European Journal of Radiology 84 (2015) 2130–2136

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Contrast-enhanced ultrasound -guided axillary lymph node core biopsy: Diagnostic accuracy in preoperative staging of invasive breast cancer

Rautiainen Suvi[a,f,*], Sudah Mazen[a], Joukainen Sarianna[b], Sironen Reijo[c,e,f], Vanninen Ritva[a,d,f], Sutela Anna[a]

[a] Department of Clinical Radiology, Kuopio University Hospital, Kuopio, P.O. Box 100, Puijonlaaksontie 2, 70029 KYS, Finland
[b] Department of Plastic Surgery, Kuopio University Hospital, Kuopio, P.O. Box 100, Puijonlaaksontie 2, 70029 KYS, Finland
[c] Department of Clinical Pathology, Kuopio University Hospital, Kuopio, P.O. Box 100, Puijonlaaksontie 2, 70029 KYS, Finland
[d] Unit of Radiology, Biocenter Kuopio, University of Eastern Finland, P.O.B. 1627, FI-70211 Kuopio, Finland
[e] Unit of Pathology and Forensic Medicine at Institute of Clinical Medicine, Biocenter Kuopio, University of Eastern Finland, P.O.B. 1627, FI-70211 Kuopio, Finland
[f] Cancer Center of Eastern Finland, University of Eastern Finland, P.O.B. 1627, FI-70211 Kuopio, Finland

ARTICLE INFO

Article history:
Received 1 June 2015
Received in revised form 9 July 2015
Accepted 12 August 2015

Keywords:
Breast neoplasms
Axilla
Biopsy
Ultrasonography
Contrast media

ABSTRACT

Objectives: To evaluate accuracy of contrast enhanced ultrasound (CEUS)-sentinel procedure followed by core biopsy (CB) and marking in patients with breast cancer. To compare the axillary metastatic tumour burden in patients with positive vs. negative CB results.
Methods: Two radiologists in our tertiary care hospital performed axillary CEUS sentinel procedures on consecutive US node negative breast cancer patients. The first enhancing lymph node (LN) was core biopsied and marked with a breast coil. The results were compared to final histopathology. We analysed the diagnostic performance of CEUS CB and its ability to detect patients with higher axillary burden (>2 metastasis).
Results: During the study period between January 2013 and December 2014, altogether 54 patients (mean age 60.4 years) were included in the statistical analysis. The sensitivity for CEUS CB was 66.7%, specificity 100%, PPV 100%, NPV 93.8% and overall accuracy 94.4%. The method correctly recognised all the axillae with higher tumour burdens (sensitivity 100%, $N = 3$) and 59.3% of coils marking the LNs were discovered.
Conclusion: CEUS -guided axillary CB proved to be feasible and accurate procedure with moderate sensitivity and it clearly identified the higher axillary tumour burden. The coil marking of LNs as used cannot be recommended. In clinical routine, CEUS procedure might be recommended in selective patient populations.

1. Introduction

During the past few decades, staging of the axilla in patients with breast cancer has shifted from routine axillary lymph node dissection (ALND) towards sentinel lymph node biopsy (SLNB), which has become the standard of care. SLNB has achieved high sensitivity (97–98%), with similar survival outcomes but with less morbidity compared to ALND [1,2]. Moreover, the need for routine ALND after positive SLNB findings was recently challenged by randomized trials (ACOSOG and AMAROS) in patients with T1-2 tumours and clinically node negative axilla [3,4]. The concept of low (<2 positive LNs) vs. high axillary tumour burden (>2 positive LNs) has recently been introduced also in radiological studies, which aim to determine the role of preoperative investigations in the evolving axillary staging [5–7].

