New and Emerging Techniques - Surgical

Horizon Scanning Report

Intraoperative Radiation Therapy

April 2004

ASERNIP-S

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

New and Emerging Techniques – Surgical

Horizon scanning reports are for information only

Royal Australasian College of Surgeons

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Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP-S) in conjunction with the Royal Australasian College of Surgeons has undertaken a Horizon Scanning Report to provide advice on the state of play of the introduction and use of intraoperative radiation therapy for early stage breast cancer.

This Horizon Scanning Report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of intraoperative radiation therapy, its present use, the potential future application of the technology, and its likely impact on the Australian health care system.

This Horizon Scanning Report is a concise update of an existing ASERNIP-S systematic review of the safety, effectiveness, cost-effectiveness and ethical considerations associated with intraoperative radiation therapy.

Background

Background to the Condition

Breast cancer is the most common form of cancer in women in the developed world (Battle *et al.* 1999). Early operable breast cancer is defined as a tumour confined to the breast (and/or ipsilateral axillary nodes) that measures less than 5 cm in diameter and can be surgically excised (Stages I and II) (Early Breast Cancer Trialists' Collaborative Group 2004).

Increasing age is the greatest risk factor for breast cancer in women (NHMRC 2001). Other factors such as family history, previous history of breast cancer or benign disease, an increased body size and heavier body weight may also increase the risk (NHMRC 2001).

There are many forms of treatment available for breast cancer. However, this report focuses on comparing breast conserving surgery with intraoperative radiation therapy (IORT) to the current standard treatment for early breast cancer of breast conserving surgery with postoperative radiation therapy (BCT).

Description of the Technology

The Procedure

Breast conserving surgery is usually accompanied by a postoperative radiotherapy schedule (six week course of radiation) within six weeks after surgery unless the patient is also receiving adjuvant chemotherapy, whereby radiotherapy can be delayed up to seven months after surgery (National Breast Cancer Centre 2003).

Intraoperative radiation therapy, alternatively known as intraoperative electron radiation therapy (IOERT) or intraoperative electron beam radiation therapy (IOEBRT), is not a new concept. Its use during the resection of gastric and colorectal cancers was reported in 1915 (Beck 1919). However, its application in breast cancer surgery is relatively new.

The radiotherapy treatment is delivered in a single, intensive fraction in the operating theatre immediately following surgical resection of the tumour (Valentini *et al.* 2002). Special applicators have recently been developed for use during breast conservation surgery, which are capable of emitting a uniform rate of radiation that enables the delivery of an accurately calculated radiation dose to the breast tumour bed at a previously determined depth. IORT devices utilise "soft" x-rays, where the beam has the ability to attenuate rapidly to reduce the radiation to more distant tissue (Vaidya 2001).

IORT is administered by either a linear acceleration electron beam or a high dose rate remote afterloading system (Veronesi *et al.* 2003). The linear acceleration electron beam method involves the detachment of the remaining breast tissue from the underlying skin, which is retracted to avoid skin necrosis. An electron beam is delivered to the exposed breast tissue via a perspex tube attached to an aluminium-lead disc placed between the breast tissue and the chest wall. With the high dose rate remote afterloading system, the iridium source (radioactive material) is directly applied to the tissue via catheters embedded in a silastic template. This technique differs from the linear acceleration electron beam in that detachment of the breast tissue from the skin is not required as the radiation distribution occurs along the catheters, so the skin and pectoral surface receive minimal radiation.

Currently, there is no firmly established standardised IORT dose or dose rate for use in early breast cancer. Doses have ranged from 5 Gy to 22 Gy using a variety of IORT systems. There are several mobile IORT devices available:

- Intrabeam system[1] (Photoelectron Corporation, Lexington MA, USA)
- Mobetron System (Oncology Care Systems Group of Siemens Medical Systems, Intraop Medical Inc, Santa Clara CA, USA)
- Novac 7 System (Hitesys SpA, Italy).

[1] The Australian distributor of the Intrabeam system is Nucletron Pty Ltd, Suite 4/26 Sparkes Street, Camperdown, NSW 2050. Ph: (02) 9517 1300 Fax: (02) 9517 1311

Currently, the recommended radiotherapy dose in Australia is 2.0 Gy/fraction (NHMRC 2001).

