Treatment of the primary tumor in breast cancer patients with synchronous metastases

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Data from the Surveillance, Epidemiology, and End Results program and the European Concerted Action on survival and Care of Cancer Patients (EUROCARE) project indicate that ~6% of women newly diagnosed with breast cancer have stage IV disease, representing ~12,600 new cases per year in the United States in 2005. Historically, local therapy of the primary tumor in this setting has been aimed solely at symptom palliation. However, several studies suggest that surgical excision or exclusive irradiation of the primary tumor can prolong these patients’ survival. In contrast, the impact of surgical dissection of regional lymph nodes and postoperative radiotherapy is poorly documented, and the patient subgroups most likely to benefit from treatment of the primary tumor remain to be identified. Two prospective studies are currently examining the benefits of locoregional therapy compared with systemic therapy alone in this setting. Here, we discuss current issues regarding treatment of the primary tumor in breast cancer patients with synchronous metastases.

Key words: local treatment, metastatic breast cancer, radiotherapy, surgery

Introduction

Data from the Surveillance, Epidemiology, and End Results (SEER) program and the European Concerted Action on survival and Care of Cancer Patients (EUROCARE) project indicate that ~6% of women newly diagnosed with breast cancer have stage IV disease, representing ~12,600 new cases per year in the United States in 2005 [1, 2]. The 5-year overall survival (OS) rate among such patients rarely exceeds 20% [3]. Survival can be improved by endocrine therapy, chemotherapy, and biological therapy [4, 5]. Local treatment is often recommended to prevent or relieve symptoms but is traditionally considered to have no noteworthy impact on survival [4, 5]. However, several recent observational studies have shown that 35%–60% of breast cancer patients with stage IV disease at diagnosis receive treatment of the primary tumor and that this treatment is associated with a survival advantage [6–18]. The impact of treatments targeting regional lymphatics is unclear, and the patient subgroups most likely to benefit from treatment of the primary tumor remain to be identified. Two prospective studies are currently examining the benefits of locoregional therapy compared with systemic therapy alone in this setting. The main objective of this review is to highlight current issues regarding treatment of the primary tumor in breast cancer patients with synchronous metastases in order to highlight clinicians in their therapeutic decision.

Search strategy and selection criteria

Data for this review were compiled by searching the PubMed and Medline databases using the search terms: breast cancer and metastatic or stage IV and also surgery or radiotherapy or local treatment. The reference lists of full articles thus identified were checked for additional material when appropriate. Abstracts and conference reports were also included. Only articles published after 1981, in English, were considered.

Surgical treatment of the primary tumor in women with metastatic breast cancer at diagnosis

At least 13 retrospective studies have evaluated surgery of the primary tumor in breast cancer patients with synchronous metastases. The results of these studies, coming from the SEER database, the National Cancer Database (NCDB), the Geneva Tumor Registry, and several large comprehensive cancer center databases, show that surgical resection of the primary tumor was carried out in 35%–60% of breast cancer patients with synchronous metastases and that surgery of the primary tumor was associated in most series with a relatively constant reduction in the risk of death of ~40% [6–13, 15–19] (Table 1). The largest series was published by Khan et al. [13], who investigated the use and impact of local therapy among 16,023 breast cancer patients with synchronous metastases registered in the NCDB of the American College of Surgeons from 1990 to 1993. Fifty-seven percent of these patients had surgical resection of the primary tumor [partial mastectomy (PM) or...
total mastectomy (TM)], while the remainder had biopsy or no surgery at all. Free resection margins were more frequent in women who had TM than in those who had PM (63% versus 45%). Women who had TM were also much more likely than those with PM to have node dissection (78.5% versus 18.9%). The majority of patients received systemic therapy, which consisted of endocrine and cytotoxic therapy, alone or in combination. Complete surgical removal of the primary tumor,

