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Review

Breast cancer: Actual methods of treatment and future trends

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ABSTRACT

The recent ten to twenty years have seen a substantial progress in the diagnosis and treatment of breast cancer. A rapid development of various curative options has led to the improvement of treatment outcomes, while paying more and more attention to the aspects of quality of life and cosmetic effect. In our publication, we wish to outline certain trends in the development of modern treatment of breast cancer. Among topics discussed are new forms of molecular diagnostics, new approach to the idea of sentinel node biopsy, as well as new techniques for delivery of medical procedures, the increasing use of nomograms, progress in the techniques of breast conservative treatment, modern approach to occult breast lesions, the increasing use of neoadjuvant treatment and intraoperative radiotherapy.

1. Introduction

In Poland, over 14,000 women are diagnosed with breast cancer (BC) each year (48/100,000), with mortality of 5000 (14.5/100,000). The incidence of BC increases with age reaching its peak at 50–59 years (approximately 32% of all cases). The disease occurs particularly in post-menopausal women (78%), with only 22% of patients below 50 years of age. BC below 35 years occurs rarely, representing just 3% of all cases, and exceptionally in women below 25 years.[1–5]

Notably, the breast cancer mortality rate in Poland shows a declining trend, which may indicate an improvement in BC diagnosis and treatment methods (0.64 in 1963, 0.38 in 2005).[1,6] The novelties in BC diagnosis and treatment are presented in this report.

The last decades have witnessed profound transformations in BC therapy. The prognosis has improved considerably and patient's quality of life has become a matter of concern for both medical professionals involved in the diagnostic and therapeutic process and scientists developing new approaches and treatment modalities which determine progress in this area. Only a few decades ago, women with diagnosed BC were treated with radical mastectomy including axillary lymph node dissection (ALND) to achieve a proper locoregional control and enable full recovery. While this treatment goal has remained valid up to the date, the surgical approach has come to be more conserving and selective both with regard to the breast and axillary lymph nodes. The impact of surgery on patient's quality of life is manifested with less mutilating procedures or the application of novel techniques which allow to deliver satisfactory cosmetic effect on the appearance of the breast.

It is now believed that patients with diagnosed BC should be referred to specialised breast units which are able to ensure diagnosis and therapy adequate for that disease. Decisions

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regarding individual treatment are from the very beginning taken by a multidisciplinary team composed of a surgeon, clinical oncologist, radiation therapist, psychologist, physical therapist, nurse, and social worker. Such a system makes it possible to plan an optimal treatment being a resultant of available treatment methods for each stage of the disease, patient's expectations, logistics, costs, as well as possible complications and distant treatment outcomes.

It is estimated that around 30–50% of patients referred to breast units have their treatment plans changed after re-assessment of their examination results, mainly regarding surgery, but also the interpretation of imaging and histopathology test results,[7] hence a significant need for such units to be established.

The European Society of Breast Cancer Specialists (EUSOMA) has defined a set of criteria to be met by a breast unit and conditions of eligibility for accreditation and European Cancer Care Certification. They are aimed to raise the quality of diagnosis, treatment and care of breast cancer patients across Europe. Soon, as it seems, each diagnosis of breast cancer will lead to patient being referred to a specialised breast unit.

2. Fundamental science

Recently, apart from the standard determination of cancer stage according to the TNM classification, expression of oestrogen and progesterone receptors and HER2 receptor, the genetic profile of cancer has increasingly been determined.[8–12] The molecular profile of a tumour helps in taking therapeutic decisions and establishing more precise prognosis of oncology patients. There are several tests available at the moment. The first of them, a 21-gene recurrence score assay Oncotype DX®. The result, referred to as recurrence score (RS) evaluates the response to hormonal therapy and chemotherapy in oestrogen positive BC. Another commercially available test is a 70-gene MammaPrint assay.[13] That test allows to evaluate the risk of distant metastases in patients with early BC. Tests are performed on a fresh tissue collected from the tumour by biopsy or during surgery.

Yet another test to help differentiate BC subtypes is the division proposed by Perou into the following subgroups: luminal A, luminal B, basal, HER-2 over-expressing, and normal-like.[14] The basal type of BC is the one with negative oestrogen and progesterone receptors, and HER2 protein. This excludes hormonal and trastuzumab-based treatment. The division helps in determining the response to chemotherapy and evaluating prognosis. Soon, owing to the molecular cancer evaluation, treatment personalisation will become a basic tool to identify treatment method and patient prognosis.