Intended Purpose

The aim of intraoperative radiation therapy is to reduce the recurrence of breast carcinoma in women undergoing breast surgery, by destroying residual cancer cells in the area surrounding the primary tumour. It also has the potential to provide increased treatment choice for breast cancer patients.

Clinical Need and Burden of Disease

Breast cancer is the leading cause of cancer deaths in women (16% of all female cancer deaths) (Australian Bureau of Statistics 2003) with a mortality rate of 21.5 per 100 000 women in 2000 in Australia (BreastScreen Australia monitoring report 1998-1999 and 1999-2000) and 22.1 per 100 000 women in 2000 in New Zealand (New Zealand Health Information Service 2004).

The incidence of breast cancer, as reported by the Australian Institute of Health and Welfare, was 98.7 new cancers per 100 000 women in 1999 (BreastScreen Australia monitoring report 1998-1999 and 1999-2000). In 2000, 11 400 new cases of breast cancer were reported in Australia of which 86 were male (Australian Institute of Health and Welfare 2003). In the same year, New Zealand reported 2 306 new female breast cancer registrations, and an incidence rate of 89.4 new cancers per 100 000 women (New Zealand Health Information Service 2004).

Stage of Development

Since 1983, the Department of Radiation Oncology at the Medical College of Ohio has been the site of nearly 400 IORT procedures.

IORT is currently in Phase III trials (randomised controlled trials) in Australia. University College London has commenced a trial on Targeted Intraoperative Radiotherapy for Early Breast Cancer (TARGIT) with participating sites in Italy, Germany and Australia (Sir Charles Gairdner Hospital, Western Australia). IORT is currently not available in New Zealand.

Treatment Alternatives

Existing Comparators

The current postoperative radiotherapy schedule involves the administration of 50 Gy at 2 Gy per fraction prescribed to the isocentre, corrected for lung transmission, daily for five to six weeks (Royal Australian and New Zealand College of Radiologists 2003). The

radiotherapy treatment is delivered by external beam radiation therapy with or without a boost dose.

IORT could potentially provide an increased treatment choice for breast cancer patients, particularly rural patients, who may be more likely to choose breast conserving surgery over mastectomy as it would not require prolonged travel to large metropolitan centres for six-week courses of radiotherapy.

IORT is purported to have the following advantages over postoperative electron beam radiotherapy:

- IORT spares normal tissues by marked dose attenuation.
- There is a greater physical capacity to move/retract normal soft tissue around the applicators to minimise irradiation of normal tissue.
- The radiation dose can be delivered directly to the tumour bed with minimal chance of geographic miss as a direct visualisation approach is used rather than relying on "simulation" and "target approximation" techniques.
- There is virtually no delay between surgery and the irradiation of any residual cancer cells.
- A larger single dose can be administered because the radiation field can be more precisely tailored to the target volume than in conventional postoperative radiotherapy.
- The entire course of radiotherapy treatment could possibly be shortened to only one intraoperative episode or the postoperative boost dose could be eliminated (provided that a sufficiently high intraoperative dose could be tolerated by the patient).
- The new mobile technology affords greater radiation protection to hospital personnel.

One disadvantage of current radiotherapy techniques is that it is difficult to deliver a 'tumouricidal dose' without compromising vital adjacent anatomical structures. In the case of breast cancer, many of the adjacent structures such as the coronary vessels, lungs and skin are particularly sensitive to radiation damage.

Clinical Outcomes

Included in this review were nine IORT studies - one RCT (Fortuna 2001[2]), two non-randomised comparative studies (Dubois 1997[2];Reitsamer 2004) and six non-comparative studies (Baum 2000[2];Merrick 1997;Odantini 2001;Proulx 2001[2];Vaidya 2001;Veronesi 2001). Appendix A provides a descriptive summary of the included IORT studies.

[2] IORT versus RT alone; other unmarked studies were IORT + RT versus RT alone.

