Current Breast Cancer Reports (2019) 11:67–73
https://doi.org/10.1007/s12609-019-0309-z

LOCAL-REGIONAL EVALUATION AND THERAPY (DM EUHUS, SECTION EDITOR)

Surgical Therapy for Women with Multiple Synchronous Ipsilateral Breast Cancer (MIBC): Current Evidence to Guide Clinical Practice

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Published online: 1 May 2019

Abstract

Purpose of Review Based on retrospective, historic data, surgeons have long recommended mastectomy as the surgical approach for women with multiple ipsilateral synchronous (multifocal or multi-centric) breast cancer (MIBC). In the modern era, however, local recurrence rates have significantly decreased due to improved imaging techniques and earlier detection through breast cancer screening, more accurate delivery of radiation, and the advent of targeted systemic therapies. Given the significant non-surgical advancements in the field of breast cancer care, the role of maximally invasive surgery in improving breast cancer outcomes has diminished. This raises the question as to whether the routine recommendation for mastectomy in MIBC is rooted in current evidence or archaic data. This review summarizes data regarding surgical options for women with MIBC.

Recent Findings The incidence of MIBC is increasing as a result of improved imaging modalities and the use of breast MRI for breast cancer screening and staging. MIBC tends toward more aggressive biology and higher rates of nodal positivity but recent data contradict the notion that more aggressive surgery improves outcomes. Retrospective studies and meta-analyses performed in the current era of targeted therapy and more sensitive breast cancer detection have demonstrated equivalent rates of local regional recurrence (LRR) in women with MIBC undergoing breast-conserving therapy (BCT) when compared stage to stage with women with unifocal disease. Alliance Z11102, the first national, prospective trial of breast conservation in the MIBC population in the USA, demonstrated the feasibility of BCT in this patient population with acceptable rates of conversion to mastectomy in the MIBC cohort. Prospective data regarding LRR and cosmetic outcomes for women undergoing BCT from completed clinical trials continue to mature, and new randomized clinical trials investigating the biology and treatment of MIBC are under design.

Summary The incidence of MIBC is increasing due to screening mammography, improved quality of imaging, and the utilization of breast MRI for breast cancer screening and staging. Local regional recurrence rates in women with unifocal disease have decreased due to earlier detection and improved regional and systemic therapy. As adjuvant therapy improves, the extent of surgery is less impactful on LRR and long-term survival. Current data demonstrate acceptable LRR in women undergoing BCT for MIBC for whom negative surgical margins are achieved and appropriate adjuvant therapy is administered. While additional prospective data regarding biology, LRR, cosmesis, and long-term survival in women with MIBC continue to be collected, current evidence supports the role of patient choice in deciding between breast conservation and mastectomy in this population.

Keywords Multicentric breast cancer · Multifocal breast cancer · Multiple ipsilateral breast cancer

Introduction

Retrospective studies published in the 1980s and early 1990s reported an increased risk of local regional recurrence (LRR) in women with multi-centric or multifocal breast cancer who underwent breast-conserving therapy (BCT) [1–5]. These trials were performed in an era prior to modern multimodality care including neoadjuvant and adjuvant systemic therapy, routine use of endocrine therapy, the advent of targeted systemic therapies, and more precise radiation techniques.

This article is part of the Topical Collection on *Local-Regional Evaluation and Therapy*

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Additionally, the data were collected in an era of limited analysis of surgical margins. Based on the concern for local recurrence demonstrated in these historic trials, many surgeons continue to recommend mastectomy for women with more than one site of synchronous cancer in the ipsilateral breast.

More recently, mammographic quality has improved and utilization of new imaging techniques including breast MRI has increased. Between 14 and 51% of women diagnosed with breast cancer will undergo breast MRI [6–9]. These more sensitive imaging modalities have led to a significant rise in the pre-operative diagnosis of previously occult MIBC [10, 11, 12•, 13, 14]. Multiple ipsilateral breast cancers are now detected at rates ranging from 13 to 75% [10, 12•, 13–23] although the true incidence is difficult to discern given lack of a standard definition. With this increased detection rate, surgeons are more frequently faced with the dilemma of how to best treat women with MIBC. A perceived contraindication to BCT in this patient population is speculated to be one of the forces driving the national and international increase in mastectomy rates [15].

