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Intraoperative imagining in breast cancer surgery

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Abstract:

Breast cancer is the most common cancer in the female population. It is the second leading cause of cancer death in this population. The current technique of nuclear medicine combined with oncological surgery requires the improvement of known imaging methods.

In addition to generally available methods, such as MRI, CT, PET or mammography, scientists try to modify the diagnostic process and treatment of the patient in such a way that it is as effective and the least harmful as possible.

Breast cancer surgery is experiencing an infamous boom due to the increase in diagnoses, but looking at the positive side, it is also experiencing an amazing development: clinical and technological.

Increasingly, surgeons are accompanied by nuclear medicine, which precisely defines the methods of excision of breast tumors with a margin, while giving a satisfactory cosmetic effect, which is especially important for women.

Thanks to the development of these two fields, it is becoming easier to identify specific sentinel lymph nodes (SLNs) that require resection during surgical treatment and to suggest postoperative treatment.

The progress of science and medicine has undoubtedly contributed to the development of methods of intraoperative imaging in breast cancer. Today, practically simultaneously in the conditions of the operating room, a multidisciplinary team can determine the area of resection faster and more accurately.

Based on the research, it was decided to compare several methods used in today's advanced breast cancer surgery, supported by nuclear medicine.

Keywords: Breast cancer surgery, Breast cancer, Intraoperative imagining, IUOS, Indocyanine-green-dye, ICG, Micro-CT, BCS, BSG, Breast Specific Gamma Camera, Gamma Camera, IART, Intraoperative Avidination for Radionuclide Therapy, Biotin, SLN, Sentinel Lymph Node.

Methods:

1. IUOS - intraoperative ultrasound in breast cancer.
2. BSG - breast-specific gamma camera, the intraoperative gamma camera.
3. Micro CT- non invasive research imaging technique 3D utilizing X-rays to see inside an object, slice by slice: in this study- breast.
4. ICG- indocyanate green is fluorescence mapping with the highly available dye- indocyanate green in breast cancer include real-time.
5. IART - combining avidin with biotin tracer to determine appropriate Gy dose for breast cancer treatment.

Introduction:

Breast cancer is the most commonly occurring malignancy in women, with second highest mortality rate (after lung cancer) among both sexes. [1] According to this fact, there is a high clinical value on striving to determine the most effective, efficient and most simple-to-use diagnostic method within the operative field.

Intraoperative imagining strives to determine the value of tissue margin which is free from cancerous cells with highest precision possible. This is due to the fact that cancer needs to be removed with highest possible precision, with concurrent preservation of the highest amount of healthy breast tissue. This procedure allows for effective treatment at the same time maximizing the esthetic outcome.

According to the newest guidelines breast cancer treatment is multimodal and consists of surgery, radiation and drug therapy [1]. Patients with metastatic disease are treated with palliative intent.

Within this report research five different intraoperative imagining methods will be analyzed and compared: ultrasonography, gamma camera, micro-CT, indocyanine-green-dye method and Intraoperative Avidination for Radionuclide Therapy.

[6] The intraoperative imaging in breast cancer is important because it allows for precise detection of the lesion. In addition, due to intraoperative imaging methods, we can very

accurately determine the size of the tumor and a margin of tissue that needs to be cut (ie. without a change in prime-weave of a tumor in the surgical incision).

[6] It should be indicated that the method of tumor removal defined the division into:

- close margin - obtaining a margin of unchanged tissues <2 mm wide, which, according to Bolger and colleagues, is associated with a significantly higher risk of the presence of additional tumor foci in the postoperative bed.
- focally positive margin - the presence of ink on the surface of tumor area up to 4 mm., which qualifies for adjuvant radiotherapy.

Despite very careful preoperative diagnostics, a common phenomenon occured, namely tumor excision in a non-radical manner, which was associated with repeated excision of the cancer and surgery. The introduction of intraoperative imaging has reduced the performance of re-procedures in the case of insufficient excision of the neoplastic lesion, which in turn is associated with the cosmetic effect of the breast, very important for women.

[6] Close margin lesions required appropriate breast reconstructions, which were often scarred or not, which was associated with the amputation of the entire breast. After a mastectomy, the aesthetic possibilities are limited. These are: reconstruction of the entire breast, mainly with the use of LAT (dermal and muscle flap in the back area) or TRAM (in the lower abdomen area), which is associated with scarring of skin transplants in order to restore the breast, so the cosmetic effect is often not accepted by women. In turn, in focally positive margin lesions, breast conserving procedures are preferred: excision of the tumor, lymph nodes, margin. [6] BCT (Breast Conservation Procedure) provides an optimal aesthetic effect, much better than a breast amputation. Moreover, the tissues around the tumor after removal of the neoplastic tumor are healthy, so they are not marked with ink and do not have scars, which increases the aesthetic value. It also allows for breast enlargement undergoing a sparing procedure and has a very positive effect on the psychological and social aspect of the patient.

