Surgery of Metastases in Stage IV Breast Cancer

31

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31.1 Introduction

Breast cancer is the most common cancer among women worldwide.

Mortality rates have been decreasing since the 1990s, as a result of earlier detection through screening, increasing awareness, as well as advances in adjuvant therapies. Nonetheless, 3–4% of patients show synchronous metastasis at time of diagnosis [1–3].

As a result, over three million women in the United States live with a history of breast cancer, representing 41% of all female cancer survivors [4] and 3.6% of the whole American population [4, 5].

In Italy, about 50,800 new cases are recorded every year (AIRTUM, Italian Association of Tumor Registry, 2015).

The prognosis of stage IV breast cancer patients is poor with a median survival of 18–24 months, but has improved due to advances in systemic therapy. Surveillance, Epidemiology, and End Results (SEER) analysis data supports the concept that surgery may contribute to a better outcome advantage by reducing the burden of disease [6].

Patients with a higher overall survival tend to be younger females with an excellent performance status and a limited metastatic disease, for whom an intensified multidisciplinary approach combining systemic therapies with local treatment may prevent local complications and prolong survival [7, 8].

Metastatic disease is normally treated with systemic therapy, but sometimes surgery may play a role in symptom management, on a case-by-case basis. Recurrences, when they do occur, normally do so within the first 5 years, particularly in hormone receptor-negative or human epidermal growth factor 2 (HER-2)-positive disease, but sometimes they tend to be more indolent (hormone receptor-positive or HER-2-negative disease) [9].

31.2 Selection of Patients

The selection of candidates for surgery requires a careful assessment of medical conditions, extent and clinical behavior of the disease, and feasibility of resecting the metastasis with a negative margin.

The relative risks and benefits of surgery must be weighed for each individual patient.

Predictive factors are described in Table 31.1, with identification of different determinants related to the patients and to the disease.
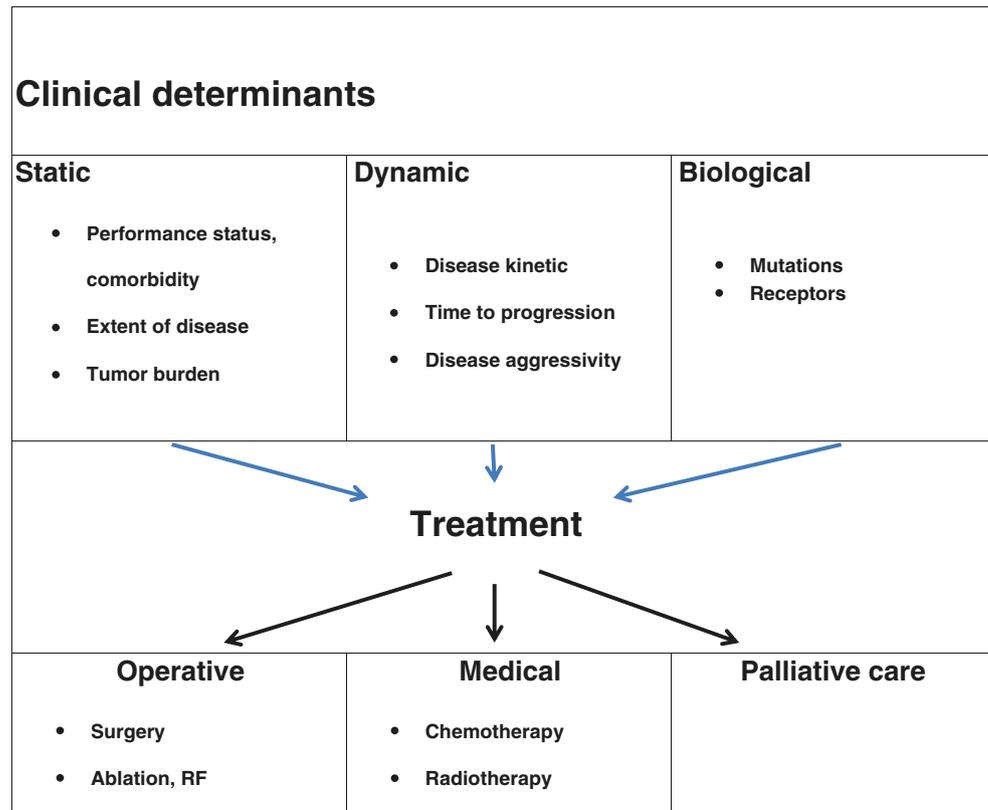
31.2.1 Clinical Determinants

- Static clinical determinants:
  - Performance status, comorbidity
  - Extent of disease (life-threatening organs, brain mets)
  - Tumor burden
- Dynamic determinants (before and during therapy):
  - Kinetics of the disease
  - Time to progression
  - Disease aggressivity

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Table 31.1 Determinants which may help the selection of appropriate patients for surgical consideration