Retrospective data and meta-analyses from the modern era of breast cancer care demonstrate the feasibility and safety of breast conservation in appropriately selected patients with MIBC resulting in acceptable LRR [2, 24–26, 27•]. This improvement in LRR reflects advances in radiation techniques, targeted systemic therapies, the increasing role of neoadjuvant chemotherapy, and improved pathologic analysis of surgical samples.

Incidence, Diagnosis, and Prognosis

The true incidence of MIBC is unknown. Studies in the 1980s demonstrated incidentally detected MIBC (tumors separated by over 2 cm) in over 40% of breast specimen on pathologic review of mastectomy specimens from patients deemed to be candidates for BCT [28]. Despite the significant number of women with occult MIBC, multiple large, randomized, multicenter trials in the 1980s confirmed equivalent survival and acceptable rates of LRR in women undergoing BCT for presumed unifocal disease in comparison with those undergoing mastectomy. The data from the NSABP B-06 [29], with confirmatory data from similar trials, demonstrated the safety of breast conservation therapy with partial mastectomy and whole breast radiation in achieving acceptable outcomes when compared to mastectomy [30]. Although patients on these studies did not have modern imaging, systemic therapy, or margin analysis, the LRR was acceptable suggesting that adjuvant therapies adequately controlled recurrence in the group with occult MIBC who did not randomize to mastectomy.

Over the last few decades, the incidence of MIBC detected on pre-operative imaging has increased significantly. This increase in diagnosis is related to improved imaging techniques (digital mammography, tomosynthesis, ultrasound, and novel imaging techniques) and increased use of breast MRI which detects previously occult cancer in the ipsilateral breast in nearly 20% of women diagnosed with breast cancer [12•, 31]. The true incidence, however, is elusive as the definitions of MIBC are varying and nonspecific.

The American Joint Committee on Cancer (AJCC) version 8.0 defines two macroscopic cancer foci in the same breast as multiple cancers if they are at least 0.5 cm apart. No distinction is made as to whether these are multifocal breast cancers (foci no more than 5 cm apart in the same quadrant) or multi-centric breast cancers (foci in different quadrants or foci in the same quadrant, but more than 5 cm apart) [32]. Older studies similarly defined multifocal breast cancer as more than one tumor in a single quadrant of the breast while multi-centric disease was defined as more than one tumor in more than one quadrant. With improved understanding of cancer biology, however, these distinctions are considered arbitrary, and more appropriate nomenclature is the all-encompassing term "multiple ipsilateral breast cancer" (MIBC). In most current literature, the moniker MIBC includes more than one tumor in the breast separated by over 2 cm of normal breast tissue.

In addition to variance in definitions obscuring the data regarding numbers of women diagnosed with MIBC, the incidence is difficult to precisely capture as AJCC guidelines continue to stage breast cancer based on the largest single focus of tumor and do not encourage documentation of number of foci of disease [32]. By all objective measures, however, there is an increase in diagnosis of MIBC. This is partly due to the use of preoperative staging MRI [12•, 15–19] and frequent utilization of bilateral whole breast sonography in women with a new breast cancer diagnosis [10, 13, 14]. Other novel imaging modalities such as positive emission mammography (PEM), breast specific gamma imaging (BSGI), and molecular breast imaging (MBI) may continue to increase the detection of MIBC. One recent study revealed 14% of patients enrolled on a PEM/MRI study were converted to mastectomy based on detection of additional abnormalities with this modality [11].

Mastectomy rates in the USA are rising [10, 20, 23]. The impetus for this trend is likely multi-factorial but one causative factor is the increase in MRI and other imaging modality detected MIBC. When identified on preoperative imaging, additional lesions should undergo biopsy prior to surgery in order to avoid unnecessary mastectomies. Once MIBC is diagnosed, surgeons should be cognizant of surgical options for these patients. In the past, mastectomy was the only oncologically accepted option. Current data, however, are evolving and support patient choice regarding possible BCT for MIBC.

