Breast Cancer Online
www.bco.org

Breast Cancer Online, 2006, **9**(8), Page 1 of 5, ***e30***
doi:10.1017/S1470903106002288

ISSN 1470-9031

Focus On

The role of surgery for pulmonary metastases in breast cancer patients

D. A. Hess[a,b], H. M. Klomp[a]

[a]*Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Department of Surgery, Amsterdam;*
[b]*Red Cross Hospital, Department of Surgery, Beverwijk, The Netherlands.*

Abstract In breast cancer, oligometastatic disease is a controversial concept. Generally, solitary pulmonary lesions are detected on chest imaging made for other reasons (unintentionally). The majority of these pulmonary lesions in breast cancer patients prove to be unrelated (bronchogenic carcinoma or benign lesions), 33–40% are in fact breast cancer metastases. Only a small number of breast cancer patients (0.4–1%) will have potentially resectable isolated metastasis to the lung.

Controlled studies comparing pulmonary metastasectomy to systemic therapy or best medical care are lacking. Overall survival (OS) data in patients who underwent metastasectomy are favourable despite the high incidence of recurrences. Long-term survival is seen primarily in patients with only one or two lesions and long initial disease-free interval. Radical resections with unnecessary loss of pulmonary parenchyma should be avoided, since there is no benefit of such resection in terms of survival and the incidence of complications is higher.

Foremost justification of surgical resection for lung lesions in breast cancer patients is differentiation of metastatic breast cancer from new primary lung cancer. The survival impact of pulmonary resection in 'oligometastatic' breast cancer is probably limited and attempts should be made to limit the amount of tissue removed.

Introduction

Patients with metastatic breast cancer are a heterogeneous population with considerable differences in prognosis. Metastatic breast cancer usually presents as disseminated disease and is regarded as incurable, although a few long-term survivors are observed. In general, treatment intent is palliative, expanding survival with optimal quality of life. Therapeutic strategies are commonly systemic (chemotherapy, hormonal therapy) or aimed at symptom relief (irradiation of painful bone metastases). However, a subgroup of patients with limited metastatic disease may benefit from more aggressive local treatment. Consequently, surgical resection may be an option for patients with isolated pulmonary metastasis.

In breast cancer, oligometastatic disease is a controversial concept [1]. Unlike in other tumour types like sarcoma or colorectal carcinoma, isolated metastasis in breast cancer is commonly perceived as part of widespread (occult) dissemination. For that reason, surgical resection of distant metastases is a matter of debate, despite some encouraging reports especially from patients with hepatic and pulmonary disease [3–6]. Nevertheless, oligometastatic disease represents lower tumour load and is associated with more favourable prognosis [2].

This article describes the role of diagnostic techniques and discusses the indication of surgery for pulmonary nodules in breast cancer patients.

Correspondence to: MS H. M. Klomp, MD, Department of Surgery, Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital, Plesmanlaan 121, NL-1066 CX, Amsterdam, The Netherlands; E-mail: h.klomp@nki.nl Tel: +31 20 5122565; Fax: +31 20 5122554

Received Date: 12/04/05
Accepted Date: 04/07/06
First published online 24/07/06
BCO/228/2004/FO

Patients

In the Netherlands, as in most of the industrialized world, breast cancer is the most prevalent cancer

among women. After initial treatment, 30–40% of these patients have recurrent disease, involving locoregional recurrences in about one-third and distant spread in the remainder of patients [3]. Metastatic spread to the lungs occurs regularly, but only a very small percentage of patients (0.4–1%) have limited or solitary pulmonary metastasis [7,8].

Diagnosis

Breast cancer follow-up does not include routine chest X-ray, thus most pulmonary lesions are detected on chest imaging made for other reasons (unintentionally). The majority of these pulmonary lesions in breast cancer patients prove to be unrelated (bronchogenic carcinoma or benign lesions), 33–40% are in fact breast cancer metastases [7,9].

