

Brest experience in intraoperative radiotherapy for breast cancer

Petra Miglierini¹, Stéphane Key¹, Pierre-François Dupré², Emmanuelle Le Fur¹, Omar Miranda¹, Anne-Sophie Lucia¹, Sarah Quillevere¹, Olivier Pradier¹

¹Department of Radiotherapy, ²Department of Gynecology and Obstetrics, Regional University Hospital Morvan, 29 200 Brest, France

Correspondence to: Petra Miglierini, MD. Department of Radiotherapy, Institute of Oncology and Haematology, Regional University Hospital Morvan, 2 Avenue Foch, 29 200 Brest, France. Email: petra.miglierini@chu-brest.fr.

Purpose: Targeted intraoperative radiotherapy (TARGIT) of an early breast cancer is a novel and promising treatment approach. For carefully selected patients, it permits to omit external beam breast radiotherapy (EBRT) and thus reduce the treatment duration. Moreover it offers an excellent precision without risk of tumour site miss and normal tissue sparing. Various techniques of intraoperative radiotherapy (IORT) are available. The first technique being tested in randomised trial was the TARGIT using a device developed by clinical academics in collaboration with the industry, Intrabeam[®] system that consists of a small low-energy X-ray generator. Strict criteria for TARGIT eligibility need to be respected, i.e., age ≥ 45 years and invasive ductal carcinoma that is unifocal on conventional imaging ≤ 3.5 cm, without gross lymph node involvement.

Methods: Our inclusion criteria were significantly stricter than those of the TARGIT-A trial and we only included patients ≥ 55 years with unifocal ductal invasive carcinoma of grade 1 or 2, tumour size ≤ 2 cm (based upon clinical and ultrasound evaluation), significant expression of hormone receptors ($\geq 10\%$), no ErbB-2 expression. Intrabeam[®] system has been established within Regional University Hospital in Brest on April 2011. Between Mai 2011 and September 2013, 74 female patients were scheduled for TARGIT of an early stage breast cancer. Patients submitted a breast-conserving surgery (BCS) and sentinel lymph node (SLN) search. In case of respect of inclusion criteria patients benefited of TARGIT using a spherical applicator of a diameter depending upon the tumour and breast size. A total dose of 20 Gy was prescribed to the surface of the applicator and delivered into the surgical cavity. If any unfavorable histological modification appeared in the final pathological examination, a further EBRT needed to be done with a dose of 46-50 Gy. Patients were evaluated clinically 3-4 weeks post-operatively and possible side effects were documented.

Results: Sixty five patients received TARGIT. For 66% of them, the TARGIT was the only radiation treatment. For 33% also a complementary EBRT was required and thus the TARGIT has replaced the boost, only. Among the first side effects observed induration of surgical bed, radiation dermatitis, seroma, and delayed healing were the most frequent ones that have appeared in 20%, 14%, 12.5%, and 12.5% of patients, respectively.

Conclusions: Intraoperative irradiation during BCS is a feasible and promising alternative to conventional external fractionated radiotherapy. Strict eligibility criteria need to be taken into account before TARGIT is proposed to the patients. At present, only women with an early-stage breast cancer with low risk of recurrence can be candidates for this treatment modality.

Keywords: Breast cancer; intraoperative radiotherapy (IORT); tolerance; side effects

Submitted Dec 20, 2013. Accepted for publication Mar 04, 2014.

doi: 10.3978/j.issn.2218-676X.2014.03.01

View this article at: <http://www.thetcr.org/article/view/2368/2963>

Introduction

Breast cancer is a leading cancer site and the first cause of death from cancer in women in the whole Europe. It represented the third most frequent cause of death from cancer in general population in 2012 (1). Appropriate treatment approaches are required according to every disease stage. Regardless of particular cases, main breast cancer management consists of breast-conserving surgery (BCS), adjuvant chemotherapy if indicated, and external beam radiotherapy (EBRT) of whole ipsilateral breast. These might be further associated with hormonal therapies depending upon tumour pathological characteristics.

