Metastatic disease of the breast and local recurrence

Mark Verrill

Abstract

Multimodality primary therapies for breast cancer combined with earlier detection have led to a sharp decline in the death rate from breast cancer in the UK over the last 40 years in the face of a rising incidence. The latest UK statistics from Cancer Research UK report 55,122 new cases of breast cancer in 2015 with 11,563 deaths from breast cancer recorded in 2016. Crudely, this equates to a cure rate of around 80% for all comers and demonstrates a clear improvement in outcome with 50,285 new cases in 2011 and 11,716 deaths in 2012. Despite this good news, there are still significant numbers of women (and men) who suffer from either a local recurrence or metastatic disease following apparently successful treatment for early breast cancer (Stage I to III). Only a minority of individuals, 6.6% with the stage recorded at diagnosis, present with stage IV disease. This review considers the treatment options available to individuals with locally recurrent and advanced breast cancer (ABC).

Keywords Breast cancer; local recurrence; metastatic disease

Considerations when assessing a patient with ABC

There are four main considerations when assessing a patient with recurrent or metastatic breast cancer; the patient, tumour burden and distribution, tumour biology and previous treatments (Figure 1). These build a picture of the available treatment options which range from excision of locally recurrent disease with curative intent, through aggressive multimodality treatment of oligometastatic disease, systemic anticancer therapies (SACT) modifying the natural history of the disease, to best supportive care.

Patient engagement in treatment choices at any stage of disease is paramount. The patient should be involved at all stages of decision making and the gold standard of care is for a specialist secondary breast cancer nurse specialist to be present at each consultation and available to support decision making. In the absence of a dedicated nurse, external organisations such as Maggie's Centres provide invaluable support, which are situated adjacent to an increasing number of cancer centres and with more planned. In patients scheduled for SACT, there may be options to use drugs with different routes of administration and specific toxicities and patient preference in these situations should be considered.

Physical patient characteristics are also fundamentally important. There is a clear link between poor functional status and early mortality following drug treatment as well as an impact on longer term outcomes. Disturbance of organ function and residual toxicity from previous treatment can limit the ability to use particular drugs. Patients with visceral crisis, characterized by rapid and symptomatic progression of disease with disordered liver biochemistry may require treatment with a high likelihood of producing a brisk tumour response.[1] This may lead to selection of a cytotoxic chemotherapy in patients where endocrine therapy would otherwise be the treatment of choice. Assessment of menopausal status is required to select antiendocrine therapies.

The distribution and burden of disease at recurrence defines the presenting symptoms and the goals in controlling them. While the systemic nature of metastatic breast cancer lends itself to "whole body" treatment with systemic therapies, there are cases where local therapies or organ directed treatments may be used. Local recurrences, brain metastases and spinal cord compression are most effectively treated with surgery and/or radiotherapy. Meningeal disease may require intrathecal chemotherapy. Bone metastases may need orthopaedic intervention to maintain function, radiotherapy for pain and specific bone directed therapies to prevent skeletal related events. Isolated liver metastases or liver metastases in the context of limited and well-controlled bone disease may be amenable to resection, ablation or stereotactic radiotherapy.

Locoregional recurrence

Following primary local therapy, there is an ongoing, albeit small, risk of recurrence in the conserved breast, the skin flaps following mastectomy or the axilla regardless of axillary treatment. In these sites, further surgery may allow macroscopic complete clearance of the recurrent disease and this should be considered in the Multidisciplinary Team (MDT) meeting. Local recurrence in a conserved breast is an indication for mastectomy and cannot usually be followed by radiotherapy due to the limitations to radiation dose resulting from previous treatment to the conserved breast. There is evidence that systemic therapy with endocrine therapy in ER positive patients and with chemotherapy in ER negative patients improves outcomes after excision and/or radiation for locoregional recurrence and, by extrapolation, anti-HER-2 therapy should be considered in HER-2 positive disease.[2] In cases where there is no option for locoregional therapy, the management options are the same as for overt metastatic disease. This includes many supraclavicular, infraclavicular and internal mammary nodal recurrences.

