NATIONAL
BREAST CANCER CENTRE
Incorporating the Ovarian Cancer Program

JULY 2007 | Incorporates published evidence to July 2006

The use of intraoperative radiotherapy

FOR THE TREATMENT OF PATIENTS WITH EARLY BREAST CANCER

In 2006, the National Breast Cancer Centre (NBCC) commissioned a review about the use of intraoperative radiotherapy (IORT) for the treatment of patients with early breast cancer. This review was designed to update the report *A Systematic Review of Intraoperative Radiotherapy in Early Stage Breast Cancer* published in 2002[1] by ASERNIP-S (Australian Safety and Efficacy Register of New Interventional Procedures - Surgical).

A summary of the status of IORT in the treatment of breast cancer is provided below. This summary is based on outcomes from the 2002 ASERNIP-S review and the NBCC update and includes evidence to July 2006. New data are constantly emerging. The conclusions of this summary are likely to change in light of results from trials, which are yet to be published.

To access the full ASERNIP-S 2002 systematic review go to the Royal Australasian College of Surgeons website http://www.surgeons.org.

To obtain a full copy of the NBCC systematic review update please contact the NBCC on 1800 624 973.

BACKGROUND

Conventional treatment for early breast cancer involves breast conserving surgery or mastectomy, usually accompanied by sentinel node biopsy or axillary dissection. Radiotherapy is recommended for all women following breast conserving surgery and for women at high risk of relapse following mastectomy.[2] The aim of radiotherapy after breast cancer surgery is to destroy any breast cancer cells that may be left in the breast after breast conserving surgery or in any breast tissue left on the chest after mastectomy. The current standard treatment is at least 6 weeks of postoperative whole-breast external beam radiotherapy with or without an external 'boost' dose. External beam radiotherapy may also be used to treat lymph nodes in the armpit and/or lower neck. Systemic adjuvant therapy may also be used.

Common local side effects of external beam radiotherapy include redness and soreness of the skin around the treated area, which usually resolves within a week or two of completion of treatment. Patients may also experience feelings of tiredness during treatment and up to 4 weeks after treatment has ended. Later effects may include a tightening of the skin, and arm lymphoedema if the axilla is irradiated. Rare side effects may include cardiac damage, osteitis of the ribs, acute radiation pneumonitis, brachial plexopathy and development of a second malignancy.[2]

WHAT IS INTRAOPERATIVE RADIOTHERAPY?

Intraoperative radiotherapy (IORT) is radiotherapy that is administered at the same time as breast conserving surgery directly to the tumour bed. It involves the delivery of a uniform single dose of radiation at a predetermined depth in the operating theatre immediately following the removal of the breast cancer. IORT allows breast cancer surgery and radiotherapy to be given on a single day.

IORT is one of a number of approaches designed to deliver radiation to only a part of the breast tissue.

Other techniques include:

- accelerated partial breast irradiation (APBI) using a linear accelerator
- conformal radiotherapy techniques
- interstitial brachytherapy
- intracavity brachytherapy (Mammosite®).

Collectively these techniques are called partial breast irradiation. Trials to examine the efficacy and safety of these techniques are ongoing. This fact sheet describes the current status of IORT. NBCC will continue to monitor emerging evidence about this and other forms of partial breast irradiation on an ongoing basis.

CURRENT USE OF INTRAOPERATIVE RADIOTHERAPY IN AUSTRALIA

In Australia, IORT for the treatment of breast cancer is only available to patients participating in clinical trials. The most common application of IORT is as a boost therapy after breast conserving surgery. After surgery, IORT is applied at a dose ranging from 5 to 20 Gray (Gy). This is followed by a course of whole-breast external beam radiotherapy, and may be accompanied by systemic adjuvant therapies if appropriate.

Trials are also ongoing to assess the use of IORT as a single therapy without postoperative radiotherapy following breast conserving surgery or mastectomy. The optimal dose of IORT is still being investigated; studies have applied IORT doses ranging from 5 Gy to 22 Gy.

THEORETICAL BENEFITS OF IORT

The theoretical benefits of IORT when compared to postoperative radiotherapy include:

- IORT is applied directly to the tumour bed rather than relying on simulation techniques to estimate the area to be irradiated
- dose attenuation and the ability to physically move soft tissue around the applicators reduces irradiation of surrounding tissues and organs
- administration of a precise target volume in a single dose to the target area allows more targeted treatment
- there is virtually no delay between surgery and delivery of radiation therapy
- for patients who are unable or unwilling to have postoperative radiotherapy, IORT provides a way of delivering at least some radiotherapy.

