whole-body assessment with one test (PET/CT is highly accurate for soft tissue and bony sites of disease). Although current 18F-FDG PET/CT cannot rule out microscopic disease, it does provide a reliable assessment of the true extent of macroscopic metabolically active disease. It is also a highly effective and useful test to define treatment response: its key strengths are early response assessment and the differentiation of active from inactive disease sites. Bony response assessment, which is difficult with other imaging approaches, is a particularly exciting area. Although PET/CT is now widely available in some countries, scanner resource availability is currently limited in a number of countries, including the UK. As the modality becomes more widely available in the coming years, patient management pathways will be change; PET/CT will be increasingly used early in the patient journey.

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INTRODUCTION

External beam radiotherapy (teletherapy) is a highly cost-effective and reliable modality in the palliation of metastatic breast cancer. It is useful in the management of localised lesions that can be targeted, and contributes to symptom relief through local control but rarely to survival benefit. In this chapter, theoretical and practical issues surrounding the role of radiotherapy in the management of bone deposits, chest wall disease, and choroidal and cerebral metastases will be discussed.

FRACTIONATION

When considering palliative radiation in general, it is important to address the issue of dose fractionation. External beam radiotherapy is delivered in a number of treatments (fractions) that make up the overall dose. The total radiation dose (measured in grays, abbreviated Gy) will have a biological effect that is dependent on the number of fractions, the dose per fraction, the total time taken to deliver all treatments and the radiosensitivity of the tissues being irradiated. The biological effects of treatment may be crudely separated into acute and late effects, which are in turn mediated by the rate of turnover in the tissue under study. In radical treatments, the therapeutic ratio is respected by delivering a dose unlikely to cause late effects while maximising acute effects within the tumour; this is achieved by delivering doses in the range of 1.8–2.2 Gy five times weekly over 5–7 weeks. In the palliative setting, much larger doses per fraction may be delivered over shorter overall treatment times in order to achieve rapid tumour kill. This approach is unlikely to achieve the level of cell kill required to completely eradicate tumour at the site, and normal tissues will undergo late changes that are not usually clinically relevant in the palliative patient’s lifetime.

Through a combination of radiobiological modelling and clinical experience the trend in palliative fractionation has been to give smaller numbers of treatments at
higher doses per fraction (hypofractionation). There are clear advantages to the patient: clinical isoeffectiveness, including dose-limiting complications, with a reduced number of visits for treatment. Most palliative treatments may therefore be delivered in 1–5 fractions, with the caveat that in those patients where survival may be measured in years a larger number of smaller doses may be appropriate.

**BONE METASTASES**

Bone is the most common site of metastatic disease in breast cancer and ultimately may affect up to 70% of women with metastases. Disease will most often be found in the axial skeleton but all bones may be affected including base of skull and skull vault. The prevalence of bone metastases is twice the incidence, and the prevalence is likely to increase as systemic therapies for metastatic disease improve in efficacy. Two-thirds of patients with bone metastases will experience skeletal-related events (fracture, orthopaedic intervention, spinal cord compression or radiotherapy).

Median survival after development of bone metastases is 19–25 months, with a median survival of 12 months following pathological fracture. There is a long tail on the survival curve, with a small number of very long-term survivors. Good prognostic factors for survival are low histological grade, positive oestrogen receptor status, bone disease at initial presentation, a long disease-free interval and increasing age. Bone-only disease has a better prognosis than disease associated with visceral involvement, and disease may remain confined to the skeleton.

Bone-dominant metastatic disease may be adequately controlled by endocrine therapies and bisphosphonates. However, radiotherapy remains an important and highly cost-effective part of the treatment algorithm. Indeed, patients receiving radiotherapy for bone metastases form the largest group of patients receiving any form of palliative radiotherapy. It is of particular benefit for those patients with painful bone disease or spinal cord compression and as an adjuvant to orthopaedic intervention (either prophylactically or after pathological fracture), and can be a useful treatment even in the face of a large burden of metastatic disease due to the high response rate and low toxicity.

**Effect of radiotherapy on bone**

Within bone affected by metastatic tumour there are conflicting processes of destruction and new bone formation. The majority of bone destruction is mediated by osteoclasts, which in turn are influenced by humoral factors released by tumour. New bone formation is predominantly reactive (as seen in healthy bone after fracture), but may be exuberant, generating new bone that often lacks the strength of normal lamellar bone. Whereas it is often not possible to determine histologically the balance of destruction and new bone formation, radiological studies may indicate whether the metastatic process is predominantly sclerotic, lytic or mixed. Another non-malignant
process increasingly affecting the bones of women with breast cancer is osteoporosis, which is associated with premature ovarian ablation and endocrine therapies and which may exacerbate the local effects of bone metastases.

Bone pain is the most common complication of metastatic bone disease. Such pain may be either nociceptive (mediated by prostaglandins, substance P and other cytokines) or neuropathic, usually as a result of bone destruction (and increased resorption), periosteal irritation and nerve entrapment. The mechanism by which radiotherapy improves this pain is not well understood. It has been recognised for many years that the very rapid improvement in pain that is often associated with radiotherapy treatment makes it unlikely that the effect is mediated entirely through a reduction in tumour size.4

Although it has been postulated that a prompt reduction in peritumoural oedema may rapidly relieve neuropathic pain, recent research has focused on markers of bone turnover. A study of urinary markers of bone resorption (pyridinoline and deoxypyridinoline), measured before and at 4 weeks after radiotherapy for metastatic bone pain, demonstrated an association between radiotherapy efficacy and low marker concentrations pre- and post-treatment. This finding supports a theory that relief of metastatic bone pain by radiotherapy relates to effects on bone physiology rather than direct tumour effects.5

Further work in other solid malignancies lends weight to the theory that mediation of osteolysis is an important aspect of the radiotherapy effect and has identified the urinary marker N-telopeptide as a potentially useful predictive factor.6

**Fractionation in the treatment of localised bone metastases**

For many years, fractionation has been the major focus of research into radiotherapeutic treatment of bone metastases. The body of evidence addressing this question since 1982 now amounts to at least 22 published trials, 5 published overviews, an overview of the overviews and a Cochrane review! These trials have studied over 6000 patients. Despite these numbers, only a small fraction of the total number of patients treated over this time have entered clinical trials; the largest single randomised study – The Dutch Bone Metastasis Study (DBMS)7 – randomised only 29% of eligible patients. All of the randomised studies included multiple different tumour types, but in all cases breast cancer formed the predominant patient group. In the DBMS, 49.7% of the 1157 patients randomised had breast cancer.

In the most recent overviews8,9 neither overall response rate nor complete response rate (by intention to treat) was significantly different in the multiple- or single-fraction arms of the study (Table 8.1). A single fraction of 8 Gy delivered for palliation produced a 60% response rate on intention-to-treat analysis. Approximately one-third of patients treated had a complete pain response. Overall, mean time to response was 3 weeks and mean duration of remission was 18 weeks, although in breast cancer
patients in the Dutch study response rates were higher than average (78%) and response rates longer (24 weeks) than all other tumour types.

The consistently repeated message from these studies and overviews is that multiple fractions of radiotherapy offer no advantage over a single fraction of treatment. This finding represents a clear advantage for the patient in reduced inconvenience and for the treating centre in increasing treatment capacity. Delivering treatment as a single fraction further increases the cost efficiency of an already cost-effective treatment.10 The estimated cost of a single fraction of radiotherapy for pain is £280 for each effective treatment, as compared with £2200 for a single intravenous infusion of bisphosphonate.11

Despite this considerable body of evidence (which continues to grow), the ongoing controversy is reflected in a discrepancy between published recommendations and clinical practice. Some of this relates to considerable methodological problems with the studies (Table 8.2), but persistent physician bias must also exist to explain the continued variation in prescribing habits.

Retreatment of bone deposits

Critics of single-fraction treatment have pointed to the higher levels of retreatment required in the single-fraction arms of the randomised studies. Retreatment after a single fraction is recorded for 21.5% of patients as compared with 7.4% of those receiving multiple fractions. However, pain relief levels are similar, and the higher retreatment rates are likely to reflect a bias amongst treating physicians not to retreat those patients who have previously received a higher dose through multiple fractions. This view is strongly supported by reanalysis of the DBMS, controlling for the effect of retreatment.12

What dose should be given to a previously treated area?

Retreatment is worthwhile and produces good responses. Amongst breast cancer patients experiencing progressive pain who had previously responded to treatment,
89% responded again to retreatment. Perhaps more importantly, 82% of those who had not previously responded gained a response to a retreatment.

Many physicians have taken the view that if the patient previously received a single fraction yet progressed or failed to achieve a complete response, then the retreatment should be delivered to a higher fractionated dose. Neither retrospective studies\(^\text{13}\) nor final analysis of the retreatment data from the Dutch bone study support this view and a single fraction may be delivered for retreatment as efficaciously as multiple fractions.

It is worth noting that if patients treated with a single fraction required retreatment at a rate of 21.5%, the overall number of fractions delivered to the population would still be 4 times less than if 5 fractions were given as first treatment, even if none of the latter required further treatment. This reflects a significant impact on radiotherapy capacity. Yet, in a recent audit of all palliative radiotherapy practice within the UK, only 37% of treatments delivered were single fractions.

**Neuropathic bone pain**

Single-fraction treatment has also been tested against multiple fractions in the treatment of neuropathic bone pain, where it has been argued that multiple fractions are required to reduce tumour mass and relieve pressure on nerves. The Trans-Tasman group\(^\text{14}\) randomised 272 patients with neuropathic bone pain between 20 Gy in 5 fractions and a single 8 Gy fraction. The difference between overall response rates in the two arms (53% for single fraction and 61% for multiple fractions) was small and not statistically significant \((p=0.18)\). It therefore seems appropriate to conclude that whereas 20 Gy in 5 fractions may be a slightly better choice for patients with neuropathic pain, a single fraction is still entirely appropriate for patients with poor performance status, limited prognosis or difficult access to radiotherapy facilities.

**Radiotherapy for bone metastases: techniques**

Magnetic resonance imaging (MRI) of the whole spine is recommended prior to the treatment of spinal lesions, as this investigation reveals excess lesions in a large
number of cases\textsuperscript{15} as well as allowing calculation of treatment depth. For other sites, information from bone scan and plain radiographs is usually sufficient.

The patient requires immobilisation before simulation and treatment. In the majority of patients rigid cushioning will be adequate but vacuum bag fixation may be required to assure the comfort of some patients. Rigid fixation is almost never required. Fluoroscopic simulation should always be available and, with treatment possible from under the couch, it should not be necessary to move the patient to an uncomfortable and unstable prone position.

For the majority of sites, treatment should be prescribed as an applied dose for single-incident fields and a mid-plane dose for opposed fields. The treatment volume should include at least one vertebral body above and below the painful vertebra(e) and a minimum of a 2 cm margin on long bones.\textsuperscript{16} Because there is a high rate of retreatment or later treatment of adjacent areas, simulation and verification films are recommended to document target localisation along with permanent skin marking of the treatment field with tattoos. When orthovoltage energies are used, the dose correction ($f$ factor) that may be applied to compensate for the higher absorbed dose in bones from photons in the kilovolt range is not routinely recommended, particularly as these energies should be restricted to treatment of superficial bones such as ribs, sternum and clavicle.

For spinal bone metastases, it is suggested that the radiation dose should be prescribed to mid-vertebral body. This requires, as a minimum, a lateral spine X-ray or a CT image to determine the depth. If it is not possible to obtain exact measurement of cord depth, an averaged depth of 5 cm may be chosen. Prescribing to mid-vertebra should give a relatively homogeneous dose across the vertebral body. When the shoulders can be moved low enough, cervical spine metastases should be treated with lateral opposed fields to reduce exit-dose toxicity to the larynx and oesophagus.

Radiotherapy toxicity

The major toxicity of radiotherapy to bone is its effect on bone marrow. This cannot be avoided, since a dose of radiation as low as 2 Gy will arrest mitosis in erythropoietic cells. In terms of bone marrow regeneration, the amount of marrow included in the treatment volume seems to be a more important factor than the radiation dose delivered. If large volumes are treated with a single dose (as in wide-field radiotherapy), rapid compensation is observed. Normalisation of the full blood count does not necessarily indicate recovery of the irradiated marrow; however, since the response may occur within unirradiated marrow. After irradiation of smaller volumes the stimulus to the uninvolved marrow may be less significant and, paradoxically, compensation may be slower.\textsuperscript{17}

Longer-term recovery of marrow depends on the age of the patient and sequencing of therapies. Breast cancer patients heavily pretreated with chemotherapy are likely to have slower haemopoietic recovery after radiation; indeed, experience suggests that many of these patients will experience clinically relevant falls in haemoglobin after palliative radiotherapy treatment.
Normal bone formation is a relatively radioresistant process and bone healing continues after radiation doses in the therapeutic range. Healing and reossification is seen in 65–85% of lytic lesions after radiotherapy in unfractured bone. The process of reossification is relatively slow, however, and radiological evidence of the process may not be present until at least 6 months (Figure 8.1).

At higher doses of radiotherapy there are discrepancies in the literature over bone healing. Radiation doses above 30 Gy may prevent long bone healing, yet doses above 40 Gy may assist the healing of vertebral fractures. These results are not necessarily inconsistent: long bones repair by a process of endochondral bone formation mediated by a relatively radiosensitive chondrogenic phase, whereas vertebrae depend on direct osteogenesis for intramembranous bone formation, which is more radioresistant.

**Adjuvant radiotherapy following surgical fixation**

Patients whose metastases involve the cortex of long bones preserve mobility for longer with improved pain control and likely consequent gains in quality of life if orthopaedic intervention is offered in a timely manner before pathological fracture occurs. The theory that radiotherapy interferes with osteogenesis (see above) has been invoked to argue that adjuvant radiation should not be given after surgical fixation. It is clear, however, that failure to follow this practice leads to high rates of failure of the surgical fixation, regardless of theoretical considerations. Adjuvant radiation should therefore be considered standard and, since there is no evidence to suggest that it compromises post-surgical recovery, should be given as promptly as is practicable.

**Wide-field radiotherapy**

Many patients have multiple, widespread bone metastases. For some of these patients, irradiating multiple areas of the skeleton simultaneously is an attractive policy that will reduce the overall number of treatments for the patient and may treat early lesions prophylactically. As predicted by the gate theory of pain, restricting treatment to the most painful lesion in patients with multiple bony deposits often does not improve the patient’s symptoms, as adequate local treatment simply ‘unmasks’ pain from the other untreated lesions.

For these reasons the practice of wide-field radiotherapy (WFRT) has developed. The term WFRT is preferred to hemi-body irradiation, as it is often not the hemi-body which is covered by these treatment fields. Within the RTOG (Radiation Therapy Oncology Group) studies of this technique, in which the majority of patients were men with prostate cancer and the number of breast cancer patients was small, the approach was associated with appreciable haematological toxicity (12% of patients experienced grade 3–4), and even after premedication with steroids many patients experience immediate and delayed emesis. Because of concerns about longer-term erythropoiesis in patients who may receive further multiple lines of chemotherapy, WFRT has become less popular in breast cancer than localised radiotherapy.
Figure 8.1  X-rays taken prior to (left panel), immediately after (right panel) and 1 year after (lower panel) surgical fixation and adjuvant radiotherapy of a large lytic deposit. (a) Plain radiograph of hip showing lytic metastasis in femoral neck. (b) Metastasis internally fixed with surgical nail and palliative radiotherapy delivered. (c) Patient’s hip radiograph 6 months later showing recalcification around the nail following radiotherapy.
Further research directions

The number of methodological problems in previous bone pain studies led to formation of an international consensus study group who have worked to identify future criteria for research and to achieve consensus on the following:

- eligibility criteria for future trials
- pain and analgesic assessments
- radiation techniques
- follow-up and timing of assessments
- parameters at follow-up
- endpoints
- reirradiation
- statistical analysis.\(^\text{16}\)

It is expected that all future trials will be designed according to this consensus (Table 8.3).

### Table 8.3 Ongoing and future research priorities in palliative bone radiotherapy

<table>
<thead>
<tr>
<th>Question</th>
<th>Trial arms</th>
<th>Trial</th>
<th>Trial status</th>
</tr>
</thead>
<tbody>
<tr>
<td>What dose is required for neuropathic bone pain?</td>
<td>20 Gy in 5 fractions vs 8 Gy in 1 fraction</td>
<td>TROG</td>
<td>Closed</td>
</tr>
<tr>
<td>What dose is required for reirradiation?</td>
<td>20 Gy in 5 fractions vs 8 Gy in 1 fraction</td>
<td>SC20 MRC/NCRN</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Is an infusion of bisphosphonate as effective as radiotherapy for relieving pain?</td>
<td>8 Gy in 1 fraction vs Single iv infusion of ibandronate</td>
<td>RIB (MRC/NCRN)</td>
<td>Recruiting</td>
</tr>
</tbody>
</table>

TROG = Trans-Tasman Radiation Oncology Group; RIB, Radiotherapy or Ibandronate study (Medical Research Council/National Cancer Research Network); SC20, a phase III international randomised trial of single vs multiple fractions of reirradiation of painful bone metastases.

### Further research directions

The number of methodological problems in previous bone pain studies led to formation of an international consensus study group who have worked to identify future criteria for research and to achieve consensus on the following:

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### RADIOTHERAPY IN THE TREATMENT OF LOCAL RECURRENCE AND FUNGATION

#### Local cutaneous metastasis in chest wall

Treatment of extensive local recurrence or cutaneous metastasis to the chest wall presents particular problems in those cases where the chest wall has previously been
irradiated in the adjuvant setting, as is often the case (Figure 8.2). Further delivery of radiation doses in the therapeutic range would exceed normal tissue tolerances and may be expected to lead to ulceration or necrosis of underlying soft tissue. For these reasons, radiotherapy is often avoided and endocrine or chemotherapy treatment preferred. When these options have been exhausted, radiotherapy may offer useful palliation for unpleasant fungation or malodorous recurrence and may ‘dry’ the affected tissues, reducing the need for dressings and analgesia.

In order to reduce toxicity to underlying connective tissues from retreatments, the beam may be delivered using electrons rather than photons. The physical properties of electrons are such that the energy required for cell kill is transferred over short distances such that deeper connective tissue and lung receive a much lower radiation dose. The technique is occasionally limited by the requirement to treat a relatively flat surface; where disease extends around the curvature of the chest wall, multiple fields (with problems of overlap) may be necessary to achieve coverage.

Photon fields may be delivered either directly or as a reprise of the previous tangential fields. In choosing a dose/fractionation schedule, there needs to be consideration of the likelihood of late effects of overdose through retreatment becoming clinically significant within the patient’s expected lifetime. The prescriber should also be aware that some radiobiological recovery of normal tissues takes place over years.

**Hyperthermia**

In an attempt to overcome the problems of normal tissue tolerance, hyperthermia has been used as a method of increasing therapeutic ratio. Hyperthermia enhances the cytotoxic effects of radiotherapy and if delivered synchronously can increase cell kill. Since heating of tumour cells to 41–45°C is itself cytotoxic to both tumour and normal tissues, tumours must be selectively heated if the therapeutic ratio is to be increased.

This is usually achieved by methods that rely on the thermal absorbance of the soft tissue (electromagnetic current or ultrasound), with a cooling water bolus at the surface. All methods risk hot spots within the treatment field, which may affect

![Figure 8.2 Fungating chest wall recurrence requiring palliation.](image)
the patient’s ability to cope with the treatment or cause burns at the edge of the treated area. Current technology limits the amount of heat that can be effectively delivered to tumours deeper than 3 cm.

Initial studies were small and therefore an international effort to randomise patients to larger studies in Canada, the UK and Europe took place in the late 1980s. These studies failed to recruit large numbers and reported a combined analysis of 307 breast patients in 1996. All patients had locally recurrent breast cancer and the majority (68%) had previously received radiotherapy. Only half of the patients had evidence of metastatic disease (although only a Canadian study mandated comprehensive staging).

The studies delivered radiotherapy doses in the order of 28–32 Gy in 8 fractions, treating twice a week with or without heating to 43°C, and showed a convincing benefit for hyperthermia in achieving local control (Table 8.4). No survival benefit was shown for the approach, and curiously no benefit for hyperthermia in previously unirradiated patients (where a biological rationale for radiosensitisation by hyperthermia still exists despite the higher radiation doses used).

In the collaborative study, only 28% of patients had received prior systemic hormone therapy and 9.8% prior chemotherapy. Developments in these areas have largely superseded hyperthermia and radiation as a treatment in this situation, and because of the practical and radiobiological concerns, the technique is rarely used in the UK, despite advocacy in Europe.

### Table 8.4 Hyperthermia trial data

<table>
<thead>
<tr>
<th></th>
<th>Radiotherapy alone</th>
<th>Radiotherapy with hyperthermia</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>135</td>
<td>171</td>
<td></td>
</tr>
<tr>
<td>CR overall</td>
<td>55 (41%)</td>
<td>101 (59%)</td>
<td>2.3 (1.4–3.8)</td>
</tr>
<tr>
<td>CR in area not previously irradiated</td>
<td>27/45 (60%)</td>
<td>32/51 (63%)</td>
<td>1.24 (0.46–3.32)</td>
</tr>
<tr>
<td>CR in previously irradiated area</td>
<td>28/90 (31%)</td>
<td>68/120 (57%)</td>
<td>4.7 (2.4–9.5)</td>
</tr>
</tbody>
</table>

Toxicities:
- Blistering: 2% (Radiotherapy alone), 11% (Radiotherapy with hyperthermia)
- Ulceration: 2% (Radiotherapy alone), 7% (Radiotherapy with hyperthermia)

CR, complete response; OR, odds ratio; CI, confidence interval.

* Receiving ‘radical’ doses in region of 40 Gy.

