A Role for Curative Surgery in the Treatment of Selected Patients with Metastatic Breast Cancer

S. Eva Singletary, a Garrett Walsh, b Jean-Nicholas Vauthey, a Steven Curley, a Raymond Sawaya, c Kristin L. Weber, a Funda Meric, a Gabriel N. Hortobágyi d

Departments of aSurgical Oncology, bThoracic and Cardiovascular Surgery, cNeurosurgery, and dBreast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas, USA

Key Words. Breast cancer · Metastasis · Surgery · Median survival

ABSTRACT

Although metastatic breast cancer is widely believed to carry a grim prognosis, treatment developments over the past 25 years have greatly improved survival outcomes in these patients. In selected cases, aggressive treatment approaches may occasionally result in long-term survival of 15 years or more. This review considers the role of surgery in the treatment of single or multiple metastatic lesions restricted to one site. For each site, available literature from 1992-2002 was assessed to determine the role of surgery on survival outcomes and to determine appropriate criteria for selecting the best candidates for surgery. For lung, liver, brain, and sternum metastases, the use of surgery with or without adjuvant therapy resulted in greater median survival times and 5-year survival rates. The best candidate for surgery had no evidence of additional metastatic disease, good performance status, and a long disease-free interval after treatment of the primary tumor. Current treatment standards for breast cancer follow-up do not include imaging studies other than mammography. The addition of chest x-rays as part of routine follow-up should be considered as a cost-effective approach for early assessment of metastases to the lung or sternum that may be appropriate for surgical excision.

The Oncologist 2003;8:241-251

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Explain how surgery in combination with systemic therapy may offer significantly improved survival outcomes in selected patients with metastatic breast cancer.

2. Appreciate the value of chest x-rays in follow-up to identify patients with pulmonary or sternal metastases who may be candidates for surgical resection.

3. Recognize that the concept of a “cure” in breast cancer is evolving to mean a prolonged period of survival without significant symptoms.

ABSTRACT

INTRODUCTION

The traditional belief of both patients and their physicians has been that metastatic breast cancer offers only the grimmest prognosis, with average survival times of 1-2 years. This belief has fostered treatment regimens based on the notion that palliative treatment is the optimal choice for
most patients, with more aggressive therapeutic approaches likely to result in useless patient distress.

It is certainly true that, in the absence of intercurrent causes of death, most patients who develop breast cancer metastases ultimately die of their disease, with an overall survival rate of approximately 2% at 20 years after diagnosis with metastases [1]. It is equally true, however, that new treatment modalities developed over the past 25 years have resulted in significantly improved median survival times for patients with metastatic disease. A recent study by Giordano and colleagues [2] examined outcomes in 1,986 breast cancer patients who received similar treatment for their primary disease at a single institution between the years of 1974 and 2000. Of the original patient sample, 843 developed recurrent disease. Those patients who were diagnosed with recurrent disease in the interval from 1974-1979 had a median survival of 15 months, with 3- and 5-year overall survival rates of 15% and 10%, respectively. Patient outcomes improved steadily over the following 20 years, with patients diagnosed with recurrent disease in the interval from 1995-2000 showing a median survival of 51 months, and 3- and 5-year overall survival rates of 61% and 40%, respectively.

With these longer median survival times, the treatment paradigm for metastatic breast cancer is evolving. A recent paper by O’Shaughnessy [3] outlines a clinical strategy based on prolonged tumor control with minimal toxicity. For patients who have no significant symptoms and who respond to first-line therapy (typically hormonal for patients whose metastatic disease is estrogen-receptor or progesterone-receptor positive), such a strategy can result in long progression-free intervals and postponement of the need for more toxic therapies.