Effectiveness

Disease-free Survival

Comparative and Non-comparative IORT Studies

Only one non-randomised comparative study (Reitsamer 2004) reported disease-free survival, which was 92% at 2.2 years for IORT and 97 % at 4.6 years for radiotherapy (RT). None of the other included IORT studies reported disease-free survival rates.

Overall Survival

Comparative IORT Studies

Reitsamer (2004) reported an overall survival rate of 96% at 2.2 years for IORT and 99% at 4.6 years for RT. Fortuna (2001) anticipate publishing 5-year survival rates from their RCT in 2006.

Non-comparative IORT Studies

Three of the six non-comparative studies (Merrick 1997, Odantini 2001, Proulx 2001) reported overall survival rates of 91% at 5.9 years, 100% (follow-up length unknown) and 86% at 10.3 years, respectively.

Local Cancer Recurrence

Comparative IORT Studies

Dubois (1997) reported no local cancer recurrences at two years follow-up in either the IORT or RT group. Reitsamer (2004) reported no local cancer recurrences at 2.2 years for IORT and a 4.3% recurrence rate at 4.6 years for RT. Fortuna (2001) anticipate publishing local recurrence rates from their RCT in 2006.

Non-comparative IORT Studies

The ranges in local cancer recurrence reported from four of the six non-comparative studies (Baum 2000, Merrick 1997, Proulx 2001, Vaidya 2001) ranged from 0% at 1.5 years to 29% at 10.3 years. It is important to note that the Baum study (2000) reporting 0% at 1.5 years was a case report on one patient, and the Proulx study (2001) reporting 29% at 10.3 years had a sample size of only seven patients. The two patients, from the Proulx study (2001), who did develop a local recurrence had recurrences that originated at the surgical scar in one case and the tumour bed in the other.

Cosmesis

The measurement of postoperative cosmetic outcome (cosmesis) differed between studies making comparison difficult, with most developing their own non-validated rating scales of 'excellent, good, average or poor cosmetic result'.

Comparative IORT Studies

In the RCT by Fortuna (2001), 80% of patients in the IORT group and 76% of patients in the RT group reported 'good to excellent' cosmetic results. However, no statistical tests were performed on these data. Cosmetic outcome was measured using photographic assessment and a specific predetermined aesthetic evaluation.

The non-randomised comparative study (Dubois 1997) did not report outcomes separately for the IORT and RT groups.

Non-comparative IORT Studies

Three of the six non-comparative studies measured cosmetic outcome (Odantini 2001, Proulx 2001, Vaidya 2001). Vaidya (2001) reported that 21 of 25 patients (84%) rated their cosmetic outcome as better than they had expected. All seven patients in the study by Proulx (2001) also expressed general satisfaction with their cosmetic outcome. Six of the 101 patients (6%) in the Veronesi (2001) study developed fibroses that were disfiguring enough to affect breast cosmesis. Odantini (2001) reported a 'good' cosmetic outcome in 26 of 27 patients (96%); however, the technique used to measure this outcome was not stated.

Table 1. Efficacy Outcomes for IORT versus BCT

Outcomes	IORT	BCT (based on 8 RCTs[#])
Survival	Range 86% at 10.3 years to 100% unknown follow-up* (median 93.5%)	Range 62% at 15 years to 92.9% at 5 years (median 79%)
Recurrence	Range 0% at 1.5 years to 29% at 10.3 years^ (median 0%)	Range 3.6% at 5 years to 19.7% at 13.4 years (median 10.6%)

*Based on 4 studies - Merrick 1997, Odantini 2001, Proulx 2001, Reitsamer 2004.
^Based on 6 studies - Baum 2000, Dubois 1997, Merrick 1997, Proulx 2001, Reitsamer 2004, Vaidya 2001.
[#]Eight RCTs on BCT (ten articles) were included to provide an indirect comparison with IORT (Bartelink 2001, Blichert-Toft 1992, Clark 1996, Fisher 2001, Magee 1996, Mariani 1998, Romestaing 1997, Van Dongen 2000, Veronesi 1995, Whelan 2000). Only the results from the comparator procedure arm (i.e. breast conserving surgery with postoperative radiotherapy) were extracted.