† Receiving palliative doses in region of 28–32 Gy.

### RADIOTHERAPEUTIC MANAGEMENT OF CHOROIDAL METASTASES

Choroidal metastasis, a devastating complication of breast cancer, is not uncommon (Figure 8.3). In prospective studies asymptomatic disease has been documented in 5%...
of patients with metastatic breast cancer, and symptomatic disease in 1–2% of patients. In 41% of these patients the metastases were bilateral. Although the development of choroidal disease is associated with poor prognosis (median survival 10 months) the complication of reduced visual acuity is devastating and therefore palliative treatment to prevent deterioration is warranted. Prior to the advent of highly active chemotherapies, radiotherapy was the treatment of first choice, with an 80% response rate and complete resolution in 25%. More recently, authors incorporating systemic therapies into their treatments (in 55% of cases) have reported complete regression in 57.8% of eyes treated. No chemotherapy study has reproduced the results of the early radiotherapy studies.

The authors know of no published randomised studies of dose for treatment. The largest prospective series, the ARO-95-08 from Germany, recruited 56 patients (65 eyes), of whom 62% had breast cancer. Patients were treated with 40 Gy in 20 fractions. Visual acuity was stabilised (50%) or improved (36%) for the majority and no treated asymptomatic patients (n = 15) developed ocular symptoms during follow-up. The 70% of patients in the study with unilateral disease were treated with a unilateral radiotherapy beam arrangement; that none of these developed clinically apparent disease contralaterally suggests that a lower total dose may have been adequate for tumour control.

In delivering the treatment, modern computed tomography (CT)-planned virtual simulation enables the application of a simple direct beam that targets the choroid and is angled posteriorly to avoid entering the lens of either eye. Where this is not available, a 4 cm × 4 cm field covering the bony orbit but sparing the lens anteriorly may simply be angled posteriorly by 5° to reliably spare the contralateral eye.

RADIOTHERAPEUTIC MANAGEMENT OF CEREBRAL METASTASES

For patients with breast cancer, the development of cerebral metastases is associated with significant physical and psychological distress. Quality of life may be severely
affected by neurological symptoms accompanied by diminished independence, and the prognostic implications are bleak. Unfortunately, this development is relatively common, and conventional treatment has been limited in its efficacy.

According to population-based studies, brain metastases are diagnosed in approximately 5% of women with breast cancer. Postmortem examinations have suggested that the actual incidence may be as high as 20–30%, with many cases going unnoticed during the patient’s lifetime. There is a growing feeling amongst clinicians that the incidence of cerebral metastases is increasing, particularly in heavily treated patients who have lived with metastatic disease for a number of years. Recent reports have documented the incidence of cerebral metastases in women receiving combination chemotherapy for advanced disease to be between 25 and 48%.27,28 Many clinicians have also suspected patients with disease overexpressing Her-2 to be at increased risk: of two small retrospective studies addressing the issue, however, one study found no increased incidence in this group,27 whereas the other study demonstrated a non-significant reduction in time to diagnosis of brain metastases amongst the Her-2 overexpressing patients.29

Although inconclusive, these figures illustrate a number of issues. First, the need for effective treatment is greater than ever. Secondly, cerebral metastases can develop and progress in the face of effective systemic treatment. Thirdly, management of disease in the brain has failed to keep pace with the remarkable improvements in systemic therapies that have taken place over the past 20 years. Another consequence of improved control of disease at other sites is that a number of patients with cerebral metastases survive long enough to experience the potentially devastating long-term effects of radiation upon the normal brain. Care must therefore be taken to ensure that improvements in the efficacy of treatment do not occur at the expense of increased toxicity.

**Whole-brain radiotherapy**

For many years, the standard therapy for symptomatic brain metastases has been whole-brain radiotherapy (WBRT). Various factors underlie this approach:

- adenocarcinoma of the breast is generally radiosensitive
- metastases are likely to be numerous and at multiple intracranial locations, even if not all are appreciated by standard imaging
- most systemic treatments do not penetrate the blood–brain barrier effectively and so are unlikely to be delivered to the target lesions at effective concentrations.

Since the prognosis for this patient group is poor, attempts at radical dose treatments are rarely justified, so the dose of radiation applied is generally in the palliative range.

**WBRT technique**

WBRT is delivered using parallel opposed, lateral fields encompassing the contents of the cranium but avoiding radiosensitive normal tissues, particularly the eyes.
Megavoltage photon treatment using a linear accelerator has the advantage of reducing radiation dose to the scalp. Traditionally, patients have been immobilised using a personalised thermoplastic mask that is secured to the treatment couch, and the treatment fields simulated fluoroscopically. Some patients find immobilisation claustrophobic, however, so in many centres the palliative nature of the treatment has been acknowledged and patients are treated without rigid immobilisation devices. Similarly, treatment fields may be planned on the treatment couch using anatomical landmarks – the accuracy of the set-up can then be checked at the first treatment session using electronic portal imaging (Figure 8.4). Additional advantages of this more pragmatic approach are a reduction in number of patient visits and the opportunity to minimise delays in starting treatment. Both factors may be helpful in alleviating patient anxiety at what is often an emotionally demanding time.

**WBRT radiation dose**

The delivered dose of radiotherapy varies widely between centres. In many countries, the standard dose for WBRT is 30 Gy in 10 daily fractions, but alternative regimens range from 12 Gy in 2 fractions up to 45 Gy in 15 fractions. In many cases, the dose and duration of treatment will be determined by the patient’s general condition and performance status. Outpatient treatment is entirely appropriate in most cases. In the UK, 20 Gy in 5 daily fractions is commonly delivered on the basis that a more prolonged course of treatment is not justified for patients whose life expectancy is a matter of weeks.

This array of treatment regimens reflects the paucity of evidence to support the use of any particular radiation schedule. The vast majority of studies have been retrospective, and thus subject to the important confounding factor of patient selection. Generally, patients offered more aggressive regimens are those with better performance status, whose prognosis has been shown to be better regardless of treatment.
Most of the published data are derived from heterogeneous groups of patients with various primary tumours, amongst which breast cancer patients are often in a minority. Very few randomised trials addressing radiation dose have been conducted. Hence, interpretation of the available data is problematic.

Median survival from time of diagnosis of brain metastases for patients receiving symptomatic treatment only has been reported as 4–6 weeks, whereas patients receiving WBRT have a life expectancy of 4–6 months. Rates of symptomatic response have been quoted as 60–85%, but clinical experience suggests that steroid treatment alone is often associated with a prompt improvement in neurological symptoms. In one study, 67% of patients were able to discontinue steroids shortly after completing radiotherapy, although 38% restarted this medication during the follow-up period.30 Perhaps more relevant was the observation that 30–40% of surviving patients showed improved or stable functional status (Karnofsky performance status) at 1- and 3-month follow-up. Radiological response rates are rarely reported, and the available data are often biased by preferential imaging of patients experiencing new or worsening neurological symptoms.

The majority of attempts to improve response rates and survival by increasing radiation dose have been unsuccessful. In those studies where a survival benefit was identified, this was attributable to beneficial effects of the higher dose on a small subgroup of patients displaying favourable prognostic features.31 The largest randomised controlled study of radiation dose was the RTOG 9104 study in which the control protocol was 30 Gy in 10 daily fractions and patients in the experimental arm received accelerated, hyperfractionated treatment of 32 Gy in 20 twice-daily fractions to the whole brain and a boost of 22.4 Gy in 14 fractions. No difference in median or 1-year survival was demonstrated.32 Amongst the published data derived specifically from breast cancer patients, the only consistent predictor of improved survival is performance status.30,33

**WBRT toxicity**

Acute toxicity associated with WBRT includes alopecia, which is inevitable but temporary, and fatigue and nausea, one or both of which occur in 8–12% of patients. The latter two may be ameliorated by corticosteroid and antiemetic therapy. A rare but debilitating complication of WBRT in adults is ‘somnolence syndrome’, a subacute consequence of cranial irradiation that occurs in up to 60% of children receiving such treatment for leukaemia. The clinical features are overwhelming fatigue and apathy, typically commencing 4–6 weeks after completion of radiotherapy. The syndrome is self-limiting, and there is some evidence for a partial symptomatic response to steroids, but the development of this complication in a woman with a life expectancy of only a few months clearly represents a failure of palliative therapy. Unfortunately there are few data to inform any estimate of the risk of somnolence for an individual. In a small prospective study of patients receiving high-dose cranial radiotherapy for primary brain tumours, the incidence of somnolence symptoms was 84%.34 In the setting of metastatic brain involvement, the dose of radiation delivered
is generally lower, but the volume of brain irradiated is greater. Specific questioning for and reporting of symptoms of somnolence would be a useful component of any future study in this area. At present, it is perhaps wise to inform patients of the nature of this possible complication, since its occurrence is usually associated with marked anxiety about the possible implications of the symptoms experienced.

Documentation of the late complications of WBRT has also been scanty, partly because of the poor prognosis of the patient group and partly because the symptoms of cerebral radiation toxicity overlap significantly with those of progressive disease. The most important manifestations of late radiation damage are white matter necrosis, which may occur as early as 6 months after treatment, and cerebral atrophy associated with vasculopathy, which becomes apparent after 1–10 years. Generalised clinical symptoms include lethargy, short-term memory loss and impaired cognitive function. More specific symptoms may arise from areas that were subjected to a higher radiation dose, or to localised damage of vascular origin. Symptoms do not always correlate with the radiological features of white matter changes and cerebral atrophy. In one retrospective study of patients who had received WBRT, actuarial rates of cerebral atrophy and white matter abnormalities, respectively, were 50% and 25% after 1 year, and 84% and 85% after 2 years. Clinical symptoms of late radiation toxicity at these time points occurred in 32% and 49% of patients, rising to 83% at 5 years.35

One of the few studies to address specifically the effect of WBRT on neurocognitive function demonstrated no significant change in Mini-Mental State Examination (MMSE) scores compared with pretreatment values. The capacity of this study to demonstrate an effect was limited by the short follow-up period (3 months). However, an important finding to emerge was that the average MMSE score of patients whose metastases were not controlled by treatment fell by a significant and clinically meaningful extent.36

Despite the generally disappointing overall results presented to date, it has been clear that a subgroup of patients with cerebral metastases has a substantially better outlook than the average, and that these patients might benefit from more intensive therapy. The results of neurosurgical intervention support this view. A randomised trial comparing surgical excision + WBRT against needle biopsy + WBRT in the treatment of solitary brain metastases (various primary tumour types) reported overall survival and duration of functional independence to be significantly longer in the resected group (median survival 40 weeks vs 15 weeks).37 Considering breast cancer specifically, retrospective data suggest that surgical excision may be associated with median survival rates of around 16 months in this highly selected patient group.38

**WBRT and surgery**

In many centres, neurosurgical excision of cerebral metastases is followed routinely by adjuvant WBRT. This approach is supported by two retrospective analyses that, subject to the usual concerns about patient selection, demonstrated delivery of postoperative WBRT to be associated with increased survival39 and time to neurological
A cautionary finding of the latter study was that 11% of irradiated patients surviving for more than 1 year developed severe radiation-induced dementia. In the context of increasing survival of patients with metastatic breast cancer, it may now be appropriate to reconsider the routine use of postoperative WBRT.

These considerations, and the awareness that craniotomy and metastasectomy are associated with considerable inconvenience, morbidity and risk, have contributed to increasing enthusiasm for alternative, non-surgical modes of localised treatment.

**Stereotactic radiotherapy**

Stereotactic radiotherapy involves the precise delivery of radiation to a localised target volume by relating its anatomical location to a three-dimensional image data set using numerical coordinates. The aim of treatment is to achieve a relatively high radiation dose at the tumour target while delivering a minimal dose to the surrounding normal tissue. Patient immobilisation is critical and requires the fitting of a rigid stereotactic frame to the patient’s head (Figure 8.5). This frame is in place during the imaging and treatment phases and enables precise and reproducible localisation of the target relative to components of the frame, and hence to the radiotherapy delivery system.

For the treatment of brain metastases, the dose to the tumour deposit is usually delivered in a single fraction, a scenario that has led to the widespread use of the term ‘stereotactic radiosurgery’ (SRS). It should be stressed that SRS is a non-invasive procedure that differs from stereotactic radiotherapy only in the magnitude of the dose delivered per treatment session. Two techniques are in general use. The first technique exploits the capacity of a linear accelerator (linac) to move through a predefined arc around
its isocentre while continuously delivering a collimated beam of X-rays (linac-based SRS – Figure 8.6). The second technique utilises a stationary treatment device that houses around 200 small radioactive sources (cobalt-60), the gamma radiation emissions from which are collimated into narrow beams that intersect at the site of the tumour. The most widely used machine of this type is the gamma knife (Figure 8.7).

Both linac-based and gamma knife SRS are capable of accurately delivering therapeutic single doses of radiation to cerebral metastases. Differences between the two techniques affect the internal and external dose gradients achieved, and the number

Figure 8.6 Reconstructed digital image showing arcing beams of a linear accelerator delivering stereotactic radiation to a single cerebral metastasis. (Courtesy of Dr M Brada and Mr K Burke, Royal Marsden Hospital, London.)

Figure 8.7 The multiple radioactive sources of the gamma knife machine and its treatment couch. (Courtesy of Dr PN Plowman, London Radiosurgical Centre.)
of lesions that can be treated in a single episode. Logistical considerations also mean that linac-based treatments usually take place alongside conventional radiotherapy and may thus be subject to more stringent time restrictions than might apply in gamma knife treatment units. Perhaps because of this, the gamma knife facility has more often been used to treat multiple deposits in a single session. This is clearly more convenient for the patient, although it does entail a lengthy period of immobilisation that requires sedation. At present, there is no evidence to suggest that either technique is associated with a superior outcome.

Patient selection is clearly an important component of this treatment strategy. Accuracy and homogeneity of the delivered dose fall as target volume increases, so many centres restrict treatment to tumour deposits no larger than 3 cm in diameter. Larger or irregularly shaped lesions may be treated by using multiple isocentres. The radiation dose prescribed varies between 12 and 20 Gy, with more conservative doses for larger lesions. The dose is usually prescribed to the 90% isodose, which corresponds to the tumour margin (Figure 8.8). Hypofractionated linac-based stereotactic radiotherapy regimens delivering 24 Gy in 4 fractions have been employed in the treatment of larger metastases.

Figure 8.8 Radiation isodose contours generated during planning of linac-based stereotactic treatment for a solitary cerebral metastasis. The treatment dose is prescribed to the 90% isodose contour at the tumour margin. (Courtesy of Dr M Brada and Mr K Burke, Royal Marsden Hospital, London.)
SRS toxicity

The evidence to date suggests that the risk of late toxicity associated with the delivery of large radiation doses in single fractions is largely counterbalanced by the superior dose distribution achieved. Cerebral necrosis has been reported in between 3 and 17% of patients, of whom the majority experienced symptoms. The risk of necrosis appears to rise with the volume irradiated: in one study the incidence at 5 years was 16% for tumours greater than 2 cm in diameter compared with 3.7% for smaller tumours.41 Haemorrhage is a rare complication, and long-term effects on cognition and memory have not been reported. Acute toxicity relates to the stereotactic frame, which can cause transient headaches and local irritation, and to radiation-induced oedema. The latter effect is minimised by the use of prophylactic high-dose steroids, but may cause nausea, vomiting and drowsiness in a proportion of patients. That SRS does not cause alopecia may be an important consideration for some women.

SRS efficacy

The stereotactic approach appears to yield impressive rates of control within the irradiated volume, with many studies quoting local control rates of over 90%. SRS enthusiasts consider it to be a valid alternative to neurosurgical excision: this view is supported by a retrospective study of 97 patients with solitary brain metastases treated either by surgery or SRS, which revealed no difference in survival, but significantly enhanced local control in the SRS group.42

Patients remain vulnerable to relapse at other sites in the brain, however, unless they receive WBRT as an adjunct to the stereotactic treatment. One of the very few multi-centre, randomised studies to address the question of the optimum combination of therapies allocated patients with 1–3 deposits (various primary malignancies) to receive WBRT alone or WBRT + stereotactic boost(s). In this study, SRS treatment was associated with a higher incidence of improved or stable performance status, and with superior survival in patients with good performance status at baseline.43 WBRT followed by SRS boost has become standard therapy for suitable patients in some centres.

A number of reports describing the outcome of SRS in the treatment of patients with breast cancer have been published. The median survival from time of diagnosis of brain involvement varied from 8 to 18 months, and the reported toxicity was low.44,45 The results compare favourably with those of neurosurgical series, especially when taking into account that many of the SRS patients were treated for multiple lesions. Many of the patients included in these studies had received WBRT or neurosurgery at some stage of their disease process, so it is difficult to make specific recommendations about the scheduling of different interventions in the treatment of breast cancer patients.

One treatment philosophy has been to use SRS for symptom control and to avoid or delay the use of WBRT in as many patients as possible. Whether the omission of WBRT impacts upon survival has been assessed in a multi-institutional, retrospective study of 569 patients whose initial management was either SRS alone or WBRT
and SRS. No difference in survival was detected, regardless of performance status. In a prospective study of patients with four or less metastases, in which linac-based SRS was given as first-line therapy and for treatable relapses, salvage WBRT was delivered to only 29% of patients.

SRS appears to be a useful addition to the treatment options for this patient group. Its suitability for an individual patient depends on the number and size of intracerebral deposits, the status of their extracranial disease, their performance status and the local availability of linac-based SRS or gamma knife facilities. Concerns over the financial implications of SRS treatment may have been alleviated by a cost utility analysis of surgery, WBRT and SRS, in which the combination of WBRT and SRS yielded the lowest cost per week of survival. Patients with a life expectancy of >6 months may benefit from the first-line use of SRS to avoid the potential long-term complications of WBRT. Other roles are the palliation of patients whose intracranial disease has progressed after WBRT, or as part of a more aggressive approach in combination with WBRT.

Radiotherapy for cerebral metastases: summary

In the treatment of cerebral metastases from breast cancer, whole-brain radiotherapy increases survival but the extent and duration of palliation are limited, and toxicity may be significant. Stereotactic radiotherapy techniques offer a useful addition to the repertoire of treatments for this disease entity, and may be used as an alternative to surgical excision in suitable patients. The optimum timing of these different treatment modalities remains to be elucidated.

REFERENCES


INTRODUCTION

Breast cancer is the most common cancer in women. In the UK in 2000 there were 40,707 new patients diagnosed with breast cancer with a 5-year survival rate of 77%. In autopsy studies central nervous system (CNS) metastases are reported to occur in 30% of patients. These lesions can cause severe functional deficits, which may be irreversible, even with adequate treatment. As the systemic treatment for metastatic breast cancer has improved markedly over recent years, survival is more likely to be influenced by effective treatment of CNS metastases than in other solid tumours. Therefore, these patients should be evaluated and treated rapidly to improve the functional outcome. Management of CNS metastases can be divided by their anatomical location. This chapter deals with the neurological management of brain and spinal metastasis as well as the major technical advances in spinal reconstruction necessary for tumour control.

BRAIN METASTASIS

Epidemiology

Brain metastases are the most common intracranial tumour in adults, outnumbering primary brain tumours. In cancer patients brain metastases occur in 15–40% of patients, with an associated high mortality and morbidity rate. Brain metastasis, with breast cancer as the primary site of disease, is reported in 10–20% of all cases, making breast cancer after lung cancer the second most common source of brain metastases. In breast cancer patients, metastasis to the CNS is the fourth most common distant metastasis after bone, lung and liver metastases. It is associated with aggressive tumour biology, the presence of lung metastasis and hormone receptor-negative disease and has the propensity to occur in a younger patient group. Breast cancer
rarely presents with brain metastasis. With the improved systemic management of breast cancer and prolonged survival rate, there is a suggestion that the incidence of brain metastases will increase, thereby emphasising the need for better treatment options.9,10

**Symptoms**

Symptoms and signs associated with CNS metastases result from the location of the tumour or the raised intracranial pressure resulting from the space-occupying lesion, surrounding oedema or obstruction to the cerebrospinal fluid (CSF) flow. Headache is the most frequent presenting symptom (40–50%). However, only 15–20% of these patients have papilloedema. Focal neurological deficits are present in 40% and seizures occur in 15–20% of the patients. Nausea and vomiting may develop with further increase of the intracranial pressure and altered mental status or impaired cognitive function are often present.11 When patients with known metastatic breast cancer develop neurological symptoms, urgent diagnostic imaging studies are mandatory. The gold standard diagnostic study is a gadolinium-enhanced magnetic resonance imaging (MRI) scan of the brain, which has been shown to be more sensitive than contrast-enhanced computed tomography (CT).12 MRI can detect lesions that are missed by CT, especially when lesions are situated in the posterior fossa and in the brain stem. It is also more sensitive in detecting multiple lesions,13 thereby influencing management (Figure 9.1).
Therapy

The therapy of brain metastasis is a subject of much debate. The prognosis is often dependent on disease activity at extracranial sites of disease. However, in breast cancer, systemic therapy is superior to most solid tumours and consequently up to 50% of patients with brain metastases will die due to neurological problems. In order to preserve quality of life, treatment is important to control symptoms and reduce the risks of, or delay CNS relapse.

In CT studies authors report that approximately half of patients present with a single CNS lesion. Without treatment the prognosis is poor, with a median survival of 1 month. Dexamethasone is given to treat the cerebral oedema by stabilising the disrupted blood–brain barrier. There is no class I evidence for the dosage in metastatic brain tumours, but in most studies a dose of 4 mg every 6 hours is used. During therapy it can be tapered to the patient needs.

