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Using a New Marker Clip System in Breast Cancer: Tumark Vision® Clip – Feasibility Testing in Everyday Clinical Practice

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Keywords

Ultrasound · Breast cancer · Clip · Targeted axillary dissection

Summary

Background: This study presents first feasibility experiences with a new 3-dimensional (3D) marker clip system in clinical practice. The rate of clinical complete responses in the treatment of breast cancer patients is increasing; additionally, a change to targeted axillary dissection is being considered after neoadjuvant chemotherapy (NACT). Consequently, marker clips are needed which are reliable and easy to handle even in the axillary lymph node system. **Methods:** A total of 50 patients from the Breast Care Unit of the Kliniken Essen Mitte were included. Clip marking of all 50 primary breast cancer lesions as well as 23 lymph nodes was performed using the Tumark Vision® clip. Following application, the position and visibility of the marker clip were monitored and documented in 2 axes. **Results:** The feasibility of the Tumark Vision clip was excellent in everyday clinical practice as none of the markers dislocated. After clip marking of the tumor region and/or suspicious lymph nodes, all Tumark Vision clips could be detected in both axes. The 3D shape could be observed in all cases after application. **Conclusion:** The new 3D-shaped marker clip seems to be a promising tool for marking breast cancer lesions and even lymph nodes before NACT. As there are many studies ongoing to prove the feasibility of a shift from standard axillary dissection after NACT towards targeted axillary dissection, the Tumark Vision clip seems to provide good visibility even in lymph nodes after NACT. Further studies are warranted.

Introduction

The rate of breast cancer in women is increasing each year while the age at initial diagnosis is shifting to a younger age [1]. While therapy regimens are becoming more individualized, neoadjuvant chemotherapy (NACT) has become the standard of care more so in patients with aggressive disease [2, 3]. In these patients, NACT has several advantages over adjuvant treatment: First, NACT results in improved surgical options as tumor shrinkage might offer breast-conserving surgery instead of mastectomy in certain situations. Second, information on treatment response can be gained [3, 4], and chemotherapy or the surgical approach might be changed if tumor progression is observed during NACT [5]. Third, response to NACT can be used as a surrogate marker for disease-free and overall survival [6]. If complete tumor response can be achieved, accurate and reliable detection of the former tumor region after NACT by radiology and pathology is required [7, 8]. The use of radiodense marker clips has been shown to be an effective method to identify the region of interest [9]. The clip can be detected by either ultrasound or mammography, and wire marking of the clip can be performed to guide the surgeon to the region of interest.

Since the first description of metal clips in the late 1990s, many different clips have been developed to improve the reproducibility and reliability of breast cancer lesion marking [10, 11]. Moreover, as the axillary management of biopsy-confirmed positive lymph nodes might shift from axillary lymph node dissection towards targeted axillary dissection, clip marking of affected lymph nodes might become standard procedure as well [12]. Precise and reliable clipping of the tumor and lymph nodes determines the further treatment and thus the prognosis of the patients. Often, after NACT, the clip cannot be detected by ultrasound, especially if there is a complete clinical response. In these situations, mammog-

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raphy is necessary to identify the lesion, resulting in extra radiation and organizational requirements, loss of time, and added costs [13]. In addition, unintended movement and unreliable detection of the clips because of migration after image-guided clip marking have been reported [14, 15]. Different mechanisms of unintended clip migration have been described: clip migration in the biopsy track, a clip floating in a hematoma, clip displacement by a hematoma, change in clip site due to resorption of air at the biopsy cavity, and change in clip site after NACT and after reduction mammoplasty [14].

The newly available clip marker Tumark Vision® (SOMATEX Medical Technologies, Berlin, Germany) has been developed to provide improved ultrasound characteristics and long-term stability.

The purpose of this study is to report the worldwide first experience with using the new ultrasound-guided clip marker system for tumor localization in both breast and lymph nodes. To examine the feasibility and identifiability of the Tumark Vision clip, the new clip system was applied both in breast tumors and in affected lymph nodes.

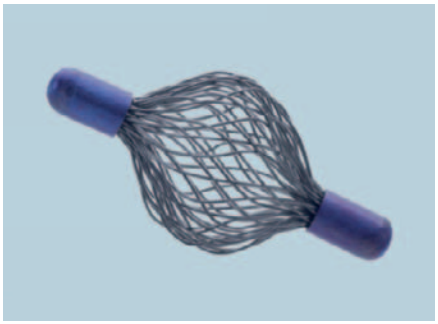

Fig. 1. Tumark Vision® clip marker (SOMATEX).

