Vladimir Franzevich Baytinger et al /J. Pharm. Sci. & Res. Vol. 9(12), 2017, 2479-2485

ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Contemporary View of Potential Methods Used to Identify Lymphatic System in Case of Breast Cancer

Vladimir Franzevich Baytinger
Research Institute of Microsurgery, 96 Ivan Chernykh str., Tomsk 634063 Russia

Artem Shamilyevich Bureev
Diagnostika + LLC, 472 - 8 Razvitiya Ave., Tomsk 634055 Russia;
National Research Tomsk State University, 36 Lenina Ave, Tomsk 634050 Russia

Oksana Sergeevna Kurochkina
Research Institute of Microsurgery, 96 Ivan Chernykh str., Tomsk 634063 Russia

Ekaterina Yuryevna Dikman
Diagnostika + LLC, 472 - 8 Razvitiya Ave., Tomsk 634055 Russia
National Research Tomsk State University, 36 Lenina Ave, Tomsk 634050 Russia

Andrey L'vovich Shum
Elecard Devices CJSC, 522 - 3 Razvitiya Ave., Tomsk 634055 Russia

Abstract

The article describes contemporary clinical methods used to visualize lymphatic drainage in case of breast cancer of different location. The evolution of lymphatic system visualization methods is given. The contemporary view of the lymphatic drainage of the mammary gland and upper extremity from the viewpoint of the mapping procedure are described. The risks associated with metastatic spread into lymph nodes responsible for the lymphatic drainage of the upper extremity and potential cross-over in the axillary region have been analyzed. The article describes the ways of improving the method of contemporary diagnostics via a device with a dual-channel mode and simultaneous use of two contrast agents.

Key words: lymphatic system, sentinel lymph node, lymphatic drainage, breast cancer, fluorescent dye

INTRODUCTION

In the late 17th century, Anton Nuck (1650-1692) developed the method of injecting mercury into lymph vessels. In the 18th century, this method was used as a basis for further studies of the human lymphatic system [1, 2, 3]. This method allowed scientists not only to see lymph nodes but also determine specific morphology aspects of the lymphatic system.

Now it is generally accepted that Italian anatomist from the University of Siena Paolo Mascagni (1755-1815) made the most considerable contribution to the study of the anatomy of the lymph nodes and thoracic duct. Among contemporary oncologists, this famous anatomist is known as the author of "Mascagni's rule" according to which "lymph that runs through lymph vessels to the thoracic duct and large veins of the neck passes at least one or, more often, 8-10 lymph nodes." The physiological essence of this rule has become clear only recently. It has been found out that the cellular composition of lymph outflowing from different organs and that of lymph that has passed through lymph nodes are not identical. In this connection, scientists have singled out peripheral lymph (that has not passed through any lymph node yet), intermediate lymph (that has passed through 1-2 lymph nodes) and central lymph contained in the lymphatic trunks and thoracic duct that run into the large veins of the neck. That is why lymphatic drainage from different organs implies that lymph passes a different number of lymph nodes and, eventually, the venous bed (neck veins) receives lymph with a standard cellular composition (white blood cell differential). It is also relevant to the protein components of lymph, as organ lymph contains different protein components as compared to the lymph from the thoracic duct and blood [4].

One hundred years after Paolo Mascagni, French anatomist Constant Sappey (1810-1896) used the "mercury" method and managed to receive a clear visualization of the superficial lymph nodes of the entire human body. He singled out specific regions (upper and lower parts, right and left sides of the body) from which lymph run off. Also, he divided the lymphatic drainage of the human body with lines that were called Sappey's lines [5]. Soon after that, the "mercurial contrasting of lymph vessels" was abandoned, as mercury was very toxic for researchers. In 1896, this method was replaced with a technique proposed by Romanian physician D. Gerota – mercury was substituted with a blue oil paint (Berlin blue). However, this substance could only travel short distances from the point of administration, which did not allow visualizing the lymphatic bed completely [6].

The idea of mapping the lymph nodes of the human body belongs to surgeon L.R. Braithwaite who accidently detected a lymph node chain that got the black

color under the impact of an inflammatory process in the regions of the appendix and greater curvature of the stomach. L.R. Braithwaite called them "glands sentinels." Doctor J. Weinberg was inspired by these achievements and developed a technology to map lymph nodes with a blue dye agent in stomach cancer patients. He administered a blue dye agent (pontamine sky blue or direct blue 1) into the stomach during a surgery related to malignant stomach tumors to identify "sentinel" lymph nodes [7]. In 1952, J. B. Kinmonth developed and introduced lymphangiography (lymphography) into clinical practice. This method allowed visualizing lymph basins by means of oily X-ray contrast agents (lipiodol, neohydrin and etiodol). The procedure consisted in the subcutaneous administration of Patent Blue V to color a lymph vessel. Then this clearly visualized vessel was cannulated for the further administration of an X-ray contrast agent. Since then, English surgeon J. B. Kinmonth has been called the "farther" of clinical morphology [8]. However, those oily fluids had a negative impact on the endothelium of injected lymph vessels thus leading to obliteration. In 1953, A. Shermam and M. Ter-Pogossian developed a new method to visualize lymph nodes using a radioisotope (radioactive colloid Au^{168}) [9]. Other radioisotopes (e.g., technetium 99mTc) were introduced into practice a bit later. The principle of their method was very simple, which allowed it to become a routine diagnostic test and spread very quickly all over the world. The method was called "indirect lymphoscintigraphy."

