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Surgery in the Setting of Metastatic Breast Cancer

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Abstract

Purpose of Review Among individuals with metastatic breast cancer, surgical resection of the primary tumor remains controversial, and its benefit is unclear. In this review, we highlight select retrospective and prospective studies which have sought to address this clinical scenario. In addition, we discuss further considerations that may be relevant.

Recent Findings Numerous retrospective studies have suggested a potential survival benefit associated with surgical resection of the primary breast tumor in women with metastatic disease; however, three randomized controlled trials more recently have challenged these findings. Mixed results have demonstrated no survival benefit with locoregional treatment versus limited benefit in select patient groups.

Summary Prospective studies suggest that most patients with metastatic breast cancer are unlikely to experience a survival benefit related to resection of their primary tumor. However, ongoing work seeks to further define if there may be select subgroups that could benefit from surgery.

Keywords Stage IV breast cancer · Metastatic breast cancer · Breast surgery · Patient outcomes

Introduction

Over 260,000 women in the USA are diagnosed with breast cancer annually [1]. While 20−30% of women with early stage breast cancer eventually progress to distant metastases [2], de novo metastatic breast cancer (MBC) accounts for 5−10% of new diagnoses [1,3,4]. Improvements in systemic therapies over recent years has led to an increasing number of women living with MBC due to improved overall survival in this population [5]. As of 2017, an estimated 150,000 patients were living with MBC in the USA [5,6].Although outcomes are improving [6,7], the median survival remains around 2−3 years, and prognosis among patients with metastatic disease varies widely [8,9]. Survival depends on numerous factors, including but not limited to extent of disease, biomarker status, patient demographics, and sustainability of treatment [10–15]. Based on some of these factors, we previously developed a novel staging system to stratify patients with de novo MBC into 3 subgroups (IVA, IVB, and IVC) in order to better discriminate prognosis [16•] and validation studies are ongoing. Others are investigating the significance of circulating tumor cells [17] and genomic assays to help tailor treatments [18,19], although tumor genomic profiling in particular may not always impact clinical management decisions [20].

Given the advancements in systemic therapies and continually improving survival, there continues to be ongoing controversy regarding the risks and benefits associated with surgical resection of the primary breast cancer in women with stage IV disease. Current national guidelines state that "the role and timing of surgical removal of the primary tumor in patients presenting with de novo stage IV (M1) is the subject of ongoing investigations and must be individualized…[and may be] reasonable in select patients responding to initial systemic therapy." [21] The

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included review will summarize some of the significant studies related to the surgical considerations for patients with MBC, including a historical perspective, review of prospective studies, and additional issues that may also be important.

Looking to the Past (Retrospective Studies)

Retrospective studies evaluating the utility of locoregional surgery for patients with MBC have yielded mixed results, with some reporting improved survival and others demonstrating no significant difference between those who do and do not undergo surgery (Table 1). One of the earliest and largest studies from the National Cancer Data Base (NCDB) included 16,023 patients diagnosed with de novo MBC between 1990 and 1993, of whom 57.2% underwent partial or total mastectomy [22]. After adjustment, women who underwent surgical resection were found to have a superior prognosis (HR 0.61, 95% CI 0.58−0.65). Administration of systemic therapy, the number of metastatic sites, and the type of metastatic disease were also associated with an improved overall survival (OS), while the type of breast surgery (lumpectomy or mastectomy), tumor size, extent of axillary surgery, and the number of involved nodes were not. As recognized by the authors, there was likely some degree of selection bias inherent in the retrospective nature of the study [22]. Regardless, the results appeared promising, and numerous retrospective studies using other data sources were subsequently published (Table 1).