Since almost 90% of local recurrences appear within the tumour bed, its complementary irradiation, i.e., boost, aims to reduce the risk of this relapse and became an inevitable part of the breast irradiation protocol in invasive breast carcinomas. This can be delivered simultaneously together with the whole breast EBRT or consecutively in 5 to 8 fractions of 2 Gy by reduced fields using photons or electrons.

Recently, numerous clinical research teams dealt with a possibility of a complementary boost delivery into the tumour bed during BCS in order to shorten the duration of subsequent radiotherapy. Another advantage of an targeted intraoperative radiotherapy (TARGIT) is to avoid a “geographic miss” of tumour site during later EBRT (2). For the purpose of TARGIT different techniques are available up today, e.g., linear accelerators, brachytherapy or mobile devices generating low-energy X-rays such as Intrabeam® system from Carl Zeiss Surgical company. This miniature X-ray source with 50 kV maximum has already been tested on large series of patients with very promising results in terms of recurrence rates, acute or late side effects, cosmetic outcomes, or quality of life (3-9). The Intrabeam® device permits acceleration of electrons that are forwarded towards a gold target and induce a formation of radiation field with an isotropic dose distribution. Thus, low-energy X-rays are generated and spread homogenously upon the whole surface of a spherical applicator which is particularly adapted for mammary gland treatment. Because of its steep dose fall-off it requires relatively modest precautions of radiation protection.

As it was demonstrated by Vaidya *et al.* (6), in some very carefully selected patients with early-stage breast cancer a restriction of radiation therapy exclusively to the tumour bed during surgery, i.e., TARGIT alone, should be considered as an alternative to EBRT delivered over several

weeks.

An Intrabeam® system has been established at our Regional University Hospital in Brest on April 2011. At present, the irradiation using this device is performed in two main indications, breast cancer and vertebra bone metastasis. For the latter, TARGIT is followed by a kyphoplasty which is done at the same operation time. A trained staff consisting of three radiation oncologists, three surgeons (gynecologists), and three physicists performs breast intraoperative radiotherapy (IORT) treatments once or twice a week since May 2011.

In this paper, we describe our experience with this low-energy X-ray generator device in patients with early-stage breast cancer.

Methods

Between May 2011 and September 2013, 74 female patients were scheduled for breast TARGIT using a mobile device Intrabeam® (Carl Zeiss Surgical, Oberkochen, Germany) according to strict inclusion criteria. BCS as well as TARGIT were performed in a dedicated operation room with leaded walls although these are not essential. For this study in our center, we included only female menopausal patients 55-year old and more. Prior to BCS, tumour histological characteristics were evaluated on a microbiopsy piece. Our inclusion criteria were significantly stricter than those of the TARGIT-A trial and we only included patients with the following tumour characteristics: unifocal ductal invasive carcinoma of grade 1 or 2, tumour size ≤ 20 mm (based upon clinical or ultrasound evaluation), significant expression of hormone receptors ($\geq 10\%$), no ErbB-2 expression. Sentinel lymph node (SLN) was inevitably explored during every BCS and we performed TARGIT IORT only if this was negative although this is not in the TARGIT-A trial protocol. The TARGIT exclusion criteria in this study in our center were the following: ductal invasive carcinoma with diffuse microcalcifications, multifocal or bilateral carcinoma, lobular invasive carcinoma, lymph node involvement, personal history of malignant disease and life expectancy < 10 years, previous thoracic irradiation (m. Hodgkin), homolateral breast cancer or BRCA mutation.

Intraoperatively and prior to TARGIT, frozen section analysis of tumour piece was performed at the Department of Pathological Anatomy of the Regional University Hospital Brest for each patient and permitted to confirm the retention of TARGIT indication or not. Depending on initial tumour and breast size, the choice of spherical

applicator diameter was done by the surgeon. This could vary from 2 to 5 cm. A total dose of 20 Gy was prescribed to the surface of the applicator. Although this is no longer considered necessary, in our center, prior to positioning of the applicator itself, a small tungsten impregnated plaque is placed at the bottom of the surgical cavity in order to ensure a radiation protection of the ribs, lung, and heart.

