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Wire localization of clip-marked axillary lymph nodes in breast cancer patients treated with primary systemic therapy

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ABSTRACT

Introduction: Clipping and selective removal of initially suspicious axillary lymph nodes in breast cancer patients who have been sonographically down-staged by primary systemic therapy improves the accuracy of surgical staging and provides the opportunity for more conservative axillary surgery. This study evaluated whether preoperative ultrasound-guided wire localization of the clipped node is useful for routine clinical practice.

Material and methods: This prospective, single-center feasibility trial included patients with invasive breast cancer (cT1-3N1-3M0) treated by primary systemic therapy. They underwent ultrasound-guided core needle biopsy and clip placement into the most suspicious axillary lymph node prior to chemotherapy. After primary systemic therapy the clipped lymph node was localized by a wire. All patients underwent target lymph node biopsy, completion axillary lymph node dissection and, if yiN0, axillary sentinel lymph node biopsy. The primary study endpoint was the identification rate of the target lymph node.

Results: All patients (n = 30) underwent successful clip insertion into the lymph node. After chemotherapy, the clipped target lymph node was visible by ultrasound in 83.3% (25/30). Wire localization was possible in 24 cases (80%), and the clipped node identification rate was 70.8% (17/24 cases). In 9/30 patients (30%) clipped node removal was not confirmed by intraoperative radiography.

Conclusion: Ultrasound-guided wire localization of the target lymph node is not suitable for clinical practice because of limitations regarding clip visibility and selective surgical preparation of the target lymph node. Further prospective evaluation of alternative techniques is needed.

Introduction

Management of the axilla in breast cancer patients has changed over recent decades. In clinically node-negative cases axillary sentinel lymph node biopsy (SLNB) has replaced completion axillary lymph node dissection (ALND), a procedure associated with a high risk of complications, such as pain, paresthesia, shoulder dysfunction and lymphedema [1,2]. The ACOSOG Z0011 trial revealed no benefit for patients with one or two involved sentinel lymph nodes (SLN) who received completion axillary lymph node dissection (cALND), compared with patients with SLNB only, when primary breast-conserving surgery (BCS) was conducted [3].

Patients who present initially with clinically positive axillary lymph nodes and are treated by primary systemic therapy (PST) convert to node-negative disease (ypN0) in 40–74% [4–6]. Three prospective multicenter trials (ACOSOG Z1071, SENTINA, SN FNAC) consistently reported unacceptably high false-negative rates (FNR) >10% for SLNB in this situation; the FNR rate decreased only if dual mapping with radiocolloid and blue dye was performed or if two or more SLNs were retrieved [7–9]. In a subset of 141 patients from the ACOSOG Z1071 trial, a clip was placed into the biopsy-proven metastatic lymph node before PST. The FNR was 6.8% where the clipped node was within the SLN specimen compared with 19.0% where the clipped node was not in one of the SLNs [10]. It was therefore suggested that identifying and removing the clipped or target lymph node (TLN) could be a safe alternative to SLNB in breast cancer patients following axillary down-staging with PST.

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Different target lymph node biopsy (TLNB) techniques have been published in recent years. The MARI (marking the axillary lymph node with radioactive iodine seeds) procedure, developed in the Netherlands [11], and the TAD (targeted axillary dissection) procedure, originating in the United States [12], involve identifying the TLN using radioactive ^{125}I seeds. Although the dose of these ^{125}I seeds is low, their use for application into axillary lymph nodes is not authorized under German law and requires complex radiation safety procedures and documentation. A simpler option might be wire localization of the TLN, a technique routinely used for the targeted removal of suspicious, nonpalpable breast lesions. The only retrospective investigation of ultrasound-guided wire localization reported a 97% identification rate (IR) for TLN [13]. Given the limited data regarding this technique, we conducted a prospective trial (CLIP study, DRKS-ID: DRKS00009793) to evaluate the IR and clinical utility of wire localization and selective removal of the clipped TLN after PST.