Systemic anticancer therapies for advanced breast cancer

Knowledge of tumour biology is crucial to inform SACT strategies and it is vital to know hormone receptor (HR) and HER-2 status. There are distinct strategies for management of each subgroup defined by HR and HER-2, including for triple negative cancers (oestrogen, progesterone and HER-2 negative).[1] There are also emerging therapies specifically directed at patients with BRCA gene mutation associated cancers. As a general principle, where there is a validated biological target with an appropriate associated therapeutic, use of a targeted therapy should be the first consideration in selecting anticancer drug therapy. Chemotherapy is increasingly regarded as an old fashioned and rather

Mark Verrill *MA MB BChir FRCP is Head of the Department of Medical Oncology at the Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, UK. Conflicts of interest: none.*

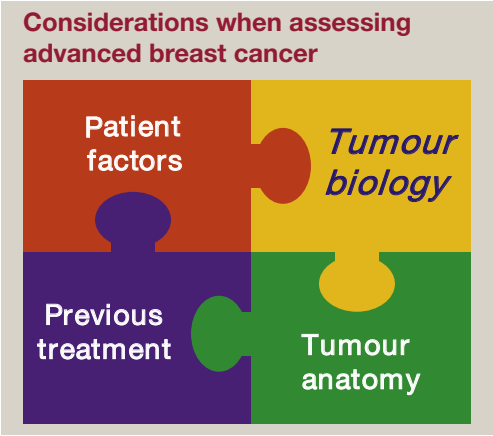

Figure 1

blunt tool although it remains the standard of care in triple negative ABC and in combination with the majority of anti HER-2 therapies. Many patients with local or metastatic recurrence have previously been exposed to SACT in the adjuvant setting. This impacts on choice of therapies for ABC because of drug resistance, cumulative toxicities and, increasingly, funding restrictions based on tightly defined treatment pathways. Recently, standard definitions of primary and secondary (acquired) resistance to endocrine therapies have been agreed and published.[1] There is no corresponding consensus for cytotoxic treatments.

HR positive HER-2 negative disease

The majority of breast cancers are oestrogen receptor (ER) positive and so have the potential to benefit from anti endocrine therapies (ET). Most patients with ER positive cancers and regardless of recurrence risk based on other parameters will receive adjuvant anti-endocrine therapy as part of the treatment package for early breast cancer. In the advanced setting, patients with potentially endocrine sensitive disease should be considered for anti endocrine treatment. Endocrine sensitivity in this context is defined as relapse more than 12 months after completing adjuvant endocrine therapy.[1]

Tamoxifen was the first licensed anti-oestrogen and remains the standard of care in premenopausal women. Gonadotrophin releasing hormone (GnRH) analogues can be used to render premenopausal women post menopausal and have the advantage over surgical or radiotherapy ovarian ablation of reversibility. The majority of recent clinical data in MBC are from trials in postmenopausal women so it is important to assess menopausal status in all women for whom anti endocrine therapy is planned.

Trials of the non-steroidal aromatase inhibitors (AIs) anastrozole and letrozole in the late 1990s and their publication thereafter led to the establishment of this drug class as the standard of care as first line treatment for post menopausal women with ER-positive (HER-2 negative) advanced breast cancer.[3] Initially this choice was not affected by adjuvant treatment, which in the overwhelming majority of patients was tamoxifen. However, AIs are now part of the adjuvant therapy treatment standard and so in MBC their use as monotherapy is typically reserved for patients who are endocrine therapy naïve or with endocrine sensitive disease. The addition of the cyclin dependent kinase (CDK) 4/6 inhibitor palbociclib to letrozole in the first line treatment of ER positive HER-2 negative ABC extended progression free survival (PFS) from 10 to 20 months in a randomised phase II trial[4] and has led to accelerated approval by US Food and Drug Administration (FDA). The follow-up phase III trial (PALOMA-3) compared treatment with fulvestrant and palbociclib with fulvestrant alone and found close to a tripling of PFS. NICE approved the use of CDK 4/6 inhibitors with an aromatase inhibitor for previously untreated, hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer in late 2018.

