Eur Radiol (2014) 24:288–293
DOI 10.1007/s00330-013-3009-5

BREAST

Is imaging the future of axillary staging in breast cancer?

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Received: 19 June 2013 / Revised: 2 August 2013 / Accepted: 18 August 2013 / Published online: 14 September 2013

Abstract Axillary management in patients with breast cancer has become much less invasive with the introduction of sentinel lymph node biopsy (SLNB). However, over 70 % of SLNBs are negative, questioning the generic use of this invasive procedure. Emerging evidence indicates that breast cancer patients with a low axillary burden of disease do not benefit from axillary lymph node dissection (ALND). Non-invasive techniques such as paramagnetic iron oxide contrast-enhanced magnetic resonance imaging (MRI) may provide genuine alternatives to axillary staging and should be evaluated within clinical trials. Selective axillary surgery could then be offered based on imaging findings and for therapeutic intent. This non-operative approach would reduce morbidity further and facilitate interpretation of follow-up imaging.

Key Points

- *Modern imaging and biopsy greatly help the axillary staging of breast cancer.*
- *Superparamagnetic iron oxide (SPIO)-enhanced MRI offers a further advance.*
- *Sentinel lymph node biopsy may become redundant with SPIO-enhanced MRI.*
- *Selective therapeutic axillary surgery should be based upon preoperative imaging findings.*

Keywords Sentinel lymph node biopsy · Magnetic resonance imaging · Paramagnetic iron oxide · Axillary staging · Selective axillary surgery

Sentinel lymph node biopsy (SLNB) is the standard of care for axillary staging of patients with breast cancer who have a clinically and radiologically negative axilla [1–6]. Preoperative ultrasound with fine-needle aspiration (FNA) or core biopsy of abnormal lymph nodes is used to identify node-positive patients who can proceed directly to axillary lymph node dissection (ALND) and therefore avoid an additional unnecessary surgical procedure. However, the sensitivity of ultrasound-guided FNA/biopsy for the preoperative detection of axillary nodal metastases is variable with figures ranging between 25 and 97 % [7, 8]. Houssami et al. [9] in a meta-analysis found the sensitivity and specificity of ultrasound-guided FNA/biopsy for axillary staging to be 79.6 and 98.3 % respectively. The inclusion of only patients undergoing ultrasound-guided FNA or biopsy in their calculations as opposed to all patients undergoing ultrasound imaging artificially inflates the sensitivity rates for studies [10, 11] within the systematic review [9]. More realistic figures are described by Britton et al. [12] whose assessment of 139 patients with proven invasive breast cancer demonstrated that the sensitivity of ultrasound-guided core biopsy for the identification of involved axillary lymph nodes was 53.4 %. Core biopsy sensitivity also varied between macro- and micrometastatic lymph node involvement with figures of 60.3 % and 30 % respectively. Of the 73 lymph node-positive patients confirmed on SLNB, only 5 (7 %) exhibited suspicious ultrasound appearances with an irregular outline and absence of a fatty hilum, and all of these yielded a malignant core biopsy result. From the