A more aggressive treatment approach may be appropriate for those patients in whom metastatic disease is limited to a solitary lesion or to multiple lesions at a single organ site. When those patients can be rendered clinically disease free by local treatment (surgery or radiation), there is the potential of achieving a complete remission from chemotherapy, and patients can remain disease free for prolonged periods of time (15-20 years or more). In a clinical trial conducted at the M.D. Anderson Cancer Center by Holmes and colleagues [4], patients with solitary metastases were treated with surgical resection with or without radiation therapy, followed by systemic chemotherapy, consisting of fluorouracil, doxorubicin, and cyclophosphamide, and hormonal therapy, consisting of tamoxifen. Nearly 25% of patients were alive without disease 15 years after treatment, and only two additional events occurred at a maximum follow-up of 26 years [4, 5]. Related reports from Borner and colleagues [6] and from Nieto and colleagues [7] provide additional evidence that an aggressive multimodal therapy can significantly increase disease-free survival in selected patients with limited metastatic disease.

Breast cancer metastases isolated to a single organ commonly occur in lung, liver, brain, and bone. This review article considers the role of surgery with or without adjuvant therapy in the treatment of single or multiple metastatic lesions restricted to one of these specific sites. For each site, available literature from 1992-2002 was assessed to determine the role of surgery on survival outcomes and to determine appropriate criteria for selecting the best candidates for surgery.

**Sites of Breast Cancer Metastasis**

**Lung**

Approximately 3% of all women with breast cancer develop a solitary pulmonary lesion detectable by chest x-ray, of which 33%-40% will be breast metastases [8, 9]. Lung resection for metastatic disease was first reported in 1882 by Weinlechner [10] and, in 1939, Churchill performed the first resection of a pulmonary metastasis leading to long-term survival [11]. Since that time, surgery has become a standard treatment in patients with solitary pulmonary metastases, with 5-year survival rates of approximately 35%, depending on the primary site [12].

Table 1 presents the results of eight retrospective studies that examined survival outcomes in breast cancer patients with isolated metastases to the lung treated with surgery with or without postsurgical systemic therapy [9, 13-19]. Median survival times ranged from 42 months to 79 months, with 5-year actuarial survival rates ranging from 35%-80% and 10-year actuarial survival rates ranging from 8%-60%. In two studies that presented outcomes from patients who received medical treatment only (usually chemotherapy) for pulmonary metastases [15, 18], survival was significantly lower for those patients. In a study by Staren and coworkers [15], the mean survival time was 55 months in the group receiving surgery compared with 33 months in the group receiving medical treatment only. Murabito and colleagues [18] reported a mean survival time of 79 months in patients receiving surgery versus 9 months in patients receiving medical treatment only. Across all eight studies, there was no apparent survival advantage related to treatment with postsurgical systemic therapy in addition to surgery, but precise data bearing on this issue were not available from many of these studies.

Positive survival outcomes after surgery, with or without chemotherapy, were associated with a long disease-free interval (DFI) after treatment of the primary tumor (12-36 months) [14, 16, 19], with complete resection of the tumor [9, 17, 19], and with estrogen-receptor-positive status [14]. In the largest study in that series (n = 467) [19], the best candidates (DFI greater than 36 months and complete resection)
had a 5-year survival rate of 50% and a 15-year survival rate of 25% after surgery, with or without chemotherapy, indicating that this treatment approach is curative in this select group of patients.

Even without the potential survival benefit associated with surgical resection of metastases, there is an obvious additional reason for recommending at least limited surgery for breast cancer patients with isolated pulmonary lesions. As indicated above [8, 9], only about one-third of such lesions will prove to be breast cancer metastases, while the remaining two-thirds will be other types of tumors, chiefly primary lung cancer. Early identification of the tumor is critical for determining appropriate treatment strategies.

Liver

More than half of all patients with metastatic breast cancer will have liver involvement at some point [20]. Typically, this is a late finding, when metastases are already present at other sites. Those patients with obvious multisite liver disease are usually treated with systemic therapy, although intra-arterial regional chemotherapy may be used for treatment of multiple liver metastases.