<table>
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<td>Khan et al. [13]</td>
<td>American College of Surgeons</td>
<td>1990–1993 S</td>
<td>16 023/9162/6861</td>
<td>S, systemic therapy, number of metastatic sites</td>
<td>HR OS (R0) = 0.61 (0.58–0.65), HR (R1) = 0.751 (0.71–0.793)</td>
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<td>Gnerlich et al. [11]</td>
<td>SEER</td>
<td>1988–2003 S</td>
<td>9734/4578/5156</td>
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<td>HR OS = 0.57 (0.55–0.60)</td>
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<td>Bafford et al. [7]</td>
<td>Dana Farber Cancer Institute, Brigham and Women's Hospital, and Massachusetts General Hospital</td>
<td>1998–2005 S</td>
<td>147/61/86</td>
<td>S, ER+, Her2+, no CNS metastasis</td>
<td>HR OS = 0.47 (P = 0.003)</td>
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<td>Shien et al. [18]</td>
<td>National Cancer Center Hospital</td>
<td>1962–2007 S</td>
<td>326/160/184</td>
<td>S, age &lt;50, soft tissue or bone metastasis</td>
<td>HR OS = 0.89 (0.79–1)</td>
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<td>Blanchard et al. [8]</td>
<td>Laboratory of the University of Texas Health Science Center</td>
<td>1973–1991 S</td>
<td>395/242/153</td>
<td>S, ER +, PR+, number of metastatic sites</td>
<td>HR OS = 0.609 (0.489–0.757)</td>
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<tr>
<td>Fields et al. [10]</td>
<td>Washington University Medical Center</td>
<td>1996–2005 S</td>
<td>409/287/222</td>
<td>S, Bone-only metastasis</td>
<td>HR OS = 0.53 (0.42–0.67), no difference in time to metastatic progression between the two groups</td>
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<td>Babiera et al. [6]</td>
<td>MD Anderson Cancer Center</td>
<td>1997–2002 S</td>
<td>224/82/142</td>
<td>Only one site of metastasis, HER2+, Caucasian ethnicity</td>
<td>HR OS = 0.5 (0.21–1.19), HR TTFP = 0.54 (0.38–0.77, P = 0.0007)</td>
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<td>Hazard et al. [12]</td>
<td>Lynn Sage Breast Center (Northwestern Memorial Hospital)</td>
<td>1995–2005 S</td>
<td>111/47/64</td>
<td>NA</td>
<td>HR OS = 0.798 (P = 0.52), HR TTFP = 0.49 (P = 0.015)</td>
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<td>Cady et al. [9]</td>
<td>Massachusetts General Hospital and Brigham and Women’s Hospital</td>
<td>1970–2002 S</td>
<td>622/234/388</td>
<td>Young age, RH+, bone-only metastasis</td>
<td>Matched-pair analysis: benefit of surgery P &lt; 0.0001</td>
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<td>Ruiterkamp et al. [17]</td>
<td>Eindhoven Cancer Registry</td>
<td>1993–2004 S</td>
<td>728/288/440</td>
<td>Surgery, age, no more than one metastatic site, no concomitant disease (P = 0.06), systemic therapy</td>
<td>HR OS = 0.62 (0.51–0.76)</td>
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<td>Leung et al. [19]</td>
<td>Medical College of Virginia Campus of Virginia Commonwealth University</td>
<td>1990–2000 S</td>
<td>157/52/105</td>
<td>Chemotherapy</td>
<td>No benefit in multivariate analysis</td>
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<td>Rapiti et al. [16]</td>
<td>Geneva Cancer Registry</td>
<td>1977–1996 S</td>
<td>300/127/173</td>
<td>Age &lt; 60, none N3, ER+, none visceral metastasis, none CNS metastasis, hormonal treatment, surgery with negative margins</td>
<td>HR OS = 0.6 if R0 (0.4–1.0), NS if R1</td>
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<tr>
<td>Le Scodan et al. [14]</td>
<td>Rene Huguenin Cancer Center</td>
<td>1984–2004 RT</td>
<td>581/320/261</td>
<td>Only one metastatic site, young age, LRT, no visceral metastases, N0</td>