Safety

IORT Complications

Perioperative Morbidity/Mortality

None of the included IORT studies reported on perioperative morbidity or perioperative mortality.

Postoperative Morbidity/Complications

Comparative IORT Studies

The RCT reported a 2.9% wound infection rate and 4.3% (3/70) of patients developed seromas (Fortuna 2001). However, it was not clear whether the patients were from the IORT or RT groups.

Scleroses developed in 11.6% of the IORT group in the non-randomised comparative study, but was not reported from the RT group (Dubois 1997). There were no significant differences between the RT and IORT groups in terms of healing time, lymphocele development, hospital length of stay and the number of postoperative days requiring postoperative drainage (4.5 days for control and 4.4 days for IORT).

Reitsamer (2004) reported rib necrosis in two patients (1%) in the IORT group and cases of wound infection and wound healing problems were 'very low and comparable in both groups'.

Non-comparative IORT Studies

Wound Infections and Delayed Healing

Of the 25 patients in the Vaidya case series (2001), one (4%) developed a wound infection and three (12%) experienced short-term erythema. Two case series reported delayed healing in 7.4% (2/27) (Odantini 2001) and 8% (2/25) (Vaidya 2001) of their patients. Mastitis was also reported to have developed in 14.8% (4/27) of patients (Odantini 2001).

Lymphocele Development

Only one non-comparative study reported lymphocele development and this occurred in one patient with delayed healing (Odantini 2001). It is unclear whether other lymphoceles were observed but not reported.

Fibroses (Scarring)

Two of the six non-comparative studies (Merrick 1997, Veronesi 2001) reported the development of palpable fibroses. Two of the 21 patients in the Merrick study (Merrick 1997) developed fibrosis at the lumpectomy site. Fibrosis developed in six of the 101 patients (6%) in the Veronesi study (2001), five of which had received an IORT dose ≥ 15 Gy.

Other Complications

There were also reports of transient oedema (Veronesi 2001), pain at lumpectomy site (Veronesi 2001) and mild residual breast defects (Merrick 1997).

See Appendix B for tables of safety and efficacy data extracted from each included IORT study.

Potential Cost Impact

Cost Analysis

There is a lack of evidence on the cost effectiveness of IORT, as it is still an experimental treatment modality. Cost effectiveness studies will be required if RCTs indicate IORT to be a safe and efficacious alternative for treatment of patients with breast cancer, as it is

an expensive treatment method and it would therefore be important to determine which method would be the best and most convenient for the patient.

Ethical Considerations

Informed Consent

Except for the Department of Radiation Oncology at the Medical College of Ohio, patients receiving IORT treatment are those who are participating in a clinical trial. To date, there are two ongoing randomised controlled trials (please refer to Sources of further information for full details of these two trials).

Access Issues

There are access issues for remote or rural patients with the current standard radiotherapy treatment, as it requires the patient to come back for daily radiation therapy for six weeks postoperatively. IORT may shorten this course or even eliminate it if only one high dose of radiation is sufficient, which would reduce the amount of time otherwise required for prolonged travel to large metropolitan centres for the six-week postoperative radiotherapy course.

Training and Accreditation

Training

The use of IORT in other indications is included in the clinical training programme for all radiation oncologists in Australia.

Clinical Guidelines

General guidelines for breast conserving surgery and radiotherapy exist (NHMRC 2001) but no guidelines specifically addressing IORT could be found.

Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of Health Technology Assessment. However, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study

or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A Horizon Scanning Report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost effectiveness of a technology.

In the context of a rapidly evolving technology, a Horizon Scanning Report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of intraoperative radiation therapy, its present and potential use in the Australian health system, and future implications for the use of this technology.