Clinical determinants

Static	Dynamic	Biological
• Performance status, comorbidity • Extent of disease • Tumor burden	• Disease kinetic • Time to progression • Disease aggressivity	• Mutations • Receptors

Treatment

Operative	Medical	Palliative care
• Surgery • Ablation, RF	• Chemotherapy • Radiotherapy	

31.2.2 Biological Determinants

- Receptors
- Mutations

31.2.3 Treatment Strategy

- In fast disease kinetics (i.e., immediate danger), the first objective is to preserve life and relieve symptoms in the short term:
  - Fast-acting treatment.
  - Long-term survival is only a secondary objective.
- In intermediate disease kinetics, the first objective is to prolong survival:
  - The ideal strategy is to start with the treatment that will give the highest chance of a prolonged survival (3–5 years).
- In slow disease kinetics, the first objective is to prolong survival with the best possible quality of life:
  - The current strategy is to start with treatments such as surgery, radiosurgery, low toxicity, low morbidity, and some potential to preserve long-term survival.

31.2.4 Performance Status and Comorbidity

Perhaps the most important issues in choosing patients for local treatment of metastatic disease are the performance status and the estimation of the relative risks of a planned operation. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or worse or those with significant medical comorbidity should be considered carefully for local treatment, especially surgery, as they are likely to have high rates of postoperative morbidity and mortality.

31.2.5 Extent of Disease

Overall indicated as oligometastatic disease, disease extent is an important parameter which considers not only the number of metastatic sites but also the location in a single or multiple organs.

Multivariate analysis of local treatment outcomes suggests that those patients with limited metastatic disease, i.e., solitary or few detectable lesions, and limited to a single organ are more likely to benefit from local therapy than those with multiple metastases [10–14].

A small number of studies have reported no difference in long-term outcomes in patients undergoing hepatic resection in the presence or absence of extrahepatic disease (predominantly the bone) [15–17].

Successful surgery for metastatic disease is limited to patients with a single-organ involvement, as reported in some studies, even though there is a lack of experience in multi-organ resected patients.

31.2.6 Disease-Free Interval

A long disease-free interval (DFI) is associated with a better outcome with local therapy [18–20].

The specific cutoff value of DFI that best discriminates between favorable and unfavorable outcomes is unclear.

31.2.7 Complete Resection

Breast cancer has the potential to metastasize to almost every organ in the body. The most common sites of metastases are the bone, liver, and lung, while 15–40% of recurrences involve the chest wall and axillary or supraclavicular lymph nodes.

Approximately 50–75% of patients relapse distantly in a single organ, while the rest develop diffuse metastatic disease.

Fewer than 5% of patients manifest central nervous system (CNS) involvement as the first site of metastatic disease.

A careful preoperative evaluation is necessary to determine the feasibility of a complete resection of the metastatic deposit. The impact of positive margins is unclear, even though in some series they are associated with worse outcomes [10, 18, 20–22].

Surgical resection should be proposed when can be margin-free, alone, or in association with other means of local therapy (such as radiation therapy, radiofrequency ablation, or cryotherapy).

Several small studies have shown that treatment of isolated metastases is associated with a better progression-free survival and overall survival than oligometastatic cases.

However, with the exception of brain and spinal cord metastases, there are no prospective randomized clinical trials to determine whether or not such approaches really improve palliation and/or survival.

31.2.8 Resection of the Primary Tumor in Stage IV Breast Cancer

Management of the intact primary tumor in women presenting a stage IV breast cancer has classically been determined by the presence or absence of symptoms. However, multiple retrospective reviews suggest a survival advantage with resection of the intact, asymptomatic primary tumor in these cases [23]. Recently completed randomized trials (NCT00193778 [India] and NCT00557986 [Turkey]) do not support a significant survival benefit, although local control benefits may exist. The biases of the retrospective data include the use of surgery in younger women with smaller tumors, single sites of metastasis, and less visceral disease. Timing of surgery in relation to the diagnosis of metastases and use of systemic therapy has not always been specified in the published retrospective literature, although several authors have attempted to address this matter with varying conclusions [24–26].

Until additional unbiased data are available, surgery and/or radiotherapy should not be routinely recommended for patients with stage IV breast cancer with an intact primary tumor.

In particular, there is no basis for recommending surgery to women with distant disease if:

- The distant disease is not well controlled, and survival will likely not be long enough for the primary site to become a problem.
- Both local and distant sites are well controlled, in which case the primary site is likely to remain well controlled for the patient's life span.

The only possible exception to these general rules may be the patient with well-controlled or ablated oligometastatic distant disease, who would be rendered stage IV NED (no evidence of disease) through resection of the primary tumor.

For the patient whose distant disease is controlled but whose primary site is progressing, surgery provides a reasonable approach, although whether radiotherapy following surgery is beneficial is unproven; its use may be justified if the risk is high of early local recurrence and uncontrolled chest wall disease.

