SENTINEL LYMPH NODE BIOPSY FOR BREAST CANCER USING INDOCYANINE GREEN FLUORESCENCE VISUALIZATION

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Abstract

We presented the preliminary results of sentinel lymph node biopsy (SLN) using the method of fluorescent visualization with the indocyanine green. The study included 40 breast cancer patients with the prevalence of the cTis-2N0M0 process. 1 ml of Indocyanine Green (ICG) aqueous solution was administered periareolarly and subcutaneously from the tumor side with total drug dose of 5 mg. In the following few minutes the ICG trail along the lymphatic vessels was observed by its fluorescence in the infrared spectral range using a special camera with image transmitted to a computer screen. After the trail reached the axillary region and broke off, skin and subcutaneous tissue incision in axillary area was made, and the superficial fascia was dissected. The first contrasted lymph nodes were extracted. The incidence of SLN was 92.5%. Metastases were detected in 20% of cases. On average, it took 17.6 minutes to identify and remove the SLN. In 7 patients the use of the fluorescent SLN detection method was combined with radioisotope (Technefite ^{99m}Tc colloid) – in all cases the same SLN was identified. The use of the ICG lymphotropic dye with the subsequent detection of SLN by the fluorescence method makes it possible to diagnose the status of SLN with a high degree of accuracy and can be comparable in effectiveness with the isotopic method. The specificities of lymphatic drainage were found out with the use of fluorescence lymphography: inverse dependence of the lymphatic drainage rate on the body mass index and breast size, and absence of dependence on degree of ptosis of breast.

Keywords: breast cancer, sentinel lymph node biopsy, fluorescence lymphography, indocyanine green.

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БИОПСИЯ СТОРОЖЕВОГО ЛИМФАТИЧЕСКОГО УЗЛА ПРИ РАКЕ МОЛОЧНОЙ ЖЕЛЕЗЫ С ПРИМЕНЕНИЕМ МЕТОДА ФЛУОРЕСЦЕНТНОЙ ВИЗУАЛИЗАЦИИ КРАСИТЕЛЯ ИНДОЦИАНИН ЗЕЛЕНЫЙ

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Резюме

В работе представлены результаты исследования биопсии сторожевого лимфатического узла (СЛУ) с помощью метода флуоресцентной визуализации красителя индоцианин зеленый. В исследование были включены 40 пациенток с раком молочной железы с распространенностью процесса cTis-2N0M0. 1 мл водного раствора красителя индоцианина зеленый вводили периареолярно внутрикожно и подкожно со стороны опухоли в дозе активного вещества 5 мг. В ближайшие минуты наблюдали движение красителя по лимфатическим путям в виде «дорожки» способом флуоресценции в инфракрасном спектре с помощью специальной камеры с передачей изображения на экран компьютера. После того, как дорожка подходила к подмышечной области и обрывалась,

производили разрез кожи и подкожной клетчатки в подмышечной области, рассекали поверхностную фасцию. Выделяли первые контрастированные лимфатические узлы. Частота выявления СЛУ составила 92,5%, из них метастазы выявлены в 20% случаях. В среднем на этап идентификации и удаления СЛУ уходило 17,6 мин. У 7 больных комбинировали применение метода флуоресцентного (краситель ICG) определения СЛУ с радиоизотопным (коллоид Технефит ^{99m}Tc) – во всех случаях идентифицировали одни и те же СЛУ. Применение лимфотропного красителя индоцианина зеленого с последующим выявлением СЛУ методом флуоресценции позволяет с высокой степенью точности диагностировать состояние СЛУ, а также сопоставимо по эффективности с изотопным методом. Выявлены особенности лимфооттока в молочной железе с помощью флуоресцентной лимфографии: обратная зависимость скорости лимфооттока от индекса массы тела и размера молочной железы, отсутствие зависимости от степени птоза железы.

Ключевые слова: рак молочной железы, биопсия сторожевого лимфатического узла, флуоресцентная лимфография, индоцианин зеленый.