Treatment of patients with endocrine resistant disease

Patients relapsing after prior endocrine therapy for breast cancer are regarded as having endocrine resistance. Primary resistance is defined by either relapse during the first two years of ET or progression within the first 6 months of first line ET for MBC. Secondary or acquired resistance is defined as relapse during adjuvant ET but after the first 2 years or within 12 months of completing adjuvant ET or 6 or more months after the initiation of ET for MBC.[1] (Table 1) Until recently there were surprisingly few data to inform optimal ET after a non-steroidal AI and the tendency was to cycle through the available antiendocrine drugs or to use cytotoxic chemotherapy. The best evidence for anti-endocrine monotherapy in this setting is for Fulvestrant at a dose of 500 mg given 4-weekly with an additional loading dose 14 days after the first administration. In the CONFIRM trial comparing this schedule with a lower, 250 mg dose, time to progression was 6.5 months and overall survival 26 months.[5]

As our understanding of molecular biology increases, we have been able to target signalling pathways involved in endocrine resistance. Everolimus is a tyrosine kinase inhibitor directed at mTOR (mammalian target of rapamycin) and was tested in the Bolero-2 trial in which the combination of exemestane with everolimus was compared with exemestane alone. There was a statistically significant improvement in investigator assessed time to progression (6.9 months vs. 2.8 months) although no significant survival advantage.[6] Everolimus adds a number of toxicities to endocrine therapy and its use requires close clinical supervision.

Palbociclib has also been tested in second line in patients who had not previously received the drug and the combination of palbociclib with fulvestrant is clearly superior to fulvestrant alone although, to date, the licensing authorities have not considered this combination, with NICE approval limited only to the first line usage.[7]

HER-2 positive disease

First line treatment

Interest in HER-2 as a target for breast cancer therapy arose from the observation in 1987 that HER-2 positivity shortened median overall survival by around 50%. Trastuzumab, a recombinant antibody directed at the extracellular domain of HER-2 was the first in class targeted antibody therapy for HER-2 positive breast cancer. 15–20% of breast cancers are HER-2 positive. Compared to chemotherapy alone, which achieves approximately 6 months of PFS and 15 months of OS, the addition of trastuzumab to docetaxel extends these intervals to approximately 12 and 30

Considerations in endocrine therapy

Visceral crisis

- Severe organ dysfunction as assessed by signs and symptoms, laboratory studies, and rapid progression of disease.
- Visceral crisis is not the mere presence of visceral metastases, but implies important visceral compromise leading to a clinical indication for a more rapidly efficacious therapy, particularly since another treatment option at progression will probably not be possible.

Endocrine resistance

Primary endocrine resistance

- relapse while on the first 2 years of adjuvant ET, or
- PD within first 6 months of 1st line ET for MBC, while on ET

Secondary (acquired) endocrine resistance

- relapse while on adjuvant ET but after the first 2 years, or
- relapse within 12 months of completing
- adjuvant ET, or
- PD 6 months after initiating ET for MBC, while on ET.

Table 1

months respectively.[8] Combinations of HER-2 targeted therapies have also been tested. The Cleopatra trial tested the addition of pertuzumab to docetaxel with trastuzumab. Pertuzumab is an anti HER-2 antibody targeting the receptor dimerization domain of HER-2, a different binding site to trastuzumab causing what is known as dual blockade. Dual blockade further extended PFS to 18 months and OS to 53 months.[9] The combination of docetaxel + trastuzumab + pertuzumab has become the standard of care for the treatment of patients with de-novo HER-2 positive metastatic disease or those who suffer a systemic recurrence more than a year after completing trastuzumab containing adjuvant therapy.

