# Surgical Treatment of the Primary Tumor in Patients with Metastatic Breast Cancer (Stage IV Disease)

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The widespread uptake of breast cancer screening, together with heightened population awareness, means that most breast cancers in the Western world are detected at an early stage. Recent tumor registry studies from the United States and Europe have shown that metastatic breast cancer (BC) accounts for 4–5% of all cases [1–3]. However, in developing nations, the proportion of patients with metastatic BC at diagnosis is greater, ranging from 10% in Malaysia [4] to 24% in Nepal [5] and 44% in Nigerian women [6]. In early breast cancer, high-quality evidence from randomized controlled trials and meta-analyses is available to support the majority of treatments we perform. In comparison, there is a lack of level I evidence and accepted standard-of-care therapies available for patients with metastatic BC.

Metastatic BC is considered to be a fatal disease, regardless of whether distant metastases are discovered at initial presentation (de novo stage IV) or following apparently successful therapy of localized disease and an intervening disease-free interval (metachronous stage IV). As stage IV disease is considered incurable, the goals of treatment are only the prolongation of life and the palliation or prevention of symptoms. In both the situations de novo stage IV and metachronous stage IV, the primary and most important and effective treatment modality is systemic therapy. Recent rapid advances in medical therapy, with the discovery of new therapeutic targets and drugs directed at these targets, have led to the concept of stage IV BC as a chronic disease. With the ever-increasing medical therapy armamentarium, and perhaps with better palliative care, survival of patients with metastatic BC has improved steadily over the past two decades [7, 8]. Moreover, improvements in imaging technology, especially combined positron emission tomography with computed tomography (PET-CT), now enable the detection of minute foci of metastases that previously would have remained undetected. Today's patients with metastatic BC are frequently asymptomatic and systemically well controlled. They often have small primary breast cancers rather than locally advanced cancers. Consequently, the question of management of the primary tumor in women with de novo stage IV BC has attracted significant interest, particularly as loss of control at the primary site can have a profound effect on the quality of life. Retrospective data published over the past decade suggest that primary tumor resection and possibly radiotherapy (RT) may improve survival when used in conjunction with effective systemic therapy. These data have led to some new enthusiasm for the resection of asymptomatic primary tumors, in contrast to the classical, dogmatic approach of reserving resection only for palliation of symptomatic primary tumors.

## 29.1 Arguments Against Primary Surgery in Stage IV Breast Cancer

There are several, historical arguments against performing primary surgery in metastatic BC. Traditional teaching tells us that surgery may not provide any survival advantage, but may be associated with postoperative complications; by not performing surgery, we can avoid potential complications. How surgical procedures can carry inherent risk is well known. There is the possibility of hematoma, infection, and poor healing of the surgical site, particularly if combined with axillary surgery or postmastectomy reconstruction. There is a 16% risk of lymphedema for patients undergoing axillary dissection [9], which is roughly doubled by the addition of radiation following axillary dissection [10]. In the metastatic setting, this may only add to a patient's distress in the last few months or years of life. Moreover, complications from surgery may delay systemic treatment, which is of paramount importance in patients with metastatic disease. This delay in systemic therapy may adversely affect the control of distant disease in some patients. If mastectomy is performed, questions about breast reconstruction arise, which increases the risk of surgical complications and may further delay adjuvant

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U. Veronesi et al. (eds.), *Breast Cancer*, DOI 10.1007/978-3-319-48848-6_29

therapy [11]; other data suggest that delays in systemic therapy can negatively affect survival. Lohrisch et al. [12] found a decrease in survival when chemotherapy was started more than 12 weeks after surgery in patients with early-stage BC, and this is likely to be even more true of metastatic BC. Finally, women with metastatic disease who are offered primary site surgery are inquiring about (and anecdotally receiving) contralateral prophylactic mastectomy, a clearly inappropriate intervention for this patient population. However, the fact that patients consider it points to the need for definitive, unbiased information to guide treatment plans for a patient population that is highly motivated to pursue any and all options with a possibility of benefit. Apart from the risks and quality-of-life hazards of locoregional therapy for BC, it is also important to remember that this population of patients is often stretched to the limit in terms of out-of-pocket expenses for imaging and therapy, even when insurance plans are generous. Locoregional therapy adds considerably to this burden, which must be considered when arriving at a management plan for this vulnerable population of patients.

Another argument against primary surgery in stage IV BC is that the intact primary breast cancer is easily accessible and provides measurable disease that can be used to gauge the response to systemic treatment; removing this makes the clinical assessment of response to therapy more difficult. Patients with stage IV BC may represent an anesthetic challenge because of debilitation, as well as a surgical challenge because of locally advanced cancer with bulky lymph node involvement; the likelihood of adverse outcomes may be increased. Additionally, in a rodent cancer model, the primary tumor has been shown to inhibit its remote metastases. Following excision of the tumor, neovascularization and growth of the metastases occurred; it is feared that perhaps this could also happen in patients after primary surgery in metastatic BC [13].

## 29.2 Arguments in Favor of Primary Surgery in Stage IV Breast Cancer

The validity of these arguments against primary surgery in metastatic BC has been apparently challenged. First of all, there have been several studies indicating improvement in survival of women with metastatic BC over the past three decades [8, 14, 15]. A single-institution review of women diagnosed with metastatic disease treated from 1974 to 1979 showed a median survival of 15 months compared with those treated from 1995 to 2000 who had a median survival of 58 months [3]. Similarly, Andre et al. [8] reported temporal trends in improvement of survival for patients with metastatic disease based on treatment period, comparing the intervals 1994–2000 and 1987–1993. Although some of these improvements are undoubted because of better systemic therapy, lead time bias related to more sensitive imaging and therefore earlier diagnosis of metastatic disease in later periods are also likely contributing factors, given the retrospective nature of these studies. More recently, Dawood et al. [15] examined the outcomes between patients with de novo stage IV breast cancer and those who experienced metachronous distant relapse. From a large cohort of patients examined from a single institution, they found the median survival for patients who presented with de novo stage IV breast cancer was 12 months longer than in women with relapsed breast cancer. This difference was statistically significant in both univariate and multivariate analyses. The authors also noted that disease-free interval was also associated with outcomes. Specifically, those patients whose disease relapsed with shorter disease-free interval had worse outcomes when compared with those patients who presented with de novo stage IV disease. The reasons for this difference in outcomes maybe partially related to the fact that women with de novo stage IV disease are treatment naïve and therefore may respond better to systemic therapy, whereas those with metastatic relapse have demonstrated therapeutic resistance of their tumors in the adjuvant setting. There may also be biological differences dictated by the presence of the primary tumor in de novo stage IV disease, as suggested by Retzky et al. [16], vs. reactivation of dormant, resistant clones in metachronous metastases; however, present knowledge regarding interactions between the primary tumor and metastatic sites in humans, and any influence these may have on the course of disease, is limited.

The second argument in favor of primary surgery in metastatic BC comes from evidences accumulated over the past 15 years in non-breast cancer treatment, suggesting that a reduction in tumor burden at the primary site may add to the efficacy of systemic therapy and aid survival. These include a randomized trial of patients with de novo stage IV renal cell carcinoma, which demonstrated a modest but significant survival advantage for the nephrectomy group [17, 18]. An improved survival with resection of primary disease with or without resection of distant disease has also been observed in advanced stages of ovarian cancer [19], in which tumor debulking in the abdominal cavity has become a standard component of overall treatment strategy, despite the lack of a randomized trial testing this approach. Thus, based on retrospective data, these cancers are frequently managed with tumor debulking before chemotherapy [20, 21], drawing on the theory that a smaller tumor burden increases the efficacy of chemotherapy [22]. Again, in colorectal and gastric cancer and in melanoma and sarcoma, resection of the primary tumor, tumor debulking, tumor burden reduction, metastasectomy, re-metastasectomy, multiple metastasectomies, and combined surgery for primary and secondary tumor are widely accepted and routinely performed in clinical practice, being accepted their role in improving survival and quality of life [23–27].