<td>HR OS = 0.7 (0.58–0.85)</td>
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95% CI, 95% confidence interval; CNS, central nervous system; ER+, tumor-positive estrogen receptor; Her2+, Her2 positive status; HR, hazard ratio; LRT, locoregional treatment; MST, median survival time; N0, clinical N0 lymph node status; OS, overall survival; NS, not statistically significant; PR+, tumor-positive progesterone receptor; R0, surgery with negative margins; R1, surgery with positive margins; RT, radiation therapy; S, surgery of the primary tumor; SEER, Surveillance, Epidemiology, and End Results; TTFP, time to first progression.
i.e. with free margins, was associated with a 39% reduction in the risk of death: the 3-year survival rate was 35% compared with 26% and 17.3%, respectively, among patients with positive margins and patients who did not have surgery \( (P < 0.0001) \). This survival benefit of breast surgery persisted in multivariate analysis. Similar conclusions were reached by Rapiti et al. [16]: among 300 women included in the Geneva Cancer Registry from 1977 to 1996, complete surgical resection of the primary tumor was associated with improved OS. The 5-year breast cancer-specific survival rate was 27% [95% confidence interval (CI) 16% to 39%] among women who had surgery with free margins, 16% (95% CI 3% to 28%) among those with positive margins, and 12% (95% CI 7% to 17%) among those who did not have surgery \( (P = 0.0002) \). Women with negative surgical margins had a 40% reduction in the risk of death from breast cancer [multi-adjusted hazard ratio (HR) 0.6, 95% CI 0.4–1.0] relative to women who did not have surgery \( (P = 0.049) \), whereas women with positive or unknown margin status derived no significant survival benefit \([HR 1.3, 95\% CI 0.8–2.1 and HR 1.1, 95\% CI 0.7–1.7, respectively]\). Analysis of the 1988–2003 SEER dataset, involving 9734 women, also showed that surgical resection of the primary breast tumor (surgical margin status was not available) was associated with prolonged survival, with a HR for death of 0.63 (95% CI 0.60–0.66) [11]. Smaller series from other institutional databases, such as the Baylor College [8] the Washington University/Barnes Hospital [10] or the MD Anderson [6], also pointed to a benefit of surgical treatment of the primary breast tumor in stage IV breast cancer patients, based on samples of between 147 and 728 women. In the MD Anderson study, there was a nonsignificant trend toward improved survival after surgical resection of the primary tumor and also a significant improvement in the time to first progression, with a HR of 0.55 (95% CI 0.4–0.8) relative to women who did not have surgery [6]. In the report from Baylor College of Medicine, surgery was associated with a multi-adjusted HR for death of 0.7 \( (P = 0.0059) \) [8]. Following the change in the treatment paradigm in this setting, Morrow et al. [20] recently reported that, in the Memorial Sloan-Kettering Cancer Center, the rate of symptom control mastectomy fell from 41% to 25% over time, while the rate of local control mastectomy rose from 34% to 66%. In the studies reported by Leung et al. [19], median survival for patients who underwent surgery was 25 months compared with 13 months for those who did not \( (P = 0.004) \). However, when taking the delivery of chemotherapy into account, surgery no longer appeared to have a significant impact on OS in multivariate analysis. Cady et al. [9] suggested that case selection bias may explain an important part of the beneficial effect of surgery on OS. However, surgery was associated with improved survival in the entire population study and in nearly all case-matched subgroups.