Whole-brain radiotherapy

Whole-brain radiotherapy (WBRT) is the palliative treatment of choice for patients with multiple lesions or for patients with disease inaccessible to neurosurgical or radiosurgical approaches. WBRT alone improves survival and quality of life compared with corticosteroids alone and is still the mainstay of the treatment for the majority of patients. In a retrospective analysis of patients with brain metastases from breast cancer, the median survival following the start of radiotherapy is reported to be 4–5 months. Nausea, vomiting, headache, alopecia, fever and transient worsening of neurological symptoms can occur in the initial phase of therapy. WBRT is usually combined with corticosteroid therapy. The best clinical results are witnessed in patients <65 years old, with good performance, and in patients with the CNS as the only site of metastatic disease.

Surgery

Surgical therapy should be considered for younger patients of good performance status who have a solitary lesion with stable systemic disease. In a recent Cochrane review, the authors concluded that there is currently no evidence that surgery extends survival. However, there is a clear benefit for the duration of functionally independent survival. This benefit is probably due to a direct lowering of the raised intracranial pressure following surgery and by reducing the need for long-term steroids.

Surgery for superficial lesions is technically straightforward. The tumour is approached by a standard craniotomy. Surgery is often assisted by an image-guided system to reduce the craniotomy extent and to maximise safe removal of tumour. Other developments such as functional MRI will improve the safety of operating in eloquent areas (e.g. speech area or motor strip). In general the patients will be required to stay 4–5 days in hospital. Potential complications of surgery include postoperative complications.
haematoma formation, brain oedema, infection and epilepsy. The rate of major complications is 12%, with neurological deficit occurring in 6% of patients. The mortality rate associated with such procedures is 2–3%.

To reduce the residual disease in the tumour bed and to treat micrometastases in other parts of the brain, postoperative WBRT is usually advised. A randomised controlled trial (RCT) reported improved local control when WBRT was given following surgery for single brain metastases but found no difference in survival.

**Radiosurgery**

An increasing number of patients with single metastatic brain lesions are being treated with stereotactic radiosurgery. Multiple lesions can also be treated, but the risks of radionecrosis causing cerebral swelling and irritability increase. Stereotactic radiosurgery is administered either by a linear accelerator (linac) or by multiple cobalt sources (gamma knife). The gamma knife has the advantage of a sharply confined therapy field, with a rapid dose fall-off, thereby minimising the risk to surrounding brain tissue. In contrast to primary malignant brain tumours, brain metastases are well-demarcated, minimally invasive lesions, which make them ideal candidates for stereotactic radiotherapy.

This therapy is restricted to lesions <3–3.5 cm; with larger lesions, there is an unfavourably high level of toxicity. Early complications resulting from oedema occur in 7–10% of patients within 2 weeks of treatment. Patients may report symptoms such as headache, nausea, vomiting, focal neurological deficits and seizures. Normally these symptoms are well treated with corticosteroids. The major long-term complication is radionecrosis (5–11%), rarely requiring a further operation. The advantage of radiosurgery is that it is a non-invasive 1-day treatment and lacks many of the major complications of neurosurgery. In the authors’ opinion, neurological improvement with conventional surgery is perhaps more reliable and consistent. The role of radiosurgery, conventional neurosurgery and whole-brain irradiation is reviewed in the article by Patchell et al.

With radiosurgery in highly selected patients with 1–3 lesions, a very high level of 1-year local control can be achieved (80–90%), with a median survival comparable to surgical resection and WBRT. Distant brain control is much lower (40–70%) than WBRT. WBRT in combination with radiosurgery improves the CNS relapse rate, but has no effect on median survival. Stereotactic radiosurgery alone is now promoted with careful follow-up and, if necessary, salvage therapy with WBRT or further stereotactic radiosurgery.

The role of stereotactic radiosurgery in patients with more than 3 metastatic brain lesions has not been clearly defined. A recent study suggests there is a value of radiosurgery in this category of patients, but randomised trials are necessary to confirm this. Other new forms of radiosurgery include the cyberknife (Figure 9.2), which unlike the gamma knife (which is limited to brain lesions) can be used for the spine as well.
LEPTOMENINGEAL METASTASIS

General considerations

Leptomeningeal metastases or meningeal carcinomatosis (MC) is an increasingly common manifestation of metastatic disease, probably due to the prolonged survival associated with improved systemic therapy. Breast cancer is the primary tumour most frequently associated with MC. About 2–5% of patients with metastatic breast cancer have MC. Symptoms are related to the site and extent of tumour infiltration, to CSF flow disturbance with associated hydrocephalus and to local inflammatory responses. The patient may suffer from raised intracranial pressure, with associated headache and vomiting. Other symptoms include focal neurological deficits and seizures. The diagnosis is made by gadolinium-enhanced MRI and occasionally (multiple) lumbar punctures are required in the case of diagnostic uncertainty. The prognosis of MC in general is very poor, with a median survival in untreated patients of 4–6 weeks and in treated patients of 4 months. In metastatic breast cancer the survival is slightly better as a result of improved chemosensitivity of the tumour, with reported median survival of between 5 and 7 months.31,32

Radiotherapy

Radiotherapy of the whole brain and spinal cord is not possible because of bone marrow toxicity. Intrathecal chemotherapy is a possibility, combined with local radiotherapy to space-occupying or symptomatic lesions. Systemic chemotherapy is sometimes also considered. Intrathecal chemotherapy can be administered by repetitive lumbar puncture or through an intraventricular route via a catheter.
(Figure 9.3) with a subcutaneous reservoir (Ommaya catheter). An Ommaya is preferred because of the superior delivery of the drugs through the subarachnoid space and the achievement of adequate ventricular therapeutic drug concentrations. Early complications are common (10–20%) and include aseptic chemical meningitis, bacterial infections of the Ommaya, intracranial haemorrhage and focal encephalopathy by leakage of CSF along the Ommaya reservoir. Late neurotoxicity includes necrotising leucoencephalopathy, with a clinical picture of progressive ataxia and dementia, and occurs in about half of the long-surviving patients.

**INTRAMEDULLARY METASTASIS**

**Overview**

Intramedullary spinal cord metastasis is very rare indeed, with a reported incidence of 0.1–6% in metastatic disease, with breast cancer the second highest cause. The
overall median survival is 3 months; however, in breast cancer it may be of the order of 13 months. The clinical presentation depends on the level of the tumour, and consists of back pain with a partial or complete spinal cord lesion with motor, sensory and autonomic deficits. The most common site is the cervical spinal cord (Figure 9.4). Clinically, there are no features which distinguish an intramedullary metastasis from an extradural lesion compressing the cord. The diagnosis is made by MRI, with an isointense lesion on T1-weighted images and a nodular contrast enhancement on T1 and a pencil-shape hyperintensity on T2-weighted images. Therapy usually consists of steroids and radiotherapy. In selected cases, with patients of good performance status, stable systemic disease and no evidence of leptomeningeal metastases, surgery is an option. As the lesions tend to be well circumscribed, gross total resection can be performed with an improvement of the neurological deficit. The surgeon uses microsurgical techniques such as an ultrasonic aspirator (CUSA). Spinal cord monitoring using somatosensory and motor evoked potentials (SSEPs and MEPs) is desirable.

**EPIDURAL METASTASIS**

**Epidemiology and clinical presentation**

In metastatic breast cancer, spinal epidural metastasis is a common problem and is considered critically important because of the devastating effect on the quality of life.
with ensuing spinal cord compression. The highly vascular posterior portion of the vertebral body is the place where vertebral metastases usually develop.

Epidural metastases occur most commonly in the thoracic (50–60%) and lumbar spine (30–35%) and less frequently in the cervical spine (10–15%), correlating with the volume of bone marrow in each region. Spinal cord compression may evolve due to direct extension of the tumour into the anterior epidural space. Less often, due to mechanical compromise, a vertebral collapse may occur, precipitating spinal cord compression. About two-thirds of patients with breast cancer develop bone metastasis involving the vertebral column, and in about 2–5% the clinical diagnosis of spinal epidural metastasis is made. Multiple lesions can be found in 20% of the patients with epidural metastasis. Symptoms result from spinal cord compression and instability of the spinal column.

For the majority of patients, back pain is the initial symptom. This is a red flag in a patient with breast cancer, particularly if the pain is in the thoracic spine. Radicular symptoms may develop after a few months. Myelopathy signs due to spinal cord compression may develop slowly, but can also present progressively over a few days. Sensory disturbances, weakness of arms or legs, spasticity and autonomic dysfunction are all part of the myelopathy, depending on the spinal level of the tumour. Rapid recognition and treatment is the key to optimising outcome. The preferred diagnostic method is MRI of the whole spine. Conventional X-rays can be useful in evaluating the stability of the spine, but are not advocated as a screening method because a plain spinal radiogram will not demonstrate pathology until 50% of bone is destroyed.

**Treatment**

There are three goals of treatment in this palliative neurosurgical setting: to restore or preserve neurological function, to treat pain and to restore or preserve spinal stability. The timing of therapy is of paramount importance. The pretreatment ambulatory status is the strongest predictive factor of outcome. The majority of patients who are able to walk before therapy remain ambulatory. They have a shorter hospital stay, fewer complications and a better functional outcome. Only 30% of non-ambulatory patients regain the ability to walk. The median survival with spinal epidural metastasis in breast cancer is approximately 6–9 months after the diagnosis of epidural disease. The survival of bedridden patients is approximately 6 weeks with complications of metastatic disease and the non-ambulatory state.

Dexamethasone is important in the early stage and is appropriate when there is symptomatic spinal cord compression. Normally an initial bolus of 10 mg is followed by a dosage of 4 mg 4 times a day during the first week, which is then tapered off in 1 or 2 weeks.

Radiotherapy is traditionally the therapy of choice, with a radiation area of two levels above and below the affected vertebra. Ninety per cent of treated ambulatory
patients remain ambulant, with a local relapse rate of 10% after a median of 3–6 months. Radiotherapy, on the other hand, will not restore or preserve spinal stability.

There is a long-standing discussion whether surgery in metastatic epidural disease is of benefit. A great advantage of surgery is direct spinal decompression, with arguably a better neurological outcome. Early studies comparing the efficacy of radiotherapy and surgery (laminectomy) found no difference in neurological outcome and survival. However, metastatic epidural disease typically arises from the vertebral body, precipitating anterior compression, which may not be helped by a laminectomy. In patients with instability secondary to vertebral body destruction, laminectomy (removal of the last portion of healthy bone) will further compromise the spinal stability. This historical surgical error has now been recognised in most centres. Therefore if a laminectomy is performed, stabilisation is mandatory.

Surgery of metastatic epidural tumours has advanced significantly over the last 10 years with the widespread availability of spinal stabilisation techniques. With anterior and posterolateral approaches, the goal is to remove the tumour, decompress the spinal cord and stabilise the spinal column with instrumentation. The mortality rates in this kind of surgery are very low, with an acceptable morbidity rate of 10–20%, most of which result from wound complications. A recent randomised study by Patchell et al comparing direct decompressive surgical resection with radiotherapy vs radiotherapy alone demonstrated improved neurological outcome in the surgical cohort with less narcotic and steroid use.

Adjuvant radiotherapy should be given after surgery to prevent local relapse. We recommend delaying this for 3 weeks to facilitate safe wound healing. Radiotherapy before the operation is not advised because of the higher frequency of postoperative complications. There are many studies demonstrating a higher frequency of wound complications (2–3-fold) if radiotherapy precedes spinal surgery.

Surgery involves decompression. This may be anterior and involve a corpectomy (removal of vertebral body/tumour). For the cervical spine this is straightforward surgery. The spine is commonly reconstructed using a hollow titanium cage and secured by an anterior locking plate. In the thoracic spine, a thoracotomy is required to expose the spine. Reconstruction is afforded by a similar but larger titanium cage. In the lumbar spine, a retroperitoneal approach is typically used and reconstructed with a cage supported by an anterior plate or screw rod system. Expandable cages afford very good support and a tight fit.

Posterior decompression involves a laminectomy (removal of lamina). This is straightforward surgery but it will destabilise the spine. Fixation is therefore required. In the neck this is achieved by lateral mass screws connected to a titanium rod. In the thoracic and lumbar spine, a similar result is achieved by pedicle screws. Typically, screws are inserted 2 levels above and below the area of disease. This is based on detailed biomechanical testing (Figures 9.6–9.8).
Spinal fixation facilitates reliable stability and aggressive tumour removal. However, it is relatively unusual for the surgeon to achieve complete tumour removal. Surgery is palliative and reduces the risks of paralysis. Spinal fixation has a beneficial effect on reducing pain (reduced narcotics), and usually will significantly improve the quality of life.

New treatment modalities for spinal involvement include percutaneous vertebroplasty or kyphoplasty. These techniques involve injection of biological cement (methyl methacrylate) into the vertebral body, usually via the pedicle. It is a difficult technique and requires good radiological imaging: either biplanar fluoroscopy or CT fluoroscopy. Early results are promising in tumours. It helps pain mainly, but the exothermic effect of the methyl methacrylate cement may have a cytotoxic effect. It has mainly been used for osteoporotic fractures. It is contraindicated if the posterior vertebral body wall is compromised by fracture or direct tumour infiltration. Risks include extravasation of the cement into the canal, causing cord compression, or through the basivertebral venous system into the pulmonary tree, causing pulmonary embolism. Vertebroplasty involves simple injection into the vertebral body. Kyphoplasty involves inflation of a balloon first, which may restore sagittal balance and arguably decrease the risk of cement embolus (Figure 9.9).

Radiosurgical techniques have also been developed for the spine. Computer algorithms modified from intracranial computer guidance systems allow accurate delivery of high-dose radiotherapy to the mobile spine (see Figure 9.2). Small percutaneous
bony screws are required as fiducial markers for the radiotherapy planning, which co-registers and fuses CT scans with ‘real-time’ fluoroscopic images. Long-term results are not yet available. This technique shows promise in all osseous spine tumours.

**SUMMARY**

Patients with metastatic breast cancer have a limited life expectancy and therapy is palliative. Systemic therapy in metastatic breast cancer is more effective than with other
Figure 9.7  Intraoperative photograph of posterior upper thoracic pedicle screws.

Figure 9.8  Pedicle screws in vertebral body cross-sectional view.

Figure 9.9  Schematic illustrations of percutaneous vertebroplasty for pathological fracture. (Reproduced with permission of Kyphon.)
Figure 9.10  Protocol for spinal metastasis and surgical referral.
solid tumours. With prolonged survival encountered with improved systemic endocrine and chemotherapies, more neurological sequelae will be witnessed by physicians. Immediate and aggressive therapy in selected patients can improve outcome and preserve quality of life. New developments in spinal fixation allow for safer and more reliable outcomes. Evidence for improved outcomes with spinal surgery followed by radiotherapy from RCTs is now forthcoming.

REFERENCES

10
Thoracic complications

George Ladas

INTRODUCTION

One of the body compartments most commonly affected by metastatic breast cancer is the thorax. The thoracic surgeon has an important role as a member of the extended multidisciplinary breast cancer team and can help with diagnosis and staging, provide surgical palliation, but also occasionally perform potentially curative resection of localised metastatic disease. It is fair to say that with the significant progress in the systemic treatments of patients with advanced breast cancer in recent years, with resulting prolongation of their survival, the successful surgical palliation achieved by modern thoracic surgery has really transformed patients’ quality of life.

The thoracic surgeon has a role in the management of the following:

• surgical palliation of pleural effusions
• surgical palliation of pericardial effusions
• endoscopic palliation of airway obstruction, including stents
• pulmonary metastasectomy
• metastatic involvement of the chest wall and sternum.

SURGICAL PALLIATION OF PLEURAL EFFUSIONS

Pleural effusions are common during the course of malignant disease, with 16% of patients dying of malignancy found at autopsy to have a pleural effusion. Carcinomas of the lung and breast combined account for 60% of all malignant pleural effusions. These effusions can cause significant morbidity, including dyspnoea in 96%, chest pain in 57% and persistent cough in 44% of the patients. At the same time, the overall prognosis of patients with malignant pleural effusions is poor, with reported 1- and 6-month mortality rates of 54% and 85%, respectively, so that quality of life is of paramount importance. Patients with malignant pleural effusions from metastatic breast cancer had a longer life expectancy as a group, with a median survival of 7.1 months in our experience, even before the introduction of the newest systemic treatment modalities. As a result of the effectiveness of modern systemic treatments for breast cancer, we would normally wait to see whether an effusion responds to such
treatment initially before deciding to proceed to surgical palliation. Since dyspnoea in patients with advanced malignancy is often multifactorial, an initial needle aspiration will confirm diagnosis in 65% of the patients, but will also help define to what extent the pleural effusion itself is responsible for the symptoms.

In frail patients with very short life expectancy of 1–2 months, repeated needle aspiration can be helpful in controlling symptoms. In the majority of patients with recurrent symptomatic malignant effusions, lasting palliation can be achieved by one of a spectrum of techniques used to achieve chemical pleurodesis, i.e. fusion of the visceral and parietal pleura with the use of a ‘sclerosing agent’. The basic prerequisite for a successful chemical pleurodesis by any technique is that the lung can re-expand following drainage of the pleural effusion, so that the visceral and parietal pleura can remain apposed while adhesions are formed. However, the presence of a malignant restricting cortex on the visceral pleura prevents re-expansion of the lung and apposition to the parietal pleura.

The presence of such a trapped lung (Figure 10.1), means that any attempt at chemical pleurodesis is destined to fail. The treatment options in these circumstances are very few and most of them unattractive. Repeated aspirations require frequent hospitalisation, are painful, and detrimental to the quality of life of the patients. Furthermore, they carry the risk of the devastating complication of infection of the fluid and empyema formation. This is the major concern that also limits the popularity of permanent chest drain devices such as PleurX. Thoracotomy and decortication of the lung, combined with chemical pleurodesis or pleurectomy on the other hand, involves major surgery with very significant morbidity and mortality, unacceptable for a palliative procedure. In contrast, pleuroperitoneal shunts provide an elegant, effective and lasting solution to this difficult problem and can be used with minimal morbidity and mortality in properly selected patients.

**Sclerosing agents**

Sclerosing agents all act by triggering an intense inflammatory reaction of the pleura by chemical irritation, the produced fibrin acting as the ‘glue’. A wide variety of substances have been used in the past for this purpose, e.g. Adriamycin (doxorubicin), bleomycin, intrapleural tetracycline, or quinacrine. Currently, the most widely used agent is talc. This consists of a powder containing 20% medical-grade, asbestos-free iodised talcum, mixed with starch. In frail patients, unfit for general anaesthesia, it is used as sterile slurry via a tube thoracostomy. For the fitter patients, we use video-assisted thoracoscopic surgery (VATS) under general anaesthesia and an insufflation technique, which has been shown to be effective in up to 93% of the patients.

**Pleuro-peritoneal shunts**

Wesse and Schouten in 1982 first reported the use of a modified peritoneoatrial Holter valve as a pleuroperitoneal shunt. Since then, successful use of a purpose-built
device has been reported for the treatment of benign, but also (and mainly) malignant pleural effusions. The pleuroperitoneal shunt (Denver Biomedical Inc., Denver, Colorado, Figure 10.2a) is made of inert silicone rubber. It is composed of a central pump body, which contains two unidirectional valves. The pressure gradient required for the valves to open is 1 cmH₂O, and consequently spontaneous flow occurs from the pleural to the peritoneal cavity at expiration or during cough. The presence of a pleural effusion results in greater pressure gradient, which further enhances flow. The stroke volume of the pump itself is about 1 ml, and so periodic compression ensures a minimum throughput but also clears the valve leaflets from deposited fibrin. The proximal catheter of the shunt is introduced into the pleural cavity and the distal one into the peritoneal cavity (Figure 10.2b).

Figure 10.1 (a) Chest radiograph of patient with a malignant right pleural effusion following insertion of chest drain. The presence of a trapped lung is obvious. (b) Computed tomography (CT) scan of the same patient. A right hydropneumothorax is present. Note the thickened, restricting visceral cortex overlying the right middle and lower lobes, preventing re-expansion of the lung. Indication for immediate referral for insertion of pleuroperitoneal shunt. The drain should not be put on suction, to avoid barotrauma.
During the initial postoperative period, the nursing staff operate the pump every 3–4 hours for 2–3 minutes at a rate of around 30 strokes per minute. With the help of appropriate audiovisual training material, the patients are able to assume responsibility for the shunt within 3–4 days postoperatively (Figure 10.3).

We recently performed a retrospective review of 280 consecutive patients – 109 male, median age 60 years old (range 26–89) – undergoing 312 surgical procedures for

Figure 10.2 (a) The pleuroperitoneal shunt. Note the central compressible pump chamber with the two unidirectional valves, and the thoracic and peritoneal limbs of the shunt. (b) Schematic diagram of the function of pleuroperitoneal shunt.
palliation of malignant pleural effusions (MPEs) over a 72-month period at the Royal Brompton Hospital. The commonest malignancies were breast (29%), mesothelioma (25%), lung (12%), ovary (9%) and adenocarcinoma of unknown primary (5%). Procedures performed were VATS talc pleurodesis, 198; insertion of pleuroperitoneal shunt, 39; pleurodesis via an intercostal drain, 37; pleural biopsy alone, 28; and long-term drainage, 9. The overall hospital mortality rate was 4.3% and the complication rate 17%. Follow-up was 100% for a median of 1288 days (range 173–2329). Median postoperative survival was 210 days. Patients with breast cancer and mesothelioma had significantly better median survival (258 and 297 days, respectively) than those with ovarian cancer, adenocarcinoma of unknown primary and lung cancer (133, 123 and 142 days, respectively, \( p = 0.02 \)) (G Ladas, unpublished work).

Result from our series, one of the largest reported to date,\(^9\text{–}^{11}\) show very low mortality and low treatment-related morbidity, combined with effective palliation in the vast majority of patients. Avoiding the need for repeated hospital admissions for thoracocentesis not only dramatically improves the quality of life of these patients but also reduces the overall cost of their care.

