Limiting Axillary Surgery for Patients with Initial Biopsy-Proven Axillary Metastases After Preoperative Chemotherapy: To Clip or Not to Clip?

Henry M. Kuerer, MD, PhD, FACS and Kelly K. Hunt, MD

Division of Surgery, Department of Breast Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Much has been learned about the biology of breast cancer; key among the advances has been our understanding regarding the importance of molecular subtype and the relationship to patient prognosis and prediction of response to therapy. At the same time, our armamentarium of new and improved agents has increased the response rates. This has allowed us to offer less extensive breast and nodal surgery following preoperative systemic therapy. Trials are even underway to test the hypothesis that surgery in the breast and nodal regions might be eliminated safely among exceptional responders.¹

Beginning in the 1970s, preoperative therapies were initially utilized for patients with inoperable breast cancer. When significant clinical responses were realized, they were extended to patients with earlier stages.^{2,3} Some patients even had dramatic responses such that the pathologist was no longer able to find any residual tumor in the surgical specimens. It became clear that pathologic complete response (pCR) was an endpoint that could be achieved after only a few months of systemic therapy, and this was associated with improvements in overall and disease-free survival. Now, the pCR endpoint is being utilized by the Food and Drug Administration as a pathway for early expedited drug approval of promising new agents.^{2,3} For the surgeon, the use of preoperative systemic therapy led to increased use of breast-conserving therapy and the possibility of less axillary surgery, even among initially documented node-positive breast cancer patients.

Conversion from node-positive to pathologically node-negative has been reported in approximately 40 % of cases and as high as 74 % in patients receiving HER2-targeted preoperative therapy.^{4,5}

Armed with this information on response rates to systemic therapy and the radical success of lymphatic mapping with sentinel lymph node biopsy among patients with early-stage clinically node-negative disease, our group and others embarked on testing sentinel lymph node biopsy after systemic therapy in patients with initial biopsy-proven axillary nodal metastases.^{5–7} The initial retrospective and prospective studies demonstrated that the false-negative rates with sentinel lymph node biopsy were as high as 25 % among patients with documented nodal metastases treated with preoperative systemic therapy compared with patients receiving surgery first.^{8–11} With the hypothesis that we could reduce false negative rates, our group developed a procedure to ensure that the accuracy of nodal staging among patients with initial documented nodal metastases was improved. This involved placing a marker clip in the biopsy proven node at diagnosis, similar to the practice of placing a clip in the primary breast tumor. We found that false-negative rates were markedly decreased when the clipped node was targeted for removal along with the sentinel nodes and that this axillary staging procedure was an accurate reflection of the remaining lymph nodes.^{12,13} The concept intuitively makes sense, because the lymph node most important to assess after systemic therapy would be the actual lymph node that had metastatic carcinoma prior to therapy. The new technique, called targeted axillary dissection (TAD), in which a radioactive seed is placed within the clipped node following preoperative chemotherapy and removed along with any other sentinel lymph nodes, reduced the false-negative rates to

approximately 2 % in the MD Anderson Cancer Center clinical trial recently published by Caudle et al.¹⁴

With TAD, we found that the clipped node is not retrieved as a sentinel lymph node in approximately 25 % of patients. This may be the fundamental reason why lymphatic mapping with sentinel lymph node biopsy among node-positive breast cancer patients after preoperative chemotherapy has higher false-negative rates as the lymph node with the initial documented metastases will not be retrieved as a sentinel lymph node almost 25 % of the time. This may be due to lymphatic vessels being blocked by debris associated with tumor and/or immune surveillance removal, although this is only a hypothesis and has not been definitively demonstrated in patients. Our group has shown that ensuring removal of the clipped lymph node appears to improve the accuracy of axillary staging when combined with sentinel lymphadenectomy, because approximately 25 % of the time, the clipped node with documented carcinoma is not retrieved as a standard sentinel lymph node.¹⁴ Other groups have published their experience with this technique and alternative methods to ensure removal of the actual lymph node that had documented metastasis prior to therapy.^{13,15–17} This practice appears to have been adopted broadly as 87 % of participants during a 2016 American Society of Breast Surgeons plenary session responded that lymphatic mapping and sentinel node biopsy with localization of the clipped node is the preferred method for staging the axilla in patients with documented nodal metastases prior to systemic therapy. The practice of placing a metallic marker at the time of initial biopsy has facilitated our routine practice for identification and successful removal of image-detected breast cancers. The marking of known metastatic disease in the axilla to ensure identification and removal is an extension of this routine practice for management of the breast.

