Utility of indocyanine green injection in avoiding unnecessary axillary lymph node dissection in breast cancer patients

Nicolae Bacalbașa[1,2], Irina Bălescu[3], Roxana Bohîlțea[1,4], Sorin Petrea[5], Sorin Aldoescu[5], Mihaela Vîlcu[5,6], Iulian Brezean[5,6], Lucian Pop[7], Alexandru Ciulcu[8], Dragoș Romanescu[9], Claudia Stoica[10,11], Cristina Martac[12], Alexandru Filipescu[1,13], Cezar Laurențiu Tomescu[14,15], Adnan Ad Aloul[16,17]

1. Department of Obstetrics and Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

2. Department of Visceral Surgery, Center of Excellence in Translational Medicine, Fundeni Clinical Institute, Bucharest, Romania

3. Department of Visceral Surgery, Ponderas Academic Hospital, Bucharest, Romania

4. Department of Obstetrics and Gynecology, "Filantropia" Clinical Hospital of Obstetrics and Gynecology, Bucharest, Romania

5. Department of Surgery, "Dr. I. Cantacuzino" Clinical Hospital, Bucharest, Romania

6. Department of Surgery, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Abstract

Breast cancer represents the most frequently encountered malignancy affecting women worldwide, with an increasing incidence especially when it comes to early-stage lesions, due to the wide implementation of the national screening programs. In this direction, attention was focused on developing the concept of conservative surgery in regard to both breast and axilla. Once innovative techniques have been implemented, the rates of patients submitted to unnecessary surgical procedures, such as axillary lymph node dissection for early-stage breast cancer, decreased, while the number of cases submitted to conservative procedures, such a sentinel node dissection, increased. Meanwhile, the wide use of the dual method of sentinel node detection led to a significant increase of the sensibility and specificity of the method. The aim of the current paper is to investigate the role of indocyanine green in avoiding unnecessary axillary lymph node dissection in early breast cancer patients.

Keywords: *early-stage breast cancer, sentinel lymph node, indocyanine green, axillary lymph node dissection*

Rezumat

Neoplasmul de sân reprezintă cel mai frecvent întâlnită malignitate care afectează femeile, având o incidență crescută, în special în ceea ce privește cazurile diagnosticate în stadiile incipiente, mai ales datorită implementării pe scară largă a programelor naționale de screening. Drept urmare, atenția a fost concentrată asupra dezvoltării conceptului de chirurgie conservatoare în ceea ce privește atât chirurgia sânului, cât și cea a axilei. Odată ce au apărut tehnicile inovatoare, rata pacientelor supuse procedurilor chirurgicale extensive, cum ar fi limfodisecția axilară pentru neoplasmele mamare diagnosticate în stadii incipiente, a scăzut, în timp ce rata cazurilor supuse intervențiilor conservatoare, de tipul exciziei ganglionului-santinelă, a crescut. În același timp, utilizarea metodei duale de detecție a ganglionului-santinelă a condus la o creștere semnificativă a sensibilității și specificității metodei. Scopul acestei lucrări este de a investiga rolul verdelui indocianin în evitarea limfodisecției axilare la pacientele cu neoplasm de sân diagnosticat în stadii incipiente.

Cuvinte-cheie: *neoplasm mamar diagnosticat în stadii precoce, ganglion-santinelă, verde indocianin, limfodisecție axilară*

Submission date: 25.11.2021
Acceptance date: 3.12.2021

Utilitatea injectării cu verde de indocianină în evitarea disecției inutile a ganglionilor limfatici axilari la pacientele cu cancer de sân

Suggested citation for this article: *Bacalbașa N, Bălescu I, Bohîlțea R, Petrea S, Aldoescu S, Vîlcu M, Brezean I, Pop L, Ciulcu A, Romanescu D, Stoica C, Martac C, Filipescu A, Tomescu CL, Ad Aloul A. Utility of indocyanine green injection in avoiding unnecessary axillary lymph node dissection in breast cancer patients. Ginecologia.ro. 2021;34(4):82-84.*

