Is there a role for sentinel node biopsy in the pre-operative ultrasound positive axilla?

M. Ahmed¹ · F. Jozsa¹ · M. Douek¹

Received: 25 March 2017 / Accepted: 23 May 2017 / Published online: 8 June 2017
© Springer Science+Business Media New York 2017

Abstract Axillary management in breast cancer is becoming increasingly conservative. This approach is based on the identification of low axillary burden on sentinel node biopsy (SNB). The modern practice of routine pre-operative axillary ultrasound has meant that patients are ‘fast tracked’ to axillary node clearance (ANC) in the presence of a histologically confirmed positive axilla. This practice reduces the number of patients undergoing SNB compared to the original trials, which evaluated the role of SNB, and those assessing safety of omission of ANC in low axillary burden. The risk of depriving patients with low axillary burden the opportunity to avoid ANC as a consequence of pre-operative ultrasound is discussed.

Keywords Axillary ultrasound · Sentinel node biopsy · Low axillary burden · Axillary node clearance · Breast cancer

What constitutes adequate management of the axilla has evolved from a traditionally low threshold for performing axillary node clearance (ANC) towards increasing surgical conservatism. This shift has been the consequence of a succession of studies [1–3] reporting unaffected locoregional control following omission of ANC in patients with low axillary burden undergoing upfront breast conserving surgery (BCS) with radiation and systemic therapy. The application of the minimally invasive technique of SNB

with its reduced associated morbidity—including lymphoedema—compared to ANC has accelerated this process rapidly. Consequently, the ability of axillary staging techniques to evolve to distinguish between low and high nodal burden is increasingly clinically imperative. This is particularly the case when pre-operative axillary ultrasound is being performed. The use of routine axillary ultrasound was absent from the ACOSOG Z0011 trial [4] and also from all of the large randomized controlled trials (RCTs) of sentinel node biopsy (SNB) [5–10]. This has meant that these trials differed in their eligibility of patients—for SNB—compared to the established modern practice of routine pre-operative axillary ultrasound and ‘fast-track’ to ANC on histological confirmation of a positive axilla, which is reducing the number of patients undergoing SNB from these original trials.

The practice of ‘fast-track’ ANC is based on the concept of higher axillary burden in the ultrasound positive axilla and is supported by meta-analysis—although the review by van Wely et al. [11] categorized nodal burden as 1–3 involved (micro and macrometastases) nodes, or more than three nodes for ultrasound positive and negative groups, making it redundant for interpretation in the context of ACOSOG Z0011 findings. However, if we consider a series of subsequent trials, which have stratified groups according to a more clinically relevant 1–2 or greater than two macrometastatically involved nodes, then the clinical picture may be slightly different. In a retrospective study of 1060 breast cancer patients, Moorman et al. [12] identified that in 181 patients with a positive pre-operative ultrasound, 64% were found to have low nodal burden at ANC (≤ 2). Similarly, Caudle et al. [13] and Boone et al. [14] report 52 and 50% of patients, respectively, possessed low nodal burden following positive pre-operative ultrasound on ANC. Other studies report lower but still significant

✉ M. Ahmed
muneer.ahmed@kcl.ac.uk

M. Douek
michael.douek@kcl.ac.uk

¹ Division of Cancer Studies, Research Oncology, King’s College London, London SE1 9RT, UK

ranges for this patient subgroup ranging between 25 [15] and 48% [16–18]. These studies demonstrate that pre-operative axillary ultrasound is not currently sufficiently specific to identify clinically relevant high nodal burden, and its role in stratifying patients to ‘fast-track’ ANC leads to overtreatment in up to two-thirds of patients. In its current form, one can conclude that routine pre-operative axillary ultrasound is incompatible with the implementation of ACOSOG Z0011 recommendations. The identification of a clinically node negative axilla—as within ACOSOG Z0011—is automatically an important stratification technique to identify patients with a likelihood of ‘low axillary burden’ [17].

