

RESEARCH COMMUNICATION

Marking Non-palpable Breast Masses with Injected Methylene Blue Dye, an Easy, Safe and Low Cost Method for Developing Countries and Resource-limited Areas

Alavi Nasrinossadat^{1*}, Fonooni Ladan¹, Ensani Fereshte², Olfatbakhsh Asieh¹, Chaman Reza³, Sadjadian Akramossadat¹, Mehra Golshan⁴

Abstract

Introduction: The widespread use of improved mammographic techniques has led to increased detection of nonpalpable breast masses. Preoperative localization is important for reducing false negative results and decreasing the size of tissue resection needed and the resulting breast deformity. We used ultrasound guided methylene blue injection in the mass for localization of breast masses that were clinically nonpalpable but detectable by ultrasound. **Materials and methods :** 57 masses from 51 patients were marked 20 to 180 minutes before surgery with 0.4-0.7 cc methylene blue and resection was done in operating room under local or general anesthesia. success of radiologist for localization and success of surgeon for complete resection and pathology results were reviewed and follow up ultrasound was done 3-5 month after surgery for patients whom pathology results were non specific (such as FCC) to confirm complete resection. **Results:** 57 masses were excised successfully by the surgeon, localization was successful in all patients but injection in the mass was not feasible in 4 patients and dye was injected on the surface of the mass and led to successful excision. Only one mass was not found at surgery because dye washed out before surgery, and the mass was resected by use of intra operative ultrasound. 5.3% patients reported the procedure was painful and 28% reported tolerable pain during injection and 66.7% of patients said that the injection was painless or with minimal discomfort. Allergic reaction was not seen in any patient and no interference was reported by the pathologist in slide preparation or diagnoses and IHC study. **Conclusion:** Marking with blue dye injection is a safe and low cost method for localization of non palpable breast lesions that are detectable by Ultrasound. In one patient failure to find the mass was because of location of the mass that was in axillary tail of breast and time of surgery that was 100 minutes after injection that led to absorption of blue dye before surgery and it is advised to do surgery as soon as possible after blue dye injection especially in peripheral and deeply located masses.

Keywords: Breast cancer - non-palpable - physical markers - resection

Asian Pacific J Cancer Prev, 12, 1189-1192

Introduction

With the advent and widespread use of screening mammography there has been a decrease in breast cancer specific mortality (Shapiro et al., 1982; Tabar, 1985), however findings on imaging have led to new challenges in breast cancer surgery. The resection of non palpable breast masses during surgery requires a marking method for precise resection. In the case of non-palpable lesions if the surgeon forgoes the marking of the lesion prior to surgery, there would be risk of sacrificing a large amount of normal breast tissue, or the mass may be missed. There are many techniques that have been used for non palpable breast masses in the breast. Image guided core biopsy and wire localization under ultrasound or mammography

are two standard methods that are widely used in many countries around the world (Liao et al., 2004; Surry, 2007). There are some reported complications such as pain during the procedure and vasovagal incidents have also been reported. Others have describe displacement of wires especially in fatty breasts (Rapaport et al., 1991; Homer et al., 1992; Canavese et al., 1995). Other methods such as intraoperative ultrasound (Fornage et al., 1994; Kaufman and Kaufman, 1994; Ngo et al., 2007), hematoma guided excision after core biopsy (Hert et al., 2009) and radio labeled occult lesion localization (Mena et al., 1996; Mercado, 2008), are used in some centers based on preference of the surgeon and radiologist. Some of these techniques require expert radiologist and expensive equipment that are not readily available in many

¹Iranian Center for Breast Cancer, Academic Center for Education, Culture and Research, ²Cancer Institute, Tehran University of Medical Sciences, ³Dept. of Basic Sciences, School of Medicine, Shahroud University of Medical Sciences, Tehran, Iran, ⁴Dept of Surgery Brigham and Women's Hospital, Harvard Medical School, Boston, USA *For correspondence: dralavin@gmail.com

developing countries.

