BREAST INTEREST GROUP OF SOUTHERN AFRICA

BIGOSA

BIGOSA Council Comment on IORT – July 2022

The BIGOSA Council has been asked to comment regarding the use of intraoperative radiotherapy (IORT) for the treatment of breast cancer patients. Important endpoints to consider are efficacy (in this instance the most important end point to consider is local recurrence), treatment safety, convenience, and financial implications of the treatments. Also, paramount to the discussion is international guidelines regarding breast cancer radiotherapy.

Most of the data on IORT are based on two randomised studies with updated results, the ELIOT trial using electron IORT which accrued patients from 2000 - 2007, and the TARGIT-A trial using an orthovoltage source which recruited from 2000 - 2012.

The views of the BIGOSA Council are as follows:

1) Regarding efficacy, in both studies, IORT has higher rates of local recurrence compared to external beam radiotherapy (EBRT).

In the ELIOT trial, 1305 patients were randomised to whole breast irradiation (WBI) or electron IORT, the recurrence rate for the IORT arm was 11% vs 2% for the WBI arm. In the lower-risk patients, the recurrence rate was 8.1% for IORT vs 3.1% for WBI.[1]

In the TARGIT-A trial, 3451 patients were randomised to orthovoltage IORT or WBI. Patients receiving IORT at the time of surgery were defined as the "prepathology" cohort while patients receiving IORT as a second procedure were defined as the "postpathology" cohort. A risk-adapted strategy was employed for the IORT group with 15% of the IORT group going on to receive WBI – 21.5% of the prepathology group and 3.6% of the postpathology group. The updated local recurrence rate at 5 years for the prepathology cohort was 2.11% for IORT vs 0.95% for WBI (but within the non-inferiority criteria of the study) and for the postpathology cohort was 5.3% for IORT vs 1.7% for WBI (exceeding the non-inferiority criteria).[2]

A recent review on breast cancer radiotherapy published in JCO Oncology Practice raised concerns regarding this trial's methodology, given that results for the entire IORT group were not presented. Furthermore, questions were raised regarding the lack of long-term outcome data (8 or 10 years), as well as the lack of local recurrence data for the prepathology IORT group based on those who had IORT alone and those who went on to receive WBI (21.5% of the cohort).[3]

In breast irradiation for early stage, low risk breast cancers, local recurrence is the most relevant endpoint to consider as these patients have good survival, hence it is unlikely for there to be a survival benefit. However, subjecting these patients to a possible mastectomy for salvage of a local recurrence which could have been avoided with EBRT as opposed to IORT, is unacceptable.

The local recurrence rates of the TARGIT study are comparable to the local recurrence rates in studies omitting radiotherapy entirely for similar low-risk patient populations. An example is the 4.1% local recurrence rate observed in the PRIME trial for select patients receiving no radiotherapy, vs 1.3% in those having radiotherapy.[4] This begs the question – is IORT even better than doing nothing for these low-risk patients?

2) Regarding treatment safety, in the ELIOT trial toxicity data was not collected and in the TARGIT-A trial wound complication rates were similar.[3] Regarding EBRT, with excellent 3D-conformal radiotherapy (3DCRT) as well as intensity modulated radiotherapy (IMRT) planning techniques, as well as with the increasing availability of respiratory-motion-management techniques, such as deep inspiration breath hold (DIBH) and active breathing control (ABC), at many radiotherapy units, it is possible to effectively reduce the radiation dose to the heart, lungs and other organs at risk, so the suggested benefit of IORT having considerably less potential side effects is negated.

3) Regarding convenience, IORT results in the delivery of 1 fraction (#) of radiotherapy at the time of surgery. This makes it an attractive alternative to EBRT, however, regarding EBRT for breast carcinoma, there has been a move toward hypofractionation, reducing the 5-7 weeks traditionally required for most patients. Hypofractionation is already a standard of care and the preferred treatment schedule for patients with early breast cancer requiring WBI, and there is also mounting evidence for safety of hypofractionation even in more advanced disease. Many patients should not require more than 15 fractions of radiotherapy, and this is possible using IMRT to give a simultaneous integrated boost (SIB) to the tumour bed, to reduce the overall number of treatments required, in the interests of patient convenience.

Furthermore, for many low-risk patients, a 5# schedule (as per the FAST trial[5] and FAST Forward trial[6]) is also a reasonable option, especially for older patients, so for these patients the comparison is between 1# IORT treatment vs. 5# EBRT.

4) Regarding financial implications, although 1# of IORT may seem more cost effective than 5 – 15# EBRT, funders should consider the overall costs of both treatments – including the additional theatre time (which is usually billed at hundreds of rands per minute) and additional anaesthetic time taken to deliver IORT – which usually adds 40 – 60 minutes to the theatre time. This is often overlooked by funders and patients, as this is funded out of a separate benefit (the hospital benefit rather than the oncology benefit), however, the overall costs to the funder should be considered. An accurate cost analysis should be undertaken by funders, considering all these factors, to ascertain the true costs involved for the various treatment options.

5) Regarding the option of using IORT as the boost to save the patient one additional week of EBRT (meaning the patient still receives WBI for 15# after IORT), there is no good data supporting this approach. Also, this would likely be the most expensive option of all, given that the patient would receive EBRT as well as IORT – again considering the 40 – 60 minutes of additional hospital theatre time and anaesthetic time. So, once again, if patient convenience is the aspect being considered, then the most convenient option is again delivery of the boost by use of a SIB given concurrently with the WBI – this way there are no additional trips required for the patient for the boost.

Finally, BIGOSA supports current international guidelines. The American Society of Breast Surgeons (ASBrS) consensus statement recommends that all IORT patients be treated within the setting of a clinical trial or registry.[7] The American Society of Radiation Oncologists (ASTRO) consensus statement recommends that “suitable” patients be counselled regarding the higher rate of local recurrence with IORT and the need for prospective monitoring.[8] The American Brachytherapy

Society provides a weak recommendation for use of this technique.[9] Of interest, IORT is not referenced as an option in the latest version of the NCCN guidelines.[10]

In summary, the BIGOSA Council recommends that IORT only be used in the setting of a clinical trial, and that potential patients should be informed about all the aspects related to IORT including that, as per available evidence, local recurrence rates are higher for IORT compared to EBRT. Funders should consider all aspects of costs related to the various treatment options.

References:

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