Locoregional therapy for the primary tumor should be offered to patients only with full disclosure of the lack of evidence of a survival benefit.

31.2.9 Lung Metastases

Isolated lung metastases occur in 10–25% of patients with metastatic breast cancer [11, 19] (Fig. 31.1). While pulmonary metastasectomy is a commonly performed operation, belief in its effectiveness is based on tumor registry data and surgical follow-up studies.

The necessity to rule out lung cancer in a breast cancer patient presenting with pulmonary nodes is clear; pulmonary resection may be diagnostic as well as therapeutic, since a significant number of solitary pulmonary nodules are primitive lung cancer [27–30].
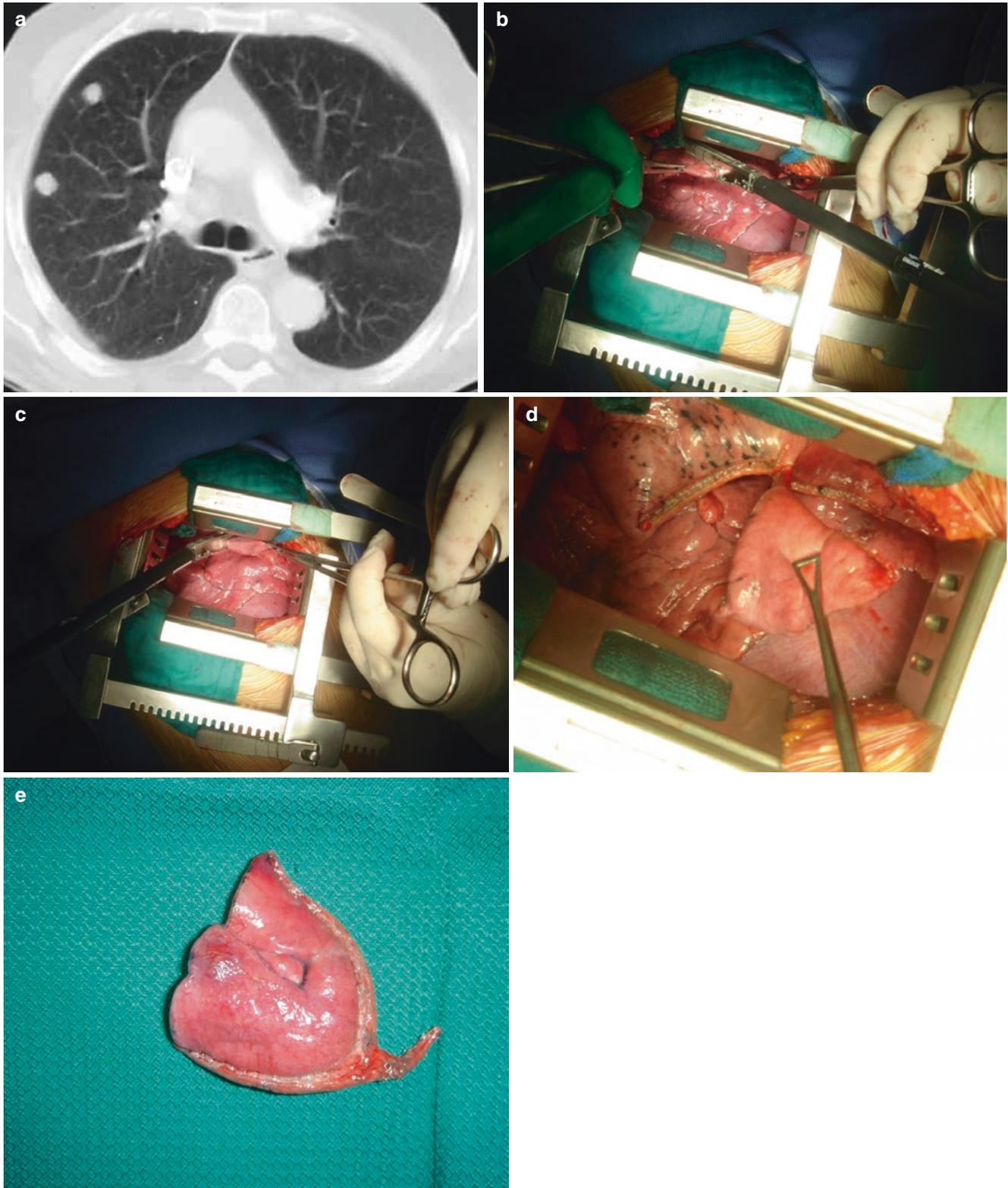
Fig. 31.1 (**a**) Monolateral lung metastases, amenable to surgical resection. (**b**) Identification and resection planning of a peripheral lung nodule. (**c**) Wedge resection using a surgical staple. (**d**) Result of lung resection. (e) Specimen with the evidence of a metastatic node

