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The TARGIT-A Randomized Trial: TARGIT-IORT Versus Whole Breast Radiation Therapy: Long- Term Local Control and Survival

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The TARGIT-A trial demonstrated that targeted intraoperative radiotherapy (TARGIT-IORT) during lumpectomy as a risk-adapted approach achieves breast cancer outcomes (local control, breast preservation, freedom from distant disease and breast cancer mortality) comparable with whole breast external beam radiotherapy (EBRT), in both the short-term, and the long-term[1-3], and provides survival benefits. Randomisation at such a large scale has ensured that risk factors for death and breast cancer outcomes were equally distributed between the two arms of the trial, so that the differences or equality observed for *both* these outcomes must be attributed to the differences or equality in the effects of the treatment.

We are pleased that Ward_et_al see the potential for normalisation of lifespan after treatment of local recurrence, but they should recognise that this is of course true only when local recurrence occurs after TARGIT-IORT. The hazard of death after local recurrence after TARGIT-IORT (9%), was much the same as without a local recurrence[2], but for local recurrence after EBRT, the hazard of death was nearly 5 times higher (43%)[2]. This difference in outcome will not be captured in the one-way competing-risk graph that Ward_et_al propose. This approach only accounts for deaths *before* local recurrence, and gives local recurrence an equal weighting in each arm. In reality, death is a more substantial competing risk for local recurrence in the EBRT arm, and local recurrence is a risk factor for death *only in the EBRT arm*. This complex interaction can be realistically captured by the chance of being alive without local recurrence (local control) – showing what patients actually experience. We are pleased that others have now started providing their trial results in this manner, without censoring the dead[4]. The bottom line is that both TARGIT-IORT and EBRT have the same rate of long-term local control of breast cancer.

Their claim of additional treatments is untrue. In fact, over the whole 19-year maximum follow up, a comparable number of patients underwent mastectomy in the TARGIT-IORT and EBRT arms: (66/1140 (5.8%) vs 53/1158 (4.6%), p=0.19). The breast preservation rate (mastectomy-free survival) was identical - HR 0.96 (95%CI 0.78 to 1.19), P=0.74)[1-3].

Importantly, the randomised evidence shows that TARGIT-IORT confers an overall survival benefit (HR of 0.72, 95%CI 0.53 to 0.98, p=0.036) in the large number (n=1797) of grade 1 and 2 cancers[2], which taken together form over three-quarters of all the cases in our study. Not only is this an accurate reflection of case distribution in the US and Europe, but in this group, the degree of survival benefit of TARGIT-IORT is similar in magnitude to a year's course of trastuzumab (HR 0.69 and absolute benefit of 3.8% at 8 years with trastuzumab[5 6] vs HR 0.72 and 4.4% absolute benefit at 12 years with TARGIT-IORT[2]). For grade 3 cancers, the survival was identical (HR 1.09, 95%CI 0.69 – 1.71, p=0.71)[2].

Contrary to their key accusation, we have not altered the endpoint of the trial; rather it is they who have altered the endpoint by their statistical smoke and mirrors. The pre-specified endpoint was *non-inferiority of local recurrence* of TARGIT-IORT to EBRT, calculated at 5-years[1]. This is quite different from a *superiority analysis*. With complete follow-up, the published paper shows that original endpoint was indeed reached, and that TARGIT-IORT was demonstrated to be non-inferior to EBRT in terms of local recurrence[1-3]. Moreover, in the longer term, key additional endpoints such as overall survival and quality of life, both so critically important for patients, will help them towards a far more realistically informed decision. These long-term outcomes were specified in the statistical analysis plan that was signed off by the independent trial steering committee and independent senior statisticians, *before* the data were unblinded and describe what actually happens to patients during a maximum 19-year follow up[1-3].

Ward_et_al's hypothetical estimates are based on incorrect and misleading assumptions. First, that no one dies during follow up; secondly, that no one dies after local recurrence; and thirdly, that patients who die have the same chance of local recurrence as those who are still alive. Now they use rhetorical devices, keep restating their erroneous estimates, and accuse us in Latin of being silent, even though we have systematically disproven their estimates, and given detailed descriptions of all the real data[7].

TARGIT-IORT has many clear benefits in terms of survival, quality of life, as well as its environmental and social advantages[1-3]. Patient preference studies have found that patients overwhelmingly prefer TARGIT-IORT[8 9]. Moreover, regardless of the doctor's or any professional body's preference, the offering all options to patients is now a mandatory requirement for doctors in the UK, both professionally https://www.gmc-uk.org/-/media/documents/updated-decision-making-and-consent-guidance_pdf-84160128.pdf and legally https://www.bmj.com/content/357/bmj.j2224.