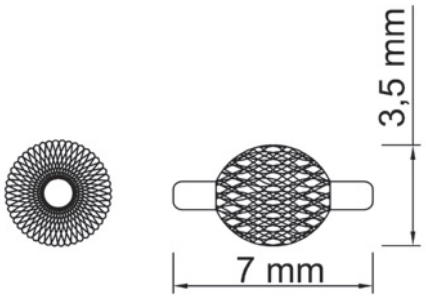

Fig. 2. Tumark Vision® clip in 2 cross sections (SOMATEX).

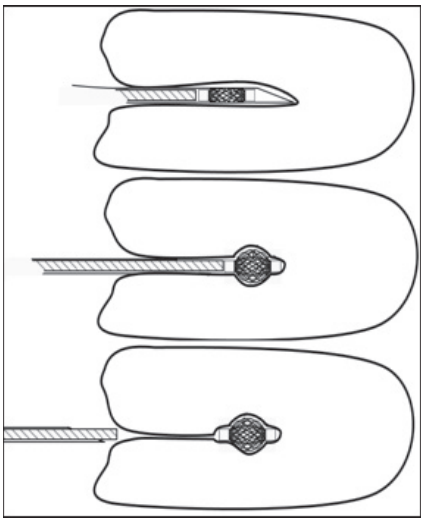

Fig. 3. Deployment of the marker into breast tissue (SOMATEX).

Patients and Methods

Novel Clip System

The reflection of ultrasound waves at the interface of 2 materials depends on the difference in acoustic impedance (Z_F) of these materials. For instance, Z_F of body tissue is relatively low and Z_F of air is very high; therefore almost 100% of ultrasound waves are reflected at a tissue/air interface. This value is similarly high for metallic materials (approximately 80% reflection for titanium) causing their bright appearance in an ultrasound image.

The Tumark Vision clip is entirely made of nitinol, a biocompatible metallic alloy, which results in hyperechogenic behavior of the marker material. 48 single nitinol wires are twisted into a wire mesh and fixated by 2 nitinol caps (figs. 1, 2). In the development phase, different mesh designs were compared in laboratory trials with regard to their echogenicity. The best results were considered for the final product design. The roundish shape of each wire leads to the reflection of sound waves. The configuration of 48 single wires in a spherical shape leads to a 3-dimensional (3D) design. This makes the clip marker highly visible from different angles and transducer positions.

Reasons for the Choice of Implant Material

Nitinol is a titanium-nickel alloy with superelastic characteristics. This means the wire material can return to a certain shape – in this case the spherical shape of the clip marker – after being released from the cannula of the application system. This effect is utilized to compress the marker into a highly compact 18G cannula. When it is released, it instantly expands to the spherical shape even in harder tissues (fig. 3).

Due to its high chemical stability, nitinol is biocompatible and used in several medical implants such as vascular stents. Laboratory trials show that there is almost no release of material into the tissue [16]. Therefore, it is expected that the marker will remain stable in the tissue for several months, in contrast to some non-metallic clip markers.

To meet clinical needs, the product needed to fulfil further requirements:

- Magnetic resonance imaging (MRI) compatibility of the clip marker.
- Application system for single-handed operation (ultrasound- or mammography-guided).
- Visibility of the clip marker in all imaging modalities.
- Sharp cutting cannula for precise application.

Study Cohort

From January to May 2017, 61 patients with a suspicious tumor underwent an ultrasound-guided core needle biopsy (2D, Acuson S2000™, 13/11 Mhz, Siemens Healthcare, Erlangen, Germany) with a reusable biopsy system (Bard® Magnum® Reusable Core Biopsy, Bard Biopsy Systems, Tempe, AZ, USA). In 30 cases, the axillary lymph nodes were also suspicious. In these patients, an ultrasound-guided axillary core needle biopsy was performed as well. Informed consent was obtained from each patient.