**type of surgery; importance of surgical margins and timing**

Khan et al. [13] directly compared different surgical procedures in this setting. Differences in the survival benefit experienced by surgically treated patients were entirely explained by the pathologic status of the resection margins but not by the type of surgery (PM versus TM). The 3-year survival rate was similar, regardless of the type of surgery, among patients with involved margins (26.4% and 26.1% after PM and TM, respectively). When the margins were free, the 3-year survival rate was also similar after PM and TM (34.7% and 35.7%, respectively), even though free margins were obtained more frequently with TM than with PM. Same conclusions have been reached in the study by Ruiterkamp et al. [17] where the type of surgery was not associated with survival in multivariate analysis. Similarly, in the study by Rapiti et al. [16], only surgery with negative margins was associated with a lower risk of dying from breast cancer relative to no surgical treatment (multi-adjusted HR 0.6, 95% CI 0.4–1), whereas no difference was shown for women with positive surgical margins (multi-adjusted HR 1.3, 95% CI 0.8–2.1) or unknown margin status (multi-adjusted HR 1.1, 95% CI 0.7–1.7).

The optimal timing of surgery is controversial, although one would expect early treatment to be more beneficial based on theories of metastases and tumor biology: first, the primary tumor could functions as a source of new metastases [21]; second, the surge of angiogenesis at distant metastatic sites after removal of the primary tumor might enhance chemoresensitivity; and third, systemic therapy may be more effective after a reduction in the tumor burden because surgery removes necrotic and nonvascularized tumor regions that may be inaccessible to drugs, thereby limiting the emergence of chemoresistant cell lines [22–26]. Unfortunately, clinical data are equivocal. In the study by Bafford et al. [7], surgery-only benefited patients who were operated on before metastases were diagnosed: survival among those operated on later was similar to that among women who did not have surgery. In the study by Hazard et al. [12], 10 of 64 patients who were not operated on immediately went on to have local delayed palliative surgery. There was no significant difference in OS between these 10 patients and the other 54 patients, suggesting that delayed surgery is not beneficial. The MD Anderson dataset was recently reanalyzed to determine the optimal timing of surgery in this setting [15]. The patients were divided into three groups, based on the interval between diagnosis and first surgery. Patients who had surgery within 3 months after diagnosis (group 1) had shorter metastatic-progression-free survival (MFS) than those who were operated on later \( (P = 0.008) \). One explanation could be that patients in group 1 were not immediately identified as having metastatic disease, which may have delayed systemic therapy. In the recently published study by Cady et al. [9], the benefit of surgery was observed whenever surgery was carried out before, after, or concomitant to chemotherapy. Thus, whether surgery should take place initially or after a first line of chemotherapy remains an open question. Moreover, in the case of initial medical treatment, the influence of the response on the decision to carry out surgery is unclear and will be discussed later.

**axillary dissection and role of adjuvant radiotherapy**

The impact of surgical dissection of regional lymph nodes is poorly documented in this setting, and so is the benefit of postoperative radiotherapy.
**axillary dissection**

Axillary dissection has often been regarded as a staging rather than a therapeutic procedure but a meta-analysis of nearly 3000 patients included in six randomized controlled trials reported an average survival benefit of 5% from axillary dissection in the non-metastatic setting [27]. Several studies also suggest that uncontrolled regional disease can act as a source of tumor reseeding [28, 29] and question the benefit of axillary dissection in the metastatic setting. Axillary dissection did not affect survival in series by Khan et al. [13], possibly owing to a link between axillary dissection and complete surgical excision of the primary tumor. Similarly, axillary dissection was not a prognostic factor in multivariate analysis in study by Ruiterkamp et al. [17]. In series by Rapiti et al. [16], the risk of death from breast cancer was reduced in patients who had complete surgery, whether or not they had axillary dissection, but the effect tended to be more obvious (albeit without reaching statistical significance) in the group of women who also had axillary dissection (HR 0.2, 95% CI 0.02–1.9 versus HR 0.7, 95% CI 0.4–1.2 for women with and without axillary dissection, respectively). In the MD Anderson study, axillary dissection was associated with improved survival in univariate analysis only [15]. These results suggest that axillary dissection provides an additional benefit when combined with complete tumor removal, and it also questions the benefit of regional node irradiation.

**adjuvant radiotherapy**

Radiation therapy was received by 5806 of the 16 023 women in series by Khan et al. [13], but no information was provided on whether it was directed to the breast, the chest wall, or osseous or symptomatic metastatic sites; Rapiti et al. [16] reported that women who had surgery (and especially breast-conserving surgery) were more likely to have local radiotherapy too (21% versus 5%, P < 0.0001). Radiation therapy, delivered to 266 patients (89%), was associated with significantly improved survival in the multi-adjusted model [HR for death without radiation therapy 1.6 (95% CI 1.0–2.5)], but the authors did not state whether irradiation was delivered in the adjuvant setting or to treat metastatic sites. Gnerlich et al. [11] found that 41% of patients received radiation therapy in the surgery group compared with 34% of patients in the no-surgery group and that irradiation was associated with a reduction in the risk of death in univariate analysis (HR 0.83, 95% CI 0.79–0.87), but it was unclear whether or not irradiation was a prognostic factor in multivariate analysis. In the recent series reported by Ruiterkamp et al. [17], locoregional radiotherapy (LRR) was not associated with better OS in multivariate analysis. In the study by Le Scodan et al. [14], the median survival times and 3-year OS rates were 26 months and 46% (95% CI 29.60% to 63.60%) for the 30 patients treated with surgery alone, 31 months and 41.5% (95% CI 35.50% to 47.90%) for the 249 patients treated with exclusive LRR, and 39 months and 52.6% (95% CI 37.60% to 67.20%) for the 41 patients treated with surgery followed by LRR, respectively (P = 0.07). However, comparisons between a multimodality treatment targeting the primary tumor and regional lymphatics and surgery alone must be undertaken with care, owing to the potential selection bias. Thus, the possible benefit of postoperative radiotherapy is unclear. Several randomized trials have supported the use of hypofractionated whole breast radiotherapy and have shown good results in the adjuvant setting [30, 31]. If LRR following surgery of the primary tumor is considered to be of significant interest in this metastatic setting, accelerated radiotherapy may represent an active alternative to normofractionated schedules.