Introduction

Breast cancer has reported an increasing incidence in the last decades, especially when it comes to the early stages of the disease, due to the wide implementation of the national screening programs, due to a higher adherence of women to these programs and due to the improvements reported in the field of imagistic methods such as ultrasound, tomosynthesis or magnetic resonance imaging[1,2]. Therefore, attention was further focused on developing the concept of conservative surgery for both breast and axilla. While during the 19th century the most commonly performed surgical procedure were Halstead or Madden mastectomy, these procedures are now recognized as mutilating gestures and are exceptionally used[3-5]. Therefore, they were further replaced by less radical procedures such as sectorectomies or quadranectomies. Thus, a de-escalation of the breast surgery occurred; meanwhile, a similar process was described in regard to the axillary approach, standard axillary lymph node dissection being de-escalated to sentinel lymph node identification[6-9]. The method has been associated with significant improvement of the quality of life, leading to a diminished rate of postoperative complications such as wound dehiscence, infection or upper limb lymphedema. However, the initial sensitivity and specificity of the method were not as high as expected and, therefore, the attention was focused on other techniques with the aim of obtaining improved results[10].

The concept of dual method of sentinel node identification

In order to increase the chances to have a correct identification of the sentinel node, certain study

groups proposed a double check of the identified node; thus, the initial method of sentinel node detection – via Technetium injection at the periareolar site followed by sentinel node identification in the same day or at 24 hours after injection – has been doubled checked by an intraoperative injection of another tracer. In this regard, the concept of a dual method of sentinel node identification developed; one of the first proposed dyes for sentinel node detection was represented by methylene blue[10]. The method was associated with improved rates of lymph node detection, but also with increased risks of perioperative complications, such as cutaneous necrosis, that can significantly modify the postoperative outcome, especially in cases in which conservative breast surgery is performed. It should not be omitted the fact that in such cases methylene blue is injected in the periareolar area irrespective to the site of the tumor in order to identify the sentinel node.

Furthermore, if conservative breast surgery is planned and local complications such as skin necrosis occur after methylene blue injection, the aim of a good cosmetic result is entirely compromised. Consequently, the attention was focused on identifying other potential markers which could be injected in the periareolar area and which could provide an adequate detection of the sentinel without increasing the rates of development of local complications such as skin necrosis[11,12].

The rationale of indocyanine green injection for medical purposes

Indocyanine green was approved by the Food and Drug Administration in 1959 and has rapidly gained popularity, being used with multiple purposes. Initially used for the evaluation of hepatic, renal and cardiac functions, this molecule is now widely used for its optical properties in order to provide a real-time angiographic and/or lymphographic mapping of different regions[13]. The optical properties are based on the capacity of indocyanine green to absorb between 600 nm and 900 nm, with a maximum *in vivo* absorption at 800 nm, and to emit fluorescence between 750 nm and 950 nm[14]. Due to the fact that it presents a low degree of absorption, it is considered to have a low systemic toxicity and therefore can be widely administrated to different categories of patients, including pregnant women[15].

The rationale of indocyanine green injection for sentinel node excision

Also known as the first lymphatic node in which lymph from a certain region is drained, sentinel node seems to play a crucial role in establishing the further therapeutic strategy in different malignancies, such as breast cancer, digestive cancers or malignant melanoma. Once identified and excised, it is sent for histopathological analysis in order to establish the presence or absence of isolated tumoral cells, micrometastasis or macrometastasis; furthermore, according to the status of the sentinel node, the further therapeutic strategy remains to be established[16]. Thus, a correct identification of this node is mandatory, a double check of this lymph node bringing more confidence in regard to the real stage of the disease. Due to the fast-learning curve, indocyanine green based lymphography has been widely implemented and became part of the therapeutic protocol for sentinel node identification. In this direction, the rates of unnecessary lymph node dissection decreased, conducting to a lower level of postoperative complications, such as upper limb lymphedema or chronic wound related issues[17].