Material and methods

Thirty female patients with histologically proven invasive breast cancer (T1-T3), presenting with sonographically suspicious ipsilateral axillary lymph nodes were included in this prospective single-institution feasibility trial in the Department of Obstetrics and Gynecology of the University of Rostock, Germany, between February 2016 and June 2017. Distant metastases were excluded by computed tomography (CT) scans of chest and abdomen and bone scintigraphy. All patients were scheduled to undergo PST. The study was approved by the local institutional ethics committee and informed consent was obtained from all participants. Suspicious lymph nodes were defined by a cortex $\geq$ 3 mm, asymmetrical hilar fat or rounded shape (Solbiati-Index >2) on ultrasound. If more than one suspicious lymph node was found on ultrasound, the largest of these suspicious nodes was defined as the TLN. Before starting PST, ultrasound-guided core needle biopsy (CNB) using a 14-gauge needle (ARGON Medical Devices, Athens, TX, USA) of the TLN was performed, followed by immediate placement of a tissue marker (HydroMARK, Devicor Medical, Norderstedt, Germany) into the cortex of the TLN (Fig. B.1). After PST, all patients underwent TLNB and cALND. Axillary SLNB (dual mapping with blue dye and radiocolloid) was performed only in patients presenting with yiN0, i.e. where ultrasound revealed no further suspicious axillary lymph nodes after PST (Fig. B.2). Wire localization of the TLN with a flexible marking wire (Somatex Duo-System correctable localization kit, Somatex Medical Technologies GmbH, Teltow, Germany) was performed under ultrasound or mammographic guidance, depending on the visibility of the axillary clip. Successful removal of the clip-containing TLN was confirmed by intraoperative radiography (Fig. B.3). All lymph nodes were assessed using standard histopathology methods and were stained with hematoxylin and eosin without routine immunohistochemical staining. Pathologic complete response (pCR) was defined as the absence of invasive tumor in the breast and axillary lymph nodes after PST [14].

Results

Patient and tumor characteristics

Clinicopathologic and treatment details of the 30 enrolled patients are listed in table A.1. The median patient age was 52 years (range 24–73 years), the median diameter of the TLN at clip insertion was 17.6 mm (range 10–29 mm). Thirty seven percent (n = 11) were HER2-positive, 37% (n = 11) were triple negative breast cancers. Anthracycline-containing chemotherapy was administered in all cases, taxanes were added for 28 patients (93.3%) and platinum in 7 cases (23.3%). All patients presenting with HER2-positive tumors received anti-HER2-targeted therapy.

Clip insertion and axillary ultrasound

Clip insertion into the TLN was successful in all 30 participants. Immediately after insertion, the clip was visible on ultrasound in all cases. During CNB/clip-placement one patient sustained an adverse event (bleeding which was managed without surgery). Lymph node metastases were confirmed by pathology after CNB in 25 patients (83.3%). During PST the clip was located sonographically inside the TLN in 21 cases (70.0%), and beside the TLN in 9 cases (30.0%). The clip was located on ultrasound immediately before surgery/after completion of PST in 25 patients (83.3%). In 23 patients (95.8%) with yiN0, SLNB was conducted as per the study protocol, and one patient refused SLN mapping despite being yiN0.

Wire localization and surgery

Wire localization of the TLN was possible in 24 out of 30 patients (80%, ultrasound-guided n = 20, mammography-guided n = 4). Of the six patients, in whom wire localization was not possible, one had sonographically suspicious post-PST lymph nodes (16.7%), compared with 21% (5/24 cases) in the wire localization group. In 20 out of 24 patients (83.3%) with wire localization, the clip was verifiable on specimen radiography, either in the TLNB (n = 17) or the ALND (n = 3) specimen. The IR for the TLN (defined as clip localized inside the TLN specimen) was 70.8% (17/24 cases). SLNs were detected and removed in 20/23 of mapped cases (IR for SLN 87%, median number of SLNs 1.6, range 1–5 SLNs). In 14 patients both TLN and SLN were successfully detected and removed. They were congruent in five cases (concordance rate 35.7%). Extirpation of the clipped node was not shown in nine cases (30.0%). In eight patients, intraoperative radiography failed to verify the clip. In one case without wire localization no specimen radiography was performed and the clip was not found by the pathologist. In 4/9 (44.4%) of these patients, the clip was located beside (not inside) the TLN and in 4/9 (44.4%), the clip was not visible on ultrasound after PST. In the twenty-one patients with successful clip removal as documented by specimen radiography, the clip was located beside the TLN in 23.8% (n = 5/21) and not visible at ultrasound in 4.8% (n = 1/21).

Accuracy of axillary interventions

FNR for SLNB and TLNB was 0% for both procedures. FNR for post-PST ultrasound of axillary lymph nodes was 25.0%. In three of seven patients (42.9%) with metastatic TLN and three of six with metastatic SLN (50%), additional lymph node metastases were found (Table A.2).

Discussion

Standard care for patients receiving PST and presenting initially with suspicious axillary lymph nodes is completion ALND, although pathologic down-staging rates of the axilla may exceed 50% [4,15]. Reliable identification of patients achieving nodal pCR would result in avoidance of ALND and its complications. Axillary ultrasound does not reliably exclude metastases (FNR after PST 55.9%) [16], and neither does ultrasound-guided needle biopsy (sensitivity 79.6%) [17]. SLNB, with an FNR >10% in three multicenter prospective trials [7–9], is not an oncologically safe option after down-staging the axilla by PST. Therefore, different conservative techniques for axillary exploration are under investigation. Recent studies have focused on TLNB, which includes marking the most suspicious

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