**exclusive LRR for the primary tumor**

Exclusive LRR is an alternative form of locoregional treatment (LRT) in this setting and has the advantage of breast conservation. Le Scodan et al. [14] retrospectively studied the impact of LRT, consisting mainly of exclusive LRR, on the survival of breast cancer patients with synchronous metastases. Among 581 patients, 320 received LRT and 261 received no LRT. LRT consisted of exclusive LRR in 249 cases (78%), surgery of the primary tumor with adjuvant LRR in 41 cases (13%), and surgery alone in 30 cases (9%). With a median follow-up of 39 months, the 3-year OS rates were 43.4% and 26.7%, respectively, among patients who received or not LRT (P = 0.00002). LRT was an independent factor of favorable outcome in multivariate analysis [HR 0.70 (95% CI 0.58–0.85), P = 0.00002], and the adjusted HR for late death (21 year) was 0.76 (95% CI 0.61–0.96, P = 0.02). Although few patients were treated with surgery alone, the median survival times and 3-year OS rates were 26 months and 46% (95% CI 29.60% to 63.60%) among the 30 patients treated with surgery alone and 31 months and 41.5% (95% CI, 35.50% to 47.90%) among the 249 patients treated with exclusive LRR, respectively, suggesting that exclusive LRR might be an effective treatment of the primary tumor. Other series have also supported the use of exclusive LRR in the management of breast cancer and have shown good locoregional control [14, 32–34].

**subgroups of patients qualifying for local treatment**

It is not clear which patients—those with estrogen-responsive tumors, bone metastases only [6, 16], a low disease burden at diagnosis, or those who respond to medical treatment—are most likely to benefit from treatment of the primary tumor. In the study by Rapiti et al. [16], the effect of surgery on breast cancer mortality did not differ between patients with bone metastasis only and patients with metastases in other sites. After stratifying the study population according to the sites of metastasis, however, the survival benefit of complete surgery was particularly evident among women who had only bone metastases at diagnosis (adjusted HR 0.2, 95% CI 0.1–0.4, P < 0.001), whereas it was not statistically significant in women with metastases at other sites (adjusted HR 0.7, 95% CI 0.4–1.2, P = 0.310). A similar beneficial effect of surgery in the subgroup of patients with bone metastases alone was found by Babiera et al. [6]. In his recently published study, Shien et al. [18] found that surgery was beneficial only among patients <50 years old who had no visceral metastases. Conversely, Blanchard et al. [8] found no benefit of surgery in the subgroup of patients with bone metastasis alone. Le Scodan et al. [14] reported that patients with extensive metastatic disease at diagnosis also benefited from LRT, as did patients with unfavorable features at...
diagnosis (e.g. visceral or multiple metastatic sites or chemotherapy as the sole systemic treatment). In their experience, LRT was not associated with better survival among patients with bone metastases alone. Several reports show that patients with bone-only metastatic disease are more likely to have hormone-responsive tumors at diagnosis, as well as a favorable response to systemic therapy and longer survival, than those with visceral metastases [10, 35, 36]. These two latter studies suggest that this relatively indolent clinical course was not affected by the treatment of the primary tumor. Note that these contradictory findings have to be very carefully interpreted because they are a product of subgroup analyses in retrospective studies. Regarding response to a first-line chemotherapy, there is no firm clinical evidence showing whether or not only patients who respond to medical treatment should be operated on or, conversely, that surgery is beneficial only when systemic treatment fails to control local disease. If the benefit of surgery is mediated by a better local control as suggested by Hazard et al. [12], it is not clear that patients with a good metastatic and primary tumor response under medical treatment are most likely to benefit from treatment of the primary tumor. In their studies, chest wall control was associated with improved OS regardless of whether surgical resection of the tumor was carried out (HR 0.415, P < 0.0002). A recent analysis of the impact of LRT according to the response to a first-line systemic treatment in our institution reported that patients with uncontrolled disease under medical treatment were most likely to benefit from LRT, raising the question of a continual shedding of tumor stem cells from the primary tumor. In their studies, chest wall control was associated with improved OS regardless of whether surgical resection of the tumor was carried out (HR 0.415, P < 0.0002). A recent analysis of the impact of LRT according to the response to a first-line systemic treatment in our institution reported that patients with uncontrolled disease under medical treatment were most likely to benefit from LRT, raising the question of a continual shedding of tumor stem cells from the primary tumor under medical treatment (R. Le Scodan, unpublished data).

