Single-dose intra-operative breast cancer radiotherapy (TARGIT-IORT) – innovative, effective, far less trouble to the patient

RAD Magazine, 47, 552, 27-28

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The September 2020 issue of *RAD Magazine* and the front page of *The Times* on August 20, 2020, both featured the excellent long term results of the TARGIT-A trial of intra-operative radiotherapy (TARGIT-IORT) for early breast cancer that were published in *The BMJ*[1] (https://www.bmj.com/content/370/bmj.m2836.full.pdf). These results had widespread international media coverage – very unusual in trials of radiotherapy.

The study concept was straightforward: since almost all local recurrences of early breast cancer occur at the initial site – the index quadrant – rather than other parts of the same breast, might it be sufficient to target radiotherapy only at the initial site and deliver it immediately after lumpectomy, under the same anaesthetic? The great advantage, of course, would be the avoidance of unnecessary treatment to the rest of the breast. It would also avoid scattered irradiation to other organs such as the lung and heart.

Working with colleagues in the USA and Germany, we developed the Zeiss Intrabeam system, a type of miniature linear accelerator producing 50kV x-rays. This low energy radiation is delivered from the centre of various sized spherical applicators that can be introduced into the surgical cavity immediately after the cancer has been excised (**figure 1A**). The idea is that the device is placed into the tumour bed and left for 20 to 40 minutes depending on the size of the applicator. Various sizes (1.5-5cm diameter) can be used depending of course on the specific requirement in each individual patient. The length of exposure is set to provide a very high dose at the surface of the applicator (20Gy, which gives a depth-dose of 6Gy at 1cm beyond the surgical cavity). We gave the procedure a name: TARGIT, for TARGeted Intraoperative radioTherapy, which is now more commonly called TARGIT-IORT (www.targit.org.uk) to differentiate it from other forms of IORT.

Because of efficient exponential decay, substantially enhanced by absorption by the tissues, the dose to other organs especially heart and lung is virtually zero. As the linear energy transfer of kV photons is considerably higher than for megavoltage, the biologically effective dose from this single treatment has been shown to be greater than it might seem at first sight.

We started with a pilot study in 1998 and from 2000 onwards we designed a pragmatic multicentre international randomised trial – the TARGIT-A trial – using this approach as the 'experimental arm', with conventional external beam whole breast radiotherapy (EBRT), normally given daily for three to six weeks, as the 'control arm'. We were fortunate in working with a large collaborative network of centres of excellence and patient representatives were on the steering group from very early on. The TARGIT-A trial was academically driven and mainly funded by a large grant from the HTA programme of NIHR and other international bodies.

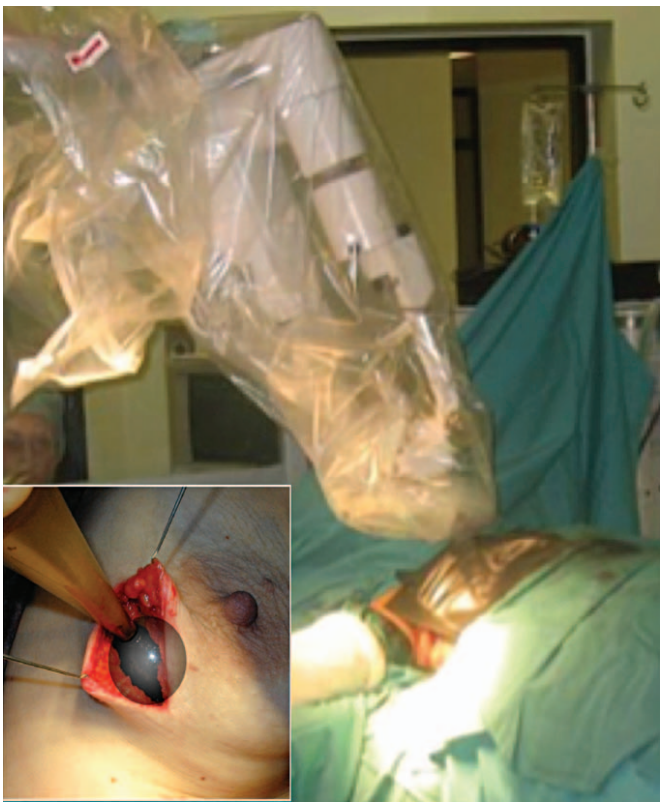

Figure 1
(A) Position of the TARGIT-IORT applicator in the breast tumour bed and a view of the operation theatre. (B) The front page masthead of *The Lancet* 2010 publication.