Although the search for a non-invasive approach to preoperatively stage the axilla has attracted much interest, the diagnostic figures have not achieved the results of SLNB [6,8,9]. The sensitivity and specificity of axillary ultrasound (US) has been reported

Abbreviations: ALND, axillary lymph node dissection; CB, core biopsy; CEUS, contrast-enhanced ultrasound; FNA, fine-needle aspiration; LN, lymph node; SLN, sentinel lymph node; SLNB, sentinel lymph node biopsy; UNB, ultrasound-guided needle biopsy; US, ultrasound.

* Corresponding author at: Department of Clinical Pathology, Kuopio University Hospital, Kuopio, P.O. Box 100, Puijonlaaksontie 2, 70029 KYS, Finland. Fax: +358 17 173 341.
E-mail addresses: suvi.rautiainen@kuh.fi (S. Rautiainen), mazen.sudah@kuh.fi (M. Sudah), sarianna.joukainen@kuh.fi (S. Joukainen), reijo.sironen@kuh.fi (R. Sironen), ritva.vanninen@kuh.fi (R. Vanninen), anna.sutela@kuh.fi (A. Sutela).

http://dx.doi.org/10.1016/j.ejrad.2015.08.006
0720-048X/

between 61% - 62% and 82% - 86%, respectively [6,10]. US-guided needle biopsy (UNB) has improved the sensitivity (80%) with perfect specificity (100%) [6,9,10] and finds approximately half of axillary metastasis preoperatively [11]. The US-positive axillae is more frequently associated with higher axillary tumour burden (>2 positive LNs) [12] and the metastases found by US tend to be larger than average [13,14]. However, the majority of patients with small breast tumours have a low axillary tumour burden [15,16] and more accurate preoperative staging would be desired.

The false negative findings in axillary UNB can arise from failure to sample the sentinel lymph node (SLN) (45%), or the metastatic deposit within the LN (55%) [13]. The latter can be reduced by using core biopsy (CB) instead of fine needle aspiration (FNA) [17,18]. Moreover, the ability to correctly localize the SLN during biopsy would improve the detection rate of metastatic LNs.

The use of contrast enhanced US (CEUS) to localize the SLN has shown it to be both safe and feasible [19–21]. In comparison to traditional isotope SLNB and Patent Blue dye, the sensitivity of CEUS to detect SLN correctly was 89% [20]. In clinically node negative patients, the sensitivity of CEUS -guided biopsy (with either CB or FNA) was 61–65% [21,22]. However, the literature on CEUS -guided SLN biopsies is still scanty and details such as localization methods prior to subsequent surgical excision remains to be determined [20,23].

The goals of the present study were: (1) to assess the accuracy of CEUS-sentinel procedure followed by CB in patients with no ultrasonographic signs indicative of axillary metastasis and (2) to evaluate the metastatic tumour burden in patients with positive vs. negative CB results and (3) to investigate the accuracy of marking the CEUS SLN with a breast coil.

2. Materials and methods

This prospective study was approved by the National Medicines Agency (EudraCT 2012-005349-20) and by the hospital ethics committee according to the recommendation from the national ethical board for medical research. All consecutive newly diagnosed patients at least 18 years of age and with invasive breast cancer or BI-RADS 5 breast lesions were invited to participate in the study. The exclusion criteria were as follows: patients who could not provide written informed consent; clinically suspicious finding of axillary metastasis; history of previous ipsilateral breast cancer, axillary surgery or radiotherapy; no axillary surgery planned or performed; contraindication for the use of US contrast agent. In addition, exclusion criteria for axillae in the grey scale US study included morphological abnormality of the LNs were any of the following findings: any cortical thickening $\geq$5.0 mm or dislocated or absent fatty hilum. No limits were set for minimum thickness of the axillary LN, breast tumour size or tumour multifocality.

During the study period between January 2013 and December 2014, the patients in this study were referred from a screening centre, two district hospitals and private institutions. All patients were evaluated by a breast radiologist before surgery and breast lesions were classified according to the ACR BI-RADS® lexicon (American College of Radiology, Breast Imaging Reporting and Data System) [24,25]. The findings were evaluated at a multidisciplinary breast meeting.