In 1965, Doctor J.T. Halsell described the results of analyzing lymphatic drainage from the chest with the use of dye agents and radiography in his work "Lymphatic drainage of the breast demonstrated by vital dye staining and radiography" [7].

The goal of this publication is to describe contemporary clinical methods used to visualize lymphatic drainage in case of breast cancer of different location.

The main authors' objectives were as follows:

1. Describe a contemporary technology for sentinel lymph node mapping and biopsy as a new paradigm shift in the surgical treatment of breast cancer;
2. Explain a contemporary view of the lymphatic drainage of the mammary gland and upper extremity from the viewpoint of the mapping procedure;
3. Determine risks connected with the metastatic spread into the lymph nodes responsible for the lymphatic drainage of the upper extremity and consider the potential cross-over in the axillary region;
4. Discuss alternatives used to prevent secondary lymphedema when the lymphatic drainage of the upper extremity cannot be maintained.

MATERIALS AND METHODS

In the 1970s, it was found out that lymphatic drainage from organs primarily passes through specific lymph nodes, and then it passes through other lymph nodes. The first lymph nodes were called "sentinel" [10].

A sentinel lymph node is most often the first lymph node in a specific lymph basin. The lymphatic drainage of this anatomic region passes through this lymph node in the first place, and this lymph node is immunologically responsible for this region.

For the first time ever, Donald Morton performed the lymphatic mapping procedure to identify a sentinel lymph node in case of melanoma in 1992 [11]. D. Morton used a radioisotope (technetium) and dye agent (isoflurane blue) to map sentinel lymph nodes in his clinical practice.

Later, as knowledge about the routes of lymphatic drainage from different anatomic regions was accumulated, the theory of lymphosomes proposed by H. Suami was developed. According to this theory, a **lymphosome** is a defined region of the skin or soft tissues where lymphatic drainage goes through one lymph node or group of lymph nodes belonging to one and the same lymph basin [12].

Today, assessing potential metastatic spread into axillary lymph nodes is one of the most important prognostic criteria for breast cancer, that is why performing the "sentinel" lymph node biopsy prior to axillary lymph node dissection has become the standard of diagnostics [13, 14, 15].

The modern surgical treatment methods for breast cancer are based on an individual approach. This is the third revision of the surgical treatment paradigm for breast cancer. The first revision consisted in switching from radical extensive mastectomy to modified mastectomy that allowed preserving the greater and smaller thoracic muscles. The second revision of the surgical treatment paradigm consisted in switching from radical mastectomy to organ preservation surgeries (sector resection). However, these two revisions did not lead to a significant increase in patients' life expectancy and did not allow avoiding the emergence of iatrogenic (secondary) upper extremity lymphedema. Only the "sentinel" lymph node biopsy can give a complete understanding of the lymphatic drainage routes from a breast tumor and allow maintaining the lymphatic drainage of the upper extremity in some cases.

The mapping procedure was proposed by Donald Morton in 1992 as a method to identify "sentinel" lymph nodes in case of breast cancer. This method does not have a universal procedure technology even now, as different markers and points of administration are used: from radiopharmaceutical agents to various fluorescent and non-fluorescent dye agents. Some researchers administered these agents transdermally, while other used the intracutaneous route of administration; these agents were injected subareolarly, periareolarly, pretumorally and intratumorally [16, 17, 18, 19, 20, 21, 22, 23, 24, 25]. Overall, the "sentinel" lymph node biopsy is successful in most cases regardless of the point of administration. However, some diagnostic cases are unsuccessful, for instance, if an agent is accidently administered into the seroma cavity [13]. There are two absolute contraindications for the "sentinel" lymph node biopsy: inflammatory diseases of the mammary gland and clinical signs of axillary lymph node lesions [26].