Further evaluation should include examination of the primary cancer site and contralateral breast, comparison with previous chest X-rays, CT scan of chest and upper abdomen and bronchoscopy. Evaluation for metastatic spread must be thorough. FDG-PET scanning is helpful to assess the nature of the detected lesion as well as the presence of further dissemination, both in breast and lung cancer [10]. Alternatively bone scintigraphy, liver ultrasound and brain scans may be indicated. If further dissemination is discovered and systemic therapy is considered, tissue confirmation by needle biopsy should be performed.

For solitary pulmonary lesions, tissue examination is required to establish a histopathologic diagnosis. Bronchoscopic techniques or transthoracic needle biopsy may be helpful, but in most cases surgical resection is necessary to differentiate metastatic breast cancer from second primary lung cancer. Pulmonary wedge resection, either via (mini)thoracotomy or by video-assisted thoracic surgery (VATS), will generally resolve this issue, although in a few cases larger or strategically placed tumours will necessitate more radical resections (lobectomy or pneumonectomy). If, at time of diagnostic resection, the lesion cannot be differentiated from lung adenocarcinoma, the problem should be managed as primary lung cancer with formal pulmonary resection, preferably lobectomy including mediastinal lymph node sampling.

If metastatic breast cancer is diagnosed, the therapeutic role of surgical resection may be considered.

Metastasectomy

Controlled studies comparing pulmonary metastasectomy to systemic therapy or best medical care are lacking. A number of retrospective (mostly single institution) series described results of pulmonary metastasectomy in breast cancer patients (Table 1). An important database is the International Registry of Lung Metastases, started in 1991, with 467 cases of metastasectomy in breast cancer patients and a 15-year follow-up [3]. Nevertheless, all series involved highly selected patient groups and only two reports illustrated their selection sufficiently [3,11].

Median survival in these series ranged from 32 to 97 months. Reported 5-year survival rates were 31–80% and 10-year survival 8–60%. Friedel *et al.* reported 15-year survival after radical resections of 20%. Remarkably, most series did not report disease-free survival following metastasectomy. If revealed, median recurrence-free survival following metastasectomy varied from 19 to 30 months [7,8,12,13]. Staren *et al.* compared surgical treatment in 33 patients with chemo- or hormonal therapy in 30 patients [14]. The surgical group had a median survival of 58 months that compared favourably with the median

Table 1. Survival outcomes of pulmonary metastasectomy in breast cancer patients.

Study	Number of patients	Treatment	OS median (months)	RFS median (months)	5-year survival (%)	10-year survival (%)
Tanaka [23]	39	Surgery	32	NS	31	NS
Planchard [11]	125	Surgery alone ($n = 15$) or with chemo-, radio- or hormonal therapy	51	NS	45	30
Staren [14]	33	Surgery alone ($n = 20$) or with chemo- or radiotherapy	58[a]	NS	36	NS
Ludwig [12]	21	Surgery	97	28	53	NS
Friedel [3]	467	Surgery alone ($n = 313$) or with chemotherapy	37[b]	NS	38[b]	22[b]
McDonald [7]	60	Surgery alone ($n = 17$) or with chemo-, radio- or hormonal therapy	42	19	38	8
Lanza [8]	42	Surgery alone ($n = 2$) or with chemo- or hormonal therapy	47[b]	24[b]	50[b]	NS
Livartowski [13]	40	Surgery	70	30	54	NS
Murabito [24]	96	Surgery + chemotherapy[c]	79[a,b]	NS	80[a,b]	60[a,b]

[a]Mean values.
[b]Outcomes associated with complete resection of metastasis.
[c]Percentage of patients receiving chemotherapy not specified.
NS = not specified.

https://doi.org/10.1017/S1470903106002288 Published online by Cambridge University Press

survival of the systemic therapy group (34 months). The overall 5-year survival rate was 36% vs. 11%.

A longer disease-free interval (DFI $>$ 1 or 3 years) was consistently identified as a favourable prognostic factor. In some series, patients with largest metastatic lesion diameter $<$20 mm, only one metastasis and positive oestrogen-receptor status had a better prognosis [3,8,11,12]. Data on the influence of complete vs. incomplete resection were inconsistent. In three studies complete or radical resection was associated with better prognosis [3,13,15], whereas two were unable to demonstrate a difference in survival [7,11].

