Int. J. Radiation Oncology Biol. Phys., Vol. 80, No. 1, pp. 31–38, 2011
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0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2010.01.045

CLINICAL INVESTIGATION **Breast**

TARGETED INTRAOPERATIVE RADIOTHERAPY FOR BREAST CANCER IN PATIENTS IN WHOM EXTERNAL BEAM RADIATION IS NOT POSSIBLE

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Purpose: External beam radiation therapy (EBRT) following wide local excision of the primary tumor is the standard treatment in early breast cancer. In some circumstances this procedure is not possible or is contraindicated or difficult. The purpose of this study was to determine the safety and efficacy of targeted intraoperative radiotherapy (TARGIT) when EBRT is not feasible.

Methods and Materials: We report our experience with TARGIT in three centers (Australia, Germany, and the United Kingdom) between 1999 and 2008. Patients at these centers received a single radiation dose of 20 Gy to the breast tissue in contact with the applicator (or 6 Gy at 1-cm distance), as they could not be given EBRT and were keen to avoid mastectomy.

Results: Eighty patients were treated with TARGIT. Reasons for using TARGIT were 21 patients had previously received EBRT, and 31 patients had clinical reasons such as systemic lupus erythematosus, motor neuron disease, Parkinson's disease, ankylosing spondylitis, morbid obesity, and cardiovascular or severe respiratory disease. Three of these patients received percutaneous radiotherapy without surgery; 28 patients were included for compelling personal reasons, usually on compassionate grounds. After a median follow-up of 38 months, only two local recurrences were observed, an annual local recurrence rate of 0.75% (95% confidence interval, 0.09%–2.70%).

Conclusions: While we await the results of the randomized trial (over 2,000 patients have already been recruited), TARGIT is an acceptable option but only in highly selected cases that cannot be recruited in the trial and in whom EBRT is not feasible/possible. © **2011 Elsevier Inc.**

Breast cancer, Targeted intraoperative radiotherapy (TARGIT), Radiotherapy, Recurrence rate, Breast-conserving surgery.

INTRODUCTION

Wide local excision of the primary tumor, followed by postoperative external beam radiotherapy (EBRT) to the whole breast is now considered the standard management for most patients with early breast cancer. This approach ensures that the majority of patients will enjoy long-term local control of the disease with an acceptable cosmetic result (1–4). There are a number of circumstances in which treatment by this standard method proves difficult, either because of previous radiation (for example, in the case of patients with recurrent cancer in the same breast or those who have been treated with ''mantle'' radiotherapy for Hodgkin's disease) or because of comorbidities such as severe respiratory problems, collagen or autoimmune disorders, chronic lung disease with respiratory dysfunction, or painful arthritis (which might prevent adequate abduction of the shoulder). Extreme age and geographical considerations may also be confounding factors in the delivery of EBRT, bearing in mind the traveling required, generally on a daily basis for at least 3 weeks or more to the radiation oncology center.

This paper reports the experience of three major centers in the United Kingdom, Australia, and Germany, all of which have extensive experience in administering intraoperative radiation therapy (IORT) for patients with early breast cancer. These centers along with 22 others are participating in an international randomized trial targeted intraoperative

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Acknowledgment—We thank Pauline Rogers of the Biostatistics Group in the UCLH/UCL Biomedical Research Unit for statistical advice.

Received Dec 15, 2009, and in revised form Jan 22, 2010. Accepted for publication Jan 22, 2010.

Table 1. Reasons for treating breast cancer with TARGIT off-trial

Reasons for TARGIT	No. of patients	Age (IQR) years	Follow-up (IQR) months	LR
Previous EBRT	21	60 (53–70)	42 (28–66)	0
Clinical reasons including comorbidities	31	69 (61–79)	29 (18–49)	1
Compelling personal reasons	28	67 (53–76)	45 (25–60)	1
Total	80	67 (56–76)	38 (24–57)	2

Abbreviations: LR = number of local recurrences.

radiotherapy (TARGIT), comparing EBRT with IORT alone, which was launched in March 2000 and has now accrued over 2,000 patients (5–9). In each of these three centers, patients have been seen for consideration of inclusion within this randomized trial. In selected cases of patients who failed to meet the inclusion criteria and after careful consideration at the respective multidisciplinary meetings, IORT was offered outside the randomized trial, following wide local excision surgery as an alternative to EBRT (Table 1). In addition, a small group of patients with estrogen receptor-negative tumors who were considered unfit even for wide local excision or who refused surgery have been treated by ''percutaneous'' IORT alone without any surgical intervention.