3. Sentinel node biopsy

The publication of the report by Veronesi et al. marked the beginning of a new approach to surgical treatment of BC where efforts are made to limit the extent of procedure as much as possible.[15] However, the removal of the axillary lymph system remains an integral part of treatment. Why ALND? First, it is important to remove cancerous tissue, that is metastasis, in axillary lymph nodes. It has been proved that lymphadenectomy in that group of patients reduces the number of relapses and has a favourable impact on long-term survival. Second, and very importantly, pathology results of dissected lymph nodes provide full information on the stage of disease. It is a main factor determining the inclusion and extent of adjuvant treatment.

For all the above benefits, lymphadenectomy also involves a number of complications, the most common of them including: lymphatic oedema of the upper limb, movement and sensory disorders of the shoulder, pain or prolonged chylothorax. Those complications may occur in up to 80% of post-surgery patients. It is a great number considering that around 60% of patients are not found to have metastases to the lymph nodes. For them, lymphadenectomy is of no therapeutic but merely of a diagnostic value. Therefore, a method has been sought for years to safely evaluate the lymphatic system, while causing a limited number of consequences and complications [16].

The application of sentinel lymph node biopsy (SLNB) in BC was first tested in the early 1990s. Numerous randomised studies confirmed its value and efficacy in the evaluation of axillary lymph node status. Researchers agree, however, that full consequences of dropping ALND in patients with negative SLNB may only be assessed after results of prospective studies are known on large groups of patients with long-term follow-up. At present, there are nine studies of that kind being conducted in the world.[16,5,17]

Since the 1990s, when Giuliano[18] proposed the use of blue dye to identify the sentinel node, markers have mostly been based on radiocolloids or, more recently, on indocyanine green.[17–20]

As in the case of breast conserving therapy, SLNB has been found to have its indications and contraindications. Whenever possible, axillary lymphadenectomy in BC patients should be replaced with SNLB. That technique is also advisable in patients with the regional lymph node status established as N0. SNLB can be applied with lymph nodes which are palpable or visible by imaging if the clinician finds them to be clear of cancer (small, soft). For that group of patients, however, a fine-needle lymph node biopsy is recommended before the decision to perform SLNB is taken.

Excluded from SLNB are patients with metastases to regional lymph nodes (clinical or cytology confirmed) or with distant metastases; patients who do not agree for the procedure or those who report allergy to colloidal markers or methylene dye. Breast-feeding women are recommended to stop feeding before the administration of the marker and not to resume until 24 h thereafter.[16] Another issue that has been discussed recently in relation to SLNB is whether it should be used in pregnant women, especially that women tend to start their motherhood at an increasing older age.[21] Due to teratogenic properties of methylene blue being and potential anaphylactic activity of Lympahazurin,[22,23] Tc99-m has been proved to be safe in use and of very little effect to the foetus.[24,25]

The analysis of the lymph node collected by SLNB being more detailed as compared to ALND, a problem of clinical evaluation of micro metastases appeared.[26] In the NSABP B-32 study, the impact of micro metastases on five-year survival

rate was low, 94.6 versus 95.8%, thus warranting the possibility for patients with micro metastases to be followed-up without having to undergo ALND.[27]

4. Nomograms

An issue of increasing concern is the absence of metastases in the other axillary lymph nodes examined in the case of metastatic sentinel node (SN). This applies to as many as 60% of patients.[28,29] In their meta-analysis Degnim et al. identified 5 factors associated with the increased incidence of metastases in non-sentinel lymph nodes in the case of metastatic SN.[30] These include: metastasis to the sentinel lymph node of over 2 mm, cancer infiltrating beyond the node capsule, tumour size >2 cm, more than one metastatic sentinel node, invasion within lymphatic vessels.[30] Therefore, mathematical models have been developed to evaluate the risk of metastases in non-sentinel lymph nodes in the case of a metastatic sentinel node. Van Zee et al. proposed a model based on data from the Sloan Kattering Memorial Cancer Centre, New York.[31] Currently, other nomograms are also available, including the Cambridge nomogram and the Stanford nomogram. Researchers from the MD Anderson Cancer CenteR have proposed a nomogram regarding the risk of metastases to non-sentinel nodes in patients treated with neoadjuvant chemotherapy.[32–34]

The results of ACOSOG Z0011 trial published in 2011 proved to be a real breakthrough.[35] The study comprised stage I and IIa cancer patients. Patients with metastatic sentinel node were randomised into the ALND or control group. The groups were found to show no difference in terms of local recurrence, disease free survival or overall survival. It needs to be stressed, however, that patients participating in the study had received conserving therapy and post-surgery radiation therapy also for the armpit region. Results of other ongoing studies are now awaited for this type of treatment to be wider implemented into the clinical practice.