To limit some of the bias inherent in these retrospective studies, researchers have utilized various analytical and statistical approaches. For example, a retrospective, single institution review of patients with an intact primary tumor and synchronous metastatic disease (1997−2002) suggested that surgical extirpation of the primary tumor was associated with an improved progression free survival when performed > 3 months after diagnosis [23]. As such, Lane et al. excluded patients in the NCDB who died within 1 year of diagnosis in order to identify metastatic breast cancer patients that may benefit from locoregional therapy [24]. In this study of 24,015 women diagnosed with stage IV breast cancer (from 2003 to 2012), receipt of surgery was again found to be associated with an improved adjusted OS (surgery before systemic therapy, HR 0.68, 95% CI 0.62−0.73; systemic therapy before surgery, HR 0.56, 95% CI 0.52−0.61) [24]. In contrast, Dominici et al. performed a retrospective analysis using data from the NCCN Breast Cancer Outcomes Database (1997−2007), which matched patients who did and did not undergo surgery based on age at diagnosis, estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and number of metastatic sites [25]. Survival of the matched cohorts were similar (3.4 years in the nonsurgery group vs 3.5 years in the surgery group) [25]. In a retrospective study by Marks et al. of nearly 25,000 patients in the NCDB, recursive partitioning was used to stratify patients and determine if some subgroups may benefit more than others [26]. This study suggests that patients with more favorable disease likely benefit more from surgery [26]. While selection bias is likely a confounding variable in many of these retrospective studies, some have noted potential confounding from stage migration bias. In a study by Bafford et al., patients diagnosed with MBC postoperatively had a median OS of 4.0 years, compared to 2.4 years for those diagnosed preoperatively and 2.36 years for those who did not undergo surgery ($p = 0.18$) [27]. Based on this conflicting data, the breast oncology community recognized the need for and value of randomized clinical trial data and several prospective studies were pursued (Table 2).

Contemporary Insights (Prospective Studies)

The first prospective study to be published on the topic of surgery in the setting of MBC was based in India and included 350 women aged 65 or less with a life expectancy of at least 1 year. Study participants were enrolled from 2005 to 2013 and randomized to receive locoregional treatment to the breast and the axilla versus no locoregional therapy. Women were further stratified by site of distant metastases, number of metastatic lesions, and hormone receptor status [28]. Notably, sequence of systemic therapy varied by clinical presentation at diagnosis; participants with resectable primary tumors were randomized upfront, while those with unresectable primary tumors received 6−8 cycles of preoperative chemotherapy requiring objective in-breast tumor response prior to randomization. In the locoregional treatment group, the median OS was 19.2 months, compared to 20.5 months in the no locoregional treatment group ($p = 0.79$), suggesting no survival benefit with locoregional therapy for those who responded to upfront systemic therapy. This finding remained true in subgroup analyses regardless of biomarkers, menopausal status, number of metastases, and site of metastatic disease [28]. However, it is important to note that the majority of patients with HER2+ disease did not receive targeted anti-HER2 therapy.

The next randomized controlled trial to be published was based in Turkey (MF07-01) and included 274 patients that were randomly assigned at diagnosis (without stratification; from 2007 to 2012) to either locoregional treatment or systemic therapy [29]. Patients in the locoregional treatment group underwent surgical resection of the primary tumor upfront followed by systemic therapy, while those in the systemic therapy group immediately started treatment without surgery. At the primary planned endpoint (3-year OS), there was no statistical difference between the 2 groups. However, the overall hazard of death was 34% lower for participants who underwent local therapy when compared to those in

Table 1 Select retrospective studies (2002 to 2020) evaluating the survival benefit associated with surgical resection of the primary tumor in women with metastatic breast cancer