RESULTS OF THE 2002 ASERNIP-S REVIEW

In 2002, ASERNIP-S published a systematic review about the safety and efficacy of IORT compared with postoperative radiotherapy.[1]

Eight studies were identified: two comparative studies (level II and level III evidence)[3,4] and six level IV case series.[5-11] Of the comparative studies, one was a randomised controlled trial[3] of 70 patients comparing IORT followed by whole-breast external beam radiotherapy with external boost radiotherapy and whole-breast external beam radiotherapy. The other was a concurrently controlled study[4] of 101 patients, comparing postoperative whole-breast external beam radiotherapy with an IORT dose. Due to the small sample sizes the two studies lacked statistical power to detect any significant treatment differences.

In terms of safety, the studies reported only minor postoperative complications experienced with IORT, with the majority resolved within a few months of treatment completion. Reported side effects experienced by patients treated with IORT included wound infections and delayed healing, although there was no significant difference when compared to patients receiving external beam radiotherapy. In terms of cosmetic outcomes, the majority of patients who received IORT rated their cosmetic result as either good or excellent; however statistical comparisons with patients who did not receive IORT were not conducted. In terms of efficacy the follow-up periods of 5 months[3] and up to 2 years[4] for the two comparative studies were insufficient for information on long-term side effects, local recurrence rates, disease-free survival, and overall survival to be ascertained.

Within the six case series, most of the postoperative complications were reported as minor, with the exception of one patient in one study[11] who developed a severe fibrosis after receiving a 10 Gy dose of IORT. It is not possible to evaluate and make comparisons of efficacy in these studies due to the small sample sizes and low level of evidence; however the short-term follow-up results reported were similar to those for external beam radiotherapy in terms of local recurrence, disease free-survival and overall survival.

The 2002 ASERNIP-S review concluded that more research is needed to investigate the safety and efficacy of IORT. Because of the limited evidence, comparisons between IORT and postoperative radiotherapy could not be made.

RESULTS OF THE NBCC REVIEW UPDATE

In 2006 the NBCC commissioned ASERNIP-S to update their review with evidence published after 2002. Only two level III comparative studies[12,13] with small sample sizes were identified: one study[12] involving 137 patients compared IORT boost therapy followed by whole-breast external beam radiotherapy with whole-breast external beam radiotherapy alone and the other study[13] involving 378 patients compared IORT boost therapy to an external boost.

The first study reported mild toxicity in all patients regardless of radiotherapy regimen. Cosmetic outcomes were evaluated by a single doctor 4–6 months after surgery. The majority of cosmetic outcomes for patients receiving IORT were evaluated as either good or excellent. However no statistical testing was performed to determine differences between the two groups. Extensive efficacy data were not reported.

The second study focused primarily on efficacy outcomes and did not report on safety or cosmetic outcomes. An earlier paper published after a shorter follow-up time reported two patients who developed rib necrosis 6–8 months after IORT. Incidence of infections and wound healing problems were reported as very low in both groups, although absolute numbers were not provided. In terms of efficacy, the study found that in the IORT group there was a lower rate of 5-year actuarial ipsilateral breast tumour recurrence (significant, p=0.0018), a lower rate of 5-year actuarial distant recurrence (non significant) and higher 5-year disease-free survival (non significant).

Five other level IV case series were identified, two examining IORT as a single therapy and three examining the use of IORT as boost therapy following breast conserving surgery. There was no common method of IORT treatment between studies and outcomes were not uniformly investigated or reported. The lack of consistency and limited evidence precludes comparisons across these studies. As a result, it is not possible to add to the recommendations from the ASERNIP-S 2002 systematic review.

ONGOING RESEARCH

At the time of publishing there are two ongoing multi-centre randomised controlled trials enrolling large numbers of patients investigating the use of IORT in early breast cancer. A further study is examining the use of IORT in the treatment of ductal carcinoma in situ. The largest of these is the TARGIT trial which has recruited patients in UK, Australia, America, Germany and Italy. The TARGIT trial is comparing patients treated with breast conserving surgery and IORT with patients treated with breast conserving surgery and postoperative radiotherapy. Initial results from this trial are expected to be published in late 2007.

CONCLUSIONS

There is currently insufficient evidence about the impact of IORT on breast cancer recurrence or long-term side effects to recommend the standard use of IORT for patients with early breast cancer.

Based on current evidence it is not possible to say whether IORT is a safer and more effective treatment when compared with external beam radiotherapy, either as a boost or as a single therapy.

More research is required before IORT can be incorporated into standard treatment for patients with early breast cancer. Further randomised controlled trials need to investigate issues related to which patients will benefit most from IORT, short- and long-term side effects and complications, optimal dosing, potential quality of life and cosmetic benefits, local recurrence rates and disease free and overall survival rates. In addition it is still unclear whether IORT is best suited as a boost therapy or whether it should replace postoperative radiotherapy entirely.

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Systematic review

The NBCC gratefully acknowledges the work of the Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) in developing the systematic review *Intraoperative radiotherapy for early breast cancer* (2006), which informed the development of this summary.

ISBN Online: 978-1-74127-076-1

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