Data on the role of 'adjuvant' chemo- or hormonal therapy are insufficient to draw any conclusion. One study suggested a benefit in terms of OS and RFS for patients who received doxorubicin-based adjuvant chemotherapy after local treatment of stage IV breast cancer as compared to a historic control group [2].

Perioperative mortality was low, in most series around 1%. As would be expected, mortality was higher after irradical resections, and after more extensive resections (particularly after pneumonectomy). The complication rate of metastasectomy ranged from 4% to 13% and involved mainly infections and prolonged air leak [3,7,8,12,15]. No data were provided on (prolonged) postoperative pain and discomfort.

Systemic therapy

Many therapeutic drugs and combinations have been studied in patients with metastatic breast cancer. Survival of women with recurrent breast cancer has been improving over the last decades. Recent studies show median survival of 33–58 months and 5-year survival rates of 30–40%, as compared to 15–19 months median survival and 5-year survival of 10–15% in the seventies [16,17]. Survival in patients with pulmonary metastases was reported to be higher than survival of the whole group of patients with metastatic disease (all sites). Mortality of chemotherapy is low, for conventional schemes less than 1% [18]. Complications and side effects involve haematological toxicity, diarrhoea, vomiting and infections.

Several phase II trials reported promising results for high-dose chemotherapy (HDC) followed by autologous haematopoietic stem-cell transplantation. This result was perceived to be an improvement as compared to historical controls. The incidence of severe adverse effects was greater as well. However, the enthusiasm for HDC has declined since results of randomized trials showed no clear advantage of HDC over conventional-dose chemotherapy in metastatic disease [19,20]. An analysis of the failure pattern showed that most patients relapse in sites of prior macroscopic disease.

Two studies evaluated prospectively the use of HDC in combination with local therapy (surgery and/or radiation therapy) in metastatic breast cancer limited to a single organ site [2,21]. The sites of recurrence were equally distributed to local, distant, and both local and distant. Median RFS and OS were 18 and 42 months in the German study, inferior to the results reported by Nieto with corresponding values of 52 and 80 months. The results of these studies suggest that local treatment combined with systemic consolidation therapy may be a useful and well-tolerated option in a selected group of patients with oligometastatic breast cancer leading to 27% relapse-free survival (RFS) after 5 years.

Interpretation

Breast cancer patients who may be candidates for therapeutic pulmonary metastasectomy represent a very small fraction of those patients with a recurrent malignancy. Most literature reports are archive series of metastasectomies and suffer from lack of insight into the selection of patients. Population-based data should be used to estimate incidence and put the problem in perspective. Only a small number of breast cancer patients (0.4–1%) will have potentially resectable isolated metastasis to the lung.

A more difficult question is, whether a breast cancer patient with potentially resectable metastasis should undergo surgical resection. In the absence of controlled trials, criteria for therapeutic metastasectomy, in general, were extrapolated from retrospective series. These are local control of the primary malignancy, long disease-free survival since primary therapy, no effective alternative therapy, absence of extrathoracic metastases and the presence of solitary (or limited) pulmonary metastatic burden that can be completely resected [22]. Although these criteria are recognized as generally valid, some aspects ought to have consideration.

Comparison of the results of surgical treatment vs. systemic therapy is virtually impossible. At first glance, results from chemotherapy treatment seem inferior to most surgical metastasectomy results. However, selection of patients and differences in diagnostic work-up result in extremely dissimilar patient populations and mess up interpretation of data.

Disclosure of post-metastasectomy OS and post-metastasectomy recurrence-free survival is of obvious importance in determining the therapeutic role of pulmonary metastasectomy. This information is vital in determining whether survival is primarily influenced by indolent tumour biology or by tumour eradication through surgery. This distinction is often presented vaguely or not at all. If described, median RFS is 19–30 months. Consequently, OS data in patients who

https://doi.org/10.1017/S1470903106002288 Published online by Cambridge University Press

underwent metastasectomy are favourable despite the high incidence of recurrences, which downsizes the role of surgical resection. The inability to show consistent survival benefit in patients with complete vs. incomplete resection are compatible with a minor role of surgery.

Discussion

There is no modus operandi for management of breast cancer patients with oligometastatic pulmonary disease. Wait and see, surgical resection or systemic therapy are justifiable options.