Publication year and first author	Study years and data source	*N*	% Surgery	Study outcomes and findings	Additional study notes and limitation(s)
2002 Khan	1990–1993 NCDB	16,023 overall; 10,160 included in multivariate analysis	57.2%	Adjusted HR 0.612 (95% CI 0.581–0.646) for surgery with negative margins (vs no surgery)	36.6% of cohort missing data and excluded from multivariate analysis; NCDB data on adjuvant non-surgical therapy may be inaccurate or incomplete
2008 Cady	1970–2002Massachusetts General Hospital and Brigham and Women's Hospital	808 overall; 622 included in final analysis	38%	$p < 0.0001$ based on Kaplan-Meier analysis of overall cohort favoring surgery	Survival benefit with surgery was minimal after case matching patients based on age, date of diagnosis, location of metastatic sites, ER status, and use of systemic therapy
2009 McGuire	1990–2007 Moffitt Cancer Center	566	27.4%	OS: surgery 33% vs no surgery 20%, $p = 0.0012$ based on Kaplan-Meier analysis	Multivariate analysis not performed; cohorts (surgery vs no surgery) comparable based on tumor size, number and sites of metastatic sites, ER/PR/HER2 status, and receipt of systemic therapies; surgery vs no surgery patients differed by median age (60y vs 52.5y, $p < 0.001$); 74% of surgical patients underwent surgery upfront.
2009 Ruiterkamp	1993–2004 Eindhoven Comprehensive Cancer Centre, South Netherlands	728 overall; 554 included in multivariate analysis	40%	Adjusted HR 0.62 (95% CI (0.51–0.76) for surgery (vs no surgery)	Lacked information on timing of surgery or systemic therapy
2011 Dominici	1997–2007 NCCN Breast Cancer Outcomes Database	551 overall; 290 included in matched pair analysis	9.8% in overall cohort; 18.6% in matched pair analysis	Adjusted HR 0.94 (95% CI 0.84–1.05) for entire surgery cohort (vs no surgery) Adjusted HR for matched pair analysis 0.94 (95% CI 0.83–1.08) for surgery (vs no surgery)	Matched on age at diagnosis, ER/HER2 status, and number of metastatic sites; all included surgical patients underwent surgery upfront without receipt of neoadjuvant chemotherapy
2013 Lang	1997–2002, MD Anderson	208	35.5%	0.58, 95% CI 0.35–0.98	

Table 1 (continued)

2016 Thomas	1988–2011, SEER	21,372	39%	0.6, 95% CI 0.57–0.63,	Looked at HR at 10 years out; Royston-Parmar survival functions were chosen instead of a Cox model because the proportional hazards assumption was violated. Limitations; excluded patients who received radiation prior to surgery b/c anatomic site of RT unknown
2019 Pons-Tostivint	2008–2014, French Epidemiological Strategy and Medical Economics MBC database (NCT03275311)	4276	26%	HR 0.73, 95% CI 0.60–0.89, $p = 0.002$ at 6 months HR 0.65, 95% CI 0.54–0.78, $p < 0.001$ at 1 year	HR @ 6mos and 1 year; group comparison was LRT vs no LRT (LRT including radiotherapy and/or surgery)
2019 Lane	2003–2012, NCDB	24,015	43.8%	0.68, 95% CI 0.62–0.73 (before ST), 0.56, 95% CI 0.52–0.61	Included women with M1 disease alive 1 year after diagnosis who received neoadjuvant chemotherapy prior to surgery; sensitivity analysis done with 21,516 in agreement with larger cohort
2020 Lin	2010–2015, SEER	13,034	29.8%	HR 0.557, 95% CI 0.523–0.594	Matched case-control analysis

HR: hazard ratio. CI: confidence interval. NCDB: National Cancer Data Base. OS: overall survival. ER: estrogen receptor. PR: progesterone receptor. HER2: human-epidermal-growth-factor-receptor-2. NCCN: National Comprehensive Cancer NetworkHR hazard ratio. *CI* confidence interval. *NCDB* National Cancer Data Base. *OS* overall survival. *ER* estrogen receptor. *PR* progesterone receptor. *HER2* human epidermal growth factor receptor 2. *NCCN* National Comprehensive Cancer Network

Table 2 Prospective randomized clinical trials evaluating the survival benefit associated with surgical resection of the primary tumor in women with metastatic breast cancer

