National Health Committee

Intraoperative Radiotherapy (IORT)

March 2015

National Health Committee (NHC)

The National Health Committee (NHC) is an independent statutory body charged with prioritising new and existing health technologies and making recommendations to the Minister of Health.

It was reformed in 2011 to establish evaluation systems that would provide the New Zealand people and the health sector with greater value for money invested in health.

The NHC Executive is the secretariat that supports the Committee. The NHC Executive's primary objective is to provide the Committee with sufficient information for it to make decisions regarding prioritisation and reprioritisation of interventions and services. They do this through a range of evidence-based products chosen according to the nature of the decision required and timeframe within which decisions need to be made.

The New Zealand Government has asked that all new diagnostic and treatment (non-pharmaceutical) services, and significant expansions of existing services, are to be referred to the NHC.

In August 2011 the NHC was appointed with new Terms of Reference and a mandate to establish the capacity to assess new and existing health technologies. Its objectives (under Section 4.2 of its Terms of Reference – www.nhc.health.govt.nz) include contributing to improved value for money and fiscal sustainability in the health and disability sector by:

- providing timely advice and recommendations about relative cost-effectiveness based on the best available evidence;
- providing advice and recommendations which influence the behaviour of decision makers including clinicians and other health professionals;
- providing advice and recommendations which are reflected in resource allocation at national, regional and local levels; and
- contributing to tangible reductions in the use of ineffective interventions and improved targeting to those most likely to benefit.

In order to achieve its objectives under Section 4.2 and to achieve 'Value for Money', the NHC has adopted a framework of four assessment domains – Clinical Safety & Effectiveness; Economic; Societal & Ethical; and Feasibility of Adoption – in order that assessments cover the range of potential considerations and that the recommendations made are reasonable.

It is intended that the research questions asked will fall across these domains to ensure that when the Committee comes to apply its decision-making criteria, it has a balanced range of information available to it. When the NHC is setting those questions they will have the decision-making criteria in mind.

The 11 decision-making criteria will assist in the determination of the NHC work programme and in the appraisal and prioritisation of assessments.

Contents

Executive Summary

This report explores the uses of intraoperative radiotherapy (IORT) and which cancer types are highest priorities for the National Health Committee (NHC) to assess further with health technology assessments (HTAs).

IORT is delivered directly to exposed tissues during surgery, providing a large radiation dose to a target tissue while sparing normal tissues. There are several available IORT devices delivering different energy forms, which do not require a shielded room for use. Treating cancers with IORT has been investigated both as an addition to standard external beam radiotherapy treatment (EBRT), and as a substitute for usual radiation therapy for early breast cancer.

Clinical safety and effectiveness

Generally, the evidence base for the comparative effectiveness of IORT is immature and largely comprises lower quality studies. Available evidence for IORT's use as additional therapy is mainly case series, with few randomised controlled trials (RCTs). There is reasonable evidence for benefit of IORT as an intervention in the management of early breast cancer, and some suggesting potential in the treatment of colorectal cancer. There is no strong evidence for benefit of IORT as an additional intervention in other cancers.

Evidence for IORT's effectiveness as a substitute for usual radiation therapy in the treatment of early breast cancer includes the TARGIT-A RCT using the Intrabeam system and the ELIOT RCT using the Novac7 system. The TARGIT-A trial is a non-inferiority trial and the ELIOT trial is an equivalence study. It has been claimed that the results of TARGIT-A show 'non-inferiority' to standard EBRT and should be made available to low risk women with early breast cancer. However, this conclusion has been questioned, and New Zealand medical organisations have expressed doubt over the certainty of the results and consider longer patient follow up to be necessary. The UK's National Institute for Health and Care Evidence (NICE) have cautioned that the evidence is currently immature and that 'non-inferiority' has not been demonstrated.

The TARGIT-A trial also showed that breast cancer mortality was non-significantly higher and non-breast cancer mortality significantly lower in the Intrabeam group than the EBRT group. Overall mortality was non-significantly higher in the EBRT group. The authors suggested that the higher non-cancer mortality could be partly explained by the effect of the EBRT dose delivered to the heart, but this interpretation has been debated.