As to the active options, surgical intervention can be done with low mortality and acceptable morbidity. Surgical resection allows definitive histopathologic diagnosis including receptor status, with slightly lower error rate than cytological evaluation. Although speculative, patient preferences are likely toward 'one course of surgical oncology' instead of prolonged courses of chemotherapy with unpleasant side effects (hair loss, malaise, vomiting). It should be pointed out however, that removing the detectable component of systemic disease has a limited role in the management of 'oligometastatic' breast cancer.

Therefore it is vital to ensure that the intervention does not cause more physiologic harm than oncologic good. Attempts should be made to limit the amount of tissue removed. Radical resections (i.e. lobectomy or pneumonectomy) should be avoided, since there is no benefit of such resection in terms of survival and the incidence of complications is higher.

Long-term survival following pulmonary metastasectomy is not only observed among patients who have 'complete removal of all metastatic deposits' within the lung. The argument against VATS (inability of bimanual palpation with discovery of additional lesions in over 20% of patients) is illogical [12,15]. Most patients undergoing metastasectomy will develop recurrent disease and long-term survival is seen primarily in patients with only one or two lesions. Obviously the presence of occult metastatic disease is the real problem. A survival advantage, if any, primarily results from indolent tumour biology rather than from 'radical' resection procedures with unnecessary loss of pulmonary parenchyma. The frequent identification of clinically occult disease by open thoracotomy should not be the argument to avoid minimally invasive procedures (as in VATS or minithoracotomy). If more than a few lesions are found, the metastasectomy takes on a primary diagnostic role. For that reason (mini)thoracotomy, VATS or sternotomy are the suitable surgical approach options. For deeper lesions, an open surgical approach will usually be necessary.

Conclusion

Foremost justification of surgical resection for lung lesions in breast cancer patients is differentiation of metastatic breast cancer from new primary lung cancer. The majority of pulmonary nodules in breast cancer patients are found unintentionally. As many of these nodules are located peripherally in the lung, pathologic diagnosis by bronchoscopy is difficult. Surgical intervention, preferably by pulmonary wedge excision allowing pathologic differentiation, can be done with low morbidity and mortality.

Most breast cancer patients undergoing pulmonary metastasectomy will develop subsequent (pulmonary) metastases. Radical resections as pneumonectomy or meticulous removal of multiple metastatic deposits should be avoided, since there is no benefit of such resections in terms of survival and the incidence of complications is higher. Although the survival impact of surgical resection in 'oligometastatic' breast cancer is probably minor, metastasectomy may have a role in patients with one or two pulmonary lesions and long DFI. It allows for exact histopathologic evaluation and preserves alternative (systemic) treatment options for recurrence.

References

1. Tait CR, Waterworth A, Loncaster J, Horgan K, Dodwell D. The oligometastatic state in breast cancer: hypothesis or reality. *Breast* 2005; **14**(2): 87–93.
2. Nieto Y, Nawaz S, Jones RB, *et al.* Prognostic model for relapse after high-dose chemotherapy with autologous stem-cell transplantation for stage IV oligometastatic breast cancer. *J Clin Oncol* 2002; **20**(3): 707–718.
3. Friedel G, Pastorino U, Ginsberg RJ, *et al.* 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* 2002; **22**(3): 335–344.
4. Bathe OF, Kaklamanos IG, Moffat FL, Boggs J, Franceschi D, Livingstone AS. Metastasectomy as a cytoreductive strategy for treatment of isolated pulmonary and hepatic metastases from breast cancer. *Surg Oncol* 1999; **8**(1): 35–42.
5. Pocard M, Pouillart P, Asselain B, Salmon R. Hepatic resection in metastatic breast cancer: results and prognostic factors. *Eur J Surg Oncol* 2000; **26**(2): 155–159.
6. Elias D, Maisonnette F, Druet-Cabanac M, *et al.* An attempt to clarify indications for hepatectomy for liver metastases from breast cancer. *Am J Surg* 2003; **185**(2): 158–164.
7. McDonald ML, Deschamps C, Ilstrup DM, Allen MS, Trastek VF, Pairolero PC. Pulmonary resection for metastatic breast cancer. *Ann Thorac Surg* 1994; **58**(6): 1599–1602.
8. Lanza LA, Natarajan G, Roth JA, Putnam Jr JB. Long-term survival after resection of pulmonary metastases from carcinoma of the breast. *Ann Thorac Surg* 1992; **54**(2): 244–247.