Pulmonary resection or metastasectomy offers an opportunity for long-term survival in highly selected patients with metastatic breast cancer, with case series demonstrating 5-year overall survival ranging from 30% to 80% and median survival duration ranging from 40 to 100 months [10, 19, 21, 27]. Based upon these observations, aggressive resection of isolated pulmonary metastases has become a widely accepted treatment for appropriately selected patients. The decision to proceed with pulmonary metastasectomy requires a multi-disciplinary approach (a medical oncologist and thoracic surgeon). The goal is to offer surgery only to those patients who are most likely to benefit, to optimize the timing of surgical intervention. Patients who experience long-term survival after metastasectomy are those with solitary metastases and a disease-free interval greater than 36 months. In one report, the most important factor that influences survival is the positivity to HER-2; the 5-year survival moves from 12.1%, HER-2 negative, to 76%, HER-2 positive. Other prognostic factors may include size of metastases, unilateral disease, completeness of resection, and use of anatomic resection (as opposed to wedge resection) [10, 12].

31.2.10 Liver Metastases

Hepatic metastases occur in over half of patients with metastatic breast cancer, are commonly associated with disseminated disease, and result in a poorer prognosis than bone or soft tissue metastases.

Only 5–12% of patients have isolated liver involvement [31–33].

Only appropriately selected patients with breast cancer metastases may have an advantage from hepatic resection.

In a systematic review of 19 studies involving 535 patients who underwent hepatectomy for metastatic breast cancer, median overall survival was 40 months (range, 23–77 months) with a 5-year survival following resection of 40% (range, 21–80%) [34]. Postoperative mortality ranged from 0 to 6% and the complication rate ranged from 0 to 44%. Prognostic factors following hepatic resection were positive margins and hormone-refractory disease.

The ideal candidate has a solitary metastasis, no evidence of extrahepatic metastatic disease, normal liver function, a good performance status, and a long DFI [12, 14, 17].

An essential part of the diagnostic work-up in patients who are considered for hepatectomy is precise imaging of the liver (helical computed tomography scan or magnetic resonance imaging) to evaluate whether a complete resection can be achieved while retaining a sufficient volume of functional liver.

It is not clear whether multiple metastases are a negative prognostic feature for resection of liver metastases, as long as they can be completely resected [14, 15, 20].

Initial laparoscopic exploration may spare unresectable patients the morbidity of a laparotomy, since up to half of the patients considered for resection are discovered to have diffuse liver lesions or peritoneal dissemination at the time of laparotomy [35].

Hepatic resection is appropriate for highly selected patients, but alternative local therapies are being increasingly used to treat liver metastases.

Liver-directed therapy includes image-guided thermal ablation (radiofrequency ablation, microwave ablation, cryoablation, interstitial laser therapy), stereotactic body RT (SBRT), and intra-arterial therapies (selective internal RT and transhepatic arterial chemoembolization).

None of these methods has been directly compared to systemic chemotherapy in metastatic breast cancer, except in a recent paper addressing a cost-utility analysis of liver resection in breast cancer liver metastases. The authors compared postoperative conventional systemic therapy versus conventional therapy alone versus newer targeted therapy alone. The implications of using different chemotherapeutic regimens based on estrogen receptor and human epidermal growth factor receptor 2 status were also assessed. Liver resection in patients with breast cancer liver metastasis proved to be cost-effective when compared with systemic therapy alone, particularly in estrogen receptor-positive tumors or when newer agents were used [36].

31.2.10.1 Interventional Oncology

- Image-guided thermal ablation:

This category of local treatment includes modalities having the common aim of targeted tissue destruction by means of different forms of energy.

Those treatments can be used alone percutaneously, based on imaging guidance, or in combination with resection [31–34].

When radiofrequency energy is applied, an oscillating electrical current flows through the body inducing ionic agitation in tissues around the interstitial electrode. Resistive heating is produced in the areas closest to the interstitial probe [37] (Figs. 31.2, 31.3, 31.4).

Microwave (MW) ablation is based on electromagnetic energy, with frequencies greater than or equal to 900 MHz, which induces a vigorous movement of water molecules. This movement produces heat and thus tissue destruction and cell death via coagulative necrosis [38–41].