Publication year and first author	Enrollment years and study population	Trial design	End point	*N*	Adjusted HR for surgical patients	Study limitation(s)	Other notes
2015 Badwe	2005–2013, Women < 65 years in India	Primary resectable: endocrine therapy > randomized to surgery vs no surgery Non-resectable: 6 cycles chemotx > randomized to surgery vs no surgery	OS	350	HR 1.04, 95% CI 0.81–1.34	96% ($n = 336$) of the patients were randomly assigned after receiving and responding to chemotherapy as their first treatment	No survival benefit with surgery upfront vs surgery after responding to systemic therapy
2018 Soran MF07-01	2007–2012; women with de novo stage IV breast cancer in Turkey	Randomized 1:1 to either the LRT or ST group	OS	274	0.66; 95% confidence interval [CI], 0.49–0.88	All patients received systemic therapy Bony metastases determined by two imaging modalities without biopsy confirmation.	No survival benefit with surgery at 36-months; at 5 years, LRT associated with 17% survival benefit.
2020 Khan ECOG-2108	2011–2015; women with de novo MBC	All participants received systemic therapy (4–8 months) followed by randomization to surgery vs no surgery	OS	256	1.09 90% CI 0.8-1.49	70% negative margins after surgical resection	All patients received preoperative ST. No improvement in survival or health-related quality of life; improved time to locoregional progression with surgery

MBC metastatic breast cancer, *ST* systemic therapy, *LRT* locoregional therapy MBC, metastatic breast cancer; ST, systemic therapy; LRT, locoregional therapy

the systemic therapy group at 40 months (HR 0.66, 95% CI 0.49−0.88, $p = 0.005$). In unplanned subgroup analyses, the lower risk of death was most significant in participants with hormone receptor (HR) + disease, HER2- disease, age < 55 years old, and bone-only metastases (all $p \leq 0.05$) [29]. Notably, the findings of this study were limited by the unplanned stratification, inconsistencies in diagnostic confirmation of metastatic sites (particularly for bone only metastases), and differences in disease characteristics between treatment arms with the locoregional therapy group including higher rates of ER/PR+ disease and lower rates of triple negative disease.

Based on these findings, Tosello et al. conducted a systematic review including the 624 women enrolled in the previously aforementioned trials, concluding that the OS benefit with breast surgery was uncertain (HR 0.83, 95% CI 0.53−1.31) [30]. However, they also reported that breast surgery may improve local progression free survival (HR 0.22, 95% CI 0.08−0.57) and potentially worsen distant progression free survival (HR 1.42, 95% CI 10.8−10.86) due to mechanisms that remain uncharacterized [30].

More recently, the long-awaited findings from the randomized controlled trial conducted in the USA (ECOG-ACRIN 2108) were presented by lead investigator Dr. Seema Khan at the American Society of Clinical Oncology's Annual Meeting in 2020 [31,32••]. This study enrolled patients with de novo MBC diagnosed from 2011 to 2015, who received optimal systemic therapy and had no evidence of progression of distant disease following 4−8 months of therapy. Participants ($N = 256$) were then randomized to either continued systemic therapy or early local therapy, including complete tumor resection with negative margins and postoperative radiotherapy per standard of care. Although patients were of similar age and biomarker status in both groups, those in the systemic therapy alone group were more likely to have a single organ system involved. At a median follow-up of 53 months, there was no significant difference in OS (HR 1.09, 95% CI 0.80−1.49) or progression free survival (log rank $p = 0.40$) between the treatment groups. However, for the 20 women with triple negative disease, OS appeared to be significantly worse for those who received early local therapy (HR 3.50, 95% CI 1.16−10.57). No significant differences were observed for those with HER2+ (HR 1.05, 95% CI 0.49−2.24) or HR+/HER2- disease (HR 0.94, 95% CI 0.59−1.51) [32••]. The ECOG 2108 trial also included health-related quality of life and time to local progression as secondary outcomes. At 18 months post-randomization, quality of life (based on the validated FACT-B survey) was significantly lower in women who underwent locoregional treatment. Notably, local progression was significantly higher in the systemic therapy group when compared to surgery (25.6% versus 10.2%; HR: 0.37 (95% CI: 0.19−0.73), conferring a 2.5-fold higher risk of local progression without surgery [32••].

