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First Reported Use of Radiofrequency Identification (RFID) Technique for Targeted Excision of Suspicious Axillary Lymph Nodes in Early Stage Breast Cancer – Evaluation of Feasibility and Review of Current Recommendations

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Abstract. *Background/Aim: The purpose of this study was to evaluate, whether radio frequency identification (RFID) labeling of axillary lymph nodes (LNs) for the use of targeted resection is feasible in primary breast cancer patients with suspicious LNs. Patients and Methods: We analyzed 10 consecutive patients where RFID technique was used for intraoperative detection of suspicious LNs without preceding neoadjuvant chemotherapy (NACT). We compared the specifics of these procedures to 10 consecutive sentinel lymph node biopsies (SLNB) in the cN0 situation. Results: Intraoperative detection rate (DR) for the RFID-labeled target lymph node (TLN) was 100%. Perioperative complications were infrequent and comparable to SLNB. Average time for location of the RFID labeled TLN was quicker than for the SLN. In 71.4% the chip bearing TLN equaled a SLN. Conclusion: The use of the RFID technique for intraoperative localization of axillary LNs for targeted excision seems feasible. RFID technique for targeted axillary dissection (TAD) following NACT should be investigated in a prospective manner.*

The axillary nodal status has been of paramount importance for decisions on adjuvant therapies in early stage breast cancer for many decades. Since sentinel lymph node biopsy (SLNB) was developed, the axillary status can be accurately evaluated with significantly lower iatrogenic morbidity compared to historic operation techniques (1-7). Targeted axillary dissection (TAD) as a combination of SLNB and targeted excision of an initially affected lymph node (LN) to evaluate residual axillary disease after neoadjuvant chemotherapy (NACT) is proposed to replace axillary lymph node dissection (ALND) in patients with clinical complete remission of the axilla (ycN0) after NACT. A superior method for intraoperative identification and targeted excision of these LNs has not been identified yet.

While SLNB is the worldwide accepted gold standard for axillary staging in patients with initially unsuspicious LNs (cN0), recommendations on axillary staging and treatment for patients with suspicious LNs or even affected LNs proven by needle biopsy remain controversial. Patients with LNs of clinically unclear dignity upon first presentation, for long, had no access to less invasive axillary operation techniques and received therapeutic or diagnostic ALND. Nowadays nodal involvement can be ruled out preoperatively *via* core needle biopsy (CNB) (8). However, the false negative rate (FNR) of CNB of suspicious LNs is estimated to be around 20% (8) and the impression upon ultrasound can vary widely depending on the metric dimensions of the LN metastasis, which can lead to a far higher number of false negative clinical evaluations (9). LNs that were biopsied should therefore be labeled using marking devices as clips just as it is done with breast lesions. This approach of CNB and clip labeling of suspicious LNs is recommended in major guidelines beginning in 2014 (10-12) and are recommended irrespective of a following NACT. This way, patients with suspicious LNs and a negative CNB of these LNs can be offered a SLNB. The reason why this rather circuitous approach is favored in several major guidelines is to largely avoid any unbeneficial ALND in those patients that turn out to be truly LN negative upon histology (13-15). It is also advisable to resect also the clipped LN during SLNB to rule out a false negative CNB result (14). On the other hand, LN metastases that are histologically proven *via*

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CNB should be securely marked for later retrieval and reevaluation after NACT (13, 15). For the sake of semantic clarification, this clipped node is called target lymph node (TLN) further on.

As systemic treatments are getting more and more effective, even for patients with initially a pN+(CNB) status undergoing NACT, less invasive axillary staging procedures are achievable (16). Axillary pathologic complete remission (pCR) rates range from 40% to more than 70% for special subtypes (17-19). For patients with initially positive LNs and a pCR of the breast after NACT chances are almost 90% to be free of tumor residuals in their LNs as well (19). An ALND in this situation has most likely only diagnostic and no therapeutic effect. Unfortunately, attempts to use SLNB after NACT in these patients failed to display satisfactory FNRs (17, 20). Therefore, it is not advisable to try to identify the patients with a pCR of the axilla with SLNB alone after NACT. A new approach is the combination of SLNB and resection of the TLN after NACT, together called TAD (21-25). TAD is of rising importance in patients with ycN0 status after NACT and subject of multiple current investigations. Initially, Caudle and colleagues showed that the combination of SLNB and resection of the TLN has an FNR clearly below the commonly accepted threshold of 10% (21). However, in their retrospective series, the targeted resection of the TLN was performed in a proportion of the cases. For part of the patients the TLN was identified postoperatively upon pathology in the ALND specimen.