https://doi.org/10.1017/S1470903106002288 Published online by Cambridge University Press

9. Singletary SE, Walsh G, Vauthey JN, *et al.* A role for curative surgery in the treatment of selected patients with metastatic breast cancer. *Oncologist* 2003; **8**(3): 241–51.
10. Isasi CR, Moadel RM, Blaufox MD. A meta-analysis of FDG-PET for the evaluation of breast cancer recurrence and metastases. *Breast Cancer Res Treat* 2005; **90**(2): 105–112.
11. Planchard D, Soria JC, Michiels S, *et al.* Uncertain benefit from surgery in patients with lung metastases from breast carcinoma. *Cancer* 2004; **100**(1): 28–35.
12. Ludwig C, Stoelben E, Hasse J. Disease-free survival after resection of lung metastases in patients with breast cancer. *Eur J Surg Oncol* 2003; **29**(6): 532–535.
13. Livartowski A, Chapelier A, Beuzeboc P, *et al.* Surgical excision of pulmonary metastasis of cancer of the breast: apropos of 40 patients. *Bull Cancer* 1998; **85**(9): 799–802.
14. Staren ED, Salerno C, Rongione A, Witt TR, Faber LP. Pulmonary resection for metastatic breast cancer. *Arch Surg* 1992; **127**(11): 1282–1284.
15. Pastorino U, Buyse P, Friedel G, *et al.* Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The international registry of lung metastases. *J Thorac Cardiovasc Surg* 1997; **113**(1): 37–49.
16. Pierga JY, Asselain B, Jouve M, *et al.* Effect of adjuvant chemotherapy on outcome in patients with metastatic breast carcinoma treated with first-line doxorubicin-containing chemotherapy. *Cancer* 2001; **91**(6): 1079–1089.
17. Giordano SH, Buzdar AU, Smith TL, Kau SW, Yang Y, Hortobagyi GN. Is breast cancer survival improving? *Cancer* 2004; **100**(1): 44–52.
18. Farquhar C, Basser R, Hetrick S, Lethaby A, Marjoribanks J. High dose chemotherapy and autologous bone marrow or stem cell transplantation versus conventional chemotherapy for women with metastatic breast cancer. *Cochrane Database Syst Rev* 2003; issue 1: CD003142.
19. Stadtmauer EA, O'Neill A, Goldstein LJ, *et al.* Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. Philadelphia Bone Marrow Transplant Group. *New Engl J Med* 2000; **342**(15): 1069–1076.
20. Berry DA, Broadwater G, Klein JP, *et al.* High-dose versus standard chemotherapy in metastatic breast cancer: comparison of cancer and leukemia group B trials with data from the autologous blood and marrow transplant registry. *J Clin Oncol* 2002; **20**(3): 743–750.
21. Bojko P, Welt A, Schleucher R, *et al.* High-dose chemotherapy with autologous stem cell transplantation in patients with oligometastatic breast cancer. *Bone Marrow Transplant* 2004; **34**(7): 637–643.
22. Matsuzaki Y, Shimizu T, Edagawa M, Hara M, Tomita M, Ayabe T, Onitsuka T. 'The Law of 3': prognostic parameters for resected metastatic pulmonary tumors. *Ann Thorac Cardiovasc Surg* 2003; **9**(5): 290–294.
23. Tanaka F, Li M, Hanaoka N, Bando T, Fukuse T, Hasegawa S, Wada H. Surgery for pulmonary nodules in breast cancer patients. *Ann Thorac Surg* 2005; **79**(5): 1711–1714.
24. Murabito M, Salat A, Mueller MR. Complete resection of isolated lung metastasis from breast carcinoma results in a strong increase in survival. *Minerva Chir* 2000; **55**(3): 121–127.

https://doi.org/10.1017/S1470903106002288 Published online by Cambridge University Press