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Introduction

Sentinel lymph node biopsy is an objective diagnostic criterion that allows for assessing the extent of the malignant process and plays a key role in the treatment of patients with early breast cancer [1]. The "sentinel" lymph node (SLN) is the node that is the first on the path of lymph outflow from the organ under investigation; the term was introduced by L. R. Braithwaite, a British scientist, in 1923 [2]. The presence or absence of metastases in it determines the required scope of lymphodissection. The absence of metastasis in the SLN makes it possible to predict the absence of metastases in the remaining lymph nodes of the axillary and subclavian tissue in more than 90% of cases, and not to perform a full regional lymphadenectomy, a surgery that often results in complications such as long-term lymphorrhea, secondary infection, lymphedema of the arm, impaired limb function and the development of post-mastectomy syndrome [3, 4].

Currently, there are two main methods for detecting and identifying SLN, which use different lymphography techniques: the use of a radiopharmaceutical agent or fluorescent dye. These methods can be used in combination [5, 6]. The isotope method for determining SLN in breast cancer has been used since the late 1990s [7, 8]. This method is well studied and was presented in many publications, both foreign and Russian [9-13]. The method is based on the selective ability of unchanged reticular-endothelial cells of the lymph nodes to capture radionuclide-labeled colloidal particles coming with lymph from the tissue depot after their introduction. As a rule, a solution of sodium pertechnetate, ^{99m}Ts from the technetium-99m generator and lyophilizate is used, 1 ml of which is injected peritumorally or periareolarly into the tumor projection zone. To assess the state of regional lymphatic collectors and search for "sentinel" lymph nodes, scintigraphy is performed with the use of a standard tomographic gamma camera. During an intraoperative search for SLN, a portable gamma scanner (GammaFinder II, etc.) is used, with the possibility of contact detection of the radioactivity level in the lymph nodes in question. When an SLN is identified, it is removed and undergoes urgent diagnostics with the ise of histological or cytological methods [14]. The method of using a radioisotope colloid has a fairly high SLN detection rate, which varies from 91% to 97% [15]. The indicators of sensitivity, specificity, and accuracy are 83.3%, 100%, and 94%, respectively [16]. According to one of the main meta-analyses published in 2006, which included data from 8,059 patients who underwent SLN biopsy with the use of only the radioisotope method, the average SLN detection rate was 97%, and the average false-negative result was 7.4% [15]. The use of a combination of radioisotope colloid and blue dye methods led to an improvement in detection indicators (OR = 2.03, 95% CI 1.53–2.69, $P < 0.05$). And the false negative result indicator for a combination of two methods does not change significantly and is 7.5% (95% CI 4.8–11.5%) [16].

The method of determining SLN with fluorescent lymphography is relatively new: the first publication on its application appeared in 1999 [17]. SLN biopsy with the use of a fluorescent dye is a convenient and safe intraoperative method for assessing the condition of the lymph nodes, the main disadvantage of which is the rapid passage of the dye, which places great demands on the experience of the surgeon. The dye currently used is a fluorescent agent indocyanine green (ICG), the distribution of which along the lymphatic pathways is determined by fluorescence in the infrared spectrum of radiation. In a meta-analysis published by T. Sugie et al. in 2016, it was confirmed that the accuracy indicators for determining SLN with the use of the ICG method and the method with a radioisotope colloid do not differ [18].

In Russia, a minor-scale experience of the use of ICG is represented by the work of S. M. Portnoy et al. The study included 81 patients with stage 0–III breast cancer. SLNs were detected in 75 patients (93%) and not found in 6 observations. In the first group, which included 8 patients with breast cancer cTisN0M0, SLN was found in 7, all of them without metastatic lesions. In the second group, which included 56 patients with cT1–4N0M0 breast cancer, SLN was detected in 54 (96%) patients, among which metastases in the SLN were detected in 15 (28%) cases. A false negative result was obtained in 2 (4%) out of 54 cases. In the third group, consisting of 17 patients with cT1–4N1–3M0 breast cancer after effective systemic therapy with undetectable regional metastases, SLN was detected in 14 (82%) patients, while in 5 (36%) cases metastases were detected in the SLN. False-negative results were found in 2 (14%) of 14 patients. The fluorescence was performed with the Photo dynamic eye camera (Hamamatsu, Japan) [19].

In this study, we have explored the possibility of determining SLN with the technique of fluorescent lymphography based on the indocyanin green dye and SPY 2000 device. The difference between the method used and other systems of fluorescent intraoperative navigation is the use of a laser radiation source operating in a narrow-band range of 805 nm at the peak of absorption of fluorescent contrast.