Other Considerations

The Other Influences of Surgery

Although some data suggests that removal of the primary tumor may improve survival, others have postulated that excisional surgery for cancer may alter the residual disease via three main mechanisms: (1) dissemination; (2) facilitation; and (3) acceleration [33]. More specifically, surgery-induced stress has a systemic effect, which includes cytokine release, inflammation, sympathetic nervous system activation, immunosuppression, and ischemia-reperfusion injury [34]. As such, surgery may result in dissemination of tumor cells (e.g., circulating tumor cells that may add to the overall tumor burden), create a window of opportunity for tumorigenesis related to postoperative immunosuppression, and/or alter the biological properties of neoplastic cells by increasing cellular proliferation and reducing cell death [33]. Although largely based on small and preliminary studies, potential benefits from surgical intervention may be related to multiple factors. In a preclinical breast cancer mouse model, primary tumor resection resulted in a decreased tumor burden, halted metastatic progression, and enhanced the immune response [35]. Others have shown that removing the primary tumor in mice may also decrease the number of myeloid-derived stem cells, which can promote metastatic tumor growth when present and can be further suppressed by chemotherapy regimens [36]. As such, some have sought to investigate and develop pharmaceutical agents that may help mitigate the surgery stress-induced tumor progression [34]. For example, peri-operative β-blockade appeared to inhibit recurrence and metastasis in patients with triple negative breast cancer [37]. However, additional studies are needed to further delineate these potential benefits.

Regardless, surgery has been consistently shown to improve locoregional progression-free survival for women with MBC [28,31]; however, it may also result in a worse distant progression-free survival [30]. For example, in the randomized controlled trial by Badwe et al., patients who received locoregional treatment had a distant progression free survival of 11.3 months, compared to 19.8 months in those who received systemic therapy alone ($p = 0.012$) [28]. Similar behavior has been noted in multiple animal models and is supported by other clinical data [38]. Nevertheless, the exact mechanisms and associations between surgery and tumor growth remain largely unknown and require additional exploration.

The Influence of Anesthesia

Although likely difficult to separate from the impact of surgery itself, the type of anesthetic administered during surgery has also been investigated as having a potential impact on oncologic outcomes. In a retrospective study of 1458 patients who underwent surgical resection (from 2006 to 2009) for gastric, lung, liver, colon, or breast cancer, 5-year OS was compared between those who received total intravenous anesthesia (TIVA) vs volatile inhaled anesthesia (VIA) [39]. Overall, the type of anesthetic did not affect the 5-year survival rate (log rank $p = 0.21$) [39]. However, a systematic review and meta-analysis by Yap et al. including 10 independent studies did demonstrate an association between propofol-TIVA (vs VIA) and improved survival [40]. More specifically, the use of TIVA was associated with an improved recurrence-free survival (pooled HR 0.78, 95% CI 0.65−0.94) and OS (pooled HR 0.76, 95% CI 0.63−0.92) [40].

The Role of Palliation

Aside from the potential survival benefit, some patients may still require surgery for palliation. Primary breast tumors may erode through the overlying skin, causing chronic wounds that may bleed, cause pain, and/or become infected. In a study of 340 patients who developed distant MBC after being treated for early stage disease, 100 patients (29.4%) ultimately required 127 surgical procedures, including 60 of the breast (47.2%), 50 to stabilize osseous structures due to metastases (39.4%), and 6 of other metastatic sites (4.7%; 1 lung, 1 liver, and 4 brain) [41]. Similarly, in a retrospective analysis of 147 women with stage IV breast cancer, only 25 patients (22.5%) underwent surgery after being diagnosed with metastatic disease, although the indications for surgery were not provided. However, both of these studies included patients diagnosed prior to 2006, and systemic therapies have significantly improved since that time [42–44]. As such, the need for palliative breast surgery has likely declined over time and will presumably continue to do so with future advancements in our understanding of and treatment for MBC.

