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Preliminary experience in sentinel node and occult lesion localization (SNOLL) technique—One center study

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ABSTRACT

Aim: The aim of this study was to present one center experience in applying the SNOLL technique to patients with suspected occult breast lesions.

Background: In the last years, the widespread use of mammographic screening programs resulted in an increasing number of women with nonpalpable suspicious breast lesions requiring further examination. The new method called sentinel node and occult lesion localization (SNOLL) enables the intraoperative detection of nonpalpable breast tumors and sentinel node biopsy in one surgical procedure.

Materials and methods: 46 patients with suspected malignant lesions or diagnosed non-palpable breast cancer were subjected to a pre-operative SNOLL procedure. The day before the surgery, they were administered two radiotracers: one to localize the tumor and the other to localize the sentinel node. During the surgery, the breast tumor and the sentinel node, which in most cases had been examined intraoperatively, were detected with a handheld gamma probe and resected under its control.

Results: All 46 (100%) patients had their occult breast lesions resected. Histopathologic examination revealed cancer in 40 patients: in situ in 2 cases, invasive in 38 cases. All these patients had their sentinel nodes examined. In one case only, the sentinel node could not be located with a gamma probe. Intraoperative tests showed the sentinel node to be metastatic in 5 patients, who were then given a simultaneous axillary lymphadenectomy. In addition, the final histopathologic examination revealed metastasis to the sentinel node in one patient, who had to be reoperated.

Conclusion: SNOLL is a modern technique that enables a precise intraoperative localization of non-palpable suspected malignant breast lesions in combination with a sentinel node biopsy. Extended application of intraoperative management leads to significant decrease in the number of reoperations performed in patients with early bread cancer.

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1. Background

Recently, a considerable growth in the number of diagnosed cases of early breast cancer has been observed. This has become possible mainly because of the larger availability of screening assays, prevention programs, and changes in women's awareness of and approach towards the disease. Owing to the development of imaging and biopsy techniques, neoplastic lesions of the breast can now be detected at a very early stage, before becoming clinically palpable. In such cases modern medicine offers breast conserving therapy (BCT), an option providing patients a significant improvement in their comfort and quality of life.

Today, BCT often involves quadrantectomy with a sentinel node biopsy, supplemented by an appropriate post-operative procedure, i.e. radiotherapy with or without systemic treatment. This type of management often ensures good cosmetic results with minimum surgical intervention.[1–3]

The main issue with non-palpable breast lesions, which represent 30% of diagnoses, is to localize them precisely enough to be able to perform a correct excision with an adequate margin of healthy tissues, while limiting the extent of the surgical procedure from being too extensive. Therefore, efforts are being made to develop a method to permit this kind of precise localization.[1] Currently, most commonly used is the needle localization technique employing wires that are inserted into breast lesions under mammographic or ultrasound guidance. This method, however, is marked with several important drawbacks. The very process of inserting a needle into the breast is time consuming, often painful and unpleasant. The wire is likely to be displaced, particularly in breasts with a predominant fatty component.[3,4] It may also cause injuries both to the patient and to the medical staff engaged. A surgeon resecting a lesion follows a needle-marked track, thus removing a wide range of healthy tissues and undermining the cosmetic effect of the procedure.[4]

A new method for the localization of occult breast lesions has been developed in recent years. Radio-guided occult lesion localization (ROLL) was first proposed in 1997 in the European Institute of Oncology, Milan, Italy.[1,2] It involves intratumoral injection of a radiotracer under mammographic and ultrasound guidance. The injection site is located intraoperatively by means of a handheld gamma camera which also enables controlled dissection of the lesion.[1] ROLL may therefore be used as a diagnostic and therapeutic method for occult breast tumors. A great deal of research has proved this method to be superior to the commonly used guidewires.[3,5]

When a non-palpable early breast cancer is recognized preoperatively, the status of regional lymph nodes has to be determined. This is made possible by a sentinel node biopsy, which is an optional method in such cases.[1] The application of both ROLL and SNB within one surgical session has given rise to the development of SNOLL (sentinel node and occult lesion localization), first described and performed in Milan's European Institute of Oncology in 1998.[1,2]

2. Aim

The aim of this study is to present our experience in the use of SNOLL technique in patients with occult malignant breast tumors which were qualified for breast conservative surgery.