Another theoretical benefit from resection of the primary tumor in patients with overt metastases can be supported along several lines of investigation about the different possible models of progression and metastatic dissemination in BC, ranging from the potential role of BC as a source of tumor stem cells with enhanced metastatic potential [28, 29] to the possibility that tumor-induced immunosuppression is facilitated by the intact primary tumor [30, 31]. It is well known that the progression and metastatic dissemination in breast cancer are a highly selective process that depends on specialized properties of tumor cells (genetically predetermined) and multiple interactions of metastatic cells (seed) with homeostatic mechanism (soil) that tumor cells can exploit. The ongoing seeding from both the primary tumor and distant sites could be an important mechanism of continued tumor growth and metastases. Under this self-seeding theory, tumor cells have the property to escape from the primary tumor and seed distant site but also may metastasize back to the site of the primary tumor [28]. Decreasing the tumor burden could also increase the efficacy of medical treatment by reducing the chances of a resistant clone appearing, and a certain degree of immunomodulation may be achieved by eliminating the immunosuppression associated with the presence of the primary tumor [31]. The newer concepts of the metastatic progression in BC seem to support the concept that the resection of the primary tumor in this scenario would have clinical relevance. In fact, the removal of the primary tumor could theoretically reduce either self-seeding, tumor cell dissemination, or the population of native cancer stem cells, finally making more effective the systemic therapy. Conversely, there has been a concern, based on laboratory data, that primary tumor resection may accelerate the growth of metastatic lesions, but this has not been demonstrated in humans. Although these laboratory data suggest a biological basis for improved survival with resection of the primary tumor in the setting of metastatic disease, these specific models have not been validated in humans. In conclusion, it would be naïve to believe that surgery will benefit all women with metastatic breast cancer [32], but in theory no clinical or biological reason exists to exclude a priori the surgery in all patients with stage IV breast cancer.

Finally, there are important quality-of-life (QOL) hazards that relate to the primary tumor, regardless of whether primary site local treatment is used. If the intact primary tumor progresses, the QOL effect of uncontrolled chest wall disease can be disastrous for a minority of women [33, 34]. Actually, for most women with intact primary tumors and distant disease that is responsive to systemic therapy, the primary tumor tends to remain controlled and asymptomatic with medical therapy [35]. So, if all women were subjected to primary site local treatment, most of them would experience the QOL risks of surgery and potentially RT, including those who would not have developed uncontrolled local disease during the remainder of their lives. Therefore, the analysis of the QOL effect has to be very thoughtful, weighing the possibility of uncontrolled local disease in a minority of women against the potentially unnecessary costs of primary site local treatment in all women.

## 29.3 Retrospective Studies and Meta-analysis on Primary Tumor Resection

Based on these considerations and mainly following the publication of a randomized trial demonstrating the value of primary tumor resection in stage IV renal cell carcinoma, a number of retrospective studies were performed to examine the effect of surgical resection of the primary tumor on survival in the setting of metastatic BC [1, 2, 4, 33, 36–46]. These studies have come from single institutions and large data bases from the United States, Europe, and Asia. The type of local therapy has largely been a surgery alone, although a few authors have been able to evaluate surgery plus RT [47–49]. The survival outcomes in these retrospective analyses have been the subject of several reviews and meta-analyses [50–54].

A large meta-analysis by Petrelli and Barni published in 2012 [51] included 15 retrospective case series and found that surgery of the primary tumor was independently associated with longer survival, with a hazard ratio (HR) of 0.69 ($P < 0.00001$) (Fig. 29.1). On overall, surgery reduced the risk of death by 30%, especially when it was associated with systemic therapy and RT in a multimodality strategy. The survival benefit was independent of age, tumor burden, type of surgery, margin status, site of metastases, hormone receptor status, and HER2 status; the use of systemic therapy and RT was significantly associated with survival.

A similar literature has developed on the use of primary RT for the primary site, showing a similar magnitude of survival benefit. The RT studies have come mainly from single institutions in France and Canada. The first and largest was reported by Le Scodan et al. [47]. These investigators identified 581 patients with de novo stage IV BC treated between 1984 and 2004, 320 of whom received RT, with 41 women receiving both surgery and RT and 30 receiving only surgery. Nodal fields were included for most patients, and most of those receiving RT were given a boost dose to the tumor site. The overall survival rate was 43% in the group receiving locoregional therapy vs. 27% in those who did not, for an adjusted HR = 0.7 (95% CI: 0.58–0.85). A second French study of 236 patients described similar differences in outcomes with the use of primary RT to the primary site, but adjusted estimates of overall survival showed no significant advantage for the primary site local treatment group [48]. The value of postoperative RT has been difficult to assess in these retrospective studies, as large databases such as the

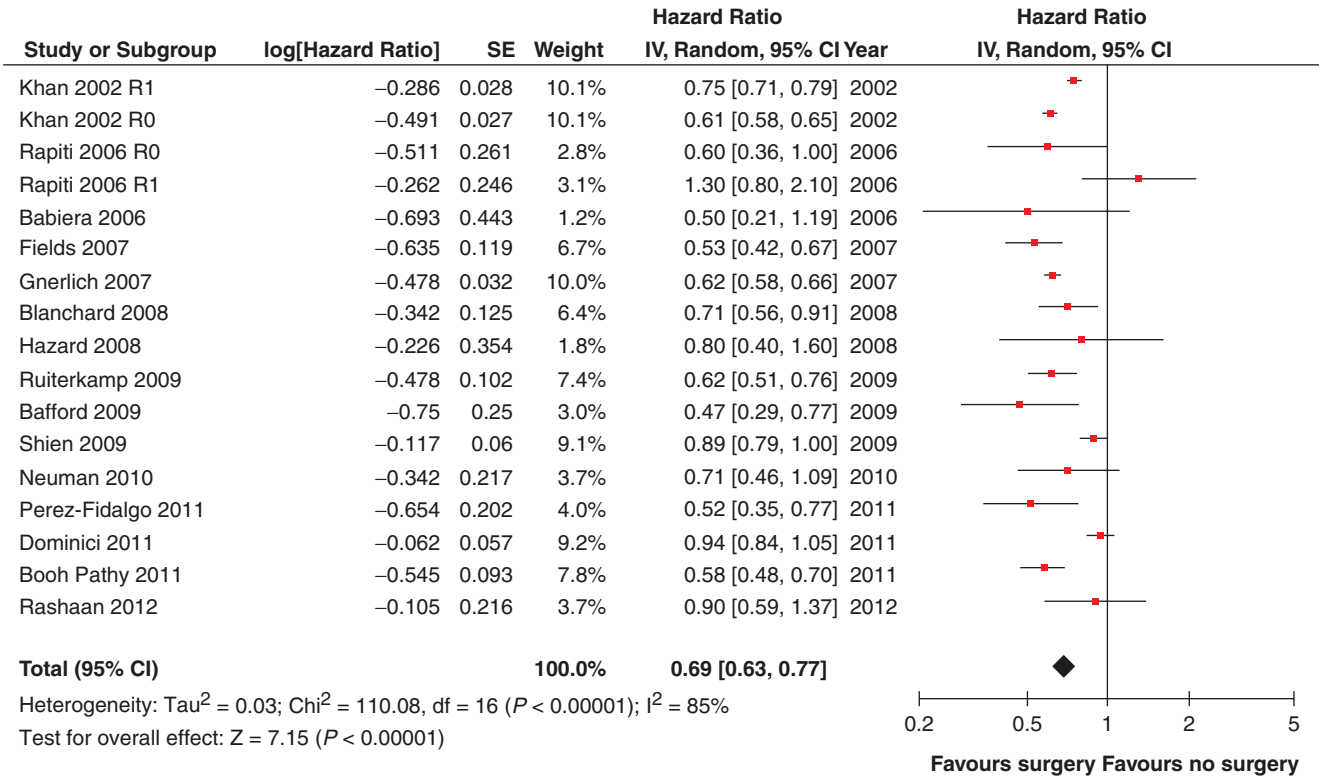


**Fig. 29.1** Meta-analysis on 15 retrospective case series, from Petrelli et al. [51]

National Cancer Database (NCDB) and the Surveillance, Epidemiology, and End Results (SEER) did not distinguish between RT to the primary and metastatic sites. The data that are available do not allow clear conclusions and do not show a significant advantage to the combination of surgery and RT to the primary site.

A larger systematic review and meta-analysis were published in 2016 by Headon et al. [55]. The analysis included 16 studies and compared 15,368 stage IV BC patients submitted to surgery of the intact primary tumor to 14,313 not operated patients. In this meta-analysis, a pooled hazard ratio of 0.63 (95% confidence interval, 0.58–0.7; $P < 0.0001$) was revealed, equating to a 37% reduction in risk of mortality in patients that underwent surgical resection of the primary tumor (Fig. 29.2). The conclusions, consistent to what previously reported, are that surgery of the primary tumor in stage IV BC apparently offers a survival benefit in metastatic patients.