Now radioactive technetium 99mTc is usually used as a radiotracer. Lymphazurin blue, isoflurane blue, methylene blue, indocyanine green and indigo carmine are used as dye agents [27]. Each of these agents has its own benefits and drawbacks. The administration of

radioisotopes requires specially equipped premises and, as a rule, lead to a specific radiation exposure. In most cases, this method is expensive. Administering some contrast agents, such as lymphazurin, isoflurane and methylene blue, can lead to the emergence of a long-term tattoo mark, while indocyanine green (ICG) does not have such an effect. Owing to its fluorescence properties, this agent is administered in a lower dose, therefore lymphoscintigraphy (with ICG) is unique in terms of its ability to visualize the lymphatic drainage of the mammary gland [27]. Some authors claim that it is advisable to avoid the use of lymphazurin blue because of its potential teratogenic effect. Therefore this research group uses only radioisotopes for the "sentinel" lymph node biopsy [13]. The opponents of lymphoscintigraphy claim that this method produces false-negative results significantly more often vs. the use of radiopharmaceutical agents: if the mapping of the upper extremity lymph nodes was performed with radioisotopes, the rate of identifying lymph nodes was 91-100% [28, 29], while fluorescent dye agents allowed identifying 88-93% of the lymph nodes [30, 31].

M.P.S. Sappey's classic research study [5] singles out two types of mammary gland lymphatic drainage – superficial lymph vessels responsible for lymphatic drainage from the skin and tissues under the mammary gland and deep lymph vessels responsible for the lymphatic drainage of the mammary gland itself [5, 32, 41].

H. Suami et al. (2008) found out that the superficial lymphatic system of the chest is represented by multiple basins forming a single lymph node located in the axillary cavity, near the lateral border of the smaller pectoral muscle. In some cases, the researchers detected another "sentinel" lymph node collecting lymphatic drainage from the superficial lymphatic system of the mammary gland [33].

The deep lymphatic system in the areola zone differs from other regions. The microscopic dissection of the areola region revealed a dense network of lymph capillaries and pre-basis in the skin. Most lymph nodes in the chest pass between the skin and gland tissue, while some lymph nodes pass between the greater and smaller pectoral muscles. When they pass the chest tissues, all lymph basins run to the lymph nodes located in the axillary cavity [33].

The internal lymph vessels of the mammary gland run down the internal thoracic artery and vein to the parietal pleura. They are accompanied by the lymph nodes located in the intercostal spaces. The researchers did not detect any connection between the superficial lymph basins and lymph basins that go along the perforating arteries [33].

The lymphatic drainage from the superficial lymph vessels directly goes to the axillary lymph nodes. The lymphatic drainage from the deep lymph vessels passes through the intermediate lymph nodes and then reaches the axillary lymph nodes [34]. There are two potential pathways of lymphatic drainage: from the parenchyma of the mammary gland directly to the axillary lymph nodes and from the parenchyma to the sub-areola region and then to the axillary lymph nodes [35]. This factor is of great importance for detecting a point where a dye agent should be administered to identify a "sentinel" lymph node in case of breast cancer. Intracutaneous injections demonstrate internal lymph nodes (axillary and intrathoracic) rarely [16, 21, 25]. Clinical trials have revealed that a contrast agent should be administered pretumorally in order to perform accurate lymphatic mapping. False-negative results in the process of identifying a sentinel lymph node can be received, if a contrast agent is administered only in the subareolar lymphatic plexus of the chest [33]. That is why the sentinel lymph node biopsy is sometimes used after the preliminary pretumoral and subareolar administration of dye agents and radioisotopes. It has been shown that the frequency of false-negative results is 7.8% in case of the pretumoral administration of contrast agents and 13.7% in case of the subareolar administration of contrast agents. However, despite the higher frequency of false-negative results in case of the subareolar administration of contrast agents, some research studies demonstrate a higher frequency of detecting a sentinel lymph node via this method vs. pretumoral administration. It can be explained with the fact that the areola region is rich with lymph vessels [36, 37, 38, 39]. At the same time, other research studies reveal a higher frequency of identifying "sentinel" lymph nodes in case of the pretumoral administration of contrast agents, when the double mapping of lymph nodes with blue and green contrast agents is performed [40]. Multiple research studies investigating various combinations of agents and points of administration have revealed that the frequency of false-negative results is reduced only in case of the simultaneous pretumoral and subareolar administration of a radioisotope and contrast agents [35, 40, 42, 43]. The accuracy of this procedure reaches 96-100% vs. 86-90% for the procedure using only one of the identifiers. Therefore it is necessary to use two contrast agents to map sentinel lymph nodes. However, the researchers make a conclusion that the latter combination is more expensive, contraindicated for pregnant women and associated with additional radiation exposure for test subjects [40]. Also, the authors determine that false-negative results are most often obtained in case of the lateral location of tumors [40].

Axillary lymph node dissection is included into the standard of surgical treatment for breast cancer. Despite this fact, the incidence of upper extremity lymphedema after this procedure varies from 7% to 77% according to different literature sources [44, 45, 46, 47, 48, 49, 50, 51]. However, Sakorafas G.H et al. and Wilke L.G. et al. say that the sentinel lymph node biopsy performed to determine the presence or absence of cancer cells and further dissection of this lymph node lead to secondary upper extremity lymphedema statistically less frequently vs. the consequences of extensive axillary lymph node dissection [47]. That is why the sentinel lymph node biopsy can become an alternative to axillary lymph node dissection. However, this method still leads to upper extremity lymphedema in 7% of the cases [52, 53].

