International Journal of Surgery Case Reports 126 (2025) 110723

Contents lists available at ScienceDirect

International Journal of Surgery Case Reports

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

Case series

Nerve autofluorescence to enhance nerve visualization during axillary lymph node dissection in three breast cancer patients: Case series

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ARTICLE INFO

Keywords:
Axillary lymph node dissection
Breast cancer
Iatrogenic nerve injury
Nerve-sparing surgery
Fluorescence imaging
Dendrite® imaging system

ABSTRACT

Introduction and importance: Iatrogenic nerve injury is a possible complication of axillary lymph node dissection (ALND), which remains standard-of-care for some breast cancer patients. Recently, several studies have demonstrated that nerves auto-fluoresce in near-ultraviolet light (NUVL). We describe three women with BC in whom a recently-developed NUVL camera was used to facilitate visualization of and prevent iatrogenic injury to the intercostobrachial, long thoracic, and thoracodorsal nerves during ALND.
Case presentation: In all three women, ALND was deemed necessary per current guidelines for the treatment of locally-advanced breast cancer following neoadjuvant chemotherapy. The surgery was performed using standard-of-care surgical techniques, except that a Dendrite® Imaging System was employed to visualize the surgical field both in white light and NUVL. In all patients, all nerves fluoresced brightly throughout their course in the surgical field. Such visualization was crucial during resection of lymph nodes close to nerves. No peri-operative complications occurred and no evidence of neurological injury was evident at one-month follow-up.
Clinical discussion: The Dendrite® Imaging System employs a NUVL light source and filter system to detect fluorescent signals emitted by neural tissue. These signals then pass through a filter system within the camera head, are captured by a chip, and are transmitted to a dedicated software platform for real-time analysis, processing, and relay to a display screen, allowing the surgical team to observe neural structures with clarity.
Conclusion: In three breast cancer patients undergoing ALND, nerve autofluorescence under NUVL aided in visualizing and preventing injury to all nerves within the surgical field.

1. Introduction

Axillary lymph node dissection (ALND) was the standard of care for all breast cancer patients until the 1990s, the underlying rationale being that achieving complete surgical removal of loco-regional tumor residues should reduce cancer recurrence and improve patient survival [1]. However, the almost ubiquitous use of ALND changed after the introduction of sentinel lymph node (SLN) biopsy [2] and its use declined even further after the landmark ACOSOG-Z0011 study [3]. This said, ALND remains the recommended surgical procedure for a sizeable number of patients, including those with residual nodal disease after neoadjuvant chemotherapy (NACT) [4,5].

One possible complication of ALND is iatrogenic injury to nerves that run through the axillary space. Such an injury that can lead to both motor and sensory sequelae which include chronic upper extremity pain, arm weakness, limited shoulder motion, and reduced grip strength [6]. The neuropathic pain that can result, especially from injury to the intercostobrachial nerve as it runs through the axilla, can be both severe and permanent [7].

Here, we report our experience using a recently-developed nerve imaging system [8–11] in three post-menopausal women with breast cancer requiring ALND to treat residual nodal disease after NACT. This imaging system, called the Dendrite® imaging system, causes axillary nerves to autofluorescence in near-ultraviolet light (NUVL), thereby

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https://doi.org/10.1016/j.ijscr.2024.110723
Received 15 October 2024; Received in revised form 5 December 2024; Accepted 7 December 2024
Available online 9 December 2024

facilitating their visualization and, by doing so, potentially aiding with nerve-sparing ALND.

2. Presentation of cases

This case series has been drafted in full compliance with 2023 SCARE guidelines [12] and all patients provided written informed consent before being enrolled in this study.

In three women, 51 to 63 years old, with breast cancer, our surgical team utilized a novel nerve autofluorescence imaging system (Dendrite®, Germany) to optimize visualization of the intercostobrachial nerve (ICBN), long thoracic nerve (LTN) thoracodorsal nerve (TDN) within the operative field during ALND. The Dendrite® Imaging System (Fig. 1) that we used employs a light source with wavelengths in the NUVL spectrum and a filter system to detect auto-fluorescent signals emitted by neural tissue. This auto-fluorescence is captured and transmitted to a dedicated software platform for real-time analysis and processing. The processed image is then relayed to a display screen within the operating theater, which permitted us to observe neural structures in real-time. In all three of these patients, ALND was deemed necessary to treat residual nodal disease within the ipsilateral axilla after NACT.

In the operating room, each of these three patients was placed supine with her ipsilateral arm abducted to 90°. A linear 8–10 cm incision then was made at the lateral margin of the pectoralis major muscle on the anterior axillary line, and subcutaneous tissue incised up to the clavipectoral/Berg's fascia. The fascia was incised at the lateral border of the pectoralis major muscle.