## 29.4 SEER (Surveillance, Epidemiology, and End Results) Data on Primary Tumor Resection

In 2016, four different analyses on primary site local therapy in stage IV BC, based on SEER data, were published. Eng et al. [56] retrieved the records of 25,323 women diagnosed with primary stage IV BC in the SEER 18 registries database from 1990 to 2012. For each case, information on age at diagnosis, tumor size, nodal status, estrogen receptor status, progesterone receptor status, ethnicity, cause of death, and date of death were extracted. The Cox proportional hazard model was used to estimate the unadjusted and adjusted hazard ratio (HR) of death due to stage IV BC, according to age group. Among 25,323 women with stage IV BC, 2542 (10.0%) were diagnosed at age 40 or below, 5562 (22.0%) were diagnosed between ages 41 and 50, and 17,219 (68.0%) were diagnosed between ages 51 and 70. After a mean follow-up of 2.2 years, 16,387 (64.7%) women died of breast cancer (median survival 2.3 years). The 10-year actuarial breast cancer-specific survival rate was 15.7% for women ages 40 and below, 14.9% for women ages 41–50, and 11.7% for women ages 51 to 70 ($p < 0.0001$). In an adjusted analysis, the risk of death from BC at 10 years was significantly lower for women ages 40 and below (HR 0.78; 95% CI, 0.74–0.82; $p < 0.0001$) and for women ages 41–50 (HR 0.82; 95% CI, 0.79–0.85; $p < 0.0001$), compared to women ages 51–70. The authors concluded that approximately 13% of women with primary stage IV breast cancer survive 10 years after diagnosis. Women diagnosed with stage IV BC before age 50 have better survival at 10 years compared to older women.

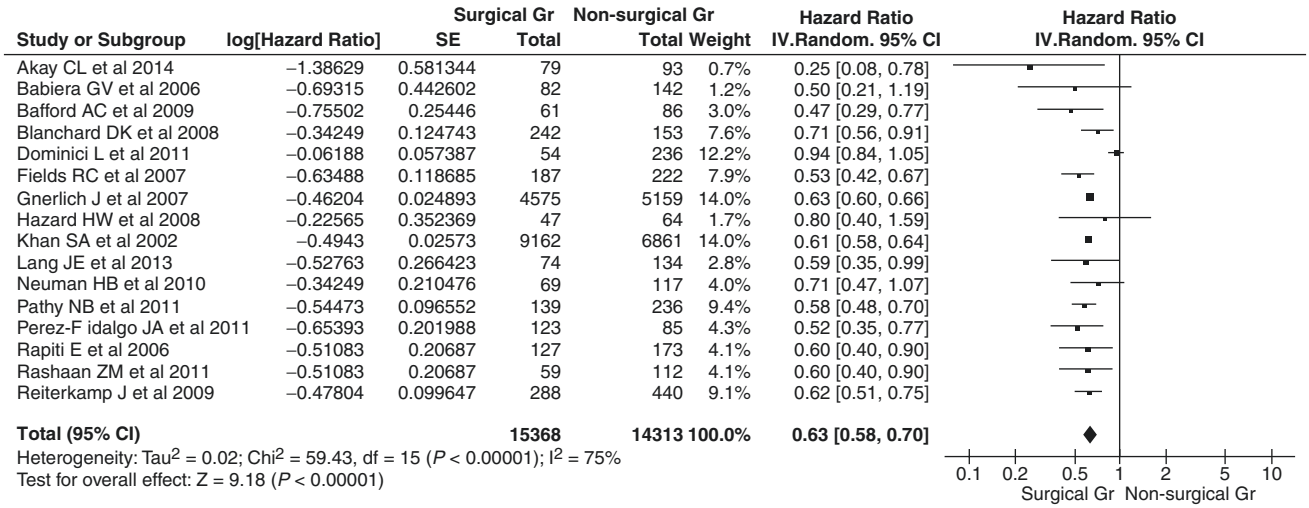


**Fig. 29.2** Meta-analysis on 16 retrospective case series, from Headon et al. [55]

Similarly, Warschkow et al. [57] assessed the effect of primary tumor surgery on overall and cancer-specific mortality using risk-adjusted Cox proportional hazard regression modeling and stratified propensity score matching in metastatic BC patients identified in the SEER registry between 1998 and 2009. Overall, 16,247 women with metastatic BC were included. Of those, 7600 women underwent primary tumor surgery although 8647 did not have any surgery at all. Primary tumor surgery decreased from 62.0% in 1998 to 39.1% in 2009 ($P < 0.001$). Primary tumor surgery was associated with decreased overall mortality (hazard ratio (HR) = 0.53, 95% CI 0.50–0.55, $P < 0.001$) and cancer-specific mortality (HR = 0.51, 95% CI 0.48–0.54, $P < 0.001$) in the propensity score-matched model. The benefit of primary tumor surgery increased from 1998 to 2009 for overall mortality (1998, HR = 0.72, 95% CI 0.59–0.89; 2009, HR = 0.42, 95% CI 0.35–0.50) and cancer-specific mortality (1998, HR = 0.72, 95% CI 0.58–0.89; 2009, HR = 0.40, 95% CI 0.33–0.48). In conclusion, the study provided evidence of a favorable impact of primary tumor surgery on mortality in metastatic BC patients. Most importantly, the benefit of primary tumor surgery increased over time from 1998 to 2009.

In order to evaluate the patterns of receipt of initial breast surgery for female patients with stage IV BC in the United States, with particular attention to women who survived at least 10 years, Thomas et al. [58] analyzed a retrospective cohort of patients using data from the SEER program. Female patients diagnosed as having stage IV BC between 1988 and 2011 and who did not receive RT as part of the first course of treatment were included ($n$ = 21,372). Kaplan-Meier estimates of median survival and descriptive statistics were used to compare patient and tumor characteristics by receipt of breast surgery at diagnosis. A Royston-Parmar survival model and logistic regression analysis assessed demographic and clinical factors associated with survival and prolonged survival (of at least 10 years). Mail outcome of the analysis was differences in survival, particularly survival of at least 10 years, by receipt of initial surgery to the primary tumor. Among the 21,372 patients, the median survival increased from 20 months (1988–1991) to 26 months (2007–2011). During this time, the rate of surgery declined (odds ratio [OR], 0.16; 95% CI, 0.12–0.21). Even so, receipt of surgery was associated with improved survival in multivariate analysis, which controlled for patient and clinical characteristics, along with time period (hazard ratio, 0.60; 95% CI, 0.57–0.63). For women diagnosed as having cancer before 2002 ($n$ = 7504), survival of at least 10 years was seen in 9.6% ($n$ = 353) and 2.9% ($n$ = 107) of those who did and did not receive surgery, respectively (OR, 3.61; 95% CI, 2.89–4.50). In multivariate analysis, survival of at least 10 years was associated with receipt of surgery (odds ratio, 2.80; 95% CI, 2.08–3.77), hormone receptor-positive disease (OR, 1.76; 95% CI, 1.25–2.48), older age (OR, 0.41; 95% CI, 0.32–0.54), larger tumor size (OR, 0.37; 95% CI, 0.27–0.51), marital status of being separated at the time of diagnosis (OR, 0.67; 95% CI, 0.51–0.88), and more recent year of diagnosis (OR, 1.43; 95% CI, 1.02–1.99). In conclusion, survival in stage IV BC was improved and was increasingly of prolonged duration, particularly for some women undergoing initial breast surgery.

Finally, Tan et al. [59] used the SEER database to explore the impact of surgery on the survival of patients with stage IV BC and included 10,441 eligible stage IV BC patients from 2004 to 2008. They were divided into four groups as follows: R0 group (patients who underwent primary site and distant metastatic site resection), primary site resection group, metastases resection group, and no resection group. The four groups achieved a median survival time of 51, 43, 31, and 21 months, respectively, $P < 0.001$. The Cox proportional hazard model showed that the R0 group, primary

resection group, and metastases resection group had a good survival benefit, with hazard ratios of 0.558 (95% CI, 0.471–0.661), 0.566 (95% CI, 0.557–0.625), and 0.782 (95% CI, 0.693–0.883), respectively. In the hormone receptor (HR)-positive population, the R0 group (median survival time = 66 m, 5-year OS = 54.1%) gained an additional survival benefit compared with the primary resection group (median survival time = 52 m; 5-year OS = 44.9%; $P < 0.001$). The metastases resection group (median survival time = 38 m; 5-year OS = 31.7%) survived longer than the no resection group (median survival time = 28 m; 5-year OS = 22.0%; $P < 0.001$). In the HR-negative population, the R0 group and primary resection group had a similar survival ($P = 0.691$), and the metastases resection group had a similar outcome to that of the no resection group ($P = 0.526$) (Fig. 29.3). In conclusion, patients who underwent surgery for stage IV BC showed better overall survival than the no resection group, especially when cytoreductive surgery is performed in HR+ stage IV BC patients.