Of all patients with metastatic breast cancer, approximately 5% will have metastasis confined to the liver with no evidence of extrahepatic disease [21, 22]. Even with systemic chemotherapy, the median survival time for patients with metastatic disease to the liver only or with limited disease elsewhere is only 19 months, with pretaxane chemotherapy regimens, or 22-26 months with taxane-containing regimens [23].

Hormonal therapy is of limited use, as most breast tumors that metastasize to the liver are hormone-receptor negative [24]. Because of the lack of effective systemic therapy, surgery has been proposed as a potential therapeutic tool for increasing survival in patients with isolated hepatic metastases.

Only a small number of retrospective studies have examined outcomes in breast cancer patients with isolated hepatic metastases treated with surgery, and the patient numbers in those studies are relatively small. Nonetheless, there is evidence that the use of surgery with or without chemotherapy in treating these patients can significantly increase survival. As shown in Table 2, the median survival times in six published studies ranged from 24-44 months, and the 5-year survival rates ranged from 22%-38%, with one study showing a 4-year survival rate of 46% [25-30]. In a study by Selzner and coworkers [28], 4 of 17 patients were alive without evidence of disease at 6 months, 17 months, 6 years, and 12 years after surgery.

In unpublished data from the University of Texas M.D. Anderson Cancer Center, 21 patients underwent resection and/or radiofrequency ablation with curative intent for isolated liver metastases between January 1987 and July 2000. Liver metastases developed after a median time of 35 months (range 0-144) from initial diagnosis. Fourteen patients had a solitary metastasis and seven had two lesions. The vast majority (81%) of patients received adjuvant chemotherapy for the primary tumor or neoadjuvant chemotherapy for the liver recurrence. The type of surgery included major hepatectomy (resection of one or more

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Treatment</th>
<th>Median (months)</th>
<th>5-year (%)</th>
<th>10-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ishida et al. [13]</td>
<td>4</td>
<td>Surgery</td>
<td>NS</td>
<td>75</td>
<td>NS</td>
</tr>
<tr>
<td>Lanza et al. [14]</td>
<td>37</td>
<td>Surgery + chemotherapy with or without tamoxifen</td>
<td>47</td>
<td>50</td>
<td>NS</td>
</tr>
<tr>
<td>Staren et al. [15]</td>
<td>33</td>
<td>Surgery</td>
<td>55*</td>
<td>35</td>
<td>NS</td>
</tr>
<tr>
<td>McDonald et al. [9]</td>
<td>60</td>
<td>Surgery alone (n = 17) or with chemotherapy (n = 43)</td>
<td>42</td>
<td>38</td>
<td>8</td>
</tr>
<tr>
<td>Simpson et al. [16]</td>
<td>17</td>
<td>Surgery alone (n = 2) or with chemotherapy (n = 15)</td>
<td>NS</td>
<td>62</td>
<td>NS</td>
</tr>
<tr>
<td>Livartowski et al. [17]</td>
<td>40</td>
<td>Surgery</td>
<td>70</td>
<td>54</td>
<td>NS</td>
</tr>
<tr>
<td>Murabito et al. [18]</td>
<td>86</td>
<td>Surgery + chemotherapy*</td>
<td>79*</td>
<td>80*</td>
<td>60*</td>
</tr>
<tr>
<td>Friedel et al. [19]</td>
<td>467</td>
<td>Surgery alone (n = 308) or with chemotherapy (n = 159)</td>
<td>50*</td>
<td>45*</td>
<td>26*</td>
</tr>
</tbody>
</table>

*Mean values
*Percentage of patients receiving chemotherapy not specified
*Survival outcomes associated with complete resection of metastatic lesion
*Survival outcomes associated with a DFI > 36 months before detection of metastatic lesion
NS = not specified

Table 1. Survival outcomes in breast cancer patients with isolated metastases to the lung treated with surgery with or without chemotherapy
lobes) in seven patients, minor hepatectomy in nine patients, and radiofrequency ablation alone or in combination with resection in five patients. There were no perioperative mortalities. The median disease-free survival time was 40 months, and the disease-free 3-year survival rate was 55%. These survival results are comparable with those reported in the literature (Table 2). The role of radiofrequency ablation should be further evaluated in larger subsets of patients. At this time, it should be reserved for patients who cannot undergo safe resection or used as an adjuvant to resection.

