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Dear Sir,

The authors of the Budapest randomised trial[1] of partial breast irradiation (PBI) recruited a very low-risk patients (T1N0, Grade 1 or 2). Their small sample size (n=258) was a little more than 1/10th of the TARGIT-A randomised trial (n=2298) published in the BMJ[2]. Yet they fail to mention it. TARGIT-A compared risk-adapted single-dose targeted intraoperative radiotherapy (TARGIT-IORT) *during lumpectomy* vs whole breast radiotherapy (EBRT). TARGIT-IORT achieved comparable long-term outcomes to EBRT for local control, distant control, breast preservation and breast-cancer mortality, along with a significant and substantial reduction in non-breast-cancer mortality by 4.4% by 12 years (5.41% vs 9.85%,p=0.005). With this magnitude of survival benefit, a new cytotoxic agent would achieve high-profile rapid adoption!

They also fail to correctly cite the trial of delayed IORT (n=1153) reported in JAMAOncology[3 4]. Instead, they selectively refer to the hypothetical and erroneous statistics from a correspondence letter, without noting our robust rebuttal[3 4] - their fundamental error was not recognising that TARGIT-A was a non-inferiority trial. The median follow-up was 9 years (they wrongly state 5 years, and give an incorrect p-value in Table 4). They overlook that the 10-year local recurrence-free survival was not statistically different (80.16% vs 84.36%,p=0.052), and mastectomy-free survival was virtually identical (83.79% vs 83.82%,p=0.38). We repeatedly stress our strong preference for TARGIT-IORT *during* the initial lumpectomy[2-4].

Then they fall prey to the temptation of comparing TARGIT-A with the PRIME-II trial of 'no-radiotherapy' vs EBRT. Unlike the wide eligibility for TARGIT-A (≥ 45 years, ≤3.5cm invasive ductal carcinoma), PRIME-II recruited only ultra-low risk patients ≥ 65 years. In fact, three-quarters of the TARGIT-A patients[2] *would not have been eligible for the PRIME-II trial* because they were either too young or had node positive (22%), grade 3 (20%) or ER/PR negative (19%) disease! Yet, even in this ultra-low risk PRIME-II trial, the reduction in local control in the absence of radiotherapy was dramatic, with a local recurrence of 9.8% vs 0.9% at 10 years(SABCS 2020 https://www.abstractsonline.com/pp8/#!/9223/presentation/579). PRIME-II found no hint of a reduction in mortality- the benefit of avoiding radiation was perhaps nullified by the harm from the large increase in local relapse. On the other hand, when TARGIT-IORT is given during lumpectomy (higher-risk patients, much larger trial), there is no reduction in the patient's chance of being free of local recurrence, preserving the breast, or

survival from breast cancer, AND there is a substantial reduction in deaths from cardiovascular causes and other cancers.

PBI whether with brachytherapy wires/balloon or external beam, is very cumbersome to patients, requiring several hospital visits or even an in-patient stay[5]. These approaches inevitably deliver significant scattered irradiation to the nearby organs at risk (OARs) such as the heart and the lung[5]. TARGIT-IORT involves much less travel, delivers the least dose to OARs, has reduced toxicity, less pain and improves quality of life and cosmetic outcome[2 6 7]. To quote many patients, single-dose TARGIT-IORT delivered during surgery is a "no-brainer".

The elephant in the room is something we have naively touted as an advantage: TARGIT-IORT is a high-value treatment, saving substantial sums (e.g. $1.5 billion over 5 years in the US[8 9]) to the healthcare system. However, from the perspective of the healthcare provider, these savings result in a substantially lower income-stream for the department or the individual, compared with any other method of radiotherapy. These considerations may reverse with the introduction of a value-based system for remuneration.

As an editorial in this journal pointed out[10], "Many careers have been built around fractionated radiation therapy for breast cancer, and it 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.".

260 centres in 38 countries worldwide have already treated 45,000 patients with TARGIT-IORT, which is now included in several national and international guidelines (https://targit.org.uk/targit-iort-in-guidelines).

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