## 29.5 Potential Biases of Retrospective Studies and Meta-analysis

Many potential biases could have affect and spoiled the enthusiastic results of all the retrospective studies, including meta-analysis. First of all, the timing of surgery on the primary tumor in relation to the diagnosis of metastases, and the use of systemic therapy, has not always been specified in the published retrospective literature, although several authors have attempted to address it [41, 46, 60, 61], with varying conclusions. This is a source of bias because women who are

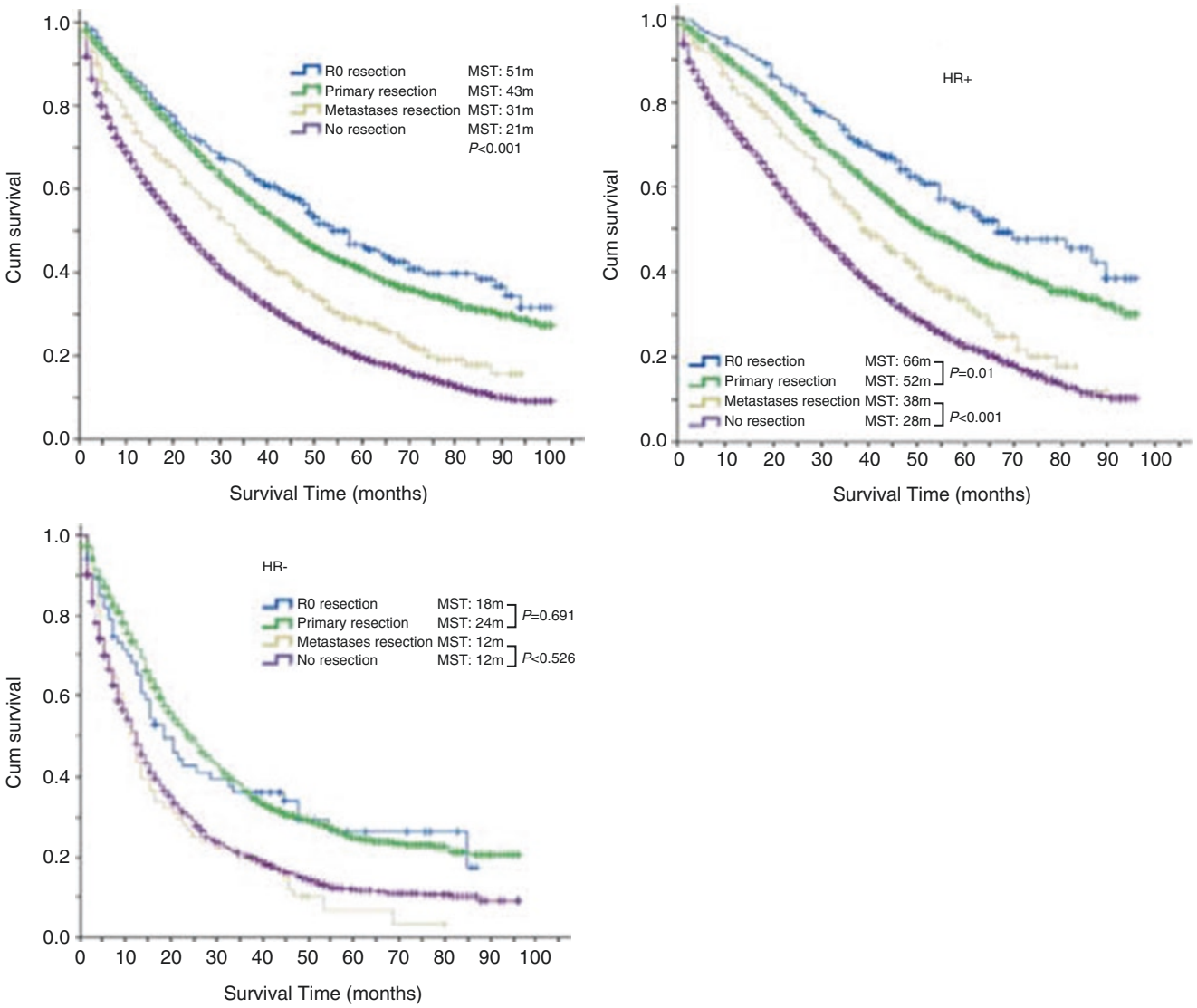


**Fig. 29.3** (**a**) Overall survival curves in four groups, (**b**) Kaplan-Meier survival curves of the four groups in the HR+ population (**c**) and in HR-population, from Tan et al. [59]

diagnosed with metastases only after they have undergone surgery for the primary tumor most likely have asymptomatic (and therefore lower-volume) metastases. In contrast, those who present with symptomatic metastases, discovered before surgery, are likely to have a higher burden of distant disease. In reviewing the available literature, we see that there is a substantial fraction of women with T1–T2 tumors, raising the possibility that these women were operated on with the assumption of nonmetastatic disease, were diagnosed with metastases postoperatively, and were then classified as having stage IV disease during the abstraction process by local tumor registrars. Other sources of bias exist in the retrospective data although all studies have attempted to control for these using multivariate regression. In fact, single-institution studies are limited by institutional biases and small numbers of well-selected patients, often treated during a long period of time and with different, and differently effective, medical therapies. In addition, some studies were multi-adjusted with exclusion of patients with short survival, delayed metastatic disease, and more advanced tumors.

Although the meta-analysis seems to definitively confirm the positive impact of surgery of the primary tumor on survival in stage IV patients, it well known that the assumption that a meta-analysis uniformly represents the final and accurate viewpoint of an area of research is not warranted. A meta-analysis combines similar trials in order to obtain a larger number of patients to improve the evaluation of whether statistically reliable differences exist between comparison groups. Meta-analyses are by no means perfect. The conclusions made by the authors of a meta-analysis are subject to the same potential for bias as the smallest of clinical studies included in it. On some occasions, a large clinical trial has subsequently been performed evaluating the same clinical question with an outcome quite different from the initial meta-analysis, and discrepancies between meta-analyses and subsequent large randomized clinical trials are documented in literature [62]. In all the retrospective studies on stage IV BC included in the recent meta-analysis, women who received surgery tended to be younger [33, 36, 37, 39, 40, 44, 46], tended to have smaller tumors [2, 4, 36, 38–40, 42], tended to have fewer comorbidities and better performance status [2, 44, 45], tended to have a lower burden of metastatic disease [2, 36–38, 41, 42, 44–46], were less likely to have visceral metastases [2, 36, 38, 43, 45], and were likely to have better access to care [38, 40]. Meta-analysis simply reflects the biases of the retrospective studies considered in it.

Finally, studies based on large population-based data sets such as administrative claim data and tumor registry data (SEER data on metastatic BC) have become increasingly common in surgical oncology research. These data sets can be acquired relatively easily, and they offer larger sample sizes and improved generalizability compared with institutional data. There are, however, significant limitations that must be considered in the analysis and interpretation of such data. Invalid conclusions can result when insufficient attention is paid to issues such as data quality and depth, potential sources of bias, missing data, type I error, and the assessment of statistical significance [62]. In fact, the population database studies on metastatic BC incorporated large cohorts of very heterogeneous patients treated during a long period of time and provided the most generalizable conclusions, but they were limited by the clinical variables recorded (HER-2/neu status, indications for the procedure, the specific procedure performed, time of surgery, surgical margin status, systemic therapy, and local RT). So, registry data should be interpreted with caution and good understanding of its limitations.

In conclusion, these consistent biases related to retrospective data and large population-based registries on metastatic BC, including meta-analysis, raise real questions as to whether the better survival of women undergoing primary site local treatment is a cause-and-effect relationship or simply means that physicians are good at picking out patients who are likely to survive longer and definitively selecting patients with the best prognosis at all. Therefore, any conclusions reached from these series should be considered exploratory, and physicians should therefore exercise appropriate caution in adopting these data to their therapeutic strategies, as the survival value of primary site local treatment clearly remains to be proven.

## 29.6 The Clinical Trials

The initial wave of retrospective data suggesting a survival advantage to primary tumor resection, the recognition of consistent biases observed in the published retrospective analyses, and the potential for harm from surgical and RT interventions led to the launching of seven randomized trials in different countries (Table 29.1). Of these, two trials are ongoing (Japan and Austria), two have been completed (India and Turkey), one has just completed enrollment (the Unites States and Canada), one has terminated for lack of enrollment (the Netherlands), and another was withdrawn before enrollment (Thailand). The two completed trials were presented at the San Antonio Breast Cancer Symposium (SABCS) in 2013 [63, 64, 66], and one (India) was recently published [64]. These presentations can be viewed at http://www.sabcs.org/PastSymposia/Index.asp#SABCS2013. Their major features are compared in the Table 29.2. In addition to the main question of whether locoregional therapy is beneficial to women with stage IV BC, these trials address the many ancillary questions regarding the selection of patients who may benefit from resection of the primary tumor, the value of surgery alone vs. surgery plus RT, the type of surgery (mastectomy vs. tumorectomy), and the optimal timing of surgery.

