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Management of the axilla: Conventional tracers vs ICG-fluorescence in sentinel lymph node biopsy

Amelia Milulescu[1,2], Cristian Gabriel Viisoreanu[2], Nicolae Bacalbasa[3], Irina Balescu[4], Tiberiu-Augustin Georgescu[5,6], Corina Grigoriu[3,7], Costin Berceanu[8], Roxana Elena Bohiltea[3,9]

[1]Department of Obstetrics and Gynecology, Faculty of Medicine, "Titu Maiorescu" University, Bucharest, Romania
[2]Breast Institute, Monza Oncology Hospital, Bucharest, Romania
[3]Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[4]Department of Visceral Surgery, Ponderas Academic Hospital, Bucharest, Romania
[5]Department of Pathology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
[6]"Alessandrescu-Rusescu" National Institute for Mother and Child Health, Bucharest, Romania
[7]Department of Obstetrics and Gynecology, University Emergency Hospital, Bucharest, Romania
[8]Department of Obstetrics and Gynecology, Craiova University of Medicine and Pharmacy of Craiova, Craiova, Romania
[9]Department of Obstetrics and Gynecology, Filantropia Clinical Hospital, Bucharest, Romania

ABSTRACT

The evaluation of regional lymph nodes is part of breast cancer staging. Biopsy of the sentinel lymph node was established, in order to evaluate the condition of the axillary lymph nodes without having to complete an axillary dissection. The concept of sentinel lymph node (SLN) is based on the theory of sequential dissemination of tumor cells through the lymph. When lymphatic dissemination occurs, the invasion initially occurs in the first lymph node that drains lymph from the tumor. This lymph node has been named GS and depending on its negative or positive status, the presence or absence of metastases in the remaining regional lymph nodes can be established. Blue dye (BD) and radioactive isotopes (RI) are routinely used markers for identification of the sentinel lymph nodes during sentinel lymph node biopsy (SLNB) in early stage breast cancer. Unlike the blue dye technique, using radioactive isotopes has lower false-negative rates. Nonetheless, the need of lymphoscintigraphy, the time needed for preoperative injection, and undetected sentinel lymph nodes in some cases cause surgeons to rely only on the combination of blue dye and radioisotopes. At present, indocyanine green (ICG) fluorescence method (ICG-SLNB) is starting to gain more and more field as an alternative to conventional mapping methods. The purpose of this review is to compare ICG with the conventional methods (blue dye and radioactive isotopes) and their role in detection of SLN.

Keywords: sentinel lymph node, ICG, TC-99, breast cancer

INTRODUCTION

Breast cancer has the highest death rate of all cancers in women worldwide, and has now topped lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases (1).

Axillary lymph node involvement is one of the most significant prognostic factors and hence, it is routinely evaluated during primary treatment. Early detection of breast cancer is associated with an improved prognosis and a significantly reduced rate of patients with positive axillary lymph nodes (N+). Sentinel lymph node biopsy (SLNB) is the golden standard used for axillary staging in breast cancer patients with clinically negative nodes, mostly because of its reduced morbidity. The notion of sentinel node biopsy is based on two fundamentals: the existence of a predictable pattern of lymphatic

Corresponding author:
Nicolae Bacalbașa
E-mail: nicolaebacalbasa@gmail.com

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drainage to a regional lymph node basin, and the idea of a first lymph node action as a filter for tumor cells (2). The concept of sentinel node is based on Halsteds theory of the loco regional spread of cancer, and the importance of loco regional treatment.

Sentinel lymph node biopsy (SLNB) is the standard method used to evaluate the status of the axilla in patients with breast cancer. It was developed, as an alternative to complete axillary lymph node dissection, in order to avoid the severity of postoperative complications, like arm lymphedema and swelling.

Due to the fact that radioactive isotopes (RI) technique can have some limitations, the need for developing other types of tracers and different technologies emerged (3). One of these methods, still studied, is the use of indocyanine green-guided sentinel lymph node biopsy. Ahmed M. et al., in a systematic review from 2014 concluded that the use of ICG was significantly better than the use of blue dye in regards to improving the identification of the sentinel lymph node (4). Another meta analysis, made from 12 studies from 2005 to 2015, stated that the ICG fluorescence method improved axillary staging compared with the RI method (5). A more recent study made in 2020 by Agrawal et al. demonstrated that ICG guided sentinel lymph node biopsy is equivalent to Tc-99 in early breast cancer (6).