Surgical Management of Primary Tumors

Small, retrospective studies from the 1980s and early 1990s documented prohibitively high rates of LRR in women with MIBC undergoing BCT [1–5]. These studies are few in number and do not extrapolate to modern-day patients given the high rates of positive surgical margins in these retrospective cohorts and the limited adjuvant systemic therapies utilized during this time period. For decades, however, mastectomy was the recommended surgical therapy for women with MIBC due to the perceived risk of LRR in patients opting for BCT. Given the significant rise in the pre-operative identification of MIBC, interest in appropriate surgical management of this disease is piqued. Numerous studies have sought to understand the surgical options and outcomes for women with MIBC.

The largest prospective trial to address the feasibility and safety of BCT in women with MIBC is the ALLIANCE Z11102 study. This trial confirmed that BCT in women with MIBC is a feasible option with a low risk of conversion to mastectomy (7%) (due to persistently positive margins or immediate cosmetic issues) and with most women successfully achieving breast conservation with negative margins in a single operation (67.6%) [33••]. Data from this study regarding LRR and long-term cosmetic outcomes continue to mature.

While strong prospective data are lacking, many recent retrospective and registry studies as well as meta-analyses, however, have confirmed equivalency of LRR and/or overall survival (OS) in women with MIBC treated with BCT and indicated adjuvant or neoadjuvant therapy in comparison with those with unifocal disease who also complete recommended adjuvant therapy [24–26, 27•, 34, 35, 36••, 37]. These studies include patients undergoing larger partial mastectomies as well as double lumpectomy through two separate incisions. The largest of these contemporary trials, by Gentilini et al. [25] published in 2008, reviewed 476 patients with MIBC treated between 1997 and 2002, all of whom underwent BCT. The LRR in this trial was 5.1% at 5 years; this was deemed an acceptable LRR in comparison with that expected in women with unifocal disease. In this study, the majority of patients (98.3%) received adjuvant systemic therapy with 12.6% receiving adjuvant chemotherapy only, 40.1% receiving hormonal therapy only, and 45.6% receiving both chemotherapy and endocrine therapy. Adjuvant whole breast radiation was delivered to 95% of patients (Table 1).

When comparing patients undergoing BCT vs. mastectomy for MIBC, many studies confirm the non-inferiority of BCT [24–26, 27•, 29, 30, 33••, 34, 35, 36••, 37–41, 42••, 43]. Nos et al. [38]compared 56 women treated with BCT for MIBC with 132 women who underwent mastectomy for MIBC. In this retrospective study, no differences in OS or LRR were detected. Similarly, Lim et al. [41] studied 478 patients with multifocal/multi-centric (MF/MC) tumors, 147 treated with BCT and 331 with mastectomy. After a mean follow-up of 59 months, they found no difference in OS, disease-free survival (DFS), or LRR (2.0% vs 0.9; $p < 0.378$) between the groups. Kadioglu et al. similarly compared women undergoing mastectomy for multifocal disease with those undergoing BCT. In this study, there was no statistically significant difference in LRR between the group undergoing mastectomy vs the group undergoing BCT. The mastectomy group, however, did exhibit a significantly higher

Table 1 LRR in patients undergoing BCT for MIBC by year of publication

Author	Year of publication	MIBC patients (*n*)	Median F/U (months)	LRR % MIBC	LRR % unifocal	*P* value
Leopold [2]	1989	10	64	40		
Kurtz [3]	1990	61	71	25		
Fowble [5]	1993	57	48	8		
Hartsell [4]	1994	57	48	4		
Wilson [1]	1994	13	71	25		
Nos [38]	1999	56	60	11		
Cho [24]	2002	15	76	0		
Kaplan [39]	2003	36	45	3		
Oh [40**]	2006	97	6	7	10	0.92
Gentilini [25]	2008	476	73	5		
Lim [41]	2009	147	59	2	1.3	0.445
Bauman [26]	2010	22	42	4.5		
Kapoor [34]	2012	7	26	0		
Yerushalmi [36••]	2012	300	95	5.5	4.6	0.77

**Patients in this study underwent neoadjuvant chemotherapy

mean number of tumor foci as well as more extensive lymphovascular invasion [43] (Table 2).

