

## Surgical Management of Multifocal and Multicentric Breast Cancers: Can We Achieve the Same, with Less?

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The characterization and management of multifocal and multicentric breast cancer is an increasingly important topic as the incidence of diagnosis increases. The true prevalence of multiple ipsilateral breast cancer (MIBC) is unknown due to variations in definitions, detection, and pathologic sampling. The reported rate, in the era of modern imaging, ranges from 13 to 75 %.<sup>1</sup> Improvements in mammographic screening, increasing use of breast ultrasound, and most significantly, the increased utilization of breast MRI for preoperative planning have increased the preoperative detection of additional lesions in many women. This trend toward increased preoperative detection of MIBC is likely contributing to rising mastectomy rates. Based on historic, retrospective studies with small number of patients that suggested an unacceptably high rate of local recurrence in women with MIBC undergoing breast-conservation therapy (BCT), many surgeons continue to recommend mastectomy for these patients.

More recently, several retrospective studies have reported low local relapse rates (LR) following BCT in the MIBC population. One of the largest of these trials, by Gentilini et al., reviewed 476 patients treated with BCT for MIBC between 1997 and 2002.<sup>2</sup> Despite relatively advanced disease in the study population (55 % of all patients were node-positive), the LR rate in this trial was 5.1 % at 5 years. This LR is similar to recurrence rates in the unifocal (UF) breast cancer population. The authors concluded that breast conservation is a reasonable option for women with MIBC. The results from a recent study by Ataseven

et al. further buttress the argument for breast conservation in the MIBC population.<sup>3</sup> This study reviewed the surgical management of women with multifocal (MF) or multicentric (MC) disease 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), disease-free survival (DFS), and overall survival (OS). A total of 6134 patients were accrued of whom 13.4 % were found to have MF cancer and 9.5 % multicentric disease. The trial concluded that in patients with negative margins or a complete pathologic response, there was no statistically significant difference in LRFS when comparing UF to MIBC disease. Of note, this trial also demonstrated a significant decrease in OS in women with MC disease compared with women with UF or MF disease.

The study by Kanurmuri et al. published in this volume of ASO offers a thorough review of publications that have studied the biology and behaviour of MIBC. This trial similarly concludes that MC, *but not MF*, disease represents a distinctly more virulent form of breast cancer that predicts a worsened OS. Women with MC breast cancer were younger with higher rates of nodal positivity and LVI. The study highlights the importance of improved definitions and characterization of MIBC to better prognosticate patient outcomes. MF and MC breast cancers appear to have distinct phenotypes—the understanding of which may lead to more tailored local therapy for these patients. This trial also identifies opportunities for improvement in local and systemic recurrence rates in women with MIBC through utilization of molecular subtyping to assess heterogeneity between separate foci of disease. Based on the data in this study, surgeons can better inform their patients about the overall risk associated with multicentric disease, including worsened recurrence-free survival and breast cancer-specific survival. This descriptive study does

not, however, provide data on LR and does not, therefore, make recommendations for local therapy. Lynch et al. similarly characterized and analysed the behaviour of MIBC compared with UF disease in two publications. Like the Kanurmuri study, Lynch differentiates MC from MF disease. In contrast to the Kanurmuri study, Lynch found that both MF and MC disease are associated with younger age of diagnosis and higher T and N stage. All patients with MC disease in this trial underwent mastectomy; 256 patients were treated for MF disease and 38 % underwent BCT with no significant increase in LR compared with UF disease despite more aggressive tumor biology.<sup>4,5</sup>

The contrast between the prohibitively high historic LR rates and those reported in these more recent trials are explained in several ways. Modern studies benefit from accurate margin analysis, routine prescription of targeted therapies, and the increased use of systemic therapy. The improved sensitivity of multiple imaging modalities has led to earlier detection of smaller tumors with fewer nodal metastases. Earlier detection reduces breast cancer-specific mortality but also benefit patients by improving LR.

Perhaps most significantly, however, the improved LR in women treated with BCT for MIBC reflects the better characterization of these tumors and the resulting understanding of systemic management. Multiple, large trials have illustrated the positive impact of appropriate systemic therapy on local control. More recently, data have demonstrated that molecular profiling can predict local recurrence risk in addition to predicting risk of systemic spread. The improved outcomes in women undergoing BCT for MIBC is likely related to better understanding and personalized treatment based on tumor biology rather than imaging and histology alone.

The surgical management of MIBC remains controversial, although significant evidence from recent trials supports the use of breast conservation in appropriately selected patients. More data are needed. The Alliance Z11102 was designed to evaluate prospectively the feasibility of BCT for MIBC. This single-arm study assessed local recurrence rates and cosmetic satisfaction in women undergoing BCT for MIBC. Results from this trial, which is currently accruing, will enhance our understanding of the surgical options available to these patients. A better understanding of potential heterogeneity between these tumors is needed to improve prognostication and treatment. As our understanding of tumor biology improves and targeted therapies continue to evolve, the need for extensive surgical extirpation will continue to diminish in importance and more women will safely undergo breast conservation if desired.

## REFERENCES

1. Bendifallah S, Werkoff G, Borie-Moutafoff C, et al. Multiple synchronous (multifocal and multicentric) breast cancer: clinical implications. *Surg Oncol.* 2010;19(4):e115–23.
2. Gentilini O, Rotteri E, et al. Conservative surgery in patients with multifocal/multicentric breast cancer. *Breast Cancer Res Treat.* 2009;113(3):577–83.
3. Ataseven B, Lederer B, Biohmer JU, et al. Impact of multifocal or multicentric disease on surgery and locoregional, distant and overall survival in breast cancer patients treated with neoadjuvant chemotherapy. *Ann Surg Oncol.* 2014.
4. Lynch SP, Lei X, Chavez-Macgregor M, et al. Multifocality and multicentricity in breast cancer and survival outcomes. *Ann Oncol.* 2012; 23:3063–9.
5. Lynch S, Lei X, Hsu L et al. Breast cancer multifocality and multicentricity and locoregional recurrence. *Oncologist.* 2013;18: 1167–73.