Second and subsequent lines

There is evidence to support the continuation of anti-HER-2 therapy after disease progression on first line anti HER-2 treatment. In trials of capecitabine on disease progression continuation of trastuzumab[10] or substitution of the small molecule tyrosine kinase inhibitor, lapatinib, improved outcome compared to capecitabine alone.[11] This strategy has been superseded by data on the use of trastuzumab emtansine. This product is a novel antibody-drug conjugate in which a potent cytotoxic, emtansine, is joined by a stable linker molecule to trastuzumab. This results in selective delivery of cytotoxic drug to HER-2 overexpressing cancer cells and results in an increase in anticancer activity with a reduction in toxicity compared to the combination of lapatinib with capecitabine, the former licensed standard of care.[12] Lapatinib and capecitabine has been displaced to third line although this combination is not funded in the UK.

ER/HER-2 co-positive disease

Based on the results of two trials testing the addition of anti HER-2 treatment to antiendocrine therapy it is clear that ER and HER-2 co-positive tumours are resistant to endocrine monotherapy.[13,14] Addition of anti HER-2 therapy to antiendocrine therapy does lead to longer PFS and support this approach but the benefit of adding anti HER-2 therapy to chemotherapy appears to be more pronounced. As a result in the UK where there are restrictions on the number of lines of anti-HER-2 therapy that can be used, anti-HER-2 therapies are more commonly combined with chemotherapy.

Chemotherapy

The indication for chemotherapy in metastatic breast cancer is for those patients when a targeted therapy would be unlikely to be effective. Patients with triple negative disease have no other option. Chemotherapy partners anti HER-2 therapies and may be used when lines of anti HER-2 treatment have been exhausted. In hormone receptor positive patients chemotherapy is used in those with a visceral crisis to achieve a response and in patients with endocrine resistant or refractory disease. Combination chemotherapy is seldom used with most clinicians preferring to give sequential monotherapies to avoid the toxicity of combinations in the palliative setting. The best evidence in first line is for the anthracyclines or taxanes, although these drugs are increasingly used in adjuvant treatment limiting their utility in patients with advanced disease.[15] Other options include capecitabine, vinorelbine, eribulin, gemcitabine and carboplatin[16,17] (Table 2).

There is evidence that the genetic mutation in BRCA carriers sensitises the tumour to the type of DNA damage caused by carboplatin and the "TNT" trial validated this concept.[18] Bevacizumab, an anti VEGF monoclonal antibody has been tested in all comers with HER-2 negative MBC. When added to paclitaxel on a weekly schedule it improved the response rate and time to progression but not overall survival.[19] The data for bevacizumab are most compelling in patients with triple negative cancers previously treated with a taxane and provides a potentially useful additional line of treatment in this patient population.

Bone specific drug treatment

Bone is the commonest site for metastatic breast cancer and is a source of very significant morbidity. Most patients with bony metastases present with pain but may also suffer from bone fractures, spinal cord compression and hypercalcaemia. Prior to the introduction of potent anti-bone resorptive therapies, skeletal related events caused significant mortality as well as morbidity. Relentless bone destruction led to progressive loss of function and refractory hypercalcaemia was a common terminal event.

Bisphosphonates are direct inhibitors of osteoclasts, reducing the ability of cancer to stimulate osteoclast mediated bone resorption. The aminobisphosphonate, pamidronate, was studied in a double blind comparison versus placebo in a randomised trial in women with at least one lytic bone lesion. Treatment was given every 4 weeks for a year and the primary endpoint was time to first skeletal related event (SRE) defined as any of: pathological fracture; the need for surgery or radiotherapy to bone; spinal cord compression or hypercalcaemia. There was a statistically significant decline in skeletal events with a corresponding improvement in quality of life indices.[20] In subsequent trials zoledronic acid was shown to be superior to pamidronate and is still commonly used in routine clinical practice for patients with bony metastatic breast cancer.[21] The bisphosphonates have been a game changer and it is now a rare event to see a breast

Metastatic breast cancer: chemotherapy efficacy from pooled analyses

	Chemotherapy	PFS (m)	OS (m)
First line[7]	Anthracycline combination	6.9	19.2
	Taxane combination	7.7	19.8
	Anthracycline monotherapy	7.2	18.6
	Taxane Monotherapy	5.1	19.5
Previous anthracycline and taxane[8]	Capecitabine	4.2	13.5
	Vinorelbine	3.8	12.6
	Gemcitabine	4.5	9.8
	Liposomal doxorubicin	2.9	10.4
	Eribulin	3.7	13.1

Table 2

cancer patient with hypercalcaemia or the extensive skeletal destruction which was so common before their introduction.