Cryoablation is based on alternating temperature decrease (-40 °C) and thawing. Rapid expansion of pressured gas within the probe creates a very low temperature and the formation of an iceball on the probe tip. Thawing of the iceball was achieved by insufflations of high-pressure gas. This system induces cell death by osmotic shock [42].
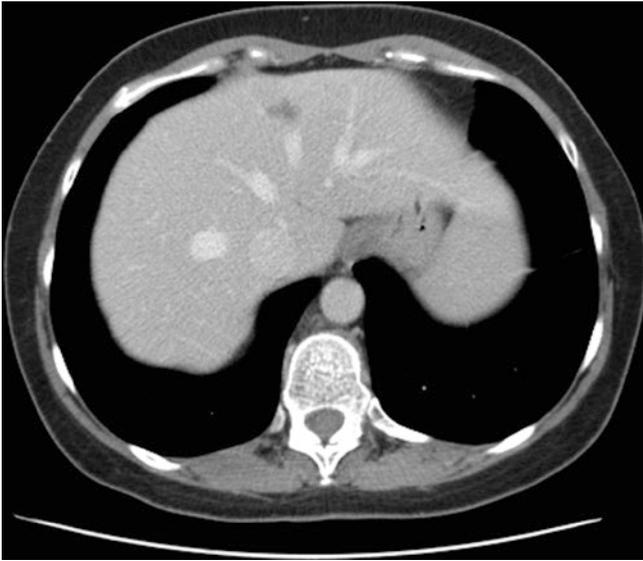
Fig. 31.2 CT scan portal venous phase: single metastatic lesion in segment II (pre)

Fig. 31.4 CT scan 5 years after treatment showing shrinkage of ablation area. Patient is still disease-free

Fig. 31.3 CT scan the day after treatment showing complete treatment: hypodense ablation area without suspicious contrast enhancement

Interstitial laser therapy (ILT) causes local tumor destruction by the application of laser light, delivered through quartz diffusing laser fibers which can be percutaneously placed within tumors [43–46].

• Intra-arterial therapies:

The rationale behind transarterial treatment is that liver tumors receive blood flow almost entirely from the artery, while normal liver tissue is supplied both by the portal blood flow and by arterial blood flow. Selective intravascular deliv-

ery of agents into arterial tumor-feeding vessels has the goal of inducing lethal damage to the pathologic tissue while reducing collateral injury to healthy liver tissue [47, 48].

Different materials have been used in past decades in the treatment of primary and secondary liver cancers.

Transarterial chemoembolization (TACE) is based on different drug carriers (Gelfoam, microparticles) that have a dual aim: to reach higher intrahepatic drug concentration than that in systemic therapy and occlude arterial vessel to induce tissue ischemia.

Selective internal RT (SIRT) is a procedure in which glass or resin microspheres incorporating the radioactive isotope 90Y are directly infused into the hepatic arteries feeding the tumor. This will allow the delivery of doses of ionizing radiation above 120 Gy to the tumor compartment without causing intolerable toxicity to the normal tissue [49].

• Stereotactic body radiation therapy (SBRT or fractionated radiosurgery) is a technique that delivers external beam radiation to the tumor.

31.2.11 Brain Metastases

Breast cancer is the second most common cancer associated with brain metastases in the United States. In a subset of women, progression in the central nervous system (CNS) has become the major life-limiting problem. The risk of central nervous system (CNS) relapse among patients with breast cancer varies significantly by disease stage. Among women presenting with early-stage breast cancer, less than 3% will
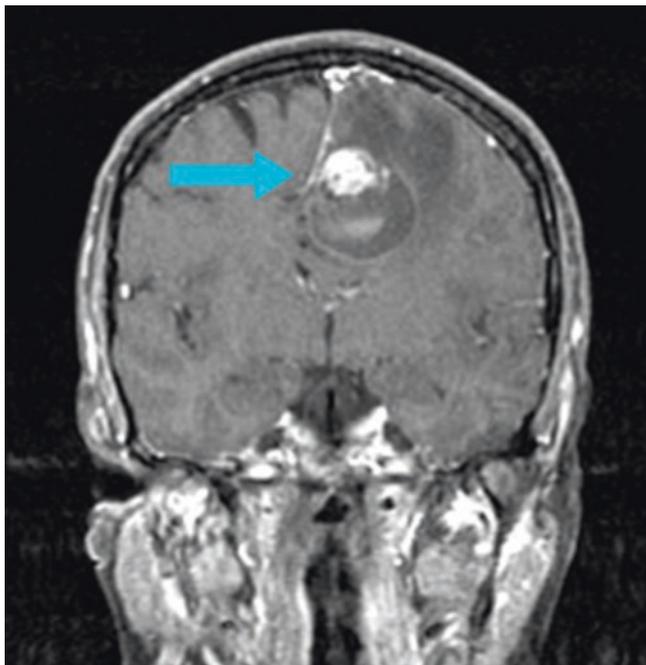
Fig. 31.5 Isolated brain metastasis

Fig. 31.6 Pathologic fracture through a metastatic lesion of the distal femur (**a**). Resection of the metastatic lesion and distal femoral replacement (**b**)

go on to develop brain metastases [1, 2]. In contrast, symptomatic brain metastases are diagnosed in 10–16% of patients with metastatic breast cancer [1, 3] (Fig. 31.5). Factors associated with an increased likelihood of CNS relapse include age under 40 years, pulmonary metastases, and African-American ancestry [1, 3–7].