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remaining positive nodes, 8 (11 %) had a smooth outline but no fatty hilum and 7 of these produced a malignant core biopsy result; 22 (30 %) were multilobulated nodes with malignant core biopsy results in 17; 11 (15 %) unilobulate nodes of which 7 were positive on core biopsy; 25 (34 %) nodes with a smooth outline and fatty hilum of which 3 were positive on core biopsy. Cho et al. [13] found in their study of ultrasound-guided needle localisation of axillary nodes and subsequent confirmatory surgical SLNB, that a significant correlation between increasing cortical thickness of nodes and the presence of malignancy was present ($P<0.001$). They found that a cortical thickness of >3.5 mm and absence of a fatty hilum was associated with 90 % malignancy compared with 2 % for a thickness of <1.5 mm. The work of Garcia-Ortega et al. [14] supports this since the ultrasonographic finding with the highest positive predictive value for malignancy was absence of a fatty hilum (93.1 %). This raises the question of how best to target axillary nodes for core biopsy if 34 % of normal-appearing nodes are positive for malignancy [12]. Certainly more intelligent targeting of the SLN using ultrasound contrast agents such as microbubbles may be of benefit. Sever et al. [15, 16] have demonstrated that contrast-enhanced ultrasound (CEUS) using intradermal injection into the breast of phospholipid-stabilised microbubbles containing sulphur hexafluoride gas with a mean diameter of 2.5 μm, can be successful. In 2 studies consisting of 44 and 80 patients they were able to confirm a sensitivity of 89 % for SLN detection compared with radioisotope and blue dye [15, 16]. However, when Cox et al. [17] consequently used CEUS with microbubbles in a larger cohort of 371 patients, the sensitivity was found to be only 61 % and therefore comparable to non-enhanced ultrasound. This technique has also been applied to a porcine model and the execution of percutaneous excision of the SLN using the Intact Breast Lesion Excision System (BLES, Intact Medical, Framingham, MA, USA) [18]. In this porcine study Sever et al. [18] demonstrated that the excision of the whole SLN was successful in the groins of the three pigs tested and that the nodal architecture of the removed nodes was preserved on microscopy. Further refinement of such a system with improved sensitivity could provide an alternative to surgical SLNB. Other techniques such as ultrasound elastography have also shown potential for preoperative axillary staging in breast cancer. Taylor et al. [19] found that the sensitivity, specificity, positive predictive value and negative predictive value of conventional ultrasound were 76, 78, 70 and 81 % respectively; 90, 86, 83 and 93 % respectively for visual ultrasound elastography; and for strain scoring, 100, 48, 58 and 100 % respectively. Wojcinski et al. [20] in their study using real-time ultrasound elastography found a significantly harder cortex in metastatic lymph nodes ($P=0.006$) and a sensitivity and specificity of 40 and 96.8 % respectively for B-mode ultrasound compared to 60 and 79.6 % respectively for ultrasound elastography. They found that the highest sensitivity of 73.3 % was achieved by the combination of conventional ultrasound and elastographic features of cortical thickness >3 mm on B-mode ultrasound or blue cortex on the elastogram. The highest specificity of 99.3 % was achieved by findings of a cortical thickness >3 mm on B-mode and blue cortex on the elastogram. These studies suggest that ultrasound elastography could act as an adjunct to conventional ultrasound to improve the performance of conventional ultrasound alone. However, in the current clinical context by using preoperative ultrasound staging of the axilla routinely, potentially up to 75 % of patients will still have a negative SLNB and undergo an unnecessary invasive procedure with its associated morbidity. Furthermore, ultrasound is of limited value for intraoperative localisation of sentinel nodes in view of limited surgical ultrasound training and the limitations of using portable ultrasound machines to identify departmental radiological findings.

A growing number of studies and trials support the concept that patients with low axillary tumour burden do not benefit from an ALND [21–24]. The recent update by Galimberti et al. [23] of the International Breast Cancer Study Group (IBCSG) trial 23–01 demonstrated that an ALND can be omitted in patients with very low volume metastatic nodal involvement. This randomised, multicentre, phase III clinical trial compared ALND with no ALND in patients with micrometastases alone in the sentinel lymph node (SLN). A total of 934 clinically node-negative patients were randomised, with a primary tumour of less than 5 cm and with less than 2-mm tumour focus in one or two SLNs. Two thirds of patients (67 %) had tumours less than 2 cm, and 89 % were oestrogen-receptor positive (ER+). The 5-year disease-free survival (DFS) and overall survival (OS) rates in the ALND- versus SLNB-only groups were 87.3 versus 88.4 % ($P=0.48$) and 97.6 versus 98 % ($P=0.35$) respectively. The SOUND trial (Sentinel node vs. Observation after axillary UltrasouND) [25] will assess ultrasound for preoperative staging of the axilla. This prospective, multicentre, randomised controlled study is recruiting patients with breast cancers less than 2 cm in size and suitable for breast-conserving surgery and SLNB, who undergo preoperative axillary ultrasound to rule out suspicious nodal involvement. Patients with a single indeterminate lymph node undergo ultrasound-guided fine-needle aspiration. Patients with either negative cytology of the single indeterminate lymph node or with negative ultrasound of the axilla, are randomised into ether conventional management (SLNB± ALND) or no axillary surgical staging. In the conventional arm, ALND is only performed in the presence of macrometastases, but not for isolated tumour cells or micrometastases. The primary endpoint is distant disease-free survival, which will act as a proxy for overall survival, allowing results to be acquired in a shorter period of time than overall survival. Secondary endpoints will be cumulative incidence of distant and axillary recurrences, disease-free survival and overall survival.

