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Targeted axillary dissection after neoadjuvant systemic therapy in patients with node-positive breast cancer

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Abstract

Background: Over the last decade, neoadjuvant systemic therapy (NAST) has gained considerable popularity and its use has been extended to include breast cancer patients with operable node-positive disease. It may no longer be necessary to commit patients who are node-positive at presentation to axillary dissection if they become clinically node-negative after completing NAST. Targeted axillary dissection (TAD) is a technique where the marked pre-NAST positive node is excised along with the sentinel nodes and its response to chemotherapy is assessed and thus helps guide further treatment to the axilla.

Methods: The aim of this study was to determine the feasibility of marking positive axillary nodes with a clip and removing the clipped node after neoadjuvant treatment. We also assessed the concordance of the sentinel node with the clipped node.

Results: We prospectively evaluated 37 clinically and/or radiologically node-positive patients who underwent NAST. The overall identification rate of the clipped node was 78%. The identification rate was 100% if the clipped node was localized preoperatively and was much lower at 68% in patients who did not have the clipped node localized. The clipped node was not retrieved as the sentinel node in 14% of patients.

Conclusion: We present the first Australian series on the feasibility of TAD. TAD is a feasible option in patients having NAST and with every new technique there is a learning curve. With the increasing experience globally and the refinement in marking and localization techniques, the accuracy of performing TAD will likely continue to improve.

Introduction

Over the last decade, neoadjuvant systemic therapy (NAST) has gained considerable therapeutic and prognostic importance and has been extended to include breast cancer patients with operable node-positive disease. Upon completion of NAST, axillary lymph node (LN) dissection (ALND) remains the standard of care for axillary staging in many centres around the world. Studies have shown that up to 40% of clinically node-positive patients can have a pathological complete response in the axilla after neoadjuvant treatment.[1,2] In the human epidermal growth factor receptor 2+ disease subgroup, the axillary pathological complete response rate can be as high as 74%.[3] Therefore, it may no longer be necessary to commit all node-positive patients to ALND to stage the axilla accurately.

In clinically node-negative breast cancer patients undergoing NAST, sentinel node biopsy (SNB) has become the standard practice for axillary staging in many breast cancer centres.[4] In clinically node-positive patients who become clinically node-negative after NAST, SNB is being considered and there are several prospective clinical trials to determine its accuracy and feasibility in the post-NAST setting. The ACOSOG Z1071, SENTINA and SN FNAC trials reported a false-negative rate (FNR) of 12.6%, 14.2% and 13.3%, and a sentinel LN (SLN) identification rate (IR) of 93%, 80% and 87.6%, respectively. The consistently high FNR and IR demonstrated in these studies fail to support the implementation of SNB after NAST in node-positive patients undergoing NAST.[5–7] Studies have explored factors that may reduce the FNR and increase the IR after NAST. The use of dual tracer (lymphoscintigraphy in combination with blue dye), the examination of three or more SLNs and the placement of a 'marker' within the biopsied positive LN with its subsequent removal during post-NAST surgery can improve the accuracy of SNB.[5,8] The National

Comprehensive Cancer Network now advocates the consideration of placing a clip in the positive node prior to chemotherapy to ensure its retrieval at the time of definitive surgery.[9]

Targeted axillary dissection (TAD) is a technique where clinically node-positive breast cancer patients have the biopsied positive node marked before NAST with a clip, dye or radioactive iodine seed (RIS).[10–12] At the time of surgery, SNB is performed and the marked node is also removed. To facilitate the identification of the marked node, preoperative localization (e.g. with a guide wire) can be performed. Where patients have an RIS within the node, the surgeon can use a gamma probe on the iodine-125 setting to detect the node intraoperatively. Regardless of the technique used for LN marking and localization, TAD is a feasible technique and may be a more accurate way to stage the axilla compared to SNB after NAST in clinically node-positive patients. Furthermore, a more limited approach to the axilla is associated with less morbidity compare to ALND and reduced risk of arm lymphoedema.[13]

The aim of this study was to determine the feasibility of TAD (success of retrieving the marked node) using a technique of marking the positive axillary node with a clip pre-NAST and removing this node at the time of SNB after NAST. The secondary aim was to assess the concordance of the sentinel node with the clipped node. We present the first Australian series of TAD.