In addition, the breast cancer subtype appears to be associated with the incidence of brain metastases [2, 6, 8–19]. In a cohort study of 1434 women treated with breast-conserving therapy plus systemic chemotherapy, brain metastases developed in 36 (2.5%).

For patients with a favorable prognosis (e.g., Karnofsky performance score [KPS] 70 or higher, age <65 years, controlled primary tumor, and controlled or absent extracranial metastases), aggressive treatment is indicated. For women with brain metastases from human epidermal growth factor receptor 2 (HER-2)-positive disease, the administration of systemic therapy may delay the use of whole-brain radiation therapy (RT) and the associated risk of neurologic toxicity.

Following initial treatment for brain metastases due to breast cancer, both surgery and stereotactic radiosurgery can be used to retreat patients who develop recurrent, symptomatic central nervous system (CNS) disease and have stable extracranial disease following their initial treatment for brain metastases. Careful selection of patients is critical in this setting. As with the initial evaluation, the absence of active systemic disease and a Karnofsky performance score of at least 70 are important. Factors indicating a probable poor outcome include a short time to recurrence and age less than 40 years.

31.2.12 Bone Metastases

The bone is the most common site of metastatic involvement in breast cancer and can be associated with significant morbidity and mortality.

Surgery, RT, and RFA can provide effective pain relief and prevent fracture (Figs. 31.6 and 31.7). Surgery and RT are also used for the palliative treatment of epidural spinal cord or nerve compression.

Bisphosphonates and other osteoclast inhibitors have been shown to reduce the morbidity of metastatic bone disease, in particular skeletal-related events (SREs), which include fracture, need for surgery or radiation to the bone, spinal cord compression, and hypercalcemia of malignancy.

Bone-confined metastatic breast cancer is usually characterized by an indolent course and good response to systemic therapy [50–52].

There is a limited role for resection as a curative option for the majority of bone metastases, except for selected patients with isolated spine or sternal involvement [53–57].

Sternal metastases may remain solitary for a long time, possibly because there is no communication with the paravertebral venous plexus through which cancer cells can spread to other bones [53, 55].

In other cases, isolated sternal involvement represents locoregional recurrence (i.e., direct extension from an internal mammary nodal recurrence) rather than true metastatic disease. Surgical resection of breast cancer confined to the sternum may improve quality of life and prolong survival.

When spine metastases become symptomatic causing severe pain, neurological deficit, and biomechanical instability, this may require surgical resection. The ideal approach is multidisciplinary and includes medical treatment (mostly for symptom control) radiotherapy, stereotactic radiosurgery, and surgery. The aim of surgery is to preserve or restore a neurological function in tumors that progress despite undergoing maximal radiation dosages and medical intractable pain. The treatment improves patient's quality of life; the indication for surgery should take into consideration anatomical location and the extension of disease [56, 58].

31.2.13 Abdominal and Pelvic Metastases

Limited data suggest that ovarian breast cancer metastases can appear many years following the initial diagnosis of breast cancer and tend to be hormone receptor-positive [59–62].

Surgical evaluation of an adnexal mass may be required to discriminate metastatic breast cancer from a primary ovarian cancer.

31.3 Summary and Recommendations

Local therapy may offer therapeutic benefits and the potential for long-term survival for highly selected patients with metastatic breast cancer.

Although most evidence exists in support of surgical resection, alternative approaches, such as radiofrequency ablation and stereotactic body radiation therapy, are gaining popularity.

Patient selection is crucial when considering local therapy. The best candidates are those with solitary metastases in a single metastatic site and a long disease-free interval.

Completeness of resection is a key factor when considering surgery.

Perhaps the main indication for resection of a new, isolated pulmonary, hepatic, or abdominopelvic lesion in a patient with a prior history of breast cancer is diagnostic, since some patients may have a new primary malignancy or a change in tumor marker status.

References

1. Greenberg PA, Hortobagyi GN, Smith TL et al (1996) Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol 14:2197
2. Falkson G, Gelman RS, Leone L, Falkson CI (1990) Survival of premenopausal women with metastatic breast cancer. Long-term follow-up of eastern cooperative group and cancer and leukemia group B studies. Cancer 66:1621

3. Hanrahan EO, Broglio KR, Buzdar AU et al (2005) Combined-modality treatment for isolated recurrences of breast carcinoma: update on 30 years of experience at the University of Texas M.D. Anderson cancer center and assessment of prognostic factors. Cancer 104:1158

4. DeSantis CE, Lin CC, Mariotto AB et al (2014) Cancer treatment and survivorship statistics, 2014. CA Cancer J Clin 64:252

5. Saphner T, Tormey DC, Gray R (1996) Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 14:2738

6. Brewster AM, Hortobagyi GN, Broglio KR et al (2008) Residual risk of breast cancer recurrence 5 years after adjuvant therapy. J Natl Cancer Inst 100:1179