The sentinel lymph node biopsy and axillary lymph node dissection performed in case of breast cancer-related mastectomy cannot eliminate the risk of upper extremity lymphedema completely. In this connection, a

concept of the reverse lymphatic mapping (RLM) of the axillary lymph nodes was first published in 2007. This method allows initially detecting the routes of the upper extremity lymphatic drainage [29, 32, 54].

In 2010, M. Noguchi [32] described a technique used to map lymphatic drainage in the chest. He simultaneously used a radioactive isotope (technetium) and the Patent Blue dye to map the lymphatic drainage of the chest and ICG to map the lymphatic drainage of the upper extremity. He believed that the lymphatic drainage of the upper extremity was not connected with lymph nodes that were primarily affected by breast cancer metastases. The concept was based on the idea that the lymphatic drainage of the upper extremity had to be studied in the first place, and then axillary lymph node dissection had to be performed during the lymphatic drainage of the upper extremity. The lymph nodes responsible for the lymphatic drainage of the upper extremity are located differently in relation to the sentinel lymph node. As a rule, they lie deeper than the sentinel lymph node. In this connection, the sentinel lymph node biopsy leads to lymphedema significantly less frequently as compared to axillary lymph node dissection [55]. In most cases, the lymph nodes responsible for the lymphatic drainage of the upper extremity are located higher than the second intercostohumeral nerve. Therefore why lower axillary lymph node dissection is safe and does not lead to lymphedema [56]. Nevertheless, the sentinel lymph node is often located higher than the second intercostohumeral nerve, which substantiates the need to perform the mapping procedure.

Some research studies have revealed that there is a limit of non-overlapping between the lymphatic drainage of the upper extremity and the lymphatic drainage of the chest. The metastatic lesion of lymph nodes responsible for the lymphatic drainage of the upper extremity is from 11 to 44% according to different authors. This can be connected with two circumstances: 1) progression of the metastatic lesion of axillary lymph nodes, which inevitably leads to the lesion of lymph nodes responsible for the lymphatic drainage of the upper extremity [31, 32, 30, 57, 58, 59, 60, 61]; and 2) central location of the lymph nodes of the upper extremity [28, 30, 57, 62]. A cross-over takes place in this case, i.e., a sentinel lymph node is a lymph node responsible for the lymphatic drainage of both the upper extremity and the chest [31, 32, 58, 59, 60]. The incidence of this process is from 2% to 20% according to different authors [30, 31, 57].

Thus, the contemporary view of lymphatic drainage testifies to a connection between the lymphatic systems of the upper extremity and the chest [34, 63]. This assumption was confirmed by M. Noguchi who developed a concept for the mapping of the upper extremity lymphatic drainage and noticed that even the partial dissection of the axillary lymph nodes (levels I and II) leads to upper extremity lymphedema in 2.5-5% of the cases [32].

Preventing secondary lymphedema when the lymphatic drainage of the upper extremity cannot be maintained.

The lymph nodes responsible for the lymphatic drainage of the upper extremity can be saved in 47% of the cases only [29]. Therefore performing a lymphatic-venous bypass can become a good alternative in this case.

For instance, F. Casabona et al. performed the visualization of the lymphatic drainage of the upper extremity and chest and identification of a sentinel lymph node and lymph nodes of the upper extremity in their research studies. They showed that the lymph basins of the upper extremity leading to the sentinel lymph node become colored in some cases. If this occurs, it is impossible to maintain the lymphatic drainage of the upper extremity [55, 64, 65]. In such cases, lymph basins are plunged into the lumen of the axillary vein branch with the application of a telescopic end-to-side suture with the Nylon 8/0 thread [65].

This technology implies creating a lymphatic drainage between one or two lymph basins and the axillary vein branch where these lymph basins are plunged into. Another method to prevent and treat secondary upper extremity lymphedema is transplanting inguinal lymph nodes into the axillary region. This method that implies inguinal lymphatic flap collection requires the use of the mapping technique. The reverse lymphatic mapping (RLM) procedure allows maintaining an adequate lymphatic drainage of the lower extremity in this case [66].

The essence of the reverse lymphatic mapping technology consists in the simultaneous administration of indocyanine green into a zone located near the area from which an inguinal lymphatic flap will be collected and technetium 99mTc into the distal regions of the extremity (second interdigital space). The gamma test (detection of technetium 99mTc traces) is used in intraoperative settings to determine the location of lymph nodes that should be avoided during a flap collection procedure. Infrared fluorescent lymphangiography is performed simultaneously (with fluorescent angiographs, e.g., SPY Elite, LifeCell Corp., Branchburg N.J.) to detect sentinel lymph nodes containing indocyanine green. As a result, fluorescent lymphangiography and scintigraphy make it possible to determine a border between the lymph nodes of the donor zone and the lymph nodes responsible for the lymphatic drainage of the extremity [66].

