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Intraoperative radiotherapy for early breast carcinoma-dissertation project with literary review

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Abstract

Breast cancer (BC) is a socially significant illness. Radiotherapy (RT) is an important part of the complex treatment of early BC after a breast preserving surgery (BPS). Partial breast irradiation (PBI) has been established as a suitable treatment option for appropriately selected women with early stage BC by numerous clinical trials dating back to the 1990s. Risk¬ adapted single¬ dose targeted intraoperative radiotherapy during lumpectomy (TARGIT ¬IORT) is a method of PBI for early BC. In this literary review, we will present the therapeutic capabilities of intraoperative radiotherapy (IORT) for early BC, the necessary patients' selection, as well as the advantages and disadvantages of this combined with surgery radiotherapeutic approach. IORT has potential efficacy advantages related to overall survival related to reduced cardiopulmonary radiation doses, as well as prior to oncoplastic reconstruction to improve accuracy of adjuvant radiation delivery, or when used as a boost in higher risk patients to improve tumor control.

The expected contributions from this research project are: 1) For the first time in Bulgaria to use IORT in the treatment of early breast cancer.;2) Local control and early toxicity for patients receiving IORT in comparison with whole breast irradiation with or without boost.

Keywords: Breast Cancer, Targeted Intraoperative Radiotherapy, Breast Preserving Surgery, Partial Breast Irradiation, Radiation Therapy.

Introduction

Breast cancer (BC) is the most common malignant neoplasm in women and the third cause of death in Europe [1]. This fact determines BC as a socially significant illness. Breast-Preserving Surgery (BPS) followed by postoperative whole breast external beam radiotherapy (WBER) is now the standard of care for suitable patients with early BC [2,3]. Currently the most commonly used schedule for whole breast irradiation (WBI) after BPS is 45 to 50 Gy delivered over 5-6 weeks with 1.8-2 Gy daily fractions, followed by an additional boost to the tumor bed of 10-16 Gy over 1-2 weeks [4]. In a meta¬ analysis of randomized controlled trials that began before the year 2000, 7.7% of women treated with BCS and radiotherapy had locoregional recurrence within 10 years of diagnosis, compared with 25.1% in the BCS only arm [5]. Partial breast irradiation (PBI) has been established as a suitable treatment option for appropriately selected women with early stage BC by numerous clinical trials dating back to the 1990s [6]. TARGIT-A compared conventional WBRT (EBRT) to single dose IORT (TARGIT) and enrolled 3,451 patients from 33 centers in 10 countries between the years 2000 and 2012. This study used a non-inferiority statistical design which anticipated a 15% probability of adverse pathologic features on final pathology leading to additional WBRT after initial IORT [7]. In this literary review, we will present the therapeutic capabilities of intraoperative radiotherapy (IORT) for early BC, the necessary patients' selection, as well as the advantages and disadvantages of this combined with surgery radiotherapeutic approach.

Discussion

Prospective and multicenter studies have shown equivalent treatment outcomes in early BC (stage I-II) after mastectomy with axillary lymph dissection and after BPS with volume of