Perhaps because of the small numbers of patients for whom data are available, there is also a limited amount of data about prognostic factors for increased survival after surgery in breast cancer patients with isolated hepatic metastases. Most would agree that the patient should show normal performance status and normal liver function tests. Two studies agreed that the size and number of hepatic metastases did not influence survival, but disagreed about whether the interval between treatment of the primary tumor and detection of the metastasis was an important factor [28, 30]. Selzner and colleagues did not find an effect on survival based on extent of liver resection [28]. Raab and colleagues reported a significant effect related to achieving a margin-negative resection of all metastatic liver lesions, with a median survival time of 42 months in patients receiving complete resection compared with 5 months in patients receiving palliative surgery [26]. Of special interest, two studies reported that the presence of extrahepatic metastases did not affect survival in patients in whom hepatic metastases had been surgically removed [28, 30]. This may be because, with the exception of brain lesions, metastases at other sites tend to develop more slowly, and the hepatic metastasis is the rate-limiting factor for patient survival.

### Brain

Brain metastases are diagnosed in approximately 10% of breast cancer patients [31]. Without treatment, the median survival for these patients is a mere 1-2 months [32-34]. With whole brain radiation therapy (WBRT), this figure increases to 3-6 months [33-36]. Brain lesions typically involve obvious and frightening neurological symptoms, and treatment has historically been aimed at the rapid palliation of these symptoms using WBRT and steroids. While this treatment approach is effective in most patients over the short term, symptoms usually return within 2-3 months [37].

In up to one-third of breast cancer patients with brain metastases, the brain is the only site of metastasis [33, 38, 39]. For those patients, depending upon the size and location of their lesions, surgical excision added to WBRT can significantly increase survival. In the five studies shown in Table 3 [31, 40-44], the median survival time for the combination of surgery and WBRT ranged from 15 to 37 months, with 5-year survival rates of 7%, 17%, 20%, and 38% reported in four studies [40-44]. The largest study in that series (n = 70) reported a median survival time of 15 months and a 5-year survival rate of 7% [43]. It should be noted that the 38% 5-year survival rate and a subsequent 20% 10-year survival rate were reported in a study with a very small sample size (n = 8) [41]. Nonetheless, it does point out the possibility of prolonged survival following surgical excision and radiotherapy for isolated brain metastases. This is

### Table 2. Survival outcomes in breast cancer patients with isolated metastases to the liver treated with surgery with or without chemotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Treatment</th>
<th>Median (months)</th>
<th>5-year (%)</th>
<th>10-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schneebaum et al. [25]</td>
<td>6</td>
<td>Surgery + regional chemotherapy*</td>
<td>42</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Raab et al. [26]</td>
<td>35b</td>
<td>Surgery alone (n = 32) with regional chemotherapy (n = 2)</td>
<td>42</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Santoro et al. [27]</td>
<td>15</td>
<td>Surgery + chemotherapy</td>
<td>44</td>
<td>38</td>
<td>NS</td>
</tr>
<tr>
<td>Selzner et al. [28]</td>
<td>17</td>
<td>Surgery + high-dose chemotherapy</td>
<td>24</td>
<td>22</td>
<td>NS</td>
</tr>
<tr>
<td>Yoshimoto et al. [29]</td>
<td>17</td>
<td>Surgery + chemotherapy (systemic or regional)</td>
<td>34</td>
<td>30</td>
<td>NS</td>
</tr>
<tr>
<td>Pocard et al. [30]</td>
<td>65</td>
<td>Surgery + chemotherapy</td>
<td>NS</td>
<td>46d</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Regional chemotherapy = intra-arterial chemotherapy via the hepatic artery
bSolitary metastasis in 59% (n = 21) of patients
cSurvival outcomes shown are for patients receiving complete resection; patients receiving palliative surgery had a median survival time of 5 months and a 5-year survival rate of 0%
dSurvival at 4 years
NS = not specified
also illustrated in a case report by Nieder and colleagues of a 51-year-old woman with a solitary brain metastasis presenting 11 months after treatment for stage II node-negative breast carcinoma [45]. She was treated with surgical excision and WBRT, followed by long-term tamoxifen treatment. At the time of the report, she was alive with no evidence of disease more than 10 years after diagnosis of the brain metastasis.