TARGIT-IORT is sometimes perceived as disruptive to concepts, pathways and reimbursement systems of traditional radiotherapy (see figure 1). The distinguished chief editor of this very journal, who served for 10 years from 2012, and has also been President and Chair of ASTRO, previously shrewdly observed that[10] "…..fractionated radiation therapy for breast cancer ..comprises a substantial proportion of the practice of the average contemporary radiation oncologist. Depending on

your perspective, intraoperative radiation therapy is thus either a very serious threat or a quantum leap forward".

However, this perceived threat could be turned into a win-win scenario: One team in Bangalore, India has successfully used TARGIT-IORT within a model of equal payment to the whole team irrespective of the choice of radiotherapy (see https://on.soundcloud.com/KfmzP , specifically at 32:00 min: https://on.soundcloud.com/uuUZs). ASTRO have now announced their intention to introduce value-based payments[11], so we can reasonably expect that they will now promote using risk-adapted TARGIT-IORT during lumpectomy for breast cancer, which provides the greatest value-for-money in improving the lives of patients with breast cancer[12].

TARGIT-A research has been called one of the five major breakthroughs by the National Institute of Health Research alongside the Oxford COVID vaccine work (https://bepartofresearch.nihr.ac.uk/Articles/Health-research-breakthroughs/). The randomised data from the TARGIT-A trial have led to global adoption, and TARGIT-IORT is included in many international guidelines (https://targit.org.uk/targit-iort-in-guidelines). By early 2020, 45,000 patients have been treated in 260 centres (including >80 in the USA) in 36 countries, with an estimated 20 million miles of patient travel saved, together with a dramatic reduction of the carbon footprint of repeated radiotherapy attendances, plus of course, 2000 deaths prevented[13].

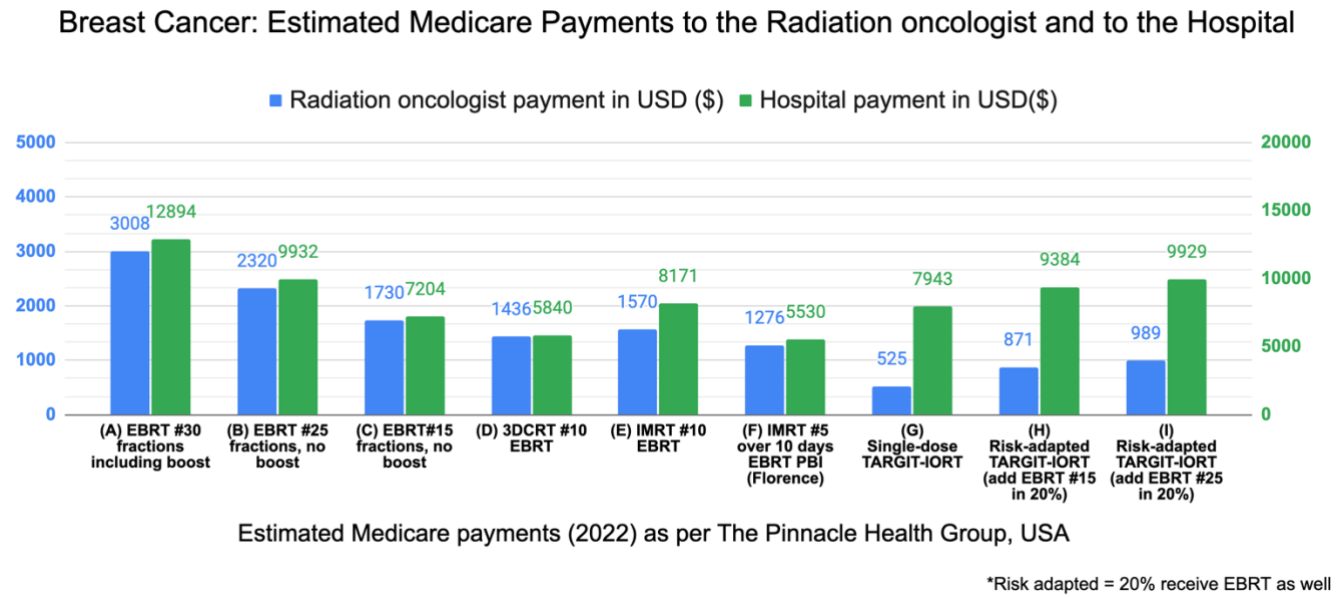

Figure 1: Current payments for various radiotherapy regimens (A to I). The payments to the radiation oncologist are separate and in addition to the payments to the hospital. The surgeon's fees for lumpectomy are $650 (for all types of radiotherapy) and an additional $169 for delivering TARGIT-IORT. In the real world, the option (G) will normally be followed by additional EBRT in 20% of cases, making the options (H) or (I) as the real-world scenarios.

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