**Pathophysiological hypotheses**

Resection of the primary tumor has been linked to better survival in other metastatic malignancies. Two phase III randomized controlled trials comparing medical treatment alone versus medical treatment plus nephrectomy for metastatic renal carcinoma showed a significant OS benefit among patients whose primary tumor was removed [37, 38]. Excision of the primary tumor is also known to be beneficial in stomach cancer [39], melanoma [40] colon cancer [41, 42], and ovarian cancer [43]. But the effect of tumor-specific biological factors, responsiveness to systemic therapies, and growth kinetics differ widely across the different types of metastatic cancer and results in one setting may not be applicable to another. Several mechanisms potentially support the use of local treatment in this setting.

First, removal or irradiation of the primary tumor may reduce the total tumor burden, increasing the effectiveness of chemotherapy, and limit an additional reseeding of tumor if one considers that the primary tumor is the only continuous source of metastases and that systemic spread from metastatic lesions is less likely [21]. Total tumor burden, i.e. the total number of tumor cells present in the organism, plays a central role in survival since the number of metastatic sites and the number of metastasis at a given site is strongly correlated with survival [23–25, 44]. There is also a correlation between the level of circulating tumor cells and the prognosis of metastatic breast cancer [45, 46]. Furthermore, it has been reported that chromosomal abnormalities in circulating tumor cells isolated from patients with metastatic epithelial cancers match those in the primary tumor, indicating that circulating cells are derived from the primary tumor [21]. Second, removal of the primary tumor may make metastases more chemosensitive, by inducing an angiogenic surge (thereby increasing tumor vascularization and drug penetration), by removing necrotic tissue and nonvascularized tumor cells (which are classically less sensitive to chemotherapy and radiation therapy), and by eliminating breast cancer stem cells from the primary tumor, limiting the emergence of chemoresistant cell lines [22–25, 47]. Third, removal of the primary tumor helps to restore immunity and to improve nutritional status. Indeed, some tumors, including breast cancer, can induce an immunosuppressive state and influence metastatic disease progression possibly owing to cytokine secretion by tumor cells [47]. In a murine model, Danna et al. [48] demonstrated that a primary tumor may influence metastatic disease progression through the release of immunosuppressive factors and that removal of the primary tumor may result in restoration of an immune response, even in the presence of metastatic disease. Fourth, surgery or exclusive LRR effectively prevents uncontrolled chest wall and in-breast disease. Prospective randomized trials of postmastectomy radiotherapy have shown that local therapy in the form of chest wall and lymph node irradiation prolongs survival in node-positive women receiving tamoxifen or chemotherapy [28, 49, 50]. This suggests that local therapy impacts survival in breast cancer that is likely to be systemic and that uncontrolled local disease may act as a source of tumor reseeding, diminishing the effectiveness of systemic therapy. This is supported by the finding that the increased local recurrence rate after lumpectomy without radiotherapy translates into poorer 15-year survival [51]. Moreover, a randomized controlled trial showed that local recurrence is predictive of distant dissemination [52]. In the study by Hazard et al. [12], surgery strongly protected against uncontrolled chest wall disease, suggesting that the impact of local therapy on survival may be mediated by better local control. Thus, both mechanisms—a reduction in tumor burden by removing the primary tumor that serves as the source of tumor cell seeding and better local control—may be involved. Indeed, these mechanisms are linked because uncontrolled local disease may serve as a source of systemic tumor reseeding. Opposite to the proposed biological mechanisms in favor of treatment of the primary tumor, other theories have been proposed regarding the effect of surgical removal of the primary tumor on the growth kinetics of micrometastases. Several authors suggested that surgical resection of the primary breast tumor may accelerate relapse due either to removal of inhibitors of angiogenesis and/or the release of growth and immunosuppressive factors in response to surgical wounding [53–56]. However, the literature review of these retrospective studies does not support this point of view.