The cohort group we studied was as follows: eligible patients were aged 45 years and older and had to be suitable for breast conservation, with a unifocal invasive ductal carcinoma on conventional imaging preferably up to 3.5cm in diameter. MRI was not necessary and was indeed performed in less than 6% of cases. There were no other absolute stipulations. This means that several patients had tumour prognostic factors putting them at medium or even high risk of local recurrence. More than three-quarters of patients had high risk factors that would make them

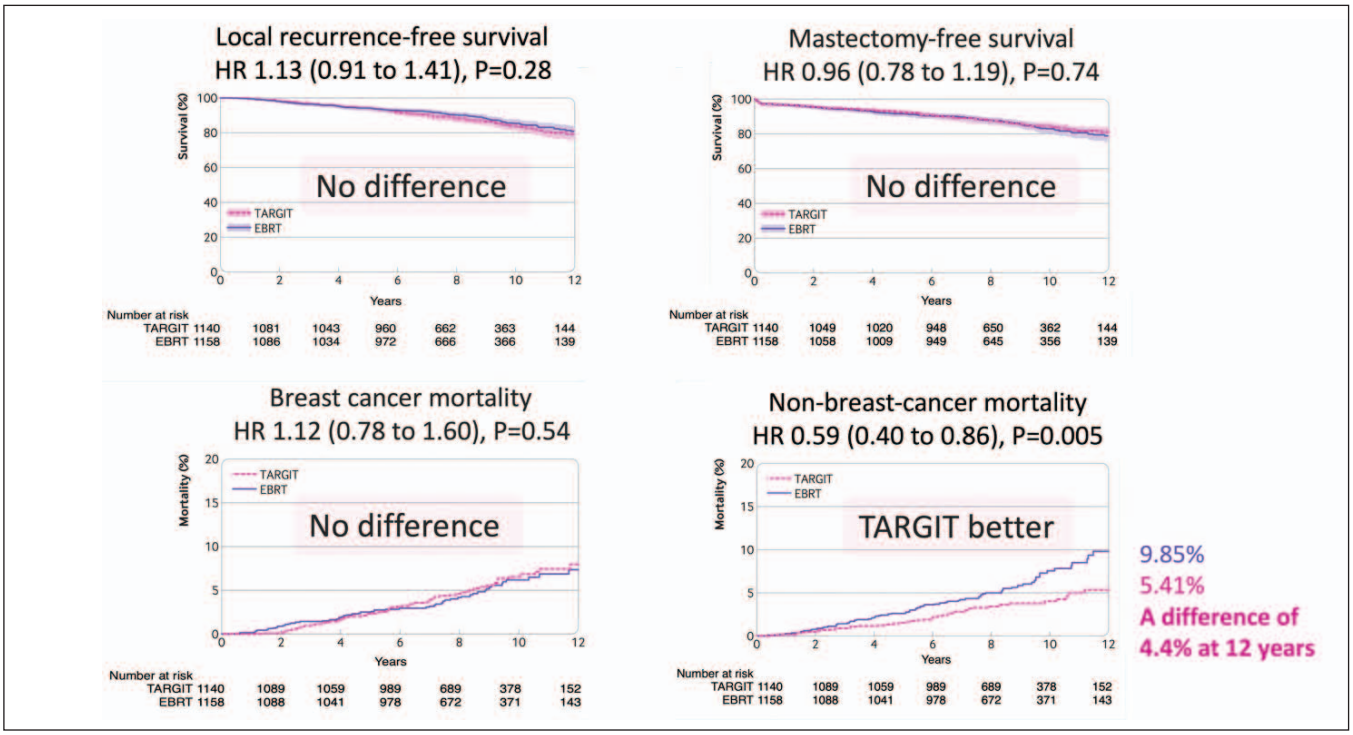

Figure 2
Long term outcomes of the TARGIT-A trial (from *The BMJ* 2020;370:m2836. https://www.bmj.com/content/370/bmj.m2836.full.pdf).