Economic

Analysis of IORT by the NHC Executive estimates that:

- IORT could be suitable for about 750 patients of the estimated 1600 per annum who are suitable for breast conservation surgery
- the number of patients taking up the treatment would depend on patient preference and whether patients at risk of non-adherence to usual treatment could be identified
- Seven machines would be needed to meet demand for the substitution of EBRT in treating selected women with breast cancer. The number of devices would depend on the number of patients opting for IORT as well as whether the devices could be used across multiple sites
- investment in IORT devices could be a substitute for future projected investment in machines for EBRT
- capital expenditure would be $8.4 million with $0.7 million in annual running costs.

Initial cost analysis by the Executive indicates IORT would give small annual cost savings of up to $0.4 million. A Tier 3 assessment is needed for more detail of the economic impact.

Societal and ethical

There may be potential benefits to patients and the health care system from IORT being used as a substitute for EBRT in the treatment of early breast cancer. A single episode of treatment may improve quality of life through the avoidance of multiple visits for EBRT. Some women do not complete recommended EBRT, so treatment in one step at operation could improve access to care.

Some women choose mastectomy rather than EBRT due to the cost, inconvenience and side effects. These are reduced with IORT, and there may be fewer mastectomies and more breast conserving surgery with IORT, which may have a societal benefit.

The UK's NICE economic assessment found Intrabeam would be cost saving, but with lost quality of life; £1,596 saved for each quality-adjusted life year (QALY) lost. There would be a particular need to ensure that patients are properly informed about the risks and benefits if IORT were used as a substitute for EBERT.

Feasibility

If a Tier 3 assessment found IORT to be a safe, effective, cost-effective and appropriate way to treat selected patients, then it would be technically feasible to adopt the technology into the New Zealand public health system. Mobility of devices and lack of need for shielding will aide adoption.

Feasibility will partly depend on the trade-off between increased theatre utilisation and reduced EBRT sessions.

1 Introduction

This report explores Intraoperative radiotherapy (IORT) as a potential therapy for some cancers to identify which uses of IORT are highest priorities for health technology assessments (HTAs). For patients with cancers suitable for treatment with IORT, the HTAs could improve health outcomes and efficiencies, including the burden of disease and the pathway of care.

The NHC became aware of IORT as a priority issue during a sector referral round. Preliminary assessment of the referral question on "the suitability of using intraoperative radiotherapy for selected women with early breast cancer using Intrabeam" suggested use of IORT offers potential for improved efficiency in the health system.

This report assesses IORT technology to determine its status and potential indications for its use. The burden of disease and pathway of care for IORT patients is discussed, along with assessment under the four NHC assessment domains (Clinical Safety and Effectiveness; Cost Effectiveness; Societal and Ethical Considerations; Feasibility of Adoption) and key decision-making criteria (Materiality and Risk) to inform a Committee decision on whether further assessment work by the Executive is appropriate at this stage.

2 Technology

Radiation therapy can be delivered by external beam or local implant (brachytherapy) that emits radiation. IORT is delivered directly to exposed tissues during surgery, giving a large radiation dose to target tissue while sparing normal tissue.[1] . The tumour and associated tissues at risk for micro-metastatic spread are visible at operation of the IORT, allowing it to be delivered directly to the tumour; while normal or uninvolved tissues are removed or shielded from the treatment field.[2]

IORT can be delivered through the use of electrons (IOERT) or low-energy photons. IOERT uses electrons via a compact linear accelerator, applicators and cones, to direct radiation to defined surface structures. Most clinical experience involves IOERT.[2] The Novac 7 and Mobetron are electron devices that are mobile within a facility and do not need a shielded room [1] Systems that deliver photons include the Intrabeam and Axxent systems. Both of these systems do not require the use of a shielded room.[1]

Brachytherapy with high-dose-rate photons uses a remote-afterloading device with a flexible applicator that allows treatment of difficult target areas and requires a shielded room.[1]

2.1 Regulatory approval

The US Food and Drug Administration (FDA) has different routes for approval of devices. Devices considered to be of low risk are passed through the class I process are subject to 'general controls' that are sufficient to protect the user. Moderate risk devices pass through the 510(k) review pathway, in which the FDA and manufacturer rely on similarities between the device at issue and a previously cleared device. If the device is shown to be 'substantially similar', additional clinical data are not usually required.[3]

The FDA gave approval to Intrabeam in 2005 through the 510(k) process.[4] Mobetron, Novac7 and the Xoft Axxent system are approved by the FDA[5],[6]

Intrabeam achieved the Conformité Européenne (CE) marking in 1999 for use as an alternative to whole breast irradiation[7] Mobetron[8] and Axxent[9] also have CE approval.