Once the final pathological examination of tumour and SLN was achieved, the decision of further additional external breast irradiation or not was discussed at a regular multidisciplinary meeting. If the TARGIT inclusion criteria were still respected, no complementary EBRT was performed and TARGIT was considered as an exclusive breast treatment. On contrary, if at least one of the above mentioned criteria was not met, or intraductal component was >25%, or there was a lymphovascular invasion (LVI), or positive surgical margins, a whole breast EBRT was done at a dose of 46 to 50 in 2 Gy per fraction. Under these conditions, the TARGIT was considered as a boost only.

Demographic and histological parameters of eligible patients were reviewed retrospectively and collected within an Excel™ system (Microsoft Corporation, Redmond, Seattle, USA). The first clinical post-operative evaluation was done 3-4 weeks after the BCS. Cosmetic outcomes and potential post-treatment toxicities were evaluated without grading at this time. No statistical analysis was performed.

Results

Seventy four patients with an early-stage breast cancer were initially eligible for TARGIT. Mean age of these patients was 68.1 years (56-86 years). Mean chest diameter of all patients was 98 cm (85-119 cm) and mean body mass index value was of 25.7 (18.7-35).

Since one of the advantages of TARGIT is to spare time consuming and several weeks lasting classic EBRT of breast cancer we have evaluated the social situation of our patients as well. Eighteen percent of patients were still actively working at the moment of cancer diagnosis and treatment, 82% were already retired. Mean distance between patient's home and Regional University Hospital in Brest was 35 km (0-135 km).

Concerning tumour characteristics, 59% of them were located in a left breast and 41% in a right one. Regarding the tumour size, no clinically palpable tumour (T0), tumour inferior to 2 cm (T1) or tumour of 2-5 cm (T2) was found in 53%, 43%, and 4% of patients, respectively. No patient

presented a clinically palpable lymph node at the moment of diagnosis. Histological grade was of 1 for 70% of tumours and of 2 for the rest 30%.

As for treatment procedure, mean time between the moment of diagnosis and treatment itself was 6 weeks and 3 days. The BCS lasted in average 2.5 hours while the mean duration of intraoperative irradiation was 28 minutes. In majority of cases (92% of patients) spherical applicators of 3-4 cm were used.

Finally, 65 out of 74 eligible patients could benefit of TARGIT. Nine patients did not receive the intraoperative treatment because of the following reasons: positive surgical margins despite the second reexcision, histological doubt in SLN, no SLN found, positive SLN, tumour not found in the piece, bifocal tumour, and one case of technical impossibility to recover the applicator by the mammary gland.

According to the final histological examination of tumour piece, in 66% of cases TARGIT was considered as an exclusive radiation treatment and in 33% of it needed an addition whole breast EBRT and, thus it was considered as a boost only. Twenty three percent of patients required EBRT because of unfavorable final histological profile, e.g., positive lymph nodes, higher histological grade, ErbB-2 overexpression. For 10% of these patients, the involved margins required a reexcision and subsequent EBRT. In the TARGIT-A trial, apart from positive margins, the other factors on their own, would not necessarily prompt the addition of EBRT.

Negative SLN was achieved in 77% of cases whereas it was positive in the remaining 23%. Micrometastases were found in 10.2%, macrometastases in another 10.2%, and 2.6% were of unknown status.

Presence of side effects was evaluated during the first post-operative medical visit 3-4 weeks after the BCS and TARGIT. Induration of the surgical bed, being the most frequent side effect, was present in 13 patients (20%). This was followed by radiation dermatitis in 9 patients (14%). In eight patients the wound was slightly inflamed and sensible even 4 weeks after the surgery. This phenomenon was assigned in our conditions as a delayed wound healing although a true dehiscence could be observed only in one patient. The approximate duration of the healing process in these 8 patients was 1.5-2 months.