In patients with nodal metastasis, the ACOSOG Z0011 trial [24] demonstrated that when ALND was omitted there was extremely low local recurrence and excellent overall survival, so long as whole breast radiotherapy and systemic therapy were administered. In this trial 27 % of patients randomised to ALND were found to have further axillary involvement and by inference a similar proportion in the other study arm would have residual axillary disease. However, about 40 % of patients entered into ACOSOG Z0011 [24] had micrometastases and the trial was criticised for not meeting the planned accrual and for lacking statistical power. Therefore, with very low axillary tumour burden and in line with the IBCSG 23–01, axillary surgery can be omitted. This leaves the questions of how to identify patients with macrometastases reliably and what the future of SLNB will be. If we are pursuing a less invasive approach, it is time to consider non-invasive techniques to assess the axilla.

Axillary MRI provides an alternative to SLNB in determining axillary burden. Diffusion-weighted MRI (DWI) has been applied to the evaluation of primary breast lesions and Kamitani et al. [26] assessed its role in the detection of axillary metastases. However, in their study they found a sensitivity and specificity of only 53.8 and 86.9 % respectively for detecting axillary metastases in the 110 breast cancers that were evaluated. Scaranelo et al. [27] assessed the use of unenhanced MRI *versus* diffusion weighted (DW) imaging for axillary staging in 61 patients with breast cancer and correlated this with histopathological findings. They demonstrated that the sensitivity, specificity and accuracy for unenhanced axial T1-weighted MRI was 88, 82 and 85 % respectively and 84, 77 and 80 % for DW imaging. They demonstrated the accuracy of preoperative axillary evaluation using unenhanced MRI and the reproducibility of DW imaging, but its unlikely clinical function. Memarsadeghi et al. [28] demonstrated that unenhanced MRI was inferior to ultrasmall superparamagnetic iron oxide (USPIO)-enhanced MRI with sensitivity, specificity and accuracy of 55, 81 and 79 % respectively for unenhanced MRI and 100, 98 and 98 % for the detection of axillary involvement. Fornasa et al. [29] performed their own characterisation of axillary lymph nodes using DW-MRI and found that the apparent diffusion coefficients (ADCs) of lymph nodes with metastases were significantly lower (mean: 0.878×10^{-3} mm^2/s; range: 0.3-1.2) than those with benign lymph nodes (mean: 1.494; range: 0.6-2.5) ($P<0.001$). By applying this refinement they established a threshold value of 1.09×10^{-3} mm^2/s DWI resulting in a sensitivity, specificity and accuracy for metastatic lymph node identification of 94.7, 91.7 and 93 % respectively. Nakai et al. [30] compared the outcomes of DW-MRI and conventional MRI using USPIO contrast enhancement. They demonstrated that whilst more axillary lymph nodes are identified on conventional MRI compared to DW-MRI (83 % versus 76 % respectively), the sensitivity, specificity and overall accuracy was 83, 98 and 95 % respectively for DW-MRI and 70, 98 and 93 % for conventional MRI respectively. Mortorello et al. [31], in their assessment of axillary staging using contrast-enhanced (gadodiamide) MRI, found that the presence of an axillary node with no fatty hilum and the number of nodes with no fatty hilum on MRI significantly correlated with pathologic node positivity ($P=0.04$), whilst kinetics, node number and node size did not correlate. Ex vivo characterisation of axillary nodes by Luciani et al. [32] demonstrated that an MR short axis threshold of 4 mm yielded the best predictive value for metastatic nodal involvement with a sensitivity and specificity of 78.6 and 62.3 % respectively. Other factors significantly correlated with metastatic lymph node involvement were irregular contours (sensitivity 35.7 and specificity 96.7 %), central nodal hyperintensity on inversion recovery T2-weighted images (sensitivity 57.1 and specificity 91.4 %) and a cortical thickness of >3 mm (sensitivity 63.6 and specificity 83.2 %).