A similar technique is used to collect axillary lymphatic flaps for their further transplantation into the inguinal region in case of lower extremity lymphedema.

RESULTS AND DISCUSSION

Until now, the mapping of lymph nodes from different lymphosomes has been performed with fluorescent dyes in combination with a radiopharmaceutical agent. Some researchers simultaneously use two contrast agents (indigo carmine and indocyanine green) to be administered peritumorally and subareolarly only to map lymph nodes from one and the same area (when searching for a sentinel lymph node) [40].

Using two contrast agents can be more promising than using only one contrast (fluorescent) agent and one radiopharmaceutical agent, since it will allow using this method to identify lymphatic drainage from two

neighboring anatomic zones in patients for whom radiation exposure is contraindicated (pregnant and lactating women). In addition, the technology of using two contrast (fluorescent) agents will not require special premises and equipment, and a proper selection of a contrast agent will allow avoiding complications and reducing the high cost of this test.

Now ICG is the most popular contrast fluorescent agent in the market, as this substance is administered in a low dose owing to its fluorescence properties and does not lead to the emergence of a long-term tattoo mark.

The second substance that could be successfully used in combination with ICG was lymphazurin (USA). However, the high price for this product made it necessary to search for an alternative to this dye in 2001. Using only one radiopharmaceutical agent was considered, which reduced the efficacy of searching for a sentinel lymph node. Oncologists did not want to get back to routine axillary lymph node dissection, as it would lead to an increase in the incidence of upper extremity lymphedema. This unwillingness to get back to routine lymph node dissection forced US oncologists to consider the use of methylene blue. As compared with lymphazurin, it [67] has a lower molecular weight, which, in theory, allows ensuring a better access of this dye to lymph vessels. Another benefit of this product vs. lymphazurin is its low price. The research study on the use of two dyes revealed that methylene blue was characterized by a higher speed of spread vs. lymphazurin. In 2006, it was shown that using only methylene blue to be administered peritumorally, without any radio colloid, was sufficient for the sentinel lymph node biopsy [63]. At the same time, the authors believe that the most serious complication associated with the administration of methylene blue is skin necrosis. Therefore the subcutaneous injections of this product are contraindicated. In this case, it is advisable to perform deep subcutaneous injections and slow administration under low pressure. Diluting the substance allows reducing the risk of getting a low-term tattoo mark.

CONCLUSION

Therefore methylene blue can be used to diagnose a sentinel lymph node in the chest in connection with its wide availability, low price and absence of serious side effects, except subcutaneous injections (the product safety profile has been confirmed with its wide 40-year use in medicine; in addition, this product has an FDA certificate). In our opinion, methylene blue can be used as an alternative to a radioactive isotope in combination with ICG for mapping a sentinel lymph node in case of breast cancer and maintaining the lymphatic drainage of the upper extremity at the same time. We have chosen this combination of agents, as the simultaneous use of these products has been clinically studied in cardiosurgery and biliary surgery, these substances have non-overlapping spectrums and can produce images, if dual-channel modes are used, and both of these products have FDA certificates [68, 69, 70].

ACKNOWLEDGMENTS

The study was performed within the framework of the Agreement #14.579.21.0146 (unique identifier for the project – RFMEFI57917X0146) entitled “Development and research of the hardware-software complex model and the experimental technique of extended photodynamic visualization for differentiation of the lymphatic pathways of closely located organs”, signed between Elecard Devices CJSC and the Ministry of Education and Science of the Russian Federation.