It is very important to use a technique that is effective, low cost and easy to learn for the countries that may have not enough access to trained radiologists and expensive equipment. Dye injection in non palpable breast masses is a method that was done for many years but with development of wire localization technique, it's use has become limited in most countries with access to trained imagers, core biopsy and wire localization. Multiple materials have been used as dye for injection such as: carbon suspension (Renoldi, 1998; Arman et al., 2001; Mathieu et al., 2001), toluidene blue (Czarnecki et al., 1989; Kopans, 2007) and methylene blue. Considering the need to decrease the cost of management for these lesions, the dye injection in the mass may be an effective tool.

Specifically methylene blue is a readily available and inexpensive dye and has a long history of use in humans with few side effects. Specific to breast cancer, It has been used for sentinel node biopsy and localization of non palpable breast masses and is safe for injection (Blessing, 2002; Varghese et al., 2007; Zakaria et al., 2008) without adversely affecting histologic and immunohistochemistry assessment (Masannat et al., 2007; Alavi et al., 2010) Our aim in this study is to detail our our experience in marking non palpable breast masses by injection of methylene dye into the mass.

Materials and Methods

Our study group were 51 patients with 57 masses that underwent surgical excision of non palpable breast masses with guide of methylene blue dye between 2006 and 2009. Approval was obtained from the institutional review board of Iranian Center for Breast Cancer. Indications for surgery were suspicious mass on ultrasound or mammography, a mass that shows interval growth on imaging or patient desire for removal of a mass. Injection was done by radiologist under ultrasound guide of the mass 20-180 minutes prior to surgery. We used 1% methylene blue for injection of all masses because of availability and lower rate of sensitivity reaction. The volume of dye was between 0.4 to 0.7 ml and an insulin syringe with a 26 gauge needle was used for injection. After injection of 0.2 -0.4 ml of dye into the mass, a tract between the mass and skin was also marked with injection of dye while withdrawing the needle. Success rate in marking with methylene blue dye and complete excision of mass were evaluated. We report the sensitivity and specificity of the exam. For cases of pathologic discordance, an ultrasound was performed 3 month after surgery to ascertain whether the mass was excised. Success was complete if the surgeon could find the mass easily with guide of discoloration of the mass. Success was partial when the surgeon had difficulty in identifying the mass during surgery for example when dispersion of dye in tissue surrounding the mass made the surgeon to search for mass in that area, but excision was complete by the guide of dye.

Severity of pain during injection was evaluated according to a questionnaire to the patient after the

procedure asking whether she experienced: no pain, tolerable pain, severe pain. The pathologist also reported adverse effect on tissue diagnosis due to staining with methylene blue. Sensitivity reactions were recorded by the radiologist or surgeon. One expert pathologist in breast pathology reviewed slides of all patients and reported any adverse effect on histologic examination.

Results

Mean age was 42 (range 27-57) year and median was 41. Mean size of the mass was 14 mm (7mm-24mm) noted in the longest dimension of length, width and height. The most common location of masses was upper outer quadrant of both breasts, upper inner quadrant, lower outer quadrant, then lower inner and subareolar region in order of frequency. We identified 57 masses from 51 patients which were marked by dye injection before surgery. In 38 (66.7%) of the patients reported the procedure as painless, 16 (28%) reported tolerable pain during injection and 3 (5.3%) of our patients had severe pain during the procedure of injection. All masses were marked with methylene blue successfully except in 4 masses (7%) the radiologist could not inject the dye into the mass, and injected the dye on the surface of the mass.

At surgery, all masses were excised completely with guidance of dye, except 1 mass that was not found based on marking with blue dye and the surgeon found the mass with the use of intra operative ultrasound, this mass was located in upper outer quadrant of the breast and time of the operation was 100 minutes. For 3 masses (5.3%) surgeon had some difficulty for finding the mass with guide of dye mainly because of dye dispersion in the area around the mass.

Our pathologist reported no adverse effect on evaluation of cells and tissue in slides of masses that were stained by methylene blue either in the benign lesions or in malignant cases and immunohistochemistry was staining for estrogen and progesterone and her2 not affected by methylene blue injection.

In Iran, localization with wire costs about 250 US dollars and methylene blue injection under ultrasound guide costs about 60 US dollars and most radiologists do not enough experience with wire localization or core biopsy under us guide. So, methylene blue injection is more available and costs less for patient and our health system. We report not adverse reactions or complications with the procedure either during injection, intra-operatively or postoperatively.