The devices used for labeling of non-palpable TLNs in clinical practice are not regulated in clinical practice guidelines and include magnetic implants, radioactive iodine seeds, tattoo ink, ultrasound detectable titanium or nitinol clips (21-25). The radio frequency identification (RFID) technique was introduced this year in Europe for intraoperative detection of non-palpable lesions (26-28). Its use for the targeted resection of axillary LNs in any situation has not been reported until now. The purpose of this analysis was to demonstrate RFID labeling of axillary LNs for the use of targeted resection. Previous reports on the LOCalizer system displayed 100% DRs of non-palpable breast lesions (26, 28). Unlike most other technologies available, the LOCalizer probe displays the distance of the probe from the tag in real-time. This intelligent feature may offer the opportunity to further refine DRs of TAD and reduce iatrogenic trauma during axillary surgery.

Patients and Methods

We retrospectively analyzed all patients that were treated for primary early breast cancer with cN+ at our institution. All of these patients had ipsilateral biopsy proven invasive breast cancer without distant metastases. Approval of local ethics committee was obtained and informed consent was obtained from all individual participants included in this analysis. All patients with initially suspicious LNs with contraindication against CNB that had targeted resection of these LNs instead of ALND for further histologic clarification were reviewed. The intention in these cases was to spare these patients with clinically unclear nodal status, who were also not suitable for CNB, from upfront ALND. All cases were analyzed according to the method that was used for TLN labelling. Ten cases with RFID placement in the TLN were identified and analyzed separately. All ten patients received preoperative marking of suspicious LNs using the Faxitron (Hologic, Inc. Company, Marlborough, MA, USA) LOCalizer™ chip combined with ultrasound guidance (GE Voluson E8 Expert, GE Healthcare Chicago, IL, USA). The procedure of RFID tag placement in suspicious axillary LNs and consecutive intraoperative detection and resection are displayed in Figure 1.

Standard RFID chip placement at our institution: For RFID chip placement, a 2 mm skin incision is required to facilitate the insertion of the applicator. Due to the resistance of the skin, the applicator should not be inserted without this preparatory step, as excessively forceful skin penetration with the applicator might be harmful to delicate structures of the axilla. At our institution, in general only the most suspicious LN, *i.e.* the TLN, is marked. As the slightly larger diameter of the RFID applicator causes resistance in the underlying subcutaneous tissue as well, movement of the desired structures, *i.e.* LNs, is possible. Continuous ultrasound surveillance during chip placement is recommended.

Surgical management: All surgical procedures were performed by experienced oncology breast surgeons only. In general, surgical management followed the principles of lymphadenectomy during SLNB. Handling of the probe to locate the TLN and tissue dissection are very similar to that in SLNB. During surgical axillary staging, the tagged TLN was located using the LOCalizer Reader. An advantage of RFID is that the device is coated in glass and does not hold the risk of thermal tissue damage in comparison to guidewire localization, as the transmission of thermal/electrical energy in guide wires can cause tissue or skin damage. For the same reason, the RFID tag should not be clamped directly as this may break the glass casing. The successful excision of the RFID tag was confirmed intraoperatively *via* specimen radiography (Biovision Faxitron) and additional SLNB was offered to these patients instead of ALND. Patients with tumor manifestation in the marked TLN received completion ALND in a subsequent procedure.

The technique of targeted resection of axillary LNs with the help of RFID tags would be beneficial if it would be feasible to securely retrieve the marked LN in a procedure with limited surgical trauma. As SLNB is the gold standard in surgical axillary staging, we compared these cases to 10 consecutive standard radiotracer-guided SLNBs at our institution.

Results

We identified 10 patients that had targeted LN resection using RFID technique between April and October 2019. Six out of 10 patients had a localization unsuitable for CNB and 4 out of 10 had objected to axillary CNB.