Methods

Ethical approval was obtained from the Western Sydney Local Health District Human Research Ethics Committee (LNR/16/WMEAD285).

We prospectively evaluated all patients undergoing TAD after NAST at Westmead Breast Cancer Institute between 2016 and 2019. These were clinically and/or radiologically node-positive (N1) breast cancer patients who had one or two biopsy-proven malignant LNs at presentation and who were recommended for NAST on the basis of tumour and patient factors after discussion

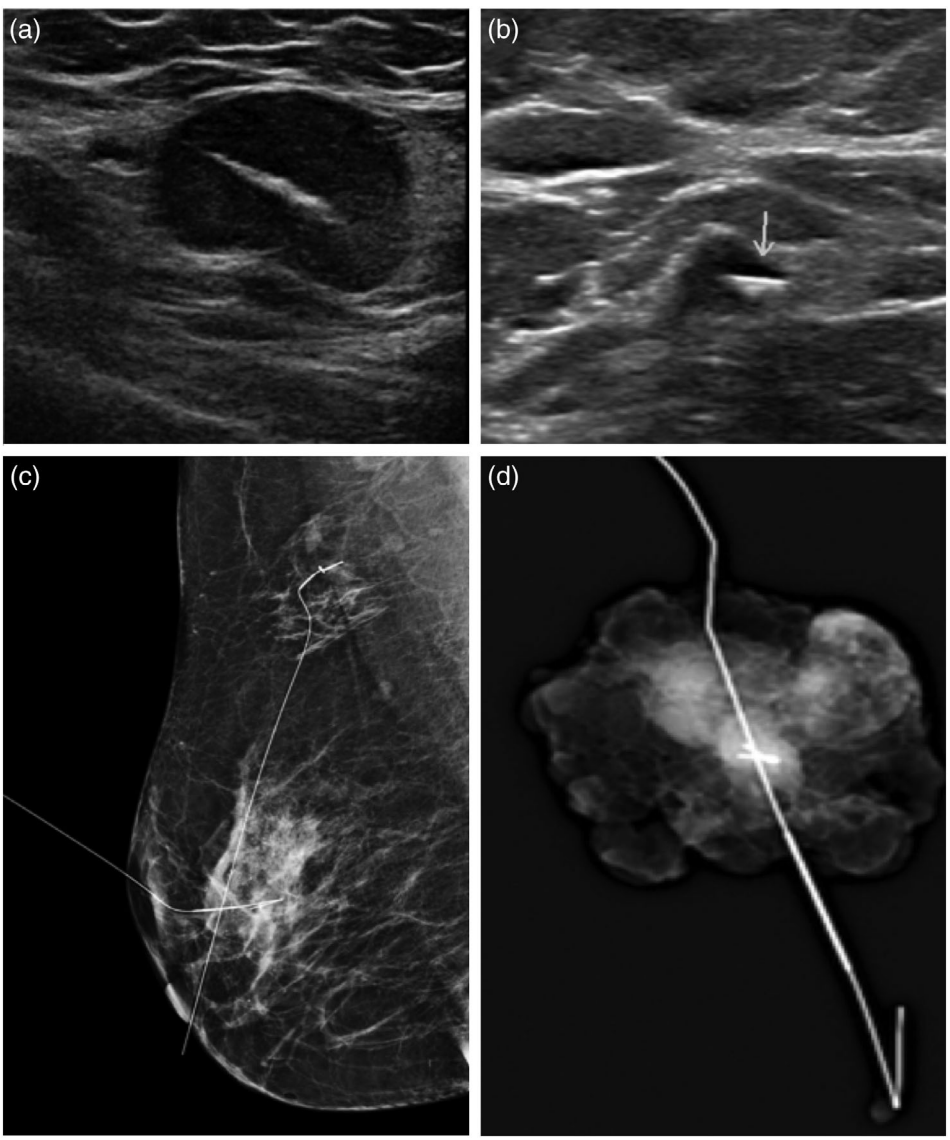

Fig. 1. Targeted axillary dissection. (a) Clip inserted into biopsy-proven positive node. (b) Progress ultrasound towards the completion of neoadjuvant chemotherapy demonstrating good response to neoadjuvant systemic therapy and marker clip (white arrow) identified within the lymph node. (c) Post-localization mammogram of breast lesion and clipped axillary node. (d) Intraoperative specimen radiograph of clipped node excision.

by the multidisciplinary team (MDT). Patients with more than two abnormal nodes were not considered suitable for TAD. A clip was placed in the malignant axillary node under ultrasound guidance prior to commencing NAST and progress clinical and imaging assessment was conducted during chemotherapy. All patients who became clinically and radiologically node-negative as a result of NAST underwent TAD at the time of their definitive breast surgery and were included in the study.