Where do these results leave axillary ultrasound in the assessment of breast cancer patients? One could argue that removal of ultrasound from the staging of the axilla would nullify the risk of overtreating this patient subgroup, and that reliance on SNB for accurate staging of the axilla is currently the safer option. This may change in future with the results of the SOUND [19] and INSEMA [20] trials—which compare SNB with no further axillary intervention following a negative axillary ultrasound—where the low sensitivity of ultrasound may prove useful in preventing the overtreatment by SNB in this subset of patients who traditionally have no or low axillary burden.

An alternative solution could be to find a way to reconcile the ACOSOG Z0011 trial recommendations with clinical guidelines for pre-operative axillary ultrasound. Caudle et al. [13] conducted subgroup analysis for patients in whom 1 or 2 suspicious nodes were seen at ultrasound. In this study, 149 out of 190 patients with a positive axilla on ultrasound possessed 1–2 visible suspicious nodes. In total, 99 patients were found at ANC to have low axillary burden (≤ 2 macrometastases). If a threshold of 1 or 2 suspicious nodes on axillary ultrasound were applied, then 82 of the 99 patients with low axillary burden would have been identified. Therefore, it could be beneficial if radiologists scanning the axilla quantified the axillary burden using a threshold of 1–2 and >2 suspicious nodes. Patients with two or fewer suspicious nodes on ultrasound could be directed to SNB and those greater than two nodes ‘fast tracked’ to ANC. This would increase the number of pre-operative ultrasound positive patients currently fulfilling Z11 criteria avoiding ANC by 43% [13]. It is acknowledged that there could always be some residual axillary disease, which will not impact upon local recurrence or survival (so long as adjuvant systemic treatment is administered) and even with this stratification there may be overtreatment of a select cohort. The marking of suspicious nodes pre-operatively at ultrasound (with clips or radioactive seeds) for targeted excision intraoperatively could also allow for more accurate staging of the axilla—as has emerged with the primary chemotherapy treated axilla

[21]. The use of primary chemotherapy itself allows downstaging of axillary burden in-between 40 and 75% of patients [22, 23]. Whether primary chemotherapy or not is administered in patients with high axillary burden will be dependent on current evidence, biological features of the cancer and patient wishes. Either way, all patients will require careful pre-operative axillary staging and cytological or histopathological assessment of suspicious nodes. The performance of SNB and targeted axillary dissection (TAD) post-primary chemotherapy may allow potential avoidance of ANC in the event that the sentinel node and TAD node were negative [21, 24] and omission of axillary radiotherapy.

The issue of patients undergoing mastectomy and their axillary burden was not addressed by the ACOSOG Z0011 trial [4]. Whilst it may be assumed that the ACOSOG Z0011 criteria could be extrapolated to mastectomy patients, radiotherapy is not routinely recommended after mastectomy unlike following breast conserving surgery. This means that some patients who undergo mastectomy otherwise meet the ACOSOG Z0011 criteria and could avoid ANC, may not receive chest wall radiotherapy or tangential fields to the lower axilla, leaving the axilla potentially undertreated. In the absence of further clinical trial data, the only safe option for patients undergoing mastectomy is to recommend axillary clearance or recruitment into ongoing clinical trials.

Alongside refining of axillary ultrasound reporting, future links between high nodal burden and histological risk factors may emerge to aid staging. Whilst limited data are available regarding difference in nodal burden according to tumour subtype, lobular histology of the primary tumour has been reported [13] as a risk factor for high burden (OR 1.77; 95% CI 1.06–2.95), and other studies report age <50 years and tumour grade as risk factors [12]. No association with receptor subtype has yet been reported, but other potential associations need to be explored including molecular profiling of tumours.

Other imaging modalities have so far not been shown to be credible alternatives with high false positive rates being recorded for MRI [25] and when combined with ultrasound no improvement in sensitivity or specificity identified [16]. Positron emission topography (PET) or PET/CT has been reported to possess a mean sensitivity and specificity of 63 and 94%, respectively, for the determination of axillary lymph node status in early breast cancer [26]. Whilst these areas warrant further evaluation, their implementation will face marked difficulties within the financial constraints of healthcare expenditure.