5. Breast conserving treatment (BCT) as a predominant technique in breast cancer management

This type of treatment is reserved for all BC cases unless contraindicated. The BCT procedure consists of a breast conserving procedure (alternatively quadrantectomy, lumpectomy or wide tumour excision), diagnostic and therapeutic procedure on the axillary lymph nodes (ALND, SLNB) and adjuvant post-surgery radiotherapy. By today's standards, radiotherapy is a prerequisite procedure following BCT.

Indications and contraindications for BCT have changed over the years. Currently, conserving procedures are applied for BC cases staged T1N0M0, T1N1M0, T2N0M0, T2N1M0. In Europe, eligible patients are those with tumours of up to 3 cm, in the USA, of up to 5 cm. Obviously, the most important condition is patient's consent and the lack of contraindications for such a procedure. The contradictions include multicentric (but not multifocal) cancer, earlier breast radiotherapy, inability to perform a total tumour dissection, inability to achieve an acceptable cosmetic effect, lack of patient's consent, connective tissue disease.[3–5,36–39]

In West Europe and the USA, BCT has in recent years replaced radical modified mastectomy as a preferred method of treating early BC. This could be achieved owing to education and a wide access to screening tests which have enabled diagnosis of cancer at early stages. According to the data presented by Morrow et al. as many as 75% of newly diagnosed BC cases in the United States are qualified for conserving therapy. The authors note, however, that large geographical differences persist in their country both in terms of diagnosis and qualification to BCT.[40]

With properly selected patients, long-term results of BCT and mastectomy are comparable, as confirmed by large randomised studies, such as Milan I or NSABP B-06.[41,42] Both methods differ significantly in the incidence of local recurrence. With correct qualification to BCT, the risk of local relapse is 1% at 1 year and 10% at 10 years.[43] The recurrence risk factors following BCT may be divided into three groups: those related to the patient, the tumour or the treatment method. The most important patient-related factors include young age (below 35–40 years) and genetic predisposition, mainly BRCA1 and BRCA2 gene mutation. The main tumour-related risk is linked with the size of resection margins. The size of the tumour and lymph node involvement are not prognostic factors for local recurrence, but rather for distant recurrence. The relevance of treatment methods for local recurrence is mainly related to the size of surgical excision (lumpectomy or quadrantectomy), radiation boost to the tumour bed and, finally, the implementation of appropriate adjuvant therapy (hormonal therapy, chemotherapy, targeted therapy).[44]

Importantly, significant principles of surgery and radiation therapy in BC treatment may be considered to be similar and mutually complementary. Each of this techniques, when applied alone, fails to control locally advanced disease or subclinical foci. Limitation in the case of surgery is the extent of tissue resection to guarantee appropriate local control – "this considered, each patient should be proposed mastectomy". The consequence in the case of BCT, but also mastectomy (higher stages of cancer) is the presence of local recurrences in 65–80% of cases in the region of the scar, that is on the boundary of the tissue removed or resection margins.[37,45–49] Things look different with radiotherapy. Average radiation doses are sufficient to control sub-clinical foci. However, with larger groups of cancer cells – primary tumour – much higher radiation doses are needed to control the disease. For example, even a small T1c tumour requires a 50% higher dose of radiation than that applied in treatment of sub-clinical cancer foci. It is too much for the surrounding healthy tissue which is threatened to be damaged.[48,36,37,50] As a consequence, cancer recurrence is mostly found in the centre of the tumour bed, where the most cancerous tissue was located. Combining the above combined makes up the image of a modern conservative treatment: a surgical excision of tumour with a narrow margin of healthy tissue followed by radiotherapy which eradicates the remaining microscopic cancer foci. The maximum loco-regional control of cancer can be achieved without compromising the cosmetic effect by surgery being too radical or radiation doses too high.

6. Occult breast cancer

The recent decades have seen a rapid growth in the rate of diagnosed early occult breast cancer. This has become possible owing to the implementation of even better equipment and techniques in the area of breast imaging, but above all owing to BC screening programmes. Occult, so-called sub-clinical BC, is assumed to represent 30% of all diagnosed tumours.[51] The increasing detection of occult BC and the approval of BCT as a primary therapeutic technique by that group of patients is the reality that surgeons are faced with today. A key to successful treatment of occult BC is a precise excision of the tumour with a proper margin of healthy tissue first of all to cure but also to reduce the risk of re-operation or recurrence. Therefore, reliable and easy-to-use methods are searched for to precisely localise and remove occult breast tumours or lesions highly suspicious to be malignant, with concurrent SLNB.