Research and biopsy of the sentinel lymph node is currently a necessary procedure in the treatment and diagnostic process, which corresponds to international clinical recommendations (NCCN, ESSMO, etc.), as well as the recommendations of the Association of Oncologists of Russia. The use of fluorescent lymphography with dye has a significant advantage over the isotope method as it does not involve the risks of radiation, and there is also no need to comply with the numerous standards and conditions or to bear the costs related to the materials and technology as it is required when working with radio sources.

Materials and methods

The study involved 40 patients, including 7 people with cTisN0M0 process prevalence, 20 people with cT1N0M0, 13 people with cT2N0M0. The patients' age ranged from 34 to 80 years, averaging 52.8. The body mass index (BMI) was calculated by the formula: BMI = m/h^2, where m is the patient's body weight (kg), h is the patient's(m). BMI values were determined according to the generally accepted scale: the normal BMI range is 18.5-25 kg/m^2, 25-29.9 kg/m^2 means the person is overweight, 30-34.9 kg/m^2 is I degree of obesity; 35-39.9 kg/m^2 is II degree of obesity; more than 40 kg/m^2 is III degree of obesity. The body mass index of the patients included in the study ranged from 18.0 to 38.9, with the body mass deficit registered in 2 people, the normal weight in 21, 10 of the women were overweight, and obesity of I-III degree was observed in 7 women in the sample. In terms of the size of the mammary glands (by bra number), the distribution of the women was as follows: 12 women with small breast size (No. 1, 2), 22 women with medium size (No. 3, 4), and 6 women with large size (No. 5, 6). As the first stage of treatment, all patients underwent organ-preserving surgery or subcutaneous mastectomy with endoprosthesis reconstruction, with SLN biopsy. Indocyanine green (ICG) was used as a staining agent. The agent emits fluorescent radiation when exposed to light in the near-infrared range of about 820 nm. The dye is supplied in a 25 mg bottle.

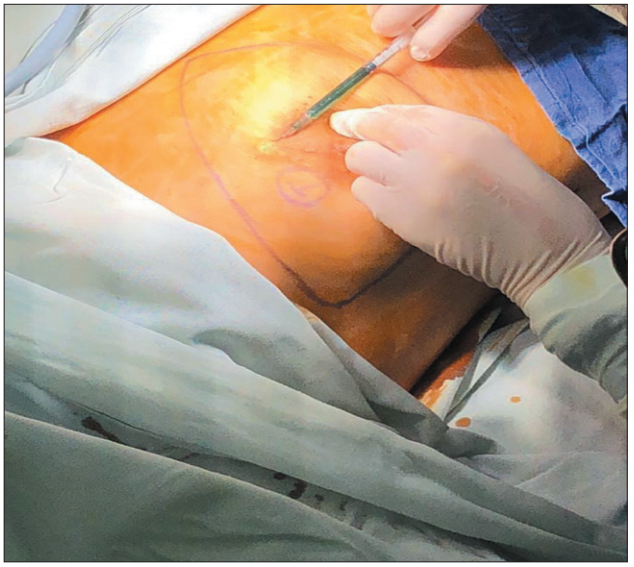

Рис. 1. Периареолярное введение раствора индоцианина зеленого
Fig. 1. Periareolar injection of Indocyanine green

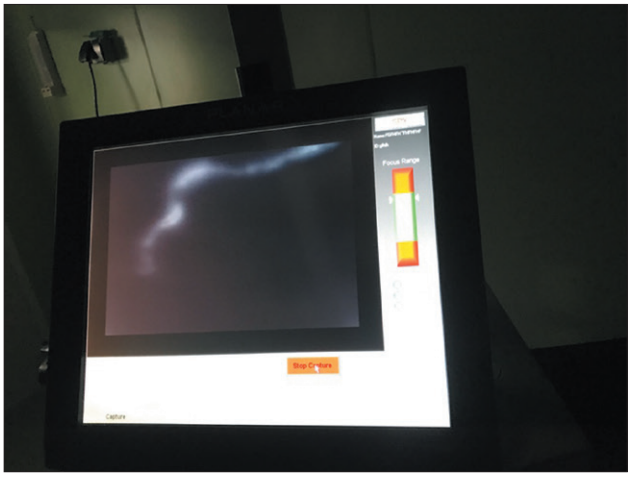

Рис. 2. Флуоресцентная «дорожка» на экране аппарата SP-2000
Fig. 2. Fluorescent "trace" on the screen of SP-2000