After the procedure, intramammary and lymph node clip marking using the new directly adapted clip system was performed. The breast cancer biopsy system was used with a 14-gauge 10-cm outer cannula and a needle advancement of 15 or 22 mm. Standard ultrasound-guided biopsy was done under local anesthesia after careful disinfection. After biopsy, the clip described above was placed directly in the tumor or lymph node under ultrasound guidance. After the intervention, the correct location was verified by ultrasonography in both horizontal and vertical axes. Invasive breast cancer was pathologically confirmed in all cases both in the breast and in the lymph nodes. In order to improve later localization and determine potential migration of the clips during

Table 1. Patient and tumor characteristics

Age, mean, years	58
Tumor stage, n (%)	
pT1	14/50 (28)
pT2	33/50 (66)
pT3	1/50 (2)
pT4	2/50 (4)
Phenotype, n (%)	
Invasive ductal	41/50 (82)
Invasive lobular	9/50 (18)
Tumor biology, n (%)	
ER+/PR+, HER2–	32/50 (64)
ER+/ER+, HER2+	6/50 (12)
ER–/PR–, HER2+	3/50 (6)
ER–/PR–, HER2–	9/50 (18)

ER = Estrogen receptor; PR = progesterone receptor; HER2 = human epidermal growth factor receptor 2.

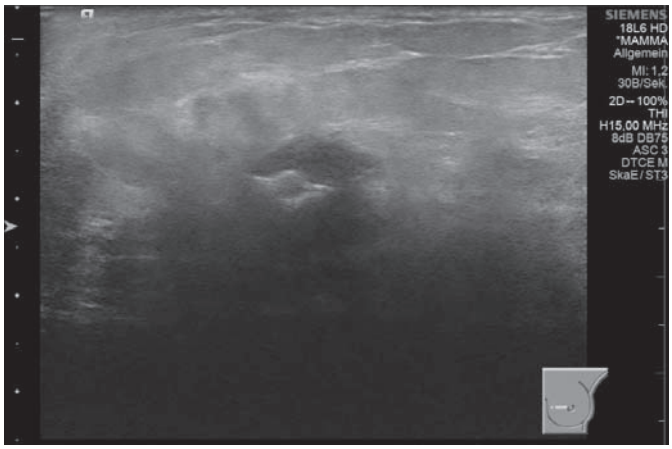

Fig. 4. Tumark Vision® clip within breast cancer.

Table 2. Quality of visibility on the day of application

Visibility	n (%)
Very good	36/50 (72)
Good	12/50 (24)
Poor	2/50 (4)
Total	50/50 (100)

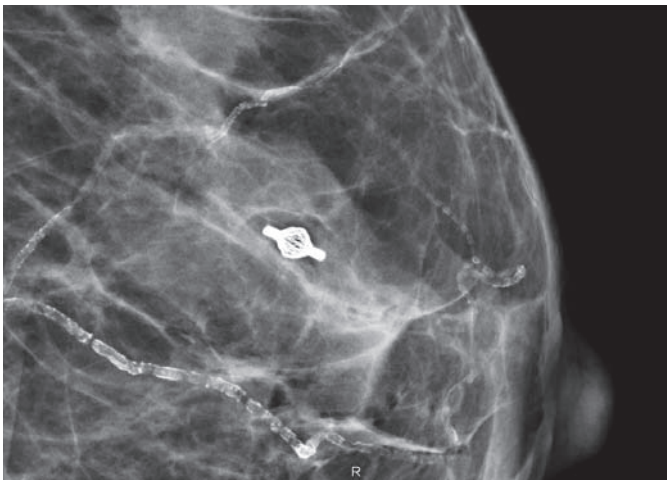

Fig. 5. Mammography showing the Tumark Vision® clip within the breast.

NACT, the position of the marker clips was described by correlating landmarks: Distance to the nipple and the skin for the primary tumor and distance to the pectoralis muscle and vessels for affected lymph nodes. Indications, measurements, and characteristics of patients and tumors are described in table 1. To monitor the correct position of the clips, sonography was repeated after 7 days before starting NACT. The aim of this was to detect immediate post-procedure displacement.