We compared these cases to 10 exemplary, consecutive SLNBs at our institution. As standard SLNB is performed nowadays after NACT, 8/10 patients received SLNB after

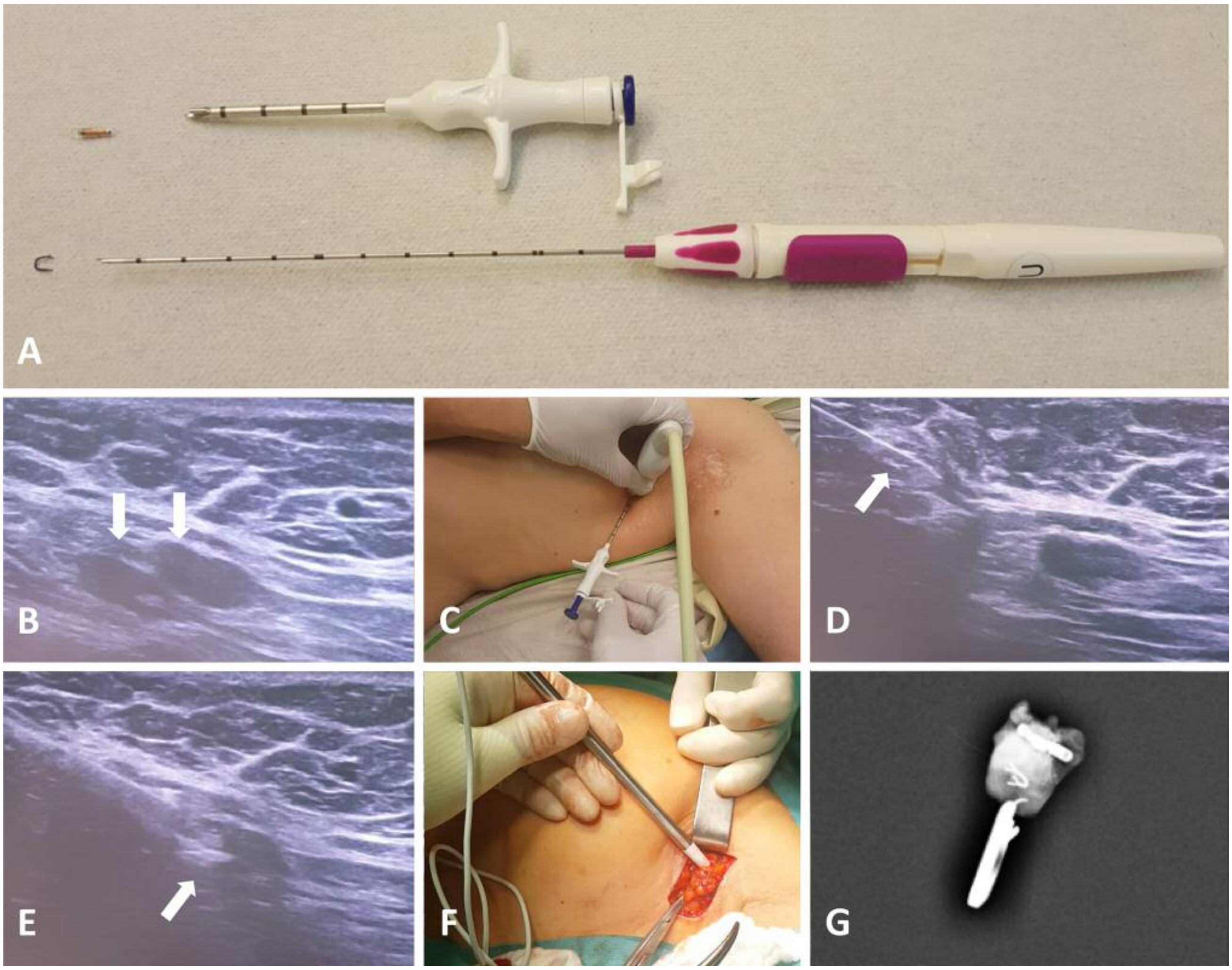

Figure 1. *RFID tag placement and intraoperative retrieval. A: LOCalizer™ RFID tag and applicator (above); Somatex Tumark® Professional; B: two suspicious lymph nodes (arrow); C-E: ultrasound guided tag application; D: needle placement (arrow); E: tag release (arrow); F: tag detection via axillary incision and LOCalizer® probe; G: intraoperative specimen radiography and confirmation of resection (specimen bears RFID tag and clip).*

