Multifocal and multicentric breast cancer, is it time to think again?

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ABSTRACT

Multifocal multicentric breast cancer has traditionally been considered a contraindication to breast conserving surgery because of concerns regarding locoregional control and risk of disease recurrence. However, the evidence supporting this practice is limited. Increasingly, many breast surgeons are advocating breast conservation in selected cases. This short narrative review summarises current evidence on the role of surgery in multifocal multicentric breast cancer and shows that when technically feasible the option of breast conservation is oncologically safe.

KEYWORDS

Multifocal – Multicentric – breast cancer – Breast conserving surgery – Mastectomy – Oncoplastic surgery

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Introduction

Early randomised controlled trials with 20 years of follow-up comparing the combination of breast conserving surgery and radiotherapy with mastectomy have confirmed non-inferior long-term survival.^{1–6} However, studies excluded tumours measuring greater than 5–4 cm, locally advanced, centrally positioned and multifocal multicentric breast cancer. Since these trials concluded, the practice of breast conservation has evolved, incorporating greater use of oncoplastic techniques. This is facilitated by the increased use of neoadjuvant treatments to downstage the primary tumour, allowing breast conserving surgery when previously mastectomy would have been necessary. This has resulted in a paradigm shift away from mastectomy towards more conservative, but potentially more technically demanding surgery, with specific oncologically tailored operations allowing breast conserving surgery for larger tumours.^{7–10} Oncoplastic techniques are now widely accepted and allow breast conserving surgery for tumours that have a high tumour to breast size ratio. However, it is

important to evaluate the oncological safety of extending these surgical practices to patients with multifocal multicentric breast cancer.

The reported incidence of multifocal multicentric breast cancer varies widely in the literature, with figures of between 6% and 60%. The higher incidence seen recently is due to improved imaging techniques.^{11–14} Many cases treated as and thought to be unifocal are actually multifocal or even multicentric on detailed radiological and pathological assessment. One study showed that, on further sectioning of mastectomy specimens for what was considered to be unifocal disease, only 37% were truly unifocal. Many showed tumours within 2 cm of the main lesion and more than 43% showed further tumours more than 2 cm away from the main lesion.¹⁵

Pathologically, multifocal breast cancer is the result of a single tumour cell clone spreading within the ductal complex and subsequently developing disease independently at various locations. In contrast, multicentric breast cancer requires the independent transformation of two separate cell groups, and is therefore less common than multifocality.¹⁶

There are numerous anatomical definitions of multifocality and multicentricity in the surgical literature. Most frequently, multifocal tumours are described as tumours located within the same quadrant and multicentric tumours as residing in different quadrants. Less commonly, the definition is based on the distance between the tumours, with multifocal tumours located within a 2-cm radius of each other (in most papers), although some papers define this as up to 5 cm, and when tumours lie beyond these distances the disease is considered to be multicentric.¹⁷ In many papers, anatomical definitions can overlap, but the overriding question in considering breast conservation is whether it is technically feasible to safely excise the full extent of multifocal multicentric breast cancer while remodelling the breast in a cosmetically acceptable way? The answer is complex and will depend upon accurate interpretation of imaging and biopsies, together with the availability of oncoplastic technical skills.

Traditionally, multifocal multicentric breast cancer has been associated with an unfavourable survival outcome, thus driving a more aggressive surgical approach. However, two small multifocal or multicentric lesions with good prognoses would be subject to a mastectomy, while currently it is acceptable to conserve a breast with a large area of ductal carcinoma in situ or invasive disease. This contrast poses two questions; is the prognosis of multifocal multicentric breast cancer really worse than unifocal disease and, if so, does the extent surgery affect this?