Pre-determined limits of ALND were the inferior edge of the axillary vein superiorly, chest wall medially, and anterior border of the latissimus dorsi muscle laterally. The depth limit for dissection was the thoraco-dorsal pedicle. Dissection started with the medial part of the fat and lymphatic tissue down to the serratus anterior muscle and chest wall. At this point, the Dendrite® camera was used to visualize and preserve the ICBN, LTN and TDN.

From this point onward, the surgeon alternated between standard operating room light and NUVL, as necessary, to visualize the various brachial plexus branches, which lay superior to the axillary vein. The lateral thoracic vessels then were ligated and disssected in a medial-to-lateral direction. The thoraco-dorsal pedicle was identified infero-dorsal to the axillary vein, after which dissection proceeded downward. Here, NUVL again was used to prevent injury to the TDN. The lower limit of dissection was identified as the crossing of the LTN, over the thoraco-dorsal pedicle, again enhanced under NUVL.

In all three patients, we were able to easily isolate and safeguard the ICBN, the TDN, and the LTN, clearly identifying each nerve's course throughout the surgical field, especially helping us to avoid iatrogenic injury to nerves lying close to lymph nodes (Figs. 2 and 3). Utilizing the camera to identify the nerves never took more than two to three minutes in total, and might have decreased the time required to dissect out the nerves since nerve autofluorescence both confirmed that the structure visualized was a nerve, and facilitated visualization of each nerve over its entire course through the surgical field. Toggling back and forth from white light to NUVL also facilitated reconfirmation of each nerve's location at different stages of dissection when visualization under white light was difficult.

No post-operative complications occurred; and, at one-month follow-up, no patient had any symptoms or signs of nerve injury during a thorough neurological assessment.

The work has been reported in line with the PROCESS criteria.

Fig. 1. Dendite® imaging system.

3. Discussion

Iatrogenic injury, especially to the LTN and TDN coursing through the axilla, is a potential complication of ALND and often leads to both motor and sensory sequelae. Since the long thoracic nerve innervates the serratus anterior muscle, injury to it results in a winged scapula and patients may complain of upper extremity weakness and/or decreased shoulder range of motion. The thoracodorsal nerve innervates the latissimus dorsi muscle, and injury causes loss of function.

In published literature, ALND is also consistently associated with a higher prevalence and intensity of chronic pain and sensory disturbances than SLN biopsy, due to the iatrogenic injury of the intercostobrachial nerve, affecting from 25 to 60 % of patients [13,14]. For example, Steegers et al. found that ALND doubled the risk of chronic pain after breast cancer surgery, observing chronic pain prevalence rates of 51 % with ALND versus 23 % without [15]. Zhu and colleagues demonstrated that, though identifying the ICBN during axillary dissection added 10–20 min to the procedure, it also significantly reduced the incidence of post-mastectomy pain syndrome and significantly improved patients' post-operative quality of life [16].

For all these reasons, avoiding unintentional nerve damage during

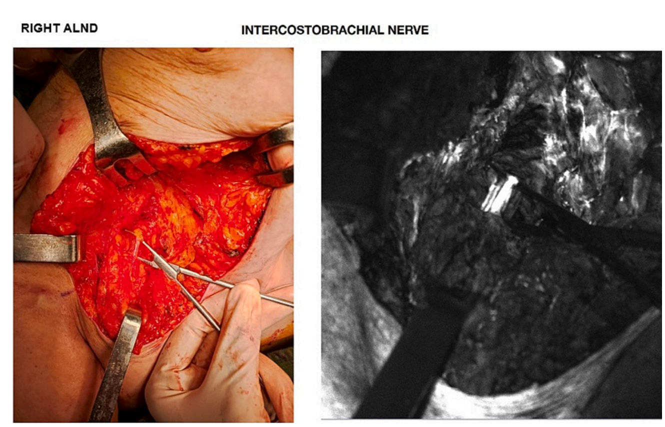

Fig. 2. Intra-operative images of the axilla under A) standard operating room (white) light and B) near-ultraviolet light (NUVL) showing the intercostobrachial nerve (ICBN).

LEFT AXILLARY LYMPH NODE DISSECTION

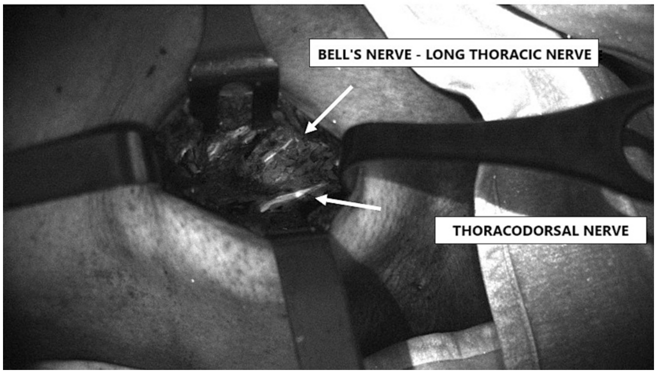

Fig. 3. Intra-operative images of the axilla under near-ultraviolet light showing the long thoracic nerve (LTN) and the thoraco-dorsal nerve (TDN).