**PALLIATION OF PERICARDIAL EFFUSIONS**

Pericardial effusions may develop in patients who develop metastatic implants on the serosa, leading to exudation of fluid into the pericardial space. When the resorptive

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**Figure 10.3** Early postoperative chest radiograph of a patient following insertion of a shunt on the right. The proximal limb is clearly visible within the right hemithorax, with the pump body lying in the soft tissues overlying the costal margin. The limited pneumoperitoneum, resulting from air entering the peritoneal cavity intraoperatively, resolves within a few days.
capacity of the pericardial serosa is exceeded, or when there is compromise of the venous or lymphatic drainage of the pericardium due to malignant infiltration, a significant effusion develops that may result in cardiac tamponade. Since the normal pericardium allows some distensibility, the rate of fluid accumulation can be as important as the total amount of fluid in defining the point at which cardiac function is compromised. Mild cardiac compression can be compensated and result only in elevation of the central venous pressure with normal systemic blood pressure. Severe compression though results in serious compromise of diastolic filling, which cannot be compensated and leads to tamponade and cardiogenic shock.

**Diagnosis**

Even large pericardial effusions can be largely asymptomatic if compensated. A high level of suspicion is important. Diminished QRS voltages on the electrocardiogram (ECG) or an enlarged cardiac silhouette and elevated central venous pressures in association with clear lung fields should point to the diagnosis. The classic triad of Beck (distended neck veins, muffled heart sounds and hypotension) is characteristic and can be associated with pulsus paradoxus. Cardiac echocardiography is widely available, simple, non-invasive and highly accurate in diagnosing the problem.

**Management**

A pericardiocentesis is helpful in proving the malignant nature of the effusion as opposed to a reactive collection secondary to chemotherapy, radiotherapy or other systemic reasons. In compromised patients with large effusions or tamponade it is appropriate to defuse the situation by introducing a catheter into the pericardial cavity under echocardiography guidance. This allows improvement in the clinical condition and ensures that a definitive procedure can be performed in safer circumstances.

An open pericardiectomy (pericardial window) can be performed in a variety of ways.

*Video-assisted thoracoscopy* or a *left anterolateral thoracotomy* can be used to create an opening towards either pleural cavity. Most of these patients though also have, or will at some point in time develop, concomitant MPEs and will require a pleurodesis. Consequently, draining the pericardial effusion towards a pleural cavity is undesirable. Furthermore, these techniques result in respiratory compromise due to postoperative chest pain from the incisions and chest drains.

A subxiphoid pericardiectomy is the preferred technique in our practice. This involves a limited midline incision extending inferiorly for 5 cm from the tip of the xiphoid process. The linea alba is incised and the peritoneal sac mobilised and displaced inferiorly, exposing the underside of the diaphragm. The peritoneal cavity is not entered. Next, a generous disc of the diaphragm with attached overlying pericardium is resected and sent for histology, and fluid specimens are sent for cytology and microbiology. The effusion is therefore drained and a wide communication is
created between the pericardial cavity and the compliant and resorptive preperitoneal space. The wound is closed by simple reapproximation of the linea alba, without the need for any drains. This procedure provides lasting palliation, is tolerated extremely well by the patients, results in minimal postoperative pain and leaves all options open regarding the management of any future pleural effusions (Figure 10.4).

**ENDOSCOPIC PALLIATION OF AIRWAY OBSTRUCTION**

Upper airway obstruction due to metastatic breast cancer is a relatively uncommon, but potentially serious problem. In an emergency, stridor and severe dyspnoea may be life threatening and demand immediate management.
Malignant disease may cause airway obstruction by (1) external compression due to mediastinal extension, usually due to nodal metastases (extraluminal component) or (2) by direct growth of tumour in the lumen of the airway with resulting occlusion (intraluminal component), or a combination of both. Disobliteration of the airway lumen can be achieved by one of several methods, usually undertaken through the rigid bronchoscope under general anaesthesia. The Nd-YAG laser is widely used,12–18 and in the case of tumours in the distal bronchi can also be undertaken through the flexible bronchoscope under local anaesthesia. Cryoablation has also been used,19,20 but requires repeated treatment. In our experience,21–23 and that of others,24 diathermy resection through the rigid bronchoscope has proved a cheap, effective and safe method of disobliteration, and can be easily combined with stenting when an extraluminal component of airway obstruction coexists. Disobliteration can be valuable as a temporising measure to allow time for systemic treatment to act25 (Figure 10.5).

In the majority of patients the extraluminal component prevails or the intraluminal occlusion recurs rapidly following disobliteration. Radiotherapy is valuable, and external irradiation is the treatment of choice. If this is contraindicated, endobronchial irradiation via remote afterloading techniques is now available. It has the advantages of not exposing staff and other patients to irradiation, and of achieving high radiation doses locally during short outpatient sessions.26–28 When dealing with critical stenosis one has to secure the airway before irradiation, to allow for the tissue oedema which ensues. Endobronchial stents and T tubes are useful in several situations in which airway obstruction is due to malignant disease. In intraluminal obstruction:

• when obstruction recurs during or shortly after disobliteration.
In extraluminal compression:

- when severe, extrinsic compression warrants immediate securing of the airway before further treatment
- if afterloading therapy is not available and external radiotherapy is not possible, or the obstruction recurs following afterloading treatment.

An accurate evaluation of the extent of airway obstruction and the interplay of the various components is only possible at bronchoscopy, and the need for stenting may only become apparent after other steps have been taken (Figure 10.6).
Types of stents

Silicone stents

The silicone T-tube stent was described by Montgomery to provide support for the upper trachea and the larynx. It consists of a length of silicone rubber with a side arm coming off at a right angle near the upper end, designed to emerge through a tracheostomy incision, allowing easy access for bronchial suction. Normally the external limb is spigotted when not being used for suction, so that the patient can speak, cough and humidify inspired gases normally. This type of stent is still in regular use, but there are now modifications in the form of T-Y stents (Figure 10.7a). T tubes require regular attention, and in common with all silicone tubes they tend to fur as sputum dries and forms concretions. If malignant disease regresses with subsequent treatment, these tubes can be removed.

Silicone endobronchial stents can be inserted through the bronchoscope without undertaking tracheostomy. They can be straight or bifurcated, and, depending on the anatomy, a collar can be sutured to one or both ends prior to insertion, to prevent stent displacement (Figure 10.7b). Such stents have the advantages and disadvantages of other silicone stents and T tubes. They are cheap, readily available, can be removed easily if no longer needed or replaced with stents of different length and calibre as needed. They are impervious to the ingrowth of granulation tissue or tumour. They have a relatively small internal diameter for the external size due to the thick wall, and tend to occlude slowly.

Figure 10.7  (a) Silicone straight and Y-type stents. (b) Silicone Montgomery T and T-Y tubes. (c) Self-expanding metal stent, partially deployed on the carrier catheter.
**Wire stents**

Bucher et al in 1951 first reported the use of stainless steel wire mesh in the treatment of tracheal and bronchial strictures. Since then, several patterns of expandable metal stents have been used in the airway. Self-expanding stents are widely used, and several designs are available. They usually come stretched and constrained on a delivery catheter within a double sheath, the outer one released once in place (Figure 10.7c). A combination of endoscopic and radiographic control is necessary to precisely position this type of stent. All patterns of wire stents must be regarded as permanent implants.

An inherent problem with all present patterns of wire stent is the presence of interstices that allow tumour or granulation tissue ingrowth and recurrent airway obstruction. They are therefore best suited for dealing with extraluminal compression where the airway wall is intact. To overcome this problem, new, covered wire stents are now commercially available.

**MANAGEMENT OF PULMONARY METASTASES**

The first, incidental, resection of an isolated lung metastasis was performed by Weinlechner in 1882, in the course of intraoperative assessment for a chest wall sarcoma. In the following 50 years, surgery was only offered to a small number of patients who presented with a single lung deposit or long disease-free interval, mainly due to the view that pulmonary metastatic disease invariably represented a manifestation of generalised systemic spread. There was a subsequent gradual recognition of the curative potential of the technique, largely due to the favourable results of work with metastatic sarcomas. In the last two decades, pulmonary metastasectomy has been systematically offered in properly selected patients with multiple or bilateral metastases from a variety of primaries, in major oncological centres in Europe and North America.

The advances in systemic treatment which can be potentially effective in micrometastases, but not to eradicate bulky, clinically detectable deposits, have further expanded the role of adjuvant or salvage surgery, to excise residual tumour after induction chemotherapy or to confirm complete pathological remission.

**Basic mechanisms**

The basic mechanisms controlling the process of metastatic spread remain largely unknown. Recent research on angiogenesis and growth factors has provided new insight into some aspects of tumour progression but a full biological explanation of the selectivity and specificity of distant metastases is still lacking.

Studies in large autopsy series have demonstrated that in 29% of patients who died of malignancies, lung was the second commonest metastatic site. Furthermore, in another series, 20% of autopsied patients’ lungs were the only site of detectable cancer.
Patient selection

The clinical incidence of isolated lung metastases varies widely with the primary tumour site. In sarcomas and germ cell tumours, many patients presenting with lung metastases will be candidates for metastasectomy. On the contrary, most patients with metastatic epithelial cancers have involvement of multiple organs and only a small fraction (1–2%) will be suitable for lung metastasectomy. This is usually the case for breast cancer patients, in whom an operation is considered normally only when there is a solitary lung lesion present.

In principle, the main prerequisites for any patient to be considered for pulmonary metastasectomy are:

- primary tumour is under control
- lung is the only site of metastasis (liver and lung acceptable in colonic cancer)
- no better treatment method is available
- complete resection of all deposits is feasible
- patient fit for planned procedure.

In any patient with a history of previous malignancy and a new, solitary lung mass, a main consideration is whether this represents a new primary lung cancer. This turns out to be the case in 63% of patients with previous breast cancer, compared with 58% when the previous malignancy was colonic cancer, 94% in head and neck tumours and only 8% of patients with previous sarcoma. Computed tomography (CT) and positron emission tomography (PET) scans are invaluable when assessing the extent of disease.

In patients with breast cancer it is very important to type the metastatic tumour, as the receptor profile often differs from that of the primary, which has significant treatment implications. Furthermore, since a lobectomy is the accepted minimum resection for primary lung cancer, distinguishing a new lung primary adenocarcinoma from a solitary breast metastasis is crucial in planning the appropriate resection. Until recently, the only method was to perform a CT-guided needle biopsy preoperatively, which was not popular due to concerns about inoculation, but there is significant progress in that field recently.

In a modern specialised thoracic surgical centre, pulmonary metastasectomy is a very safe procedure. Multi-institutional data from the International Registry of Lung Metastases (IRLM) on 5206 patients report complete resection in 88% of patients, and an overall 30-day mortality of 0.8%. In this author’s personal series of more than 300 procedures over the last 8 years, there has been no 30-day mortality (Ref 46; G Ladas, unpublished work).

In the experience of the IRLM, the actuarial survival rate after complete metastasectomy was 36% at 5 years and 26% at 10 years (median 35 months), whereas the corresponding results following incomplete resection were 13% at 5 years and 7% at 10 years (median 15 months).
A number of independent prognostic indicators, which apply universally in metastasectomy patients, were identified from the IRLM data analysis:\textsuperscript{45}

- completeness of resection
- disease-free interval (DFI) $> 36$ months
- single deposit
- tumour type.

Long-term survival is possible even in patients with more than one deposit as long as complete resection is achieved, with no clear-cut cut-off in the number of lesions. On the contrary, the identification of multiple, miliary-type micro deposits on a CT scan or intraoperatively is a contraindication to metastasectomy.

In patients with metastatic breast cancer, pulmonary involvement often results from extension via the internal mammary or mediastinal lymph nodes rather than limited hematogenous spread. Resection of isolated lung metastases represents less than 1\% of all mammary carcinomas.\textsuperscript{47} There were 411 patients with metastatic breast cancer in the IRLM cohort, and the overall survival rates were 37\% at 5 years and 21\% at 10 years (median 37 months).\textsuperscript{45}

### METASTATIC INVOLVEMENT OF THE CHEST WALL AND STERNUM

When, rarely, in the context of pulmonary metastasectomy, direct extension of the tumour to the chest wall is encountered, complete en-bloc resection is warranted and is still associated with good long-term survival.\textsuperscript{48}

Chest wall resection for breast cancer today is most often performed for recurrent local disease after failure of other forms of therapy.\textsuperscript{49,50}

Systemic recurrence is common, and chest wall resection is mainly directed towards relieving pain, removing fungating, unsightly tumour, eliminating odour, and generally improving quality of life. Due to the scale of surgery involved, careful patient selection in terms of life expectancy is very important. Surgery should be part of a multimodality treatment approach, with pre- and postoperative chemotherapy and/or hormonal treatment playing a crucial role. Chest wall lesions are often the result of spread from involved internal mammary nodes, but we have seen the occasional patient with isolated, intramanubrial bone metastasis and no nodal disease. When recurrence of previously irradiated lesions occurs, the surgeon is presented with significant technical challenges.

The surgical principles include complete en-bloc resection of all involved or previously irradiated and damaged skin, muscle and part of chest wall, including multiple ribs and sternum, as well as lung, pericardium or diaphragm, as required, with wide clear margins (Figure 10.8). The chest wall defect is then reconstructed with a prosthesis to avoid paradox and ensure protection of noble intrathoracic organs.
our practice, a composite polypropylene mesh and methyl methacrylate resin (bone cement) prosthesis is the preferred option. Once the mesh is cut into shape, the two-part resin is mixed and applied in a paste form. This sets with an exothermic reaction to form a thin yet robust plate, which is then secured at the edges of the chest wall defect (Figure 10.9). In most cases, soft-tissue reconstruction to provide cover follows, usually in the form of myocutaneous pedicled rotation flaps of various origin, with rectus abdominis, latissimus dorsi, and pectoralis major muscles being popular donor choices. Occasionally, omentum in association with free skin grafts can also be used to cover large central sternal defects. Specialist input from a plastic surgeon is invaluable in providing a high-quality service.

Breast tumours metastatic to the manubrium and the sternoclavicular area present formidable technical challenges for the thoracic surgeon due to their proximity to the noble structures of the thoracic inlet and superior mediastinum. Using complex surgical techniques developed in recent years for the management of Pancoast tumours of the lung, we have successfully resected numerous tumours of this area with no operative mortality and very low morbidity. The proven safety of these complex procedures

Figure 10.8  (a) Breast cancer metastatic to chest wall. Cross-sectional computed tomography (CT) scan, showing soft-tissue mass at the right anterior chest wall involving the sternum, ribs, overlying muscle and lung. (b) Intraoperative photograph: Note en-bloc resection of skin eclipse, muscle, sternum and ribs and (c) wedge of underlying involved lung, using staplers on this occasion. Note the size of residual chest wall defect. (d) The resected specimen (deep aspect), showing sternum, parts of three ribs bilaterally and attached wedge of lung.
in our experience, in combination with the significant advances in systemic treatment and improved survival for patients with advanced breast cancer, make them a very attractive option for the management of these very difficult problems. The most gratifying aspect of these resections is the improved quality of life that they afford, with very efficient relief of pain and tenderness, and vastly improved cosmesis.

REFERENCES

Bone is the commonest site for breast cancer to metastasise: 60–80% of patients will have bony lesions. Observational studies suggest that approximately one-third of patients with metastatic breast cancer will develop structurally significant bone destruction. The same study discovered that only half of patients with structurally significant bone destruction were referred to an orthopaedic surgeon for consideration of surgical intervention. Possible reasons for this underutilisation of orthopaedic services include the frailty of the patient, poor expected life expectancy and the effectiveness of medical management of bony breast cancer metastases, but the lack of awareness amongst referring teams of the beneficial potential of orthopaedic surgery must also play a part.

In simplest terms, the aims of orthopaedic surgery are to relieve pain and restore function. Circumstances in which surgical intervention should be considered are:

- pain due to bony metastases
- impending risk of fracture
- fracture
- spinal metastases causing spinal instability
- spinal metastases causing nerve root compression.

**PRESENTATION**

Patients with bony metastases can present with pain, fracture, hypercalcaemia and neurological symptoms secondary to nerve root compression. Although bony metastases can often be found during the standard work-up of patients with breast cancer, most patients will report pain. This is an important symptom to investigate as almost all patients with a pathological fracture have had preceding weeks of worsening pain. Pelvic and femoral metastases frequently cause pain on weight-bearing relieved by rest. Night pain is typical of bony metastases, although not all bony metastases cause night pain. A study of 498 patients showed that approximately 65% with known metastatic breast cancer had a major bone-related complication (such as pain, fracture, hypercalcaemia or nerve compression); this work also demonstrated that not all bony metastases are symptomatic.
Plain X-ray

Plain X-rays have a vital role in diagnosis, planning surgical management and in assessing response to treatment. Skeletal metastases can be lytic, blastic or mixed; this reflects the balance between osteoclastic and osteoblastic activity. Lytic lesions are usually easier to diagnose on plain films as they appear as an area of radiolucency. In contrast, blastic lesions tend to show as a denser, whiter sclerotic region (Figure 11.1). Bony breast cancer metastases tend to be mixed or lytic in character, though predominantly osteoblastic lesions are not unknown (Figure 11.2).

Fractures are identified as areas of loss of cortical integrity; recognition is easier in the presence of accompanying deformity and displacement and bone loss. However, metastatic lesions prior to fracture can be notoriously difficult to spot – especially in the case of mixed lesions. Plain X-rays tend to underestimate the amount of bone loss associated with metastases. A 30–50% loss of bone mineral density has to occur – more for primarily trabecular bone lesions – before an area of radiolucency appears. Thus, while having a high specificity, plain X-ray imaging lacks the sensitivity of other imaging modalities. Even amongst experienced orthopaedic surgeons looking at two views of the same region, there is significant inter-observer variation in assessing the size of a lytic lesion. Despite these flaws, X-rays are an inexpensive and easily accessible investigation.

If a patient is complaining of pain, a plain X-ray is the first investigation of choice. Any suspicious long bone lesions seen on radionuclide scanning should be X-rayed in order to plan management. The location and extent of a lesion will determine the type of fixation to use or whether to try conservative treatment initially. The appearance of sclerosis and new bone formation indicates response to treatment. If surgery is being considered, the whole length of the long bone must be seen to exclude the possibility of other metastases. Similarly, for vertebral metastases, the whole spine should be visualised.

Nuclear medicine scanning

Radionuclide scanning utilises the property of technetium-99m to bind to various bisphosphonates, which are taken up by osteoblasts and so can reflect metabolic bone activity. Nuclear medicine scanning is more sensitive than plain X-rays, as early disease can be detected and the whole body can be scanned in the same test. It has been estimated that radionuclide scanning can detect skeletal metastases approximately 3 months earlier than plain X-rays. In addition, lesions detected by radionuclide scanning can be as small as 2 mm in diameter, whereas the smallest lesions on plain X-rays are approximately 1 cm in diameter. However, the specificity of nuclear scanning is 78–100%, which is below that of plain X-rays, and false positives include trauma,
inflammation and even osteoarthritis. False negatives can occur with metabolically inactive metastases, typically avascular, lytic lesions with a slow bone turnover. Whole-body images are relatively inexpensive and form part of the work-up and surveillance of symptomatic breast cancer patients. Suspicious areas must be supplemented with a plain X-ray.

**Computed tomography scanning**

Computed tomography (CT) scanning, especially on the bony window setting, is a highly sensitive method of detecting bony changes. Metastases can be detected in the early bone marrow deposition stages that precede bone destruction. CT scanning
is particularly sensitive at characterising cortical destruction. Unfortunately, this benefit of sensitivity is offset by the limited anatomical exposure that CT scanning offers; it is also a relatively expensive test compared with radionuclide scanning and plain X-rays. However, CT scanning is better than X-ray imaging at demonstrating spinal metastases where surrounding soft tissue can impair definition.

**MRI scanning**

Magnetic resonance imaging (MRI) is the gold standard test for characterising bony metastases with accompanying soft-tissue involvement. Its use is vital in cases of spinal cord and nerve root compression where the extent of involvement can be clearly visualised. However, MRI provides less definition for cortical bone lesions – for these, X-rays and CT scanning are more useful.

As with CT scanning, MRI can also detect metastases at the bone marrow deposition stage. Clearly this can identify early disease but its clinical use is not clear.
**AXIAL METASTASES**

In descending order of frequency the commonest sites for skeletal breast cancer metastases are:

- vertebrae (primarily thoracolumbar)
- pelvis
- ribs
- femur (mostly proximal)
- humerus (mostly proximal)
- other bony sites (scapula, tibia, skull, for example).

The axial skeleton is the commonest site for breast cancer skeletal metastases; however, it is the appendicular skeleton which is more likely to require operative fixation. This partly reflects the scope of treatment available to the surgeon and partly the relative success of local radiation treatment to the axial skeleton. However, there are circumstances in axial disease where orthopaedic intervention can be beneficial.

**Spinal metastases**

It has been estimated that between 30 and 70% of patients with breast cancer will have spinal metastases at the time of death. This predilection for the spine is believed to be due to the venous drainage of the breast. Cancer cells are believed to seed via the lymphatics and the azygos vein into the paravertebral venous plexus of Batson and then deposit most frequently into the anterior and middle columns of the thoracolumbar spine (Figure 11.3).

Although spinal metastases can remain asymptomatic, a significant proportion (approximately 95%) will cause symptoms of pain; a smaller number will also cause deformity or neurological dysfunction. The osteoclastic activity of breast metastases creates osteolysis, which can lead to fracture, collapse and kyphosis. This in turn can result in pain, paraspinal muscle spasm and resultant scoliosis. Furthermore, nerve root and spinal cord compression can occur with fracture fragments and soft-tissue tumour response. Pain can be as a result of all these phenomena and in addition may be caused by mechanoreceptor stimulation in the peristeum and direct nociceptor stimulation by the tumour and the local release of chemical mediators such as substance P, bradykinin and histamine.

