

surgery'? Clinicians can combine two approaches for a better patients' selection for 'No axillary surgery':

1. By using nomograms predicting the risk of metastatic SLN in order to identify low risk patients. The main nomograms calculating the risk of metastatic SLN integrate the following variables: age of the patients, tumor size, lymphovascular invasion and biological subtypes with three main categories of BC (luminal-like, basal-like, HER2-like). Thresholds have to be determined in order to classify patients as low, intermediate and high risk of metastatic SLN.
2. By using ultrasound-guided needle biopsy of axillary nodes (UNB). Studies have shown that preoperative UNB of axillary nodes has good accuracy and estimates that UNB has a pooled sensitivity of 80 %, specificity of 98,3%, and a PPV of 97,1% assuming a prevalence of node metastases of 47%.

Based on these approaches, we could offer to our patients an individualized axillary surgery according to the combination of the predicting risk calculated by a nomogram and results of UNB. Three options would be possible (1) No axillary surgery in low-risk patients, (2) SLND in intermediate or high risk-patients and (3) immediate axillary lymph node dissection in case of positive UNB. Perspectives studies should be conducted to define and validate the threshold of risk groups. The decision of 'No Axillary Surgery' would eventually be shared with the patient based on her predicted individualized risk within the low-risk group.

References

- Viale G, Zurrida S, Maiorano E. Predicting the status of axillary sentinel lymph nodes in 4351 patients with invasive breast carcinoma treated in a single institution. *Cancer* 2005;103:492–500.
- Bevilacqua JL, Kattan M, Fey J et al. Doctor, what have my chances of having a positive sentinel node? A validated nomogram for risk estimation. *J Clin Oncol*. 2007; 25: 3670–79.
- Reyal F, Rouzier R, Depont-Hazelzet B et al. The molecular subtype classification is a determinant of sentinel Node positivity in early breast carcinoma. *Plos One* 2011; 6 (5)
- Mouttet D, Ngo C, De Rycke Y et al. Validation over time of a nomogram including HER status to predict sentinel node positivity in early breast carcinoma. Submitted 2011
- Houssamy N, Ciatto S, Turner R et al. Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer. *Ann Surg* 2011;254:243–251.

14

Invited

The Sentinel Node Biopsy is Positive: No Axillary Clearance?

H.S. Cody¹. ¹Memorial Sloan-Kettering Cancer Center, Surgery, New York, USA

For all cancers, the goals of lymphadenectomy (in order of importance) are staging/prognostication, local control, and the possibility of a survival benefit. Since the pioneering reports of Morton (1991), Krag (1993) and Giuliano (1994), sentinel lymph node (SLN) biopsy has become standard care for axillary lymph node staging at many institutions worldwide. What have we achieved?

First, we have demonstrated that SLN biopsy works. An overview¹ of 69 published studies of SLN biopsy validated by a backup axillary dissection (ALND) confirms an overall success rate of 96%, with a 7% false-negative rate, results which have been confirmed in 5 randomized trials^{2–6}.

Second, through an extensive literature we have asked and answered the easiest questions. There remain a few areas of debate. These include the management of non-axillary SLN, the timing of SLN biopsy relative to neoadjuvant chemotherapy, pathologic assessment of SLN (intraoperative and postoperative), the significance of SLN micrometastases, and most importantly the need for ALND in SLN-positive patients.

Finally, recent major reports from the ACOSOG Z0010–11 and NSABP B-32 trials are practice-changing.

In Z0010 (n=5184)⁷ and in B-32 (n=5611)⁸, all patients were treated on the basis of routine H&E staining of the SLN, blind to the results of immunohistochemical (IHC) stains. For IHC-positive vs IHC-negative patients, Z0010 found no differences in 5-year OS and B-32 found that 5-year OS, DFS, and DDFS were worse, but by very small margins, 1.2%, 2.8% and 2.8%, respectively.

In Z0011 (n=813), patients with H&E-positive SLN were randomized to ALND vs no further axillary treatment (all had breast conservation and whole breast but no axillary RT). Additional positive axillary nodes were found in 27% of the ALND patients, but at 6.3 years' followup there were no differences between the ALND and no-ALND arms in axillary (0.5% vs 0.9%), breast (3.6% vs 1.9%) or overall locoregional recurrence (4.1% vs 2.8%, p=0.53), or in the usage of systemic therapy⁹, or in DFS (82.2% vs 83.9%), or in OS (91.8% vs 92.5%)¹⁰.