2.1. US—contrast enhancement studies and biopsies

The CEUS procedures and consecutive biopsies were performed by two breast radiologists with 5 and 21 years of experience in breast imaging and interventions (SR, MS). Before the start of the study, both radiologists had limited experience in performing axillary CEUS procedures. The US examinations were undertaken with an Esaote MyLabClassC (Esaote S.p.A., Genova, Italy) with a 7–13 MHz linear transducer and the contrast studies using the contrast-specific software program and linear probe. During the grey scale axillary US assessment, special attention was paid to the typical location of the SLN at the caudal part of level I. If no exclusion criteria were present, the possible SLN with the thickest cortex at that location was documented. If during CEUS procedure this LN was found not the enhancing sentinel node, then the enhanced LN was biopsied and CEUS was deemed to have changed the biopsy plan. The morphology of the CEUS LN was noted as was the number of other enhancing LNs. All US and CEUS findings were recorded to a structured study form.

2.1.1. CEUS and biopsy procedures

The CEUS procedure was performed according to Sever et al. [20]. In short; the contrast agent powder, SonoVue® (Bracco Imaging, Milan, Italy) was mixed with 2.0 ml of sterile saline. The contrast was then injected intradermally into the upper outer quadrant close to the areola with a 26G needle using 1.0 ml syringe. The amount of a single injection was approximately 0.4 ml and the injection was repeated 1–2 times if needed. Breast and axillae were scanned with US and the contrast injection area was massaged for 5–15 s in cases where no enhancing lymph vessels or axillary LNs could be visualized. The rate of lymph vessel enhancement was categorised as (1) spontaneous, (2) delayed, or (3) delayed after massage.

The core biopsies were obtained from the first enhancing LN aiming at the cortex and subcapsular area using a 16G core-needle with 20-mm notch exposure (Temno Evolution, CareFusion Corporation, McGaw Park, IL, USA) or with an automated CNB gun with a 22-mm throw (Bard Magnum; Bard Biopsy Systems, Tempe, AZ, USA). A total of two samples that visually included solid non-fatty tissue were obtained. More biopsies were collected at the discretion of the radiologist if the first biopsies were deemed as being non-representative. In the case where two or more LNs were enhancing, then only the first LN to enhance was biopsied (Fig. 1). The successfully biopsied and enhanced LNs were marked with a breast coil (MReye Breast Localization coil, COOK Medical, Bloomington, IN, USA) adjacent to the biopsy area, for possible further recognition. The total number of enhancing LNs and biopsies were recorded, as well as any possible complications. The procedure was deemed as unsuccessful if no axillary LN enhancement could be observed.

2.1.2. Patient management and histopathological evaluation

Core biopsy specimens were placed into 10% formalin and embedded in paraffin after fixation. The samples were cut into 5-μm slices at 4 different levels then stained with haematoxylin and eosin (HE). CB samples were evaluated by 2 pathologists, first at diagnosis, then at the multidisciplinary meeting.

Patients underwent SLNB in case axillary CB showed micrometastasis and were directed to ALND in the cases where the preoperative CB revealed metastases. The CEUS-positive LNs were recognized from the evacuation specimens either by the surgeon during the operation or from specimen X-rays and were marked separately for the pathologist. If the biopsy result was negative, then SLNB was performed according to a standardized 2-day protocol including injections of technetium-labelled nanocolloid (Nanocoll, Technetium Tc-99M Albumin Aggregated Kit, GE Healthcare, Milan, Italy) and Patent Blue dye preoperatively as well as the intraoperative frozen sections. During surgery, the performing breast surgeon recognized the CEUS LN with the coil and removed this and any radioactive LN's and any other clinically suspicious LNs.

After formalin fixation, all of the obtained LNs were paraffin embedded, serially sectioned into 2-mm slices and stained with HE. For the detection of micrometastases, an immunohistochem-