Of course, the patients suffering from breast cancer are different and it is worth trying to explain every possible complications after breast reconstruction, resulting from the disease, and the expected cosmetic effect after surgery.

SLN it means sentinel lymph node. [9].

[9] In recent years, sentinel lymph node biopsy is one of the standard procedures in the surgical treatment of breast cancer. Surgical excision of axillary lymph nodes, axillary

surgery, increasingly serves us to determine the staging and treatment of breast cancer. It is an integral part of locoregional therapies.

Let's start with what the sentinel node is - these are the initial lymph nodes into which the lymph flows from a specific organ (in this case, the breast), before being drained to the next nodes. [9] Thus, the identification of SLN allows to refine the clinical window of regional lymphatic drainage. [9] By using different techniques lymphatic mapping can specify the area of the die cut lymph node. According to data on complications after SLNB, this biopsy has less impact on numbness, swelling of the arm or the occurrence of a deficit of shoulder abduction. In addition, SLNB in combination with fluorescence imaging using indocyanine green (ICG) has been recognized as an extremely sensitive method of sentinel lymph node detection. This method involves the injection of ICG in the lymphatic channels to SLN, where its progress is followed by the high- camera that detects the emitted fluorescence.This allows for a more precise excision of the lymph node. Research is underway to combine the ICG method with the MB method (using the dye methylene blue), which in the group of patients under study gave promising results, characterized by high precision of marking the node to be excised. The combination of both methods would be attractive due to the possibility of eliminating radioactive substances.

Body:

1. IUOS as the method of localization and precise excision in breast cancer. [3]

[3] IUOS - intraoperative ultrasound, has been used in surgical excision of breast cancer to obtain optimal excision of a small tumor with minimal sacrifice of healthy tissue and with negative resection margins. The idea of using intraoperative ultrasound in breast cancer was initially introduced into clinical practice as a way to visualize non-palpable tumors.
Research shows (table 1 [3]) that IUOS used for this purpose was 100% effective.

Table 1

Identification rate of a non-palpable breast lesion by IOUS and WGL

Author	Type of the study	IOUS				WGL			
		Nº of patients	Nº of operations	Nº of ident. tumors	Ident. rate (%)	Nº of patients	Nº of operations	Nº of ident. tumors	Ident. rate (%)
Rahusen	prosp	19	20	20	100	43	43	43	100
Snider	retro	22	22	22	100	22	22	22	100
Harlow	retro	62	65	65	100	nd	nd	nd	nd
Smith	retro	81	81	81	100	nd	nd	nd	nd
Rahusen 2	prosp	27	27	27	100	22	22	22	100
Kaufman	prosp	100	101	101	100	nd	nd	nd	nd
Gittleman	retro	15	15	15	100	nd	nd	nd	nd
Beneth	prosp	103	115	115	100	24	24	24	100
Haid	retro	299	299	299	100	61	61	61	100
Potter	retro	32	32	32	100	nd	nd	nd	nd
Ngo	prosp	70	70	67	96	nd	nd	nd	nd
Fortunato	prosp	77	77	77	100	nd	nd	nd	nd
James	retro	96	96	96	100	59	59	59	100
Bouton	retro	28	28	28	100	nd	nd	nd	nd
Berentz	prosp	120	120	120	100	138	138	138	100
Ramos	retro	225	225	224	99	nd	nd	nd	nd

IOUS Intraoperative ultrasound, *WGL* wire-guided localization, *nd* no data, *N⁰* number, *ident* identified, *ident. rate* identification rate

In the 1988 reports by Schwartz et al. It was shown that IOUS can be used in selected patients as a supplement to or instead of the used x-rays to locate the tumor. In addition, researchers showed an interesting difference in the adequacy of margin resection. Rahusen reports show 89% negative margin resections. What's more - IUOS allowed to avoid many complications resulting from resection and simplification of surgical treatment. The use of intraoperative ultrasound in the surgical treatment of non-palpable breast cancer according to Harlow's research proved that the number of positive margins after excision is smaller and more healthy tissue remains around the excised breast, compared to other methods of excising breast tumors. The studies published so far (Harlow and COBALT Krekel) on IUOS clearly show that this technique improves the effectiveness of excision of the oncological lesion and characterized by very favorable cosmetic effects - women retain most of the healthy tissue building the breast, which is of great importance in the treatment that conserves it and improves the quality of life of patients with breast cancer.