In summary pain from spinal metastases can be as a result of:

1. Enlarging tumour mass.
2. Bone defect, leading to pathological fracture.
3. Bone defect, leading to deformity – kyphosis, scoliosis or combination of both.
4. Nerve root compression – secondary to tumour mass, accompanying tissue reaction or fracture fragments.

5. Compression of spinal cord – secondary to tumour mass, accompanying tissue reaction or fracture fragments.

So, not all spinal metastases are symptomatic, and not all symptoms require surgical intervention. A scheme for directing patients to surgical or medical management was described by Harrington (Table 11.1).10

In all patients without neurological deficit considered for surgery, there is instability or impending instability. This means bone defects in the anterior and middle vertebral columns, as described by Denis (see Figure 11.3). Spinal surgery can be a major undertaking, with many attendant risks; therefore, it is important to have an understanding of indications, methods and outcomes.

The goals of spinal surgery include:

- neural decompression
- spinal stability
- correction of spinal deformity.
Frequently, two or more of these aims have to be addressed in the same procedure. The general principles are to replace bone loss, stabilise the spine to maintain height and alignment and decompress neural compromise if present. Bone defects in the spine have to be replaced with either autologous bone graft, exogenous bone graft or bone cement. In the non-tumour setting, bone graft is an excellent way to replace bone loss and aid fusion of vertebral bodies; however, in cancer patients we cannot expect bony fusion due to local and systemic changes affecting bone healing and therefore bone cement is more commonly used. Whichever bone substitute is used, it is rare for it to have the strength to maintain height and alignment – particularly in the case of a progressive osteolytic lesion – and therefore supplementation with internal fixation is required. Instrumentation either distracts or compresses vertebral bodies and can provide an aid to fusion. Examples of instrumentation include pedicle screws, rods and cages, depending on the size of the metastatic lesions and the number of levels involved in the instability. Whichever form of internal fixation is used, it must extend to unaffected bone or disc both above and below the lesion – hence, the need for whole-spine imaging.

The need for stabilisation means the anterior approach or a combined anterior–posterior approach is usually required in tumour surgery. Anterior approaches involve accessing the cervical spine through the neck, the lumbar spine through the abdomen and the thoracic spine via the chest. The posterior approach to spinal surgery involves an incision to the back followed by a laminectomy to access the foramen, spinal canal and vertebral bodies. In cases of spinal metastases, the laminectomy can itself destabilise an already collapsing vertebral body. Comparative research shows that patient outcome for spinal decompression surgery is twice as favourable after an anterior rather than a posterior approach.\textsuperscript{10} However, metastases affecting only the posterior half of the vertebral body may need a posterior approach, and patients with multilevel involvement requiring extensive internal fixation may necessitate a combined anterior and posterior approach.\textsuperscript{11} Anterior approaches are obviously more invasive, so traditionally

### Table 11.1 Managing spinal metastases

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<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Management</th>
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<tbody>
<tr>
<td>I</td>
<td>No neurological involvement</td>
<td>Chemotherapy and/or local radiation</td>
</tr>
<tr>
<td>II</td>
<td>Bone involvement but no collapse</td>
<td>Chemotherapy and/or local radiation</td>
</tr>
<tr>
<td>III</td>
<td>Neurological impairment without body involvement</td>
<td>Local radiation and/or steroids</td>
</tr>
<tr>
<td>IV</td>
<td>Vertebral collapse or instability without significant neurological involvement</td>
<td>Surgical stabilisation via anterior approach</td>
</tr>
<tr>
<td>V</td>
<td>Vertebral collapse with major neurological impairment</td>
<td>Surgical stabilisation and decompression via anterior approach</td>
</tr>
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From Harrington.\textsuperscript{10}
spinal surgery has been reserved for those patients presenting with cord/nerve root compression or instability and who are also surgically fit with a good prognosis — usually taken to mean a life expectancy greater than 6 months. However, this view is beginning to change with the advent of minimally invasive spinal surgery.

There are three areas where minimally invasive spinal procedures are proliferating:

- biopsy
- replacing bone loss — namely, vertebroplasty and kyphoplasty techniques
- reconstruction and stabilisation — especially through endoscopic procedures.

**Tissue diagnosis**

With screening programmes and superior imaging methods available, metastatic spinal disease is being detected earlier so there is an increasing need for minimally invasive and targeted bone sampling where doubt exists as to the origin of the lesion. Interventional radiology is increasingly used to gain vertebral samples instead of open biopsies or core biopsies, which have associated risks of bleeding and nerve damage. CT-guided or fluoroscopic-guided biopsies can access posteriorly located lesions or those in the far lateral area of the vertebral body through the paravertebral approach, whereas lesions in the central or anterior parts of the vertebral body (where metastases typically first emerge) are more amenable to the transpedicular approach. The use of the transpedicular approach in particular has meant that metastases are being diagnosed earlier and open biopsies of deep vertebral lesions are being rendered obsolete.

**Percutaneous vertebroplasty**

Percutaneous vertebroplasty involves injecting polymethyl methacrylate (PMMA) cement directly into collapsed vertebral bodies. It is a fast emerging technique that is achieving some success in managing osteoporotic vertebral fractures, providing fast relief (within 2 weeks) and with significant reduction in pain scores at 1 year. PMMA confers a more than 195% increase in compressive strength than isolated osteoporotic vertebrae left untreated. It is being increasingly used for metastatic collapse and has the advantage over radiotherapy and conservative treatment in its faster speed of action and return to mobility.

However, in the presence of cortical osteolysis there is an increased incidence of PMMA leak and a lower incidence of pain relief. For patients with osteolytic fractures, kyphoplasty may be more appropriate. In this technique, an inflatable balloon at the tip of the needle is inflated within the vertebral body to restore height, the newly created defect being filled in with PMMA cement. The balloon is ultimately removed. These are new techniques and complications at present are known to be cement leak and infection risk. Results of published series are encouraging, but there are few data at present and long-term follow-up evidence is scanty. As techniques are modified
and newer high-viscosity cements are developed, percutaneous vertebroplasty and kyphoplasty procedures promise to have wider applications in the future (Table 11.2).

**Endoscopic spinal surgery**

Video-assisted thoracoscopic surgery (VATS), a method more commonly utilised by thoracic surgeons, is beginning to be used for approaching metastases in the thoracic vertebrae.

Vertebral bodies, discs and pedicles can be accessed by VATS to perform procedures such as decompression, tumour resection and spine stabilisation using anterior plating and bone grafting. For VATS procedures requiring greater exposure, a lung may need to be deflated for the duration of the procedure. Laparoscopic techniques are also being developed to access the lumbar vertebrae via the retroperitoneal approach – at present only a few centres are using these methods. Reduced rates of hospital stay and earlier returns to activity than with similar surgery involving open anterior approaches have been reported. Whereas endoscopic spinal surgery promises much in terms of lower rates of chest complications and reduced trauma to ribs and shoulder girdle, it must be remembered that few centres offer this type of surgery and it is associated with a long and steep surgical learning curve.

**Hip and pelvis**

Pelvic involvement in metastatic breast cancer is common and a frequent cause of immobility and loss of function. At present, lesions in the femur and in the acetabulum are amenable to reconstruction by orthopaedic surgeons, whereas lesions in the pubic rami, sacrum, sacroiliac joint, superior ilium and ischia are currently managed by conservative and medical management (Figure 11.4).

Surgery in the hip and pelvis is essentially a version of the conventional total hip replacement that has to be adapted to accommodate the bone loss particular to the patient. This is major orthopaedic surgery, especially if complex acetabular reconstruction is necessary. Patient selection is the key to management. Patients must be physiologically able to tolerate such invasive surgery and the possible complications.

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**Table 11.2** Relative and absolute contraindications to percutaneous vertebroplasty and kyphoplasty

<table>
<thead>
<tr>
<th>Relative contraindications</th>
<th>Absolute contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural cortical osteolysis – danger of cement leak compromising the spinal cord</td>
<td>Coagulopathy</td>
</tr>
<tr>
<td>70% or greater loss of height – danger of fracture fragments displacing with cement injection</td>
<td>Osteomyelitis and discitis in the affected area</td>
</tr>
<tr>
<td></td>
<td>Lack of surgical back-up in the event of complications</td>
</tr>
</tbody>
</table>
Furthermore, they must be physically and emotionally able to tolerate the physical rehabilitation required postoperatively. Although no specific patient-selection guidelines exist, a reasonable function and more than 6 months’ life expectancy are believed to be essential by most surgeons.

The pattern and extent of acetabular bone loss influences the type of reconstruction that is done: options include a conventional total hip replacement with a cemented cup, a protrusio cup with a cemented total hip replacement (uncemented prostheses are not successful in metastatic disease) and a custom-made protrusio cup with pin/screw fixation into the pelvis. A protrusio cup is a specially reinforced cup which extends into the pelvic cavity; it is indicated in cases of extensive bone loss in the floor and walls of the acetabulum (Figure 11.5). Tumour involvement of most of the acetabular walls would be an indication for fixation devices to fix the cup to the pelvis – these include Steinmann pins, threaded rods and screws. All of the acetabular cups may need to be reinforced with reinforcement rings, bone graft, methyl methacrylate cement or silastic and wire meshes. An anatomical guideline to influence the choice of acetabular reconstruction in metastatic bone disease was formulated by Harrington based on plain X-rays. Although this is the most frequently used classification system, it must be remembered that it is a guide for all metastatic disease and not just breast cancer; this is particularly pertinent for class IV lesions where an excision of the hip joint (Girdlestone procedure) is one of the recommendations for solitary, symptomatic lesions – this type of scenario is infrequently encountered in metastatic breast cancer.

Figure 11.4 This is an anteroposterior X-ray image of a pelvis with extensive metastatic disease. Metastatic deposits are seen in the right pubic rami, right acetabulum and in the right proximal femur.
Although total hip replacement is a frequently performed procedure, metastatic breast cancer is a special case and an orthopaedic surgeon specialising in hips is recommended. Meticulous preoperative planning is essential – both in terms of patient preparation and prosthesis selection. Intraoperative bleeding is generally worse than with routine pelvic surgery and methods such as rapid, thorough curettage of tumour and the use of substances such as methacrylate cement, bone wax, absorbable sponge and thrombin may be necessary. The risk of major complications – such as neurovascular injury, infection, thromboembolic disease, death – are all higher in cancer patients. Some studies report the risk of major complications to be as high as 30%. However, despite the technical difficulty and the risks of acetabular reconstruction, total hip replacement for the correct patient will mean reduced pain and early return to function.

**APPENDICULAR SKELETON**

**Long bone metastases**

As mentioned previously, although axial metastases are more common, the need for orthopaedic fixation is higher in the appendicular skeleton. Treatment is largely for the management of fracture or for prophylaxis of fracture. Appendicular metastases
may present with pain or fracture. Fractures are often associated with low-energy trauma and there can be minimal external signs such as bruising or swelling. The occurrence of any fracture in metastatic breast disease is a poor prognostic indicator. Observational data\textsuperscript{14} demonstrate a median time from fracture to death to be 12 months; this is approximately half the survival time of patients with bony metastases and no fracture. A fracture in a long bone results in pain and loss of mobility and function. An upper limb fracture can have significant implications for self-caring and independence and for patients with coexistent mobility issues the use of walking aids can be near impossible. Thus, a fracture is a disastrous event for the breast cancer patient and the aim of all clinicians should be to diagnose and manage bone at risk of impending fracture. From the surgeon’s point of view, an intact bone, however weak, is technically easier to stabilise than a broken one; from a patient’s point of view, a broken bone can mean a longer, more painful postoperative period and a reduced life expectancy.

Most fracture patients will report pain in the weeks preceding the fracture and X-rays may demonstrate an area of bone loss (a 30–50% loss in bone mineral density has to occur before a metastatic lesion is visible on plain films – see section on Plain X-rays above). Numerous attempts have been made to describe radiological changes that signify structurally significant weakening of bone. We know that osteolytic lesions are more likely to result in fracture than sclerotic metastases. We also know that even a small area of cortical bone loss (0.5 cm diameter) can act as a stress riser and break when subjected to sufficient force. fifty per cent of cross-sectional cortical bone loss on plain X-rays is the critical amount which signifies impending fracture; an osteolytic lesion $\geq 2.5$ cm is also considered significant.\textsuperscript{7} These observations have been supported by others; but different bones will break with less bone loss, depending on the forces they have to withstand. Mirels drew all these factors together to formulate a scheme to direct the decision to prophylactically internally fix a bone based on his observations of 78 metastatic lesions undergoing radiation therapy.\textsuperscript{15} He has formulated a scoring scheme where $\geq 8$ points is an indication for internal fixation, whereas $< 8$ points indicates medical or conservative management (Table 11.4).

### Table 11.4

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Reconstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Lateral cortices, superior and medial walls remain structurally intact</td>
<td>Conventional cemented total hip replacement</td>
</tr>
<tr>
<td>II</td>
<td>Deficient medial wall</td>
<td>Protrusio cup, cemented total hip replacement</td>
</tr>
<tr>
<td>III</td>
<td>Deficient lateral and superior acetabulum</td>
<td>Protrusio cup with fixation (e.g. screws or Steinmann pins) with cemented total hip replacement</td>
</tr>
<tr>
<td>IV</td>
<td>Solitary metastasis</td>
<td>Resection of lesion – Girdlestone, saddle prosthesis or custom-made prosthesis</td>
</tr>
</tbody>
</table>

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Mirels’ scheme, though in widespread acceptance in breast cancer, should be treated more like a guideline than an edict. In breast cancer most lesions are mixed – lytic and blastic; mixed lesions tend to respond well to radiation therapy, though new bone can take 2–3 months to reconstitute. The ability of a particular patient to tolerate pain and restriction in activity (e.g. partial weight-bearing) for a few months while radiation therapy takes effect means that surgical management decisions have to be directed individually. However, if fracture is believed to be imminent, fixation should take precedence.16 To guide clinicians managing breast cancer, the recommendations of the 1997 Working Party on Metastatic Bone Disease in Breast Cancer in the UK 17 are useful. This multidisciplinary group, composed of breast surgeons, orthopaedic surgeons and oncologists, advised to prophylactically fix those lesions which score 9 or above before commencing radiotherapy on that lesion – provided the patient can tolerate the surgery.

**General surgical considerations**

Absolute contraindications to fixation would include imminent death and severe frailty – either due to the effects of the cancer or co-morbidity. Two-thirds of patients undergoing orthopaedic surgery for skeletal metastases have cardiovascular or respiratory co-morbidity.18 All other contraindications are relative and should be considered on an individual basis. These include coagulopathy, presence of infection (particularly in the surgical field), acute thromboembolic disease, severe neurovascular impairment and inability to comprehend or cooperate with rehabilitation.

Fractures and bone defects through a metastatic lesion cannot be relied upon to unite. There should be secure fixation above and below the lesion so it should be mandatory to obtain complete full-length plain films of the limb being treated in order to look for other metastases, as further lesions will influence the type of fixation used. When choosing fixation, the aim is towards absolute, rigid fixation with a load-bearing device. The bone–metalwork interface must be secure and this means cementing or fixing the prosthesis into bone, as bony healing and incorporation cannot be

**Table 11.4  Mirels’ scoring system for appendicular metastases**

<table>
<thead>
<tr>
<th>Points</th>
<th>3</th>
<th>2</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Peritrochanteric</td>
<td>Lower extremity</td>
<td>Upper extremity</td>
</tr>
<tr>
<td>Lesion type</td>
<td>Lytic</td>
<td>Mixed – lytic and blastic</td>
<td>Blastic</td>
</tr>
<tr>
<td>Amount of cortical loss</td>
<td>&gt;2/3</td>
<td>1/3–2/3</td>
<td>≤1/3</td>
</tr>
<tr>
<td>Pain</td>
<td>Functional</td>
<td>Functional, moderate</td>
<td>Moderate</td>
</tr>
</tbody>
</table>

From Mirels.15

expected in the presence of tumour. The aim is to achieve rapid mobilisation of the patient: immediate full weight-bearing for lower limb surgery should be the goal. Intramedullary nailing is the most common method of internal fixation in tumour surgery as it achieves these goals most efficiently. Open fixation using plate and screws means a larger surgical exposure and the problem of managing a bone defect either with a longer plate or the use of cement or bone graft. The advent of gamma nails and the development of humeral nails (see below) mean that plate and screw fixation is becoming more infrequent.

**Femoral metastases**

The femur is the commonest site in the appendicular skeleton for metastases. Most lesions occur in the proximal femur, and pain on weight-bearing is a prominent feature. In addition to the Mirels’ score, avulsion of the lesser trochanter on plain X-rays is a sign of impending fracture.

Lesions in the femoral neck are usually treated with a cemented total hip replacement – with close attention paid to any lesions in the pelvis which may dictate choice of the acetabular cup. Periachonderic lesions and metastases in the femoral shaft are generally treated with an intramedullary nail device. These have largely supplanted older techniques of tumour curettage followed by plate and screw fixation and replacement of bone defects with methacrylate cement or bone graft. Plate and screw fixation are prone to long recovery times and failure in tumour patients due to a combination of problems such as poor bone healing, and weakening of the bone partly due to the lesion itself and partly due to the stress risers caused by the new screw holes. Procedures using intramedullary devices – such as standard intramedullary nails, retrograde nails and nails with fixation into the femoral neck (e.g. the gamma nail) – are relatively straightforward and commonly performed in normal trauma practice. The gamma nail and the recon nail are a type of femoral intramedullary nail with a large screw that extends through the femoral neck and fixes into the femoral head (Figure 11.6). This device stabilises both the shaft and neck of femur simultaneously; it is easy to use and has been found to have significantly similar results than the previously used spiral blade devices.

Intramedullary nailing involves a small surgical incision followed by the introduction of a nail into the medulla of the long bone traversing the tumour or fracture. The nail is fixed in position with locking screws, which prevents axial rotation and shortening; this is important in cancer patients as tumours can enlarge and further destabilise the integrity of the bone. Therefore, however small and stable the lesion may be at presentation, it is recommended to use an intramedullary nail that goes the full length of the bone and to always use locking screws. Intramedullary nails can be reamed or unreamed: the latter are smaller solid nails that are introduced directly into the medullary cavity of the long bone. Reamed nails are wider ‘hollow’ nails with greater load-bearing capacity. Reaming is a process which enlarges the medullary cavity of a long bone by using a long drill to accommodate a wider-diameter nail.
A reamed nail usually takes longer to introduce and the reaming process is associated with high intramedullary pressures and a small but significant incidence of thromboemboli and fat emboli resulting in cardiopulmonary compromise and even sudden death. Studies comparing reamed versus unreamed nails in metastatic femoral disease have not shown a significantly higher incidence of embolic disease amongst the reamed group of patients, contrary to traditional belief.

When treating skeletal metastases it is generally recommended that all nails are locked both proximally and distally: this provides stability against rotational and shortening forces, especially relevant as the bone destruction process can continue long after the procedure; locking will also prevent nail migration.

Intramedullary nails are sturdy enough to allow immediate weight-bearing and can be used for both prophylaxis and treatment of fracture. Disadvantages of an intramedullary nail include the complications associated with the reaming process where showers of emboli can be sent around the circulation causing problems such as strokes and pulmonary emboli. It is known that tumour cells can also embolise throughout the medullary cavity during the reaming process and theoretically may seed through the systemic circulation. For this reason if there is any doubt to the underlying diagnosis when treating someone with a femoral lesion, a full tumour work-up including bone biopsy is indicated. In patients with known breast metastases,
the whole femur will need to receive radiotherapy after the introduction of an intramedullary nail.

For widespread femoral metastases with severe accompanying bone loss, an intramedullary nail may be insufficient. In this circumstance an amputation may be the only operative choice. In practice this is rarely done, partly because extensive bone involvement is usually a feature of advanced disease and an amputation, though it may reduce pain, would not realise the aim for early return to mobility.

**Humeral fractures**

The humerus is the second most common site of long bone metastases after the femur. Both the diagnosis and management can be challenging. When considering a metastatic lesion in a long bone, the differential diagnoses such as primary bone tumour, osteomyelitis, Paget’s disease, giant cell tumour and post-radiation osteitis, must all be borne in mind. The humerus is more prone to post-radiation osteitis, as the chest is such a common site for radiation therapy. In situations of real doubt, a biopsy is indicated. Guidelines to humeral lesion management advise that lesions greater than 2.5–3 cm in diameter, with 50% or greater cortical involvement and ongoing functional pain after radiotherapy, are those that will benefit from fixation.

The proximal third of the humerus is the commonest site for humeral metastases. Lesions in this area are treated with curettage and packing with methacrylate cement if relatively small or with a shoulder hemiarthroplasty if bigger or more unstable. Problems with any surgical exposure in the shoulder are of bleeding, close proximity of the axillary nerve and brachial plexus and of balancing the soft tissues. Shoulder hemiarthroplasty, regardless of the indication, is a procedure dependent on good rotator cuff positioning and rehabilitation. Months of physiotherapy are required, and even then functional results are often suboptimal; therefore, the use of shoulder replacement in breast cancer patients is uncommon.

For diaphyseal lesions around or below the insertion of the deltoid muscle, as with femoral shaft lesions, surgical management options are either intramedullary nailing or cortical fixation. Intramedullary fixation includes antegrade intramedullary nails, retrograde nails and multiple Enders nails or Rush rods. Intramedullary nailing is the least-invasive technique involving a limited surgical exposure, a relatively fast operative time and immediate stabilisation (Figure 11.7). The choice of rigid antegrade or retrograde nailing is made depending on the location of the lesion and surgical preference of the surgeon. Disadvantages of nailing are with the entry point of the antegrade nail and the proximal locking screw which can impinge upon the rotator cuff muscles and thus create problems with mobilising postoperatively.