There is little in the published literature to help with difficult judgments regarding the appropriateness of EBRT in patients with significant comorbidity. For example, some radiation oncologists are reluctant to offer EBRT to patients with systemic lupus erythematosus (SLE), as the oncologists are concerned about significant risk of excess radiation damage to which can be long-lasting (10–12). Likewise, in the case of patients with respiratory dysfunction, the radiation oncologist might well be more concerned with the inevitable ''splash'' of the radiation field to the outer portion of ipsilateral lung than would normally be the case. In patients previously treated with radiotherapy, such as those with Hodgkin's disease treated and cured by mantle irradiation, most oncologists would be unwilling to agree to conventional dose EBRT, even with a gap of 20 years or more between the initial radiation and the second course.

Recently, we have discovered a novel mechanism of action of radiotherapy (13). We found that wound fluid collected over the first 24 hours immediately after lumpectomy stimulates the proliferation, motility, and invasiveness of breast cancer cells. All these stimulatory effects of normal wound fluid were abrogated if the patient had received targeted intraoperative radiotherapy. Thus, this action of TARGIT creates a microenvironment that is not conducive to tumor growth, and this novel mechanism could act synergistically with its tumoricidal effect.

In this paper, we describe 80 patients who were not suitable for the TARGIT randomized trial by virtue of their inability to accept the EBRT arm of the trial but nonetheless had compelling indications for breast-conserving surgery, and refusal to accept mastectomy as an option, we felt that TARGIT was at least better than no radiotherapy at all. We have compiled this brief report to point out to colleagues that even in these difficult circumstances, where EBRT is felt to be impossible or ill-advised, it may still be possible to avoid mastectomy by offering wide local excision surgery followed by IORT. The median follow-up of these patients was 38 months.

This paper focuses mainly on the efficacy of the treatment in a selected, albeit heterogeneous, group of patients, as the safety of using IORT has already been reported widely (14–17).

METHODS AND MATERIALS

Technique of intraoperative radiotherapy

The rationale, justification, and methodology of the technique have been previously reported (6, 7). In brief, the equipment used was an Intrabeam system (Carl Zeiss Surgical, Oberkochen, Germany). It is a mobile, miniature X-ray generator which is powered by a 12-volt supply and taken to the operating theatre at the time of surgery (Fig. 1a). Accelerated electrons strike a gold target at the tip of a 10-cm-long drift tube with a diameter of 3 mm, resulting in the emission of low-energy X-ray (50 kV) in an isotropic dose distribution around the tip. The irradiated tissue is kept at a distance from the source by spherical applicators to ensure more uniform dose distribution. Depending on the size of the surgical cavity, various sizes of applicator spheres are available (Fig. 1b). The dose rate depends on the diameter of the applicator and the distance from the applicator surface. For example, a dose of 20 Gy is delivered to the tissue immediately adjacent to a 3.5-cm applicator, and 6 Gy at 1 cm, with administration time of about 25 minutes. The steep attenuation of the radiation dose protects normal tissues and allows the treatment to be safely carried out in unmodified operating theatres. A full discussion of the dosimetry and radiobiology of the technique has been published previously (18–20).

After obtaining informed consent and excision of primary tumor, the excised specimen and the resultant cavity are measured, and a sterilized spherical applicator which best fits the cavity (ranging from 1.5 to 5.0 cm in diameter) is selected and placed over the intrabeam drift tube which is positioned inside the surgical cavity. A purse-string suture is run all around the tumor bed, which pulls the breast tissue into close proximity of the applicator surface, therefore molding the target tissue to the source (conformal radiotherapy) (Fig. 2). Care is taken to ensure that the skin is kept at least 1 cm away from the applicator surface.

Technique of percutaneous radiotherapy

After informed consent has been obtained, the patient is positioned on a MammoTest table (Fisher Imaging, Broomfield, CO, USA) in prone position (21). After local anesthetic has been administered, a small incision is made and a Mammotome vacuum biopsy (Ethicon Endo Surgery, Cincinnati, OH, USA) device is targeted to remove a core of tissue up to the center of the tumor. An Intrabeam drift tube is covered by a sterile sheet and positioned in the breast through the tract created by the Mammotome device (21). The manner of dose prescription been described in detail previously (21). Briefly, the typical prescribed physical dose is 20 Gy at the surface of the tumor, which falls off to 5 to 7 Gy at 1 cm from the tumor edge. At the center, the physical dose is approximately 130 Gy. The dosimetry is similar to interstitial brachytherapy but does not

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