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Use of the Patent Blue and Air in the Preoperative Marking of Impalpable Breast Lesions

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ABSTRACT

Objective: The goal of this study is to analyze the applicability of the patent blue dye and air in the preoperative marking of impalpable mammary lesions with indication of surgical resection.

Materials and Methods: A prospective cohort study was performed. We selected 49 patients with detection of impalpable lesions on a breast mammography or breast ultrasonography. The patients received the dye injection as close to their surgery time as possible. The criteria analyzed included: 1) complete marking and identification of the lesion; 2) complete removal of the lesion; 3) in cases of malignant lesions, presence of free margins for successful surgery; 4) occurrence of allergic events; 5) necessity of reoperation; and 6) difficulty in locating lesions.

Results: All lesions were marked, and they were successfully excised. In cases of malignancy, free margins were obtained in 100% of the cases. There were no allergic events or reoperations. Only 8.9% of the lesions were difficult to locate.

Conclusion: The marking with patent blue and air is an effective alternative for the labeling of impalpable breast lesions, and it has satisfactory surgical oncology results. All lesions were resected, 91.1% of them were performed with no difficulties, and free margins were obtained in 100% of cases of malignancy.

Keywords: Breast neoplasms, coloring agents, biopsy, mammography, patent blue

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Introduction

The dissemination of breast cancer screening, associated with more accurate imaging techniques, has resulted in an increase in the incidence of non-palpable breast lesions (1). This approach follows the proposal of the Breast Imaging Reporting and Data System (BI-RADS®) (2), published by the American College of Radiology and recommended by the Brazilian College of Radiology. When the impalpable lesions are classified as BI RADS IV and V, the cytological and/or histological diagnosis is crucial to define the appropriate therapy (3). This diagnosis can be established by minimally invasive diagnostic methods, such as large-core needle biopsy or vacuum-assisted biopsy (mammotomy). Once the surgical removal of the lesion is indicated, it is recommended to perform the preoperative marking of the lesion. It may be guided by ultrasonography, mammography or magnetic resonance imaging (3).

The current widespread methods use techniques with radioactive material (Radio-guided occult lesion localization (ROLL)), metallic suture, activated charcoal or dyes, such as patent blue, methylene blue and indocyanine green. ROLL and Wire-Guided Localization are currently the most commonly used techniques, and they obtain important results in the marking. However, these techniques have significant limitations, such as their high cost, the need for a nuclear medicine specialist on the team (in the case of ROLL), and possibility of breakage or displacement of the wire during surgery (4-6). Thus, it becomes important to search for new more readily accessible and less invasive methods for marking lesions.

To date, only 1 study has described the use of air associated with a dye in the preoperative marking of impalpable breast lesions (5). Injection of air, concomitantly used with the dye, improves the ultrasound identification of the lesions and can allow a better dissection of the tissues, causing less trauma and improving aesthetic results. Thus, air use may be an alternative to improve both the accuracy of the lesion location and the surgical outcomes of marking impalpable lesions with dyes. Therefore, the objective of this study was to evaluate the performance of the use of the patent blue dye and air in the preoperative marking of non-palpable breast lesions with indication of surgical resection and its ability to locate and allow the complete resection of the non-palpable lesion.

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Material and Methods

This was a prospective and descriptive study. We initially selected all patients who were diagnosed with non-palpable breast lesions by imaging methods in three hospitals of a capital city located in the northeast of Brazil. These patients had undergone surgical excision between February 2012 and March 2015. Patients who were not operated on by the same surgical team were excluded from the study in order to account for variations due to differing levels of experience that could influence the outcomes of operations.

The diagnostic imaging was made through mammography and/or breast ultrasonography. According to their radiological characteristics, the lesions were classified in microcalcifications (calcium deposition seen in the mammography), cysts (the presence of liquid inside the lesion identified by the ultrasound) and nodules (solid lesions). At first, we selected 53 patients who presented suspicious lesions. Some of them were undergoing removal of the lesions for another reason, such as family history of breast cancer. The inclusion criteria were: 1) the patients have to accept marking of the lesions with patent blue dye and air; 2) they must not have had previous breast surgeries; 3) and they must have no allergic history. Three patients were excluded because they chose not to participate in the study. Another patient was not included because she had an allergic history, so the technetium marking was performed instead of the blue patent. A total number of 49 patients were included in the study.