These results suggest a diminishing role for ALND in SLN-positive patients, particularly those who will receive whole breast RT, and in turn

demand a reappraisal of many 'standard' practices, including ultrasound for preoperative axillary node assessment, intraoperative examination of SLN, and the use of nomograms to predict non-SLN status. Whether a policy of 'no ALND' can be extended *beyond* the Z0011 selection criteria to include patients with (for example) T3 tumors, mastectomy, neoadjuvant chemotherapy, and partial-breast RT is a subject for future study.

References

- [1] Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma. *Cancer* 2006; 106:4–16.
- [2] Veronesi U, Paganelli G, Viale G et al. A Randomized Comparison of Sentinel-Node Biopsy with Routine Axillary Dissection in Breast Cancer. *The New England Journal of Medicine* 2003; 349:546–553.
- [3] Krag DN, Anderson SJ, Julian TB et al. Technical outcomes of sentinel-lymph-node resection and conventional axillary-lymph-node dissection in patients with clinically node-negative breast cancer: results from the NSABP B-32 randomised phase III trial. *Lancet Oncol* 2007; 8:881–888.
- [4] Mansel RE, Fallowfield L, Kissin M et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst* 2006; 98:599–609.
- [5] Zavagno G, De Salvo GL, Scalco G et al. A Randomized clinical trial on sentinel lymph node biopsy versus axillary lymph node dissection in breast cancer: results of the Sentinella/GIVOM trial. *Ann Surg* 2008; 247:207–213.
- [6] Gill G. Sentinel-lymph-node-based management or routine axillary clearance? One-year outcomes of sentinel node biopsy versus axillary clearance (SNAC): a randomized controlled surgical trial. *Ann Surg Oncol* 2009; 16:266–275.
- [7] Cote R, Giuliano AE, Hawes D et al. ACOSOG Z0010: A multicenter prognostic study of sentinel node (SN) and bone marrow (BM) micrometastases in women with clinical T1/T2 N0 M0 breast cancer. *J Clin Oncol (Meeting Abstracts)* 2010; 28:CRA504.
- [8] Weaver DL, Ashikaga T, Krag DN et al. Effect of occult metastases on survival in node-negative breast cancer. *N Engl J Med* 2011; 364:412–421.
- [9] Giuliano AE, McCall L, Beitsch P et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg* 2010; 252:426–433.
- [10] Giuliano AE, Hunt KK, Ballman KV et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011; 305:569–575.

15

Invited

The Management of the Axilla Around Neo-Adjuvant Chemotherapy

G. van Tienhoven¹, N. Bijker¹. ¹Academic Medical Center, Radiation Oncology, Amsterdam, The Netherlands

The role of treatment of regional lymph nodes in breast cancer is unclear. For clinically node negative disease, Axillary Lymph Node Dissection (ALND) is replaced by the Sentinel Node (SN) procedure. In series where no axillary treatment is performed in case of a positive SN, the incidence of axillary recurrence is extremely low. Large clinical trials of regional treatment are either negative or suffer from lack of events. On the other hand, for clinically node positive or locally advanced disease, aggressive treatment, consisting of neo adjuvant chemotherapy, and locoregional treatment including full ALND and Axillary Radiation Therapy (ART) is generally applied. Several trials have shown that ALND leads to considerable arm and shoulder morbidity, particularly in combination with ART.

Since the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview of 2000 it is clear that better locoregional treatment, in particular radiotherapy, improves longterm overall survival of breast cancer. It is unknown whether the survival benefit of locoregional radiotherapy is due to adjuvant treatment of the regional lymph node areas, or to the prevention of local recurrences in the breast or chest wall as such as a result of local irradiation. The recent EBCTCG overview of breast conservation trials with or without local radiotherapy and the lack of events in the regional treatment trials suggest that local treatment may be more important than regional treatment.

We should investigate overtreatment of the axilla not only in patients with clinically node negative disease but also in patients with node positive or locally advanced disease treated with neo adjuvant chemotherapy. In case of yN0 disease after neo adjuvant chemotherapy ART alone or even no axillary treatment at all may well be sufficient. In case of residual axillary disease after neo adjuvant chemotherapy ALND alone or ART alone may be as effective as the combination. These issues should be addressed in randomized clinical trials.