REFERENCES

[1] Cruikshank W. C. The Anatomy of the Absorbing Vessels of the Human Body. London: G. Nicol, 1786.
[2] Loukas M., Bellary S.S., Kuklinski M. et al. The lymphatic system: a histotical perspective. J. Clin. Anat. 2011; 24: 807–816.
[3] Mascagni, P. Vasorum Lymphaticorum Corporis Humani Historia et Iconographia. Sienne: P. Carli, 1787.
[4] Di Matteo B., Tarabella V., Filardo G. et al. Art in science: Giovanni Paolo Mascagni and the at rog anatomy. J. Clin. Orthop. Relat. Res. 2015; 473: 783–788.
[5] Sappey M.P.C., Delahaye A., Lecrosnier E. Anatomie, Physiologie, Pathologie des vaisseaux Lymphatiques consideres chez L’homme at les Vertebres. Paris: Adrien Delahaye, 1874.
[6] Gerota, D. Zur Technik der Lymphogeffassinjection: Eine neue Injectionsmasse fur Lymphgefasse. Polychrom Injection. J. Anat. Anz. 1896; 12: 216.
[7] Sato K, Shigenaga R, Ueda S. et al. Sentinel lymph node biopsy for breast cancer. J. Surg Oncol. 2007; 96(4): 322–9.
[8] Kinmonth, J. Lymphoangiography in man: A method of outlining lymphatic trunks at operation. J. Clin. Sci. 1952; 11: 13.
[9] Sherman, A., Ter-Pogossian, M. Lymph node concentration of radioactive colloidal gold following interstitial injection. J. Cancer. 1953; 6: 1238.
[10] Cabanas R.M. An approach for the treatment of penile carcinoma. J. Cancer. 1977; 39(2): 456–66.
[11] Morton D.L., Wen D.R., Wong J.H. et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. J. Arch Surg. 1992; 127(4): 392–9.
[12] Suami H., Yamashita S., Soto-Miranda M.A., Chang D.W. Lymphatic Territories (Lymphosomes) in a Canine: An Animal Model for Investigation of Postoperative Lymphatic Alterations J. PLOS ONE. 2013; 8: 1-13.
[13] Chatterjee A., Serniak N., Czerniecki B. J. Sentinel Lymph Node Biopsy in Breast Cancer: A Work in Progress. J. Cancer. 2015; 21(1): 7–10.
[14] Lyman G.H., Giuliano A.E., Somerfield M.R. et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J. Clin Oncol. 2005; 23(30): 7703–20.
[15] McMasters K.M., Tuttle T.M., Carlson D.J. et al. Sentinel lymph node biopsy for breast cancer: a suitable alternative to routine axillary dissection in multi-institutional practice when optimal technique is used. J. Clin Oncol. 2000; 18(13): 2560–6.
[16] Borgstein P.J., Meijer S., Pijpers R.. Intradermal blue dye to identify sentinel lymph nodes in breast cancer. J. Lancet 1997; 349: 1668–9.
[17] Giuliano A.E., Kirgan D.M., Guenther J.M., Morton D.L. Lymphatic mapping and sentinel lymphadenectomy for breast cancer. J. Ann. Surg. 1994; 220: 391–8.
[18] Kern K.A. Sentinel lymph node mapping in breast cancer using subareolar injection of blue dye. J. Am. Coll. Surg. 1999; 189: 539–45
[19] Kimberg V.S., Rubio I.T., Henry R. et al. Subareolar versus peritumoral injection for location of the sentinel node. J. Am. Surg. 1999; 6: 860–5.
[20] Krag D.N., Weaver D.L., Alex J.C., Fairbank J.T. Surgical resection and radiolocalization of the sentinel node in breast cancer using a gamma probe. J. Surg. Oncol. 1993; 2: 335–9.
[21] Linehan D.C., Hill A.D., Akhurst T. et al. Intradermal radiocolloid and intraparenchymal blue dye injection optimize sentinel node identification in breast cancer patients. J. Ann. Surg. Oncol/ 1999; 6: 450–4.