The emergence of trials demonstrating the lack of therapeutic benefit for surgical intervention in the low burden axilla, so long as systemic treatment is administered, has raised questions about the future role of pre-

operative axillary ultrasound and SNB. In the absence of further data, and in the continued application of axillary ultrasound, it would appear prudent that radiologists attempt to quantify the axillary status as accurately as possible. This includes numerical quantification as well as accurate ultrasound characterization of nodes, which currently is missing from the literature and should form the basis of future research. These findings should be considered within clinical context in the multidisciplinary team (MDT) meeting. Those patients with more than 1–2 abnormal nodes or those with abnormal nodes who are about to commence primary chemotherapy should be considered for biopsy and clipping of the node(s) within ongoing clinical trials. Further studies are needed to refine the technique of clipping the node and SNB with removal of the clipped node. Any other option—aside from stopping the performance of pre-operative ultrasound—results in overtreatment of the axilla.

Compliance with ethical standards

Conflict of interest The authors have no disclosures to make concerning financial and personal relationships with other people or organizations that could inappropriately influence their work.

References

- Giuliano AE, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Hunt KK, Morrow M, Ballman K (2010) 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* 252(3):426–432 (discussion 432–423)
- Galimberti V, Botteri E, Chifu C, Gentilini O, Luini A, Intra M, Baratella P, Sargenti M, Zurrada S, Veronesi P et al (2012) Can we avoid axillary dissection in the micrometastatic sentinel node in breast cancer? *Breast Cancer Res Treat* 131(3):819–825
- Imoto S, Ochiai A, Okumura C, Wada N, Hasebe T (2006) Impact of isolated tumor cells in sentinel lymph nodes detected by immunohistochemical staining. *Eur J Surg Oncol* 32(10):1175–1179
- Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, Leitch AM, Saha S, Morrow M, Hunt KK (2016) Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 randomized trial. *Ann Surg* 264(3):413–420
- Gill G (2009) Surgeons STGotRACo, Centre NCT: 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* 16(2):266–275
- Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Ashikaga T, Weaver DL, Miller BJ, Jalovec LM, Frazier TG et al (2007) 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* 8(10):881–888
- Mansel RE, Fallowfield L, Kissin M, Goyal A, Newcombe RG, Dixon JM, Yiangou C, Horgan K, Bundred N, Monypenny I et al (2006) Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC trial. *J Natl Cancer Inst* 98(9):599–609
- Veronesi U, Paganelli G, Viale G, Luini A, Zurrada S, Galimberti V, Intra M, Veronesi P, Robertson C, Maisonneuve P et al (2003) A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. *New Engl J Med* 349(6):546–553
- Zavagno G, De Salvo GL, Scalco G, Bozza F, Barutta L, Del Bianco P, Renier M, Racano C, Carraro P, Nitti D et al (2008) 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* 247(2):207–213
- Kim T, Giuliano AE, Lyman GH (2006) Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. *Cancer* 106(1):4–16
- van Wely BJ, de Wilt JH, Francissen C, Teerenstra S, Strobbe LJ (2015) Meta-analysis of ultrasound-guided biopsy of suspicious axillary lymph nodes in the selection of patients with extensive axillary tumour burden in breast cancer. *Br J Surg* 102(3):159–168
- Moorman AM, Bourez RL, Heijmans HJ, Kouwenhoven EA (2014) Axillary ultrasonography in breast cancer patients helps in identifying patients preoperatively with limited disease of the axilla. *Ann Surg Oncol* 21(9):2904–2910
- Caudle AS, Kuerer HM, Le-Petross HT, Yang W, Yi M, Bedrosian I, Krishnamurthy S, Fornage BD, Hunt KK, Mittendorf EA (2014) Predicting the extent of nodal disease in early-stage breast cancer. *Ann Surg Oncol* 21(11):3440–3447
- Boone BA, Huynh C, Spangler ML, Sumkin J, Johnson R, McGuire KP, Soran A, Ahrendt GM (2015) Axillary lymph node burden in invasive breast cancer: a comparison of the predictive value of ultrasound-guided needle biopsy and sentinel lymph node biopsy. *Clin Breast Cancer* 15(5):e243–e248
- Boland MR, Ni Cearbhaill R, Fitzpatrick K, Walsh SM, Evoy D, Geraghty J, Rothwell J, McNally S, O'Doherty A, Quinn CM et al (2016) A positive node on ultrasound-guided fine needle aspiration predicts higher nodal burden than a positive sentinel lymph node biopsy in breast carcinoma. *World J Surg* 40(9):2157–2162
- Barco I, Chabrera C, Garcia-Fernandez A, Fraile M, Gonzalez S, Canales L, Lain JM, Gonzalez C, Vidal MC, Vallejo E et al (2016) Role of axillary ultrasound, magnetic resonance imaging, and ultrasound-guided fine-needle aspiration biopsy in the pre-operative triage of breast cancer patients. *Clin Trans Oncol* 19(6):704–710
- Pilewskie M, Mautner SK, Stempel M, Eaton A, Morrow M (2016) Does a positive axillary lymph node needle biopsy result predict the need for an axillary lymph node dissection in clinically node-negative breast cancer patients in the ACOSOG Z0011 era? *Ann Surg Oncol* 23(4):1123–1128
- Verheul NC, van den Hoven I, Ooms HW, Voogd AC, Roumen RM (2015) The role of ultrasound-guided lymph node biopsy in axillary staging of invasive breast cancer in the post-ACOSOG Z0011 trial era. *Ann Surg Oncol* 22(2):409–415
- Gentilini O, Veronesi U (2012) Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: sentinel node vs observation after axillary UltraSound). *Breast* 21(5):678–681
- Reimer T, Hartmann S, Stachs A, Gerber B (2014) Local treatment of the axilla in early breast cancer: concepts from the National Surgical Adjuvant Breast and Bowel Project B-04 to the Planned Intergroup Sentinel Mamma Trial. *Breast Care* 9(2):87–95

