Accelerated partial breast irradiation: the new standard?

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In today's Lancet, Professor Strnad and colleagues present 5-year results of a large, international randomised trial testing standard whole breast radiotherapy (WBI) against accelerated partial breast irradiation (APBI) after breast conserving surgery, in a selected lower risk population of women. The APBI technique involved a 4-5-day postoperative course of radiotherapy delivered via radioactive sources inserted into breast tissue surrounding the operation site, the so-called tumour bed. The study design tested for non-inferiority with a primary endpoint of local recurrence in 1184 patients recruited from 16 centres and the 5-year local recurrence rates were <2% in both arms. A predefined 3% non-inferiority margin was upheld by a difference in local relapse rates of 0.53% (95% CI: -0.72 – 1.75%) in favour of WBI. There were no statistical differences in disease-free or overall survival, and adverse effects were similarly mild in both groups.

So what is the background to APBI? Firstly, it is not a new concept. The first randomised trials comparing APBI with WBI began in the 1980's with the observation that the majority of breast cancers recur close to the original tumour bed. Therefore, it was hypothesised that treating this region alone may reduce side effects with no detriment in local control. An added bonus could be less treatments and a shorter overall treatment time. Unfortunately, these early pioneering trials showed an unacceptable increase in local recurrence rates, probably due to inadequate patient selection and less sophisticated radiotherapy techniques.

A resurgence of enthusiasm for APBI returned around a decade ago, coinciding with rapid improvements in radiotherapy techniques, and a flurry of new randomised trials were launched. The APBI techniques were heterogeneous, including some that placed radioactive sources into the tumour bed itself and others that used external radiation delivered via a linear accelerator. In addition, there was considerable variation in both the volume of breast tissue treated and the dose delivered. A recent systematic overview of APBI, albeit with inclusion of the older studies, demonstrated excess local recurrence compared with WBI[1]. The Forest plot of hazard ratios (HR) for local recurrence from this publication are displayed in figure 1, demonstrating HRs as high as 7.

So how does the trial from Strad and colleagues compare with others? It is a welcome relief to comment on a carefully designed and conducted trial, presented and discussed in a measured fashion. Primary analysis at a median follow up of 6.6 years using Kaplan-Meier statistics has been carried out "as treated", which is appropriate for a non-inferiority trial[2]. The 3% non-relevant, non-

inferiority threshold settled upon by the investigators looks large in the light of dramatic falls in local recurrence rates since study inception, but the current absolute difference is acceptable by any standards. The research team also acknowledge the importance of continuing follow up for at least 10 years and this is essential given the linear rate of recurrence for lower risk patients and the on-going effect of radiotherapy after 5 years of the treatment.

The authors suggest that their technique is superior to APBI delivered with a linear accelerator by highlighting the 3-year results of the RAPID study, which showed high rates of adverse cosmesis[3]. This is very likely to be due to the radiation dose schedule, as the "equivalent" dose in standard 2Gy daily treatments is far higher than that used routinely for WBI[4]. In contrast, the UK IMPORT LOW APBI trial uses a standard radiation dose across all arms and the 5-year results will be reported in 2016[5].

So does this trial herald the death knell for WBI with APBI becoming the new standard? We think not. This trial presents maturing data and further evidence is required from the 14,000 patients in 5 unreported APBI phase III trials. Furthermore, possible attractions of APBI such as short overall treatment time and decreased heart dose are now reflected with modern WBI. The 10-year results of UK and Canadian trials comparing 5 versus 3 weeks of WBI show that local control is equivalent, but side effects are reduced with the 3-week treatment[6,7]. The UK Fast Forward study is going further and investigating just 5 treatments for WBI over one week[8]. In addition, recent advantages in cardiac-sparing WBI techniques have reduced the heart dose dramatically[9].

So how does this trial fit with the future for breast radiotherapy? We know that breast cancer represents a spectrum of different diseases with variation in prognosis and radiotherapy is no longer "one size fits all", but ranges from highly complex treatments to the breast and regional lymph nodes, to complete avoidance of any radiation. It is likely that APBI will have a place within this array of treatments. The challenge will be to select the most appropriate treatment for the individual patient and personalise radiotherapy based on tumour biology[10].

References

1. Marta GN, Macedo CR, Carvalho Hde A, Hanna SA, da Silva JL, Riera R. Accelerated partial irradiation for breast cancer: systematic review and meta-analysis of 8653 women in eight randomized trials. Radiother Oncol. 2015 Jan;114(1):42-9.
2. Haviland JS, Bliss JM, Bentzen SM, Cuzick J. In Regard to Vaidya et al. Int J Radiat Oncol Biol Phys. 2015 Aug 1;92(5):954-5.
3. Olivotto IA, Whelan TJ, Parpia S, Kim DH, Berrang T, Truong PT, Kong I, Cochrane B, Nichol A, Roy I, Germain I, Akra M, Reed M, Fyles A, Trotter T, Perera F, Beckham W, Levine MN, Julian JA. Interim cosmetic and toxicity results from RAPID: a randomized trial of accelerated partial breast irradiation using three-dimensional conformal external beam radiation therapy. J Clin Oncol. 2013 Nov 10;31(32):4038-45.
4. Yarnold J, Bentzen SM, Coles C, Haviland J. Hypofractionated whole-breast radiotherapy for women with early breast cancer: myths and realities. Int J Radiat Oncol Biol Phys. 2011 Jan 1;79(1):1-9.
5. Coles C, Yarnold J; IMPORT Trials Management Group. The IMPORT trials are launched (September 2006). Clin Oncol (R Coll Radiol). 2006 Oct;18(8):587-90.
6. Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR; START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol. 2013 Oct;14(11):1086-94.
7. Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C. Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med. 2010 Feb 11;362(6):513-20.
8. Coles CE, Brunt AM, Wheatley D, Mukesh MB, Yarnold JR. Breast radiotherapy: less is more? Clin Oncol (R Coll Radiol). 2013 Feb;25(2):127-34.
9. Taylor CW, Kirby AM. Cardiac Side-effects From Breast Cancer Radiotherapy. Clin Oncol (R Coll Radiol). 2015 Jun 28. pii: S0936-6555(15)00241-1. doi: 10.1016/j.clon.2015.06.007. [Epub ahead of print]
10. Personalized Radiation Oncology for Breast Cancer: The New Frontier. J Clin Oncol. 2015 Jun 20;33(18):1998-2000. Bellon JR.

Conflict of Interest: None

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