The role of indocyanine green in avoiding unnecessary lymph node dissection in early-stage breast cancer patients

One of the first studies which came to demonstrate the effectiveness of indocyanine green injection for sentinel node detection, to validate the method and to investigate the possibility of avoiding the unnecessary lymph node dissection, was conducted by Chi et al., being published in 2013. The study included 22 patients with early-stage breast cancer – defined as less than 5 cm tumors and negative lymph nodes – who were submitted to sentinel lymph node detection by using indocyanine green and near infrared system of visualization. In all cases, at least one sentinel node was identified, the total number of retrieved nodes being of 59; furthermore, all cases were submitted to axillary lymph node detection, a total number of 361 lymph nodes being retrieved. The histopathological studies demonstrated that eight of the 59 retrieved sentinel nodes presented metastases and 27 of the non-sentinels retrieved nodes also showed the presence of metastatic deposits. Among these cases, there was a single case that presented metastatic deposits in the non-sentinel nodes, while the sentinel node was negative. Thus, the authors demonstrated that, by using this method, the detection rate of sentinel node reaches 100%, being therefore higher when compared to the one reported by the dual method (consisting of radioactive colloid and blue dye injection)[18,19].

Meanwhile, we should not omit the fact that indocyanine green does not only offer a very high rate of sentinel node detection rate, but also avoids the disadvantages related to radioisotope usage, such as radiation exposure, licensing, costs and special conditions of injection and detection[20].

Conclusions

Indocyanine green has proven its utility in order to provide a higher rate of sentinel node detection and to improve both oncological and cosmetic outcomes in early-stage breast cancer patients, decreasing in this way the rates of unnecessary lymph node dissection. Therefore, it seems to provide an efficient de-escalation of the axillary management from routine axillary lymph node detection to sentinel node identification and excision. ■

Conflicts of interests: The authors declare no conflict of interests.

7. Department of Obstetrics and Gynecology, "Alessandrescu-Rusescu" National Institute for Mother and Child Care, Bucharest, Romania