The presence of leptomeningeal disease is a very poor prognostic sign and contraindicates surgical excision of brain metastases [43]. Patients are generally considered good candidates for surgical therapy if they have a single, operable brain lesion and well-controlled systemic disease. However, a study by Wronski and colleagues [43] did not find any significant differences in outcomes among patients with single or multiple brain metastases or patients who had concurrent lung metastases. They also did not find any difference in outcome related to the interval between diagnosis of the primary tumor and diagnosis of the metastasis, but two other studies [40, 41] did report longer survival associated with a longer DFI.

Over the past 10 years, there has been increasing interest in the use of single-fraction stereotactically delivered radiation therapy (commonly called stereotactic radiosurgery or SRS) as a substitute for surgical excision in the treatment of brain metastases. SRS delivers an intense dose of radiation to a well-defined area within the brain. It has the advantage of being noninvasive and, because of the sharp dose gradient used, collateral damage to surrounding normal tissue is minimized. In three studies that have used SRS for the treatment of brain metastases of various origin, median survival times have ranged from 6-8 months, and 1-year survival rates have ranged from 38%-44% [46-48]. One study reported a 5-year survival rate of 16% [48]. While these results are an improvement over the use of WBRT alone, they still lag behind results obtained using a combination of surgical excision and WBRT. In addition, larger lesions (>3 cm maximum diameter) may not respond as well to SRS [43]. Intuitively, treatment of these larger lesions also carries a higher risk of radiation damage to surrounding normal tissue. At present, the most prudent therapeutic strategy may be to use surgical excision where possible, reserving SRS for those cases in which the tumor is located in an inaccessible site or is otherwise inoperable.

Bone

Bone is one of the earliest and most common sites of breast cancer metastasis. The invasion of cancer cells into bone initiates a cycle that involves destruction of the bone (through activation of osteoclasts) and subsequent release of cellular growth factors leading to increased cancer cell growth [49]. The typical presenting symptom for bone metastasis is pain. As bone destruction progresses, fractures become more likely. In weight-bearing bones, this can lead to problems of mobility. Spinal cord compression can be an acute, life-threatening complication.

The usual first treatment choice for bone metastases not at risk for fracture is systemic therapy, either hormonal therapy or chemotherapy. This is especially true for isolated lesions, which account for approximately 20% of all bone metastases [50]. Isolated bone metastases have a somewhat indolent course and generally respond well to hormonal therapy.

### Table 3. Survival outcomes in breast cancer patients with isolated metastases to the brain treated with surgery with or without WBRT