Marking of positive node and progress imaging

Breast cancer patients suitable for NAST with node-positive disease (N1) were assessed by the MDT and, if potentially eligible for TAD, a clip was inserted into the biopsy-proven positive node (Fig. 1a). Towards the end of NAST, a progress ultrasound and mammogram were performed to assess the breast and axillary response. Clip position within node was confirmed (Fig. 1b) Patients who became clinically and radiologically node-negative were consented for TAD.

Wire localization of clipped node

Preoperatively, a hook wire or RIS localization of the clipped node was attempted based on radiology service availability and ease of visualizing the clipped node on ultrasound (Fig. 1c).

Surgical procedure

A standard surgical approach for SNB was used for TAD. All patients had peritumoral and/or subareolar injection of technetium 99 (Tc^{99}) administered the day before surgery and a lymphoscintigram was performed. Patent blue dye was administered intraoperatively.

Using a standard approach, dissection down to the localized node was performed. For RIS removal, a gamma probe on I^{125} setting was used. This node was then removed, and it was recorded if the node was 'blue' and/or 'hot'. Intraoperative X-ray confirmed that the excised wired node contained the clip and the node was subsequently sent for histology. Any residual sentinel nodes or palpable abnormal nodes were excised and examined separately. If a preoperative wire was not placed, a routine SNB was undertaken. Specimen radiograph was performed to ensure removal of the clipped node and this was documented in the operative report (Fig. 1d). In the case of a clipped node not being seen in the specimen, further axillary sampling was performed and X-ray was taken for all the specimens.

Results

Thirty-seven patients underwent NAST and TAD. The patient and tumour characteristics are outline in Table 1.

Radiological response to chemotherapy

Close to the completion of NAST, progress ultrasound scans showed favourable response to chemotherapy in the breast and axilla in all patients. If a poor response was noted in the axilla, the patient was considered ineligible for TAD and underwent ALND. The median size of the residual breast cancer was 11 mm on preoperative ultrasound. The position of the clip in the axilla was confirmed on ultrasound or mammogram in 22 (60%) patients.

Table 1 Patient and tumour characteristics (n = 37)

Characteristic	*n*	%
Median age (years)	49	—
Median breast cancer size prior to NAST (mm)	30.0	—
Median breast cancer size after NAST (mm)	11.0	—
Breast operation		
BCS	22	59
Mastectomy	15	41
Receptor status		
TNBC	3	8
Triple+	5	13
ER+ PR+/– HER 2–	21	57
ER– PR+ HER 2–	1	3
HER 2+ (ER– PR– and ER+ PR–)	7	19
TNM stage		
2a	3	8
2b	26	70
3a	5	14
4	3	8

BCS, breast conservation surgery; ER, oestrogen receptor; HER 2, human epidermal growth factor receptor 2; NAST, neoadjuvant systemic therapy; PR, progesterone receptor; TNBC, triple negative breast cancer; TNM, tumor, node, metastasis staging classification.

Identification rate

Median number of nodes removed was 4 (2–17). The clipped node was retrieved in 29 of 37 patients resulting in an overall IR of 78%. Eleven patients had the clipped node localized with a wire on the day of surgery and one patient had the clipped node localized with I-seed. The clipped node was successfully retrieved in all 12 patients who had preoperative localization (IR 100%). The clipped node was not localized in 25 patients and it was in this group that the clipped node was not successfully retrieved in eight patients resulting in a reduced IR of 68%. This has been summarized in Table 2.

Table 2 Identification of clipped node

	n (%)
Overall identification rate of clipped node	29/37 (78)
Wire/I-seed localized clipped node	12/12 (100)
Not localized clipped node	17/25 (68)

Table 3 Sentinel node localization and concordance with the clipped node

	n = 29 (%)
Intraoperative blue dye uptake	17 (58)
Intraoperative Tc^{99} uptake	24 (83)
Clipped node not SLN	4 (14)

SLN, sentinel lymph node; Tc^{99}, technetium 99.