lumpectomy, axillary dissection, and postoperative radiotherapy (RT) [8-11]. In well selected early breast cancer patients accelerated partial breast irradiation (APBI) has demonstrated in many large, randomized studies no differences in ipsilateral recurrence or survival with accelerated partial-breast irradiation vs whole-breast irradiation after breast-conserving surgery among women with early-stage breast cancer. APBI was associated with less toxicity and better cosmesis outcomes [12-14]. According to ASTRO APBI was initially suitable for patients older than 60 years, in the absence of a BRCA1/2 mutation, estrogen receptor positive tumors in stage I/pT1N0, with clean resection lines (R0 resection), and those without multifocal spread in the breast. Invasive intraductal carcinoma without Extensive Intraductal Component (EIC) and without Lobular Carcinoma In Situ (LCIS) is subject to this radiation approach [15]. They later revisited their statement and now consider suitable patients older than 50 years and patients with low or intermediate grade DCIS [16]. WBER after BPS is not recommended for patients >70 years of age, pT1N0 estrogen-positive invasive carcinoma with negative resection margins. After this selection, the missing postoperative RT does not worsen the disease-free and overall survival [17-19]. If RT is delivered intraoperatively, it would avoid a temporal miss and enable the shortest possible interval between surgical resection of the cancer and accurate delivery of RT [20]. Consequently, because the definitive RT treatment can be completed at the time of the surgery or shortly afterwards in a single session with targeted intraoperative RT, two of the patients' major concerns are immediately addressed, and perhaps fewer patients should feel obliged to choose mastectomy over BPS either because they live far away from a RT facility or to avoid prolonging their treatment [21]. APBI with low-energy photons from a miniature X-ray machine is undergoing a randomized clinical trial (Targeted Intra-Operative Radiation Therapy [TARGIT]) in a selected subgroup of patients treated with BPS [22]. Although new validated hypofractionated schedules have been explored to shorten treatment, the delivery of WBI remains long lasting from three to six weeks, and may affect women's quality of life, whether in active young or in older patients [23-25]. The TARGIT randomized trial with the Intrabeam system is enrolling patients in centers in the UK, Europe, the USA, and Australia. The trial is designed to test the hypothesis that the strategy of targeted intraoperative RT in patients eligible for breast-conserving therapy with a facility to add WBRT in patients at high risk of recurrence elsewhere in the breast is equivalent to standard postoperative RT [26]. There are two recently published large prospective randomized controlled trials comparing post-lumpectomy standard WBRT to IORT, one using electrons and one using 50 kV photons, which have shown low-local recurrence rates for IORT with acceptable toxicity and excellent overall survival outcomes [6]. Risk¬ adapted single¬ dose targeted intraoperative radiotherapy during lumpectomy (TARGIT ¬IORT) is a method of PBI for early breast cancer. Most patients (80%) receiving TARGIT¬ IORT during their lumpectomy complete their local treatment entirely during this single session, under the same anesthetic. Supplemental WBRT is only recommended for a minority of patients (20%) if unexpected prespecified tumor related factors such as invasive lobular cancer and positive margins are found postoperatively [7]. Peter D. Sasieni and Elinor J. Sawyer/2020 argue that the evidence remains insufficient for use of intraoperative radiotherapy (IORT) in women with early stage breast cancer outside of a clinical trial, as the recently reported TARGIT-A trial does not provide sufficient evidence to conclude that IORT is superior to no RT [27]. However, most patients with conventional 'high risk' features were treated without supplemental WBRT, including four¬ fifths of those with grade 3 or ER¬ negative disease, and two¬ thirds of node positive cases [7]. While the RT with TARGIT¬ IORT is given from within the breast with minimum additional dissection of the breast, the ELIOT technique requires the breast tissue to be dissected off the skin and the chest wall and brought together for irradiation from outside the breast [28]. Compared to other APBI techniques, IORT with electrons (ELIOT) offers the most homogeneous dose distribution, with an average dose inside the target volume closest to the prescribed dose (29). There are several other trials of PBI that use various techniques, including the ELIOT [28], NSABP-B39, GEC ESTRO, and Hungarian trials [30].

Relative Biological Effectiveness

It is well known that the relative biological effectiveness (RBE=Dx/D) of photons increases with decreasing energy, explained by a decrease in energy of secondary electrons with an increase in linear energy transfer (31,32) A published review summarized RBEs for 10% cell survival established using different systems and tumor cell types for low energy X-rays (10-240 kV) to range from 1.1 and 1.7 [32,33]. Herskind C. et al./2008 have employed a linear-quadratic formula to model the RBE of 50 kV X-rays modeled as an equivalent to a fractionated dose of 2 Gy (EQD2) as a function of depth, with the probability of local control estimated from clinical dose response data. The model calculations show that, for a cohort of patients, the increase in local control in the high-dose region near the applicator partly compensates the reduction of local control at greater distances. Thus a "sphere of equivalence" exists within which the risk of recurrence is equal to that after external fractionated radiotherapy [22]. Mathematical models of radiotherapy suggest that a smaller number of well targeted doses of radiotherapy are probably more effective than fractionated radiotherapy, which accords with the results of the START trial [34,35]. Intraoperative radiotherapy (IORT) is the only APBI technique that favors the performance of surgery and radiotherapy in the same day, offering a radiobiological advantage, minimizing the risk of repopulation of residual cancer clonogen cells before and during radiotherapy delivery; moreover, it is very convenient for the patients [36]. The biologically equivalent dose (BED) for an alpha/beta of 4 in the linear-quadratic model for a prescribed single dose of 10 Gy is isoeffective to about 24 in 2 Gy fractions [6]. The Intrabeam device provides a point source of low energy x-rays (50 kV maximum) at the tip of a 3•2 mm diameter tube that is placed at the center of a spherical tumor bed applicator [2]. Systems. that use soft X-rays have a small high

