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EDITORIAL – BREAST ONCOLOGY

Restaging Patients With Locoregional Relapse: Is There Any Benefit?

Commentary on "Radiological Staging for Distant Metastases in Breast Cancer Patients with Confirmed Local and/or Locoregional Recurrence: How Useful are Current Guideline Recommendations?" by Elfgen, Constanze et al.

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The recent *Annals of Surgical Oncology* article entitled "Radiological Staging for Distant Metastases in Breast Cancer Patients with Confirmed Local and/or Locoregional Recurrence: How Useful are Current Guideline Recommendations?"[1] poses the important and practical question of whether it is necessary to restage breast cancer patients for possible synchronous distant metastasis at the time of the first locoregional relapse, and what possible implications this may have for local and systemic patient management.

The most important finding of this study was that one-third of breast cancer patients with locoregional recurrences have distant metastasis at restaging with positron emission tomography (PET) and/or computed tomography (CT) scans. Even patients at low risk for metastasis at their first diagnosis were found to have a 20–25% risk of distant metastasis at the time of locoregional relapse, supporting the postulated role of local relapses as independent prognostic factors for distant disease.[2]

The authors disclosed a limitation of their study when they described it as retrospective. However, the data from the study were extracted from a prospectively maintained modern database with detailed biology and staging of cancers, making the overall analysis more robust.

No clear guidelines currently exist regarding how to assess patients with locoregional recurrences. The current National Comprehensive Cancer Network (NCCN) guidelines recommend staging all patients with locoregional relapses, even if the recommendations are based on a low level of evidence consisting primarily of data from the National Cancer Database showing a 27% risk of distant metastases in patients with locoregional relapses.[3] The NCCN recommendations were stronger for patients with lymph node metastasis or chest wall relapses after mastectomy, whose risk of distant metastasis is higher.

The current study had a relatively high number of locoregional relapses after conservation (35%), and the risk of distant metastasis after breast-conservation surgery was lower (23% vs. 48% after mastectomy) but still consistent with the finding that the guidelines for restaging patients with locoregional relapses should be extended to all breast cancer patients. This raises a question: When can patients benefit from a diagnosis of synchronous distant metastasis, thus justifying the restaging tests? The most obvious answer is that patients benefit when the diagnosis avoids unnecessary surgery for stage 4 breast cancer, indicating surgical and systemic treatments that are merely palliative.

Surgical management for the local recurrence of breast cancer can often be complex, especially in the reconstruction phase of a pre-irradiated breast. The complication rate has been shown to increase 29.7% with implant reconstructions.[4] The high complication rate for the implant base reconstruction procedure predisposes these patients for more complex reconstruction with free or pedunculated flaps, together with the possible morbidity, high cost, and unproven benefits of this procedure.[5] In

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some patients, avoiding surgery is of significant importance, especially in cases involving local relapses after conservation surgery and radiation, in which patients are candidates for mastectomy and complex reconstructions.

The possible benefit of a surgical procedure for stage 4 restaging-detected patients may be extrapolated from a similar population of patients with de novo stage 4 breast cancer, for whom the debate regarding the role of surgery still is open. Since the first publication of retrospective data[6–9] in large databases showing the benefit of surgery performed with curative intent in terms of both overall and disease-free survival, randomized clinical trials have been reporting controversial results.

A recently published article reports that the prospective phase 3 Austrian Breast and Colorectal Cancer Study Group (ABCSG)-28 POSYTIVE (*Primary Operation in Synchronous Metastasized Invasive Breast Cancer*) trial could not demonstrate an overall survival benefit from surgical resection of the primary tumor for breast cancer patients presenting with de novo stage 4 disease. However, this trial was ended early because of poor accrual of patients, raising questions regarding the power of its statistical analysis.[10]

One notable recent study of surgery for de novo stage 4 breast cancer is the MF07-01 trial sponsored by the Turkish Federation of the National Societies for Breast Disease.[11] In this study, the last statistical analysis in a median follow-up period of 40 months showed results that differed from those of the previous 36-month follow-up period, in which no difference in survival was noted between the surgery and no-surgery groups. The longer follow-up period showed a significant improvement in median overall survival of about 9 months. The 5-year overall survival rate was 42% with surgery versus 25% with systemic therapy alone. The greatest benefit was observed for patients with estrogen receptor (ER) positive/human epidermal growth factor receptor 2 (HER2) negative disease, patients with solitary bone metastases, and patients younger than 55 years of age. Patients with multiple liver and/or pulmonary metastases had a significantly worse prognosis with initial surgery.[12] Other similar trials are in progress internationally, and may contribute to a better understanding of this controversial issue and how to best select patients for whom surgery may give the most benefit.

We are aware that the population with local relapses and synchronous distant metastases differs markedly from the population with systematically untreated de novo stage 4 breast cancer, in which systemic treatments may have a much greater effect for patients already exposed to adjuvant treatments at the first diagnosis. If it is difficult to compare the two populations in terms of overall survival, some attempt may be made in the setting of palliative surgery to avoid chest wall disease or bulky axillary disease with plexopathy, which adversely affect patient quality of life.