Search Strategy Used for Report

Databases Searched

- Ovid MEDLINE from 1984 to February Week 1, 2004
- ISI Current Contents Connect from 1993 to Week 6, 2004
- The Cochrane Library
- Ovid EMBASE from 1988 to Week 6, 2004
- PubMed up to February 11, 2004

Search Terms

In the Cochrane Library the search terms used were:

1. Intraoperative radiation therapy OR IORT OR IOERT OR IOEBRT
2. (breast surgery OR early breast cancer OR breast cancer).ti

With limits set to dates (1992-2004) and publication type (limited to "systematic reviews")

For MEDLINE, Current Contents Connect, PubMed and EMBASE the following search terms were used:

1. ((intraoperative AND radio*) OR (intra-operative AND radio*) OR IOERT OR IORT OR IOEBRT) AND breast
2. (intraoperative radiotherapy OR IORT OR IOERT OR IOEBRT) AND breast
3. breast conserv* AND radiotherapy
   With limits set to dates (1992-2004)
4. radiotherapy AND breast conserv.ti
   With limits set to dates (1992-2004) and publication type (limited to "reviews")

The National Research Register, Clinicaltrials.gov and Meta-Register were also searched using the above search terms for RCTs in progress and the Internet was searched for product information and relevant articles.

Availability and Level of Evidence

Included IORT Studies:

Total number of studies	9
Randomised controlled trials	1
Non-randomised comparative studies	2
Case series	6

Six of the nine studies consisted of Level IV evidence (National Health and Medical Research Council 2000). Two of the three comparative studies (Dubois 1997, Fortuna 2001) had very small sample sizes (70 patients and 101 patients, respectively) and lacked sufficient statistical power to be able to detect small treatment effects. The data from these two studies were also presented in a manner that made it difficult to separate the IORT from the BCT results. The other comparative study (Reitsamer 2004) had a sufficient sample size but patients were not randomised and follow-up times for each group differed, making some comparisons difficult.

Sources of Further Information

There are currently two ongoing randomised controlled trials investigating the use of IORT in early breast cancer.

1. Targeted Intraoperative Radiotherapy for Early Breast Cancer (TARGIT) trial. Co-chaired by Clinical Professor David Joseph (Radiation Oncologist at Sir Charles Gairdner Hospital, Western Australia) and Professor Michael Baum (Surgeon – UK).
   The trial commenced in the UK with participating sites in Italy, Germany and Australia, and has recruited just under 100 patients globally. TARGIT needs approximately 1100 patients per arm (standard radiation therapy and IORT) of the trial.

   IORT technology used: Intrabeam Technology (Photoelectron Corporation, Lexington MA, USA)

2. Electron Intraoperative Therapy (ELIOT) trial. [expected to finish in three years]
   Chief investigator: Umberto Veronesi
   Instituto Europeo di Oncologia (European Institute of Oncology)
   University of Milan
   Via G. Ripamonti 435
   Milan, ITALY 20141
   IORT technology used: Novac 7 system (Hitesys SpA, ITALY)

Impact Summary

Radiation therapy is often used to destroy any remaining breast cancer cells in the breast, chest wall or axilla (underarm) area after surgery. For those who have undergone breast conserving surgery for early breast cancer, surgery is typically followed by at least six weeks of radiation therapy. Though IORT is not a new concept, its development and use in early breast cancer is relatively new. The application of IORT in breast cancer surgery provides an alternative method to administer radiation therapy that has the potential to shorten the course of radiotherapy treatment and minimise irradiation of normal tissue.

The available data represent the early stages in the development and use of IORT in early breast cancer treatment. It is still unclear whether IORT may be more suited for use as a replacement to the boost dose or whether it could replace the entire postoperative radiotherapy dose. The latter would offer an alternative mode of treatment for patients who would otherwise have to travel long distances to attend their radiotherapy sessions or opt for mastectomy instead. Further investigation is required before the safety and efficacy of IORT and its use in early breast cancer can be definitively evaluated.

Conclusions

Based on the current level of evidence, the relative safety and efficacy of IORT in comparison with breast conserving surgery with postoperative radiotherapy is still uncertain. However, early IORT results suggest only minor complications in the short-term and the cosmetic outcome from IORT appears to be as good as breast conserving surgery with postoperative radiotherapy. More rigorous studies with adequate sample sizes and long-term follow-up periods are required to assess the long-term rate of radiotherapy complications, local recurrence rates and disease-free or overall survival. In addition to this, studies on the cost-effectiveness of IORT will also need to be determined before IORT can be applied in routine clinical practice.