**Consistent selection bias?**

The results of these observational studies raise two possibilities: either local treatment of the primary provides...
a substantial survival benefit in women with metastatic breast cancer at diagnosis or there is a strong and consistent selection bias driving the use of this treatment in women who have already factors of better outcome [37]. All retrospective studies are likely to suffer from selection biases. Current clinical decision making seems to reliably identify women who will do better, as most of the studies discussed in this review showed an association between surgery or exclusive radiotherapy and known factors of good prognosis. Indeed, women in the surgical groups were younger, had smaller tumors and fewer metastatic sites, and were more likely to have bone/soft tissue metastases rather than visceral disease. This bias could be attenuated by multivariate analysis including the other prognostic factors as covariables. Yet, even this approach would not take into account unrecorded prognostic factors or physicians' subjective prognostic assessment, based for example on performance status or the response to a first line of chemotherapy. In their studies, Cady et al. [9] suggest that case matching either reduced or eliminated the survival advantage apparently achieved by primary site surgery compared with patients without surgery. Similarly, Leung et al. [19] reported that the survival benefit associated with surgery was not achieved when their data were adjusted for chemotherapy. In studies by Le Scodan et al. [14], performance status was not prospectively recorded but the survival benefit associated with LRR was also observed after excluding patients who survived for <6 months. Similarly, LRR was beneficial in patients who received chemotherapy (with or without endocrine treatment), whose performance status was probably compatible with LRR. Moreover, the lower risk of late death (≥1 year after diagnosis) after LRR strongly suggests that LRR improves OS and that this effect is not only due to a treatment-assignment bias. Finally, it is also possible that surgery is a surrogate marker of more aggressive therapy overall, including more aggressive systemic therapy, translating into better survival. This possibility is supported by the fact that, in several studies, patients were more likely to receive radiotherapy [7, 12, 16, 17] or chemotherapy [6, 14, 17] when they had treatment of the primary tumor. Nonetheless, in the studies reported by Le Scodan et al. [14], the use of taxans and new aromatase inhibitors was prospectively recorded and did not differ according to the treatment group.

phase III studies

This review of all published observational studies suggests that unrecognized selection biases may account for the observed survival benefit provided by treatment of the primary tumor breast cancer patients with synchronous metastasis. Only a large prospective randomized trial could settle this issue. Given the relatively minor adverse effects associated with the treatment of the primary tumor, along with the relatively consistent survival benefit observed in the different retrospective studies of local surgery or radiation—and the estimated 12 000 breast cancer patients with synchronous metastases diagnosed each year in the United States—a prospective randomized trial is more than justified, although issues of design, feasibility, and priority of such a trial are more complex. Such a study is under discussion among USA and European cooperative groups and two randomized trials, one sponsored by the Turkish Federation of the National Societies for Breast Diseases and the other by Tata Memorial Hospital, India, are currently recruiting. The Turkish trial is intended to enroll 271 patients in a comparison of upfront surgery (mastectomy or breast-conserving surgery with levels I–II axillary clearance in clinically or sentinel lymph node-positive patients) with adjuvant therapies and systemic therapy only [38, 39]. In the systemic chemotherapy group, patients will only receive surgery to control local complications. The primary end point is mortality and the secondary end point is the assessment of quality of life within the two groups. The estimated completion date of this study is October 2012. The Tata Memorial Hospital trial should enroll 350 patients in a comparison of locoregional therapy (i.e. surgery and adjuvant radiotherapy if indicated) and no locoregional therapy, given after six cycles of anthracycline-based chemotherapy [40]. Primary end points are time to progression and OS and secondary are correlative science points such as change in angiogenics factors. The estimated study completion date is February 2011. In a preliminary report of this trial (NCT00193778) (125 patients: 53 patients randomized to surgery and 72 patients randomized to observation; median follow-up: 18 months), surgery of the primary tumor was not associated with better PFS or OS [61]. However, if positive, the results of these studies will be of interest not only to women with initial stage IV disease but also those with synchronous local and distant recurrences of previously treated breast cancer.

In conclusion, several studies suggest that surgical excision or exclusive irradiation of the primary tumor is associated with better survival in breast cancer patients with synchronous metastases. In this setting, the impact of surgical dissection of regional lymph nodes and postoperative radiotherapy is poorly documented, and the patient subgroups most likely to benefit from treatment of the primary tumor remain to be identified. Two prospective studies are currently examining the benefits of locoregional therapy compared with systemic therapy alone and such studies are under discussion among USA and European cooperative groups.

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disclosure

None of the authors declare conflicts of interest.

references