7. Lee CG, McCormick B, Mazumdar M et al (1992) Infiltrating breast carcinoma in patients age 30 years and younger: long term outcome for life, relapse, and second primary tumors. Int J Radiat Oncol Biol Phys 23:969

8. Vogel CL, Azevedo S, Hilsenbeck S et al (1992) Survival after first recurrence of breast cancer. The Miami experience. Cancer 70:129

9. Ly BH, Nguyen NP, Vinh-Hung V et al (2010) Loco-regional treatment in metastatic breast cancer patients: is there a survival benefit? Breast Cancer Res Treat 119:537

10. Friedel G, Pastorino U, Ginsberg RJ et al (2002) Results of lung metastasectomy from breast cancer: prognostic criteria on the basis of 467 cases of the international registry of lung metastases. Eur J Cardiothorac Surg 22:335

11. Friedel G, Linder A, Toomes H (1994) The significance of prognostic factors for the resection of pulmonary metastases of breast cancer. Thorac Cardiovasc Surg 42:71

12. Pagani O, Senkus E, Wood W et al (2010) International guidelines for management of metastatic breast cancer: can metastatic breast cancer be cured? J Natl Cancer Inst 102:456

13. Fields RC, Jeffe DB, Trinkaus K et al (2007) Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. Ann Surg Oncol 14:3345

14. Pocard M, Pouillart P, Asselain B et al (2001) Hepatic resection for breast cancer metastases: results and prognosis (65 cases). Ann Chir 126:413

15. Yoshimoto M, Tada T, Saito M et al (2000) Surgical treatment of hepatic metastases from breast cancer. Breast Cancer Res Treat 59:177

16. Sofocleous CT, Nascimento RG, Gonen M et al (2007) Radiofrequency ablation in the management of liver metastases from breast cancer. AJR Am J Roentgenol 189:883

17. Selzner M, Morse MA, Vredenburgh JJ et al (2000) Liver metastases from breast cancer: long-term survival after curative resection. Surgery 127:383

18. Ludwig C, Stoelben E, Hasse J (2003) Disease-free survival after resection of lung metastases in patients with breast cancer. Eur J Surg Oncol 29:532

19. Planchard D, Soria JC, Michiels S et al (2004) Uncertain benefit from surgery in patients with lung metastases from breast carcinoma. Cancer 100:28

20. Raab R, Nussbaum KT, Behrend M, Weimann A (1998) Liver metastases of breast cancer: results of liver resection. Anticancer Res 18:2231

21. Pastorino U, Buyse M, Friedel G et al (1997) Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. J Thorac Cardiovasc Surg 113:37

22. McDonald ML, Deschamps C, Ilstrup DM et al (1994) Pulmonary resection for metastatic breast cancer. Ann Thorac Surg 58:1599

23. Patrick J, Khan SA (2015) J Natl Compr Cancer Netw 13:487–493

24. Neuman HB, Morrogh M, Gonen M et al (2010) Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? Cancer 116:1226–1233

25. Ruiterkamp J, Ernst MF, van de Poll-Franse LV et al (2009) Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. Eur J Surg Oncol 35:1146–1151

26. Shien T, Kinoshita T, Shimizu C et al (2009) Primary tumor resection improves the survival of younger patients with metastatic breast cancer. Oncol Rep 21:827–832

27. Yoshimoto M, Tada K, Nishimura S et al (2008) Favourable long-term results after surgical removal of lung metastases of breast cancer. Breast Cancer Res Treat 110:485

28. Meimarakis G, Rüttinger D, Stemmler J et al (2013) Prolonged overall survival after pulmonary metastasectomy in patients with breast cancer. Ann Thorac Surg 95:1170

29. Cahan WG, Castro EB (1975) Significance of a solitary lung shadow in patients with breast cancer. Ann Surg 181:137

30. Casey JJ, Stempel BG, Scanlon EF, Fry WA (1984) The solitary pulmonary nodule in the patient with breast cancer. Surgery 96:801

31. Hoe AL, Royle GT, Taylor I (1991) Breast liver metastases—incidence, diagnosis and outcome. J R Soc Med 84:714

32. Atalay G, Biganzoli L, Renard F et al (2003) Clinical outcome of breast cancer patients with liver metastases alone in the anthracycline-taxane era: a retrospective analysis of two prospective, randomised metastatic breast cancer trials. Eur J Cancer 39:2439

33. Zinser JW, Hortobagyi GN, Buzdar AU et al (1987) Clinical course of breast cancer patients with liver metastases. J Clin Oncol 5:773

34. Chua TC, Saxena A, Liauw W et al (2011) Hepatic resection for metastatic breast cancer: a systematic review. Eur J Cancer 47:2282

35. Maksan SM, Lehnert T, Bastert G, Herfarth C (2000) Curative liver resection for metastatic breast cancer. Eur J Surg Oncol 26:209