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Appendix A

Included IORT Studies

Study	Level of Evidence	Follow-up	Stage or Histology (N)	IORT/RT Delivered	N	IORT Device
Comparative Studies						
Fortuna 2001	II	5 months	I + II	IORT: 10 Gy RT: 50.4 Gy	41 29	Novac 7
Dubois 1997	III-2	Minimum 2 years	I (22), II (20)	IORT: 10 Gy RT: 45 Gy in 2 Gy fractions, 5 times/week	51 50	CRLC purpose built, portable IORT unit
Reitsamer 2004	III-2	25.8 months IORT 55.3 months RT	I (258 = 128 IORT + 130 RT) II (120 = 60 IORT + 60 RT)	IORT: 9 Gy IORT + 51 to 56.1 Gy in 1.7 Gy fractions RT RT: 12 Gy in 2 Gy fractions EBEBI + 51 to 56 Gy RT	190 188	Linear accelerator (Philips Elektra SL 18)
Non-comparative Studies						
Baum 2000	IV	18 months	1.0 cm tumour size, node-negative	IORT: dose not reported Patient declined an RT dose	1	Intrabeam
Merrick 1997	IV	0 to 13 years	I (14), IIA (5), IIB (2)	IORT: 10 Gy (n=18), 15 Gy (n=3) RT: all patients then received 45-50 Gy RT over 5-6 weeks	21	MCO Varian 1800 linear accelerometer
Odantini 2001	IV	Not stated	I + II	IORT: 8 to 15 Gy RT: 40 Gy on 'conventional' schedule 8 Gy + RT (n=6), 10 Gy + RT (n=6), 12 Gy + RT (n=10), 15 Gy + RT (n=5)	27	IORT dedicated linear accelerometer
Proulx 2001	IV	10.3 years	I (3), IIA (2), IIB (2)	IORT: 15 to 20 Gy (120 kV) RT: None	7	A modified, purpose built Picker Zephyr 120 portable unit
Vaidya 2001	IV	12 months	25 with tumours between 0.42 to 3.5 cm	IORT: 5 Gy RT: 50 Gy over 5 weeks	25	Intrabeam
Veronesi 2001	IV	8 months	Infiltrating cancer with a tumour size <2.5 cm	IORT: 10 to 21 Gy RT: 0 to 44 Gy 10 Gy + 44 Gy RT (n=10), 15 Gy + 40 Gy RT (n=7), 17 Gy + no RT (n=8), 19 Gy + no RT (n=6), 21 Gy = no RT (n=70)	101	Novac 7

Abbreviations: IORT – intraoperative radiation therapy, RT – postoperative radiotherapy, Gy – Gray, MCO – Medical College of Ohio, CRLC – Centre Regional de Lutte contre le Cancer, EBEBI – external-beam electron-boost irradiation.

Appendix B

Efficacy Outcomes for IORT – Comparative and Non-comparative Studies

Study		Outcomes				
		Cosmesis	**Operating Time**	**Local Cancer Recurrence**	**Disease-free Survival**	**Overall Survival**
Comparative Studies						
Fortuna 2001 (Level II)	IORT (n=41)	80% reported 'good to excellent' cosmetic result	'increased by 10 to 15 minutes'	To be evaluated at 5 years postop	To be evaluated at 5 years postop	To be evaluated at 5 years postop
	RT (n=29)	77% reported 'good to excellent' cosmetic result	Not reported			
Dubois 1997 (Level III-2)	IORT (n=51)	Results were not partitioned by IORT and RT groups: 6/51 (11.6%) received a Stage 4 (worst) classification for sclerosis 45/51 (88.4%) were judged to have 'no visible sequelae' Overall comments: all patients judged their own cosmetic results as 'excellent'	'increased by 30 to 35 minutes'	0% at 2 years	…	…
	RT (n=50)		Not reported	Not reported	…	…
Reitsamer 2001 (Level III-2)	IORT (n=190)	…	…	0% at 2.2 years	92% at 2.2 years	96% at 2.2 years
	RT (n=188)	…	…	8/188 (4.3%) at 4.6 years	97% at 4.6 years	99% at 4.6 years
Non-comparative Studies						
Baum 2000 (n=1)		'cosmetic result pleasing'	…	0% at 18 months	…	…
Merrick 1997 (n=21)		'generally excellent with 4.2% left with a mild residual deficit'	…	0% at 2 years	…	91% with a median follow-up of 5.9 years
Odantini 2001 (n=27)		26/27 (96.2%) of patients had a 'good' cosmetic outcome	…	…	…	100%
Proulx 2001 (n=7)		5/7 (71.4%) had some form of scarring 100% of patients expressed satisfaction with cosmetic result	…	2/7 (29%) at surgical scar or tumour bed	…	86% (1 patient died of other causes)
Vaidya 2001 (n=25)		'cosmetic outcome has been good to excellent'	…	0% at 2 years	…	…
Veronesi 2001 (n=101)		5/101 (5%) developed palpable fibroses (all 15 to 21 Gy IORT patients) 1/101 (1%) developed very severe Grade III, palpable fibroses	…	Not reported, although it was reported that 1 patient developed evidence of bony metastases	…	…