The Patient's Perspective

Although most studies related to surgery and MBC focus on survival, some have also sought to explore the potential impact of surgery on patient reported outcomes. In a recent study by Bjelic-Radisic et al., 90 patients with primary operable MBC were randomized to surgery followed by systemic therapy or to primary systemic therapy alone [45]. Quality of life (QoL) questionnaires were administered at baseline, 6, 12, 18, and 24 months. Overall, no statistically significant differences in any of the scales were noted over time between the two groups [45]. As previously mentioned, patients with de novo MBC enrolled in the prospective study ECOG 2108 reported no significant differences in health-related QoL at most time points [31]. For this study, QoL was assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) Trial Outcome Index (TOI), which includes physical and functional well-being and breast cancer specific symptoms. Notably, a higher score represents a better QoL. Patients in the locoregional and systemic therapy groups had similar scores at registration, randomization, 6 months post-randomization, and 30 months post-randomization, with the only difference observed at 18 months when those who received early local therapy had significantly lower scores ($p = 0.001$; indicating a worse QoL) [31]. Interestingly, a study of 3660 patients with T4M1 disease in a SEER-Medicare database (2005−2011) evaluated the morbidity of local therapy and found that receipt of local therapy was associated with more locoregional morbidity compared to those who did not undergo local therapy [46]. This study suggests that the risks of local therapy may outweigh the potential benefits in patients without pre-existing locoregional morbidity without improvements in cancer outcomes or patient quality of life.

Applying the Data and Looking Forward

If and When to Operate

Some have proposed that patients with limited distant disease may benefit from surgery, as suggested by the prospective study by Soran et al. [29] However, the incidence of oligometastatic disease, typically defined as ≤ 5 deposits, has been difficult to characterize [47]. In a study of > 16,000 patients with de novo MBC in the NCDB, 65.2% presented with a single site of metastatic disease although the exact number of deposits at that site was not specified [16•]. Furthermore, patients with a single site of metastatic disease in this study generally had better survival outcomes [16•]. Others have reported a similar improved survival in patients with oligometastatic disease [48]. As such, several groups have sought to explore the potential benefit of radiotherapy in patients with oligometastatic disease, particularly those with bone only disease, and many suggest a survival benefit [49,50].

Given the complexities associated with surgical decision-making in this population, some have sought to develop clinical tools that may assist with these decisions. In a recent study by Zheng et al., a preoperative nomogram based on data from the SEER database (2010−2015),

incorporating variables that would be available prior to surgery, was developed for predicting long-term survival in MBC patients who did and did not undergo surgical intervention (C-index > 0.70 in both training and validation data sets) [51].

Extent of Surgery

Once the decision has been made to proceed with surgery, there is also debate over how much surgery to perform. Axillary staging and clearance have become controversial even in women with breast cancer undergoing treatment with curative intent; sentinel lymph node biopsy or axillary lymphadenectomy may provide even less benefit to women with known metastatic disease. Although removal of axillary lymph nodes is not generally believed to be of therapeutic value for many women with breast cancer, there is some evidence to suggest that axillary surgery may be associated with an improved survival. In a retrospective study of 152 patients presenting with breast cancer and synchronous metastases between 2005 and 2014, the 5-year OS was 59.8% for women who underwent breast and axillary surgery versus 23.5% for those who underwent breast surgery only and 9.8% for women who did not undergo any surgery [52]. In a larger study of 11,645 patients in SEER with stage IV breast cancer (diagnosed 1990−2010), patients who underwent an axillary lymph node dissection (ALND) had an improved breast cancer specific and OS in multivariate analyses, which was particularly true for those with bone, liver, and single site of distant metastasis [53].

Perhaps inspired by other cancer types (i.e., colorectal, ovarian, renal cell), other investigators have explored the potential benefit of radical resections/treatments not only for the primary breast cancer but also for the distant metastatic site, particularly in those with oligometastatic disease. Using the SEER database, 10,441 patients with stage IV breast cancer (2004−2008) were divided into 4 groups: R0 group (resection of primary site and distant metastatic site), primary site resection group, metastases resection group, and no resection group [54]. In multivariate analyses, the R0 and primary resection groups had the most significant survival benefit (R0 group, HR 0.558, 95% CI 0.471−0.661; primary resection group, HR 0.566, 95% CI 0.557−0.625; vs the no resection group). While the R0 group gained an additional survival benefit in the hormone receptor positive population (vs the primary resection group, 5-year OS 54.1% vs 44.9%, $p < 0.001$), this difference did not persist among those with hormone receptor negative disease ($p = 0.691$) [54].