Occasionally, the site and size of the lesion may require flexible intramedullary fixation; here Enders nails or Rush rods may be inserted into the lesion and passed proximally and pushed distally to span the lesion – more than one nail is required and cement augmentation may be necessary. Enders nails and Rush rods are more likely to be used for large, distal lesions. Their use involves a technically challenging
procedure, a poorer fixation than can be obtained with a nail and the postoperative risk of device migration. Unsurprisingly, they are becoming increasingly uncommon.

Using cortical fixation with plate and screws, a stable fixation can be achieved, but a large bone defect will need methacrylate cement augmentation. A long plate is usually required, ideally with three screws above and three screws below the lesion passing through both cortices. This necessitates a large surgical exposure through muscle and puts neurovascular structures at risk. But as explained in the Femoral metastases section, plate and screw fixation has a higher risk of failure in the tumour patient as a result of bone loss and the formation of stress risers with new screw hole formation.

Distal humeral lesions (within 12 cm of the elbow joint) usually require plate fixation as intramedullary fixation is not possible both because of the proximity of the elbow joint and also because of the flatter, triangular shape of the humerus in this area. A triceps-splitting approach is required and methacrylate cement augmentation is likely. For more extensive bone destruction, a custom-made elbow prosthesis may be indicated.

Figure 11.7 This X-ray image is of a humerus with extensive metastatic disease which has been treated with a reamed intramedullary humeral nail. This is an antegrade nail with the entry point in the proximal humerus. Proximal and distal locking screws have been used to provide rotational stability – the distal screws are seen ‘end-on’ in this image. There is a fracture which has occurred intraoperatively at the mid-shaft – a risk when reaming bone weakened by tumour deposit.
In circumstances where the amount of bone destruction precludes fixation but long-term survival of the patient is anticipated, a salvage procedure using modular segmental prostheses for diaphyseal lesions may be used. Similarly, a custom-made shoulder or elbow prosthesis for proximal and distal lesions, respectively, may be required. This is specialised surgery, and an orthopaedic surgeon specialising in tumour surgery is required. However, as with the femur, it is rare in metastatic breast cancer that such large bone defects will require operative management; big areas of bone loss are relatively uncommon, and when they do occur are usually a feature of advanced disease.

In general, proximal and distal humeral lesions, however they are fixed, will result in a variable level of function impairment. Diaphyseal lesions – especially if treated with rigid intramedullary nail fixation – will result in an earlier return to function and a reduction in pain.

CONCLUSION

The functional results of orthopaedic intervention – particularly in lower limb fixation – can be life-altering, and the analgesic effects of rendering a fractured or unstable bone stable must not be underestimated. It is hoped that technical developments in the field of periarticular metastases – such as at the hip, elbow and shoulder – and in managing areas of extensive bone loss will improve the results in these patients. It is recommended that a member of an orthopaedic trauma service be designated to manage appendicular skeletal tumours, with a specialist orthopaedic oncology team managing large endoprostheses or custom-made prostheses. The 1997 Working Group advised liaison between breast surgeons, oncologists, radiologists and orthopaedic surgeons, with combined clinics to be considered if workload permitted.

The average life expectancy of patients with breast cancer presenting with bone-only metastases has improved from 24 to 36 months, and 20% of these patients will be alive at 5 years. The medical management of metastatic breast cancer is also improving, and screening programmes are selecting patients at an earlier stage of their disease. Thus, the role for operative fixation is likely to expand, requiring increasing need for closer work between breast cancer and orthopaedic teams.

REFERENCES

Radiofrequency ablation of hepatic metastases

Andreas Adam

INTRODUCTION

The liver is the third most common site of metastases from carcinoma of the breast, after the bone and lung. Two-thirds of women with metastatic breast cancer eventually have it spread to the liver. Complete evaluation of the extent of metastatic disease, both within and outside the liver, is important before considering treatment options. Although systemic treatments are the mainstay of therapy, there has been an increasing interest in the role of local therapy of liver metastases in specific circumstances for women with metastatic breast cancer.

The best established method of local treatment of hepatic metastases is surgical resection. It is valuable to review the evidence relating to surgery, as this provides the rationale for considering other types of local treatment as well. The most extensive experience with this type of surgery is in patients with colorectal metastases.

ROLE OF SURGERY IN LIVER METASTASES

Approximately 25% of patients with liver metastases from colorectal cancer have no other site of metastasis and can be treated with regional therapies directed towards their liver tumours. Hepatic resection results in survival rates of 55–80% at 1 year and 25–50% at 5 years. However, because of advanced disease, unfavourable location of the metastases, or poor physical condition, fewer than 20% of patients are eligible for hepatic resection. In general, only patients with fewer than four or five metastases, limited to one lobe, and with no evidence of extrahepatic disease, are eligible for surgery. Without resection, patients with hepatic metastases from colorectal carcinoma have a median survival of less than 1 year.

Hepatic resection is less well established in patients with carcinoma of the breast. Many surgeons have been reluctant to operate on such patients because of the high risk of undetected extrahepatic disease. However, some patients with apparently isolated hepatic metastases have been operated on with good results. Yoshimoto et al studied 25 patients with breast cancer treated with hepatic resection: 14 patients had solitary
lesions and 11 patients had multiple metastases; 8 patients had extrahepatic disease. All of the metastases were resected and all but 1 patient also received chemotherapy. After the hepatectomy, recurrent tumours were detected in 18 of the patients, being located in the liver in 12 (67%) of them. Overall, however, hepatectomy ensured that the liver was clinically recurrence-free for a median of 24 months (range 2–132 months). The 2- and 5-year cumulative survival rates after hepatectomy were 71% and 27%, respectively, and the median survival duration was 34.3 ± 3.2 months, much better than the period of 8.5 months for another series of patients treated with standard or nonsurgical therapies at the author’s institution. The number and the size of hepatic metastases, the interval between treatment of the primary lesion and hepatectomy and the existence of extrahepatic metastases were not adverse prognostic factors.

In another study, Pocard et al examined 65 patients with breast cancer liver metastases. The selection criteria for surgery were normal performance status and liver function tests; radiological objective response to chemotherapy and/or hormone therapy; in cases of non-isolated hepatic metastases, patients were included if there had been complete response of the associated metastatic site (usually bone) and no brain metastases. The median follow-up was 41 months (6–100 months). The survival rate after surgery was 90% at 1 year, 71% at 3 years and 46% at 4 years; 13 patients were alive at 4 years. The recurrence rate in the liver remnant at 36 months differed according to the lymph node status of the initial breast cancer – 40% for N0–N1 vs 81% for N1b–N2 (p = 0.01) – and according to the type of liver resection – 45% for minor liver resection vs 73% for major liver resection (p = 0.02). These, and other similar, studies, although limited and highly selective, suggest that surgical treatment of hepatic metastases from breast cancer may prolong survival in certain subgroups of patients.

**LOCAL ABLATION TECHNIQUES**

Recently developed minimally invasive techniques for local ablation of hepatic metastases may provide reasonable alternatives for patients who are not candidates for surgery. Such techniques include cryotherapy and thermal ablation with laser, microwaves or radiofrequency. This chapter focuses on radiofrequency ablation, the most widely used method of percutaneous ablation.

**RADIOFREQUENCY ABLATION**

Radiofrequency (RF) radiation produces local heat in tissues. Needle-like electrodes are placed percutaneously directly into the tumour, with the use of ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI) guidance. The RF electrode is typically comprised of a metal shaft, which is insulated except for an exposed conductive tip that is in direct electrical contact with the targeted tissue volume. The RF generator supplies RF power to the tissue through the electrode. It is connected
both to the shaft(s) of the RF electrode and to the reference electrode, usually a large conductive pad in contact with the patient's skin in an area of relatively good electrical thermal conductivity (such as the thigh). The RF generator produces RF voltage between the active electrode and the reference electrode, thereby establishing lines of electric field within the patient's body between the two electrodes. At the low RF frequencies used for this procedure (less than 1 MHz), the electric field pattern is governed essentially by electrostatic equations. The electric field oscillates with the alternating RF current, which causes oscillatory movement of ions in the tissue in proportion to the field intensity. The mechanism of tissue heating for RF ablation is frictional, or resistive, energy loss being caused by the motion of the ionic current.\textsuperscript{13,14} All RF generators are operated at 460 kHz at a power setting of 50–200 W.

**Patient selection and technique**

The goal of RF thermal ablation is to destroy the tumour as well as a 5–10 mm circumferential cuff of adjacent normal hepatic parenchyma. Each ablation requires exact placement of the electrode tip in the tumour. A single ablation treatment raises local tissue temperatures to 60\degree–100\degree C and produces a spherical thermal injury approximately 3–5 cm in diameter (Figure 12.1). The size of each ablation is delineated sonographically by echogenic microbubbles that are produced during the ablation.

Most investigators are limiting treatment with RF ablation to patients with four or fewer, 5 cm or smaller, primary or secondary malignant hepatic tumours, with no evidence of extrahepatic disease. However, patients with a small number of pulmonary metastases are sometimes treated, as such metastases do not usually have a significant impact on survival. Ideal tumours are smaller than 3 cm in diameter, completely surrounded by hepatic parenchyma, 1 cm or more deep to the liver capsule, and 2 cm or more away from large hepatic or portal veins. Subcapsular liver tumours can be ablated, but their treatment is usually associated with greater procedural and post-procedural pain. Tumours adjacent to large blood vessels are more difficult to ablate completely because the blood flow in the vessels causes loss of heat, thus limiting the extent of the ablation (Figure 12.2). Ablation of tumours adjacent to the large portal triads causes increased pain and poses the risk of damage to the associated bile duct. Contraindications to treatment include sepsis, severe debilitation and uncorrectable coagulopathies.

Percutaneous RF ablation is usually carried out with the use of conscious sedation alone and can be performed on an outpatient basis. However, many operators prefer to keep the patients in hospital overnight, partly in order to treat any discomfort and partly because of the small risk of haemorrhage accompanying the procedure.

Tumours smaller than 2 cm in diameter can be treated with one or two ablations. Tumours 2–3 cm in diameter require at least six overlapping ablations, and tumours greater than 3 cm require at least 12 overlapping ablations. Each ablation usually lasts 12–15 minutes and two or three ablations can be carried out during the same session.
Complications are unusual. The main ones are intraperitoneal haemorrhage, liver abscess and seeding along the tumour tract. There is often some pain after the procedure, but this usually settles within 24 hours. Approximately 10–20% of patients have a 1–3°C rise in temperature, as a response to tumour necrosis; this mild pyrexia usually begins the day after the procedure and can last up to a week. However, prolonged, marked pyrexia should always raise the suspicion of infection and merits further investigation.

**Assessment of treatment effectiveness**

CT and ultrasound cannot demonstrate the result of the procedure at the time of treatment. MRI has the potential of measuring temperature and providing ‘online’
Figure 12.2 (a) Residual tumour adjacent to the right hepatic vein. The fast-flowing blood carried away some of the heat and thus prevented complete coagulation. (b) The procedure was repeated after occluding the vein with an occlusion balloon inserted via the right internal jugular vein. (c) Successful coagulation of the residual disease.
monitoring, but this capability is limited by several other practical considerations, including the difficulty of using RF in an MRI machine.

In practice, patients are followed up with contrast-enhanced CT or MRI carried out the day after the procedure or later. Remaining viable tumours appear as an enhancing area, which can be targeted at a subsequent session of treatment.

In some patients CT cannot clearly determine whether there is residual or recurrent tumour. In such cases, positron emission tomography (PET) can be helpful, as viable tumour will give rise to increased activity. However, the study should not be performed within 3 months of treatment as the reactive processes in the liver can also result in 'hot spots' on the PET images.

Most studies that have assessed patient outcome have focused on patients with colorectal metastases, although some have included a mixture of tumours, including metastases from carcinoma of the breast. The results of several clinical series, which have used different methods of radiofrequency ablation, appear promising, with a 52–67% complete ablation rate at 1 year and survival rates of 96%, 64% and 40% at 1, 3 and 5 years, respectively. Approximately 39% of lesions develop local recurrence following treatment. The frequency and time to local recurrence are related to the size of the lesion. In one series of 117 patients, survival was not found to be influenced by the number of metastases at the time of initial therapy. This is contrary to the results of some surgical series that reported tumour recurrence and/or survival following surgical treatment were negatively influenced by the number of metastases removed. However, authors of larger and/or more recent reports have failed to confirm this correlation and have suggested that – in the range of the analyses (generally one to eight metastases removed) – survival following surgical resection is not correlated with the number of metastases removed. These findings suggest that the decision to treat should be guided more by the likelihood of achieving tumour control than the number of lesions present. In a prospective study of predictors of survival after radiofrequency ablation of colorectal metastases to the liver, only the largest tumour size more than 5 cm was found to be a significant predictor of mortality, with a 2.5-fold increased risk of death vs the largest tumour size less than 3 cm. The median Kaplan–Meier survival for all patients was 28.9 months after radiofrequency treatment, whereas historical survival with chemotherapy alone is 11–14 months, suggesting that thermal ablation has a positive impact on survival.

Radiofrequency ablation was used by Livraghi et al to treat 24 patients with 64 hepatic metastases from carcinoma of the breast. The treatment was carried out with 17-gauge, internally cooled electrodes, with the patient under conscious sedation and analgesia or general anaesthesia. A single lesion was treated in 16 patients, and multiple lesions were treated in 8 patients. Follow-up with serial CT ranged from 4 to 44 months (mean 10 months, median 19 months). Complete necrosis was achieved in 59 (92%) of 64 lesions. Among the 59 lesions, complete necrosis required a single treatment session in 58 lesions (98%) and two treatment sessions in one lesion (2%). In 14 (58%) of 24 patients, new metastases developed during follow-up. Ten (71%) of these 14 patients developed new liver metastases. Ten (63%) of 16 patients
whose lesions were initially confined to the liver were free of disease at the time of publication of this study. One patient died of progressive brain metastases. No major complications occurred. The authors concluded that RF ablation appears to be a simple, safe and effective treatment for focal liver metastases in selected patients with breast cancer.

**RADIO FREQUENCY ABLATION AHEAD OF SURGICAL RESECTION**

Some surgeons have advocated delaying resection of liver metastases to allow additional metastases which may be present, but are undetected, to be identified. This ‘test-of-time’ approach can limit the number of resections performed on patients who ultimately will develop additional metastases. Livraghi et al evaluated the potential role and possible advantages of performing RF ablation during the interval between diagnosis and hepatic resection as part of a ‘test-of-time management approach’. They treated 88 consecutive patients who were potential candidates for surgery and who had 134 colorectal carcinoma liver metastases. Complete necrosis was obtained in 53 of 88 patients (60%) and in 85 of 134 lesions (63%). During follow-up of these 53 patients, 16 (30%) remained free of disease and 37 (70%) developed new metastases. New lesions were intrahepatic in 26 of 37 patients (70%), extrahepatic in 4 patients (11%) and both intrahepatic and extrahepatic in 7 patients (19%). Of 26 patients whose new lesions were intrahepatic only, 15 (58%) were retreated with RF and 7 were free of disease at the time of last follow-up (median follow-up 28 months). Ten additional patients with only intrahepatic new lesions were deemed untreatable and 1 patient underwent resection. Overall, among the 53 patients in whom complete tumour necrosis was achieved after RF ablation therapy, 52 (98%) were spared surgical resection: 23 (44%) because they have remained free of disease and 29 (56%) because they developed disease progression. Among all 88 patients, 21 (24%) underwent resection after RF ablation (8 were free of disease at the time of last follow-up), 23 (26%) remained free of disease after successful RF ablation, and 56 (64%) developed untreatable disease progression (44 after RF alone, 12 after RF and surgery). Lesions in 35 of 88 patients (40%) demonstrated local tumour recurrence on follow-up imaging studies. Twenty of these 35 patients (57%) underwent surgical resection, whereas the remaining 15 patients (43%) developed additional, untreatable metastases. New lesions were intrahepatic in 9 of 15 patients (60%), extrahepatic in 1 of 15 patients (7%) and both intrahepatic and extrahepatic in 5 of 15 patients (33%). No patient who had been treated with RF ablation became unresectable due to the growth of metastases, and there was no evidence of needle track seeding in any patient after RF ablation. Overall, among the 35 patients in whom complete tumour necrosis was not achieved after RF ablation therapy, 15 (43%) were spared surgical resection. This important study suggests that current RF ablation techniques, when used as part of a test-of-time management approach, can decrease the number of resections performed. The approach used by these authors results in
complete tumour necrosis in some patients and provides an interval for others, who ultimately will develop new intrahepatic and/or extrahepatic metastases, to do so.

The ‘test of time’ approach has not been formally studied in patients with metastases from carcinoma of the breast. Such a study seems worthwhile in view of the additional contraindications for hepatic resection in this group of patients.

CONCLUSIONS

When attempting to evaluate the benefits of percutaneous radiofrequency ablation for hepatic metastases, the questions that must be asked are:

1. Can it reliably ablate liver metastases?
2. Can it improve survival?
3. Is it safe?

Interpreting the results of ablation is more difficult than assessing the outcome of hepatic resection. Radiofrequency treatment can ablate metastases in 50–90% of cases and is much safer than hepatic resection. With respect to overall survival, there has been no randomised comparison to show that radiofrequency treatment alters long-term survival compared with chemotherapy alone. However, this may be related to the fact that most patients being referred for ablative treatment are considered unsuitable for hepatic resection and have more extensive disease that can be difficult to eradicate. The ideal patient for ablative therapy would be one who, several years after resection of the primary neoplasm for an early-stage well-differentiated cancer, develops a small metastasis in the middle of a lobe of the liver. Such a patient is, however, also ideally suited to surgical treatment and for such a patient the long-term results of surgery are good. Interventional therapy tends to be used in patients who are otherwise considered to be beyond the scope of conventional surgical treatment. It is possible that ablative therapy would achieve similar results to surgery if only similar patients were referred for this method of treatment.

In view of the rarity of use of hepatic resection in patients with hepatic metastases from carcinoma of the breast, it is unlikely that a randomised comparison with radiofrequency ablation will ever be carried out. It seems appropriate to employ thermal ablation in patients with a small number of hepatic metastases, especially following completion of first-line chemotherapy. A study comparing chemotherapy alone with radiofrequency treatment + chemotherapy in patients with more extensive disease would require careful planning; however, such a study would help to define the role of thermal ablation in this large group of patients.

REFERENCES

Palliative care

Andrew Davies and Fiona Bailey

to care sometimes

to relieve often

to comfort always

(Anonymous, 15th century)

THE ROLE OF PALLIATIVE CARE

The World Health Organisation (WHO) has redefined palliative care as:

An approach that improves the quality of life of patients and their families facing the problems-associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual.1

Table 13.1 demonstrates the characteristics of palliative care as described by the WHO.1 One of the most important points is that palliative care may be as applicable to patients with early cancer as to patients with advanced cancer, i.e. palliative care is not synonymous with terminal care. Figure 13.1 demonstrates a model of oncological care and palliative care as endorsed by the WHO.1

Many of the characteristics of palliative care are also the characteristics of high-quality oncological care. Indeed, the majority of palliative care provided by the multidisciplinary team (MDT) is provided by the non-specialists within the MDT. However, this provision is not usually viewed as ‘palliative care’, but rather as ‘supportive care’ or ‘holistic care’. The main role of palliative care specialists is to empower the other members of the MDT to provide this type of care: palliative care specialists should provide ongoing education, training and support (physical, emotional) for the other members of the MDT in order that they may provide this type of care. In addition, palliative care specialists should have a direct input into the care of patients with complex palliative care problems.
Cancer patients often experience a variety of different physical problems. For example, Portenoy et al reported that the median number of symptoms experienced by a mixed group of cancer patients was 11.2 There was no difference in the number of symptoms experienced by patients with different tumour types (breast, colon, ovary, prostate) or different tumour stages (unknown, no disease, local disease, metastatic disease). However, there was a difference in the number of symptoms experienced by patients with differing performance status, i.e. the worse the performance status, the more symptoms experienced (and vice versa). Table 13.2 shows the symptoms reported by patients with breast cancer.2 It should be noted that the majority of patients (63%) had metastatic disease, and half the patients (50%) had a Karnofsky performance status of >80%.

