The Royal Australian and New Zealand College of Radiologists®

The Faculty of Radiation Oncology

Faculty of Radiation Oncology Comments on pre PASC Applicant Proposed Protocol 1189 – Targeted Intraoperative Radiotherapy for Early Breast Cancer (INTRABEAM)

The Faculty's position on intraoperative radiotherapy for early breast cancer is contained within 2013 Radiation Oncology Horizon Scan. The faculty is aware there are emerging data for its use in breast cancer but the appropriateness of that uptake will depend on the results of ongoing studies. The data currently available for breast cancer are based on trials of patients with (usually) very favourable histology, where the natural history is long and can be lengthened by the use of adjuvant hormonal therapy. Therefore, it is the Faculty's view that minimum follow up data of 10 years is appropriate before reviewing the outcome data. Therefore, the Faculty does not currently support intraoperative radiation therapy (IORT) as established non-inferiority for treatment of early breast cancer outside of ongoing clinical trials.

This application concerns INTRABEAM, one of the devices available to deliver IORT for early breast cancer. The application is based on one randomised trial, the TARGIT-A[1] randomised trial, reported in November 2013. This trial appropriately compared whole-breast external beam radiation therapy with IORT using the INTRABEAM device with a risk adapted design. This is a form of partial breast radiation therapy with many studies ongoing to look at efficacy of partial breast techniques. The applicant Carl Zeiss did provide some support for the TARGIT-A trial although it is acknowledged they did not have any part in the concept, design, or management of the trial, or in data analysis, data interpretation, or writing of the report.

The faculty is of the view that longer follow-up and more supportive evidence is required, with a minimum of 10 year follow-up data suggested. In this recent publication 3451 patients had a median follow-up of 2 years and 5 months, 2020 of 4 years and 1222 of 5 years i.e. only 1/3 of patients have experienced 5 years of follow-up. The Cancer Australia follow-up guidelines for early breast cancer recommend annual follow-up after 5 years, given there are recurrences 5 years and more after treatment. The 5 year risks for local recurrence in the conserved breast for TARGIT alone versus EBRT were 3.3% (95% CI 2.1-5.1) versus 1.3% (0.7-2.5; p=0.042). There were two groups of patients treated with INTRABEAM, those treated concurrently with lumpectomy and those treated after pathology analysis with a delayed procedure by reopening of the lumpectomy cavity. Only in the group treated concurrently was non-inferiority of INTRABEAM over EBRT established. It is noted that supplemental external beam radiation therapy was required in 15.2% of patients who received the IORT – this will impact on the economic analysis.

The Faculty's concern about early adoption of a partial breast radiation therapy technique is based on:

1. At this time for the INTRABEAM device there is only one trial that supports its use and it has relatively short follow-up,
2. There is conflicting evidence for intraoperative radiation therapy with a trial[2] (ELIOT) of intraoperative radiation therapy using a different technique (ie electrons) showing significantly higher local recurrences with the partial breast radiation therapy and greater toxicity.
3. There is substantial (much older) data on partial breast external beam radiotherapy showing high relapse rates.

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We look forward to further assessment and opportunity to provide comment as the logistics and possibly cost benefit of approaches like these may ultimately benefit an important sub set of patients.

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[1] Vaidya JS, Wenz F, Bulsara M, et al; **TARGIT** trialists' group. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the **TARGIT**-A randomised trial. *Lancet*. 2014 Feb 15;383(9917):603-13.

[2]Veronesi U, Orecchia R, Luini A, et al. Full dose intraoperative radiotherapy with electrons (ELIOT) during breast conserving surgery: experience with 1246 cases. *Ecancermedicalscience* 2008; **2**: 65.