Before the procedure, the contents of the vial were dissolved in 5 ml of water for injection. Next, a G30 thickness needle was used to draw 1 ml of the resulting solution into a U100 insulin syringe. After the patient was put under general anaesthetic, 1 ml of ICG solution (5 mg/ml) was administered periareolarly, subcutaneously (Fig. 1). Then, for 10 seconds, manual massage of the breast was performed (5-7 circular movements) at the injection site, which provided an increase in pressure in the tissues and contributed to faster penetration of the drug into the lymphatic vessels. A few minutes later, with the operating room light turned off, the dye movement along the lymphatic pathways was detected by fluorescence in the infrared spectrum, which was achieved with a laser radiation source with a wavelength of 805 nm, SPY 2000 device (Novadaq Technologies Inc., Canada) with a special camera, which made it possible to see the image of the fluorescent "track" on a computer screen (Fig. 2). After the "path" approached the axillary area and broke off, an incision of the skin and subcutaneous tissue was made in the projection of the "break" in the axillary area, the superficial fascia was dissected, and contrasted lymph nodes were isolated with surgical instruments (Fig. 3, 4). The isolated lymph nodes were removed and cut along the length in 2-3 parallel planes, depending on their size (Fig. 5). Scrapings were taken from the surfaces of lymph nodes and placed on the slides, stained with hematoxylin-eosin, followed by an urgent cytological study, the results of which resolved the question of whether to perform lymphodissection. Upon detection of metastases, regional (axillary) lymph node dissection was performed . A revision of cellular tissue of the subclavian zone was performed. In the absence of suspicious areas, the subclavian tissue with lymph nodes was preserved. Statistical processing of the obtained results was performed by STATISTICA supplied by StatSoft, Inc. (2014).

Results

The method of determining the SLN with ICG agent was used on 40 patients. The rate of SLN detection was 92.5% of the cases (37 patients) ($p<0.0047$). Metastases were detected in 20% of cases (8 patients) ($p<0.0016$), of which in 6 cases, as a result of urgent intraoperative cytological examination, in 2 cases, by planned histological examination (false negative result). All patients identified with metastasis underwent level I or II lymph node dissection. The metastatic focus looked like a whitish area on the green plane of the stained lymph node. In 4 observations (10%), the dye fluorescence was present not only in the SLN, but also in the usual area of axillary cellular tissue. Skin pigmentation at the site of dye administration remained from several hours to 2 days. No local or general reactions were observed. On average, it took 17.6 minutes to identify and remove the SLN, and the time was further reduced due to sufficient practice

Рис. 3. Разрез кожи и подкожно-жировой клетчатки в аксиллярной области
Fig. 3. Skin and subcutaneous tissue incision in axillary area

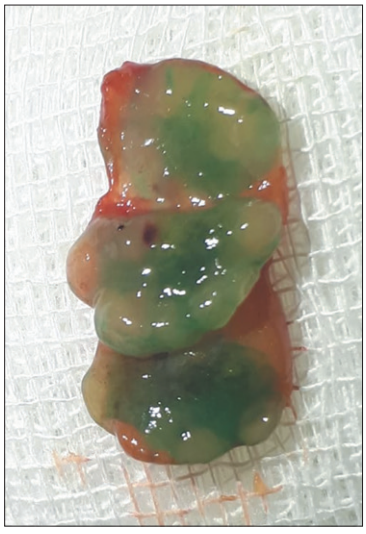

Рис. 4. Сторожевой лимфатический узел с накопленным индоцианином зеленым
Fig. 4. Sentinel lymph node with accumulated Indocyanine green