On the day of surgery, the lesions were marked with patent blue dye (Delpharm Tours, Chambray Lês Tours, France) and air as close as possible to the scheduled time for the surgical procedure. The marking was performed by a highly skilled breast radiologist. Lesions classified as nodules and complex cysts were labeled during ultrasonography (Figure 1) while microcalcifications were labeled during mammography (Figure 2). The interval between the injection of the dye and the surgical procedure ranged from 30 to 980 minutes with a mean of 152 minutes. After the marking, the patients were referred to the operating room, where three highly skilled breast surgeons performed the excision of the lesions.

In order to perform the preoperative marking of the lesions, 5 to 10 mL of lidocaine hydrochloride 2% (Cambrex Corporation, East Rutherford, New Jersey, USA) was infiltrated into the puncture site where the dye was injected. Subsequently, 0.2 mL of patent blue dye and 0.4 mL of air were injected by means of a syringe that was guided by stereotaxis or ultrasonography. The purpose of air injection was to facilitate the localization of the lesion by ultrasonography (air-injected artifact) and to identify the nearest possible point to perform the incision on the skin. The ultrasound was preoperatively used aiming to identify both the exact position of the lesion and the best path of its dissection. Moreover, it intended to confirm that the marking was successful by identifying the air bubble in the mammary parenchyma. This procedure has its outmost importance in cases of non-visualized lesions on ultrasound since it allows the precise visualization of the lesion immediately before the surgery.

The surgical procedure was performed under general anesthesia and sedation. Antibiotic prophylaxis was not administered. An incision that obeys the Kraissl's lines in the breast was performed. The underlying tissues were dissected until the area marked by the blue patent found (Figure 3). The samples with microcalcifications were radiographed intraoperatively for confirmation of complete excision. For the patients who already had a cancer diagnosis, the margin examination

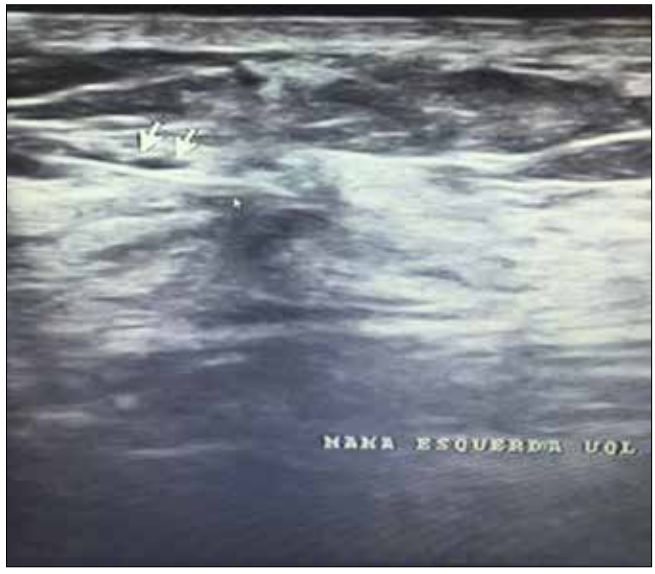

Figure 1. Marking of impalpable lesion with patent blue and air during ultrasonography

Figure 2. Marking of impalpable lesion with patent blue and air during mammography

Figure 3. Impalpable surgical nodule resected after marking with patent blue

was performed intraoperatively; if the margins were positive, they were surgically enlarged. Surgical margins were identified by marking with surgical wires in order to guide the pathologist. Absence of a tumor at the margin was considered as free margin, regardless of the margin size.