Seroma within the surgical bed was seen in eight patients, from whom two presented simultaneously a delayed wound healing. Three patients suffered from a surgical site hematoma and one patient experienced an infection of the surgical bed.

Discussion

A decline in breast cancer mortality was reported in recent years as a consequence of the combined effects of earlier cancer detection and a range of improvements in its treatment (1). Post-operative radiotherapy of mammary gland is a recommended and inevitable approach in treatment of invasive and intraductal breast cancers. Because invasive carcinomas have a particular tendency to induce a recurrence at the initial tumour site, an additional boost targeting tumour bed is required. At present, this one can be delivered in several different radiation forms using either photons or electrons. The use of a mobile low-energy X-ray generator Intrabeam® presents a novel and promising technique. Its major advantage is the possibility of direct irradiation of tumour bed without a risk of target miss as it can happen during EBRT boost. Furthermore, intraoperative irradiation permits immediate treatment of surgical bed avoiding a delay between surgery and EBRT. In selected patients with favorable early stage breast cancer, the studies demonstrated non-inferiority of TARGIT to the conventional EBRT with respect to the local control, safety and cosmetic outcomes (6,10).

Early and late side effects of IORT using Intrabeam® system have already been evaluated by several research teams (3,5,11). Sperk *et al.* (5) observed that concerning late radiation toxicities in patients treated with IORT exclusively compared to external breast radiotherapy there were no significant differences in terms of fibrosis, breast edema, ulceration, hyperpigmentation, lymphedema or pain incidence. As for early complications, Tuschy *et al.* (3) noticed particularly the appearance of surgical bed induration, seroma, erythema of grade I and II, and mastitis in 24%, 17.3%, 13%, and 3.4% respectively. These results seem comparable to early side effects observed among the group of patients treated at our institution.

Regarding the local control rates, the first results were already published. Vaidya *et al.* (12) observed in their TARGIT-A trial that the 5-year risk of local recurrence in conserved breast was 3.3% for IORT versus 1.3% for EBRT. These outcomes may appear statistically significant but the P value of 0.04 was above the pre-defined P value of 0.01; also they were simultaneously acceptable in terms of the threshold of the pre-defined non-inferiority margin. The authors recommend the use of TARGIT during the initial lumpectomy rather than as a delayed procedure by reopening the wound. When used in this manner, the recurrence rates were 2.2% versus 1.2%, and the difference

was not statistically significant. In addition, while breast cancer mortality was similar, non-breast cancer mortality was significantly reduced with TARGIT.

The recently published ELIOT study carried by Veronesi *et al.* (13) showed that the 5-year event rate for ipsilateral breast tumour recurrence (IBTR) was 4.4% for IORT with electrons and 0.4% for a whole-breast irradiation. Although the rate for IBTR in the IORT group was within the prespecified equivalence margins, the rate was significantly greater than with the EBRT. No difference in terms of the overall survival was found.

In our study, the late radiation complications incidence and local control rates are yet difficult to define because of a relatively short clinical experience so far.

The IORT during BCS is a promising alternative to the conventional external whole-breast irradiation in a carefully selected group of patients with early breast cancer.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editors (Frederik Wenz and Elena Sperk) for the series “Intraoperative Radiotherapy” published in *Translational Cancer Research*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.3978/j.issn.2218-676X.2014.03.01>). The series “Intraoperative Radiotherapy” was commissioned by the editorial office without any funding or sponsorship. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki. The study was approved by Institutional Review Board and informed consent was obtained.

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Cite this article as: Miglierini P, Key S, Dupré PF, Le Fur E, Miranda O, Lucia AS, Quillevère S, Pradier O. Breast experience in intraoperative radiotherapy for breast cancer. *Transl Cancer Res* 2014;3(2):175-179. doi: 10.3978/j.issn.2218-676X.2014.03.01