physical dose region and thereby offer an advantage over systems that use electrons to deliver a uniform dose of radiation: a high physical dose delivered over a small region would increase acute tumor effects while reducing damage to healthy tissue and long-term toxic effects [26].

Advantages and disadvantages of IORT

Among the different methods, IORT offers the advantage of a very precise delineation of tumor bed, which is identified under visual control, solving the problem of potential geographic miss [4]. Since the skin and the subcutaneous tissue can be placed outside of the irradiated volume, any changes in breast appearance are not expected even in superficial tumors, leading to a better cosmesis [37]. The advantages of IORT for PBI include: direct visualization of the target tissue ensuring treatment of the high-risk tissue and eliminating the risk of marginal miss; the use of a single dose coordinated with the necessary surgical excision; favorable toxicity profiles; patient convenience and cost savings; radiobiological and tumor microenvironment conditions which lead to enhanced tumor control. There is no time for tumor repopulation. IORT immediately after the removal of the tumor modifies the cytokines like oncostatin-M, leptin and IL-1β in the wound fluids (38,39). Wound fluids from IORT-treated patients significantly inhibit mammary mesenchymal stromal cells proliferation in comparison to wound fluids of non-irradiated patients. Single high dose of radiation can also simulate T cells and their infiltration around the remaining tumor cells [40]. The main disadvantage of IORT is the lack of final pathologic information on the tumor size, histology, margins, and nodal status [6]. IORT and other PBI techniques are likely to be more widely adopted in the future because they improve patient convenience by offering an accelerated course of treatment [41].

Patient selection for IORT

In applying the modality of risk-adapted RT, the key to success is grounded on selecting patients at low risk of harboring occult microscopic disease at distance from tumor bed, in order to ensure an annual rate of LR lower than 1% [4]. Patient selection is important when recommending IORT, as the final pathology is not available at the time of treatment, so to avoid the potential use of subsequent WBI, careful pre-operative, and intraoperative assessment can help ensure that high-risk features such as positive margins or positive sentinel nodes are minimized [6]. The ASTRO and GEC-ESTRO guidelines for APBI could be used as references when selecting suitable patients for IORT [42-45]. Among the TARGIT-A patients randomized pre-surgery, EBRT was given in addition to IORT if post-surgery histopathological analysis suggested the patient had a high risk of local recurrence (<1 mm tumor-free margin, >25% in situ component, or lobular carcinoma; and at some centers the presence of a grade 3 tumor, positive lymph nodes or lymphovascular invasion) [46]. In univariate analysis performed in the ELIOT study, tumor size, number of positive lymph nodes, proliferative index (Ki-67), young age, LVI, overexpression of HER2 and ER negative status, increased the risk of LR. In multivariate analysis age under 50 years, tumor size greater than 2 cm, remained independent predictors of local relapse [47]. Multivariate analysis in the ELIOT trial found that some factors doubled the risk of IORT, including a tumor size greater than 2cm, the presence of 4 or more positive lymph nodes, a poorly differentiated tumor, and a triple-negative subtype [48]. The NSABP B39/RTOG 0143 [49], which randomizes women between conventional WBI versus three APBI techniques, closed the accrual to low-risk group in 2007, and now is enrolling patients defined at high-risk (age >50, 1-3 nodes positive, ER negative) [4]. The patient's selection for IORT was carried out in two stages: 1/The first preclinical step for the tumor size (at clinical and radiological examination) and for other specific features evident from mammography, ultrasound, and magnetic resonance imaging; breast size, site of the tumor; 2/The second decisional step was during the surgery, soon after primary breast tumor excision. The histological examination of frozen specimen sections provides additional data for suitability of IORT delivery: histology not lobular without extensive intraductal carcinoma (EIC), not ductal carcinoma in situ (DCIS), negative margins of resection (at least 5 mm free margins) and negative node status [36].