Moreover, according to Olsh and colleagues, it was found that this method can help keep the frequency of reoperations low and does not require re-excision and breast resection.

The authors recommend the use of a number of studies IUOS two methods. The first is the use of ultrasound during surgery to measure the distance of the resection line from the edge of the tumor (in all possible directions), and the second is the use of markers as landmarks, which are determinants of tumor resection.

2. The intraoperative gamma camera detectormore effective than MRI? [10]

This a method used for determination of sentinel lymph nodes within the operative field. This technique requires usage of a device containing a scintillation counter, and for intraoperative use - previous injection of a radionuclide in a vicinity of a tumour, or the lesion itself is performed. For breast cancer tumours a Technetium-99m based radiopharmaceutical is most commonly used.
After the injections with radionucleotide are performed, the operator within the surgery is capable of precise determination of the localisation of sentinel nodes for the tumour operated. Gamma camera is used as a detector of Technetium-99m previously injected in the vicinity of the tumour in the day preceding the operation, at the moment of surgery being stored in the most proximal to the tumour lymph node.
Zhang et al. (2017) [10] implies that effectiveness of usage of intraoperative gamma probe exceeds even the effectiveness of MRI. Compared between these two methods, and included to the advantages of gamma probe, compared with MRI are similar sensitivity, higher specificity, better diagnostic performance, and can be widely used in clinical practice. Such observation should encourage breast surgeons to wider usage of the intraoperative imaging with gamma probe.

3. Micro-CT- the future of intraoperative breast cancer imaging. [11]

The goal of breast cancer surgery is to remove all of the cancer with a minimum of normal tissue, but absence of full 3-dimensional information on the specimen makes this difficult to achieve. Micro-CT is a high resolution, X-ray, 3D imaging method, widely used in industry but rarely in medicine. Imaging is simple and rapid. The size and shape of the cancers seen on Micro-CT closely matches the size and shape of the cancers seen at specimen dissection.

Micro-CT provides full 3D images of breast cancer specimens, allowing one to identify, in minutes rather than hours, while the patient is in OR, margin-positive cancers together with information on where the cancer touches the edge, in a fashion more accurate than possible from the histology slides alone. In the researchers' study, images obtained by Micro-CT were compared with the stastus of a standard histopathological sample. The high-resolution micro-CT imaging allowed detailed assessments of calcifications in breast tissue and distinguished benign from malignant lesions already at the intraoperative level. [11]

Around 15%-30% of patients receiving breast-conserving surgery (BCS) for invasive breast carcinoma or ductal carcinoma in situ (DCIS) need a reoperation due to tumor-positive margins at final histopathology [11]. Currently available intraoperative surgical margin assessment modalities all have specific limitations.

Whole lumpectomy specimen micro-CT scanning is a promising technique for intraoperative margin assessment in BCS, reveals changes in the tumor location and margin status over the entirety of the surgical surface in a clinically relevant time frame, as compared to single-projection radiography readings [11]. May be a potentially useful BCS guidance tool and lead to a reduction in the number of reoperations.

<u>4. Indocyanine green as a new, more effective method of imaging sentinel nodes in breast cancer?</u> [4] [5] [8]

[5] The most common available method of imaging lymph nodes in breast cancer, which is a kind of
a diagnostic standard, is labeling 99m Tc with a blue dye, which visualizes sentinel lymph nodes and their excision.
New imaging approaches in breast cancer include real-time fluorescence mapping with the dye-indocyanate green (ICG), a highly available dye.
This dye is used in mapping axillary lymph nodes. Clinical trials are ongoing comparing ICG to technetium mapping in patients with breast cancer. [4] They are compared in terms of: safety, allergic reactions, sentinel lymph node mapping planning (SLN). Promising observations are saying that using green indocyanine for lymphatic mapping and sentinel node detection has many advantages. Among others: the possibility of injecting the material when the patient is anesthetized in the operating room during the resection; immediate visualization of lymphatic flows and SLN node anatomy. The sentinel node is the first node to find stained ICG lymphatic flow. A problem which is associated with this method is an

excessive number of detected sentinel lymph nodes, which is not desirable for the upper limbs, as with an increase in cut SLN increased morbidity and complications from upper limbs. It takes dispute which may settle research.