**Table 29.1** Completed and ongoing randomized trials testing locoregional therapy with systemic therapy vs. systemic therapy alone

| Country | Accrual period | Sample size | Initial therapy | Radiotherapy | Status |
|---|---|---|---|---|---|
| India [63, 64] NCT00193778 | 2005–2012 | 350 | Chemotherapy | If indicated | Closed, published |
| Japan [65] JCOG 1017 | 2011–2016 | 410 | Systemic therapy | Not addressed | Enrolling |
| US and Canada EA2108 NCT01242800 | 2011–2015 | 368 | Systemic therapy | Per standards for stages I–III | Closed July 2015 |
| Turkey [66, 67] NCT00557986 | 2008–2012 | 271 | Surgery | For breast conservation | Closed, F-up immature |
| Netherlands [68] SUMBIT trial NCT01392586 | 2011–2016 | 516 | Surgery | For positive margins or palliation | Closed. Lack of enrollment |
| Austria POSYTIVE trial NCT01015625 | 2010–2019 | 254 | Surgery | Per standards for stages I–III | Enrolling |

**Table 29.2** Comparison of randomized Indian and Turkish trials presented at SABCS 2013

| | Tata memorial (2005–2012) | Turkey MF 07-01 (2008–2012) |
|---|---|---|
| Randomization time point | After systemic therapy | At diagnosis |
| Number randomized | 350 | 271 |
| Primary end point | Overall survival | Overall survival |
| Stratification | Number and type of metastases and hormone receptor | None described |
| Preplanned subset analysis | Age, ER and HER2 status, number, and type of metastases | None described |
| Tumor size | Not described | More T2 and T4 tumors in systemic therapy arm |
| Receptor status | Balanced | More triple-negative tumors in systemic therapy arm |
| Metastatic Burden | Balanced >3 lesions | Single organ site more frequent in surgical arm |
| Bone-only metastases | Balanced | Fewer in systemic therapy arm |
| Hazard ratio for survival | 1.04 (95% CI: 0.8–1.3) | 0.76 (95% CI: 0.49–1.16) |
| Hazard ratio for local control | 0.16 (95% CI: 0.10–0.26) | Too few events |

## 29.7 Trials Requiring Randomization to Local Therapy After Systemic Therapy

The rationale for initial systemic therapy is based on the notion that PSLT can provide survival value only if disease at distant sites is responsive to systemic therapy. There are four trials that have been initiated that adopt this approach.

The first trial to open was in India, at the Tata Memorial Cancer Institute in Mumbai, in 2005 (NCT00193778), and was published in 2015 [64]. In this open-label, randomized controlled trial, previously untreated patients (≤65 years of age with an estimated remaining life expectancy of at least 1 year) presenting with de novo metastatic BC were recruited. Patients were randomly assigned (1:1) to receive locoregional treatment directed at their primary breast tumor and axillary lymph nodes or no locoregional treatment. Randomization was stratified by site of distant metastases (bone, viscera, or both), number of metastases (more than 3 vs. <3), and hormone receptor status of the tumor. Use of induction endocrine therapy occurred in 4% of patients in each arm. Patients with resectable primary tumor in the breast that could be treated with endocrine therapy were randomly assigned upfront, whereas those with an unresectable primary tumor were planned for chemotherapy before randomization. Of the patients who had chemotherapy before randomization, they randomly assigned patients who had an objective tumor response after six to eight cycles of chemotherapy. The primary end point was an overall survival analyzed by intention to treat. The trial was powered to detect a 6-month improvement in 2-year survival (from 18 to 24 months). Between February 2005 and January 2013, of the 716 women presenting with de novo metastatic BC, 350 patients were randomly assigned: 173 to locoregional treatment and 177 to no locoregional treatment. At data cutoff of November 2013, median follow-up was 23 months (IQR 12.2–38.7) with 235 deaths (locoregional treatment $n = 118$, no locoregional treatment $n = 117$). Median overall survival was 19.2 months (95% CI, 15.98–22.46) in the locoregional treatment group and 20.5 months (16.96–23.98) in the no locoregional treatment group (HR 1.04; 95% CI, 0.81–1.34; $p = 0.79$), and the corresponding 2-year overall survival was 41.9% (95% CI, 33.9–49.7) in the locoregional treatment group and 43.0% (35.2–50.8) in the no locoregional treatment group (Fig. 29.4). The only

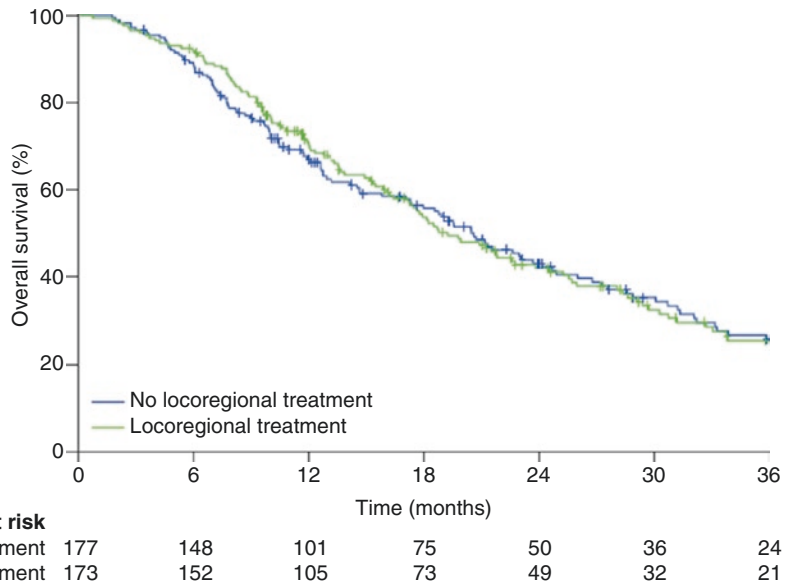


**Fig. 29.4** Kaplan-Meier plot of overall survival (From: Badwe et al. [64])

adverse event noted was wound infection related to surgery in one patient in the locoregional treatment group. The authors concluded that there is no evidence to suggest that locoregional treatment of the primary tumor affects overall survival in patients with metastatic BC at initial presentation who have responded to frontline chemotherapy and this procedure should not be part of routine practice. Planned subset analyses examined survival outcomes for premenopausal vs. postmenopausal women, those with bone-only metastases vs. those with bone plus visceral metastases, more than 3 vs. 1–3 metastatic lesions, and hormone receptor or HER2 subsets, with no significant differences noted. However, where the odds ratio deviated from unity, it favored the systemic therapy only arm (1.4 for bone-only disease and 1.6 for 3 or fewer metastases) (Fig. 29.5). It is noteworthy that the usual approach to systemic therapy for the population in this trial (per Indian standards) was that following induction, therapy was not continuous. Therapy was suspended following good response or stable disease and was resumed on progression. This may explain the difference in 3-year survival seen in this trial and the registry trial in the United States [69] (TBCRC 0013, discussed later). As expected of course, the local progression-free survival rate was significantly better in the surgical group (80% at 5 years compared with 20% in the nonsurgical group, $P < 0.001$).

Currently, two trials with similar design are ongoing. In Japan, JCOG 1017 [65] seeks to enroll 410 patients with newly diagnosed metastatic BC to compare the efficacy of primary tumor resection plus systemic therapy vs. systemic therapy alone. After 3 months of systemic therapy, women who show no disease progression are randomized to undergo surgery or to continue systemic therapy; RT is not required. The primary outcome is overall survival. Secondary outcomes are local recurrence rate, local control rate, and effect on distant metastasis after resection of the primary site. More than 350 patients have been enrolled to date.