Prognosis

There has been debate in the literature about the impact of multifocality and multicentricity on prognosis and outcomes. A recent meta-analysis of 22 studies including 67,557 women reported multifocal disease in 9.5% of patients and showed a trend towards worse prognosis for multifocal breast cancer (although without statistical significance on many occasions).¹⁵ Multivariate analysis showed significantly worse overall survival (hazard ratio, HR, 1.65; $P = 0.02$) and a non-significant association with disease-free survival (HR 1.96; $P = 0.07$). However, there

was significant interstudy heterogeneity for both overall and disease-free survival data and, on excluding the studies with significant heterogeneity, the overall survival rate was similar (HR 1.07; $P = 0.31$). Univariate analysis showed poorer disease-free, overall and disease-specific survival rates and locoregional recurrence over 5 years, but the 10-year data reached significance only for disease-specific survival and locoregional recurrence. There was also considerable heterogeneity between the studies, which rendered the conclusions weak.¹⁵

Another important paper by the BRENDA Study Group retrospectively analysed breast cancer data from 17 centres comparing multifocal multicentric breast cancer with unifocal disease. It examined outcomes, mortality and the impact of adhering to treatment guidelines.¹⁴ Of 8935 patients with breast cancer, 15.6% had multifocal breast cancer and a further 5.2% had multicentric disease. The Nottingham prognostic index for multifocal multicentric breast cancer was higher than for unifocal disease, implying a worse prognosis with a significantly higher percentage of node-positive disease, younger patients and higher-grade tumours. However, on correcting for stage and nodal status, the prognosis did not differ between patient groups who had surgery and adjuvant treatment adherent to the guidelines. Additionally, the MINDACT study (Microarray in Node-Negative and 1 to 3 Positive Lymph Node Disease May Avoid Chemotherapy) looked at 3090 patients at clinically low risk, of whom 238 had multifocal disease, and showed that multifocal tumours were more likely to have a higher genomic risk profile compared with unifocal disease. However, the study failed to show any significant association between tumour multifocality and disease-free survival (Table 1).¹⁸

In routine clinical practice, when staging multifocal multicentric breast cancer, irrespective of type of surgery, the parameters of the most aggressive tumour (which is usually the largest tumour) are used to calculate the Nottingham prognostic index or other prognostic tool to aid management decisions.¹⁹ Thus, to a certain extent it is accepted in clinical practice that, stage for stage, multifocal

Table 1 Papers comparing multifocal multicentric breast cancer with unifocal breast cancer (not including the meta-analysis).

Study	Type of breast cancer			Conclusion
	Multifocal multicentric	Multifocal	Multicentric	
Oh <i>et al</i> (2006) ²⁶	97			609 No significant difference in overall or disease-free survival
Lynch <i>et al</i> (2012) ¹¹	1171	924	247	2753 MFMCBC is associated with poorer prognostic factors but not an independent factor for disease-free or overall survival
Wolters <i>et al</i> (2013) ¹⁴	1862	1398	464	7073 No difference in overall or disease-free survival
Alders <i>et al</i> (2013) ¹⁸	238 ^a	–	–	2852 Low-risk patients; multicentric cancer had higher genomic risk profile but no association with disease-free survival

^a No segregation in type of breast cancer

multicentric breast cancer has a similar prognosis to unifocal disease, and yet this is disregarded in the surgical decision making. Is there evidence that more aggressive surgery results in a better prognosis?

The role of surgery

Does surgery change the prognosis in multifocal multicentric breast cancer, and is mastectomy really the oncologically safer option? At the time that breast conserving surgery was developing, early studies in the 1980s and 1990s explored the feasibility of performing breast conserving surgery in multifocal multicentric disease. When compared with mastectomy, some studies observed a significantly higher rate of locoregional recurrence, reaching up to 40% in some patients. It was on this basis that breast conserving surgery was considered unsafe for multifocal multicentric breast cancer; however, breast conservation for unifocal disease was a new technique at that time.^{20–22} Further analysis of the three most widely quoted studies raises questions regarding their results and conclusions, revealing historical surgical practice and pathological assessment that is not comparable with current practice. These studies included low patient numbers. Leopold *et al* had 10 only patients in the multifocal multicentric breast cancer arm of the study,²¹ Wilson *et al* had 13,²² while Kurtz *et al* included 61.²⁰ The adequacy of the excision margins of the tumour was not routinely assessed histologically in the first two studies and only one of the 15 patients who had recurrences in the study from Kurtz *et al* had a clear histological margin on the first excision.^{20–22} It is possible that the high recurrence rate in these studies is more likely due to inadequate surgery in achieving clear excision margins than to multifocal multicentric breast cancer.