36. Spolverato G, Vitale A, Bagante F, Connolly R, Pawlik TM (2016) Liver resection for breast cancer liver metastases: a cost-utility analysis. Ann Surg. doi:10.1097/SLA.0000000000001715

37. Orsi F, Varano G (2015) Minimal invasive treatments for liver malignancies. Ultrason Sonochem 27:659–667. doi:10.1016/j.ultsonch.2015.05.030

38. Lubner MG, Brace CL, Ziemlewicz TJ et al (2013) Microwave ablation of hepatic malignancy. Semin Interv Radiol 30(1):56–66

39. Wood TF, Rose DM, Chung M et al (2000) Radiofrequency ablation of 231 unresectable hepatic tumors: indications, limitations, and complications. Ann Surg Oncol 7:593

40. de Baere T, Elias D, Dromain C et al (2000) Radiofrequency ablation of 100 hepatic metastases with a mean follow-up of more than 1 year. AJR Am J Roentgenol 175:1619

41. Pawlik TM, Izzo F, Cohen DS et al (2003) Combined resection and radiofrequency ablation for advanced hepatic malignancies: results in 172 patients. Ann Surg Oncol 10:1059

42. Bala MM, Riemsma RP, Wolff R et al (2013) Cryotherapy for liver metastases. Cochrane Database Syst Rev 6:CD009058

43. Livraghi T, Goldberg SN, Solbiati L et al (2001) Percutaneous radio-frequency ablation of liver metastases from breast cancer: initial experience in 24 patients. Radiology 220:145

44. Ahmed M, Brace CL, Lee FT Jr, Goldberg SN (2011) Principles of and advances in percutaneous ablation. Radiology 258(2):351–369

45. Izzo F (2003) Other thermal ablation techniques: microwave and interstitial laser ablation of liver tumors. Ann Surg Oncol 10:491

46. Nikfarjam M, Christophi C (2003) Interstitial laser thermotherapy for liver tumours. Br J Surg 90:1033

47. Geschwind JF, Salem R, Carr BI et al (2004) Yttrium-90 microspheres for the treatment of hepatocellular carcinoma. Gastroenterology 127(5 Suppl. 1):S194–S205

48. Camacho LH, Kurzrock R, Cheung A et al (2007) Pilot study of regional, hepatic intra-arterial paclitaxel in patients with breast carcinoma metastatic to the liver. Cancer 109:2190

49. Ikeda T, Adachi I, Takashima S et al (1999) A phase I/II study of continuous intra-arterial chemotherapy using an implantable reservoir for the treatment of liver metastases from breast cancer: a

Japan clinical oncology group (JCOG) study 9113. JCOG breast cancer study group. Jpn J Clin Oncol 29:23

50. Arai Y, Sone Y, Inaba Y et al (1994) Hepatic arterial infusion chemotherapy for liver metastases from breast cancer. Cancer Chemother Pharmacol 33(Suppl):S142

51. Li XP, Meng ZQ, Guo WJ, Li J (2005) Treatment for liver metastases from breast cancer: results and prognostic factors. World J Gastroenterol 11:3782

52. Briasoulis E, Karavasilis V, Kostadima L et al (2004) Metastatic breast carcinoma confined to bone: portrait of a clinical entity. Cancer 101:1524

53. Sherry MM, Greco FA, Johnson DH, Hainsworth JD (1986) Metastatic breast cancer confined to the skeletal system. An indolent disease. Am J Med 81:381

54. Coleman RE, Smith P, Rubens RD (1998) Clinical course and prognostic factors following bone recurrence from breast cancer. Br J Cancer 77:336

55. van der Linden YM, Dijkstra SP, Vonk EJ et al (2005) Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. Cancer 103:320

56. Dürr HR, Müller PE, Lenz T et al (2002) Surgical treatment of bone metastases in patients with breast cancer. Clin Orthop Relat Res 396:191

57. Incarbone M, Nava M, Lequaglie C et al (1997) Sternal resection for primary or secondary tumors. J Thorac Cardiovasc Surg 114:93

58. Noguchi S, Miyauchi K, Nishizawa Y et al (1988) Results of surgical treatment for sternal metastasis of breast cancer. Cancer 62:1397

59. Quan ML, Fey J, Eitan R et al (2004) Role of laparoscopy in the evaluation of the adnexa in patients with stage IV breast cancer. Gynecol Oncol 92:327

60. Abu Rustum NR, Aghajanian CA, Venkatraman ES (1997) Metastatic breast carcinoma to the abdomen and pelvis. Gynecol Oncol 66:41

61. Curtin JP, Barakat RR, Hoskins WJ (1994) Ovarian disease in women with breast cancer. Obstet Gynecol 84:449

62. Bigorie V, Morice P, Duvillard P et al (2010) Ovarian metastases from breast cancer: report of 29 cases. Cancer 116:799