Hemostasis was performed. The incision of the skin was closed subcutaneously with absorbable suture. The closing of the breast parenchyma was performed as tight as possible. After the end of the procedure, compression dressing was prescribed, and the surgical bra was placed. The criteria analyzed were: 1) complete marking and identification of the lesion; 2) complete removal of the lesion; 3) in cases of malignant lesions, presence of free margins for successful surgery; 4) occurrence of allergic events; 5) necessity of reoperation; and 6) difficulty in locating lesions, characterized as a surgical time greater than 1 hour from the initial incision to the closure of the skin.

All patients signed a free and informed consent form before surgery. The study was started after obtaining the approval of the Ethics Committee of Federal University of Piauí Institution (0478.0.045.001-11).

Statistical Analysis

Data were analyzed by Statistical Package for the Social Sciences for windows version 23.0 (IBM Corp, Armonk, New York, USA) and Microsoft Office Excel 2007 for Windows (Microsoft Corporation, Redmond, Washington, USA). The results were presented in tables, supported by the statistical service of the institution.

Results

Forty-nine patients underwent resection of an impalpable breast lesion with patent blue marking. The median age of the patients was 52 ranging from 27 to 78 years. The classification according to the BI-RADS system is described in Table 1. The classification according to the radiological study is shown in Table 2. In all cases, the lesions were marked, and they were properly excised.

According to the pathological analysis on excised samples, 82% of lesions were benign, 4% were atypical hyperplasia, and 14% were malignant (Table 3). All malignant lesions were excised with free margins. No BI-RADS II or III lesion was malignant. The percentage of breast cancer among BI-RADS IV lesions was 11%.

The BI-RADS III lesions were operated because in one of these cases, the patient already had palpable lesions, and she decided not to follow up for the development of non-palpable nodules. In another case, the nodule grew, so surgical removal was indicated. One patient with BI-RADS III had an intraductal papilloma with excessive leaking of secretions, and one lesion was removed due to cancerphobia. A patient with a BI-RADS II lesion had a surgical indication due to a family history of breast cancer. In the other cases of BI-RADS II and III, the patients requested the removal of the lesions because they were not able to continue the follow up.

No patient presented any allergic events or needed reoperation. The mean operative time of the 45 patients with single lesions was 46 minutes with a standard deviation of 19.3, ranging from 15 to 90 minutes. In 4 cases (8.9%), the surgeons were presented with difficulties in removing the lesion. In these cases, the operative time ranged from 70 to 90 minutes. In the 4 cases of multiple nodules, the operative time ranged from 105 to 120 minutes.

Discussion and Conclusion

The main diagnostic methods for impalpable breast lesions are fine needle aspiration biopsy (FNAB), large-core needle biopsy or mammotomy (1). When the diagnosis of cancer is established, or the biopsy is inconclusive, resection of the lesion is indicated (3). Several methods have been developed for the localization and resection of non-palpable breast lesions. The use of dyes in the preoperative marking of impalpable lesions is a poorly explored technique. There are only 10 studies evaluating the use of dye for localization of non-palpable breast lesion (Table 4).

The wire-guided excisional biopsy is secure, accurate, and has been widely adopted. However, the management of these metallic sutures presents limitations during their implantation and during the surgical procedure. Local discomfort, wire migration within the breast parenchyma, poor introduction of the wire, or section of the wire during the surgery are common limitations. The section of the wire may lead to the formation of granulomas if the fragments are not removed properly. From an aesthetic point of view, the surgical access is not always satisfactory, mainly because the smallest incision is not always possible. Furthermore, the wire-guided excisional biopsy presents a failure rate between 2 and 6% at the location of non-palpable lesions (4).

