

Indocyanine green guided resection of non-palpable breast cancer

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ABSTRACT

Screening tests and national programs of early detection of breast cancer have been widely implemented worldwide, subsequently increasing the number of cases diagnosed in incipient stages, when the lesion has no clinical expression. In such cases a proper identification of the lesion is mandatory in order to achieve a radical result of the surgical procedure. Therefore, attention was focused on identifying the best imagistic methods regarding the accomplishment of an exact identification of the lesion which could further provide an adequate surgical resection and a proper oncological outcome and, in the meantime to provide the possibility of achieving a good cosmetic result. The aim of this paper is to study the role of indocyanine green as part of the therapeutic armamentarium which provides a correct identification of non-palpable breast lesions.

Keywords: non-palpable, breast cancer, indocyanine green, conservative surgery, identification

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INTRODUCTION

Breast cancer still represents the most commonly encountered malignancy affecting women worldwide with increasing incidence especially due to the wide implementation of the national programs of screening and early detection of this malignancy (1). Therefore, due to the permanent improvement of the imagistic techniques such as tomosynthesis mammography or magnetic resonance imaging the rates of non-palpable lesions significantly increased. In such cases, fortunately the lesion is detected in early stages of the disease and is further suitable for breast conservative surgery; however, in such cases attention should be focused in developing a method which is able to provide an adequate identification and excision of the lesion, with negative resection margins offering for the patient both oncologic and cosmetic benefits (2,3).

METHODS FOR TUMOR IDENTIFICATION IN NON-PALPABLE BREAST CANCER PATIENTS

So far, the most commonly used methods for non-palpable breast cancer localization were represented by radioguided resections (by the means of intraoperative ultrasound) or by wire guided localization (4,5). Although initially these methods have been considered as invincible ones, in time they proved to have certain disadvantages such as the risk of modification of the wire position, patient's discomfort at the moment of wire placement or the possibility of mal identification of the lesion during the intraoperative ultrasound; in this direction, it is widely recognised the fact that ultrasonographic identification of the lesion depends on both human and logistic factors. Therefore, the appropriate identification of a non-palpable breast cancer depends on the accuracy of the used ultrasound device as well as on the expertise of the radiologist or surgeon performing the imagistic study. Meanwhile, even if a wire is positioned and resection is performed in an ultrasound guided manner, there is still a risk of having positive resection margins especially in cases presenting in situ ductal carcinomas (5-8). Last but not least, it should not be omitted the fact that an adequate scheduling between the moment of wire placement and the one of surgery is mandatory, the two procedures preferably being performed during the same day or during consecutive days (6).

In regard of these limitations, the attention was focused on identifying other diagnostic methods which are able to provide a more safe and more effective tumoral identification, with lower risks of incomplete excisions.

INDOCYANINE GREEN'S UTILITY IN THE IDENTIFICATION OF NON-PALPABLE BREAST CANCER

Known for the fluorescent properties when exposed to infrared light, indocyanine green molecule has been widely used with multiple purposes in breast cancer surgery; initially proposed for sentinel lymph node identification, prevention and treatment of breast or upper limb lymphedema as well as for minimizing the risks of postoperative complications after breast reconstructive surgery, the method has been recently added as part of the therapeutic strategy for non-palpable breast lesions identification (9).

The utility of the method is based on the principle of fluorescence: injected molecules of indocyanine green are rapidly bounded to serum globulins and, when excitation light of 760 nm is achieved, fluorescence with a peak at 845 nm is emitted; this process is captured by a special system using a photodynamic eye. In these conditions, fluorescence at a depth of maximum 10-15 mm beneath the skin is achievable and structures can be further identified (10).

The protocol of lesion localization of non-palpable breast tumors consists of tumor location through intraoperative ultrasound followed by intra-tumoral injection of indocyanine green; the procedure continues with skin and subcutaneous tissue incision under the photodynamic eye guidance and identification of the fluorescent area which should be further completely resected; however, in cases in which the tumor is located more profoundly than 1 cm to the skin, a second indocyanine green injection is needed in the subcutaneous area corresponding to the breast lesion (9).

THE EFFICACY OF THE INDOCYANINE GREEN

An interesting study which came to demonstrate the efficacy of the method was conducted by Liu et al. and included 56 patients diagnosed with non-palpable breast cancer lesions; after injecting indocyanine green at the tumour lever, complete resection of the fluorescent territories and checking the absence of residual fluorescence on the remaining breast tissues the specimens were sent to the histopathological examination and demonstrated complete excision with negative resection margins in 53 out of the 56 cases; in the remaining three cases re-intervention was needed – in two cases due to the presence of positive margins for ductal carcinoma in situ and in one case due to the presence of multifocal lesions. By using this method, the mean volume of the excised tissue was of 38,2±16,5 cm³. After a mean follow up of 19 months there was no reported local or systemic recurrence (9). According to the same authors, the mean excised volume of breast tissue when this method is used is signifi-

cantly lower when compared to the tissue excised after wire or ultrasonographic guidance, thus increasing the chances of obtaining a better cosmetic outcome (11,12).

