

Editorial

Is Intraoperative Radiotherapy a Standard Technique for Early Breast Cancer?

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EDITORIAL

Recently, two pivotal papers with Intraoperative radiotherapy (IORT) are published [1,2]. The standard treatment for early breast cancer is breast-conserving therapy (BCT) with whole breast external irradiation therapy (WBI) [3]. Even in highly selected patients, omission of radiotherapy increases the risk of local recurrence [4]. In actuality some women are still encouraged to proceed to mastectomy, because of the lack of access to radiotherapy centers or the long course of treatment of WBI. Then shorter treatment option of irradiation is needed, Partial breast irradiation (PBI) has been tested in clinical trials for selected patients. The rationale for PBI is that local recurrences after BCT with or without WBI arise most in the same quadrant as the primary cancer [5]. The main objective of radiotherapy after BCT is considered to be the destruction of residual cancer cells in the operative field. PBI administered around the tumor bed has been comparable to WBI in selected patients in phase II studies [6-9]. Adequate local control, minimal toxicity, and good cosmetic appearance are shown in studies of PBI [10]. IORT is one of these PBI methods, makes it possible to remove the need to attend a radiotherapy center for 25 fractions for WBI. At present, outside the setting of a clinical trial, use of IORT as well as PBI has not been recommended yet [10,11]. They had been remained investigational until the information of phase III on its long-term efficacy compared with WBI and safety becomes available [12], although more than 1,000 IORT procedures were used in the Milan Institute [13,14].

In the ELIOT trial [1], 1,305 patients aged 48-75 years with early breast cancer, a maximum tumor diameter of up to 2.5 cm were randomly assigned to receive either WBI (50 Gy in 25 fractions followed by a boost of 10 Gy in five fractions using an external electron beam without node irradiation) or IORT with electrons (21 Gy in one fraction to the tumor bed using electrons of 6-9 MeV, prescribed to the 90% isodose). The primary endpoint was occurrence of ipsilateral breast tumor recurrences (IBTR). This is an equivalence trial; the equivalence margin was local recurrence of 7.5% in the IORT group. After a medium follow-up of 5.8 years, 35 patients in the IORT group and 4 patients in the WBI group had had an IBTR ($p < 0.0001$). The 5-year event rate for IBTR was 4.4% (95% CI: 2.7-6.1) in the IORT group and 0.4% in the WBI group (hazard ratio 9.3 [95% CI: 3.3-26.3]). 5-year

Special Issue on

Breast Cancer Therapeutics

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Submitted: 26 December 2013

Accepted: 15 January 2014

Published: 19 January 2014

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overall survival (OS) was 96.8% (95% CI: 95.3-98.3) in the IORT group and 96.9% (95.5-98.3) in the WBI group. Significantly fewer skin side-effects in the IORT group were observed than in those in the WBI group ($p = 0.0002$). The rate of local recurrence with IORT was within the estimated equivalence margin. In this paper, two important issues are pointed out. First, selection of the patients could reduce the rate of IBTR with IORT. The rate of IBTR in IORT group was significantly greater than that of WBI group, although the rare was under prespecified equivalent margin. The important information gained from these results regards the site of IBTR; the authors distinguished true local relapses from new ipsilateral breast tumors. Repeatedly, the main objective of radiotherapy after BCT is considered to be the destruction of residual cancer cells in the operative field; especially the target in IORT is tumor bed with direct visualization. In this paper, factors associated with IBTR among patients received IORT were studied in multivariable analysis; tumor size (> 2 cm), lymph node metastasis (involved 4 or more), pathological type (poorly differentiated tumor), and triple-negative subtype. The American Society for Radiation Oncology (ASTRO) Task Force recommendations also suggested relevant inclusion criteria for APBI [15]. Second, Toxicity and cosmetic appearance of IORT compared with WBI could be available; these are very important new information. Significantly fewer skin side-effects in the IORT group were observed; erythema, dryness, hyper-pigmentation, and dryness were more common in WBI group, and only fat necrosis was higher in IORT group. In addition, in patients who had been undergone CT scans, pulmonary fibrosis was more common in WBI group than IORT. IORT makes it possible to minimize several side effects, since skin and the subcutaneous tissue can be spared; and to reduce radiation dose to lung and heart; and to be able to achieve early initiation of radiation and to be given without delaying administration of chemotherapy; and to be able to decrease healthcare cost in some countries and spare time required for outpatient treatment due to one fraction [16].