### Table 13.1 Characteristics of palliative care.1

- Provides relief from pain and other distressing symptoms
- Affirms life and regards dying as a normal process
- Intends neither to hasten nor postpone death
- Integrates the psychological and spiritual aspects of patient care
- Offers a support system to help patients live as actively as possible until death
- Offers a support system to help the family cope during the patient's illness and in their own bereavement
- Uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated
- Will enhance quality of life, and may also positively influence the course of illness
- Is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications

From WHO.1

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**Figure 13.1** Model of palliative care. (Reproduced with permission from WHO.1)

### MANAGEMENT OF PHYSICAL PROBLEMS

Cancer patients often experience a variety of different physical problems. For example, Portenoy et al reported that the median number of symptoms experienced by a mixed group of cancer patients was 11.2 There was no difference in the number of symptoms experienced by patients with different tumour types (breast, colon, ovary, prostate) or different tumour stages (unknown, no disease, local disease, metastatic disease). However, there was a difference in the number of symptoms experienced by patients with differing performance status, i.e. the worse the performance status, the more symptoms experienced (and vice versa). Table 13.2 shows the symptoms reported by patients with breast cancer.2 It should be noted that the majority of patients (63%) had metastatic disease, and half the patients (50%) had a Karnofsky performance status of >80%.
The aetiology of physical symptoms includes:

- a direct effect of the underlying cancer
- an indirect effect of the underlying cancer
- an effect of the cancer treatment

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Prevalence amongst a mixed group patients with breast cancer (%)</th>
<th>Prevalence amongst a mixed group of patients with different cancers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lack of energy</td>
<td>80</td>
<td>74</td>
</tr>
<tr>
<td>Worrying</td>
<td>75</td>
<td>71</td>
</tr>
<tr>
<td>Feeling sad</td>
<td>69</td>
<td>65</td>
</tr>
<tr>
<td>Pain</td>
<td>60</td>
<td>64</td>
</tr>
<tr>
<td>Feeling nervous</td>
<td>69</td>
<td>61</td>
</tr>
<tr>
<td>Feeling drowsy</td>
<td>68</td>
<td>60</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>63</td>
<td>54</td>
</tr>
<tr>
<td>Difficulty sleeping</td>
<td>49</td>
<td>52</td>
</tr>
<tr>
<td>Feeling irritable</td>
<td>49</td>
<td>47</td>
</tr>
<tr>
<td>Lack of appetite</td>
<td>51</td>
<td>44</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>44</td>
</tr>
<tr>
<td>Difficulty concentrating</td>
<td>44</td>
<td>41</td>
</tr>
<tr>
<td>Numbness/tingling in hands and feet</td>
<td>34</td>
<td>37</td>
</tr>
<tr>
<td>Feeling bloated</td>
<td>44</td>
<td>37</td>
</tr>
<tr>
<td>Change in taste</td>
<td>37</td>
<td>35</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>35</td>
</tr>
<tr>
<td>Cough</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>‘I don’t look like myself’</td>
<td>37</td>
<td>28</td>
</tr>
<tr>
<td>Itching</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Weight loss</td>
<td>31</td>
<td>27</td>
</tr>
<tr>
<td>Swelling of arms or legs</td>
<td>33</td>
<td>27</td>
</tr>
<tr>
<td>Problems with sexual interest or activity</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Dizziness</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27</td>
<td>21</td>
</tr>
<tr>
<td>Problems with urination</td>
<td>16</td>
<td>17</td>
</tr>
<tr>
<td>Hair loss</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>Mouth sores</td>
<td>20</td>
<td>12</td>
</tr>
<tr>
<td>Urinary accidents</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Nightmares</td>
<td>10</td>
<td>12</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>15</td>
<td>11</td>
</tr>
</tbody>
</table>

* Breast, colon, ovary, prostate.
From Portenoy et al.2
an effect of a concomitant physical disease
an effect of concomitant psychological problems or
a combination of the aforementioned factors.

Indeed, individual patients may experience a number of different symptoms secondary to a variety of different aetiologies. It is important not to assume that symptoms are always related to the cancer, since this may result in inappropriate treatment of those symptoms. For example, abdominal pain due to hepatic metastases should be managed with appropriate analgesics, whereas abdominal pain due to constipation should be managed with laxatives. Thus, all physical symptoms should be fully assessed using a combination of good clinical skills (taking a history, performing an examination) and the appropriate use of investigations.

The management of physical symptoms involves:

- assessment
- treatment of the underlying cause of the symptom
- treatment of the symptom
- reassessment and (if necessary)
- secondary referral.

As discussed above, assessment is essential to determine the aetiology of the symptom, and hence the most appropriate form of treatment for the symptom. However, assessment is also essential to determine the response of the symptom to treatment: the assessment of response should take into account not only the efficacy of the treatment but also the tolerability of the treatment. If the treatment is not effective, then the patient should be reassessed, and an alternative treatment initiated. Similarly, if the treatment is not tolerated, then an alternative treatment should be initiated. In cases of continued poor efficacy and/or poor tolerability, the patient should be referred for a second opinion or alternative therapeutic options.

In many circumstances the most appropriate treatment is further oncological treatment (surgery, radiotherapy, chemotherapy, hormone therapy). Studies suggest that such treatment can result in good symptomatic improvement, and that the degree of symptomatic improvement is related to the degree of tumour response. The decision about embarking on further oncological treatment should be based on an individualised appraisal of the cost/benefit ratio: patients should have an active role in the decision making, although they will often accept treatments with relatively little chance of benefit (even if they are associated with side effects). Patients often require symptom control measures while they wait for a response to oncological treatment. Moreover, patients require symptom control measures when there is no further oncological treatment.

A detailed discussion of the symptom control measures is beyond the scope of this chapter. However, the management of pain is briefly discussed below, and the management of other common symptoms is briefly summarised in Table 13.3. Further
Exercising may lead to increased energy levels, whilst adaptation, occupational therapy and social services may allow better use of stable energy levels.

Corticosteroids tend to have a relatively short duration of effect, i.e. 2–4 weeks.

Sleep hygiene measures involve the adoption of common sense guidelines in relation to sleeping, e.g. avoidance of stimulants before bedtime.

Benzodiazepines tend to have a relatively short duration of effect. Moreover, benzodiazepines are associated with a number of problems, including daytime sleepiness, physical dependence (withdrawal syndrome) and psychological dependence. Pharmacological measures should always be used in conjunction with sleep hygiene measures.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Management options</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td><strong>Non-pharmacological</strong></td>
<td>Exercising may lead to increased energy levels, whilst adaptation, occupational therapy and social services may allow better use of stable energy levels.</td>
</tr>
<tr>
<td></td>
<td>Adaptation of ADL⁷</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physiotherapy (graded exercise)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Occupational therapy (physical aids)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Social services (practical assistance)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pharmacological</strong></td>
<td>Corticosteroids tend to have a relatively short duration of effect, i.e. 2–4 weeks.</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Progestogens</td>
<td></td>
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<tr>
<td></td>
<td>Psychostimulants (e.g. amphetamines, modafinil)</td>
<td></td>
</tr>
<tr>
<td>Drowsiness</td>
<td><strong>Pharmacological</strong></td>
<td>Sleep hygiene measures involve the adoption of common sense guidelines in relation to sleeping, e.g. avoidance of stimulants before bedtime.</td>
</tr>
<tr>
<td></td>
<td>Psychostimulants (e.g. amphetamines, modafinil)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td><strong>Non-pharmacological</strong></td>
<td>Benzodiazepines tend to have a relatively short duration of effect. Moreover, benzodiazepines are associated with a number of problems, including daytime sleepiness, physical dependence (withdrawal syndrome) and psychological dependence. Pharmacological measures should always be used in conjunction with sleep hygiene measures.</td>
</tr>
<tr>
<td></td>
<td>Sleep hygiene measures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cognitive-behavioural techniques</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pharmacological</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Benzodiazepines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other hypnotic agents (e.g. zopiclone, zolpidem)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other agents (e.g. tricyclic antidepressants, antihistamines)</td>
<td></td>
</tr>
</tbody>
</table>

⁷ADL, activities of daily living.
A dietician should supervise any dietary therapy.

Corticosteroids tend to have a relatively short duration of effect, i.e. 2–4 weeks.

These interventions are classified as saliva stimulants, i.e. these interventions induce the salivary glands to secrete additional saliva.

Studies suggest that the saliva stimulants are generally more effective than the saliva substitutes. In addition, saliva stimulants may improve other related symptoms, e.g. taste disturbance. The choice of intervention depends on a number of factors relating to the patient (e.g. presence of teeth), and to the underlying cause of the xerostomia (e.g. damage to salivary gland).

Dietary therapy involves use of foods that taste good, avoidance of foods that taste bad, enhancing the taste of food (e.g. salt, sugar), enhancing presentation of food (e.g. consistency, temperature).

Zinc supplements may be effective in certain circumstances.

The mainstay of management consists of pharmacological interventions.
The choice of antiemetic is determined by the cause of the symptoms: detecting the cause will help identify the relevant neurophysiological pathway, and so the relevant neurotransmitter receptors. In cases of unknown cause, or multiple causes, a broad-spectrum antiemetic (e.g. levomepromazine) should be utilised.

Maintaining fluid intake, fibre intake and mobility will help to prevent the development of constipation. Laxatives are traditionally classified according to their primary function: i.e. stimulant, softener. However, stimulant laxatives also have some softening action (and vice versa). In general, laxatives should be given by mouth; suppositories/enemas should be considered as second-line treatments. The choice of laxative is determined by the nature of the problem: patients with difficulty passing soft stool require a stimulant laxative, whereas patients with difficulty passing hard stool require a softening laxative. In many cases, a combination of laxatives is necessary.

The management of a productive cough involves measures to facilitate coughing, such as chest physiotherapy, and the use of nebulised normal saline.

The management of a non-productive cough involves measures to suppress coughing, such as systemic opioids, other drugs, and (rarely) the use of nebulised local anaesthetics. Systemic opioids are the treatment of choice for a non-productive cough. However, systemic opioids are usually ineffective in suppressing a productive cough.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Management options</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pharmacological</strong></td>
<td>Dopamine antagonists</td>
<td>The choice of antiemetic is determined by the cause of the symptoms: detecting the cause will help identify the relevant neurophysiological pathway, and so the relevant neurotransmitter receptors. In cases of unknown cause, or multiple causes, a broad-spectrum antiemetic (e.g. levomepromazine) should be utilised.</td>
</tr>
<tr>
<td></td>
<td>Anticholinergics</td>
<td></td>
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<td></td>
<td>Antihistamines</td>
<td></td>
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<tr>
<td></td>
<td>5HT3 antagonists</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other agents (e.g. corticosteroids, cannabinoids)</td>
<td></td>
</tr>
<tr>
<td><strong>Constipation</strong></td>
<td><strong>Non-pharmacological</strong></td>
<td>Maintaining fluid intake, fibre intake and mobility will help to prevent the development of constipation. Laxatives are traditionally classified according to their primary function: i.e. stimulant, softener. However, stimulant laxatives also have some softening action (and vice versa). In general, laxatives should be given by mouth; suppositories/enemas should be considered as second-line treatments. The choice of laxative is determined by the nature of the problem: patients with difficulty passing soft stool require a stimulant laxative, whereas patients with difficulty passing hard stool require a softening laxative. In many cases, a combination of laxatives is necessary.</td>
</tr>
<tr>
<td></td>
<td>Oral stimulant laxatives (e.g. lactulose, liquid paraffin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral softening laxatives (e.g. dantron, senna)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Suppositories</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Enemas</td>
<td></td>
</tr>
<tr>
<td><strong>Cough</strong></td>
<td><strong>Non-pharmacological</strong></td>
<td>The management of a productive cough involves measures to facilitate coughing, such as chest physiotherapy, and the use of nebulised normal saline.</td>
</tr>
<tr>
<td></td>
<td>Chest physiotherapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nebulised normal saline</td>
<td></td>
</tr>
<tr>
<td><strong>Pharmacological</strong></td>
<td>Systemic opioids (e.g. codeine, morphine)</td>
<td>The management of a non-productive cough involves measures to suppress coughing, such as systemic opioids, other drugs, and (rarely) the use of nebulised local anaesthetics. Systemic opioids are the treatment of choice for a non-productive cough. However, systemic opioids are usually ineffective in suppressing a productive cough.</td>
</tr>
<tr>
<td></td>
<td>Other drugs (e.g. dextromethorphan, benzonatate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Nebulised local anaesthetics</td>
<td></td>
</tr>
</tbody>
</table>
Non-pharmacological options are a very useful adjunct to pharmacological options, particularly in patients with less severe dyspnoea and/or ‘panic attacks’. Electric fans can be helpful, although the flow of air needs to be directed toward the face of the patient.

Systemic opioids are considered the first-line pharmacological agents for dyspnoea: they have been shown to be effective and well tolerated/safe in this clinical setting. Oxygen may be useful in patients that are hypoxic, but should not be routinely prescribed for patients that are not hypoxic.

All patients should be instructed about skin care, and should be encouraged to move the affected limb. The decision to use support/compression measures, and to use massage techniques, depends on an individual assessment by a lymphoedema specialist.

Non-pharmacological methods are the mainstay of the management of lymphoedema. However, in certain circumstances, antibiotics, corticosteroids and diuretics may have a role to play.

Skin care involves the use of moisturising creams, avoidance of heat, avoidance of tight clothing, avoidance of synthetic clothing and trimming of fingernails (to prevent skin damage).

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Management options</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dyspnoea</strong></td>
<td><strong>Non-pharmacological</strong></td>
<td>Non-pharmacological options are a very useful adjunct to pharmacological options, particularly in patients with less severe dyspnoea and/or ‘panic attacks’. Electric fans can be helpful, although the flow of air needs to be directed toward the face of the patient.</td>
</tr>
<tr>
<td></td>
<td>Breathing techniques</td>
<td>Systemic opioids are considered the first-line pharmacological agents for dyspnoea: they have been shown to be effective and well tolerated/safe in this clinical setting. Oxygen may be useful in patients that are hypoxic, but should not be routinely prescribed for patients that are not hypoxic.</td>
</tr>
<tr>
<td></td>
<td>Cognitive-behavioural techniques</td>
<td>Systemic opioids</td>
</tr>
<tr>
<td></td>
<td>Electric fan</td>
<td>Other systemic agents (e.g. benzodiazepines, phenothiazines)</td>
</tr>
<tr>
<td></td>
<td>Acupuncture</td>
<td>Oxygen therapy</td>
</tr>
<tr>
<td><strong>Lymphoedema</strong></td>
<td><strong>Non-pharmacological</strong></td>
<td>All patients should be instructed about skin care, and should be encouraged to move the affected limb. The decision to use support/compression measures, and to use massage techniques, depends on an individual assessment by a lymphoedema specialist.</td>
</tr>
<tr>
<td></td>
<td>Skin care</td>
<td>Non-pharmacological methods are the mainstay of the management of lymphoedema. However, in certain circumstances, antibiotics, corticosteroids and diuretics may have a role to play.</td>
</tr>
<tr>
<td></td>
<td>External support/compression</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Movement</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Massage</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Pharmacological</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Systemic opioids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other systemic agents (e.g. benzodiazepines, phenothiazines)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oxygen therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Pruritus</strong></td>
<td><strong>Non-pharmacological</strong></td>
<td>Skin care involves the use of moisturising creams, avoidance of heat, avoidance of tight clothing, avoidance of synthetic clothing and trimming of fingernails (to prevent skin damage).</td>
</tr>
<tr>
<td></td>
<td>Skin care</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Psychological techniques</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acupuncture</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Transcutaneous nerve stimulation</td>
<td></td>
</tr>
</tbody>
</table>
The choice of antipruritic is determined by the cause of the symptom. Antihistamines are not universally effective, and sedative antihistamines are more effective than non-sedative antihistamines.

Patients should be cared for in a quiet, well-illuminated room, which contains objects familiar to the patient (e.g. photographs), and objects that can help to orientate the patient (e.g. clock). In addition, patients are often reassured by the presence of non-professional carers. Antipsychotic agents are considered to be the treatment of choice for terminal agitation. Benzodiazepines (e.g. midazolam) are useful in cases associated with anxiety, whereas other sedative drugs (e.g. propofol) are useful in refractory cases. Carers should be informed that although the noise is distressing for them, the excess secretions are invariably not distressing for the patient. Repositioning may be effective and, if there is pooling of secretions in the oropharynx, suctioning may be appropriate/effective. Anticholinergic drugs are effective in ~50% of cases.

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Management options</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terminal agitation</td>
<td><strong>Pharmacological</strong></td>
<td>The choice of antipruritic is determined by the cause of the symptom.</td>
</tr>
<tr>
<td></td>
<td>Antihistamines</td>
<td>Antihistamines are not universally effective, and sedative antihistamines are more effective than non-sedative antihistamines.</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other drugs (e.g. selective serotonin reuptake inhibitors, 5HT3 antagonists)</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Non-pharmacological</strong></td>
<td>Patients should be cared for in a quiet, well-illuminated room, which contains objects familiar to the patient (e.g. photographs), and objects that can help to orientate the patient (e.g. clock). In addition, patients are often reassured by the presence of non-professional carers. Antipsychotic agents are considered to be the treatment of choice for terminal agitation. Benzodiazepines (e.g. midazolam) are useful in cases associated with anxiety, whereas other sedative drugs (e.g. propofol) are useful in refractory cases. Carers should be informed that although the noise is distressing for them, the excess secretions are invariably not distressing for the patient. Repositioning may be effective and, if there is pooling of secretions in the oropharynx, suctioning may be appropriate/effective. Anticholinergic drugs are effective in ~50% of cases.</td>
</tr>
<tr>
<td>Excess secretions ('death rattle')</td>
<td><strong>Pharmacological</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticholinergic agents (e.g. glycopyrronium bromide, hyoscine hydrobromide)</td>
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</tbody>
</table>
information about symptom control measures can be obtained from a variety of specialist supportive care and palliative care textbooks.6,7

**Management of pain**

In general, the management of cancer pain is based on guidelines produced by the WHO.8 The guidelines cover all aspects of the management of pain, although they focus on the pharmacological management of pain. The guidelines promote five main principles with regard to the pharmacological management of pain:

1. ‘By mouth’ – drugs should be given orally (if possible).
2. ‘By the clock’ – drugs should be given regularly.
3. ‘By the ladder’ – drugs are given in a stepwise manner (Figure 13.2).
4. ‘For the individual’ – opioid drugs should be individually titrated.
5. ‘Attention to detail’.

Step 1 of the WHO ladder involves the use of a non-opioid, which is usually paracetamol or a non-steroidal anti-inflammatory drug (see Figure 13.2).8 If this does not control the pain, then the treatment should be escalated to step 2, which consists of an ‘opioid for mild to moderate pain’ (e.g. codeine, dihydrocodeine) with a non-opioid. Similarly, if this does not control the pain, then the treatment should be escalated

---

**Figure 13.2** World Health Organisation three-step analgesic ladder. (Reproduced with permission of WHO.8)
to step 3, which consists of an ‘opioid for moderate to severe pain’ (e.g. morphine, oxycodone) with or without a non-opioid. At each step, adjuvant drugs may be employed: adjuvant drugs include antiemetics, laxatives, anxiolytics and co-analgesics (drugs that have a secondary/subsidiary analgesic effect).

Morphine is still considered the gold standard opioid for moderate to severe pain. Patients are usually started on a normal-release preparation – short acting: 4-hour duration of effect – and the dose is titrated upwards according to the response. Once the pain is controlled, patients are then usually converted to a controlled-release preparation – long acting: 12–24-hour duration of effect. Approximately $33\%$ of patients experience nausea and vomiting as an acute side effect, and so all patients should be given a prescription for a suitable antiemetic to take as required. Similarly, $40–70\%$ of patients experience constipation as a chronic side effect, and so all patients should be given a prescription for a suitable laxative combination to take regularly.

Studies suggest that $10–30\%$ of patients do not achieve a good outcome with morphine, i.e. have poor efficacy and/or poor tolerability. A number of strategies are used to overcome this problem, including the use of opioid switching (‘opioid rotation’). Opioid switching may result in improved efficacy and/or tolerability, but may also result in worsening efficacy and/or tolerability, i.e. opioid switching is unpredictable. Opioid switching has become feasible as a result of the increase in availability of alternative opioids for moderate to severe pain (e.g. fentanyl, hydromorphone, methadone, oxycodone). It should be noted, however, that none of the alternative opioids have been shown to have a greater efficacy, or tolerability, than morphine.

A number of co-analgesic drugs have been used to treat cancer-related pain. Co-analgesic drugs used in neuropathic pain include anticonvulsants, antidepressants and corticosteroids. Contrary to popular belief, the evidence suggests that opioids for moderate to severe pain are generally more effective than co-analgesic drugs in the management of neuropathic pain. Moreover, the evidence suggests that opioids for moderate to severe pain are generally better tolerated than co-analgesic drugs in this clinical setting. However, these drugs do have an important subsidiary role in the management of neuropathic pain. Other co-analgesic drugs used in malignant pain include bisphosphonates and muscle relaxants.

Studies suggest that the WHO guidelines are generally effective, with $69–100\%$ of patients achieving ‘adequate analgesia’. A number of strategies are available to treat patients with persistent/unresponsive pain, including:

2. Anaesthetic techniques – spinal analgesia, nerve blocks, neurolytic procedures, spinal cord stimulation.
4. Psychological interventions – behavioural techniques, cognitive techniques, psychotherapy.
Management of other symptoms

As discussed above, studies suggest that cancer patients often experience a variety of different physical problems. However, there is often a disparity between the symptoms elicited by healthcare professionals and the symptoms experienced by cancer patients. Thus, certain ‘core symptoms’ (e.g. pain, constipation) are usually elicited, whereas other ‘orphan symptoms’ (e.g. xerostomia, insomnia) are often not elicited. It is unclear why there is such a disparity, particularly as many of these orphan symptoms are associated with significant morbidity/distress.

The management of a symptom is dependent on the identification of that symptom. It is essential that patients are routinely asked about the whole range of relevant symptoms. In particular, it is essential that patients are asked about symptoms that are common in patients with breast cancer, that are common in patients with advanced cancer and that are related to the side effects of anticancer/supportive treatments. The use of validated symptom assessment tools should help to diminish the disparity between the symptoms elicited by healthcare professionals and the symptoms experienced by cancer patients.

MANAGEMENT OF PSYCHOSOCIAL PROBLEMS

Psychosocial problems are extremely common in patients with advanced disease. Patients often report subjective psychological distress (e.g. anxiety, low mood). For example, Portenoy et al reported that 75% of breast cancer patients admitted to ‘worrying’, whereas 69% of breast cancer patients admitted to ‘feeling sad’ (see Table 13.2). In many instances, these feelings are appropriate to the situation, and are not considered to represent a psychiatric disorder.

However, studies suggest that psychiatric disorders are relatively common in patients with breast cancer. For example, Hopwood et al reported that 21% of breast cancer patients met the criteria for an anxiety and/or depressive disorder using the Hospital Anxiety and Depression Scale. Thus, 9% of patients were anxious, 9% were depressed, and 9% were anxious and depressed. The management of these disorders includes psychotherapy, cognitive-behavioural therapy and drug therapy.