Data from studies using superparamagnetic iron oxide (SPIO) indicate that these contrast agents have sensitivity and specificity for the detection of axillary involvement of 98 and 96 % respectively [33]. Meng et al. [34] assessed the cost-effectiveness of MRI and PET for the evaluation of axillary lymph nodes in early breast cancer. They found that if MRI could accurately diagnose axillary involvement, the most cost-effective strategy was to replace SLNB with axillary MRI. With this strategy, true-positive patients would undergo a single surgical procedure (ALND) replacing two sequential surgical procedures (SLNB followed by ALND). True-negative patients would not require any surgery. The challenge of applying this to routine clinical practice is the false-positive rate of 6.3 % for MRI versus 0.2 % for SLNB [34]. Harnan et al. [33] in their systematic review considered the use of MRI assessment of axillary lymph node status in early breast cancer and recorded a mean sensitivity and specificity of 90 and 95 % respectively. The highest mean sensitivity and specificity were seen with superparamagnetic iron oxide (SPIO)-enhanced MRI, with values of 98 % and 96 % respectively. Stadnik et al. [35] compared the efficacy of USPIO-enhanced MRI with 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) for axillary staging in ten patients with breast cancer who subsequently underwent axillary clearance. Histopathological axillary staging was negative for nodal malignancy in five patients and positive in the remaining five. There was one false positive for USPIO-enhanced MRI and one false negative for FDG-PET. This provided a sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 100, 80, 80 and 100 % for USPIO-enhanced MRI and 80, 100, 100 and 80 % respectively for FDG-PET. However, the combination of USPIO-enhanced MRI and FDG-PET provided sensitivity, specificity, PPV and NPV of 100 %, demonstrating its ability to identify patients for direct axillary clearance and avoiding

SLNB. To this effect, the future prospect of the combination of radionuclide-based imaging techniques such as PET and single photon emission computed tomography (SPECT) with MRI could represent the next generation of imaging investigations. Torres Martin de Rosales et al. [36–38] demonstrated that dual-modality imaging agents based on the conjugation of radiolabelled bisphosphonates (BP) directly to the surface of SPIO provided excellent stability and allowed for *in vivo* co-localization of lymph nodes in a murine model. The application of these dual-imaging agents to future human studies provides exciting prospects to improve the sensitivity and specificity of preoperative axillary staging. Peare et al. [36] in their meta-analysis of FDG-PET for axillary staging assessed 25 eligible studies confirming the efficacy of FDG-PET compared to histopathological assessment after ALND/SLNB. They found that from a combined population of 2,460, there were 703 true positives and 1,288 true negatives, 339 false negatives and 130 false positives. Summary receiver-operating characteristic (SROC) curves were plotted for the aggregate data. This analysis found an area under the curve (AUC) of 0.95 (95 % CI 0.91-0.97) and a Q* value of 0.89 (95 % CI 0.85-0.92). For the AUC and Q* (sensitivity= specificity) a value closer to 1 represents perfect performance. Therefore, in radiological terms, the outcome of FDG-PET would represent good performance. However, Peare et al. [36] concluded that the performance of FDG-PET was not sufficient to replace surgical assessment of the axillary lymph nodes. The reason for this was inclusion of studies reporting on false-negative results because of the inability of FDG-PET to detect micrometastatic deposits. Cooper et al. [39] in their systematic review of PET for the assessment of axillary lymph node status in early breast cancer found that across 26 studies evaluating PET or PET/CT, the mean sensitivity and specificity were 63 and 94 % respectively. On this basis replacing SLNB with PET would avoid the adverse effects of SLNB, but lead to more false-negative patients at risk of recurrence and more false-positive patients undergoing unnecessary ALND, meaning that currently it could not be accepted as the standard of care over SLNB.

Superparamagnetic iron oxide injected interstitially into the periareolar region of the breast has also been successfully used to guide SLNB [40, 41]. Johnson et al. [41] showed that the 13 nodes containing metastases had variable quantities of iron within them, but the iron was not present in the areas of the node containing the metastasis. This study therefore demonstrated that heterogeneous enhancement of the SLNs and non-SLNs on contrast-enhanced MRI indicated a metastatic focus. This technique could potentially identify patients with significant axillary involvement preoperatively, who therefore require ALND. The current SentiMAG Multicentre Trial [42], a prospective phase II non-randomised clinical trial comparing SLNB using a magnetic tracer and handheld magnetometer versus the standard technique, will determine if the novel technique is viable in a larger patient cohort. This study has an MRI sub-protocol to evaluate preoperative axillary MRI (with a magnetic tracer) for SLN imaging and characterisation. The findings of this preoperative imaging will then be correlated with the outcome of SLNB to determine the ability of SPIO-enhanced MRI to characterise the sentinel lymph nodes preoperatively. However, this will be of limited clinical value since the CE marked magnetic dye is not a contrast agent and can only be used to localise sentinel nodes. Future contrast agents should further evaluate these findings.