Modern treatment of breast cancer focuses on patient classification to tailor adjuvant treatment. [4]"With fewer completion axillary lymph node dissections being performed due to increased morbidity and no survival benefit for early-stage breast cancer,(38) the routine use of dual tracer for the now standard SLN procedure in a clinically node-negative breast cancer might be overuse of resources and patient's time and, essentially, overtreatment." The ability of indocyanin green to identify the sentinel lymph node is similar to 99mTc. New research has shown that ICG mapping under the control of NIR infrared devices is successful in the correct and consistent identification of metabolic pathways, which translates into treatment with neoadjuvant chemotherapy. Unfortunately, the limitation of this study is the lack of segmentation, i.e. the percentage of false-negative results, when there is no cross-section of the lymph nodes after mapping.

ICG is a satisfactory method in terms of the margins of breast cancer resection. Re-excision of the edges is proposed for patients with ductal carcinoma in situ and invasive cancer of the multifocal.

[8] ICG provides the opportunity to develop an alternative method for double tracking SLNs that is non-radioactive and therefore has less impact on the health and recovery of the breast cancer patient. It seems that this method will bring many advantages in terms of accuracy and also in sensitivity in collecting additional SLNs undetectable by staining alone.

5. IART - Intraoperative Avidination for Radionuclide Therapy - a simple future dependent on biotin. [12]

[12] Researchers set out to study the impact of combination treatment: external beam radiotherapy (EBRT) and breast-sparing surgery (BCS). Given the previous experience of treating peritoneal carcinomas and malignant gliomas with regional treatment using 90-Y-biotin with an avidin-based technique (a tetrameric, highly glycosylated and positively charged protein showing a strong affinity for biotin), it was hypothesized that the use of radioactive biotin tracer therapy could be an alternative to radiation to the operated breast. This led to the development of the IART technique, which is based on avidin-biotin bonds. Diluted in 30 ml of NaCl, avidin was injected into the locus of the excised breast tumor,at three points of 10 ml each: two injections into the parenchyma at intervals of about 1.5 cm,

one injection into the margins after closure of the breast gland. One day after avidin, biotin was injected, which avidin was pursued as a highly conjugated tracer. The study determined such doses of avidin (250 mg, 150 mg and 100mg) that would be capable of delivering an optimal dose of 20Gy to the tumor area. After administration of the tracers, the patients' bodies were evaluated by scintigraphy at specific intervals.

Postoperative EBRT was administered four weeks after IART.

From the conducted dosimetry data and the estimated mass of the irradiated breast, it was concluded that the minimum dose needed to deliver the dose to the index quadrant was 100 mg of avidin.

It has been proven from ongoing observations that IART allows a radiation dose of 20Gy to be established as early as one day after surgery for women who have undergone BCS for breast cancer.

IART and EBRT therapy have gained approval among patients. No toxic systemic reactions to the administered tracers were observed, and the cosmetic effect was considered good. Patients' quality of life was assessed using the EORTC QoL questionnaire (Table 4 and 5 [12]).

Table 4:

Average quality-of-life score (EORTC QOL-30 questionnaire) at various times during treatment and follow-up for global functions. A low score (minimum 0) indicates poor quality of life and a high score (maximum 100) indicates good quality of life

	Baseline	21 days post-IART	At EBRT completion	One month post-EBRT	Six months post-EBRT
Global health status	69	70	64	71	70
Physical functioning	91	88	87	87	88
Role functioning	95	84	84	84	88
Emotional functioning	73	77	80	79	81
Cognitive functioning	85	84	87	85	83
Social functioning	91	91	90	92	93

Table 5:

Average quality-of-life score (EORTC QOL-30 questionnaire) at various times during treatment and follow-up for symptoms. A low score (minimum 0) indicates good quality of life and a high score (maximum 100) indicates poor quality of life

Symptoms	Baseline	21 days post-IART	At EBRT completion	1 month post-EBRT	6 months-post EBRT
Fatigue	9	23	22	24	22
Nausea	6	2	4	6	6
Pain	6	21	17	15	11
Dyspnoea	8	9	10	11	10
Insomnia	27	21	23	22	20
Appetite loss	4	2	7	3	9
Constipation	15	15	16	19	12
Diarrhoea	4	1	7	7	6

IART may be the future of nuclear medicine, as it is gaining opportunity in the treatment of any type of breast cancer that is qualified for breast-sparing therapy. There are no limitations on size, location or focal size. Moreover, in this method, areas marked by the surgeon, who knows the location of the tumor, are irradiated. This method is simple enough to be used in hospitals that have nuclear medicine departments and perform BCS surgeries, and can contribute to an improved quality of life and a new approach to treating breast cancer patients.