However, the method has also certain limitations, the most important one being represented by the impossibility of using it in patients with known iodine hypersensitivity and by the long-lasting tattooing of indocyanine green which ranges between 10 and 14 days (13). Another important issue is related to the timing between injection and tumor visualization; therefore, once indocyanine green injection is administrated at the level of the tumor, it migrates in the sentinel nodes through the subcutaneous lymphatics and the concentration in the tumour will diminish, decreasing the rates of complete resection (14,15).

CONCLUSIONS

Non-palpable breast cancer has an increasing incidence in the last decade especially due to the wide

implementation of the screening tests, of the national programs of early detection of this malignancy and the imagistic techniques improvement. In such cases, an early diagnostic is associated with increased chances of long-term survival and improved cosmetic outcomes; however, the exact localization of the lesion can still pose significant problems, different strategies being proposed. Although wire placement and intraoperative ultrasound might increase the rates of an adequate localization of the lesion the method can be associated with multiple limitations. Therefore, other methods such as indocyanine green injection have been proposed with promising results; it appears that the method is associated with a better identification of the lesion and with significantly lower rates of positive resection margins specimens.

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REFERENCES

1. Tabár L, Dean PB, Kaufman CS, Duffy SW, Chen HH. A new era in the diagnosis of breast cancer. *Surg Oncol Clin N Am.* 2000 Apr;9(2):233-77.
2. Inui H, Watatani M, Hashimoto Y, Hojo T, Hirai K, Yamato M, Fujishima M, Azumi T, Shiozaki H. Hematoma-directed and ultrasound-guided breast-conserving surgery for nonpalpable breast cancer after Mammotome biopsy. *Surg Today.* 2008;38(3):279-82.
3. Kaufman CS, Jacobson L, Bachman B, Kaufman L. Intraoperative ultrasound facilitates surgery for early breast cancer. *Ann Surg Oncol.* 2002 Dec;9(10):988-93.
4. Kaufman CS, Jacobson L, Bachman B, Kaufman L. Intraoperative ultrasound facilitates surgery for early breast cancer. *Ann Surg Oncol.* 2002 Dec;9(10):988-93.
5. van der Ploeg IM, Hobbelenk M, van den Bosch MA, Mali WP, Borel Rinkes IH, van Hillegersberg R. 'Radioguided occult lesion localisation' (ROLL) for non-palpable breast lesions: a review of the relevant literature. *Eur J Surg Oncol.* 2008 Jan;34(1):1-5.
6. Aydogan F, Ozben V, Celik V, Uras C, Tahan G, Gazioglu E, Cengiz A, Ferahman M, Cercel A, Yilmaz MH, Halac M, Unal H. Radioguided occult lesion localization (ROLL) for non-palpable breast cancer: a comparison between day-before and same-day protocols. *Breast.* 2010 Jun;19(3):226-30.
7. Medina-Franco H, Abarca-Pérez L, García-Alvarez MN, Ulloa-Gómez JL, Romero-Trejo C, Sepúlveda-Méndez J. Radioguided occult lesion localization (ROLL) versus wire-guided lumpectomy for non-palpable breast lesions: a randomized prospective evaluation. *J Surg Oncol.* 2008 Feb 1;97(2):108-11.
8. Zgajnar J, Hocevar M, Frkovic-Grazio S, Hertl K, Schweiger E, Besic N. Radioguided occult lesion localization (ROLL) of the nonpalpable breast lesions. *Neoplasma.* 2004;51(5):385-9.
9. Liu J, Guo W, Tong M. Intraoperative indocyanine green fluorescence guidance for excision of nonpalpable breast cancer. *World J Surg Oncol.* 2016 Oct 18;14(1):266.
10. Tagaya N, Yamazaki R, Nakagawa A, Abe A, Hamada K, Kubota K, Oyama T. Intraoperative identification of sentinel lymph nodes by near-infrared fluorescence imaging in patients with breast cancer. *Am J Surg.* 2008 Jun;195(6):850-3.
11. Cochrane RA, Valasiadou P, Wilson AR, Al-Ghazal SK, Macmillan RD. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. *Br J Surg.* 2003 Dec;90(12):1505-9.
12. Vrieling C, Collette L, Fourquet A, Hoogenraad WJ, Horiot JH, Jager JJ, Pierart M, Poortmans PM, Struikmans H, Maat B, Van Limbergen E, Bartelink H. The influence of patient, tumor and treatment factors on the cosmetic results after breast-conserving therapy in the EORTC 'boost vs. no boost' trial. EORTC Radiotherapy and Breast Cancer Cooperative Groups. *Radiother Oncol.* 2000 Jun;55(3):219-32.
13. Guo W, Zhang L, Ji J, Gao W, Liu J, Tong M. Breast cancer sentinel lymph node mapping using near-infrared guided indocyanine green in comparison with blue dye. *Tumour Biol.* 2014 Apr;35(4):3073-8.
14. Kitai T, Inomoto T, Miwa M, Shikayama T. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. *Breast Cancer.* 2005;12(3):211-5.
15. Hirche C, Murawa D, Mohr Z, Kneif S, Hünerbein M. ICG fluorescence-guided sentinel node biopsy for axillary nodal staging in breast cancer. *Breast Cancer Res Treat.* 2010 Jun;121(2):373-8.