ineligible for participation in 'low risk' population trials such as PRIME-II and other partial breast irradiation trials using EBRT or brachytherapy.[2,3]

As part of the design of the study and as a precautionary measure, we recognised that there might occasionally be some histological surprises after the full pathology review. So we stated in the protocol that if invasive lobular cancer or positive margins were found, collaborating centres were recommended to offer additional whole breast radiotherapy to the experimental arm, given in the conventional way, where the local multidisciplinary team felt it to be appropriate. We expected this to happen in 15-20% of cases, in which case the intra-operative radiotherapy already given at the time of surgery would act as the local boost to the tumour bed. It is really important to note that this was neither a 'crossover' nor a 'protocol violation' since this EBRT addition was part of the 'risk-adapted' experimental treatment. We felt it was both sensible and ethically sound, and it was formally approved as part of the trial protocol.

We mention this in detail here, because misunderstandings have sometimes arisen. It was a legitimate part of the study design. The randomised trial therefore compared risk-adapted single-dose TARGIT-IORT (20% of whom received additional EBRT) versus conventional whole breast radiotherapy-for-all. So in the experimental arm, 80% of patients simply did not need to attend further for treatment. For them, the large majority, all the treatment – at least as far as the surgery and radiotherapy were concerned – had been achieved at that one single session, under anaesthetic. Done and dusted.

Early on, the TARGIT-IORT approach stimulated a good deal of media interest: *TIME*, *Reader's Digest* and BBC's Tomorrow's World. Patients started seeking this new treatment. We were very firm that the the only way they could have the TARGIT-IORT 'one-shot' treatment was if they participated in the TARGIT-A trial. From a single centre in the UK (University College London and associated hospitals), the number of centres in Europe, USA and Australia grew quite rapidly. The recruitment target number was reached in 2012; a total of 2,298 patients enrolled from 32 centres in 10 countries. The first results were published by *The Lancet* in 2010 (**figure 1b**). The first survival results were published in 2013 and by 2018 NICE recommended TARGIT-IORT in centres that already have the equipment, while awaiting long term results. Other countries were more forthcoming. By 2019, TARGIT-IORT was included in national and international guidelines of many countries in Europe, the USA, the Far East and Australia (www.targit.org.uk/targit-iort-in-guidelines), and 260 centres in 38 countries worldwide have treated more than 45,000 patients (www.targit.org.uk/travel). Scientific papers can be accessed at www.targit.org.uk/publications.

As the long term outcomes are even more important for breast cancer, we set the bar for completeness of follow-up very high. By the time of the latest analysis published in 2020, we had achieved a very high level of completeness of follow-up (95%).

What were the long term results of this large international randomised controlled trial – the highest level of evidence one can get? In a nutshell, there was simply no difference in the breast cancer-related outcomes of the two arms of the study, none at all. Local recurrence-free survival, mastectomy-free survival, distant disease-free survival, breast cancer specific survival – all the same (**figure 2**).

Radiotherapy and surgery both completed in one sitting. In these days of the COVID-19 pandemic, this an extremely attractive solution to a common and labour-intensive radiotherapy problem. Bearing this in mind, the additional feature to remember here is that for a typical radiotherapy department, about 30% of the workload is made up of treatment of this single diagnosis. The resources freed up could be used in so many ways, including a substantial reduction in waiting times.