[22] Noguchi M. Sentinel lymph node biopsy and breast cancer. Br J. Surg. 2002; 89(1): 21–34.
[23] Noguchi M. Sentinel lymph node biopsy as an alternative to routine axillary lymph node dissection in breast cancer patients. J. Surg Oncol. 2001; 76(2): 144–56.
[24] Noguchi M., Tsugawa K., Miwa K. et al. Sentinel lymph node biopsy in breast cancer using blue dye with or without isotope localization. J. Breast Cancer. 2000; 7(4): 287–96.
[25] Veronesi U., Paganelli G., Galimberti V. et al. Sentinel-node biopsy to avoid acillary dissection in breast cancer with clinically negative lymph-nodes. J. Lancet 1997; 349: 1864–7.
[26] Krontiras H., Bland K.I. When is sentinel node biopsy for breast cancer contraindicated? J. Surg Oncol. 2003; 12(3): 207–10.
[27] Uren R.F., Howman-Giles R.B., Thompson J.F. et al. Mammary lymphoscintigraphy in breast cancer. J. Nucl Med. 1995; 36(10): 1775–80.
[28] Britton T.B., Solanki C.K., Pinder S.E., Mortimer P.S., Peters A.M., Purushotham A.D. Lymphatic drainage pathways of the breast and the upper limb. J. Nucl. Med. Comm. 2009; 30(6): 427-430.
[29] Nos C., Leiseur B., Clough K.B., Lecuru F. Blue dye injection in the arm in order to conserve the lymphatic drainage of the arm in breast cancer patients requiring an axillary dissection. J. Ann. Surg. Oncol. 2007; 14: 2490–2496.
[30] Noguchi M., Yokoi M., Nakano Y. Axillary reverse mapping with indocyanine fluorescence imaging in patients with breast cancer. J. Surg. Oncol. 2010; 101(3): 217-221.
[31] Yokoi M., Noguchi M., Nakano Y., Ohno Y., Kosaka T. Axillary reverse mapping using fluorescence imaging system in breast cancer. J. Breast Cancer Res. Treat. 2010; 119: 529-535.
[32] Noguchi M.. Axillary reverse mapping for breast cancer. J. Breast Cancer Res. Treat. 2010; 119: 529–535.
[33] Suami H., Pan W.-R., Mann G.B., Taylor G.I. The Lymphatic Anatomy of the Breast and its Implications for Sentinel Lymph Node Biopsy: A Human Cadaver Study. J. Annals of Surgical Oncology. 2008; 15(3): 863–871.
[34] Suami H., Pan W.R., Taylor G.I. Changes in the lymph structure of the upper limb after axillary dissection: radiographic and anatomical study in a human cadaver. J. Plast. Reconstr. Surg. 2007; 120(4): 982-991.
[35] Noguchi M., Inokuchi M., Zen Y. Complement of peritumoral and subareolar injection in breast cancer sentinel lymph node biopsy. J. Surg. Oncol. 2009; 100(2): 100-105.
[36] D'Eredita G., Ferrarese F., Cecere V. et al.: Subareolar injection may be more accurate than other techniques for sentinel lymph node biopsy in breast cancer. J. Ann. Surg. Oncol. 2003; 10: 942–947.
[37] Shimazu K., Tamaki Y., Taguchi T. et al.: Comparison between periareolar and peritumoral injection of radiotracer for sentinel lymph node biopsy in patients with breast cancer. J. Surgery 2002; 131: 277–286.
[38] Smith L.F., Rock L., Cross M.J. et al.: Subareolar injection is a better technique for sentinel lymph node biopsy. Am. J. Surg. 2000; 180: 434–438.
[39] Tuttle T.M., Colbert M., Christensen R. et al.: Subareolar injection of 99mTc facilitates sentinel lymph node identification. J. Ann. Surg. Oncol. 2002; 9: 77–81.
[40] Anan K., Mitsuyama S., Kuga H. et al.: Double mapping with subareolar blue dye and peritumoral green dye injections decreases the false-negative rate of dye-only sentinel node biopsy for early breast cancer: 2-site injection is more accurate than 1-site injection. J. Surgery. 2006; 139: 624–629.
[41] Noguchi M. Axillary reverse mapping for preventing lymphedema in the axillary lymph node dissection and/or sentinel lymph node biopsy. J. Breast Cancer. 2010; 17(3): 155-157.
[42] Cody H.S., Fey J., Akhurst T. et al. Complementarity of blue dye and isotope in sentinel node localization for breast cancer: univariate and multivariate analysis of 966 procedures. J. Ann Surg Oncol. 2001; 8(1): 13–9.
[43] Hung W.K., Chan C.M., Ying M. et al. Randomized clinical trial comparing blue dye with combined dye and isotope for sentinel lymph node biopsy in breast cancer. Br J. Surg. 2005; 92(12): 1494–7.
[44] Blanchard D.K., Donohue J.H., Reynolds C., Grant C.S. Relapse and morbidity in patients undergoing sentinel lymph node biopsy alone or with axillary dissection for breast cancer, J. Arch. Surg. 2003; 138(5): 482-488.
[45] Haid A., Koberle-Wuhrer R., Knauer M., Burtscher J., Fritzsche H., Peschina W., Jasarevic Z., Ammann M., Hergan K., Sturn H., Zimmermann G. Morbidity of breast cancer patients following complete axillary dissection or sentinel node biopsy only: a comparative evaluation. J. Breast Cancer Res. Treat. 2002; 73(1): 31-36.
[46] Leidenius M., Leivonen M., Vironen J., von Smitten K. The consequences of longtime arm morbidity in node-negative breast cancer patients with sentinel node biopsy or axillary clearance. J. Surg. Oncol. 2005; 92(1): 23-31.
[47] Mansel R.E., Fallowfield L., Kissin M. et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J. Natl Cancer Inst. 2006; 98(9): 599–609.
[48] Ronka R., von Smitten K., Tasmuth T., Leidenius M. One-year morbidity after sentinel node biopsy and breast surgery. J. Breast. 2005; 14(1): 28-36.
[49] Schijven M.P., Vingerhoets A.J., Rutten H.J., Nieuwenhuijzen G.A., Roumen R.M., van Bussel M.E., Voogd A.C. Comparison of morbidity between axillary lymph node dissection and sentinel node biopsy. Eur. J. Surg. Oncol. 2003; 29(4): 341-350.
[50] Schrenk P., Rieger R., Shamiyeh A., Wayand W. Morbidity following sentinel lymph node biopsy versus axillary lymph node dissection for patients with breast carcinoma. J. Cancer. 2000; 88(3): 608-614.
[51] Swenson K.K., Nissen M.J., Ceronsky C., Swenson L., Lee M.W., Tuttle T.M. Comparison of side effects between sentinel lymph node and axillary lymph node dissection for breast cancer. J. Ann. Surg. Oncol. 2002; 9(8): 745-753.
[52] Sakorafas G.H., Peros G., Cataliotti L., Vlastos G. Lymphedema following axillary lymph node dissection for breast cancer. J. Surg. Oncol. 2006; 15(3): 153-165.
[53] Suami H., Pan W.-R., Mann G.B., Taylor G.I. The Lymphatic Anatomy of the Breast and its Implications for Sentinel Lymph Node Biopsy: A Human Cadaver Study. J. Annals of Surgical Oncology. 2008; 15(3): 863–871.
[54] Thompson M., Korourian S., Henry-Tillman R., Adkins L., Mumford S., Westbrook K.C., Kimberg V.S. Axillary reverse mapping (ARM): a new concept to identify and enhance lymphatic preservation. J. Ann. Surg. Oncol. 2007; 14: 1890–1895.
[55] Casabona F., Bogliolo S., Valenzano M. M., Sala P., Villa G., Ferrero S. Feasibility of axillary reverse mapping during sentinel lymph node biopsy in breast cancer patients. J. Ann. Surg. Oncol. 2009; 16: 2459–2463.
[56] Kodama H., Mise K., Kan N. Lower axillary dissection for early breast cancer. J. Jap. Surg. Assoc. 2010; 71(12): 3031-3038.
[57] Kang S.H., Choi J.E., Jeon Y.S., Lee S.J., Bae Y.K. Preservation of lymphatic drainage from arm in breast cancer surgery: Is it safe? J. Cancer Research. 2009; 69(2): 87.
[58] Nos C., Kaufmann G., Clough K.B., Collignon M.-A., Zerbib E., Cusumano P., Lecuru F. Combined axillary mapping (ARM) technique for breast cancer patients requiring axillary dissection. J. Ann. Surg. Oncol. 2008; 15(9): 2550-2555.
[59] Ponzone R., Cont N.T., Maggiorotto F., Cassina E., Mininanni P., Biglia N., Sismondi P. Extensive nodal disease may impair axillary reverse mapping in patients with breast cancer. J. Clin. Oncol. 2009; 27(33): 5547-5551.
[60] Suami H., Taylor G.I., Pan W.R. The lymphatic territories of the upper limb: anatomical study and clinical implications. J. Plast. Reconstr. Surg. 2007; 119(6): 1813-1822.
[61] Bedrosian I., Babiera G.V., Mittendorf E.A., Kuerer H.M., Pantoja L., Hunt K.K., Krishnamurthy S., Meric-Bernstam F.M. A phase I study to assess the feasibility and oncologic safety of axillary reverse mapping in breast cancer patients. J. Cancer. 2010; 116(11): 2543-2548.
[62] Boneti C., Korourian S., Diaz Z., Santiago C., Mumford S., Adkins L., Klimberg V.S. Scientific Impact Award: Axillary reverse mapping (ARM) to identify and protect lymphatics draining the arm during axillary lymphadenectomy. Am. J. Sur. 2009; 198(4): 482-487.
[63] Suami H., O'Neill J.K., Pan W.-R., Taylor G.I. Superficial Lymphatic System of the Upper Torso: Preliminary Radiographic Results in Human Cadavers. J. Plastic and Reconstructive Surgery. 2008; 122: 1231-1239.