3. Materials and methods

Forty-six female patients aged 41–78 (mean age: 59) were subjected to the SNOLL procedure between May 2008 and May 2009.

All the patients had been diagnosed to have a solitary, non-palpable breast cancer and suspected malignant breast lesions revealed by ultrasonography and/or mammography. They had been ranked 4–5 in the BI-RADS scale and classified as T1 (size $\leq$ 20 mm). Clinical examination had not indicated any suspected axillary lymph nodes. 36 women had been preoperatively diagnosed with early breast cancer, as based on cytologic examination (22) and a thick-needle biopsy (29). In the patients diagnosed with stereotactic biopsy, the breast area after the procedure had been marked with a titanium clip which could be detected by ultrasound within 4–6 weeks post-implantation. In the case of 10 patients with suspected malignant lesions, it was necessary to perform an intraoperative examination of frozen specimens resected by means of ROLL. Patients with proven cancer were given a sentinel node biopsy to obtain specimens for intraoperative histopathologic assessment. Informed consent was obtained from all patients.

Two types of radiotracers (^{99m}Tc) were used in the SNOLL procedure:

1. human albumin macroaggregates (MAA), with particles sized 10–150 μm, used in the ROLL procedure. This is an immobile radiotracer that remains in the site of the injection (MAASOL, GE Healthcare);
2. human albumin nanocolloid (NC), with particles sized 10–80 nm which is used in the SNB procedure. This is a mobile radiotracer that migrates through lymphatic conduits from the injection point to the sentinel node, where it accumulates (Nannocol, GE Healthcare).

Radiotracers were prepared by the Nuclear Medicine Department in single doses of ^{99m}Tc-MAA of 15–20 MBq diluted in 0.2 ml saline and ^{99m}Tc-NC of 37 MBq diluted in 0.5–0.7 ml saline (volume depending on the size of the breast). Tracers were inserted one day before the planned surgery under ultrasound guidance (line probe of 7.5–10 MHz) in cooperation with a radiologist responsible for the localization of the breast lesion. First, an intratumoral ^{99m}Tc-MAA injection was made, followed by an intracutaneous ^{99m}Tc-NC injection at a site located above the tumor. A lymphoscintigraphy was performed the following day, before the surgery, usually 16–22 h after the tracer implantation. A frontal scan exposed the tracer injection sites in the breast and the axillary sentinel node(s) in the form of a hot spot (Fig. 1). A handheld gamma probe was used during the surgery (Neoprobe 2000, Johnson&Johnson) to localize the non-palpable breast lesion and the sentinel node, as well as to guide the procedure (Fig. 2). During

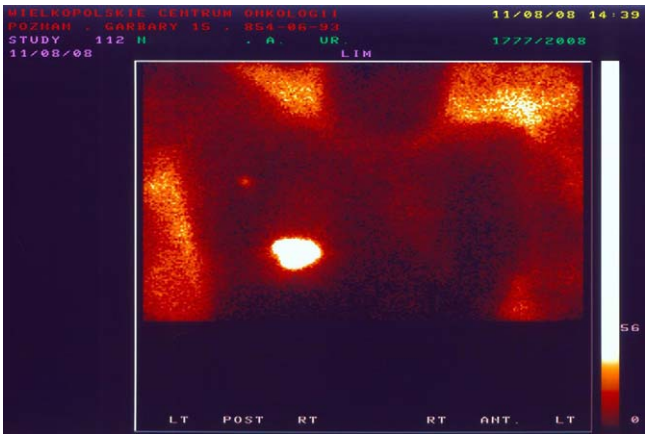

Fig. 1 – Lymphoscintigraphy (the big spot – the site of tracer injections, the small spot – the sentinel lymph node).

quadrantectomy, the skin on the breast was cut right above the hot spot indicated by the probe (Fig. 3). A specimen thus received was evaluated intraoperatively by means of a radiogram and histopathologic examination (type of tumor, size of cancer-free margins). When the pathologist reported the margin to be uncertain or too small, the surgeon responded immediately by re-excision of a concerned area of the breast. To be deemed sufficient, the margin had to be at least 0.5 cm wide or clear from the side of the breast muscle and/or skin. Patients with confirmed breast cancer were additionally treated with a sentinel node biopsy. Resected specimens of the sentinel node were also subjected to intraoperative histopathologic assessment. If metastasis was found, the patient underwent a concurrent lymphadenectomy.