Role of Radiation

For patients who do undergo surgery for the primary tumor, locoregional radiation may also be considered. In a study of patients with de novo stage IV breast cancer in SEER (2010−2013), radiotherapy was associated with an improved cancer-specific survival, particularly for those who survived > 6 months (vs surgery alone, HR 0.593, 95% CI 0.479−0.733) [55]. Unfortunately, the site of radiotherapy was not specified in SEER (could have been the primary/breast site and/or metastatic site(s)). Regardless, similar work subsequently led to the development of an online nomogram and web-based calculator that predicts survival with and without radiation [56].

For those with oligometastatic breast cancer in particular, radiotherapy may play an important role. In a study of 54 patients with oligometastatic breast cancer (≤ 5 metastatic sites) who received radiotherapy (stereotactic body radiotherapy, SBRT; or fractionated intensity modulated radiotherapy, IMRT), the 2-year local control rate was 97%, while the progression-free survival was 53%, and OS was 95%, suggesting that radical radiotherapy to all metastatic sites may achieve durable progression-free survival [49]. However, a systematic review of 41 studies related to ablative therapies (radiation and/or surgery) did not demonstrate a clear signal for improved outcomes [57]. In contrast, a recently published prospective randomized phase II trial by Palma et al. evaluated the efficacy of stereotactic ablative radiotherapy (SABR) in 99 patients with various cancers, including breast, and it noted an improved OS from 28 months in the control arm (standard of care systemic therapy) to 41 months in the SABR arm (HR 0.57, 95% CI 0.3−1.1, $p = 0.09$) [58]. Ongoing international trials continue to evaluate the benefit of surgery and/or radiotherapy to oligometastatic disease in women with metastatic breast cancer (i.e., BRe-CLIM-2; STEREO-OS; clinicaltrials.gov) .

Genetic and Molecular Considerations

Currently, how biomarker information may impact MBC prognosis is less clear, and factors not entertained in the traditional TNM staging system have been shown to hold prognostic relevance in MBC. For example, bone metastases are the single most frequent site of distant spread [2], present in 70% of patients with metastatic disease [59,60], and the presence of bone-only metastases has been associated with an improved survival [61,62]. Because pathologic evaluation of metastatic disease does not clearly predict future behavior, it is likely that biologic and genetic factors will be increasingly used for prognostication in this context. Furthermore, several studies have shown that the genetic [63,64] and molecular [65,66] changes observed in the primary tumor may differ from those observed at sites of distant metastasis, possibly suggesting that a multimodal approach may be more effective for some than

others. The emergence of next-generation sequencing has highlighted the importance of tumor biology as a critical determinant of MBC prognosis, routinely uncovering vulnerabilities, and resistance mechanisms to systemic therapies that require further investigation.

Conclusions

Although surgery is routinely recommended for patients with non-metastatic breast cancer, the role of surgical resection of the primary tumor for those with metastatic disease remains controversial. Numerous retrospective studies have suggested that some patients may benefit from surgery, while data from prospective studies do not consistently support this recommendation. In addition, the decision to operate is complex, and multiple surgical and non-surgical factors need to be considered. As with most treatment decisions for patients with breast cancer, surgical recommendations for those with metastatic disease should be reviewed by a multidisciplinary team, and patients should be counseled about the potential risks and benefits associated with surgery in order to facilitate shared cancer treatment decisions.

Declarations

Conflict of Interest Jennifer Plichta is an unpaid member of the Metastatic Breast Cancer Subcommittee for the American Joint Committee on Cancer. Mahsa Taskindoust and Rachel Greenup declare that they have no competing interests.

Human Participants, Animal Rights, and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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