In the United States and Canada, the Eastern Cooperative Oncology Group EA2108 (NCT01242800) recruited 383 patients with metastatic BC (revised downward from 880 patients because of slow enrollment), and the trial was closed on July 30, 2015. All patients receive induction systemic therapy at the discretion of the treating physician, consisting of endocrine, cytotoxic, or biologic regimens appropriate to the patient's age and tumor type. Patients without progression of disease after 16–32 weeks of treatment were randomized to either locoregional therapy including surgery and RT (to mirror standards of treatment for patients with nonmetastatic disease) or the continuation of systemic therapy. Randomization was stratified by the type of induction systemic therapy (endocrine therapy, chemotherapy, or chemotherapy with anti-HER2 agents), as that would also reflect the biological subtype of the tumor. It was estimated that 80% of registered patients would respond or demonstrate stable disease and would proceed to randomization, and a crossover of 15% was built into the design (anticipating that some patients would not accept the locoregional therapy arm that they are assigned to). Therapy for the primary site was allowed for palliation, later in the course of disease, for women who were randomized to the systemic therapy–alone arm. The primary outcome is survival; the trial is powered to detect an overall survival difference of 19% at 3 years (from 30 to 49%). The secondary outcomes are local progression-free survival and quality of life, and biological samples are being banked for correlative studies. The fraction of patients dropping out for disease progression during induction systemic therapy, and the fraction of crossing over, is within the expected range. Results are expected by 2017.

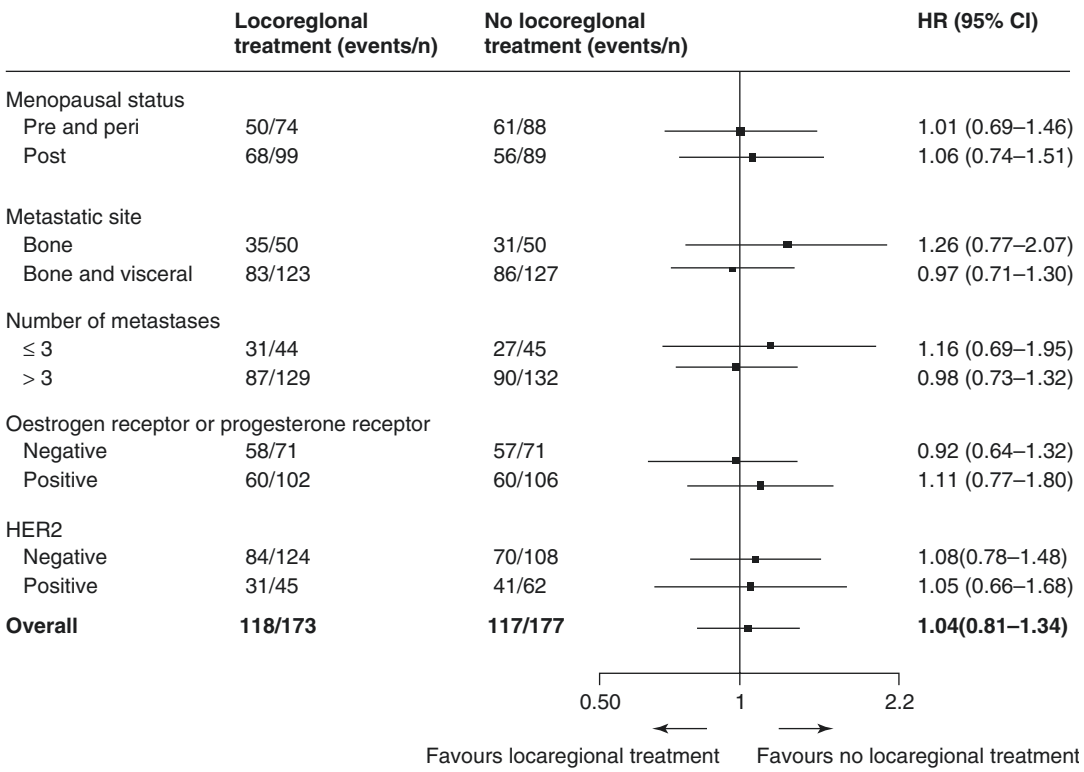


**Fig. 29.5** Forest plot of overall survival subgroup analysis unadjusted hazard ratios. (From: Badwe et al. [64])

## 29.8 Trials Requiring Randomization to Locoregional Therapy Before Systemic Therapy

Some have argued that randomization to, and delivery of, locoregional therapy before systemic therapy is a purer test of the potential benefit of primary site local treatment in the metastatic setting, as it avoids selection of only those patients who respond to systemic therapy. Although this approach avoids the "bias" of including only responders to systemic therapy, it also means that primary site local treatment is provided to some patients whose tumors are unresponsive to systemic therapy at distant sites and therefore will die early owing to their distant disease. The first trial with this design was opened by the Turkish Federation of Breast Diseases (NCT00557986) and has completed enrollment, with early data reported at SABCS 2013 [67]. The design included randomization to surgery before systemic therapy or systemic therapy alone with RT to the primary site in cases of breast conservation. The trial was powered to detect an improvement in the 3-year survival rate from 17 to 35%. A total of 271 evaluable women were recruited. The primary outcome was overall survival, with secondary outcomes related to progression-free survival, quality-of-life measures, and morbidity related to locoregional therapy. The trial was reported at SABCS 2013 with a median follow-up of 18 months and 31% of the population having died [66]. No significant survival advantage was observed at the time of reporting, with a median survival of 42 vs. 46 months, favoring surgery (HR = 0.76; 95% CI, 0.49–1.16; $P = 0.2$). Multiple unplanned subset analyses revealed only the possibility of an advantage with surgery for women with solitary bony metastases (33 women in the primary site local treatment arm and 20 in the control arm; HR = 0.23, $P = 0.02$), but these were not biopsy proven at entry. There were insufficient local recurrences for analysis.

The SUMBIT trial in the Netherlands (NCT01392586) was similarly structured but closed after enrollment of ten patients [68]. The POSYTIVE trial in Austria (NCT01015625) has a roughly similar design and aims to recruit 254 patients with synchronous metastatic breast cancer and randomly assign them to receive either PSLT (lumpectomy or mastectomy + axillary surgery/± RT) vs. nothing. This has recently been revised to allow systemic therapy before randomization. Primary outcomes are median survival. Secondary outcomes are time to distant progression and time to local progression.

## 29.9 Prospective Registry Study TBCRC 0313

A prospective study entitled "A Prospective Analysis of Surgery in Patients Presenting with Stage IV Breast Cancer" is a multi-institutional data registry [69]. The objective is to

characterize patients with stage IV BC while documenting clinical management outcomes. The planned total enrollment is 100 patients. Its primary aims are to document response to first-line therapy, frequency of surgical referral, and proportion of patients undergoing surgery, determine the incidence of uncontrolled local disease and frequency of surgical palliation, and correlate molecular characteristics of primary tumor with conventional prognostic factors. A number of correlative molecular studies of circulating tumor cells and analyses of primary and metastatic tumor samples are planned. The analysis of registered patients with stage IV disease follows two tracks: one for those with an intact primary and one for those with the primary tumor resected and metastases discovered within 3 months of surgery. Local and distant disease will be carefully monitored in women with responsive and nonresponsive disease, and the use of research biopsies during therapy will provide samples to generate biological hypotheses related to interactions between responding and nonresponding primary and metastatic sites, the frequency and effect of uncontrolled chest wall disease, quality of life, and other issues. As reported at the San Antonio Breast Cancer Symposium in 2013, the 3-year survival rate of 39 women who were responsive to induction systemic therapy and received surgery was 81%, whereas the survival rate of responders who did not receive surgery was 79%. Although the numbers are small, it is also of interest that among 15 women who were diagnosed with metastases following surgical therapy for the primary tumor, the 3-year survival rate was 87%. These numbers are remarkably different from the survival experience in the Tata Memorial trial (3-year survival rate of 25%) and point to the differences in the biological and therapeutic environment between Indian and US populations.

## 29.10 Recommendations

Although retrospective data suggest that locoregional therapy for the primary tumor may provide a survival advantage in women with metastatic BC and an intact primary tumor, this is not confirmed by randomized trials. The biases of the retrospective data include the use of surgery in younger women with smaller tumors, single sites of metastasis, and less visceral disease. The publication of data from the Tata Memorial [64] and Turkish Federation [67] trials provides information on patients treated prospectively. These and ongoing trials will allow us to evaluate the role of surgery alone or surgery plus RT and will allow us to reach solid conclusions regarding the role of locoregional therapy, how extensive it should be, and its timing in stage IV breast cancer.

Until additional unbiased data are available, surgery and RT to patients with stage IV with an intact, asymptomatic primary tumor cannot be recommended outside a clinical trial. In particular, there is no basis for recommending surgery to women with distant disease (a) if the distant disease is not well controlled, as survival will likely not be long enough for the primary site to become a problem, or (b) both local and distant sites are well controlled, in which case, the primary site is likely to remain well controlled for the patient's life span. A possible exception to these rules may be a patient who would be rendered as having stage IV NED by resection of the primary tumor, although this too is based on highly selected series. For a patient whose distant disease is controlled but the primary site is progressing, surgery provides a reasonable approach [70].