Results

A total of 61 patients with newly diagnosed invasive ductal and lobular breast cancer were included in this study. In 30 cases, the axillary lymph nodes were also biopsied, and Tumark Vision clips were placed on the affected lymph nodes. The mean age of the patients at diagnosis was 58 years. 5 patients had a pT1b, 9 patients a pT1c, 33 patients a pT2, 1 patient a pT3, and 2 patients a pT4 tumor. 64% (32/50) of the patients were hormone receptor(HR)-positive/human epidermal growth factor receptor 2(HER2)-negative, 12% (6/50) were HR-positive/HER2-positive, 6% (3/50) were HR-negative/HER2-positive, and 18% (9/50) were triple-negative. 23 patients presented with suspicious lymph nodes measuring 18–35 mm (average size 21 mm). In all cases, the suspicious lymph node was also biopsied and a Tumark Vision clip applied to the node. The application of the new marker clip could be performed in all breast cancer cases without any difficulties. In general, the clip was easily identified after application as it appears as a big round hyperechoic structure on both ultrasound and mammography (figs. 4, 5). Even in the affected lymph nodes, the Tumark Vision clip was identified as a big round hyperechoic structure. Furthermore, the Tumark Vision clip could be detected in both horizontal and vertical axes in all cases after application. In general, decreased detectability in mastopathic breast tissue was observed compared to normal breast tissue. At the follow-up visit 7 days later, the location of the Tumark Vision clip in the tumors and lymph nodes could be accurately reproduced based on our landmarks and the pictures obtained (table 2). No dislocation of the marker clip was seen in any patient.

Discussion

Accurate use of marker clips in breast cancer before NACT remains challenging due to clip dislocation and ineffective detection by ultrasonography after NACT [2, 8, 14]. Consequently, novel clip marking tools are highly needed which remain visible even after a long time following application or in the case of pathologic complete response. Furthermore, as the treatment algorithm for affected axillary lymph nodes is changing, a reliable marker clip for lymph nodes is needed before the start of NACT [12]. In this study,

2 breast cancer centers present their first experiences with a new 3D clip system that can be used both for tumor clipping and for marking affected lymph nodes. In our first evaluation, the use of the new Tumark Vision clip seems uncomplicated and reliable. Because of its roundish shape and hyperechogenic behavior, the Tumark Vision clip is highly detectable in breast ultrasound. The 3D shape provides good visibility of the Tumark Vision clip which could be observed in all cases after application. In all cases, the new marker clip could be seen in both horizontal and vertical axes, even in the lymph nodes. The marker clip unfolded in all cases. It seems that the material can also expand to its rounded shape in harder tissue. Its hyperechogenicity seems to be owing to the inclusion of fluid (blood, edema) in the 3D-shaped wires and to the reflection of the 3D stent itself. The new structure of the clip is promising in the detection of the clipped lesion even after NACT. The cave-like structure seems to grant more stability in the tumor itself so that the dislocation rate might be lower compared to the older clips. We will follow up our cases during and after NACT and will present our experience in further studies with a special interest in dense and masthopathic breast tissues.

We believe that with this novel clip system fewer investigations such as preoperative MRI or mammography might be needed to locate the lesion or lymph node after NACT as the Tumark Vision clip seems to be easily identified by sonography. This might lead to increased patient comfort. In addition, intraoperative monitoring of the removed tissue by ultrasound instead of mammography could probably confirm adequate resection by locating the clip, which would increase the efficiency of the workflow and decrease radiology costs [11]. This could result in a decrease in surgery time, re-excision rates, resection volume, and overall cost [17–19]. While we did not compare the Tumark Vision clip to other commercially available clips, comparisons between clips have shown that newer self-expanding clips show a lower displacement rate compared with bare metal clips [20].

Further studies are needed to validate the merits of this new marker clip in clinical practice, especially its visibility in patients with pathologic complete remission. At the moment, a lot of practice-changing studies are ongoing – especially concerning the operative procedures for axillary dissection. Targeted axillary dissection seems to be a safe and promising surgical alternative to standard axillary dissection after clinical complete remission following NACT [12]. The Tumark Vision clip will be used in the SenTa study because of its promising detectability especially in lymph nodes. The SenTa study is a registry trial investigating the practicability and reliability of targeted axillary dissection of affected lymph nodes. This is a very promising trial where a reliable and highly detectable clip is needed. In a next study, we will follow up on the visibility and dislocation rate of the Tumark Vision clip during and after NACT.

To summarize, we present first data concerning our experience with the Tumark Vision clip in daily practice. With its 3D shape, it combines exceptional visibility with a promisingly low dislocation rate. Further studies on visibility and dislocation rate during and after NACT are warranted.

Disclosure Statement

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