Discussion

In our series we report a high rate of success in surgical excision and radiologic/pathologic concordance. In 93% of cases the mass was found easily during surgery with guide of methylene blue and 98.2 % of cases the mass was excised by the surgeon with success. Only one mass was not excised by this method. This mass was a 1.3 cm mass of a 42 year old woman, it was located deep in upper outer quadrant of right breast near to axila and the time between injection to the mass and surgery was 100

minutes. The pathology of the mass was fibrocystic with epithelial ductal hyperplasia. Wire localization has been reported to be successful in 93-100 % of cases in different series (Abrahamson et al., 2003) and similar success rates have been reported for other techniques like hematoma assisted excision of masses and radioactive occult lesion localization (Richard, 2004; Medina-Feranco et al., 2008). Our technique also had comparable success rate with lower cost and no need for the surgeon familiar with ultrasound or special radiolabeled material or gamma probe.

The injection was without severe pain or distress in most of our patients. The injection was done in supine position and no vasovagal incidents were reported. As stated before, sensitivity reaction to methylene blue are uncommon and severe reactions are exceedingly rare. In our patients, we did not see any sensitivity reaction or skin tattoo. We used 1% solution of methylene blue at a low volume which is commonly used during the sentinel lymph node biopsy technique.

In conclusion, marking with methylene blue dye is a simple, effective and low cost method for localization of non palpable breast masses. Although new techniques in localization of non palpable breast masses like wire localization are more conventional now ,our experience shows that we can use methylene blue injection as a safe and low cost method in areas with limited facilities. This method may be useful for developing countries around the world, for ultrasound detected suspicious lesions. We recommend that hydrocortisone for injection and epinephrine should be available in the radiology center that injection of dye is done for rare cases of reaction to the dye.

Acknowledgements

This study was granted by Academic Center for Education, Culture and Research and National Cancer Research Network of Iran.

References

Alavishahreza N, Ensani N , Najarnajafi S, et al (2010). Is there any negative impact on histologic assessment of breast masses and sentinel nodes marked with blue dye? *Eur J Cancer Supple*, **8**, 172.

Arman A, Kilicoglu G, Guner HH, et al (2001). Marking of nonpalpable breast lesions using a custom carbon suspension. *Acta Radiol*, **42**, 599-601.

Blessing WD, Stoller AJ, Teng SC, et al (2002). Comparison of methylene blue and lymphazurin in breast cancer sentinel node mapping. *Am J Surg*, **184**, 341.

Canavese G, Catturich A, Vecchio C, et al (1995). Non palpable breast lesions: preoperative sonographic localization. *Int Surg*, **80**, 283.

Czarnecki D, Feider H, Splittgerber G (1989). Toluidine blue dye as a breast localization marker. *Am J Roentgenol*, **153**.

Dunlap LA, Amamoo MA, Schell MJ, et al (2003). Factors predicting successful needle-localized breast biopsy. *Radiology*, **10**, 601-6.

Fornage BD, Ross MI, Singletary SE, et al (1994). Localization of impalpable breast masses: value of sonography in the operating room and scanning of excised specimens. *Am J Roentgenol*, **163**, 569-73.

Gennari R, Galimberti V, De Cicco C, et al (2000). Use of technetium-99m-labeled colloid albumin for preoperative and intraoperative localization of nonpalpable breast lesions. *J Am Coll Surg*, **190**, 692-8, discussion 698-9.

Gray RJ, et al (2004). Radioactive seed localization of nonpalpable breast lesions is better than wire localization. *Am J Surg*, **188**, 377-80.

Hertl K, Marolt-Music M, Kocijancic I, et al (2009). Haematomas after percutaneous vacuum-assisted breast biopsy. *Ultraschall Med*, **30**, 33-6.

Homer MJ, Smith TJ, Safaii H (1992). prebiopsy needle localization methods, and expected problems. *Results, Radilology clinics of north America*, **30**, 139-53.

Joe A, Helvie MA (2008). Sonographically-guided metallic marker placement at time of wire localization for intraductal or cystic -lesions: a method to verify lesion retrieval. *Acad Radiol*, **15**, 1316-21.

Liao J, Davey DD, Warren G, et al (2004). Ultrasound-guided fine-needle aspiration biopsy remains a valid approach in the evaluation of nonpalpable breast lesions. *Diagn Cytopathol*, **30**, 325-31.