Locoregional therapy for the primary tumor should be offered to patients only with full disclosure of the lack of evidence of a survival benefit. If a clinical trial is available and the patient is willing to consider it, that is clearly the most rational choice. If primary site local treatment is decided on following the considerations described earlier, the subset of patients that may benefit from more aggressive local therapy ("ideal" patients for primary site local treatment), based on the data from retrospective series and population database studies, includes young patients with good performance status (women diagnosed with stage IV breast cancer before age 50 have better survival at 10 years compared to older women) [56], smaller primary tumor, ER-/PR-positive or HER-2/neu amplified tumor (in which more effective targeted therapies are available), oligometastatic disease (solitary and or low-volume metastatic disease) [59], and possibly with metastatic spread limited to the skeleton [36, 37, 71].

If primary site local treatment is planned, either mastectomy or lumpectomy is appropriate, but of course breast conservation (if feasible) is clearly the least harmful option, and the odds of successful breast conservation can be maximized by the use of effective systemic therapy preoperatively. In case of breast-conserving surgery (BCS), resection margins were strongly considered in the past as important prognostic factor of local recurrence and survival. The original report by Khan et al. found that for BCS or mastectomy patients, the median 3-year survival was 35–36% for patients with clear margins, 26% for those with positive margins, and 17% in nonsurgical patients ($p < 0.0001$) [1]. Two further tumor registry studies [36, 72] and an institutional study from Malaysia [4] also demonstrated that survival was improved in patients with negative margins. These findings may be easily explained by differences between groups, and currently the true significance of the resection margins in BCS has been strongly resized, either in early breast cancer [73] or in metastatic BC. So, although we should always aspire to clear surgical margins when we perform BCS in metastatic BC, this is not mandatory and a re-excision for involvement of the resection margins should be always

avoided. In case of mastectomy, plastic reconstruction is not absolutely contraindicated and must be evaluated case by case, considering the possible immunodepression related to larger reconstructive surgery.

The data on axillary surgery are extremely limited, but if surgery is undertaken, removal only of all gross and symptomatic disease seems prudent. Out of these, routine axillary dissection, axillary nodal samples, and sentinel lymph node biopsy should be categorically avoided, being unnecessary neither for prognostic information nor for local control of the disease.

The evidence supporting the use of postoperative RT is weak [47, 48], at best, and cannot be recommended presently. Primary RT can be considered with the same caveats as surgical resection, particularly if the surgical procedure required would be mastectomy. Although whether RT should follow surgery is unproven, its use may be justified if the risk of early local recurrence and uncontrolled chest wall disease is high.

### Conclusions

Stage IV disease is a chronic and incurable disease, and the goals of treatment are only the prolongation of life and the palliation or prevention of symptoms. In stage IV breast cancer patients, the primary and most important and effective treatment modality still remains a systemic therapy. The retrospective data suggest that locoregional therapy for the primary tumor may provide a survival advantage in women with metastatic BC and an intact primary tumor, but this is not confirmed by randomized trials. The publication of data from the Tata Memorial [64] and Turkish Federation [67] trials provides information on patients treated prospectively. These and other ongoing trials will allow us to evaluate the role of surgery alone or surgery plus RT and will allow us to reach solid conclusions regarding the role of locoregional therapy, how extensive it should be, and its timing in stage IV breast cancer. Until additional unbiased data are available, surgery and RT to patients with stage IV with an intact, asymptomatic primary tumor shouldn't be routinely performed or recommended outside a clinical trial. Only for selected patient whose distant disease is controlled by systemic therapy but the primary site is progressing, surgery provides a reasonable approach.

## References


1. Khan SA, Stewart AK, Morrow M (2002) Does aggressive local therapy improve survival in metastatic breast cancer? Surgery 132:620–626
2. Ruiterkamp J, Ernst MF, van de Poll-Franse LV et al (2009) Surgical resection of the primary tumour is associated with improved survival in patients with distant metastatic breast cancer at diagnosis. Eur J Surg Oncol 35:1146–1151
3. Siegel R, Naishadham D, Jemal A (2013) Cancer statistics, 2013. CA Cancer J Clin 63:11–30
4. Pathy NB, Verkooijen HM, Taib NA et al (2011) Impact of breast surgery on survival in women presenting with metastatic breast cancer. Br J Surg 98:1566–1572
5. Jha AK, Hamal PK, Jha J et al (2010) Pattern of breast cancer in a tertiary care center. J Nepal Med Assoc 49:1–5
6. Olu-Eddo AN, Momoh MI (2010) Clinicopathological study of male breast cancer in Nigerians and a review of the literature. Nig Q J Hosp Med 20:121–124
7. Gardishar WJ, Anderson BO, Balassanian R et al (2015) Breast Cancer Version 2.2015: clinical practice guidelines in oncology. J Natl Compr Canc Netw 13:448–475
8. Andre F, Slimane K, Bachelot T et al (2004) Breast cancer with synchronous metastases: trends in survival during a 14-year period. J Clin Oncol 22:3302–3308
9. McLaughlin SA, Wright MJ, Morris KT et al (2008) Prevalence of lymphedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: objective measurements. J Clin Oncol 26:5213–5219
10. Kissin MW, della Rovere GQ, Easton D, Westbury G (1986) Risk of lymphedema following the treatment of breast cancer. Br J Surg 73:580–584
11. Barry PN, Riley EC, Pan J et al (2013) Delay of adjuvant chemotherapy after elective mastectomy and immediate reconstruction in breast-conservation candidates: a matched-pair analysis. Am J Clin Oncol 37:575–579
12. Lohrisch C, Paltiel C, Gelmon K et al (2006) Impact on survival of time from definitive surgery to initiation of adjuvant chemotherapy for early-stage breast cancer. J Clin Oncol 24:4888–4894
13. O'Reilly MS, Holmgren L, Shing Y et al (1994) Angiostatin: a novel angiogenesis inhibitor that mediates the suppression of metastases by a Lewis lung carcinoma. Cell 79:315–328
14. Giordano SH, Buzdar AU, Smith TL et al (2004) Is breast cancer survival improving? Cancer 100:44–52
15. Dawood S, Broglio K, Ensor J et al (2010) Survival differences among women with de novo stage IV and relapsed breast cancer. Ann Oncol 21:2169–2174
16. Retsky M, Bonadonna G, Demicheli R, Folkman J, Hrushesky W, Valagussa P (2004) Hypothesis: induced angiogenesis after surgery in premenopausal node-positive breast cancer patients is a major underlying reason why adjuvant chemotherapy works particularly well for those patients. Breast Cancer Res 6:372–374
17. Flanigan RC, Salmon SE, Blumenstein BA et al (2001) Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. N Engl J Med 345:1655–1659
18. Mickisch GH, Garina A, van Poppel H et al (2001) Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomized trial. Lancet 358:966–970
19. Dauplat J, Le Bouedec G, Pomel C, Scherer C (2000) Cytoreductive surgery for advanced stages of ovarian cancer. Semin Surg Oncol 19:42–48
20. Griffiths CT, Fuller AF (1978) Intensive surgical and chemotherapeutic management of advanced ovarian cancer. Surg Clin North Am 58:131–142
21. Classe JM, Cerato E, Boursier C, Dauplat J, Pomel C, Villet R, Cuisenier J, Lorimier G, Rodier JF, Mathevet P, Houvenaeghel G, Leveque J, Lécuru F (2011) Retroperitoneal lymphadenectomy and survival of patients treated for an advanced ovarian cancer: the CARACO trial. J Gynecol Obstet Biol Reprod 40:201–204
22. Goldie JH, Coldman AJ (1979) A mathematic model for relating the drug sensitivity of tumors to their spontaneous mutation rate. Cancer Treat Rep 63:1727–1733