Selective axillary surgery has been evaluated in trials assessing feasibility of SLNB in patients presenting with node-positive disease and who undergo primary chemotherapy. The ACOSOG Z1071 Trial [43] evaluated the utility of SLNB after primary systemic treatment (PST) in 756 patients presenting with node-positive disease. At the time of surgery, all patients underwent SLNB followed by ALND. The SLNB identification rate was 92.5 % and SLNB correctly identified nodal status in 84 % of cases. Of those patients in whom an SLN was identified there was a complete pathological response in 40.3 %. Of the patients with a positive SLNB, the SLN was the only site of disease in 40 %. The false-negative rate for SLNB was 12.8 %. These findings are also supported by the SENTINA Trial [44], which considered the timing of SLNB in PST. In this four-arm, prospective, multicentre cohort study, patients who were clinically node negative before PST underwent SLNB and those who were found to be negative underwent no further axillary surgery (group A); those who were positive underwent post-PST SLNB and ALND (group B). Patients who wer clinically node positive before PST did not undergo any axillary intervention until completion of PST, when they were divided into those who became clinically node negative and underwent SLNB and ALND (Group C) and those who remained node positive and underwent ALND (group D). They interestingly found that 70.8 % of patients in group B and 52.3 % in group C converted to node-negative status. The false-negative rate was 14.2 % in group C but as high as 51.6 % in group B. Irrespective of the high false-negative rates in group B, both SENTINA [44] and ACOSOG Z1071 [43] suggest that there might be patients who would benefit from a more targeted surgical approach to the axilla rather than a routine, one-size-fits-all ALND. With preoperative imaging it could be possible to identify the PST responders in ACOSOG Z1071 [43] and SENTINA [44] and those who only have low axillary tumour burden (40 % of patients with only the SLN involved in ACOSOG Z1071 [43]) and surgically only excise those involved nodes, reducing the morbidity associated with ALND.

Axillary tumour burden reflects the biology of the tumour. Ideally, the extent of axillary surgery should be guided by the actual rather than the likely axillary tumour burden. To evaluate this concept a robust axillary imaging technique is required. The concept of selective axillary surgery could be used to identify and

remove only involved axillary nodes. This would rely on improved preoperative imaging combined with novel techniques to guide surgeons intraoperatively to involved nodes. Patients with a high clinical index of suspicion for axillary involvement could then be offered further imaging, and those with a low index of suspicion, conservative management. The future for SPIO contrast-enhanced MRI is promising and it is essential that funding is prioritised to include imaging trials and sub-protocols to evaluate preoperative axillary MRI. These trials will allow us to move forwards to a truly minimally invasive approach and individualised axillary management in breast cancer.

Acknowledgments This work was undertaken at both King's College London/Guy's and St Thomas' Hospitals and UCLH/UCL, which receive funding from the Department of Health's NIHR Biomedical Research Centre funding scheme. The views expressed in this publication are those of the authors and not necessarily those of the UK Department of Health.

Conflict of interest statement The authors have no disclosures to make concerning financial and personal relationships with other people or organisations that could inappropriately influence their work. No ethical approval was requested for this work.