Table 4 Clipped and other sentinel node histology

Clipped node	Negative *n* = 7	ITC *n* = 2	Micrometastasis *n* = 4	Macrometastasis *n* = 17
Sentinel/other nodes				
Negative	6	2	4	8
ITC	1	—	—	1
Micrometastasis	—	—	—	2
Macrometastasis	—	—	—	6

ITC, isolated tumour cell.

Table 5 Axillary treatment based on clipped node histology

Clipped node disease	Negative *n* = 7	ITC *n* = 2	Micrometastasis *n* = 4	Macrometastasis *n* = 17
No further axillary treatment/declined treatment	4	—	1	—
Axillary radiotherapy	3	2	1	6
Axillary dissection	—	—	2	11
Residual disease	—	—	1	5

ITC, isolated tumour cell.

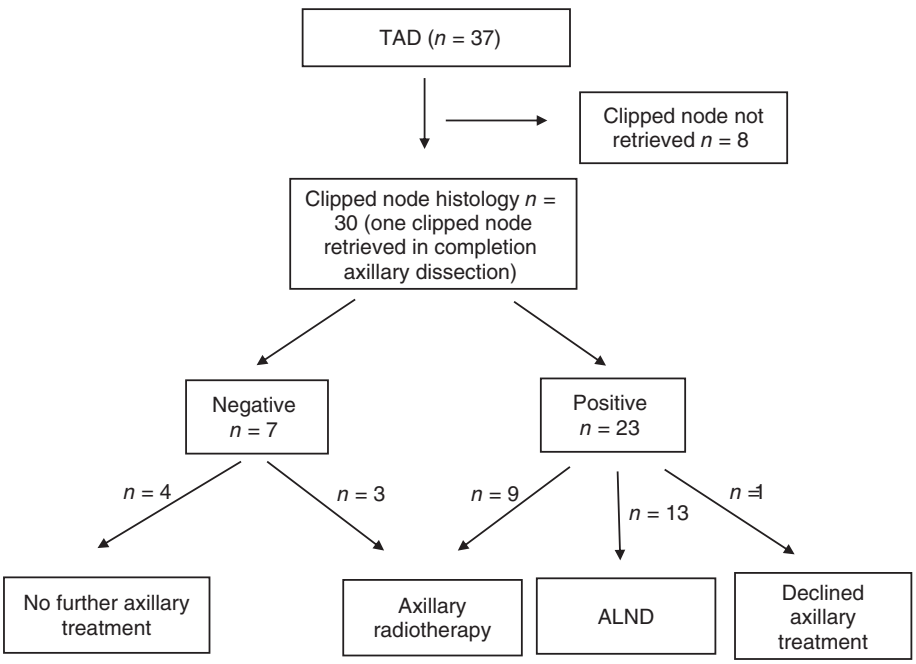

Fig. 2. Flow chart of the clipped node histology and further axillary treatment. ALND, axillary lymph node dissection; TAD, targeted axillary dissection.

Clipped node concordance with sentinel node

The dual-tracer uptake of the clipped node is summarized in Table 3. Intraoperative uptake of blue dye in the clipped node was low at 58%, whereas Tc^{99} uptake was 83%. In four (14%) patients, the clipped node was not the sentinel node (Table 3).

Clipped node histology and further axillary management

The clipped node and sentinel node histology is summarized in Table 4. Of the 30 clipped nodes retrieved (one patient had their clipped node retrieved in completion axillary clearance), seven (23%) patients had a negative clipped node and 23 had residual disease within the clipped node which included isolated tumour cells (ITCs), macrometastasis and micrometastasis. Of the seven patients with a negative clipped node, one patient had ITCs in one other sentinel node and the other six patients had no disease in any other nodes removed as part of the TAD. Of the 23 patients with disease in the clipped node, 14 (61%) had no further disease in the other nodes removed as part of the TAD.

Axillary treatment based on clipped node histology is shown in Table 5. One patient with micrometastasis in the clipped node

declined further axillary treatment. Twelve patients had axillary radiotherapy and 13 patients had ALND. Of the 13 patients who underwent axillary dissection, six had residual disease in at least one other node. Figure 2 summarizes the clipped node histology and subsequent axillary treatment. Clipped node histology with ITC, micrometastasis and macrometastasis was considered positive.