Denosumab is a monoclonal antibody directed against RANK ligand. It binds the ligand preventing it from activating RANK on the cell surface of osteoclasts and exerts a greater inhibitory effect on osteoclast function than zoledronic acid. Denosumab has the advantage of subcutaneous rather than intravenous administration and compared to the bisphosphonate is less likely to cause renal impairment. Compared to zoledronic acid, denosumab prolongs the time to first and subsequent SRE's in breast as well as other solid tumours and has been recommended by NICE for breast cancer.[22]

All of the bisphosphonates and denosumab are associated with the relatively rare but important conditions of osteonecrosis of the jaw (ONJ) and atypical (non cancer related) pathological fractures. It is important to complete any necessary dental work before starting therapy.

Organ-specific therapy for liver metastases

As organ specific therapies develop and liver resection is increasingly offered as a minimal access technique, it is important that patients with liver only disease, or those with low volume or well controlled bone metastases and liver disease are considered for organ directed therapy. All appropriate patients should be referred to a surgical liver MDT and options for resection or ablation explored. Various series have reliably reported median and 5 year survival rates of around 45 months and 41% respectively.[23] Whilst these outcomes undoubtedly represent extreme selection bias in the small numbers of patients with disease who are appropriate for consideration of resection, compared to the total number with metastatic disease. For those who can undergo successful resection or ablation, it is often possible to eliminate tumour burden for significant periods of time and whilst overall survival times may not be altered, organ specific therapy can often allow significant periods of disease control without the need for ongoing systemic cytotoxic therapies and their attendant side-effects.[24]

Conclusions

Recurrent and metastatic breast cancer continues to blight the lives of thousands of women. It is not, however, the inevitable death sentence it used to be. Women with MBC may live for many years requiring complex multidisciplinary interventions and ongoing care and support. The MDT plays a vital role in patient management, identifying patients suited to local or regional therapies and those who require a systemic approach to treatment.

When planning SACT for MBC, tumour biology is a crucial consideration and there are a host of targeted therapies already licensed or in development. These have altered the natural history of MBC and extended countless lives. Cytotoxic chemotherapy still has a role but this is, quite rightly, diminishing as we introduce these rational targeted therapies based on our greater understanding of tumour biology, along with appropriate organ directed therapies such as surgery, thermal ablation and stereotactic radiotherapy where possible.

Although the bisphosphonates are old drugs, routine use of bisphosphonates and, more recently, denosumab, has prevented many of the ravaging complications of bony metastatic disease and the routine use of drugs targeted at bone metabolism is one of the biggest advances in recent decades.

As a result of the judicious use of surgery, radiotherapy and 21st century systemic anticancer therapies, women (and men) diagnosed with advanced breast cancer in 2019, can receive multiple lines of effective treatment and have a realistic expectation of several years of good quality life despite their metastatic diagnosis. ◆

REFERENCES

1 Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol* 2014 Oct; **25:** 1871–88.

2 Aebi S, Gelber S, Anderson SJ, et al. CALOR investigators. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. *Lancet Oncol* 2014 Feb; **15:** 156–63.

3 Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the international letrozole breast cancer group. *J Clin Oncol* 2001; **19:** 2596–606.

4 Finn RS, Crown JP, Lang I, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol* 15 December 2014. Published Online, https://doi.org/10.1016/S1470-2045(14)71159-3.

5 Leo AD, Jerusalem G, Petruzelka L, et al. Final overall survival: fulvestrant 500 mg vs 250 mg in the randomized CONFIRM trial. *J Natl Cancer Inst* 2012; **106:** 1–7. 2014 Jan.