[64] Boccardo F., Casabona F., Cian F.D., Friedman D. et al. Lymphedema microsurgical preventive healing approach: a new technique for primary prevention of arm lymphedema after mastectomy. J. Ann. Surg. Oncol. 2009; 16: 703–708.
[65] Casabona F., Bogliolo S., Ferrero S., Boccardo F., Campisi C. Axillary reverse mapping in breast cancer: a new microsurgical lymphatic-venous procedure in the prevention of arm lymphedema. J. Ann. Surg. Oncol. 2008; 15: 3318–3319.
[66] Dayan J.H., Dayan E., Smith M.L. Reverse lymphatic mapping: a new technique for maximizing safety in vascularized lymph mode transfer. J. Plastic and Reconstructive Surgery. 2015; 135(1): 277-285.
[67] O'Sullivan M.J., Morrow M., Dirbas F., Scott-Conner C. Breast surgical techniques and interdisciplinary management. Springer-Verlag New York. 2011: 495-503.
[68] Ashitate Y., Stockdale A., Choi H.S., Laurence R.G., Frangioni J.V. Real-Time simultaneous near infrared fluorescence imaging of bile duct and arterial anatomy. J. Surgical Research. 2012; 176: 7–13.
[69] Dip F.D., Ishizawa T., Kokudo N., Rosenthal R. Fluorescence imaging for surgeons. Springer - International Publishing Switzerland. 2015, 360 p.
[70] Tanaka E., Chen F.Y., Flaumenhaft R., Graham G. J., Laurence R.G., Frangioni J.V. Real-time assessment of cardiac perfusion, coronary angiography, and acute intravascular thrombi using dual-channel near-infrared fluorescence imaging. J. Thorac. Cardiovasc. Surg. 2009; 138: 133-40.