Axillary management when clipped node was not identified

The outcome and management of patients where the clipped node was not retrieved is summarized in Figure 3. In eight patients, the clipped node was not retrieved in TAD, four patients had ALND, three had axillary radiotherapy and one declined further axillary treatment.

Interestingly, two of four patients not undergoing ALND had an intraoperative X-ray confirming no residual clip in the axilla. Of the four patients who had ALND, the residual clip was identified in only one patient.

Of the eight patients, one had an immediate ALND and was noted to have ITC in one node (out of 16 nodes). Among the other seven patients, only one patient had a positive SLN. This patient had a completion ALND revealing residual axillary disease in other nodes and also in the subsequently retrieved clipped node. Of the six patients with negative SLNs, three had axillary radiotherapy, two underwent ALND (no residual disease) and one patient declined further axillary treatment.

Discussion

Clinical trials have reported that TAD is a feasible option with high IRs and low FNRs for SNB after NAST.[14–16] Our study reports an IR of 78%. One of the challenges we faced was visualizing the clipped node after NAST. Of the patients who had the clipped node visualized and localized, successful retrieval was achieved in all patients. The IR was much lower when clipped node was not localized. As TAD is increasingly used, techniques of localization have been developed and refined. The Netherlands group coined the term MARI procedure (marking of axillary LN with radioactive seed).[12] Donker *et al*. performed the MARI procedure in 100 patients. The seed was inserted prior to the start of NAST and retrieved during surgery. The added advantage was further localization was not necessary. They reported an IR of 97% where three seeds were not retrieved.[15] Other methods of localization of the axillary LN using charcoal suspension, Magseed or Savi Scout radar reflectors have been described and their respective published feasibility studies reveal high IRs.[10,17,18]

The clipped node uptake of blue dye was only 58% and 83% for radioactive tracer. The clipped node was not retrieved as the SLN