References

1. Gill G, Surgeons STGotRACo, Centre NCT (2009) 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 16:266–275
2. Kim T, Giuliano AE, Lyman GH (2006) Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a metaanalysis. Cancer 106:4–16
3. Krag DN, Anderson SJ, Julian TB 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 8:881–888
4. Mansel RE, Fallowfield L, Kissin M 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 98:599–609
5. Veronesi U, Paganelli G, Viale G et al (2003) A randomized comparison of sentinel-node biopsy with routine axillary dissection in breast cancer. N Engl J Med 349:546–553
6. Zavagno G, De Salvo GL, Scalco G 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 247:207–213
7. Bedrosian I, Bedi D, Kuerer HM et al (2003) Impact of clinicopathological factors on sensitivity of axillary ultrasonography in the detection of axillary nodal metastases in patients with breast cancer. Ann Surg Oncol 10:1025–1030
8. Sahoo S, Sanders MA, Roland L, Pile N, Chagpar AB (2007) A strategic approach to the evaluation of axillary lymph nodes in breast cancer patients: analysis of 168 patients at a single institution. Am J Surg 194:524–526
9. Houssami N, Ciatto S, Turner RM, Cody HS 3rd, Macaskill P (2011) Preoperative ultrasound-guided needle biopsy of axillary nodes in invasive breast cancer: meta-analysis of its accuracy and utility in staging the axilla. Ann Surg 254:243–251
10. Baruah BP, Goyal A, Young P, Douglas-Jones AG, Mansel RE (2010) Axillary node staging by ultrasonography and fine-needle aspiration cytology in patients with breast cancer. Br J Surg 97:680–683
11. van Rijk MC, Deurloo EE, Nieweg OE et al (2006) Ultrasonography and fine-needle aspiration cytology can spare breast cancer patients unnecessary sentinel lymph node biopsy. Ann Surg Oncol 13:31–35
12. Britton PD, Goud A, Godward S et al (2009) Use of ultrasound-guided axillary node core biopsy in staging of early breast cancer. Eur Radiol 19:561–569
13. Cho N, Moon WK, Han W, Park IA, Cho J, Noh DY (2009) Preoperative sonographic classification of axillary lymph nodes in patients with breast cancer: node-to-node correlation with surgical histology and sentinel node biopsy results. AJR Am J Roentgenol 193:1731–1737
14. Garcia-Ortega MJ, Benito MA, Vahamonde EF, Torres PR, Velasco AB, Paredes MM (2011) Pretreatment axillary ultrasonography and core biopsy in patients with suspected breast cancer: diagnostic accuracy and impact on management. Eur J Radiol 79:64–72
15. Sever A, Jones S, Cox K, Weeks J, Mills P, Jones P (2009) Preoperative localization of sentinel lymph nodes using intradermal microbubbles and contrast-enhanced ultrasonography in patients with breast cancer. Br J Surg 96:1295–1299
16. Sever AR, Mills P, Jones SE et al (2011) Preoperative sentinel node identification with ultrasound using microbubbles in patients with breast cancer. AJR Am J Roentgenol 196:251–256
17. Cox K, Sever A, Jones S et al (2013) Validation of a technique using microbubbles and contrast enhanced ultrasound (CEUS) to biopsy sentinel lymph nodes (SLN) in pre-operative breast cancer patients with a normal grey-scale axillary ultrasound. Eur J Surg Oncol 39:760–765
18. Sever AR, Mills P, Hyvelin JM et al (2012) Percutaneous removal of sentinel lymph nodes in a swine model using a breast lesion excision system and contrast-enhanced ultrasound. Eur Radiol 22:545–550
19. Taylor K, O'Keeffe S, Britton PD et al (2011) Ultrasound elastography as an adjuvant to conventional ultrasound in the preoperative assessment of axillary lymph nodes in suspected breast cancer: a pilot study. Clin Radiol 66:1064–1071
20. Wojcinski S, Dupont J, Schmidt W, Cassel M, Hillemanns P (2012) Real-time ultrasound elastography in 180 axillary lymph nodes: elasticity distribution in healthy lymph nodes and prediction of breast cancer metastases. BMC Med Imaging 12:35
21. Bilimoria KY, Bentrem DJ, Hansen NM et al (2009) Comparison of sentinel lymph node biopsy alone and completion axillary lymph node dissection for node-positive breast cancer. J Clin Oncol 27:2946–2953
22. Galimberti V, Botteri E, Chifu C et al (2012) Can we avoid axillary dissection in the micrometastatic sentinel node in breast cancer? Breast Cancer Res Treat 131:819–825
23. Galimberti V, Cole BF, Zurrida S et al (2013) Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23–01): a phase 3 randomised controlled trial. Lancet Oncol 14:297–305
24. Giuliano AE, McCall L, Beitsch P et al (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 252:426–432, discussion 432–423
25. 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 21:678–681
26. Kamitani T, Hatakenaka M, Yabuuchi H et al (2013) Detection of axillary node metastasis using diffusion-weighted MRI in breast cancer. Clin Imaging 37:56–61