3 Technology uptake

The manufacturer of the Intrabeam system reports that it is used clinically in 18 countries across North America, Europe and Asia-Pacific,[10] and the other IORT devices are available in various countries.

3.1 North America

Within the United States the Intrabeam and Novac7 systems are marketed for a range of cancers[11] and are approved for restricted use in cancers by some insurers.[2, 12]

3.2 Europe

IORT is available in the UK private health sector with the Xoft system[13] and the Intrabeam system.[14] Intrabeam is available in a NHS hospital.[15] The National Institute for Health and Care Excellence (NICE) has an appraisal of Intrabeam radiotherapy for the treatment of breast cancer in development, which is expected to publish in November 2014.[16]

3.3 Asia-Pacific

Within Australia, a 2007 report noted that IORT for the treatment of breast cancer was only being performed in clinical trials and that at that point in time there was insufficient evidence to recommend its standard use.[17] However, situation has been updated and the Medical Services Advisory Committee has supported the public funding of Intrabeam for women who have breast conserving surgery and fulfil stated criteria.[18]

3.4 New Zealand

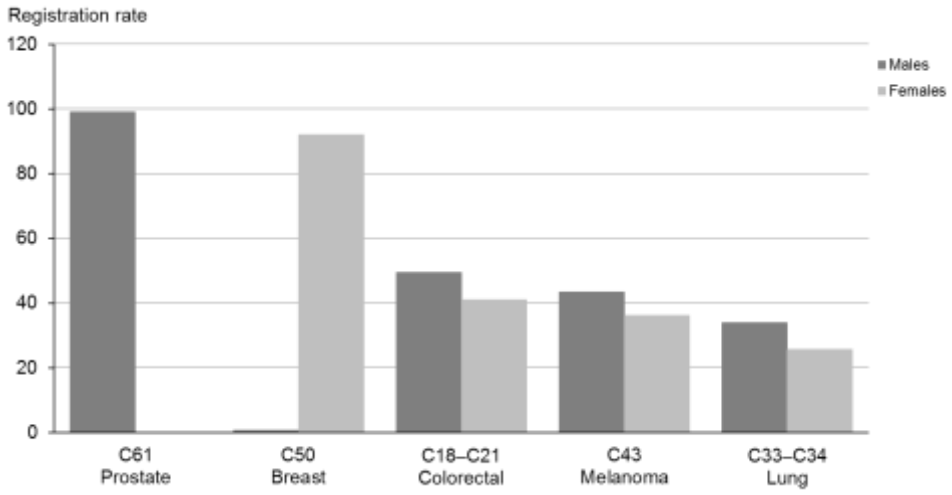
The Intrabeam device is currently used in New Zealand only for private treatment of breast cancer. It is offered by one private provider in Auckland through Focus Radiotherapy, a clinician-owned specialist radiation therapy service.[19] There is some interest in the introduction of this technology to the public health system, and there is potential for expansion within the private sector.

4 Epidemiology of cancers with potential application to IORT

As is discussed in Chapter 5 IORT has been used in the treatment of a number of cancer types. Cancer is the most common cause of death in New Zealand, accounting for nearly a third of all deaths in 2010. The following indicates the most common incident cancers in New Zealand and impact of the common cancers.

The most common cancer registrations in New Zealand in 2010 are shown in Figure 1. The top five most common cancers (prostate, colorectal, breast, melanoma and lung) account for over 60% of all cancer registrations. Almost half of all cancer deaths are accounted for by the top four causes of cancer death: lung, colorectal, breast and prostate cancer.[20] IORT has shown most promise for breast cancer and colorectal cancer (see section Clinical Safety and Effectiveness below).

Figure 1: Registration rates for leading cancer sites, by sex, 2010



Source: Cancer: New registrations and deaths 2010

Note: The rate shown is the age-standardised rate per 100,000 population standardised to the WHO world standard population.

Disability Adjusted Life Years (DALYs) are one measure of the impact of disease. They are a combined measure of years of life lost through death and years lived with disability, and thus account for both quantity and quality of life.[21]

The disability-adjusted life year (DALY)

The DALY is calculated as follows: DALY = YLL + YLD.

YLL (years of life lost) measures health loss from early death, taking into account the age when death occurred.

YLD (years lived with disability) measures health loss from time spent in less than full health, taking into account the severity of ill health or disability.