The above data dominated clinical practice and thus breast conserving surgery was not offered to patients with multifocal multicentric disease. A turning point was an influential 1999 study, when the team from the Marie Curie Cancer Centre in Paris reported comparable five-year survival and recurrence rates for patients with multifocal multicentric breast cancer treated with either breast conserving surgery or mastectomy.²³ This was a case-control study with 56 patients in the breast conserving surgery arm matched with 132 in the mastectomy arm. It provided more up-to-date evidence on the safety of breast conserving surgery in multifocal multicentric disease, generating support for a more conservative surgical approach. Subsequent studies have also found favourable outcomes of breast conserving surgery (Table 2).^{14,24–27} In 2003, Kaplan *et al* reported a prospective small cohort of 55 patients with multifocal multicentric breast cancer, 36 of whom had breast conserving surgery and 19 mastectomy, with no significant difference in the five-year recurrence rate or overall survival.²⁴ In 2009, Gentilini *et al* followed 476 patients with multifocal multicentric disease treated with breast conserving surgery for a median of 73 months, reporting a 5-year local recurrence rate of 5.1%.²⁵ This study also demonstrated better cosmetic outcomes and lower recurrence rates for breast conserving surgery compared with mastectomy.

Larger studies such as the BRENDA study assessed survival outcomes in multifocal ($n = 1398$) and multicentric ($n = 464$) breast cancer compared with unifocal disease ($n = 7073$) showing no difference in overall and disease-free survival for patients who had breast conserving surgery and mastectomy.¹⁴ Similar results were reported from the MD Anderson Cancer Centre in a cohort of 3924 patients, of whom 924 had multifocal and 247 had multicentric disease.¹¹ Here, the presence of multifocal

Table 2 Papers examining the outcomes of breast conserving surgery in multifocal multicentric breast cancer.

Study	Breast conserving surgery	Mastectomy	Conclusion
Nos <i>et al</i> (1999) ²³	56	132	No significant difference in the recurrence or survival rates
Kaplan <i>et al</i> (2003) ²⁴	36	19	Type of surgery had no impact on 5-year overall or disease-free survival
Oh <i>et al</i> (2006) ²⁶	20	27	No significant difference in disease-free or overall survival
Gentilini <i>et al</i> (2009) ²⁵	476	–	Local recurrence rate of 5.1% at 5 years
Lynch <i>et al</i> (2013) ²⁷	1757 UFBC	1059 UFBF	Breast conserving surgery is a safe option for MFBC
	256 MFBC	417 MFBC	All MCBC had mastectomy in this cohort
Wolters <i>et al</i> (2013) ¹⁴	623 MFBC	319 MFBC	No significant difference in disease-free or overall survival
	60 MCBC	40 MCBC	
Winters <i>et al</i> (2018) ²⁸	3537 MFMBC	–	Breast conserving surgery and mastectomy had similar locoregional recurrence for MFMBC. The conclusion was to support a future randomised trial
MCBC, multicentric breast cancer; MFBC, multifocal breast cancer; MFMBC, multifocal multicentric breast cancer; UFBC, unifocal breast cancer.			