<table>
<thead>
<tr>
<th>Study</th>
<th>n of patients</th>
<th>Treatment</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salvati et al. [40]</td>
<td>9</td>
<td>Surgery alone</td>
<td>15³</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>Surgery + WBRT</td>
<td>28³</td>
</tr>
<tr>
<td>Kocher et al. [41]</td>
<td>8</td>
<td>Surgery + WBRT</td>
<td>37</td>
</tr>
<tr>
<td>Boogerd et al. [31]</td>
<td>28</td>
<td>Surgery with or without WBRT with or without chemotherapy</td>
<td>23</td>
</tr>
<tr>
<td>Pieper et al. [42]</td>
<td>63</td>
<td>Surgery with or without WBRT with or without chemotherapy</td>
<td>16</td>
</tr>
<tr>
<td>Wronska et al. [43]</td>
<td>70</td>
<td>Surgery alone (n = 9) or with WBRT (n = 61)⁴</td>
<td>15³</td>
</tr>
<tr>
<td>Fokstuen et al. [44]</td>
<td>10</td>
<td>Surgery + WBRT</td>
<td>21³</td>
</tr>
</tbody>
</table>

³Figures are mean survival times

⁴Survival rate at > 3 years

₅n = 15 patients received WBRT before surgery

NS = not specified
For patients in whom the metastases are hormone-receptor negative, or who become refractory to hormonal treatment, chemotherapy has been shown to be effective [54]. In metastatic disease confined to the skeletal system and treated with hormonal therapy with or without chemotherapy, a median survival time of 48 months and a 5-year survival rate of 39% have been reported [51, 55]. More recently, osteoclast inhibitory therapy using bisphosphonates has become widely used [56]. Radiation therapy, either locally or through the systemic administration of radioisotopes, has also been used effectively in these patients, providing pain relief and, in some cases, evidence of bone healing [57, 58].

The use of surgery for the treatment of bone metastases has typically been reserved for lesions that are not responsive to systemic therapy and that are associated with a serious potential for decline in quality of life in order to reduce fractures, treat spinal cord or nerve compressions, and prophylactically fix imminent fractures. The most common goals of surgery are to maintain or restore mobility and to decrease pain, and the most common use is for the treatment of long bone fractures. Surgical treatment of impending or actual long bone fractures is generally performed to stabilize the bone rather than remove the tumor.

The use of surgery as a curative treatment option for bone metastases has been actively considered in the case of isolated metastases to the sternum. Two studies from the 1980s presented results from a limited number of patients indicating that surgical resection of solitary sternal metastases, where there was no evidence of systemic spread, may have led to significantly better survival. Takanami and Ohnishi [59] treated three patients, each with a single sternal metastasis from breast cancer, with partial resection of the sternum. Two patients died within 14 months, but the third was alive and disease free 7 years after surgery. Noguchi and coworkers [60] treated nine patients with solitary sternal metastases from breast cancer with either partial (n = 8) or total (n = 1) resection of the sternum. The median survival time for all nine patients was 30 months. Of the five patients who had no mediastinal or parasternal lymph node metastases, three survived more than 6 years. More recently, Incarbone and colleagues reviewed results from their institution from 52 patients who underwent surgical resection for tumors involving the sternum [61]. Of these, 11 involved breast cancer metastases. These patients showed a 60% 5-year survival rate and a median survival time described by the authors as “remarkably long.” Noguchi and colleagues [60] suggested that resection of sternal metastases may lead to long-term survival because these lesions remain solitary for a long time, possibly because of isolation from the venous plexus that provides a transmission route to other bones.

As shown in Figure 1, current reconstructive techniques using synthetic mesh in conjunction with autologous tissue transplants make surgical resection possible even for very large lesions. The patient shown in Figure 1 was a 69-year-old woman with a prior history of carcinoma in the right breast that had been treated with segmental mastectomy, radiation, and chemotherapy. Twenty-seven months later, she developed a large, rapidly growing sternal lesion that was a suspected metastasis from the previous breast cancer. The sternal lesion was refractory to chemotherapy. The surgeon was able to preserve a portion of the manubrium and to stabilize the bone rather than remove the tumor. The underlying right lung was compressed but not invaded; the left lung was normal. Some of the mediastinal fat and thymus was removed en bloc with the tumor. D) Positioning of a free TRAM flap for reconstruction of the surgical deficit. The base of the reconstruction was a double layer of Marlex® without methylmethacrylate. The TRAM flap was attached into the right internal mammary artery and vein. Photographs courtesy of Drs. Garrett Walsh and Pierre Chevray, M.D. Anderson Cancer Center.
reconstruct the chest wall using a double layer of Marlex® (Davol; Cranston, RI) without methylmethacrylate and a free transverse abdominis myocutaneous (TRAM) flap attached to the right internal mammary artery and vein.