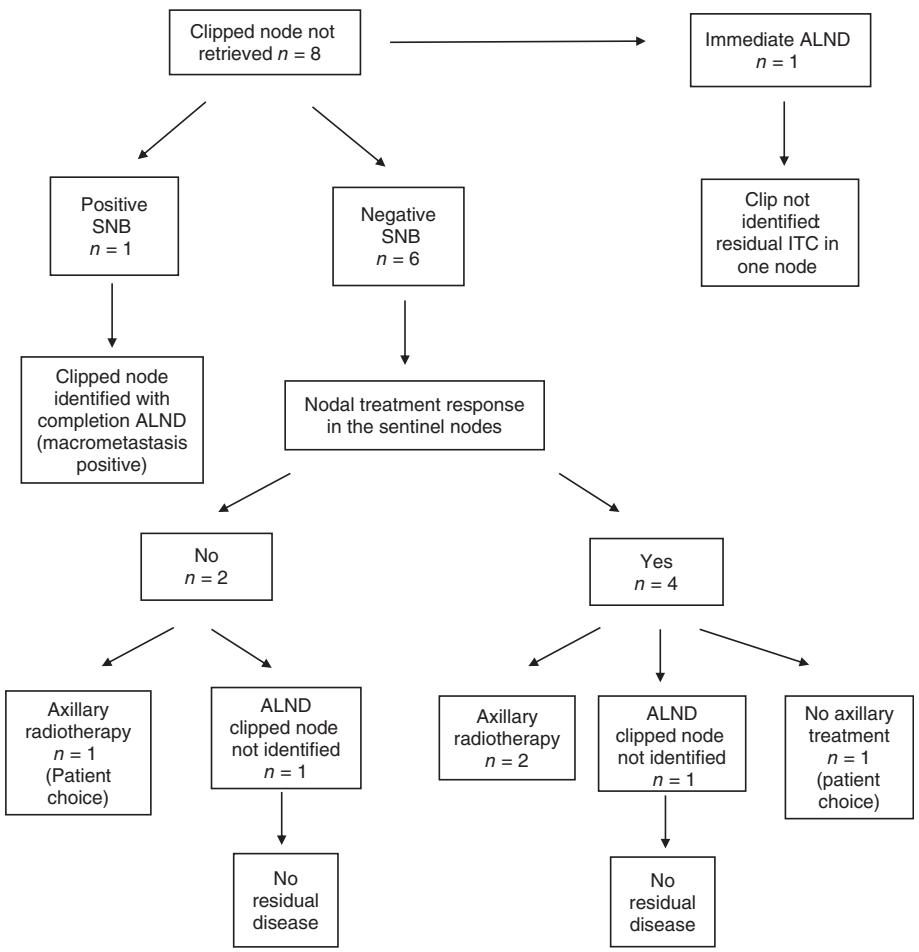

Fig. 3. Flow chart of the management of patients where the clipped node was not retrieved. ALND, axillary lymph node dissection; ITC, isolated tumour cell; SNB, sentinel node biopsy; TAD, targeted axillary dissection.

in 14% of patients in our series. The lack of concordance of the clipped node as the sentinel node could explain the high FNR with SNB after NAST. This is clearly demonstrated in the ACOSOG Z1071 trial. For patients where the clipped node was within the SLN specimen, the FNR was 6.8% and when the clipped node was in the ALND specimen and not part of the SLN specimen the FNR was 19.0%.[8] Other studies report consistently high rates of lack of concordance between the sentinel node and the clipped node ranging from 23% to 27%.[19–21] The main driving factor for performing TAD rather than SNB is that the remaining positive nodes may be missed with SNB alone (FNR >10% with SNB). In the setting of NAST, a positive clipped node represents disease that is resistant to the systemic therapy that has already been given and is therefore more significant than in the setting of upfront SNB where adjuvant therapy is likely to treat residual disease.

Of the eight patients whose clipped node was not retrieved, two patients had an intraoperative X-ray and four patients had axillary dissection of whom one patient had evidence of the residual clip in the axilla. We hypothesize that due to nodal fibrosis, the clip could have herniated through the node to lie within the perinodal fat. One of the greatest challenges we faced was accurate localization of the clipped node before surgery. Being able to locate the clipped node on post-NAST imaging predicted that the relevant node could be wire localized on the day of surgery. Not being able to see the LN marking clip meant the radiologist was unable to place a hook wire into the relevant node. Furthermore, some of the localizations were painful for the women as the wire was passed through the pectoralis major muscle from an anterior approach to ensure other axillary structures were not placed at risk. To overcome the challenge of visualization and subsequent localization of the biopsied node after NAST, our unit has commenced the utilization of a more echogenic clip (BARD UltraCoil Twirl marker).

In our study, we were unable to calculate the FNR of clipped node removal due to the small number of patients undergoing ALND. Other studies have reported acceptably low FNR for TAD. Caudle and Kuerer reported an FNR of 4.2% when only RIS clipped node was removed (95% CI 1.4–9.5; 5 of 120). With TAD, the FNR halved to 1.4% (95% CI 0.05–10; 1 of 50).[11] Donker *et al*. reported that the IR of the marked node was 97% (97 of 100) and the FNR was low at 7% (95% CI 2–16; 5 of 70).[15] Further studies have supported the accuracy of TAD and/or the removal of the marked node; however, these studies included only a small number of patients and have vast heterogeneity. An ongoing Dutch prospective multicentre study, the RISAS trial, aims to recruit 250 clinically node-positive breast cancer patients. The marked positive RIS node and SLNs are removed and examined together and this is subsequently followed by completion ALND.[22]

The limitation of this study is the small number patients from a single institution and retrospective nature of analysis. The lack of localization due to radiologist availability or inability to visualize the clipped node may have led to a lower detection rate of the clipped node. In addition, the true FNR could not be determined as not all patients went on to have ALND, at the discretion of the MDT due to the small burden of nodal disease, the number of LNs retrieved at SNB or patient choice. As this series represents the first case using a new technique, it is likely that it represents a 'learning curve' series that may underestimate the utility of the procedure in a mature practice.

Conclusion

TAD is a feasible technique for augmenting SNB for axillary staging in patients with clinically N1 breast cancer who receive NAST. Preoperative clipped node localization significantly improves the IR of the clipped node. The clipped node is not always retrieved as the SLN which could explain the high FNR of SNB after NAST. With the increasing experience globally and the refinement in marking and localization techniques, the accuracy of performing TAD will likely improve.

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Conflicts of interest

None declared.

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