In the TARGIT-A trial [2], radiotherapy using single-dose targeted intraoperative radiotherapy (TARGIT) was compared



Figure 1 IORT in our institute.

with whole-breast fractionated external beam radiotherapy (EBRT) for breast cancer. The authors used a miniature electron-beam-driven X-ray source called Intrabeam[®], which emits low energetic X-rays with 50 kV from the point source. This device is inserted intraoperatively into the tumor cavity after excision of the tumor and emits X-rays from within the breast [17]. This study was a multi-center, randomized, non-inferiority trial. 3,451 patients aged 45 years and older with invasive ductal carcinoma were enrolled and randomly assigned to receive TARGIT or whole breast EBRT (WBI). 15.2% (239 of 1,571) of patients in the TARGIT group received supplemental EBRT, if unforeseen adverse features were detected on final pathology, which was called a risk-adapted approach. The primary outcome was absolute difference in local recurrence in the conserved breast, with a prespecified non-inferiority margin of 2.5% at 5 years. After a median follow-up of 2 years and 5 months, the 5-year risk for local recurrence in the conserved breast was 3.3% (95% CI: 2.1-5.1) for TARGIT versus 1.3% (0.7-2.5) for EBRT ($p=0.042$). TARGIT concurrently with lumpectomy (pre-pathology, $n=2,298$) had much the same results as EBRT: 2.1% (1.1-4.2) versus 1.1% (0.5-2.5; $p=0.31$). With delayed TARGIT (post-pathology, $n=1,153$) the between-group difference was larger than 2.5% (TARGIT 5.4% [3.0-9.7] vs EBRT 1.7% [0.6-4.9]; $p=0.069$). Overall mortality was 3.9% for TARGIT versus 5.3% for EBRT ($p=0.099$), but there were significantly fewer non-breast-cancer deaths with TARGIT (1.4% [0.8-2.5] vs 3.5% [2.3-5.2]; $p=0.0086$), attributable to fewer deaths from cardiovascular causes and other cancers. As for adverse events, grade 3 or 4 skin complications were significantly reduced with TARGIT (4 of 1,720 vs 13 of 1,731, $p=0.029$). As a conclusion, TARGIT concurrent with lumpectomy within a risk-adapted approach should be considered as an option for eligible patients with breast cancer carefully selected patients, as an alternative to postoperative EBRT. In this paper, two important issues are pointed out. First, delayed TARGIT (post-pathology, $n=1,153$) group had worse recurrence rate. When should be delivered TARGIT; initial lumpectomy with less pathological information, or re-operation after final pathological diagnosis? The answer from the study is with initial lumpectomy, not with delayed procedure. The reason why this difference was caused is not clear, although we need to consider. The main advantages of immediate placement of the radiotherapy are follows: 1) to be able to deliver the radiation before tumor cells have a chance to proliferate under surgical intervention have a rich vascularization, which makes them more sensitive to

the action of the radiation; 2) to be able to deliver under direct visualization at the time of surgery, it has the potential capability for accurate dose delivery to the surgical bed directly [16]. These may be one of possible reasons. One area of concern in the use of IORT is the management of positive surgical margins as positivity is discovered at the final histology, a few days after surgery and IORT. The answer with this point was given by the trial. Then, in the trial it is emphasized that this trial is a risk-adapted design, if subsequent pathology suggested adverse histological features then mandatory to complete treatment to the whole breast, although only 15% of cases occurred. TARGIT is an only trial to permit addition of EBRT if the adverse pathological factors are present. Second, there were significantly fewer non-breast-cancer deaths with TARGIT group. Cardiovascular causes (cardiac disease; 8, stroke; 2, ischemic bowel; 1) were more seen in EBRT group than TARGIT group. Radiotherapy-induced cardio toxicity has been known within the first 4 years [18]. In this trial it might be possible to reduce radiation dose to lung and heart as well as ELIOT trial, although continuous monitoring is mandatory.

In these pivotal studies, most important issue is patient selection. Anatomical factors; i. e. , tumor size (>2cm), lymph node metastasis (involved 4 or more), and pathological types are very important, and addition, biological subtype features are mandatory to consider indication. Patient's age less than 45 are not included in these trials, so they should not be indicated. Pathological information is needed to perform appropriate approach, but second procedure after reopening the wound after pathological diagnosis is not recommended because of its higher recurrence rate. As for adverse events, these new methods are less toxic than WBI, mainly skin-side effects, and also cardio toxicity or pulmonary fibrosis, although a longer follow up time is needed for evaluation of late toxicity. Late cosmetic outcome is important for evaluation of radiotherapy, the majority of patients with early breast cancer treated with BCT have acceptable cosmetic outcomes [19], although there is few data evaluating for late changes of cosmesis after IORT.

These new data from ELIOT and TARGIT-A trial, IORT is an alternative to WBI for selected patients at low risk of local recurrence.

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Cite this article

Sawaki M (2014) Is Intraoperative Radiotherapy a Standard Technique for Early Breast Cancer? *J Cancer Biol Res* 2(1): 1015.