Should Surgery Referral be Standard Practice in Metastatic Inflammatory Breast Cancer?

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There is no doubt that the level of evidence desired to define practice in any disease is high and that the limitations of retrospective studies place them appropriately in the category of hypothesis generation. Randomized studies may be an unrealistic bar, however, in some uncommon diseases where patient numbers or national infrastructure are inadequate to facilitate randomized, controlled trials. Such is likely in the case of inflammatory breast cancer (IBC), although increasing development of dedicated IBC specialized centers may ultimately increase future feasibility of randomized trials.

In this issue, Warren et al. (2015) have examined the case for locoregional therapy in the setting of metastatic IBC as well as documenting local recurrence rates in the postmastectomy setting. Setting aside the controversial question of whether local therapy influences survival in the setting of metastatic breast cancer, there remains a compelling argument, unique to IBC, for local therapy in the metastatic setting. That argument is that there is a propensity for high rates of morbid local regional disease progression in patients treated with systemic therapy alone, which could be prevented or reduced with local therapy.

In the nonmetastatic IBC setting, there are not many studies of patients who do not receive postmastectomy radiation, from which to determine the locoregional recurrence rates (LRR) in the absence of radiation therapy. The Early Breast Cancer Trialists' Collaborative Group examining numerous studies of radiation versus no radiation concluded that in general, radiation reduced the risk

of LRR by approximately two-thirds.¹ Therefore, one could estimate the LRR expected without postmastectomy radiation by multiplying the LRR after trimodality therapy by three. One might then speculate the expected rate of local progression or recurrence after response in metastatic IBC patients without surgery would be higher than this and that the rate of LRR after mastectomy in the metastatic setting would be similar. Warren et al. reviewed the LRR for nonmetastatic patients treated with standard trimodality therapy and report a 3-year cumulative LRR of 21 %. A weighted average of 5-year LRR from published series, including 613 patients similarly treated with trimodality therapy (summarized in,²) yields a 5-year LRR of 20 %. Tripling this rate, one might expect LRR after surgery in the absence of radiation to be 60 % at 3–5 years and the rate of progression without surgery to be higher than this. In this ballpark, among the 54 IBC patients with metastatic disease in the Warren study, the crude LRR/progressive recurrence rate among women who did not receive local therapy was 57 %. These patients had a median 2-year follow-up after local therapy and the 1-year cumulative LRR was 17.6 % with local therapy and 48.3 % without local therapy. Convincingly, this high rate of locoregional recurrence or progression without local therapy is a clinical problem that could merit preventive therapy in some cases. The authors find that the presence of an involved nonlocoregional lymph node was the only significant independent predictor of local recurrence or progression prompting the further question of the potential role to include these in the radiation targeting when it can be done safely and the decision to deliver postmastectomy radiation has been made.

These new data are consistent with a previous study of local therapy in metastatic IBC patients. In a similar analysis of 172 patients with metastatic IBC, Akay et al. reported that local control was significantly higher at last

follow-up in patients who received surgery compared with those treated with systemic therapy alone (81 vs. 18 %; $p < 0.0001$).³ In this study, the follow-up after local therapy was 40 months and after systemic therapy alone 22 months. They reported that both surgery and response to chemotherapy were independently predictive of local control on multivariate analysis. Response to chemotherapy was not examined in the metastatic cohort in the work by Warren et al., but an obvious question is whether these analyses can overcome the bias of referring more patients who respond to chemotherapy for surgery and if good response negates the value of local therapy for local control. Interestingly Akay et al. note that surgery with radiation, but not surgery alone, is significantly associated with increased local control, potentially implying biases related to the decision to have surgery may not completely drive these results.³ Together, these studies are compelling evidence that uncontrolled local disease is a common reality for IBC patients with metastatic IBC and a strong case for considering local therapy for these patients.

But what would the Devil's advocate say? Akay et al. report that the local progression was only considered moderate to severe in 36 % of cases treated without surgery compared with 18 % treated with surgery.³ While the improvement in local control is large and statistically significant, if one offered surgery to all of those who did not receive it in the Akay study, possibly 64 % would never have had more than no or minimal local disease. Considering this, some might say that surgery would not have been worth the potential morbidity. To date, no published studies have examined how significant the impact of minimal local IBC is to patients weighed against the risks of mastectomy. For perspective, most practicing radiation oncologists would offer postmastectomy radiation to a woman with an absolute benefit in the reduction of local failure of 18 %, much less an absolute risk of moderate or severe local failure of 18 %. Weighing the role of the competing risk of death against the benefit of this reduction is the critical challenge.

So, what is the best practice given the state of the science and the unanswered questions for which additional study are needed? Speaking with the authors, the practice in their dedicated IBC clinic as well as in this author's dedicated IBC clinic is to refer potentially operable metastatic IBC patients to surgical oncology for consultation and consideration of surgery to reduce local progression in the breast or chest wall. Clearly, this is a medical decision to be made based on individual factors and with clear upfront communication of expectations and limitations of the data guiding this practice. Factors that predict for short overall survival certainly decrease enthusiasm for encouraging the risks and morbidity of surgery and radiation. So, certainly response to therapy and availability of alternative systemic therapies are important

considerations. It implies considering surgery even in those who do not currently have symptoms locally that would be palliated by surgery. Based in part on the data by Akay regarding the importance of surgery and radiation, at this time in our practice we offer postmastectomy radiation to all who have surgery and target any metastatic disease that can be treated without significantly adding to the morbidity, especially in oligometastatic patients. Most commonly, we use the same regimen decision tree we employ in nonmetastatic disease, recognizing the local control rates in the nonmetastatic setting using definitive dose still do not reach the level expected in non-IBC.⁴ The possibility of radiation alone as a less morbid, noninvasive intermediate approach to prevention of local progression deserves further study. Quality of life studies would be a critical aspect of any future studies in this area.

A final consideration on the work by Warren et al. is the missed opportunity to add data to the conversation regarding the optimal radiation dose and regimen in this disease. Broad examination of the radiation dose and techniques used in prior studies of postmastectomy radiation in the nonmetastatic setting suggests that more aggressive postmastectomy regimens may yield better control.² While the radiation therapy practice at the primary center from this institution is uniform, the authors note that regimens used in the regional centers could vary (personal communication). This makes this a good cohort to examine the question of dose and technique in future work and further refine the role of local therapy in this locally aggressive disease.

ACKNOWLEDGMENT The authors thank Gildy Babiera and Naoto Ueno from the MD Anderson Morgan Welch IBC Clinic and Beth Overmoyer and Jennifer Bellon of the Dana-Farber dedicated IBC clinic for helpful electronic conversations in considering the perspective herein. Funding for the author includes The State of Texas Grant for Rare and Aggressive Breast Cancer; National Institute of Health R01CA138239-01 and 1R01CA180061-01, and The IBC Network.

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