**PERIOPERATIVE MORBIDITY AND MORTALITY IN PATIENTS RECEIVING SURGICAL TREATMENT FOR METASTATIC BREAST CANCER**

Approximately one-half of the reviewed studies reported perioperative morbidity and mortality (Table 4). The mortality rates were very low (median 0%, range 0%–6%). The morbidity rates varied widely (median 8%, range 0%–29%), but specific types of morbidity were generally reported as minor.

**SOURCES OF BIAS IN INTERPRETING THE VALUE OF SURGERY**

It is important to note that the results shown in these studies may be influenced by selection bias. It may be that patients selected for surgery had better prognostic features than those treated with chemotherapy alone. Unfortunately, because of the lack of studies that directly compared outcomes in these two groups, there are few data that bear directly on this issue. In two lung metastasis studies that compared outcomes in patients receiving surgery compared with those receiving chemotherapy [15, 18], there were no significant differences in relevant patient characteristics including stage, histology, hormone receptor levels of the primary tumor, number of metastases, and length of DFI. However, these studies did not report whether there were differences in performance statuses between the two treatment groups, and this can be an important predictor of survival. Patients with poor performance statuses are generally considered to be poor surgical risks and are often recommended for alternative nonsurgical therapies. This could introduce an important source of bias into an assessment of the value of surgery.

Publication bias against series in which there was no survival benefit may also affect the results presented here. It might be argued that the relatively small number of cases reported in these studies (e.g., 744 lung metastases from breast) is only a fraction of the total cases in which surgery was used as a treatment option. However, the absolute number of breast metastases that are eligible for resection is likely to be relatively small. For example, while approximately 1%-1.5% of women with breast cancer develop metastasis to the lung, only about 25% of those patients may be recommended for surgery [9]. A review of the M.D. Anderson Cancer Center database starting in 1984 (most reliably captured after 1997) revealed only 56 patients who underwent thoracotomy for breast cancer metastasis to the lung. Thus, the small number of reported cases is not itself a reliable indicator of publication bias. It is also important to note that a 2002 analysis of 467 patients from the International Registry of Lung Metastases (the single largest database on metastasis to the lung) showed patient outcomes consistent with those from smaller studies reported here. Thus, we do not believe that publication bias seriously undermined our conclusions about the potential value of surgery in the treatment of lung metastases.
DISCUSSION

The data reviewed here indicate that surgery combined with adjuvant therapy, compared with radiation or systemic therapy alone, can result in significantly better survival in breast cancer patients with metastatic disease in the lung, liver, brain, or sternum. As discussed above, several kinds of bias might influence these results. Nonetheless, the data are suggestive and support the need for well-designed clinical trials to determine the exact role of surgical intervention in patients with metastatic breast cancer. Such trials will admittedly be difficult to implement. Not only are the absolute numbers of eligible patients likely to be small, but accrual of patients into clinical trials is a continuing challenge. As of 1991, only 1%-3% of the available patient population was being recruited into cooperative group adjuvant trials, with only 10%-30% of eligible patients finally enrolled in studies [62]. For breast cancer, less than 2% of patients are included in clinical trials [63]. In the case of patients with stage IV breast cancer, a significant barrier to patient accrual may be reluctance of the patient or physician to consider aggressive therapy in what has historically been considered to be end-stage disease.