Conclusion:

The development of nuclear medicine and intraoperative imaging in breast cancer is unquestionable.

The methods outlined above are being improved all the time to provide the most precise and targeted treatment possible.The methods of intraoperative imaging in breast cancer are multiplying, and each year there are more and more of them and they are more effective. Moreover, these methods are becoming more common and more readily available to doctors, surgeons and, most importantly, to the patients. The researchers continue to refine the performance of these methods with an eye to clinical and cosmetic effect. The future is full of hope.

In comparing the above methods, it is not possible to say clearly which one will take priority in the future.

IUOS is a simple method of intraoperative diagnosis and imaging based on improved visibility of nonpalpable tumors, which is associated with improved successful resection of tumor lesions. Undoubtedly, it is a method that enjoys a very good cosmetic result, due to the fact that healthy breast-building tissue is left behind. This facilitates potential breast reconstructions and, in view of this, improves quality of life.

In addition, a reduced rate of reoperation due to complications or tumor resection has been observed with IUOS. With classic ultrasound, resection lines can be drawn more precisely from the edges of the tumor or IUOS can be used as markers to indicate landmarks when resecting a tumor mass.

Increasing the availability of IUOS in oncologic surgery departments has undoubted benefits in the development of surgical treatment of breast cancer.

BSG, the intraoperative gamma camera mentioned in the above discussion, uses a radionuclide (Technet 99-m). By injecting the radionuclide, the operating surgeon is able to determine the location of the tumor and sentinel nodes very precisely during surgery.

There is some debate as to whether a gamma camera used intraoperatively is more effective than the well-known MRI scan. Comparing the two methods, it can be said without a doubt that BSG has a higher diagnostic efficiency in the surgical field and a higher specificity. Both the sensitivity of gammacamera and MRI are at a similar level. The ease of use, relatively low number of complications and wide availability argue for more frequent introduction of this type of imaging.

In view of this, the widespread clinical use of BSG seems to be a matter of time and surgical treatment options.

Micro-CT is a high-resolution method that uses the well-known X-rays. Despite fast, simple and very accurate real-time imaging, it is not a common method in medicine.In addition to the above advantages, the micro-CT method is able to very precisely assess the calcifications in the tumor mass, which makes it possible to distinguish benign lesions from. A barrier in the widespread use of this method of intraoperative imaging in breast cancer seems to be the monetary method, because despite the many advantages of intraoperative micro-CT, it is not friendly-budget method.

However, in hospital facilities that have departments of oncological surgery and nuclear medicine, they are available.

The diagnostic standard in intraoperative imaging of breast cancer has become the use of Tc 99-m. Nevertheless, the use of an indocyanate dye has become a common method. This dye is widely available, which is undoubtedly its advantage. It is currently used to map axillary lymph nodes, but research is underway to use this dye to map other lymph nodes. The problem with the use of ICG is the detection of an excessive number of sentinel nodes in the case of surgery close to the upper limb, i.e. in breast cancer surgery. There are more side effects with the ICG method than with Tc-99m.

Currently, it is a satisfactory method, which still requires refinement and appropriate devices, e.g. control with NIR infrared devices.

IART with biotin seems to be a good alternative to irradiation of the operated breast. Thanks to the precise calculation of the irradiation dose by the method with radioactive biotin, the places marked by the surgeon who knows the location of the tumor are irradiated. IART has no restrictions on the location, focus or type of breast cancer.

Moreover, it has a relatively good and acceptable cosmetic effect.

The method is so simple and unlimited that it can be widely used in hospitals.

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Author's contribution:

Conceptualization: Bigdoń A, Ćwiek M, Gorczyca P.; Metodology: Bigdoń A, Gorczyca P.; Software: Ćwiek M, Góra M., Hunek A.; Check: Woźniak A.,Wartacz M.; Formal analysis: Bigdoń A, Sydor P., Kozłowska M.; Investiagation: Bigdoń A.; Resources: Kreft R.,Bigdoń A.; Data curation: Kreft R., Kozłowska M.; Writing - rough preparation: Góra M., Wartacz M.; Writing - review and editing: Gorczyca P., Sydor P.; Visualization: Woźniak A., Kozłowska M.; Supervision: Bigdoń A.; Project administration: Ćwiek M., Bigdoń A.
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