NACT. Other patient characteristics were comparable and are displayed in Table I. DR for the TLN with targeted RFID chip retrieval was 10/10 (100%) as was DR for SLNB (10/10). In 7 of the 10 cN+ patients, the TLN turned out to be negative upon histology and axillary staging was completed with SLNB. In 5 of the 7 patients (71.4%) with SLNB, the chip-bearing TLN equaled a SLN as it also featured radiotracer uptake. Three patients had a positive TLN, therefore received completion ALND. Perioperative procedural results are summarized in Table II. Compared with 10 exemplary SLNB cases, minor complications did not differ significantly, and no major complications were observed. The slightly higher rates for seroma/hematoma formation are explained by the need for completion ALND in three patients with affected TLN, whereas no patient received ALND in the control group. Mean time for detection of the TLN was 2.2 min and thereby was quicker than detection of the SLN (6 min on average; <0.01). In 5 of the 10 patients with TLNE the chip was located within the TLN. No chip was found further away than 5 mm from the TLN. In summary, all chips (100%) were successfully excised during surgery and safety issues were not detected.

Discussion

The intraoperative identification of marked LNs in analogy to the targeted resection of non-palpable breast lesions requires further investigation. A method that warrants a secure detection of marked TLNs after a period of several months of NACT is needed for the implementation of TAD into daily routine. A

Table I. *Patient characteristics and performed axillary surgery in the two groups (TLNE versus SLNB).*

	LOCalizer TLNE	%	Control	%	*p*-Value
Number of Cases	10		10		
Gender (w)	10		10		
Median age (Range)	51.4 (30-83)		59 (41-82)		0.24
Median BMI (Range)	26.5 (22-35)		23.3 (22-26)		0.1
Nicotine	02 / 10	20	0	-	
Menopausal Status					
Pre	4	40	3	30	
Post	6	60	7	70	
N/A					
Grading					
G1	2	20	1	10	
G2	5	50	2	20	
G3	3	30	7	70	0.2
Histology					
NST	8	80	9	90	
Lobular	1	10	1	10	
Other	1	10	-	-	0.59
Hormone receptor positive	10	100	5	50	
Her2neu positive	0	-	1	10	
Median Ki67 % (Range)	32 (5-70)	-	37.3 (8-80)	-	0.67
Type of breast surgery					
BCS	7	70	5	50	
Mastectomy*	3	30	5	50	0.65
Type of axilla surgery					
SNLB**	7	70	10	100	0.21
ALND	3	30	0	-	

TLNE: Target lymph node excision; BMI: body mass index; N/A not applicable; NST: no special type; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; ALND axillary lymph node dissection. *Modified radical mastectomy or subcutaneous mastectomy; **Additional SLNB for patients with negative TLN; completion ALND for patients with positive TLN.

Table II. *Complication rates and results of TLNE versus SLNB. Successful chip retrieval during TLNE was 100%. Detection of a SLN was as well 100%. In 71.4%, the TLN equaled a SLN (chip bearing LN also shows tracer uptake). Time to detection of the TLN was quicker than for SLNB.*

	LOCalizer TLNE	%	Control	%	*p*-Value
Number of Cases	10		10		
Minor complications					
Seroma	4	40	3	30	0.639
Haematoma (operative revision)	1	10		-	-
Major complications	none		none		
Placement of RFID*					
in node	5	50	N/A		
<5 mm	5	50	N/A		
>5 mm	0	0	N/A		
Average nodes removed	5.7 (2-13)		2.9 (1-5)		0.046
Patients with nodal involvement	3	30%	1	10%	
Time to location (minutes)	2.2 (0.5-4)		7.3 (3-16)		<0.01
Failure to locate	0	-	0		
SNL equals TLN	5/7	71.4	N/A		

*RFID: Chip placement relative to lymph node. TLNE: Target lymph node excision; TLN: target lymph node; SLN: sentinel lymph node; RFID: radio frequency identification.

