

## BRIEF CLINICAL UPDATE

# The Role of Surgery in Metastatic Breast Cancer

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The incidence of breast cancer in the United States is approximately 269,000 and about 6% present with synchronous distant metastases at the time of initial diagnosis.<sup>1</sup> Stage IV breast cancer remains incurable, and improved survival in this population is driven by decreasing the progression of distant disease. Despite advances, the standard of care remains focused on systemic therapy to control the growth of metastasis and to palliate symptoms. In the metastatic setting, surgical resection of the breast primary malignancy, outside of preventing chest wall complications, remains controversial. Published guidelines, including the National Comprehensive Cancer Network (NCCN) recommend the judicious use of surgery in stage IV disease as means to prevent tumor morbidities. These complications include skin ulceration, bleeding, infection and pain.<sup>1</sup> Despite these recommendations, studies have shown that surgical resection of the primary tumor occurs in up to 50% of women with metastatic disease.<sup>2</sup>

Over the last fifteen years single-institution observational studies have conflicting conclusions as to the survival benefit of surgical removal of the primary tumor among men and women with stage IV breast cancer. Several large retrospective analyses were performed to better understand the benefits of surgery in stage IV disease.<sup>3</sup>

Some of the most encouraging results were reported in a 2012 study by Khan et al. This retrospective review of data gathered from the National Cancer Data base, included 16,203 patients with stage IV disease between 1990 and 1993. Approximately 57% underwent surgical resection of the breast. The presence of free surgical margins was associated with improved three year survival from 26% to 35% in the partial and total mastectomy groups. In a multivariate model, disease free surgical margins compared to non-surgical treated had a hazard ratio of 0.61 (95% confidence interval [CI] 0.581–0.646), p<0.0001). The improvement in overall survival was independent of the extent of chest wall resection, number and sites of metastatic disease and histologic subtype. This study called into question the historical palliative role of mastectomy in stage IV breast cancer and suggested expansion of the role of surgery in metastatic disease.<sup>4</sup>

A subsequent Cochrane review in 2018 included data from two randomized controlled trials involving a total of 624 women. Three hundred eleven women underwent breast surgery plus medical treatment, and 313 women only received medical treatment. The reviewers were uncertain as to the benefit of

surgery citing the lack of quantifiable data. While there was a trend for improved overall survival, the studies did not measure breast cancer-specific survival. They concluded that breast surgery may improve the control of local disease, but it probably worsened control at distant sites.<sup>5</sup>

Recently, a large retrospective review published the Annals of Surgery included registry data from 24,015 women. Approximately 56% underwent systemic therapy alone and 44% (10,510) underwent surgical resection along with systemic therapy. Those that underwent surgery, whether before or after systemic therapy, had improved adjusted overall survival when compared to systemic therapy alone (Hazard Ratio, 0.68; 95% confidence interval, 0.62–0.73; Hazard Ratio, 0.56; 95% confidence interval, 0.52–0.61; P < 0.001).<sup>6</sup>

Critics have questioned the quality of these trials citing significant bias. There is the possibility that healthier stage IV patients are offered surgery, while patients with poor projected survival are not, leading to a selection bias. In addition, surgery may be a surrogate for more aggressive multimodal therapy, suggesting a possibility of a treatment facility bias. Retrospective series have therefore been viewed as hypothesis-generating at best, and the call for prospective multi-center clinical trials has increased.<sup>7</sup>

To address discrepancies noted in the literature, the Eastern Cooperative Oncology Group opened a new phase III multi-center, prospective, randomized trial (ECOG 2108) to evaluate the role of resection of the primary tumor when added to standard systemic therapy in patients with stage IV breast cancer. Results from this trial are expected in June 2025.

Until prospective data is available, surgery in stage IV breast cancer remains controversial. There is consensus that every patient's case needs to be evaluated on an individual basis and a multi-disciplinary approach is paramount.

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