Patients with advanced cancer may experience a number of other psychosocial problems. Lidstone et al reported the concerns of a cohort of breast cancer patients attending clinics at an oncology centre: 58% of patients were concerned about others; 25% were concerned about their relationship with others; 35% were concerned about money; and 3% had concerns relating to spiritual/religious issues.

The family/carers of patients with advanced cancer may experience similar psychosocial problems. It is important that the MDT provide ongoing support for the family/carers of patients, since unresolved issues will not only impact on the person but also on the relevant patient. Moreover, such support needs to be offered not only while the patient is alive but also after the patient has died (bereavement care).
Unfortunately, at some stage, the majority of patients with metastatic breast cancer will progress to the terminal phase of the disease. Table 13.4 demonstrates the principles of high-quality end of life care as described by the American Medical Association (and endorsed by the American Society of Clinical Oncology). The adoption of such principles can help to minimise the distress of the patient and their carers during the terminal period. Nevertheless, the terminal phase remains a difficult period for all concerned.

The problems encountered in patients with advanced breast cancer are essentially the same as those encountered in patients with other types of advanced cancer. The physical problems include those discussed above, and specific ones related to the dying process (terminal agitation, excess respiratory secretions). The management of terminal agitation and excess respiratory secretions is briefly summarised in Table 13.3. The psychosocial problems include those discussed above, although the imminence of death may heighten the impact of specific problems.

In most cases, the terminal phase is relatively straightforward in patients with advanced breast cancer. Thus, it is feasible to consider the option of a home death, rather than an institutional death. (Studies suggest that most cancer patients would prefer to die at home, although most cancer patients actually die in an institution.) In such circumstances, it is important that the patient and their families are provided with not only adequate medical support but also with adequate other types of practical support (e.g. social services, practical aids).

**REFERENCES**

Index

Page numbers in *italics* indicate figures or tables.

ABI-007 46
Abraxane (ABI-007) 46
acetabular metastases 189, 190, 190, 192
afterloading techniques, in airway obstruction 170
agitation, terminal 219, 223
AIB1 69
aims of treatment 2–3
airway obstruction, upper 169–73, 170, 171
aminoglutethimide 12, 17
amputation 196
analgesic ladder 220, 220–1
analgesics 220–1
anastrozole (Arimidex) 9, 12
clinical efficacy 12, 13, 13–14, 14
fulvestrant following/combined with 21, 22–3
pharmacology 11–12
postmenopausal second-line endocrine therapy after 16
signal transduction inhibitors with 27
to fulvestrant 18–19, 19
to other aromatase inhibitors 15–16
androstenedione 11, 12
anorexia, management 216
anterior spinal artery, occlusion 98–9
anthracyclines 37–40, 38
cardiotoxicity 38–9, 39
in liver dysfunction 40, 55, 56
resistance, chemotherapy options 46–53
taxane combinations 44
trastuzumab combinations 46, 65, 68
see also doxorubicin; epirubicin
antiangiogenic agents 73–4
antitubulin agents, novel 45–6
anxiety 222
Arimidex see anastrozole
Aromasin see exemestane
aromatase inhibitors (AIs) 4, 9–17
chemical structures 12
clinical efficacy 11–16
comparisons between 15–16
as first-line therapy vs tamoxifen 13–15, 14
fulvestrant following 19–21, 20
mechanism of action 9, 10
non-steroidal vs steroidal 17
patient selection 8, 9
pharmacology 11–12
plus LHRH agonists 11, 24
plus targeted therapies 25–7, 27
postmenopausal second-line endocrine therapy after 16–21
resistance 25, 26
as second-line therapy post tamoxifen 12–13, 13
tolerability 15
see also individual agents
axillary node metastases, PET/CT 110–11
back pain 94–5, 154
Beck’s triad 168
bereavement care 222
bevacizumab 73–4
capcitabine combination 49, 74
paclitaxel combination 45, 74
biopsy, spinal metastases 188
BISMARK trial 84
bisphosphonates 4, 80–8, 81
clinical effectiveness 81–4, 83
toxicity 85–6
unanswered questions 84–5
bone
effect of radiotherapy on 124–5
grafts 187
healing after radiotherapy 129, 130
turnover markers 125
bone marrow toxicity, radiotherapy 128
bone metastases 79, 181–99
appendicular skeleton 191–8, 193
axial skeleton 185–91
bisphosphonate therapy 80–5
toxicity 91, 92, 181
imaging 94–5, 96, 97, 111–12, 182–4
pathophysiology 79–80
PET/CT
response assessment 114–15, 116–17
restaging recurrent disease 115–17, 119
staging metastatic disease 111, 111–12, 113
presentation 181
radiotherapy 124–31
bone pain 125, 181
investigations 182
neuropathic, radiotherapy 125, 127
radiotherapy 125–6
bone scan, isotope 182–3
symptomatic metastatic disease 91, 95, 96
at time of cancer diagnosis 89, 90, 91
vs PET/CT 111–12
brachial plexopathy, imaging 103–5, 105, 115–17
brain metastases 147–50
epidemiology 147–8
HER2 status and 67, 135
imaging 102, 102–3, 103
intrathecal chemotherapy 55
radiosurgery see stereotactic radiosurgery
radiotherapy 134–43
see also whole-brain radiotherapy
surgery 138–9, 149–50
symptoms 148
trastuzumab therapy and 67
treatment 149–50
bronchoscopic palliation, airway obstruction 169–73
buserelin 24
CA 15-3 120
capcitabine 47, 47–9
anthracycline/taxane-refractory disease 48–9
bevacizumab combination 49, 74
contraindications and dose adjustments 47–8, 48, 54
in elderly patients 54
first-line combinations 44–5, 46
trastuzumab combination 49, 67
cisplatin 51, 54, 66–7
carcinembryonic antigen (CEA) 120
cardiac tamponade 168
cardiotoxicity
anthracyclines 38–9, 39
trastuzumab 68
Cardioxane (dexrazoxane) 39
CCI-779 (tepsirolimus) 73
CEA (carnobondrymic antigen) 120
central nervous system (CNS) metastases 91, 92, 147–60
after trastuzumab therapy 67
imaging 96–103
intrathecal chemotherapy 55
see also brain metastases; leptomeningeal metastases
cerebrospinal fluid (CSF) cytology 100
chemical pleurodesis 164
chemotherapy 4, 33–60
anthracylene-naive patients 42–6, 46
anthracycline/taxane-resistant patients 46–53
choice and duration of regimen 35–7
combination vs monotherapy 35–6, 37
influence of prior therapies 34–5
intrathecal 55, 151–2, 152
leptomeningeal metastasis 151–2, 152
phase I clinical trials 53
principles 33–4
response assessment 35, 113–14
special considerations 53–5
see also anthracyclines; taxanes; individual agents
chest drainage 164, 165
chest radiography (CXR)
symptomatic metastatic disease 92–3, 94
at time of cancer diagnosis 89, 90
chest wall metastases
palliative radiotherapy 131–3, 132
palliative surgery 175–7, 176, 177
choroidal metastases
imaging 103, 104
palliative radiotherapy 133–4, 134
chromogenic in-situ hybridisation (CISH) 63
cisplatin combinations 51, 66–7
clinical trials, phase I 53
clostronate 80, 81
clinical efficacy 81, 82
CNS metastases see central nervous system metastases
covalysis drugs 221
computed tomography (CT)
after ablation of liver metastases 204–6
bone metastases 183–4
intra-abdominal metastases 105–6
myelography 99
in neurological presentations 97, 102
symptomatic metastatic disease 91, 92, 93, 93–4, 94, 95, 98
whole body imaging 106
see also positron emission tomography/computed tomography
constipation, management 217
corticosteroids
brain metastases 137, 149, 150
spinal cord compression 154
cost-benefit analysis, bisphosphonates 82
cost-effectiveness
dermocrine therapies 17
palliative radiotherapy 126
costs, advanced breast cancer 2
cost–utility analysis, radiotherapy of brain metastases 143
cough, management 217
CT *see* computed tomography

cutaneous metastasis

- palliative radiotherapy 131–3, 132
topical miltefosine 54
cyberknife 150, 151
cyclophosphamide
- anthracycline combinations 36, 37, 38
taxane combinations 44, 46
trastuzumab and 65
cytotoxic chemotherapy *see* chemotherapy
daunorubicin 38
dearth rattle (excess secretions) 219, 223
deaths, breast cancer 1, 7
depression 222
dexamethasone
- brain metastases 149
docetaxel side effects 41
spinal cord compression 154
dexrazoxane 39
diabetes, chemotherapy 54
diathermy resection, in airway obstruction 170

distant metastases, imaging 89–91, 111, 111–12
docetaxel 40–2
- contraindications and dose adjustments 42, 56
- first-line combinations 44, 45, 46, 65
- first-line monotherapy 43–4
gemcitabine combination 52
side effects 40–1
trastuzumab combinations 45, 65–7
vinorelbine combination 51
doxorubicin 37, 38, 46
- cardiotoxicity 38–9
- chemical structure 38
- in liver dysfunction 40, 56
- mono-*vs* combination therapy 36, 37
pegylated liposomal 39
- in renal impairment 54
taxane combinations 44
- trastuzumab combinations 65
vinorelbine combination 51
drowsiness, management 215
Dutch Bone Metastasis Study (DBMS) 125
dyspnoea
- intrathoracic metastases 92, 163, 164, 169
management 218

Eastern Cooperative Oncology Group (ECOG)
- performance status 34, 35
EFECT (Evaluation of Faslodex *vs*
Exemestane Clinical Trial) 21, 22
elderly patients, chemotherapy 34, 53–4
electron beam therapy, locally recurrent disease 132
end of life care 223, 223
Enders nails 196–7
endobronchial irradiation, in airway obstruction 170
endobronchial stents/T-tubes 170–3
silicone 172, 172
wire 172, 173
everodocrine therapy 2, 4, 7–32
- cost-effectiveness 17
- first-line 13–15, 14
HER2 overexpression and 68–9
- options 8–11, 10
- postmenopausal second-line, post aromatase inhibitors 11, 16–21
- premenopausal women 21–4
- resistance 24–7
- mechanisms 25, 26
- strategies for overcoming 25–7, 27
- second-line, post tamoxifen 12–13
- selection of patients for 7–8, 8, 9
*see also* aromatase inhibitors; fulvestrant;
luteinising hormone-releasing hormone (LHRH) agonists; ovarian ablation;
tamoxifen
endoscopic palliation
- airway obstruction 169–73
- spinal metastases 189
epidemiology, advanced breast cancer 1, 7
epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors 70–2, 71
epirubicin 36, 37, 37, 38
- cardiotoxicity 38–9, 39
- chemical structure 38
- in liver dysfunction 40, 56
- in renal impairment 54
- trastuzumab combinations 65
epithilones 45
erlotinib 71, 71–2
etidronate 82
exemestane 9–11, 12
- after prior non-steroidal aromatase inhibitors 17
- clinical efficacy 12–13, 13, 14, 15
- pharmacology 11–12
- *vs* fulvestrant 21, 22–3
- *vs* other aromatase inhibitors 16
eye disease *see* choroidal metastases; orbital metastases

2-[18F]-fluoro-2-deoxy-D-glucose (18F-FDG) 109
FAC regimen 38, 44
FACT (Faslodex and Arimidex Clinical Trial) 21, 23
fadrozole 12–13
farnesyltransferase inhibitors (FTIs) 72  
fluorescence in-situ hybridisation (FISH), HER2 testing 62, 63  
5-fluorouracil (5-FU)  
5-fluorouracil (5-FU) anthracycline combinations 36, 37, 38  
other combinations 51  
formestane 12, 12–13  
vs other aromatase inhibitors 16  
fractionation, radiation 123–4  
bone metastases 125–6, 126, 127  
whole-brain radiotherapy 136  
fractures, pathological 124, 191–8  
imaging 182, 183  
prophylactic fixation 193  
radiation therapy after surgical fixation 129  
signs of impending 192–3, 193  
spinal 185  
surgical fixation 193–8  
fulvestrant (Faslodex) 11, 17–21  
following/combined with aromatase inhibitors 19–21, 20, 22–3  
mechanism of action 17–18, 18, 25, 26  
signal transduction inhibitors with 27  
in tamoxifen-resistant disease 18–19, 19  
fungation, palliative radiotherapy 131–3, 132  
gamma knife stereotactic radiosurgery 139, 140, 140–1, 150  
gamma nail 194  
geftinib (Iressa) 25  
phase II monotherapy trials 71, 71–2  
plus endocrine therapy 26, 27  
gemcitabine 51–3  
dose adjustments 52, 52  
in elderly patients 54  
paclitaxel combination 44, 46, 52–3, 53  
Girdlestone procedure 110  
global impact, advanced breast cancer 2  
gonadotrophin-releasing hormone agonists  
signal transduction inhibitors with 27  
cerebral metastases and 67, 135  
detection techniques 62–3, 63  
endocrine therapy responsiveness 68–9  
prognosis 63  
trastuzumab responsiveness 64, 64  
HER2-positive tumours  
endocrine therapy responsiveness 68–9  
prognosis 63  
trastuzumab responsiveness 64, 64  
HER2 tyrosine kinases 61  
small molecule inhibitors 69–72  
HER2 61–2  
in recurrent disease 67–8  
hypercalcaemia 80  
bisphosphonate therapy 81, 81  
hyperthermia, palliative radiotherapy 132–3, 133  
ibandronate 80, 81  
clinical efficacy 81, 82, 83  
toxicity 85  
vs other bisphosphonates 84  
idarubicin 38  
immunohistochemistry (IHC), HER2 testing 62, 63  
insomnia, management 215  
intra-abdominal metastases, imaging 105–6  
intraduodenal nailing 194  
intramedullary nailing 194  
intrathecal chemotherapy 55, 151–2, 152  
intrathoracic metastases see thoracic complications  
Iressa see gefitinib  
isotope bone scan see bone scan, isotope  
ixabepilone 45  
jaw, osteonecrosis 86  
jaw, osteonecrosis 86  
kyphoplasty, percutaneous 156, 188–9, 189  
kynurenalcis 155, 187  
laminectomy 155, 187  
lapatinib 69–70, 70  
laser therapy  
PET assessment of response 114  
upper airway obstruction 170
leptomeningeal metastases (meningeal carcinomatosis) 151–2
chemotherapy 55, 151–2, 152
imaging 100, 101, 102
management 151–2
letrozole 9–11, 12
clinical efficacy 12–13, 13, 14, 14–15
pharmacology 11–12
postmenopausal second-line endocrine therapy after 16–17
signal transduction inhibitors with 27, 72, 73
vs other aromatase inhibitors 15–16

leukaemia, treatment-related 37

LHRH agonists see luteinising hormone-releasing hormone agonists
linear accelerator (linac)-based stereotactic radiosurgery 139–41, 140, 141

liver dysfunction, cytotoxic drug dose reductions 55, 56

liver metastases 91, 92, 201–8
endocrine therapy 7–8, 9
imaging 95, 97, 98
local ablation techniques 202
radiofrequency ablation see radiofrequency (RF) ablation, liver metastases
response assessment 114, 204–7
surgical resection 201–2, 207–8
local treatments 4
locally advanced breast disease
endocrine therapy 7, 9
palliative radiotherapy 131–3, 132
palliative surgery 175–7, 176, 177
PET/CT 115–17, 119

long bone metastases 191–8
Mirels’ scoring system 192–3, 193
radiotherapy after surgical fixation 129
surgical management 193–8

lung
metastases see pulmonary metastases
trapped 164, 165

luteinising hormone-releasing hormone (LHRH) agonists 10, 11, 21–4
plus aromatase inhibitors 11, 24
plus tamoxifen 11, 21–4
lymph node metastases 91, 92
imaging 92, 93, 93–4
PET/CT 110–11
lymphangitis carcinomatosa 92–3, 94
lymphoedema, management 218

magnetic resonance imaging (MRI) after ablation of liver metastases 204–5
bone metastases 184
brachial plexopathy 103–4, 105
brain metastases 102, 102, 103, 148, 148
orbital metastases 103, 104

spinal cord compression 98–9, 99, 100
spinal intramedullary metastasis 153, 153
spinal meningeal metastases 100, 101
symptomatic metastatic disease 91, 95, 96
vs PET/CT 112, 115–17
whole body 106
mammalian target of rapamycin inhibitors see mTOR inhibitors
megestrol acetate, vs aromatase inhibitors 12–13, 13
MEK inhibitors 25
meningeal carcinomatosis see leptomeningeal metastases
metastases
distant, imaging 89–91, 111, 111–12
sites of 91, 92
see also specific metastatic sites
methotrexate, intrathecal 55
miltefosine, topical 54
Mini-Mental State Examination (MMSE) scores 138
Mirels’ scoring system 192–3, 193
mitomycin C 36, 37, 46, 51
mitoxantrone 36, 37, 38, 54
morphine 221
MRI see magnetic resonance imaging
mTOR inhibitors 73
plus aromatase inhibitors 26–7, 27, 73
multidisciplinary team (MDT) 3–5, 211
MVP regimen 51
myelography 99

nausea, management 216–17
nerve root compression 185, 186
neurological complications 147–62
imaging 96–105
see also brachial plexopathy; central nervous system (CNS) metastases; spinal cord compression
neuropathic bone pain, radiotherapy 125, 127
night pain 181
nodal metastases see lymph node metastases
non-steroidal anti-inflammatory drugs (NSAIDs) 220–1
novel therapies 61–78
N-telopeptide, urinary 125
nuclear medicine scanning see bone scan, isotope

ocular metastases see choroidal metastases; orbital metastases
oestrogen, efficacy of fulvestrant and 20
oestrogen receptor or oestrogen/progesterone receptor-positive (ER+ve or ER/PgR+ve) breast cancer 7–8
endocrine therapy options 8–11, 21
resistance to oestrogen deprivation 25, 26
treatment options 34
pleurodesis, chemical 164
pleuropertonal shunts 164–7, 165, 166
polymethyl methacrylate (PMMA) cement 188
positron emission tomography/computed
tomography (PET/CT) 4, 109–22
assessing response to treatment 112–15,
116–17, 206
brachial plexopathy 105, 115–17
in clinical practice 120
distant metastatic disease 111, 111–12, 113
primary staging 109–11, 110
recurrent disease 115–20, 119
symptomatic metastatic disease 91
postmenopausal women, endocrine
therapy 8–11
first-line 15
second-line, after aromatase inhibitors 11,
16–21
premenopausal women, endocrine therapy
8–9, 11, 21–4
progesterone receptor (PgR)-positive breast
cancer 7–8
prostheses
chest wall defects 175–6, 177
hip and pelvis 190–1, 191
long bone metastases 193–4, 197–8
pruritus, management 218–19
psychosocial problems, management 222
pulmonary metastases 91, 92, 173–5
imaging 92, 93
mechanisms of spread 173
surgical resection 173, 174–5
quality of life 3
Radiouclide imaging 173
radiography, plain
bone metastases 182, 183, 184
chest see chest radiography
impending fractures 192
symptomatic metastatic disease 95, 97
radiotherapy, palliative 4, 123–45
bone metastases 124–31
after surgical fixation 129
bone healing after 129, 130
fractionation 125–6, 126, 127
future research directions 131, 131

230  Handbook of Metastatic Breast Cancer
<table>
<thead>
<tr>
<th>Treatment of Metastatic Breast Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aims 2–3</td>
</tr>
<tr>
<td>Options 3–5</td>
</tr>
<tr>
<td>Response see response to treatment</td>
</tr>
<tr>
<td>Survival benefits 3</td>
</tr>
<tr>
<td>T-tubes, endobronchial 170–3, 171, 172</td>
</tr>
<tr>
<td>Tumour markers, rising, unknown cause 117–20</td>
</tr>
<tr>
<td>Tyrosine kinase inhibitors (TKIs) 69–72, 70</td>
</tr>
<tr>
<td>EGFR 70–2, 71</td>
</tr>
<tr>
<td>Plus aromatase inhibitors 26–7, 27</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ultrasound (US)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brachial plexopathy 104–5, 105</td>
</tr>
<tr>
<td>Symptomatic metastatic disease 91, 92, 93, 95, 97, 98</td>
</tr>
<tr>
<td>At time of cancer diagnosis 89, 90</td>
</tr>
</tbody>
</table>

| Vascular endothelial growth factor (VEGF) 73 |
| Vertebral metastases see spinal metastases |
| Vertebralplasty, percutaneous 156, 158, 188–9, 189 |

| Video-assisted thoracoscopic surgery (VATS) 164, 168, 189 |
| Vinblastine 36, 37, 46, 51 |
| Vinorelbine 49, 49–51 |
| Vinorelbine combinations 50–1, 66 |
| Dose adjustments 50, 50, 54, 56 |
| Visceral metastases endocrine therapy 7–8, 9 |
| Imaging 105–6 |
| See also liver metastases |
| Vomiting, management 216–17 |
| Vorozole 12, 13 |

| Whole-brain radiotherapy (WBRT) 135–9, 149 |
| After neurosurgery 138–9, 150 |
| Radiation dose 136–7 |
| Technique 135–6, 136 |
| Toxicity 137–8 |
| With/without stereotactic radiosurgery 142–3 |
| Wide-field radiotherapy (WFRT) 129 |
| World Health Organization (WHO) analgesic ladder 220, 220–1 |
| On palliative care 211, 212 |

| Xerostomia, management 216 |
| X-rays, plain see radiography, plain |
| Zoladex see goserelin |
| Zoledronate 80, 81 |
| Clinical efficacy 81, 82, 83 |
| Toxicity 85, 86 |
| vs other bisphosphonates 84 |