Local Relapse

From our prospective study included 341 women with early BC (stage I-II) after BPS with a volume of quadrantectomy or sectoral resection, axillary lymph dissection and after completion of WBI with or without external Boost (RT in the tumor bed), we reported 5 significant pathohistological risk factors associated with local recurrence (LR)-G3, pN1, tumor necrosis, lymphatic vascular infiltration, and tumor metaplasia [3,50]. Young age (about 45 years or younger) is thought to be a risk factor for LR after breast-conserving therapy [51]. Age proved to be one of the most important predictive parameters for LR [52]. Many observational studies and randomized clinical trials have shown that more than 90% of recurrent disease occurring in the breast is within the index quadrant [53-59], which is by contrast with the findings of three-dimensional analysis of mastectomy specimens that show that 63% of breasts harbor occult cancer foci, with 80% of these situated remote from the index quadrant [60,61]. There is evidence that LR is facilitated by a local field defect: morphologically normal cells that surround breast-cancer tissue shows a loss of heterozygosity, which is in many cases identical to that of the primary tumor [62]. There are various techniques for applying an IORT for the purpose of local radiotherapy in the tumor bed during operation. Linear accelerators, brachytherapy or novel mobile devices generating fast electrons or low-energy x-rays (50 kV) are used for IORT [63]. Besides applying IORT as a boost, Vaidya et al. showed that IORT as a sole treatment in a low risk collective (women with primary unifocal ductal invasive breast cancer, aged 45 years or older) is non inferior to an EBRT regarding local recurrence [2,26,64]. The local recurrence rate in the TARGIT¬ IORT group was not significantly different from that in the external beam radiotherapy group (1•2% vs 0•95%, p=0•41 at 4 years) [2].

Clinical Results and Observations

Two large randomized trials, the TARGIT A trial establishing 50 kV IORT and ELIOT establishing electron based IOERT, both have published excellent results regarding local control and acceptable toxicity [2,19,36]. The Intrabeam® system (Carl Zeiss Meditec, Dublin, CA, USA) uses a 50 kV photon beam mobile X-ray unit that has been in clinical use since 1999 [65,66]. This system delivers low-energy photons (maximum 50 kV) at the tip of a 3.2 mm diameter tube. Spherical applicators of various sizes cover the tube and are placed in the tumor bed. Radiation is subsequently administered in the operating room over 20-35 minutes. The surface of the applicator receives 20 Gy and absorbed dose rapidly attenuates to 5-7 Gy at 1 cm depth [41]. Data from TARGIT-A have been reported as two separate trials: one in women randomized prior to surgery (46) and a second in women randomized post-surgery for whom a second operation was required to deliver IORT [5]. In the original TARGIT-A publication, all clinically significant complications occurred in 3.3% or fewer patients, including hematoma or seroma requiring intervention, infection, wound healing, or any grade 3 toxicity, and were similar between IORT and WBRT arms [67]. Complications at 6 months showed no difference between arms for any wound-related complications, with fewer grade 3-4 skin toxicities after IORT. Keshtgar reported cosmesis up to 4 years after IORT on a TARGIT-A subprotocol as assessed by photograph-analyzing software. IORT patients were about twice as likely to have excellent or good cosmetic scores as WBRT treated patients. A higher rate of radiographic fat necrosis was noted after IORT (56%) than after conventional WBRT (24%), and more scar calcifications as well [68]. Sperk et al./2012 reports a lack of difference between IORT ± WBRT versus WBRT with respect to fibrosis, breast edema, lymphedema, pain, or hyperpigmentation [69].