In the Turkish randomized study by Soran et al.[11] that investigated a group of patients randomized for no surgery, the local progression and need for palliative surgery was higher and statistically significant, with 18% of patients in the no-surgery group requiring palliation surgery. This study did not clarify how many patients lost their window of opportunity for surgery because they developed unresectable chest wall or axillary lymph node disease. We may speculate that in the local relapse group and the distant metastasis group, the potential need for palliative surgery may be higher due to the resistance of the disease to previous treatments, but this consideration also may apply to the concomitant distant metastasis, making the prognosis for the patient severe, with a shorter overall survival.

Another important consideration in this setting is the possible benefit of restaging in the migration of the stage to stage 4 from the viewpoint of systemic treatment. The CALOR study[12] did not show any benefit from using chemotherapy to treat patients with locoregional ER and progesterone receptor (PR) positive relapses. In this context, knowing that the patient with a local ER positive local relapse has a distant metastasis would not change the intent-to-cure systemic approach with the intent to palliate using hormonal therapy alone. We then can speculate that staging patients for local relapse may not alter the systemic treatment decision in all cancer subgroups.

A number of published articles suggest a possible overall survival benefit from earlier detection of asymptomatic distant metastases. Aggressive multimodality treatments such as chemotherapy, hormonal therapy, surgery, and radiosurgery for local and distant metastasis may provide an overall survival benefit for patients.[13] Unfortunately, however, these findings have a low level of evidence.

In 2010 a fascinating theory on “cancer cell self-seeding” was presented. A basic concept of metastasis is that cancer cells leaving the primary tumor can seed metastases in distant organs. But can this unidirectional process also be bidirectional? An elegant animal model study was able to show that circulating tumor cells can also colonize their tumors of origin in a process that the authors called “tumor self-seeding.” The self-seeding of breast cancer, colon cancer, and melanoma tumors in mice was preferentially mediated by aggressive circulating cancer cells, including those with bone-, lung-, or brain-metastatic tropism.[14] Academically, we cannot exclude the possibility that this also occurred in some de novo stage 4 breast cancer patients. In this situation, the cell clones of the local recurrence should be the same as those of distant

metastases, making them sensitive or resistant to second-line systemic therapy and similar in terms of progression and response.

In summary, this article by Elfgen et al.[1] provides evidence that restaging patients with locoregional relapses can show distant metastases in 25% of patients, with the main benefit of avoiding unnecessary surgery and, in some instances, complex surgery if reconstruction is involved. An earlier diagnosis of distant metastasis may not have any role in modifying the survival of patients, with minimal impact on the systemic treatment indicated. We cannot exclude a possible role for palliative surgery in improving patient quality of life, but this is a consideration that should be evaluated in the setting of personalized case management.

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REFERENCES

1. Elfgen C, Schmid SM, Tausch CJ, et al. Radiological staging for distant metastases in breast cancer patients with confirmed local and/or locoregional recurrence: how useful are current guideline recommendations? *Ann Surg Oncol.* 2019. https://doi.org/10.1245/s10434-019-07629-9.
2. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet.* 1991;338:327–31.
3. Neuman HB, Schumacher JR, Francescatti AB, et al. Risk of synchronous distant recurrence at time of locoregional recurrence in patients with stage II and III breast cancer (AFT-01). *J Clin Oncol.* 2018;36:975–80.
4. Cordeiro PG, Snell L, Heerdt A, McCarthy C. Immediate tissue expander/implast breast reconstruction after salvage mastectomy for cancer recurrence following lumpectomy/irradiation. *Plast Reconstr Surg.* 2012;129:341–50.
5. Holoyda KA, Simpson AM, Ye X, Agarwal JP, Kwok AC. Immediate bilateral breast reconstruction using abdominally based flaps: an analysis of the nationwide inpatient sample database. *J Reconstr Microsurg.* 2019;130:1125–34
6. Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. *Ann Surg Oncol.* 2006;13:776–82.
7. Cady B, Nathan NR, Michaelson JS, Golshan M, Smith BL. Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. *Ann Surg Oncol.* 2008;15:3384–95.
8. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? *Surgery.* 2002;132:620–6 (discussion 626–7.)
9. Rapiti E, Verkooijen HM, Vlastos G, et al. Complete excision of primary breast tumor improves survival of patients with metastatic breast cancer at diagnosis. *J Clin Oncol.* 20 2006;24:2743–9.
10. Fitzal F, Bjelic-Radisic V, Knauer M, et al. Impact of breast surgery in primary metastasized breast cancer: outcomes of the prospective randomized phase III ABCSG-28 POSYTIVE trial. *Ann Surg.* 2019;269:1163–9.
11. Soran A, Ozmen V, Ozbas S, et al. Randomized trial comparing resection of primary tumor with no surgery in stage IV breast cancer at presentation: protocol MF07-01. *Ann Surg Oncol.* 2018;25:3141–9.
12. Wapnir IL, Price KN, Anderson SJ, et al. Efficacy of chemotherapy for ER-negative and ER-positive isolated locoregional recurrence of breast cancer: final analysis of the CALOR trial. *J Clin Oncol.* 2018;36:1073–9.
13. Holmes FA, Buzdar AU, Kau SW, et al. Combined-modality approach for patients with isolated recurrences of breast cancer (IV-NED): the M.D. Anderson experience. *Breast Dis.* 1994;7:7–20.
14. Kim MY, Oskarsson T, Acharyya S, et al. Tumor self-seeding by circulating cancer cells. *Cell.* 2009;139:1315–26.