8. Department of Obstetrics and Gynecology, "Dr. I. Cantacuzino" Clinical Hospital, Bucharest, Romania

9. Department of Surgery, Sanador Clinical Hospital, Bucharest, Romania

10. Department of Anatomy, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

11. Department of Surgery, Ilfov County Emergency Clinical Hospital, Bucharest, Romania

12. Department of Anesthesiology, Fundeni Clinical Institute, Bucharest, Romania

13. Department of Obstetrics and Gynecology, "Elias" University Emergency Hospital, Bucharest, Romania

14. Department of Obstetrics and Gynecology, "Ovidius" University of Medicine and Pharmacy, Constanța, Romania

15. Department of Obstetrics and Gynecology, "Sf. Ap. Andrei" County Emergency Clinical Hospital, Constanța, Romania

16. Department of Surgery, Municipal Hospital Râmnicu-Sărat, Romania

17. Department of Surgery, "Titu Maiorescu" University, Bucharest, Romania

Corresponding author:
Irina Bălescu
E-mail: irina.balescu@ponderas-ah.ro

References

1. Houssami N. Can population breast screening programs be leveraged to reduce the burden of breast cancer? Breast. 2021;60:245-6.
2. Expert Panel on Breast Imaging, Weinstein SP, Slanetz PJ, Lewin AA, Battaglia T, Chagpar AB, Dayaratna S, Dibble EH, Goel MS, Hayward JH, Kubicky CD, Le-Petross HT, Newell MS, Sanford MF, Scheel JR, Vincoff NS, Yao K, Moy L. ACR Appropriateness Criteria® Supplemental Breast Cancer Screening Based on Breast Density. J Am Coll Radiol. 2021;18(11S):S456-S473.
3. Madden JL, Kandalaft S, Bourque RA. Modified radical mastectomy. Ann Surg. 1972;175(5):624-34.
4. Halsted WS. I. The results of radical operations for the cure of carcinoma of the breast. Ann Surg. 1907;46(1):1-19.
5. Veronesi U. Conservative treatment of breast cancer: a trial in progress at the Cancer Institute of Milan. World J Surg. 1977;1(3):324-6.
6. Krag DN, Weaver DL, Alex JC, Fairbank JT. Surgical resection and radiolocalization of the sentinel lymph node in breast cancer using a gamma probe. Surg Oncol. 1993;2(6):335-9; discussion 340.
7. Giuliano AE, Haigh PI, Brennan MB, Hansen NM, Kelley MC, Ye W, Glass EC, Turner RR. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. J Clin Oncol. 2000;18(13):2553-9.
8. Senofsky GM, Moffat FL Jr, Davis K, Masri MM, Clark KC, Robinson DS, Sabates B, Ketcham AS. Total axillary lymphadenectomy in the management of breast cancer. Arch Surg. 1991 Nov;126(11):1336-41; discussion 1341-2.
9. Vrdoljak DV, Ramljak V, Muzina D, Sarceviç B, Knezević F, Juzbasić S. Analysis of metastatic involvement of interpectoral (Rotter's) lymph nodes related to tumor location, size, grade and hormone receptor status in breast cancer. Tumori. 2005;91(2):177-81.
10. Veronesi U, Paganelli G, Galimberti V, Viale G, Zurrida S, Bedoni M, Costa A, de Cicco C, Geraghty JG, Luini A, Sacchini V, Veronesi P. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. Lancet. 1997;349(9069):1864-7.
11. Li H, Jun Z, Zhi-Cheng G, Xiang Q. Factors that affect the false negative rate of sentinel lymph node mapping with methylene blue dye alone in breast cancer. J Int Med Res. 2019;47(10):4841-53.
12. Zhang C, Li Y, Wang X, Zhang M, Jiang W, Ou J. Clinical study of combined application of indocyanine green and methylene blue for sentinel lymph node biopsy in breast cancer. Medicine (Baltimore). 2021;100(15):e25365.
13. Alander JT, Kaartinen I, Laakso A, Pätilä T, Spillmann T, Tuchin VV, Venermo M, Välisuo P. A review of indocyanine green fluorescent imaging in surgery. Int J Biomed Imaging. 2012;2012:940585.
14. Sabapathy V, Mentam J, Jacob PM, Kumar S. Noninvasive Optical Imaging and In Vivo Cell Tracking of Indocyanine Green Labeled Human Stem Cells Transplanted at Superficial or In-Depth Tissue of SCID Mice. Stem Cells Int. 2015;2015:606415.
15. Laperche Y, Oudea MC, Lostanlen D. Toxic effects of indocyanine green on rat liver mitochondria. Toxicol Appl Pharmacol. 1977;41(2):377-87.
16. Hutteman M, Mieog JS, van der Vorst JR, Liefers GJ, Putter H, Löwik CW, Frangioni JV, van de Velde CJ, Vahrmeijer AL. Randomized, double-blind comparison of indocyanine green with or without albumin premixing for near-infrared fluorescence imaging of sentinel lymph nodes in breast cancer patients. Breast Cancer Res Treat. 2011;127(1):163-70.
17. Kootstra J, Hoekstra-Weebers JE, Rietman H, de Vries J, Baas P, Geertzen JH, Hoekstra HJ. Quality of life after sentinel lymph node biopsy or axillary lymph node dissection in stage I/II breast cancer patients: a prospective longitudinal study. Ann Surg Oncol. 2008;15(9):2533-41.
18. Motomura K, Inaji H, Komoike Y, Hasegawa Y, Kasugai T, Noguchi S, Koyama H. Combination technique is superior to dye alone in identification of the sentinel node in breast cancer patients. J Surg Oncol. 2001;76(2):95-9.
19. Sugie T, Sawada T, Tagaya N, Kinoshita T, Yamagami K, Suwa H, Ikeda T, Yoshimura K, Niimi M, Shimizu A, Toi M. Comparison of the indocyanine green fluorescence and blue dye methods in detection of sentinel lymph nodes in early-stage breast cancer. Ann Surg Oncol. 2013;20(7):2213-8.
20. Ahmed M, Purushotham AD, Douek M. Novel techniques for sentinel lymph node biopsy in breast cancer: a systematic review. Lancet Oncol. 2014;15(8):e351-62.