4. Results

Non-palpable breast tumors were successfully localized intraoperatively and fully resected in all 46 patients.

Fig. 2 – Gamma probe for detecting "hot spot" of the breast tumor and the sentinel node.

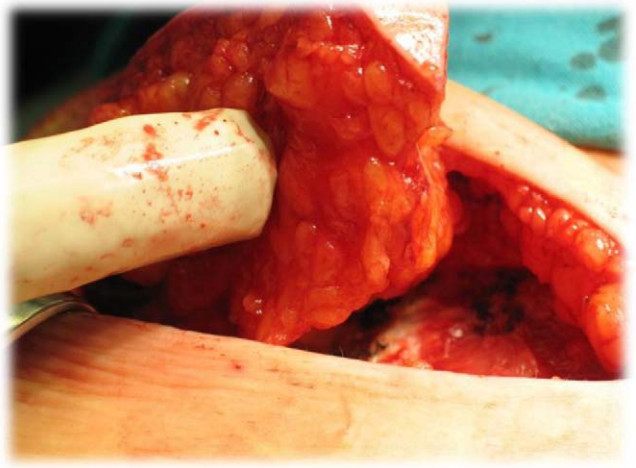

Fig. 3 – Intraoperative tumor localization using a gamma probe (ROLL).

Table 1 – Histopathological diagnosis of resected breast lesions.

Diagnosis	Number of patients	%
Benign lesions	6	13
Cancer	40	87
Non-invasive cancer		
DCIS	2	9
LCIS	0	0
Invasive cancer		
Ductal	24	63
Ductal and in situ	9	24
Lobular	2	5
Other	3	8
Total	46	100

The final histopathologic examination revealed invasive cancer in 38 patients, cancer in situ in 2 patients, and benign lesions in 6 patients (Table 1).

The average size of a ROLL-localized tumor was 12 mm (range 4–21 mm in final pathological examination). The median volume of excised specimens was $79.55 \pm 42\ cm^3$. In 95% of cases, malignant breast lesions were removed with negative surgical margins (Table 2).

Sentinel node biopsies were performed in all 40 patients with diagnosed breast cancer. An average of 1.7 of sentinel node was resected. The sentinel node could not be located

Table 2 – Margins after quadrantectomy.

Diagnosis	Number of patients	%	Radicalization
Clear margins	30	75	None
Small margins (≤4 mm)	8	20	Intraoperative (margin extension)
Involved margins	2	5	Post-operative (mastectomy/ reexcision)
Total	40	100	

Table 3 – Sentinel node status assessment in 40 patients.

	Number of patients	%
Metastatic	5	12
Non-metastatic	35	88
Lymphadenectomy		
Simultaneous	4	80
Second surgery	1	20

in one patient. In this case the axillary nodes dissection was performed. In 4 invasive cancer patients, metastasis to the sentinel node was recognized during intraoperative examination. These patients were treated with axillary lymphadenectomy within the same surgical session. The final post-surgery histopathologic examination revealed neoplastic cells in the sentinel node in another patient, who underwent a second operation. Data concerning the sentinel node are presented in Table 3.

5. Discussion and conclusions

Recently, a growth in the number of diagnosed early breast cancers has been observed due to the increased availability of imaging examinations and disease prevention programs. Now, it is necessary to develop a reliable, safe and patient-friendly method of localizing non-palpable lesions. The SNOLL procedure, currently applied in some European oncology centers, has already been recognized as an important component of breast conservative therapy.[1–3] In our department, the ROLL and SNB techniques are applied to patients with diagnosed early breast cancer. There are two reasons for that. First, with a lesion being usually small in size and clinically impalpable, the main task of a surgeon is to cut it out precisely, with an adequate margin of healthy tissues, which can be best achieved by the ROLL technique.[7–9] Besides, as small malignant tumors pose a relatively low risk of metastasis to the axillary lymph nodes, their complete excision often proves unnecessary. Therefore, the widely accepted method of sentinel node biopsy is particularly advisable in early stage breast cancer.[10] With selected patients of our center, we resort to a modern approach involving concurrent application of both techniques. The SNOLL procedure is being used in a variety of ways, depending on the experience of a medical center.