Ellipses indicate not available
Abbreviations: IORT – intraoperative radiation therapy, RT – postoperative radiotherapy.

Safety Outcomes for IORT – Comparative Studies

	Fortuna 2001 (Level II)		Dubois 1997 (Level III-2)		Reitsamer 2004 (Level III-2)	
Outcomes	**IORT (n=41)**	**RT (n=29)**	**IORT (n=51)**	**RT (n=50)**	**IORT (n=190)**	**RT (n=188)**
Postoperative complications	…	…	…	…	…	'no severe treatment complications'
Interval between surgery and RT	…	…	Mean 31.5 days Median 29 days	Mean 25 days Median 24 days	…	…
Healing time	…	…	No significant difference between groups		'very low and comparable in both groups'	
Wound infections	2.9% reported but not clear which group		0%	…	'very low and comparable in both groups'	
Sclerosis	…	…	6/51 (11.6%) had Stage 4 sclerosis 3 excellent 3 fair with visible deformation of the breast	…	…	…
Seromas	4.3% reported but not clear which group (all resolved within 3 to 6 months after surgery)		…	…	…	…
Rib necrosis					2/190 (1%)	…
Lymphocele	…	…	…	…	…	…
Length of hospital stay	…	…	Mean 7.75 days Median 7 days	Mean 7 days Median 6.9 days	…	…
Postop drainage	…	…	Mean 4.4 days	Mean 4.5 days	…	…

Ellipses indicate not available

Abbreviations: IORT – intraoperative radiation therapy, RT – postoperative radiotherapy.

Safety Outcomes for IORT – Non-Comparative Studies

Study	Outcomes				
	Postoperative complications	**Wound infections**	**Fibroses**	**Oedema**	**Pain at lumpectomy site**
Baum 2000 (n=1)	'Patient remains well and symptom-free 18 months later'	…	…	…	…
Merrick 1997 (n=21)	'No early complications associated with the delivery of IORT as a booster dose'	…	2/21 (9.5%) developed palpable fibroses at the lumpectomy site (no malignancy)*	…	…
Odantini 2001 (n=27)	…	2/27 (7.4%) had delayed healing – 1 with a prosthesis *in situ* and 1 with a serum collection in the axilla which delayed scar formation	…	…	…
Proulx 2001 (n=7)	0%	…	…	…	…
Vaidya 2001 (n=25)	0% major complications	2/25 (8%) delayed wound healing 1/25 (4%) wound infection 3/25 (12%) short-term erythema	…	…	…
Veronesi 2001 (n=101)	10/101 (10%) suffered 'mild to intermediate toxicity'	2^/101 (2%)	5#/101 (5%) developed Grades I-II fibroses 1†/101 (1%) developed severe fibrosis	3/101 (3%)	2/101 (2%)

Ellipses indicate not available.
*A further 2/21 (9.5%) also developed a palpable mass (subsequent biopsies – benign) and 1/21 (4.8%) developed mammographic calcification.
^Both patients had received a 21 Gy dose.
#1 patient had received a 15 Gy dose and 4 patients had received a 21 Gy dose.
†Patient had received a 10 Gy dose.