ALND is paramount. However, achieving this requires that surgeons accurately identify and, when needed, precisely dissect nerves within the surgical field, both of which can be challenging, even for surgeons with extensive surgical experience [8]. Nerve damage contributes appreciably to pain after breast cancer surgery, with neuropathic pain the most prevalent type of chronic post-operative pain. This is because major nerves pass through the ALND surgical field [17].

That nerves auto-fluoresce in NUVL has already been shown in various surgical scenarios, including thyroid and parathyroid surgery, parotid surgery, and both spinal and peripheral nerve surgery [10,11]. Why nerves and other tissues autofluoresce relates to various cellular metabolites and co-enzymes of metabolic pathways critical for normal cellular functions, as well in pathophysiological signal transduction [18].

We believe that ours is the first reported experience using a nerve-specific imaging device which detects auto-fluorescent signals emitted by nerve tissue during breast cancer surgery. As explained earlier, the Dendrite® imaging system that we used employs a light source that emits wavelengths in the NUVL spectrum, as well as a filter system which detects auto-fluorescent signals emitted back toward the camera by neural tissue. This auto-fluorescence is captured and transmitted to a dedicated software platform for real-time analysis and processing, after which the processed image is relayed to a display screen within the operating theater. This allows surgeons to observe neural structures in real-time. At no point using this imaging system is any contrast agent necessary.

To date, the few published studies that have generally examined the potential use of fluorescence imaging for the intra-operative detection and protection of nerves specifically examined the effectiveness of various fluorescent dyes in animal models [18,20]. However, employing neural tissue autofluorescence to visualize nerves has several advantages over using dyes. First, all dyes require administration some time prior to when target visualization is required, and then are limited in how long they provide adequate fluorescence. The same is not true of auto-fluorescence, which should appear every time the surgical field is viewed under NUVL. Second, NUVL auto-fluorescence avoids all potential toxicity from and allergenic reactions to administered dyes [21]. In our three post-menopausal women with persistent nodal disease after NACT requiring ALND, visualizing the surgical field in NUVL resulted in clear demarcation of all nerves throughout their course through the surgical field and, hence, facilitated nerve-sparing dissection of all the axillary nodes. Moreover, none of these three patients experienced any symptoms or exhibited any signs of iatrogenic nerve injury up to one month after surgery.

Limitations of our study clearly center on just having three patients, and further research remains necessary. On the other hand, in a previously-published study using Dendrite® imaging in $n = 65$ patients undergoing thyroidectomy procedures to prevent iatrogenic injury to the commonly-injured recurrent laryngeal nerve (RLN), all 81 RLNs were seen more clearly under NUVL (mean fluorescence intensity, $\mu = 134.3$ RFU) than either thyroid ($\mu = 33.7$, $p < 0.001$) or background ($\mu = 14.4$, $p < 0.001$). Moreover, scatter plots revealed no overlap between RLN intensity and that of either other tissue. Sensitivity and specificity for RLN both were 100 %, even visualizing nerve branches as small as 1 mm in diameter. All the RLNs and all the nerve branches were clearly visualized under fluorescence, versus just 56.7 % of the RLNs and 48.9 % of their branches, respectively, with white light (both $p < 0.001$). Visible nerve length also was 2.5 times as great under NUVL as under white light ($\mu = 1.90$ vs. 0.76 cm, $p < 0.001$) [10].

The main shortcoming of the Dendrite® imaging system is the limited penetration of NUVL waves to a tissue depth of just 5 mm. As such, nerves >5 mm deep to the surface require some dissection prior to the camera's use. We emphasize, however, that just like targeted fluorescent dyes that also are limited by the depth of fluorescent light penetration and typically require some dissection to visualize nerves, autofluorescence with this NUVL camera confirms the nerve's identity as a nerve, accentuates its course throughout the surgical field, and facilitates re-localization (by toggling between white light and NUVL) whenever required at the various stages of ALND.

4. Conclusions

Our experience, though limited by small sample size, suggests that using an imaging device to detect nerve autofluorescence during ALND facilitates nerve detection, which could prevent nerve injuries. Larger studies, including randomized clinical trials, are needed both to confirm the enhanced nerve visualization we observed under NUVL, and to determine if and how this might affect surgical outcomes.

Author contribution

NR was the main author of the paper. However, all the authors contributed to study design and paper writing, and all edited the manuscript prior to submission.

Consent

The patients have signed informed consent for the participation in this scientific study.

Ethical approval

We did not require ethical approval from our EC (Campania 3, Naples, Italy) for case reports or case series.

All patients provided informed written consent.

Guarantor

Dr. Ingenito is the study guarantor.

Research registration number

This is not the first time that Dendrite camera use has been reported for a human patient.

Funding

No external funding was received for this study.

Conflict of interest statement

None of the authors has any conflicts of interest to declare.

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