The New Zealand Burden of Disease, Injuries and Risk Factors Study[21] found that in 2006, cancers accounted for 17.5% of the overall population health loss. Table 1 shows the breakdown by selected cancers of DALYS and percentage of total cancers in New Zealand.

Table 1: Burden of selected cancers in DALYs in New Zealand in 2006

Cancer description	DALY	% of total for cancers
Lung	28,570	17.1
Breast (female)	17,870	10.7
Colon	15,907	9.5
Prostate	9,786	5.9
Rectum	8,105	4.8
Pancreas	6,909	4.1
Stomach	6,296	3.8
Ovary	4,046	2.4
Head & neck	3,851	2.3
Kidney	3,752	2.2
Endometrium	2,190	1.3
Cervix	1,591	1.0

Source: New Zealand Burden of Disease, Injuries and Risk Factors Study

Given the large burden of cancer in New Zealand, interventions to reduce the morbidity and mortality associated with cancer, including different approaches to radiotherapy, are a high priority.

5 Clinical safety and effectiveness

A primary search of the Cochrane library, Medline, Google Scholar and general search engine retrieved research findings (See Appendix). Literature on effectiveness of IORT for different cancers has been obtained from published reviews and reviews provided by retrieved policy statements. As the research is in an early stage, a supplementary search was made prior to submission of this paper for any systematic reviews or meta-analyses published since the start of 2013. This search included Google Scholar, DARE (Database of Abstracts of Reviews of Effects), INAHTA (International Network of Agencies for Health Technology Assessment), CRD (Centre for Reviews and Dissemination, University of York), and the Joanna Briggs Institute Database of Systematic Reviews. This supplementary search found no further research evidence to change or expand upon the findings of the original search.

Most of the published work on IORT in management of cancers focuses on single-institution series or retrospective reviews. With a few exceptions there is a scarcity of randomised controlled data on the use of IORT.[1] The Cochrane Collaboration glossary considers definition Randomised Controlled Trials and Randomised Clinical Trials to be the same. They are an experimental design in which two or more interventions, possibly including a control intervention or no intervention, are compared by being randomly allocated to participants. The external validity of a trial considers the extent to which results provide a correct basis for generalisations to other circumstances. Across the majority of conditions, including those identified as having a stronger evidence base for clinical use, IORT is an additional component of clinical management.

5.1 IORT as a substitute for EBRT

5.1.1 Breast cancer

For several decades, standard therapy for women who have breast-conserving surgery for early stage breast cancer has included EBRT to the whole breast over a five to six week period. Multiple randomised trials and meta-analyses have demonstrated the effectiveness and safety of this approach in reducing local recurrence and mortality.[22, 23]

An alternative way of delivering radiotherapy in breast cancer is accelerated or fractionated radiotherapy, where a reduced total dose of radiation is given over a shorter time than standard therapy but with a greater dose per session. RCTs of doses given over three weeks versus five weeks indicates that hypofractionated therapy results are no worse than standard therapy after breast-conserving surgery for early stage breast cancer, but duration of follow-up is a limitation to the conclusions.[24] A Cochrane review compared standard radiotherapy (50 Gy delivered in 25 fractions) with hypofractionated whole breast radiotherapy (39 to 42Gy over 13 to 16 sessions) for women undergoing breast conservation therapy. Across four trials, local recurrence at five years' follow-up was equivalent between standard and hypofractionated radiotherapy and there was equivalent local recurrence in both arms at 10 years in the two trials with sufficient follow-up. Breast appearance was unaffected by treatment method.[25]

Another alternative is partial breast irradiation, of which IORT is one method. Two RCTs analysed IORT as an alternative to EBRT in the treatment of breast cancer. The first of these was the TARGIT-A trial using the Intrabeam system;[26] the other was the ELIOT trial using the Novac7 system.[27] Both trials were 'equivalence' or 'non-inferiority' trials: that is, designed to show whether a new treatment is 'as good as' current standard therapy.[28] The intervention is 'non-inferior' or 'equivalent' if outcomes are no worse than standard treatment by no more than a pre-defined acceptable amount.[29]