The point is to excise the tumour with a proper margin of healthy tissue within one surgical procedure. It is of particular importance as patients after total cancer resection with clear margins during the first procedure are at a lower risk of recurrence compared to those who need to be re-operated due to insufficient radicality of the first excision.[52] For that reason, it is vital in the case of occult tumours to use available localisation methods before and after surgery.

Needle localisation remains to be the most popular localisation method, first described by Dodd in 1966. It involves one or two straight or crooked wires inserted into the lesion or right next to it with ends protruding above the surface of the skin. The procedure is guided by stereotactic mammography (most often), ultrasonography or MRI, with or without local anaesthesia. During surgery, following the direction of the wire inserted into the breast, the lesion is localised and excised, and then a radiogram of the specimen is performed for control.[53] This method allows to excise occult breast tumours with accuracy of nearly 100%, however, 55–83% patients require re-operation with margins being invaded by cancer.[54,55]

In the late 1990s a new method of radiooccult lesion localisation was introduced. It involves a pre-operative administration of radiopharmaceutic (99 m Technet on a protein carrier) in the form of ultrasonography- or stereotactic MMR-guided injection. A marker thus administered remains in the tumour until surgery. During the operation, occult cancer lesions are easily localised and excised using a manual gamma probe. If early BC is diagnosed pre-operatively, a second radiopharmaceutic is usually given in order to localise the sentinel node. A simultaneous application of both methods in one patients is referred to as SNOLL (sentinel node and occult lesion localisation). An increasing number of comparative studies indicate the advantage of that method over the ones used before,[51,56] first of all due to its 100% efficacy in the excision of occult tumours and a high rate of radical excisions.[57]

7. New therapeutic options in neoadjuvant therapy

Neoadjuvant (otherwise known as pre-operative or inductive) systemic therapy (NST) was first introduced in the 1970s to manage advanced inoperable BC. A good clinical response to this type of treatment made it possible to operate patients previously disqualified from surgery. Currently, the concept of NST embraces not only a standard pre-operative chemotherapy, but also pre-operative hormonal and targeted therapies. A breakthrough in this regard came with the publication of the results of two multi-centre randomised studies: NSABP B-18 and EORTC 10902, which confirmed the equivalent value of neoadjuvant and adjuvant treatment in terms of recurrence-free time and total survival. Furthermore, those studies demonstrated that NST delivers an additional benefit of increased rate of conserving treatments and, more importantly, acceptable incidence of local recurrence.[58,59] The main objective behind the use of NST is to control a potential spread of the disease (cancer cells circulating in the peripheral blood), reduce the weight of the tumour (complete pathologic response as an optimum) and, recently, enable BCT. NST also allows an in vivo evaluation of response to the selected pre-operative treatment regimen. This treatment modality is believed to have a drawback of delayed local treatment which may theoretically lead to the spread of primary cancer or disease progressing to a more advanced stage. Additionally, NST may cause the patient to become resistant to the drugs applied or more exposed to the risk of post-surgery or post-radiotherapy complications.[60]

Despite those limitations, patients with primarily operative BC who wish to have their breasts preserved are increasingly subjected to this method of treatment. If, initially, breast tumour is found to be too large to enable BCT, NST seems to be a natural therapeutic alternative. In the case when neoadjuvant therapy reduces the size of tumour, patients initially qualified for mastectomy may have their breasts preserved. Numerous publications show that the proportion of patients subjected to NST following BCT ranges from 13 to 83%. The wide spread of results is caused by different inclusion and qualification criteria applied in particular clinical trials.[61,62]

Breast conserving therapy after neoadjuvant treatment is challenging for the surgeon, as resection borders are more difficult to set with tumour being smaller in volume or even disappeared. Therefore, each patient preliminarily qualified for BCT should take necessary tests and procedures allowing a precise localisation of the tumour before NST is started. The safety of breast conserving therapy in terms of local recurrence in patients with initially large tumour remains to be a matter of controversy. A high rate of local recurrence in reports presented applies mostly to young women <40 years,[63] who are most determined to preserve their breasts. It is obvious that treatment results depend strongly on a right qualification of patients for NST.