Kaufman GS, Kaufman L (1994). Intraoperative ultrasonography guidance is accurate and efficient according to results in 100 breast cancer patients. *Am J Surg*, **186**.

Kopans DB, Deluca S (1980). A modified needle hook wire technique to simplify the preoperative localization of occult breast lesions. *Radiology*, **134**, 781.

Kopans DB (2007). Breast Imaging. *Third edition*, 927.

Mena FJ, Mena I, Diggles L, et al (1996). Design and assessment of a scintigraphy-guided biplane localization technique for breast tumours: a phantom study. *Nucl Med Commun*, **17**, 717-23.

Mercado CL, Guth AA, Toth HK, et al (2008). Sonographically guided marker placement for confirmation of removal of mammographically occult lesions after localization. *Am J Roentgenol*, **191**, 1216-9.

Mathieu M, Bonhomme-Faivre L, PhD, et al (2001). Presurgery labelling of breast tumours with a charcoal suspension for intratumour injection. *CT. J Oncol Pharm Practice*, **6**, 173-6.

Masannat YA, Shaaban AM, Speirs V, et al (2007). Adverse effects of dyes used in sentinel node biopsy on immunocytochemical determination of hormone receptors in breast cancer cells. *J Clin Pathol*, **60**, 730-2.

Mathieu MC, Bonhomme-Faivre L, Rouzier R, et al (2007). Tattooing breast cancers treated with neoadjuvant chemotherapy. *JOURNAL*, **14**, 2233-8.

Medina-Franco H, Abarca-Pérez L, García-Alvarez MN, et al (2008). Radioguided occult lesion localization (ROLL) versus wire-guided lumpectomy for non-palpable breast lesions: a randomized prospective evaluation. *J Surg Oncol*, **97**, 101-2.

Ngô C, Pollet AG, Laperrelle J, et al (2007). Intraoperative ultrasound localization of nonpalpable breast cancers. *Ann Surg Oncol*, **31**.

Gordon P (2004). An alternative clip-marking method for use after 14-gauge large core needle biopsy of the breast. *Can Assoc Radiol J*, **55**, 75-8.

Varghese P, Talaat A, Abdel-Rahman A (2007). Methylene blue Dye, a Safe and Effective Alternative for Sentinel Lymph Node Localization. *Breast J*, **14**.

Rappaport W, Thompson S, Wong R, et al (1991). Complications associated with needle localization biopsy of the breast. *Surg Gynecol Obstet*, **172**, 303-6.

Renoldi L, Sfondrini MS, Di Nubila B, et al (1998). Non-palpable lesions of the breast. Preoperative location techniques with vegetable charcoal. *Radiol Med*, **95**, 445-8.

Shapiro S, Venet W, Strax P, et al (1982). Fourteen-year effect

- of screening on breast cancer mortality. *J Natl Cancer Inst*, **69**, 349-55.
- Sittek H, Perlet C, Herrmann K, et al (1997). MR mammography preoperative marking of non-palpable breast lesions with the Magnetom open at 0.2. *Radiologe*, **37**, 685-91.
- Sittek H, Perlet C, Helmberger T, et al (1998). Preoperative marking of non-palpable mammary lesions on the magnetic resonance image using a body coil. *Rontgenpraxis*, **51**, 379-84.
- Slanetz PJ, Jain R, Kline JL, et al (1999). CT guided preoperative localization of MR image detected mamographically occult lesions. *Am J Rontgenology*, **172**, 160-2.
- Surry KJ, Mills GR, Bevan K, et al (2007). Stereotactic mammography imaging combined with 3D US imaging for image guided breast biopsy. *Med Phys*, **34**, 4348-58.
- Tabár L, Fagerberg CJ, Gad A, et al (1985). Reduction in mortality from breast cancer after mass screening with mammography. Randomised trial from the Breast Cancer Screening Working Group of the Swedish National Board of Health and Welfare. *Lancet*, **1**, 829-32.
- Zakaria S, Hoskin TL, Degenim AC (2008). Safety and technical success of methylene blue dye for lymphatic mapping in breast cancer. *Am J Surg*, **196**, 228-33.