Dutch group recently reported DRs of up to 93% in a retrospective analysis (24). The intraoperative identification of the TLN was warranted using iodine seeds in the majority of the cases (24). Other small series have also shown acceptable DRs for the TLN ranging between 85-95% using clip marking or tattoo ink (22-25). However, the applicability of the very promising initial results by Caudle and colleagues in broad clinical practice has so far not been verified in a large scale, prospective manner. The so far largest prospective multicenter registry trial has lately reported a non-detection of the TLN in 22% of 473 patients/attempted resections (29). These colleagues used almost exclusively ultrasound detectable clips.

Each labeling method unfortunately bears specific disadvantages. Remission of axillary LN metastases after NACT results in normalization of LN structures. The contrast between the device and the initially hypo-echogenic, tumor infiltrated LN cortex is thereby diminished. This explains the difficulties of clip detection in ultrasound-navigated guidewire localization of clip-marked TLNs (29). Stereotactic guidewire placement can overcome this obstacle but requires the aid of a different department. It is usually performed by a radiologist and not by the breast surgeon, thereby slowing down the preoperative workflow. Moreover, it implies additional discomfort for the patients. Initial marking of TLNs with tattoo ink for later retrieval after NACT is a further option. As detection of tattooed LNs requires intraoperative visual exposition of the axillary tissue it may contradict the goal of trauma minimization (23). Moreover, migration of the tattoo ink over time into further nodes has been described (23). Therefore, a system that stays in place and transmits an active tracking signal for intraoperative localization, seems most desirable. Due to their radioactive nature, iodine seeds actively offer intraoperative information on their localization to the surgeon, but their use bears procedural and legal complexities for the same reason (24, 30).

To warrant the oncologic safety of TAD as a staging procedure, the TLN should be identified with a high sensitivity and resected in a procedure of limited surgical trauma. Furthermore, the ideal technique for TLNE should be easily available in clinical practice and avoid legal obstacles. For example, placement of iodine seeds for TLN localization is not feasible in Germany due to radiation protection legislature. Apart from the reliable intraoperative TLN detection, TAD requires a marker enduring several months of NACT without migration or dysfunction. As the optimal labeling technique has so far not been identified and in the absence of data on oncologic long-term outcomes, major guidelines give conflicting recommendations on the use of TAD as an alternative to ALND in ycN0 patients (13, 15, 31, 32). Thus, constantly rising remission rates, that have been accomplished through costly and exhausting systemic therapies, cannot be translated into less invasive axillary staging techniques nor into tailored local treatment. Apart from axillary surgical treatment, also decisions on radiation therapy (NSABP B51 ClinicalTrials.gov Identifier: NCT01872975) as well as post-neoadjuvant therapies (33) will presumably be based on the post-NACT axillary status in the future. Our results show that labeling and intraoperative identification of axillary LNs *via* the RFID technique might be a possible solution to this dilemma.

To our knowledge, the current series is the first description of RFID technology for localization of axillary LNs worldwide. A shortcoming is that SLNBs in the control group were performed in 80% of the cases after completion of NACT. Therefore, complication rates and healing conditions might be negatively altered in these patients. An obvious limitation is that we cannot state information on the stability of the RFID-labeling of LNs over a period of several months as is necessary for NACT. Only patients not undergoing NACT or planned for targeted resection of non-palpable LNs for staging reasons before NACT were analyzed. Nonetheless, because of rapid intraoperative detection and 100% DR in our series, we deem future investigations on RFID use in TAD following NACT conceivable.

Conclusion

Data from this trial suggest that the RFID technique is an effective localization system for non-palpable axillary LNs intended for surgical removal. Unlike most other technologies available, the LOCalizer probe detects its distance from the tag and this intelligent feature may offer the opportunity to further reduce iatrogenic trauma during axillary surgery. Prospective trials are required to evaluate the sensitivity and specificity of distinct localization techniques in TAD after NACT as well as the oncologic outcomes of these patients.

Conflicts of Interest

W. Malter has received a speakers and consulting honoraria from Hologic Deutschland GmbH.

Authors' Contributions

Wolfram Malter: writing, editing, data collection, statistical analysis, trial development; Christian Eichler: writing, editing, data collection, statistical analysis, trial development; Bettina Hanstein: writing, editing; Peter Mallmann: writing, editing.

Johannes Holtschmidt: writing, editing, data collection, statistical analysis trial development.

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