Treatment of occult breast cancer aims primarily at its precise resection together with an appropriate margin of surrounding tissues. More and more emphasis is being put on preventing unnecessary removal of healthy tissues and on improvement of the post-operative cosmetic effect. Therefore, efforts are being made to develop techniques enabling precise pre-operative and intraoperative localization of occult breast lesions. There are several methods that are currently in use for this purpose, e.g. skin marking with USG, intraoperative US, carbon localization or, most commonly applied, wire-guided localization (WGL). Most of these methods, however, are characterized by insufficient accuracy. The standard technique, used in many cancer therapy centers, involves needles of various shapes and sizes inserted into the suspected breast area. The needles are usually implanted under the guidance of stereotactic mammography. While this method offers some obvious benefits, it also has a number of important weaknesses. The injection itself is rather traumatic and longlasting. Needles being inserted into a patient's breast may cause pain and bleeding. There is no practical way to adjust the position of a wire after it has been placed incorrectly. In breasts with a predominant fatty component there is a risk of needle displacement and consequent failure to collect a specimen or resect the whole of a tumor. On the other hand, breasts with a predominant glandular component are more difficult for implanting a wire.[3] The ROLL method is a way to avoid all the disadvantages of the wire-guided procedure, while providing the benefits of precise localization and access to the center of an occult breast lesion. It is a low-invasive, fast, and thus patient-friendly method of tracer implantation. There is a larger rate of clear margins of resected specimens, resulting in a lower rate of reoperations. There is more convenience of use and a better resection spacial control offered by a hand-held gamma probe. Finally, the lower volume of resected breast gland means a significant improvement in the cosmetic effect.[11]

Many comparative studies of the needle method and the ROLL technique have been conducted in recent years. Results clearly indicate the superiority of the latter.[3–5,11] Indeed, in terms of resection radicality, the ROLL method has brought about a substantial reduction in the rate of reoperations.[12] Nadeem et al. stated in their study that clear margins were found in 83% of patients treated with ROLL versus 57% of those treated with needle localization.[11] Medina-Franco et al. indicated proportions of 87.5% and 62.5% for the ROLL and the wire-guided methods, respectively.[13] The multi-center, randomized clinical study published by van Esser et al. showed a 15% advantage in the rate of clear margins achieved by ROLL.[9] Similar differences can be derived from a comparison between the sizes of breast specimens resected with the aid of ROLL and WGL. The studies made by Nadeem et al. or Mariscal-Martinez et al. did not show any statistically significant differences in the volume and weight of the specimens.[11,14] Zgajnar et al., on the other hand, demonstrated a lower mean weight of breast specimens resected with the ROLL technique (40 g and 53 g for ROLL and WGL, respectively).[15] The post-operative cosmetic effect was also compared. ROLL patients rated the effect as very good in 75% and good 25%, while WGL patients rated it as very good in 54% and good in 46%.[11,13] Both methods were also compared in terms of patient's discomfort during procedures, the costs and time required, the level of difficulty, and the rate of sentinel node identification. The studies and analyses definitely confirm the radioguided method to be more beneficial.[3,5,9,11,13–15]

The original SNOLL method, developed by the European Institute of Oncology (EIO), Milan, in 1997, which combines the ROLL technique with a sentinel node biopsy, employs two types of Technetium Tc99m carriers. Human albumin macroaggregates (Maasol, GE Healthcare, Italy) have particles large enough not to be drained by lymph vessels around the tumor and therefore stay at the site of injection, clearly indicating the location of a non-palpable breast lesion. Smaller particles of nanocolloid (Nanocoll, GE Healthcare, Italy) can in turn easily penetrate into the lymph vessels and move freely to the sentinel node, where they accumulate to make it detectable.[1,2,10] In our department, we have introduced the

original method of EIO. Other centers which have adopted SNOLL have developed their own variants of the method.