The mechanism by which systemic therapy eliminates very large tumors and metastases is complex. Depending on the type of agent utilized, the patient's immune response, and the timing of imaging and pathologic evaluation, sometimes there is a complete radiologic response and pathologic complete response. Our group published in 2010 that histologic changes, or evidence of prior metastases, were noted in approximately 50 % of cases among patients with documented initial metastases before preoperative chemotherapy who underwent sentinel lymph node biopsy with complete axillary dissection. This suggested that looking for such evidence of a histologic response could help to ensure accurate removal of the initial biopsy proven disease after preoperative chemotherapy but could not be a reliable method for axillary staging (or for assessment of the breast).¹⁸ This practice would be similar to excising breast tissue without targeting the initial clip placed at the time of biopsy and looking for a response to

assess the adequacy of resection for breast conserving surgery following preoperative chemotherapy. Our group has shown that placement of a clip to mark the initial site of cancer in the breast in patients who were receiving neoadjuvant chemotherapy and breast-conservation therapy was associated with better local control independent of stage and other clinicopathologic findings.¹⁹

In this issue of *Annals of Surgical Oncology*, Bario et al. looked at histologic nodal changes in a cohort of 204 patients who presented with biopsy-proven, node-positive disease and who had a nodal pCR following preoperative chemotherapy.²⁰ Among the patients who had a complete axillary lymph node dissection in their retrospective review, treatment effects consisting of fibrosis, histiocytes infiltrate, hemosiderin laden macrophages, increase vascularity, and thickened lymph node capsule was identified in 97 % of cases and 88 % of cases ($n = 69$) where only a sentinel lymph node biopsy was performed. Utilizing this data, they suggest that if histologic changes are seen in a sentinel lymph node and if greater than or equal to three sentinel lymph nodes are identified and removed without evidence of metastases that this may be sufficient evidence that there will be a small chance that there are additional lymph nodes with metastases. This conclusion is likely true based on multiple retrospective and prospective studies but cannot be assumed from the data presented as they did not perform a completion dissection among cases with a negative sentinel lymph node. The authors appear to be comfortable with performing sentinel lymph node biopsy in patients with node-positive disease after preoperative chemotherapy and not moving forward with the completion axillary dissection whether or not they identify histologic treatment effects in the nodes as they state “due to other factors which may influence the identification of treatment effect in node-positive patients after neoadjuvant chemotherapy, the absence of treatment effect in the sentinel nodes is not currently an indication for axillary lymph node dissection at our institution.” These authors do not support clipping of lymph nodes with documented metastases with ensuring removal of the lymph node with the clip that was identified to have carcinoma to better gauge whether a patient needs a completion dissection but do advocate completion dissection when less than three lymph nodes are removed as a sentinel lymph node. Finding three sentinel lymph nodes often is not possible, and data from prospective trials showed that this will not occur in 43–66 % of patients.^{9,11} The concept of removing “palpable” nodes to ensure more lymph nodes removed is difficult to standardize as part of a surgical approach. We believe that documentation that the clipped node is removed obviates the need for multiple sentinel and palpable lymph nodes as the false-negative rates in this scenario are extremely low in our group's experience.

In the final analysis, the ultimate issue is that we are beginning to spare many patients from the morbidity of complete axillary lymph node dissection even in the setting of documented nodal metastases prior to receiving neoadjuvant chemotherapy. This undoubtedly will decrease morbidity and improve the quality of life of our patients. The final key question is the safety of this approach with respect to local regional control and survival. As more surgical oncologists limit axillary surgery in patients with initial node positive breast cancer after preoperative chemotherapy, it is up to us to report the outcome of these various methods. Towards this end, investigators at the European Institute of Oncology in Milan Italy recently reported that sentinel lymph node biopsy alone among 147 initially clinically node-positive breast cancer patients who converted to clinically node-negative after preoperative chemotherapy had a 5-year axillary recurrence rate of only 0.7%.²¹ Key among our deliberations and discussions within our own multidisciplinary teams is the role and impact of radiotherapy use or nonuse in the residual undissected axilla in patients where only sentinel lymph node biopsy is performed. National cooperative group trials in the United States are underway and must be supported as they are designed to investigate the role of radiotherapy and surgical management among patients with initial biopsy-proven disease and in both patients with (Alliance trial A11202) and without residual nodal disease (NSABP-51/RTOG 1304 trial) following preoperative chemotherapy.¹⁰

DISCLOSURE None of the authors has any commercial interest or conflict to disclose related to the present work.