In reviewing women with MIBC undergoing neoadjuvant chemotherapy, Oh et al. [40] studied 706 women treated with mastectomy, mastectomy and adjuvant radiation, or breast conservation for MIBC following neoadjuvant chemotherapy. They concluded that MIBC did not predict for inferior outcome. Ataseven et al. [27•] similarly reviewed the surgical management of women with MIBC treated with neoadjuvant chemotherapy. Patients with operable or locally advanced breast cancer who were enrolled on several neoadjuvant cooperative group trials were evaluated for local recurrence-free survival (LRFS), DFS, and OS. Of the 6134 patients accrued, 22.9% were found to have MIBC. Patients who achieved a margin-negative resection or a pathologic complete response had no statistically significant difference in LRFS when comparing women with unifocal disease to MIBC. In this study, there was no statistically significant difference in LRR between the group undergoing mastectomy vs the group undergoing BCT. The mastectomy group, however, did exhibit a significantly higher mean number of tumor foci as well as more extensive lymphovascular invasion. This demonstrates the potential surgeon bias in retrospective studies, where higher risk patients may have been selected for mastectomy, and the persistent need for prospective, randomized data.

Guided by a growing body of literature supporting the equivalency of BCT or mastectomy for women with MIBC, the 2018 National Comprehensive Cancer Network (NCCN) guidelines [44] allow breast conservation as a surgical option in any woman for whom negative margins can be obtained through a single incision. The 2017 St. Galen International consensus panel more aggressively has de-escalated the role of surgical therapy for early-stage breast cancer in favor of greater local control with radiotherapy as indicated. The panel consensus supports breast conservation for "multifocal" breast cancer, and the majority of the panel advocated breast conservation for "multicentric" disease provided the surgical resection is achieved with clear margins (no tumor at ink) and appropriate radiotherapy can be administered [45••].

Surgical Management of Nodes

Based on data from several randomized trials confirming the accuracy of sentinel lymph node biopsy (SLNB) for patients with a single focus of breast cancer, this procedure has become the standard of care for axillary staging in women with unifocal disease and a clinically negative axilla undergoing either mastectomy or BCT [42••]. MIBC was considered a contraindication to SLNB due to concern for increased false negative results and non-consensus over possible multiple lymphatic drainage pathways to the axilla given disparate tumor locations. In 2001, Chao et al. [46] demonstrated that tumor location did not affect lymphatic drainage. Studies over the past two decades have shown no difference in false negative rates, sensitivity, or accuracy in patients with MIBC undergoing SLNB [46–49, 50•, 51]. In addition, no difference in nodal recurrence has been found among patients undergoing SLNB for MIBC vs. unifocal disease [46]. While patients with MIBC do have higher rates of sentinel nodal positivity, SLNB is indicated for women with MIBC undergoing either BCT or mastectomy with dual mapping from a central location.

Outstanding Questions and Upcoming Trials

The preponderance of data collected in the era of modern multimodality breast cancer care supports the use of BCT in appropriately selected patients with MIBC treated with margin-clearing partial mastectomy and adjuvant radiation. The equivalency of outcomes reflects improvements in non-surgical therapy and a better understanding of breast cancer behavior. Technological advances in radiation delivery as well as the advent of targeted systemic therapies increasingly negate the impact of aggressive surgery. The current data, however, are predominantly extracted from retrospective studies and possibly subject to surgeon bias as higher risk patients may have been selected for mastectomy. More rigorous, prospective level 1 evidence confirming acceptable LRR and OS in women undergoing BCT is necessary to buttress current recommendations for BCT in MIBC.