ALND remains to be a standard procedure in patients after neoadjuvant therapy. Data show that in 25% of patients NST destroys metastases in the armpit, meaning that ALND is performed unnecessarily in those cases. Can SLNB be used then to identify patients who do not need to be treated with a mutilating axillary lymphadenectomy? This remains a matter of dispute, particularly with respect to the optimal time of SLNB. Supporters of SLNB before neoadjuvant treatment believe the state of lymph nodes to be the most reliable at that particular time (evaluation at diagnosis), thus permitting to assess the stage of the disease and have an impact on the

choice of treatment (including drug regimens in chemotherapy or extent of radiotherapy fields). They also stress that NST may change the anatomical course of lymphatic tracts in the armpit. Then, SLNB performed after NST, may lead to a lower rate of sentinel node identification and higher rate of falsely negative results.[64,65]

On the other hand, numerous studies confirm that patients with initially clinically negative axillary lymph nodes benefit more when sentinel node biopsy is made after neoadjuvant treatment, resulting in conservation of axillary lymph nodes in around 20–30% of patients.[66]

Concluding, NST, apart from its traditional role in treatment of advanced breast cancer and inflammatory cancer, has in the recent decade become one of therapeutic options in treatment of early BC. However, many questions concerning this treatment modality are yet to be answered. It seems that the multicentre studies being currently in progress will soon allow to precisely define an optimal neoadjuvant treatment and select patients who can benefit the most from it.

8. Intraoperative radiation therapy (IORT) – new possibilities in BCT

For a long time the development of IORT techniques has been restricted by logistic issues (transport from the operation theatre to the radiotherapy department), unacceptable prolongation in the time of surgery and a substantial growth in the number of massive inflammations of the operated site. It was only in the mid 1990s that a prototype of a mobile linear accelerator was proposed to spur the progress of IORT as we know it today. Machines produced nowadays can be moved between surgery wards and easily docked to an operation table without requiring any structural modifications in the rooms. They also ensure an adequate level of radiation protection.[67,68] There are three mobile machines for intraoperative radiation therapy currently available in the world. These are: Intrabeam by Carl Zeiss (Oberkochen, Germany), Mobetron by IntraOpMedical Inc. (Santa Clara, USA) and Novac-11 by Hitesys (Latina, Italy). Intrabeam works with a low photon energy (30–50 KVp), the other two are linear accelerators producing electron beams (hence the term IOERT – Intraoperative Electron Radiotherapy). At present, there are six intraoperative radiotherapy machines operating in Poland.[67]

What does IORT change in terms of patient's access to BCT? Many publications report that the proportion of world's women with BC qualifying for BCT and treated with that method ranges from 10% to 80%, still a far cry from 100% level. Besides, as it turns out, 15–30% of patients who underwent lumpectomy for cancer do not receive post-surgery radiotherapy. Why then data are so poor? This results in part from the duration of radiotherapy which, as mentioned before, is 6–7 weeks and, as such, causes problems of convenience, access and cost. Actual logistic limitations often relate to such issues as distance from the place of residence to the radiotherapy department, limited means of transport, lack of sufficient social support, lower status of ambulatory patients. For those reasons, many patients chose to have their breasts removed as a basic surgical procedure.[48] Another problem that continues to be discussed even in developed countries is the fact that women treated with breast conserving techniques represent up to 30% of radiotherapy department patients, thus restricting a wider access to radiotherapy for other groups of patients. For example, in Spain there were just 177 teleradiotherapy machines in 2004, whereas the needs of that country are at the level of 266–316.[48] All the above considered, it needs to be said that IORT may considerably improve BC patients' access to BCT.

Here are the main clinical benefits of using IORT:

- irradiation of cancer cells (sub-clinical cancer foci) before they become capable of further proliferation,
- owing to better blood and oxygen supply to the intraoperatively irradiated tissue, it becomes more sensitive to treatment (oxygenation effect),
- owing to a direct visualisation of the operated site, the above-mentioned problem of "geographical loss" is avoided, irradiation is fit exactly within the surgical margins,
- part of radiotherapy side effects are avoided as the radiation field is surrounded by subcutaneous tissue and skin, and dose to the heart and lungs is largely reduced,
- the compromise related to a possible delay in chemotherapy is eliminated,
- treatment costs are reduced and radiotherapy patient waiting list shortened.[67–69]

Before oncology results for IORT in BCT are evaluated, a note should be taken of the results obtained in a classical procedure. It constitutes the basis for a proper comparison. Approximately 5% of patients will have cancer recurrence within five years following the end of treatment for invasive breast cancer with BCT. The group will grow to 10% within the ten-year follow-up. 85–90% of recurrences are located directly in the tumour bed (true recurrence). Over six years after treatment patients are observed to show an increased incidence of cancer in other parts of the breast. Such cases are believed to be new primary foci rather than recurrence of the disease.[36,69,70] Analysis of the literature and oncology results in BCT shows that the lowest rates of recurrence are follows:

Age > 50 years; 0.4% annually (START B), 0.7% (Bartelink).
Age 41–50 years; 0.72% annually (Whelan), 1.2% (Bartelink).
Age 35–40 years; 0.72% annually (Whelan), 2.0% (Bartelink) [45,71,72].