6 Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor–positive advanced breast cancer. *N Engl J Med* 2012; **366:** 520–9.

7 Turner NC, Ro J, Andre F, et al. PALOMA3: a double-blind, phase III trial of fulvestrant with or without palbociclib in pre- and postmenopausal women with hormone receptor-positive, HER2-negative metastatic breast cancer that progressed on prior endocrine therapy. *ASCO Annu Meet LBA502 J Clin Oncol* 2015; **33**(suppl)**:** 2015. abstr LBA502.

8 Marty M, Cognetti F, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2—positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005; **23:** 4265—74.

9 Swain SM, Baselga J, Kim S-B, et al. for the CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; **372:** 724—34. February 19, 2015.

10 von Minckwitz GI, Schwedler K, Schmidt M, et al. for the GBG 26/BIG 03-05 study group and participating investigators. Trastuzumab beyond progression: overall survival analysis of the GBG 26/BIG 3-05 phase III study in HER2-positive breast cancer. *Eur J Cancer* 2011 Oct; **47:** 2273—81.

11 Cameron D, Casey M, Oliva C, Newstat B, Imwalle B, Geyer CE. Lapatinib plus capecitabine in women with HER-2-positive advanced breast cancer: final survival analysis of a phase III randomized trial. *Oncologist* 2010; **15:** 924—34.

12 Verma S, Miles D, Gianni L, et al. for the EMILIA study group. Trastuzumab emtansine for HER2-positive advanced breast cancer. *N Engl J Med* 2012; **367:** 1783—91.

13 Kaufman B, Mackey JR, Clemens MR, et al. Trastuzumab plus anastrozole versus anastrozole alone for the treatment of postmenopausal women with human epidermal growth factor receptor 2—positive, hormone receptor—positive metastatic breast cancer: results from the randomized phase III TAnDEM study. *J Clin Oncol* 2009; **27:** 5529—37.

14 Johnston S, Pippen Jr J, Pivot X, et al. Lapatinib combined with letrozole versus letrozole and placebo as first-line therapy for postmenopausal hormone receptor-positive metastatic breast cancer. *J Clin Oncol* 2009 Nov 20; **27:** 5538—46.

15 Taxanes alone or in combination with anthracyclines as first line therapy of patients with metastatic breast cancer, Piccart-Gebhart et al. *J Clin Oncol* 2008; **26:** 1980.

16 Efficacy and safety of palliative chemotherapy for patients with advanced breast cancer pretreated with anthracyclines and taxenes: a systematic review, Oostendorp et al. *Lancet Oncol* 2011; **12:** 1053.

17 Cortes J, O'Shaughnessy J, Loesch D, et al. on behalf of the EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice versus E7389) investigators. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 12 March 2011; **377:** 914—23.

18 Tutt A, Ellis P, Kilburn L, et al: The TNT trial. 2014 San Antonio Breast Cancer Symposium. Abstract S3-01. Presented December 11, 2014.

19 Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. *N Engl J Med* 2007; **357:** 2666—76.

20 Hortobagyi GN, Theriault RL, Porter L, et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia Breast Cancer Study Group. *N Engl J Med* 1996 Dec 12; **335:** 1785—91.

21 Rosen LS, Gordon DH, Dugan Jr W, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. *Cancer* 2004 Jan 1; **100:** 36—43.

22 Stopeck AT, Lipton A, Body JJ, et al. Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: a randomized, double-blind study. *J Clin Oncol* 2010 Dec 10; **28:** 5132—9.

23 Adam R, Aloia T, Krissat J, Bralet MP, Paule B, Giacchetti S. Is liver resection justified for patients with hepatic metastases from breast cancer? *Ann Surg* 2006; **244:** 897—907.

24 D'Angelica M. Hepatic resection for metastatic breast cancer: an exercise in selection bias. *HPB* 2016; **18:** 631—2.

FURTHER READING

http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/breast-cancer (accessed Aug 2015).