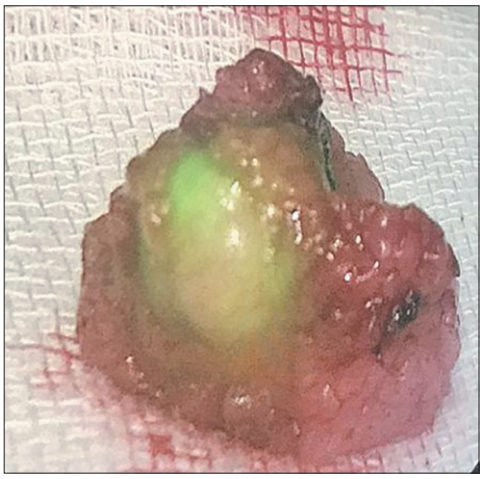

Рис. 5. Сторожевой лимфатический узел на разрезе
Fig. 5. Dissected sentinel lymph node

with the technique. The waiting period for an urgent cytological response was 15-20 minutes. Special attention was paid to the time of the appearance and development of the "track" of the dye movement. In the vast majority of cases (92%), the dye was distributed along a single radial main path running in the direction from the areola to the area of the axillary collector. A rare finding was a reticular type of lymph outflow (4%) with a dominant direction to the axillary area.

In 3 (7.5%) observations, it was not possible to trace the path of the lymph flow due to the absence of a dominant pathway. Of these, in 1 case, a marked SLN was detected, despite the absence of a dye path leading to it. In one more observation, the fluorescent focus in the axillary region was found to be a section of axillary fiber without a lymph node. The distance from the ICG injection site to the axillary area varied from 9 to 24 cm, with an average of 15.2 cm. In 65% of the observations, the track developed and reached the axillary area within 2 to 6 minutes. The maximum time was 21 minutes. The rate of ICG spread had an inverse correlation with the body mass index (6.1 minutes for the normal BMI versus 8.3 minutes for overweight persons) and the size of the breast ($p<0.005$), and demonstrated almost no dependence of the path length, i. e., the distance from the areola to the axillary area and the degree of breast ptosis. In other words, ICG was slower to reach and accumulate in women with excessive fat development, i.e. in cases where a less developed lymphatic drainage system can be expected. In 8 randomly selected patients, for the purpose of double simultaneous control, the use of the fluorescent (ICG dye) method for determining SLN was combined with the use of a radioisotope (Technefit ^{99m}Tc colloid). The same SLNs were identified in all the observations. In one case, it was not possible to identify the SLN, since no accumulation of either radiopharmaceutical or dye was detected. This case is of particular interest, as it further confirms the objectivity and comparability of both methods for determining SLN.

Discussion

The high accuracy of SLN determination with a fluorescent dye makes the technique the method of choice. A significant advantage of ICG in comparison with the more common alternative radioisotope method is the absence of radioactivity and a simpler procedure, as it is not necessary to comply with many standards established by the sanitary and epidemiological authorities, such as the use of a special room, protective aprons for personnel, etc. A disadvantage is the need to strictly follow the sequence of stages of the operation: a separate incision has to be made in the projection of the suspected SLN, since damage to the lymphatic pathways before they flow into the SLN will cause rapid diffuse staining of tissues making it impossible to identify the SLN. Moreover, for the detection of an isotope preparation by the sensor, the depth of the SLN occurrence is practically unimportant. When ICG is used, the overdeveloped subcutaneous fat layer in the axillary area requires the surgeon to work in the required speed mode, as slowing down results in the risk of staining the remaining non-sentinel lymph nodes, which seriously hinders identification of the true SLN. Taking into account the high accuracy of both fluorescent lymphography (92.5%) and radioisotope methods of SLN identification (91-97% according to the literature), we do not believe it is practical to combine them, due to the complexity and lengthening of the procedure, not to mention a significant increase in the cost of the use of a combination of the two methods.

Conclusion

The use of the lymphotropic dye indocyanin green for the detection of SLN by fluorescence in the infrared range allows for a high degree of accuracy in the diagnosis of the condition of SLN, and is comparable in efficiency to the isotope method in the group of patients without excess weight. A limitation is the superficial visualization of the lymph flow pathways, which makes it difficult or impossible to apply the technique in a methodically accurate way in overweight patients.

It is also worth noting that the use of the fluorescent lymphography method allowed us to study the specifics of lymph outflow in the mammary glands depending on some clinical and constitutional parameters, this data being absent in the world literature.

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