It is the above results that intraoperative radiotherapy results should be compared to.

Merrick in 1997 and Sedlmayer and Reitsamer in 1998 were the first to introduce an innovative technique of intraoperative boost application. A single dose of 10 Gy was delivered by an electron beam from a linac machine during a surgical breast conserving procedure. Owing to that procedure, the period of post-surgery radiotherapy was shortened by 1–2 weeks.[73] In 2004, Reitsamer published results for a group of 190 women treated in the above manner. A control group, who received classical treatment, consisted of 188 patients. No local recurrences were found in the study group versus 4.3% in the control group. What is important, the study group had a higher rate of large intraductal component, which is a recognised negative predictor.[74] Another interesting report came from researchers

of the International Society Intraoperative Radiation Therapy (ISIORT). It presented results from six centres applying intraoperative electron boost in BC treatment. The study group consisted of 1131 patients. Local recurrence was found in 0.6% of patients within a mean follow-up of 52.3 months.[75] Another study with a follow-up of 71.53 reported a recurrence rate of 0.2%.[76] In his publication, Murawa reported no local recurrence in a group of 118 patients treated with electron boost with a follow-up of 22.81 months.[67] The above reports and the position of ISIORT define intraoperative electron boost followed by whole breast post-surgery radiotherapy as the best currently available golden standard in BCT.

The literature provides much more information on the competitive Intrabeam kilo-voltage system, such type of machines being much more numerous than mobile linear accelerator systems. Intrabeam is much cheaper and has provides the benefit of high actual mobility. However, its radiobiological value is quite often criticised. Dose delivered is observed to fall considerably already at 1 cm from the applicator surface. In Wenz's report from the Mannheim centre, 197 patients were treated with photon boost by means of Intrabeam at dose of 20 Gy on the applicator surface. Local recurrence was found in 6 patients within a follow-up of 37 months.[77,78] Vaidya and Baum reported results for a group of 299 patients with a mean follow-up of 60.5 months. Local recurrence was found in just 1.73% of patients at 5 years.[79] Clearly then IORT boost delivers much better results than classical BCT procedure.

An active discussion is now being carried on about the application of IORT not as a boost but a stand-alone radiation technique following a surgical excision of BC under the BCT procedure. This approach is referred to in literature as APBI (Accelerated Partial Breast Irradiation). There are two clinical studies being conducted in the world to analyse IORT techniques in APBI. The first one is the TARGIT-A study using an Intrabeam machine. In 2010, the first report was published concerning 996 patients treated with that technique. The control group comprised 1119 patients treated managed with a classical BCT. The mean follow-up was 24.6 months. The local recurrence rate in 4 years was 1.2% in the study group and 0.95% in the control group.[80] The other study is ELIOT which is being performed in the Milan Institute of Oncology using a mobile linear accelerator. A total of 1822 were treated with the APBI technique with a mean follow-up of 36 months. Local recurrence was found in 3.6% of patients at 3 years.[81] When comparing the two above studies in her publication, Sautter-Bihl first of all noted the difference in the patient selection criteria. The ELIOT study included a much larger group of patients with G3 cancers and metastatic lymph nodes. Further, she strongly criticises the APBI technique indicating numerous deficiencies of both series, particularly the TARGIT.[82] One thing is certain, follow-up periods in both studies are too short to be able to appraise the value of APBI, as many local recurrences occur between 5 and 10 years after treatment. Nonetheless, in the wake of the above studies and similar ones employing brachytherapy techniques, recommendations of the American Society for Radiation Oncology and Groupe Europeen de Curietherapie – European Society for Therapeutic Radiology and Oncology were issued in 2010 regarding the application of APBI in breast cancer patients with favourable carcinogenic factors outside the clinical trial regimen. Those guidelines are, however, criticised as being premature by many researchers including: the German Society for Radiation Oncology and the National Comprehensive Cancer Network.[81,82]

Conflict of interest

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