Additional questions remain regarding MIBC as the clinical behavior is still not fully understood. Several studies have

Table 2 Local recurrence rates in women with MIBC treated with BCT vs mastectomy

Author	Year	BCT (*n*)	Mastectomy (*n*)	Median Follow up (months)	LRR BCT %	LRR Mastectomy %	*P* value
Nos [38]	1999	56	132	60	11	11	
Kaplan [39]	2003	36	19	45	3	0	0.54
Yerushalmi [36••]	2012	300	887	94	5.5	6.5	
Kadioglu [43]	2014	119	103	55	5	5.8	0.06

demonstrated various poor prognostic factors (younger age, increased risk of nodal positivity, higher N stage, lymphovascular invasion, high proliferative activity, absence of estrogen receptors, epidermal growth factor receptor 3 (HER2neu) positivity, and extensive ductal or lobular carcinoma in situ) associated with MIBC although there is conflicting data over whether these poor prognosticators translate into a statistically significant decrement in overall survival in patients treated with guideline-adherent therapy. The majority of these trials demonstrate equivalent OS on multivariate analysis [52, 53••, 54, 55]. Additionally, while many in breast MIBC tumors share morphology and biologic markers, MIBC at times demonstrates heterogeneity across sites of disease that may impact treatment recommendations.

Additional research regarding the treatment and biology of MIBC will continue to inform clinical behavior and treatment options for MIBC. The British Safe Surgery for Multiple Breast Cancers (MIAMI) trial is a planned prospective, randomized feasibility study of BCT vs. mastectomy for MIBC [56]. If successful, a larger, multicenter study is planned to track long-term outcomes of LRR and OS and increase the understanding of MIBC behavior.

Other outstanding areas of concern regarding the safety and feasibility of BCT for MIBC include adequacy of radiation delivery to larger or multiple lumpectomy cavities, the side effects of radiation and long term cosmetic outcomes. These issues are secondary endpoints of the Alliance Z11102 trial. The trial will report how frequently radiation is delivered in accordance with RTOG contouring guidelines and whether radiation boosts are administered when indicated. The long-term side effects of radiation will also be documented.

From a cosmetic perspective, surgeons are increasingly utilizing oncoplastic techniques when performing BCT for unifocal disease or MIBC. To optimize cosmetic outcomes, women with MIBC benefit from oncoplastic reconstruction following BCT. Prior studies have documented acceptable cosmetic outcomes in retrospective studies of women undergoing BCT for MIBC [57, 58]. Additional cosmesis data will accumulate via both the Z11102 and MIAMI trials.

Summary and Recommendations

The incidence of pre-operatively detected MIBC is increasing. Breast cancer recurrence and survival continue to improve as the role of surgery in treating breast cancer de-escalates in favor of increasingly efficacious neoadjuvant and adjuvant local and systemic therapies. Despite clear improvements in breast cancer outcomes (OS and LRR) related to non-surgical therapies, mastectomy rates have increased in the last decade due in part to the diagnosis of MIBC and surgeon perceptions that BCT is contraindicated in this population. While a woman may opt for mastectomy based on her own values or perceptions, the emotional impact of mastectomy on body image and quality of life is well documented [59–61]. BCT is associated with improved patient satisfaction and quality of life and has been shown to be cost effective [62–64]. For these reasons, BCT is the preferred surgical treatment of breast cancer when safe and feasible.

Based on currently available data from the contemporary era of breast cancer care, the surgical management of MIBC warrants shared decision-making between surgeon and the patient to formulate an appropriate surgical plan. For women with MIBC, BCT is a safe oncologic choice if the surgeon can achieve negative margins with an acceptable cosmetic outcome and radiation can be administered in accordance within RTOG contour guidelines. The use of oncoplastic reconstructive technique for larger or dual lumpectomy cavities will improve long-term cosmetic outcome. In women with a clinically negative axilla, sentinel node biopsy is recommended for axillary staging in women with MIBC. If these parameters are met, LRR and OS rates in this population are acceptable independent of surgical approach. Although more prospective data are needed regarding long-term outcomes and biologic behavior of MIBC, surgeons should offer properly selected women with MIBC the option of BCT or mastectomy.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflict of interest.

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

Disclaimer The findings/opinions included in this article are that of Jennifer Tonneson and not of the U.S. Air Force Medical Service.

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