21. Caudle AS, Yang WT, Krishnamurthy S, Mittendorf EA, Black DM, Gilcrease MZ, Bedrosian I, Hobbs BP, DeSnyder SM, Hwang RF et al (2016) 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* 34(10):1072–1078
22. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, Wilke LG, Taback B, Leitch AM, Kuerer HM, Bowling M, Flippo-Morton TS et al (2013) Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA* 310(14):1455–1461
23. Dominici LS, Negron Gonzalez VM, Buzdar AU, Lucci A, Mittendorf EA, Le-Petross HT, Babiera GV, Meric-Bernstam F, Hunt KK, Kuerer HM (2010) Cytologically proven axillary lymph node metastases are eradicated in patients receiving pre-operative chemotherapy with concurrent trastuzumab for HER2-positive breast cancer. *Cancer* 116(12):2884–2889
24. Donker M, Straver ME, Wesseling J, Loo CE, Schot M, Drukker CA, van Tinteren H, Sonke GS, Rutgers EJ, Vrancken Peeters MJ (2015) Marking axillary lymph nodes with radioactive iodine seeds for axillary staging after neoadjuvant systemic treatment in breast cancer patients: the MARI procedure. *Ann Surg* 261(2):378–382
25. Meng Y, Ward S, Cooper K, Harnan S, Wyld L (2011) Cost-effectiveness of MRI and PET imaging for the evaluation of axillary lymph node metastases in early stage breast cancer. *Eur J Surg Oncol* 37(1):40–46
26. Cooper KL, Meng Y, Harnan S, Ward SE, Fitzgerald P, Papaioannou D, Wyld L, Ingram C, Wilkinson ID, Lorenz E (2011) Positron emission tomography (PET) and magnetic resonance imaging (MRI) for the assessment of axillary lymph node metastases in early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 15(4):iii–iv, 1–134