

Targeted Intra-operative Radiotherapy—TARGIT for Early Breast Cancer

Can We Spare the Patient Daily Journeys to the Radiotherapist?

Michael Baum^a and Jayant S. Vaidya^b

^a*University College London, The Portland Hospital, London, United Kingdom*

^b*Department of Surgery and Molecular Oncology, Ninewells Hospital and Medical School, University of Dundee, Scotland, United Kingdom*

Breast conservation by wide local excision for early breast cancer is now considered safe and should be considered default therapy wherever possible. Unfortunately, this requires access to costly radiotherapy centers. Many women in the developing world or for that matter in wealthy countries with large land masses and small populations do not have access to radiotherapy and are therefore denied the option of breast-conserving surgery. Whole-breast radiation by external beam after tumorectomy is predicated on the belief that latent foci of subclinical cancer outside the index quadrant are responsible for local recurrence. We do not think this is the case, as over 90% of these recurrences occur in the index quadrant. In this paper we describe a novel system for intra-operative radiotherapy using a mobile unit that should, in theory, be able to replace 6 weeks of external beam from a linear accelerator. The technique, TARGIT, is currently undergoing a multinational clinical trial in comparison with conventional external beam. If we can prove at least equivalence in outcome, then breast-conserving surgery might become available to all women in the developing world and to those living long distances from the nearest radiotherapy center.

Key words: early breast cancer; intra-operative radiotherapy; technology for developing world

Introduction

We would like to begin this paper with an anecdote. One of us (MB) frequently looks after patients with breast cancer from the UAE. They come to London for diagnostic work-up and surgery and return home for postoperative radiotherapy and adjuvant systemic therapy. One woman, who lives in Dubai, had to make the daily trek by car, one and a half hours

each way, to Al Ain for her radiotherapy. This involved 42 return journeys. On one occasion her driver fell asleep and they were involved in a serious crash. The injuries she received have to be considered as serious adverse events related to postoperative radiotherapy.

It is of course a pity that a wealthy city like Dubai with over 2 million inhabitants, does not support a radiotherapy unit, but this pattern is repeated every day around the world in equally wealthy countries with large rural areas and difficult access to the nearest major city. Furthermore, in the poorest countries in the world, women with early breast cancer cannot be offered breast-conserving surgery

Address for correspondence: Prof. Michael Baum, University College London, Portland Hospital, 212-214 Great Portland Street, London W1W 5QN, UK. michael@mbaum.freereserve.co.uk

because of inadequate provision of radiotherapy units. Assuming there never will be a golden age when all women in the world suffering with breast cancer have easy access to postoperative radiotherapy, we need some original thinking “outside the box” to offer a solution. If the woman cannot get to the radiotherapy unit, then the radiotherapy unit must come to the woman.

In this paper, we wish to describe the rationale and the technique that may answer the problem with a simple mobile radiotherapy unit that can provide a one-shot intra-operative treatment targeting the area around the primary tumor, that in theory might be equivalent or even better than 5–7 weeks of conventional external beam treatment.

Rationale—Logical

The rationale for targeting the area around the primary tumor comes from clinical correlation of whole organ analysis of mastectomy specimens. It has been well demonstrated that the female breast frequently harbors more than one tumor and these are found if one looks hard enough. This has been demonstrated in autopsy studies (e.g., undiagnosed cancer present in 20% of women with a median age of 39¹) as well as in mastectomy specimens.² However, this widespread three-dimensional distribution does not correspond to the location of recurrences after breast-conserving surgery,^{3,4} which occurs most commonly (in about 90% of cases) in the area around the scar of primary excision (that is, in the index quadrant). Hence it follows that radiotherapy after surgical excision should be targeted to the area around the primary tumor—the tumor bed.