23. Rosen SA, Buell JF, Yoshida A et al (2000) Initial presentation with stage IV colorectal cancer: how aggressive should we be? Arch Surg 135:530–534
24. Martin R, Paty O, Fong Y et al (2003) Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg 197:233–241
25. Tanaka K, Shimada H, Matsuo K et al (2004) Outcome after simultaneous colorectal and hepatic resection for colorectal cancer with synchronous metastases. Surgery 136:650–659
26. Hallissey MT, Allum WH, Roginski C, Fielding JW (1988) Palliative surgery for gastric cancer. Cancer 62:440–444
27. Essner R, Lee JH, Wanek LA et al (2004) Contemporary surgical treatment of advanced-stage melanoma. Arch Surg 139:961–966
28. Norton L, Massague J (2006) Is cancer a disease of self-seeding? Nat Med 12:875–878
29. Karnoub AE, Dash AJ, Vo AP et al (2007) Mesenchymal stem cells within tumour stroma promote breast cancer metastasis. Nature 449:557–563
30. Campbell MJ, Scott J, Maecker HT, Park JW, Esserman LJ (2005) Immune dysfunction and micrometastases in women with breast cancer. Breast Cancer Res Treat 91:163–171
31. Danna EA, Sinha P, Gilbert M et al (2004) Surgical removal of primary tumor reverses tumor-induced immunosuppression despite the presence of metastatic disease. Cancer Res 64:2205–2211
32. Morrow M, Goldstein L (2006) Surgery of the primary tumor in metastatic breast cancer: closing the barn door after the horse has bolted? J Clin Oncol 20:2694–2696
33. Hazard HW, Gorla SR, Scholtens D et al (2008) Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. Cancer 113:2011–2019
34. Dalberg K, Liedberg A, Johansson U, Rutqvist LE (2003) Uncontrolled local disease after salvage treatment for ipsilateral breast tumour recurrence. Eur J Surg Oncol 29:143–154
35. Cady B, Nathan NR, Michaelson JS, Golshan M, Smith BL (2008) Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. Ann Surg Oncol 15:3384–3395
36. Rapiti E, Verkooijen HM, Vlastos G et al (2006) Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. J Clin Oncol 24:2743–2749
37. Babiera GV, Rao R, Feng L et al (2006) Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol 13:776–782
38. Blanchard DK, Shetty PB, Hilsenbeck SG, Elledge RM (2008) Association of surgery with improved survival in stage IV breast cancer patients. Ann Surg 247:732–738
39. Fields RC, Jeffe DB, Trinkaus K et al (2007) Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. Ann Surg Oncol 14:3345–3351
40. Gnerlich J, Jeffe DB, Deshpande AD et al (2007) Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988–2003 SEER data. Ann Surg Oncol 14:2187–2194
41. Bafford AC, Burstein HJ, Barkley CR et al (2008) Breast surgery in stage IV breast cancer: impact of staging and patient selection on overall survival. Breast Cancer Res Treat 115:7–12
42. Neuman HB, Morrogh M, Gonen M et al (2010) Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? Cancer 116:1226–1233
43. Shien T, Kinoshita T, Shimizu C et al (2009) Primary tumor resection improves the survival of younger patients with metastatic breast cancer. Oncol Rep 21:827–832
44. Rashaan ZM, Bastiaannet E, Portielje JEA et al (2012) Surgery in metastatic breast cancer: patients with a favorable profile seem to have the most benefit from surgery. Eur J Surg Oncol 38:52–56
45. Perez-Fidalgo JA, Pimentel P, Caballero A et al (2011) Removal of primary tumor improves survival in metastatic breast cancer. Does timing of surgery influence outcomes? Breast 20:548–554
46. Dominici L, Najita J, Hughes M et al (2011) Surgery of the primary tumor does not improve survival in stage IV breast cancer. Breast Cancer Res Treat 129:459–465
47. Le Scodan R, Stevens D, Brain E et al (2009) Breast cancer with synchronous metastases: survival impact of exclusive locoregional radiotherapy. J Clin Oncol 27:1375–1381
48. Bourgier C, Khodari W, Vataire AL et al (2010) Breast radiotherapy as part of loco-regional treatments in stage IV breast cancer patients with oligometastatic disease. Radiother Oncol 96:199–203
49. Leung AM, Vu HN, Nguyen KA, Thacker LR, Bear HD (2009) Effects of surgical excision on survival of patients with stage IV breast cancer. J Surg Res 161:83–88
50. Ly BH, Nguyen NP, Vinh-Hung V, Rapiti E, Vlastos G (2010) Loco-regional treatment in metastatic breast cancer patients: is there a survival benefit? Breast Cancer Res Treat 119:537–545
51. Petrelli F, Barni S (2012) Surgery of primary tumors in stage IV breast cancer: an updated meta-analysis of published studies with meta-regression. Med Oncol 29:3282–3290
52. Ruiterkamp J, Voogd AC, Bosscha K, Tjan-Heijnen VC, Ernst MF (2010) Impact of breast surgery on survival in patients with distant metastases at initial presentation: a systematic review of the literature. Breast Cancer Res Treat 120:9–16
53. Harris E, Barry M, Kell MR (2013) Meta-analysis to determine if surgical resection of the primary tumour in the setting of stage IV breast cancer impacts on survival. Ann Surg Oncol 20: 2828–2834
54. Khan SA (2007) Primary tumor resection in stage IV breast cancer: consistent benefit, or consistent bias? Ann Surg Oncol 14: 3285–3287
55. Headon H, Wazir U, Kaem A, Mokbe K (2016) Surgical treatment of the primary tumour improves the overall survival in patients with metastatic breast cancer: a systematic review and meta-analysis. Mol Clin Oncol 4:863–867
56. Eng LG, Dawood S, Sopik V et al (2016) Ten-year survival in women with primary stage IV breast cancer. Breast Cancer Res Treat 160(1):145–152
57. Warschkow R, Guller U, Tarantino I et al (2016) Improved survival after primary tumor surgery in metastatic breast cancer. A propensity-adjusted, population-based SEER trend analysis. Ann Surg 263:1188–1198
58. Thomas A, Khan SA, Chrischilles EA, Schroeder MC (2016) Initial surgery and survival in Stage IV Breast Cancer in the United States, 1988–2011. JAMA Surg 151:424–431
59. Tan Y, Li X, Chen H et al (2016) Hormone receptor status may impact the survival benefit of surgery in stage IV breast cancer: a population-based study. Oncotarget 7(43):70991–71000
60. Rao R, Feng L, Kuerer HM et al (2008) Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Ann Surg Oncol 15:1696–1702
61. Ruiterkamp J, Voogd AC, Bosscha K et al (2011) Presence of symptoms and timing of surgery do not affect the prognosis of patients with primary metastatic breast cancer. Eur J Surg Oncol 37:883–889
62. Le Lorier J, Grégoire G, Benhaddad A, Lapierre J, Derderian F (1997) Discrepancies between meta-analyses and subsequent large randomized, controlled trials. N Engl J Med 337:536–542
63. Badwe RA, Parmar V, Hawaldar R et al (2013) Surgical removal of primary tumor and axillary lymph nodes in women with metastatic breast cancer at first presentation: a randomized controlled trial. Cancer Res 73: Abstract nr S2-02 [supplement SABCS Proceedings, S-02-03]
64. Badwe R, Hawaldar R, Nair N et al (2015) Locoregional treatment versus no treatment of the primary tumour in metastatic breast cancer:

an open-label randomised controlled trial. Lancet Oncol 16: 1380–1388
65. Shien T, Nakamura K, Shibata T et al (2012) A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC). Japan Clinical Oncology Group Study JCOG1017. Jpn J Clin Oncol 42:970–973
66. Soran A, Ozmen V, Ozbas S, et al (2013) Early follow up of a randomized trial evaluating resection of the primary breast tumor in women presenting with de novo stage IV breast cancer; Turkish study (protocol MF07-01). Cancer Res 73: Abstract nr S2-03 [supplement SABCS Proceedings, S-02-03]
67. Soran A, Ozbas S, Kelsey SF, Gulluoglu BM (2009) Randomized trial comparing locoregional resection of primary tumor with no surgery in stage IV breast cancer at the presentation (Protocol MF07-01): a study of Turkish Federation of the National Societies for Breast Diseases. Breast J 15:399–403
68. Ruiterkamp J, Voogd AC, Tjan-Heijnen VCG et al (2012) SUBMIT: systemic therapy with or without up front surgery of the primary tumor in breast cancer patients with distant metastases at initial presentation. BMC Surg 12:5
69. King TA, Lyman JP, Gonen M et al (2013) TBCRC 013: a prospective analysis of the role of surgery in stage IV breast cancer. Cancer Res 2013; 73: Abstract nr P2-18-09 [supplement SABCS Proceedings]
70. Khan SA (2016) Surgical management of de novo Stage IV breast cancer. Semin Radiat Oncol 26:79–86
71. Botteri E, Munzone E, Intra M et al (2013) Role of breast surgery in T1-3 breast cancer patients with synchronous bone metastases. Breast Cancer Res Treat 138:303–310
72. Nguyen DH, Truong PT, Alexander C et al (2012) Can locoregional treatment of the primary tumor improve outcomes for women with stage IV breast cancer at diagnosis? Int J Radiat Oncol Biol Phys 84:39–45
73. Moran MS, Schnitt SJ, Giuliano AE et al (2014) Society of Surgical Oncology—American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. J Clin Oncol 32:1507–1515