Across the four sites (lung, liver, brain, bone), better patient outcome after surgery was associated with good performance status, long DFI after treatment of the primary tumor, complete resection of the tumor, and restriction of metastasis to single tumors or to multiple tumors at a single site. Complete resection constitutes proper surgery for any tumor, and it is not surprising that it would also have a significant effect on outcomes for metastatic lesions. In metastasis to the lung, for example, complete resection can offer 5-year survival rates as high as 50% compared with the 18% associated with incomplete resection [19]. The last criterion (restriction to a single tumor or a single site) argues for the early detection of the metastatic lesion(s), before more advanced disease progression occurs. Early detection of lung, liver, and bone metastases would require the routine use of chest x-rays, abdominal ultrasounds, and bone scans as part of the routine follow-up for breast cancer. In the case of brain metastases, even very small lesions generally result in neurological symptoms that are clinically detectable, removing the need for advanced imaging techniques in asymptomatic patients.

In the practice guidelines of the National Comprehensive Cancer Network [64], the current recommendations for follow-up of breast cancer patients are: A) history and physical exam every 4-6 months for 5 years, then every 12 months; B) mammogram every 12 months (or 6 months, after radiotherapy if breast-conserving surgery was used); and C) pelvic exam every 12 months in women on tamoxifen, if the uterus is present. These guidelines were based in part on the results of a large multicenter trial conducted in Italy comparing outcomes in patients with differing follow-up protocols [65, 66]. One group of patients received yearly mammograms and physical examinations, and the second group received intensive surveillance that included bone scans, liver sonograms, chest x-rays, and laboratory tests in addition to the mammogram and physical exam. The results of the trial indicated that the tests used in the intensive surveillance regimen did not improve survival or influence quality of life and, thus, should not be included in routine follow-up. However, as suggested by Cocconi [67], it may not be surprising that the outcomes in the two groups were similar, since the recommended treatment protocol would have been largely palliative, regardless of when the metastasis was discovered. The question then becomes: would the inclusion of these tests in routine breast cancer follow-up be more cost effective if a different treatment protocol with the potential for an improved outcome was recommended for patients with solitary metastases?

For bone metastases in the spine or long bones, it seems unlikely that earlier detection would significantly alter current treatment recommendations. Since bone resections constitute radical surgery, with extended and painful recovery times, most metastases would continue to be treated primarily with hormonal therapy or chemotherapy, with surgery reserved for fracture reduction or stabilization. Brain metastases, as mentioned above, are typically symptomatic from a very early stage, and patients would derive little benefit from the addition of costly screening tests. Metastasis to the liver is generally a late event, usually accompanied by systemic disease. Ultrasound imaging is effective in detecting hepatic lesions, but the cost to include this in routine screening to detect the rare isolated event may be prohibitive.

It may, however, be cost effective to reconsider the routine use of chest x-rays for follow-up of breast cancer patients. This diagnostic tool would be effective in detecting early metastasis to the lung or sternum, which often occurs as a solitary lesion. Based on current estimates of breast cancer incidence [68], this would involve screening 192,000 patients per year for the detection of approximately 3,000 metastases to the lung or sternum. In both of these sites, the use of surgical excision in addition to standard medical treatment has been shown to significantly improve median survival.

As the treatment recommendations for breast cancer continue to evolve, so too does the definition of what constitutes a “cure.” We are perhaps approaching a time where breast cancer can be “cured” in the sense that it can be rendered harmless. By moving away from the treatment paradigm aimed at removing or destroying every cancerous cell, we can redefine a “cure” as a prolonged period of survival without significant symptoms. Under this new paradigm, cancer
can be thought of as being reduced to a commensal organism, the biological equivalent of an epiphyte, such as Spanish moss, that depends on the oak tree to live but does nothing to harm its host organism. Metastatic breast cancer to the lung or sternum, if detected early and treated aggressively, holds the possibility of such a cure.

**References**


65 Liberati A. The GIVIO trial on the impact of follow-up care on survival and quality of life in breast cancer patients.