Table 1. BI-RADS[1] classification of patients who underwent surgical resection of impalpable lesions after marking with patent blue dye and air

BI-RADS[1]	Number of patients (%)
II	2 (4)
III	9 (18.4)
IV	35 (71.5)
V	0 (0)
VI	3 (6.1)
Total	49 (100)

[1]Breast Imaging Reporting and Data System

Table 2. Radiological features of lesions of patients who undergone surgical resection of impalpable lesions after marking with patent blue dye and air

Type of lesion	Number of patients (%)
Complex cyst	2 (4)
Nodule	36 (73.5)
Microcalcification	11 (22.5)
Total	49 (100)

Table 3. Histopathological evaluation of surgical samples obtained after resection of nonpalpable lesions with blue dye and air marking

Histopathological feature	Number of patients (%)
Carcinoma	7 (14)
Benign	40 (82)
Atypical hyperplasia	2 (4)
Total	49 (100)

Table 4. Studies using dyes for labeling of impalpable breast lesions and their main results

Author	Year	Number of patients	Number of lesions	Type of dye	Associate technique	Number of cancers	% Compromised Margins
Liu J	2016	56	56	Indocyanine green	[1]	56	5.4
Eulálio Filho WMN	2015	49	49	Blue patent	[1]	7	0
Vieira SC	2014	64	64	Blue patent	[1]	13	7.7
Aydogan F	2012	2	2	Indocyanine green	Injection of 99 m-TC	2	0
Nasrinossadat A	2011	51	57	Methylene blue	[1]	N[2]	0
Tang J	2011	78	78	Methylene blue	Injection of 99 m-TC	42	0
Tang J	2009	138	138	Methylene blue	[1]	84	0
Zgajnar J	2003	17	17	Blue patent	Injection of 99 m-TC	17	0
Zografos GC	2003	1	1	Blue patent	Guide wire	0	0
David J	1989	22	22	Toluidine blue, methylene blue, Blue patent	Guide wire	N[2]	N[2]

[1]Absent
[2]Not commented

Radio-guided occult lesion localization was proposed as an alternative for the excision of non-palpable wire guided breast lesions. A small dose (3.7 MBq) of 99m Tc-labeled albumin is injected during ultrasonography or mammography using the stereotaxis. During surgery, the lesion is localized by a gamma probe, emitting a sound and a count of radioactive material (6-9). However, the main disadvantage of this technique is the difficulty in establishing the depth of the impalpable lesion in the mammary parenchyma, since the probe cannot distinguish between superficial or deep lesions. This may lead to a mammary segmental resection larger than desirable (5, 6).

This difficulty is reduced when a dye is associated with the ROLL for marking the impalpable lesions. In a study involving 157 patients with non-palpable breast lesions, the labeling was evaluated using a metallic suture and a ROLL association with methylene blue. This technique with the dye was performed in less time, and a greater number of free surgical margins were obtained. Furthermore, the size of the sample was smaller, and there was a lower rate of reoperation. In addition, the size of the skin incision was smaller when compared to the skin cut made by the wire-guided resection (7). However, only the use of the dye for labeling is sufficient for a complete resection of the lesion according to other studies (10, 11).

Another disadvantage is the presence of one more professional in the team, the nuclear medicine specialist, which makes the procedure expensive, as it also includes performing a mammary scintigraphy. In contrast, the cost of marking lesions with dyes is much lower since it does not require a nuclear medicine specialist in the team and special metal wires (5). An Iranian study shows that the cost of using metallic wires is four times greater than the dye labeling by ultrasonography (12). In this way, the use of dyes for marking lesions is a more feasible alternative financially in areas with fewer resources.

The patent blue marking has as main advantage in the removal of the lesion by direct visualization of the blue area. It can be indicated for the removal of any palpable or non-palpable breast lesion. The only contraindication is in patients with a history of allergic reactions; in such cases, the labeling with technetium is most appropriate. In the past, after the dye was injected, the puncture trajectory was dyed, and a small amount of dye was injected during withdrawal of the needle. The incision was made along the trajectory of the puncture. If the puncture site was far from the nodule, larger incisions and trauma to the tissues were inevitable, compromising the aesthetic results of the procedure. Currently, a small amount of air is used between the plunger of the syringe and the dye, which facilitates the location of the lesion by the ultrasound (artifact determined by injected air). The point closest to the lesion to be excised is then marked. This way, the path of the puncture does not impregnate with the dye. It causes less tissue trauma. The surgical resection is only initiated when we visualize the area colored with blue. It provides a smaller area of resected mammary parenchyma, improving cosmetic results (5, 13).