multicentric disease was associated with poor prognostic factors such as advanced disease and locoregional spread, which themselves impact on prognosis and survival. However, multicentricity and multifocality alone were not independent factors for either breast cancer recurrence or survival. The same group also looked at locoregional control in a separate paper where breast conserving surgery was performed on 256 of the 673 patients with multifocal (not multicentric) cancer and concluded that breast conserving surgery is a safe option with patients with multifocal breast cancer.²⁷ This is further supported by yet another study of 706 patients receiving neoadjuvant chemotherapy, where 97 patients with multifocal multicentric breast cancer had no significant differences in recurrence-free or overall survival when compared with unifocal disease, regardless of they had breast conserving surgery or a mastectomy. Importantly, there were no in-breast recurrences in patients with multifocal disease treated with breast conserving surgery.²⁶ A recent meta-analysis including 17 comparative studies and 7 case series totalling 3537 women undergoing breast conserving surgery demonstrated a locoregional recurrence rate of 2–23% following breast conserving surgery in multifocal multicentric breast cancer at a median follow-up of 59.5 months (range 56–81 months) with equivalent rates to mastectomy (risk ratio 0.94, 95% confidence interval 0.65–1.36).²⁸ This meta-analysis concluded that the evidence was lacking for breast conserving surgery in multifocal multicentric breast cancer and suggested the need for a clinical trial.

Further evidence will be generated by the upcoming UK MIAMI trial (multiple ipsilateral breast conserving surgery vs mastectomy) which is randomising patients with multifocal multicentric breast cancer into therapeutic mammoplasty or mastectomy.²⁹ The preliminary ACOSOG Z11102 (Alliance) trial looked at breast conserving surgery in multifocal multicentric breast cancer and preliminary data showed that two-thirds of the patients who underwent breast conserving surgery achieved negative margins at the first operation. Although the remaining third required further surgery, the conversion rate to mastectomy was only 7.1%.³⁰

Additionally, it is also important to address the lack of prospective data on radiotherapy, especially the general lack of reporting of local boost radiotherapy and tumour bed marking in the majority of studies on oncoplastic breast conserving surgery.³¹ In multifocal multicentric breast cancer there is more than one tumour bed and while planning may be more difficult, the main issue will be for patients requiring radiotherapy boost to the tumour bed when there are two beds to boost (ie, separate boosts to each tumour site) increasing the overall dose to the breast with the risk of additional severe fibrosis.³² Phantom studies on positioning and delivery of radiotherapy are included in the MIAMI trial.

Surgical approach

There are three broad surgical approaches to breast conserving surgery in multifocal multicentric breast cancer:

multiple wide local excisions, volume displacement and volume replacement techniques. The first approach is appropriate in patients who are not suitable for or prefer not to have more extensive surgery. This is not the preferred option for many surgeons, as many would prefer en-bloc resection of the tumours in one specimen, if possible, to ascertain sufficient margin clearances. Patients with larger breasts are good candidates for volume displacement techniques. These techniques are a prime example of cross-fertilisation across specialties, initially developed as pure breast reduction techniques that were applied successfully in breast cancer surgery. Their flexibility permits a tumour in any quadrant to be excised using a number of therapeutic mammoplasty techniques and various pedicles.^{7,17} Although this allows multifocal tumours to be excised, it is not always easily applicable to multicentric tumours.

Volume replacement, or partial breast reconstruction, was first pioneered by Noguchi using the latissimus dorsi mini-flap.^{33,34} Adoption of this technique was slow but, importantly, it ushered in the development of chest wall perforator flaps.³⁵ This technique can be based on a choice of perforators from the lateral chest wall or the upper abdomen and has introduced flexibility into the management of disease in patients with smaller breasts. Tumour size becomes less relevant, as the amount of recruited tissue does not depend on breast size. Tumour location may restrict this choice, although parenchymal mobilisation techniques can be incorporated in carefully selected patients. This technique can also be recommended to patients wishing to avoid breast reduction or contralateral surgery.

Conclusion

With the best evidence currently available indicating that multifocal multicentric breast cancer has a similar prognosis to unifocal cancers and equipped with over 30 years' experience in breast conserving surgery in the management of unifocal cancers, there remains valid consideration for a conservative approach in multifocal multicentric breast cancer. In particular, there is no evidence that surgical approach affects prognosis, provided that tumours are completely excised. Current evidence points to breast conservation as being safe for multifocal multicentric breast cancer (when technically feasible and provided that acceptable cosmetic results can be achieved). While some patients may opt for mastectomy over breast conservation, their choice should not be limited by lack of surgical skill and local expertise in oncoplastic breast surgery.

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