Thus, it is very difficult to draw a conclusion, due to the fact that the results comparing ICG with traditional tracers (blue dye and Tc-99) are usually contradictory. From what we know until the present moment, whether ICG can be a valid option for clinical use as a viable tracer and if it can be a feasible substitute for traditional standard procedures has not yet been determined.

SLNB WITH BLUE DYE

The surgeon injects 3 to 5 ml of blue dye around the tumor. One of the most important aspects of this method is not to inject the dye directly into the tumor (due to the possibility of the lympathics being ocluded by tumor), because this error is very likely to lead to a failure of mapping.

The use of isosulfan blue dye for SLNB can be associated with anaphylactic reactions (7). Methylene blue is a feasible alternative to isosulfan blue dye due to its lower rate of possible allergic reactions. But even so, methylene blue can also have side effects, such as skin necrosis, induration and erythema with associated pain. Following tracer injection, the breast should be massaged for five minutes to dilate breast lymphatics (8). The axillary fascia is then opened through an axillary incision; this incision should be made inferiorly, rather than centered within the axilla. A meticulous search is made for blue stained lymphatic channels. Once identified, these lymphatic channels should be followed, until they guide the surgeon to the blue-stained lymph nodes. All blue lymph nodes and any lymph nodes at the end of a blue lymphatic channel should be removed and identified as sentinel nodes. Also, all suspicious palpable nodes should be evaluated, being considered peri-sentinel lymph nodes.

SLNB WITH RADIOACTIVE COLLOID

Usually, the radioactive tracer can be injected peritumorally, intradermally, or into the subareolar plexus. There is still a matter of debate regarding the best site for injection.

The quantity of radioactive colloid injected differs based on the time of injection; usually, 0.5 mCi is injected on the day of surgery, or 2.5 mCi if the patient is injected one day before surgery. The surgeon then uses a gamma probe in order to identify the maximum radioactivity in the axilla.

The lymph node with the highest radioactivity found by the gamma probe is first removed. The mean number of sentinel lymph nodes removed is usually two to three sentinel; any other extra sentinel lymph nodes removed, have a very low value (9). As for the methilen blue lymph node technique, all suspicious palpable nodes should be removed, irrespective of whether they are radioactive.

SLNB WITH INVESTIGATIONAL TECHNIQUES

Indocyanine green is injected directly into the breast and the sentinel lymph nodes are localized using a fluorescent imaging system (5,10).

There are also other types of tracers, such as superparamagnetic iron oxide (SPIO), and microbubble contrast agent. Nevertheless, all these techniques have wide variability in results between studies, because of small patient cohorts, and short patient follow-up. At present, all these types of tracers are being considered investigational until there is strong evidence that they can securely identify sentinel lymph nodes.

CONCLUSIONS

SLN is described as being the first lymph node in a regional lymphatic basin that receives lymph flow from a primary tumor, and its status indicates the regional spread of the primary tumor: if the sentinel lymph node is negative, the other nodes in the same basin are most probably also free of disease.

Several methods are used for the biopsy of the SLN, such as blue dye, radioactive isotopes and combination techniques, but many disadvantages still remain.

The blue dye method is known to be safe, practical and cost-effective but also has several limitations. Radioactive isotopes grant superior tissue penetration but expose both surgeons and patients to radiation and can only be identified with a gamma probe. It is also expensive and requires additional facilities.

To overcome these limitations, ICG is being used in order to improve the accuracy of sentinel node detection. Fluorescence-guided axillary SLNB offer a safe and efficient option to blue dye or radiocolloids. Sentinel lymph node biopsy with ICG doesn't have poorer results compared to the dual technique or the use of radioactive isotopes alone, but is better to blue dye. The use of ICG would not only be justified in terms of SLNB efficacy, but would cancel the risks associated with radiation of the patient and the medical staff, skin tattooing, and hypersensitivity reactions.

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