An initial concern with this method was the leaking of the dye, which could prevent the technique from being successful if the surgery was not performed immediately after the injection of the dye. In the present study, one patient was operated on for 980 minutes after the injection of the dye. Despite this, the patient still had the dye at the site of injection, and the dye had not disseminated to the adjacent parenchyma by the time of surgery, which allowed adequate resection. Preliminary studies analyzing the staining and diffusion properties of various dyes have concluded that patent blue is the best dye for marking this type of lesion, as it diffuses adequately, allowing for safe margins without leading to unnecessary dissection of adjacent tissues. Moreover, in these studies, the amount of dye injected was around 1 to 2 mL. Nowadays, only 0.2 mL of dye is injected into the lesion, and it is enough for an oncologically safe resection with good cosmetic results (13, 14).

In our experience, the main advantage of performing a combined surgical marking of blue patent and air is to allow a more accurate visualization of the lesions in the immediate preoperative period by the ultrasound. In addition, in cases of non-visualized breast lesions on ultrasound, the air artifact in the mammary parenchyma allows the use

of intraoperative imaging, so it can facilitate the location of the lesion during the intraoperative period. In our institution, ultrasonography was only used in the immediate preoperative period, which significantly improved surgical planning in both cases of non-visualized lesions (microcalcifications) and visible lesions (nodules and cysts).

In the present study, all lesions were marked, and they were adequately resected. The mean operative time was 46 minutes. Only in 8.9% of the cases, the surgeons had difficulty in resecting the lesions. In these cases, the depth and size of the lesions may have worsened the location and dissection of the lesion. In cases of multiple lesions, the operative time was much longer (ranging from 90 to 120 minutes), which implies that the greatest determinant of operative time is the number of lesions to be resected.

The possibility of allergic events prevents the widespread use of dyes for the marking of lesions. In the literature, the incidence of allergic events with the use of patent blue dye has been 0.06 to 2.7% with an average value of 0.71%. The incidence of allergic events is related mainly to the surgery for the screening of the sentinel lymph node, which requires a larger volume of dye, usually 2 to 4 mL. In contrast, the volume of patent blue used for marking non-palpable lesions is 0.2 mL. A precaution that should be taken is to avoid performing the procedure in patients with a major allergic history, such as severe urticaria and angioedema. Instead, in these patients, resection should be indicated with technetium or metallic guidewire (5, 9, 15). In our study, no adverse reactions to the patent blue were observed. In addition, we did not find any case in the literature of allergic reactions during the marking of impalpable lesions with patent blue.

Another possible complication of the procedure is the development of gas embolism from the injected air. However, experimental studies have shown that it takes a large amount of air in the circulation to cause systemic problems. It is necessary to inject at least 1.5 cm^3/kg/sec of air into the bloodstream to provoke a death of a dog. This value is much higher than the 0.4 mL of air injected in our technique. Therefore, the risk of severe gas embolism in the marking of breast lesions is negligible (16).

In the present study, all lesions were successfully resected. In the cases of malignancy, the margins were free. After review of the literature, it was observed that from the 510 patients submitted to preoperative staining with dyes, 143 were carriers of malignant neoplasia. Free margins were obtained in 97.4% of the operations (Table 4), proving that the resection of impalpable lesions in the breast with dyes is a method with satisfactory oncological results (5, 17).

In conclusion, resection of impalpable breast lesions marked with patent blue dye and air was possible in all cases. In the patients with malignant lesions, the margins were free in 100%. 91.1% of the surgeries presented no difficulties. The combined use of air in the surgical marking did not lead to any complications to the procedure, but instead its application allowed a better surgical planning, especially in cases of non-visualized lesions on ultrasound. Randomized prospective studies are necessary in order to show superiority of this technique in relation to other existing ones.

Ethics Committee Approval: Ethics committee approval was received for this study from Eastern Michigan University Human Subjects Review Committee (UHSRC).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

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