Aspects for our Dissertation Project Related to an Intraoperative Raying of an Early BC

The expected contributions from this research project include the introduction of IORT for the first time in Bulgaria and that the method can be safe and effective treatment for well selected Bulgarian breast cancer patients [70]. We will analyze the first 100 IORT patients treated in our center between 2015 and 2021 and compare them with control group of patients treated with WBI in our institute during the same time interval. We will evaluate the early side effects and tumor control in both the control the experimental group. All patients have tumor been evaluated by mammography, ultrasonography, and contrast enhanced MRI, unless contraindicated. In our center we consider patients suitable for IORT if preoperatively and intraoperatively they meet the GEC-ESTRO low risk group criteria: including patients ageing at least 50 years with unicentric, unifocal, pT1-2 (<or=30 mm) pN0, non-lobular invasive breast cancer without the presence of an extensive intraductal component (EIC) and lympho-vascular invasion (LVI) and with negative surgical margins of at least 2mm. The IORT is delivered through the Intrabeam device (Carl Zeiss Meditec, Oberkochen, Germany) in a single treatment under the same anaesthetic as the primary surgery and is the only radiotherapy for most patients. Radiation is delivered from a point source of 50 kV energy x rays at the center of a spherical applicator over 20-50 minutes (Figure 1/A,B). The appropriately sized (1.5-5 cm diameter) applicator is surgically positioned in the tumor bed so that breast tissues at risk of local recurrence receive the prescribed dose while skin and other organs are protected (Figure 2/A,B). The surface of the tumor bed typically receives 20 Gy that attenuates to 5-7 Gy at 1 cm depth. If after the release of the pathologist's final report any patient is no longer found in the low risk group, she is offered postoperative whole breast irradiation (50 Gy in 2 Gy fractions) without additional boosting.

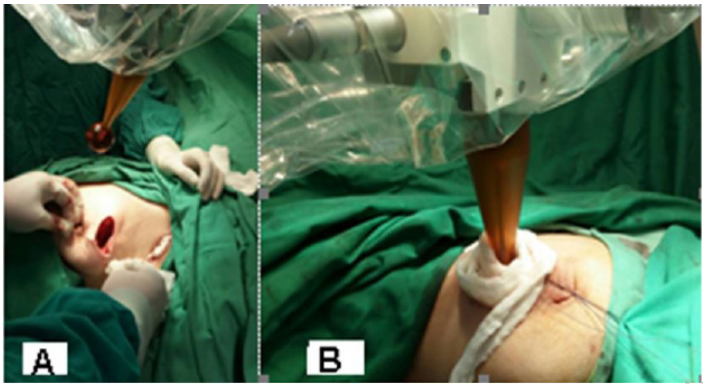

Figure 1: Radiation is delivered from a point source of 50 kV energy x rays at the center of a spherical applicator over 20-50 minutes.

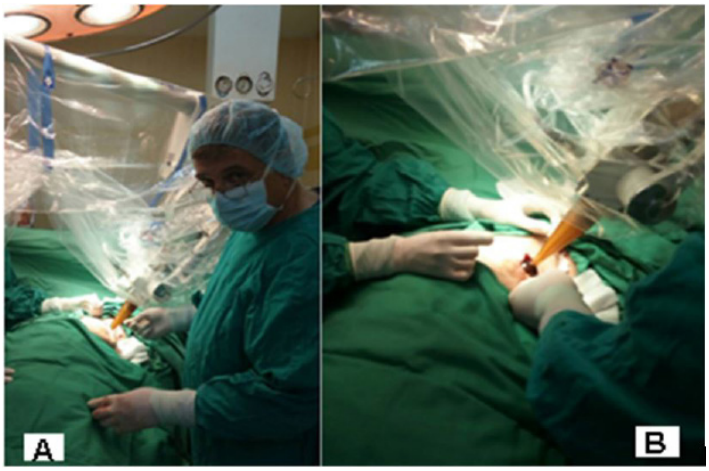

Figure 2: The appropriately sized (1.5-5 cm diameter) applicator is surgically positioned in the tumor bed so that breast tissues at risk of local recurrence receive the prescribed dose while skin and other organs are protected.

Conclusion

When considering use of IORT techniques for partial breast treatment after lumpectomy, it is recommended to select patients who fall into the low-risk categories among published guidelines, using the "suitable" or "good risk" criteria for patients who are general candidates for APBI [6]. IORT has potential efficacy

advantages related to overall survival related to reduced cardiopulmonary radiation doses, as well as prior to oncoplastic reconstruction to improve accuracy of adjuvant radiation delivery, or when used as a boost in higher risk patients to improve tumor control. An additional advantage of the procedure is reduced therapeutic times, which is not comparable to the five weeks, that are necessary for the WBI after a PBS.

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