Studies published in recent years have shown comparable effects of applying the SNOLL method with a single radiotracer [12,16,17]. Feggi et al. proposed the use of a nanocolloid labeled with Technetium-99m (NC-Tc99m) of 0.3–0.4 ml for simultaneous performance of ROLL and sentinel node identification. One day before surgery, half of the dose was injected intratumorally and half superficially, but very close to the tumor. The procedure was 100% effective in permitting the excision of occult breast lesions and 97.3% effective in permitting the localization of the sentinel node. The authors of the study stressed that the single tracer method is a useful option in that it saves time and costs, as well as facilitates the procedure.[16] Similar conclusions were drawn by Lavoue et al., who only injected technetium-labeled nanocolloid peritumorally: 0.2 ml above and 0.2 ml below the tumor.[12] Although all patients had their non-palpable breast lesions removed, the sentinel node identification rate of 90% was not fully satisfactory, calling for further improvement of the technique.[16]

The single tracer method also has the inconvenience of failing to determine the exact scope of radioactivity for a certain group of patients. This may result from the broadening of the signal emitted from two insertion sites located close to each other and nanocolloid migration to adjacent lymph vessels. Nevertheless, most of the studies referred to in this article confirm the feasibility of a single radiopharmaceutical in the SNOLL technique. This is certainly a way to facilitate the procedure, while reducing the time and costs needed to perform it.[12,16,17]

Another disputable issue regarding SNOLL is where to inject a radiopharmaceutical to achieve the best possible identification of the sentinel node. Studies concerning sentinel node localization have proposed a large variety of possible locations for injecting Tc99 nanocolloid. The most frequently described are: intratumoral, peritumoral, subdermal/intradermal and periareolar/subareolar injections.[10]

In our study, we followed the experience of the European Institute of Oncology by administering a tracer intradermally with a typical bubble on the skin right above the tumor, at a point marked by a radiologist with a felt-tip pen. We did not apply additional patent-blau staining, relying on our own long experience in sentinel node biopsy and so as to avoid possible tattoos that clearly deteriorate the post-operative cosmetic effect. Utilizing this method, we achieved 98% sentinel node identification. Barros et al. confirmed in their study that a combination of two tracers – radioisotope and patent-blau – in a medical center having extensive experience in the application of radioisotopic techniques does not produce significant benefits with respect to sentinel lymph node identification.[18] It has to be assumed that in a certain number of cases the sentinel node simply cannot be localized. The reasons for this may be the variable anatomy and size of the breast, blockage of a lymph vessel, massive invasion of neoplastic cells into the lymph node, or even incorrect preparation of radiopharmaceuticals or an inadequate time interval between the tracer injection and the surgery. With some of these possible factors being beyond control, the sentinel node remains undetectable in a small percentage of patients despite proper implementation of the method.[10]

The study by de Cicco demonstrates a higher rate of sentinel node localization with Tc99m-labeled nanocolloid injected subdermally (98.8%) as compared to peritumoral injection (80.6%) and intratumoral injection (88.6%).[2] Opposite results were published by Feggi, who recorded a higher rate of sentinel node identification after injecting a radiotracer in the immediate vicinity of the tumor.[16] Patel, apart from ^{99m}Tc-nanocolloid, performed a periareolar intradermal/subcutaneous injection of patent blue-V dye in order to optimize sentinel node localization.[19] Out of many possible nanocolloid injection sites proposed by multiple studies, the periphery of the tumor seems to be the most advisable location. Further research in this area is necessary though, as findings regarding sentinel node identification in the SNOLL method vary across centers.

The radioisotopic method, with all its benefits, is beyond any doubt an interesting alternative to the needle technique, which is still regarded as a standard approach. Our study confirms that the SNOLL technique allows an exact intraoperative localization of clinically occult breast cancer and the sentinel node within one surgical session. The method enables a precise and fast excision of a breast tumor with a minimum necessary margin of healthy tissue. Reoperations forced by positive margins had to be performed in 5% of patients only. The simultaneous intraoperative performance of a sentinel node biopsy and sentinel node status assessment in patients with confirmed cancer has also largely contributed to the reduction of necessary reoperations. The results of this study have encouraged us to use SNOLL in our department's everyday practice as a method of effective therapy for early non-palpable breast cancer.

At present however, its widespread development is somewhat restricted by factors such as limited access of breast cancer treatment centers to nuclear medicine facilities. Many authors also emphasize that good cooperation between the radiologist, the nuclear medicine physician and the surgeon is a necessary condition for optimal utilization of the SNOLL method.[13] Considering that the current approach to early breast cancer treatment is targeted towards minimalization of patients' discomfort and injury, it seems that general implementation of the SNOLL technique is just a matter of a short time and the proper organization of breast units.

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