As a patient, what would you prefer? The approach outlined above, which gives you an eight out of 10 chance of not needing EBRT at all after your breast-conserving surgical excision, or the traditional approach? This would involve, at the very least, using the recently introduced whole breast FAST-Forward regimen (itself a highly compressed type of EBRT), which requires a minimum of five treatment visits to the radiotherapy department (10 to 15 in a quarter of cases in whom a tumour bed boost is given), preceded by a radiotherapy planning session. All this takes

Figure 3
Screenshot of the map of the world with each dot representing a centre that has treated breast cancer with TARGIT-IORT. The name of the centre and number of cases treated by the centre (if available) is seen in the left-hand pane when you click on the centre. This map is interactive and available at www.targit.org.uk/travel.

time to organise, and most departments would insist on a two or three-week period of post-surgical recovery even before planning the patient, to ensure that everything had settled down, that the patient's chest contour was stable, and that the ipsilateral arm was not tethered or restricted in raising or abduction. Perhaps a total of two months at best between surgery and completion of the radiotherapy and, sadly, often longer. And the result of such an intensive whole breast regimen even at a short follow-up shows a higher incidence (25%) of patients reporting a 'hardened/firm' breast. By contrast, we know that patients treated by TARGIT have less in the way of long term side effects, with a better cosmetic outcome and a higher level of patient satisfaction as well – all well documented and published.[4-7]

There is another major point not yet mentioned. We found that the risk of death from other (ie non-breast cancer) causes is substantially lower with TARGIT-IORT than with conventional EBRT. Many still find this a surprising result even though excess cardiovascular and other cancer mortality among patients receiving EBRT has been recognised since the 1980s. The effect was first seen in the analysis published in 2013. The long term data have strengthened the results: by 12 years the reduction in non-breast cancer mortality is 4.4% (from 9.85% with whole breast radiotherapy to 5.41% with TARGIT-IORT). If this level of reduction had been observed in a chemotherapy drug trial, one might imagine it would have been rapidly adopted.

We feel that TARGIT-IORT offers the benefits of other partial breast irradiation (PBI) approaches plus several more, notably the total integration of surgery and radiotherapy, with completion of all the local (ie non-systemic) treatment all at once, in eight out of every 10 patients.[3] It gives the lowest possible scattered radiation to organs at risk (OAR). One interesting result from the much awaited PRIME-II trial is that the local recurrence rate without radiotherapy is as high as 9.8% at 10 years (compared with 0.9% with radiotherapy), even in an ultra low risk group (65 years and older, less than 3cm, mostly grade 1 and 2, all node negative and ER positive) (Kunkler et al, SABCS 2020 www.abstractsonline.com/pp8/#!/9223/presentation/579). By contrast, the TARGIT-A eligibility was much broader and applicable to most standard risk patients in our breast clinics, such that over three-quarters of these patients would not even have been eligible for participation in PRIME-II. Of the TARGIT-A patients, 64% were ≤65 years, 22% had node-positive disease and 20% had grade 3 tumours, making them ineligible for PRIME-II. Despite this, there was no difference found in the long term local control between TARGIT-IORT and EBRT.

The new approach with 'single pit-stop' intra-operative radiotherapy is certainly an example of 'disruptive technology'. The plain fact is that by removing much of the breast cancer treatment, a significant reduction of the workload of a typical radiotherapy department would eventually be bound to alter the work pattern and therefore income generation in a major way. Equipment would of course be freed up for other uses, and this should be recognised as a benefit. There is already a recommendation by NICE (January 2018) that this treatment should be offered to patients in departments that have the equipment and expertise. The recently published long term data robustly confirmed and even amplified the initial results, as we point out above in more detail.

Elsewhere in the world (**figure 3**), the treatment has been enthusiastically received, and more than 45,000 patients have now been treated in 260 centres in this way.[8] To satisfy 'valid consent', doctors in the UK are now obliged to follow the new GMC guidelines underlining the essential nature of adequate patient information (https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent). In the UK this powerful principle is now fully enshrined in law (Montgomery v Lanarkshire Health Board, 2015). Too often in this country we have shown ourselves as pretty good at creativity but far less fleet-footed when it comes to implementation.

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