27. Scaranelo AM, Eiada R, Jacks LM, Kulkarni SR, Crystal P (2012) Accuracy of unenhanced MR imaging in the detection of axillary lymph node metastasis: study of reproducibility and reliability. Radiology 262:425–434
28. Memarsadeghi M, Riedl CC, Kaneider A et al (2006) Axillary lymph node metastases in patients with breast carcinomas: assessment with nonenhanced versus uspio-enhanced MR imaging. Radiology 241: 367–377
29. Fornasa F, Nesoti MV, Bovo C, Bonavina MG (2012) Diffusion-weighted magnetic resonance imaging in the characterization of axillary lymph nodes in patients with breast cancer. J Magn Reson Imaging 36:858–864
30. Nakai G, Matsuki M, Harada T et al (2011) Evaluation of axillary lymph nodes by diffusion-weighted MRI using ultrasmall superparamagnetic iron oxide in patients with breast cancer: initial clinical experience. J Magn Reson Imaging 34:557–562
31. Mortellaro VE, Marshall J, Singer L et al (2009) Magnetic resonance imaging for axillary staging in patients with breast cancer. J Magn Reson Imaging 30:309–312
32. Luciani A, Pigneur F, Ghozali F et al (2009) Ex vivo MRI of axillary lymph nodes in breast cancer. Eur J Radiol 69:59–66
33. Harnan SE, Cooper KL, Meng Y et al (2011) Magnetic resonance for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. Eur J Surg Oncol 37:928–936
34. 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 37:40–46
35. Stadnik TW, Everaert H, Makkat S, Sacre R, Lamote J, Bourgain C (2006) Breast imaging. Preoperative breast cancer staging: comparison of USPIO-enhanced MR imaging and 18F-fluorodeoxyglucose (FDC) positron emission tomography (PET) imaging for axillary lymph node staging–initial finding. Eur Radiol 16:2153–2160
36. Peare R, Staff RT, Heys SD (2010) The use of FDG-PET in assessing axillary lymph node status in breast cancer: a systematic review and meta-analysis of the literature. Breast Cancer Res Treat 123:281–290
37. Torres Martin de Rosales R, Finucane C, Mather SJ, Blower PJ (2009) Bifunctional bisphosphonate complexes for the diagnosis and therapy of bone metastases. Chem Commun (Camb). doi:10.1039/b908652h:4847-4849
38. Torres Martin de Rosales R, Tavare R, Glaria A, Varma G, Protti A, Blower PJ (2011) ((9)(9)m)Tc-bisphosphonate-iron oxide nanoparticle conjugates for dual-modality biomedical imaging. Bioconjug Chem 22:455–465
39. Cooper KL, Harnan S, Meng Y et al (2011) Positron emission tomography (PET) for assessment of axillary lymph node status in early breast cancer: a systematic review and meta-analysis. Eur J Surg Oncol 37:187–198
40. Joshi T, Pankhurst Q, Hattersley S, Brazdeikis A, Hall-Craggs M, De Vita E, Bainbridge A, Sainsbury R, Sharma A, Douek M (2007) Magnetic nanoparticles for detecting sentinel lymph nodes. Eur J Surg Oncol 33
41. Johnson L, Pinder SE, Douek M (2013) Deposition of superparamagnetic iron-oxide nanoparticles in axillary sentinel lymph nodes following subcutaneous injection. Histopathology 62:481–486
42. Douek M (2010) SentiMag Multicentre Trial (NIHR) UKCRN ID12178
43. Boughey J, Suman V, Mittendorf E, Ahrendt G, Wilke L, ACOSOG Z1071 Trialists Collaborative (2012) The role of sentinel lymph node surgery in patients presenting with node positive breast cancer (T)-T4, N1-2) who receive neoadjuvant chemotherapy-results from the ACOSOG Z1071 trial. Cancer Res 72:94s
44. Kuehn TBI, Fehm T, Fleige B, Helms G, SENTINA Trialists Collaborative (2012) Sentinel lymph node biopsy before or after neoadjuvant chemotherapy-final results from the prospective multiinstitutional SENTINA Trial. Cancer Res 72:95s