REFERENCES

- van la Parra RF, Kuerer HM. Selective elimination of breast cancer surgery in exceptional responders: historical perspective and current trials. *Breast Cancer Res.* 2016;18:28.
- Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol.* 1998;16:2672–85.
- Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol.* 1999;17:460–9.
- Dominici LS, Negron Gonzalez VM, Buzdar AU, et al. Cytologically proven axillary lymph node metastases are eradicated in patients receiving preoperative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. *Cancer.* 2010;116:2884–9.
- Kuerer HM, Sahin AA, Hunt KK, et al. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. *Ann Surg.* 1999;230:72–8.
- Shen J, Gilcrease MZ, Babiera GV, et al. Feasibility and accuracy of sentinel lymph node biopsy after preoperative chemotherapy in breast cancer patients with documented axillary metastases. *Cancer.* 2007;109:1255–63.
- Alvarado R, Yi M, Le-Petross H, et al. The role for sentinel lymph node dissection after neoadjuvant chemotherapy in patients who present with node-positive breast cancer. *Ann Surg Oncol.* 2012;19:3177–84.
- Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. *J Clin Oncol.* 2015;33:258–64.
- Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA.* 2013;310:1455–61.
- Caudle AS, Kuerer HM. Targeting and limiting surgery for patients with node-positive breast cancer. *BMC Med.* 2015;13:149.
- Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. *Lancet Oncol.* 2013;14:609–18.
- Caudle AS, Yang WT, Mittendorf EA, et al. Selective surgical localization of axillary lymph nodes containing metastases in patients with breast cancer: a prospective feasibility trial. *JAMA Surg.* 2015;150:137–43.
- Donker M, Straver ME, Wesseling J, et al. Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. *Ann Surg.* 2015;261:378–82.
- Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. *J Clin Oncol.* 2016;34:1072–8.
- Choy N, Lipson J, Porter C, et al. Initial results with preoperative tattooing of biopsied axillary lymph nodes and correlation to sentinel lymph nodes in breast cancer patients. *Ann Surg Oncol.* 2015;22:377–82.
- Plecha D, Bai S, Patterson H, et al. Improving the accuracy of axillary lymph node surgery in breast cancer with ultrasound-guided wire localization of biopsy proven metastatic lymph nodes. *Ann Surg Oncol.* 2015;22:4241–6.
- Diego EJ, McAuliffe PF, Soran A, et al. Axillary staging after neoadjuvant chemotherapy for breast cancer: a pilot study combining sentinel lymph node biopsy with radioactive seed localization of pre-treatment positive axillary lymph nodes. *Ann Surg Oncol.* 2016;23:1549–53.
- Brown AS, Hunt KK, Shen J, et al. Histologic changes associated with false-negative sentinel lymph nodes after preoperative chemotherapy in patients with confirmed lymph node-positive breast cancer before treatment. *Cancer.* 2010;116:2878–83.
- Oh JL, Nguyen G, Whitman GJ, et al. Placement of radiopaque clips for tumor localization in patients undergoing neoadjuvant chemotherapy and breast conservation therapy. *Cancer.* 2007;110:2420–7.
- Barrio AV, Mamtani A, Edelweiss M, Eaton A, Stempel M, Murray MP, Morrow M. How often is treatment effect identified in axillary nodes with a pathologic complete response after neoadjuvant chemotherapy? *Ann Surg Oncol.* 2016. doi:10.1245/s10434-016-5463-1.
- Galimberti V, Ribeiro Fontana SK, Maisonneuve P, et al. Sentinel node biopsy after neoadjuvant treatment in breast cancer: five-year follow-up of patients with clinically node-negative or node-positive disease before treatment. *Eur J Surg Oncol.* 2016;42:361–8.