Rationale—Biological

The conventional standard radiotherapy is very successful and reduces the rate of local recurrence by two-thirds, but conversely, it fails

in one-third of cases. This could be because of intrinsic resistance or due to the radiotherapy dose “geographically” missing the target tissues and “temporally” missing the window of optimal opportunity. It is interesting that the proportional reduction of the risk does not change with increasing size of excision. Hence just excising the cancer with a larger margin will not eliminate the risk. This raises the question as to whether the trauma of surgery itself may contribute to the risk. The wound fluid after surgery is found to stimulate cancer cell growth, motility, and invasiveness, and we have found that targeted intra-operative radiotherapy impairs the stimulatory effect of surgery.⁵ As it is delivered immediately after surgery, targeted intra-operative radiotherapy may avoid both the geographical and temporal missing of the target.

Rationale—Mathematical Model

We have devised a mathematical model^{6,7} that simulates breast cancer growth, recurrence, and response to radiotherapy. In this model we have introduced the cells that have suffered a loss of heterozygosity in the tumor suppression genes. These cells would have been derived from the same ductal tree and would surround the area of the primary tumor. They would be morphologically normal and would withstand the usual fractionated (low) doses of radiotherapy, but would not be able to tolerate the high dose delivered in the single shot of intra-operative radiotherapy. Our model predicts that the single well-directed dose may be superior to conventional radiotherapy.

The New Approach

In 1998 we pioneered the approach of *targeted* intra-operative radiotherapy (TARGIT).^{8–10} With our technique, using the IntrabeamTM system (Carl Zeiss Meditec, Jena, Germany), a single fraction of 20 Gy is

delivered to the surface of the tumor bed using a spherical applicator, from within the breast. The surgeon “wraps” (or conforms) the pliable tumor bed around the applicator (something we discovered while testing out our initial applicator designs), ensuring close apposition of the target tissue to the radiotherapy source. The technique¹¹ needs to be meticulous but is relatively straightforward, and over 1000 patients have been treated worldwide.

Although the approach of concentrating on the tumor bed is not new, modern technology has allowed it to be used with relative ease in a routine operating theater and with a potential for significant economic savings. The latest analysis of our large phase II study using Intrabeam in place of a conventional boost, has given us the courage of our convictions to go ahead and test the approach in a large multicenter randomized clinical trial.¹¹ Several other investigators have also started testing the same approach: the ELIOT trial in Milan, the NSABP-B32 trial in the United States, and the GEC-ESTRO, RAPID, and IMPORT trials in Europe and the United Kingdom.

The Randomized Trials

After successful completion of a pilot study,⁹ we launched the TARGIT (Alone) trial in March 2000. In this trial, we are selecting women who are older than 45 years and who do not face a high risk of developing recurrent or multiple cancers in the breast. In fact, these women form the majority of breast cancer patients. The randomly allocated treatment that follows wide excision of the cancer (lumpectomy) is either targeted intra-operative radiotherapy or the usual 4- to-7-week course of external beam radiotherapy. The initial slow uptake of the trial has now accelerated as confidence with this approach has grown, and currently 21 centers on three continents contribute to a steep recruitment curve. The aim of the trial is modest—to investigate if the two treat-

ments are equivalent. But if proven, the prize is great—women could then avoid the 30–40 visits to the radiotherapy center and still conserve their breast. If it turns out to be superior then that will be an added bonus.

For women outside the criteria for entry to the trial who may need “prophylactic” radiotherapy to the whole breast in addition, the intra-operative dose to the tumor bed could be the better way of giving the usual tumor bed boost for the reasons already stated. In our series of 302 cancers, we found a very low recurrence rate,¹² and this has prompted us to launch a second trial, TARGIT-B, to assess if it yields superior results to an external beam boost. The prize if this trial is successful would be a significant reduction in local recurrence, which may translate into a definite, albeit small, survival benefit.

Conflicts of Interest

Michael Baum declares a consultancy arrangement with Karl Zeiss that pays 1,000 euros a month. Jayant S. Vaidya’s salary was partly funded by a research grant from Photoelectron Corporation (PeC), the initial manufacturer of Intrabeam from October 1996 to September 1999.

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