5.1.1.1 TARGIT-A

The TARGIT-A trial was a randomised trial of low energy x-rays-IORT with Intrabeam compared with standard EBRT in 3451 women with early breast cancer aged 45 years and over. Of participants 86% had tumours 2cm or less in size, 85% had tumour grades 1 or 2, 83% were free of nodal involvement and 92% were oestrogen-receptor positive.[30] The predetermined non-inferiority limit was an increase of 2.5% (absolute value) in the incidence of local recurrence. This margin was chosen "because it seemed clinically acceptable to physicians and patients".[30] The authors extrapolated the difference in recurrence rate to a predicted increase in mortality they considered could be acceptable, a difference in mortality of 0.625% at 15 years. The estimation of mortality difference is taken from the EBCCTCG analyses that indicate that for every four recurrences avoided by year 10 post treatment, one breast cancer death is avoided by year 15.[22] The authors note the acceptability in patient preference studies of this margin. Results have been published for four years[30] and five-year follow-up.[26]

Participants were women who were suitable for wide local excision for invasive ductal carcinoma that was unifocal on conventional examination and imaging. They were randomised to IORT or EBRT either before or after lumpectomy (pre-pathology or post-pathology). For the post-pathology patients, a further operation to deliver the IORT was performed within 30 days of the original surgery.[26] If the pathology report for women in the IORT group showed unpredicted pre-specified adverse features, then EBRT was added to IORT.[26]

The primary outcome measure was local cancer recurrence in the treated breast, and the most recent (2014) results include five-year follow-up of some patients. The local rate of recurrence at five years for all patients was higher In the Intrabeam group (3.3%; 95% CI: 2.1-5.1%) than the standard treatment group (1.3%; 95% CI: 0.7%-2.5%), an absolute difference of 2% and within the predetermined acceptable difference. In the pre-pathology stratum the local recurrence rate was 2.1% (95% CI: 1.1%-4.2%) in the Intrabeam arm and 1.1% (95% CI: 0.5%-2.5%), an absolute difference of 1.0%, within the predetermined margin. However, in the post-pathology group the difference was 3.7% (5.4% with IORT vs 1.7% with EBRT), exceeding the 2.5% margin of acceptability.[26]

The TARGIT-A trial also showed that breast cancer mortality was non-significantly higher in the Intrabeam group (2.6%) than the EBRT group (1.9%), and non-breast cancer mortality significantly lower (1.4% vs 3.5%). Overall mortality was non-significantly higher in the EBRT group (5.3% vs 3.9%). Non-breast cancer causes of death included other cancers, cardiac disease, stroke and other causes. The authors suggested that the higher non-breast cancer mortality could be partly explained

by the effect of the EBRT dose delivered to the heart,[26] but this interpretation has been questioned because the various causes of deaths cannot all be aetiologically linked to radiation therapy.[31, 32] Complication rates for infection and skin breakdown or delayed wound healing were not statistically different between the arms of the trial. Seroma needing more than three aspirations was more frequent in the Intrabeam arm and the difference was statistically significant. RTOG toxicity grade 3 or 4 was greater in the EBRT arm and the difference was statistically significant. [30]

Issues with the TARGIT-A trial include:

- there is debate regarding the results of the trial and opinion that longer follow up is needed[33, 34]
- the 2.5% margin of inferiority was chosen when the risk of local recurrence after standard treatment was 6%. But the risk of recurrence for standard treatment in the current trial was noticeably lower, which inflates the relative risk. It is suggested that within non-inferiority trials relative measures should be reported as well as absolute measures as relative differences tend to be more stable over time[28]
- correspondence in the Lancet calculated a hazard ratio of 2.56 for local recurrence between the two arms with a confidence interval that could indicate a recurrence rate of up to 7.1% for IORT, which is outside of the predefined margin.[33]

With respect to the duration of follow up the study authors note that the peak of local recurrence occurs within the first 2-3 years and radiotherapy provides protection during the first five years of follow up. The method for the calculation of the above hazard ratio and its accuracy has been questioned.[35]

The TARGIT-A trial is being followed up by the recently started TARGIT-B, an RCT comparing the effectiveness of IORT and EBRT in delivering the boost component of radiotherapy.[36]

5.1.1.2 ELIOT

The ELIOT trial was an RCT comparing EBRT with electron-delivered IORT using the NOVAC 7 system. The prespecified equivalence margin was local recurrence of 7·5% in the intraoperative radiotherapy group. This level was considered acceptable in most institutions during study design.[27] Participants were aged between 48 and 75, suitable for breast conservation surgery, and with a maximum tumour diameter of 2.5 cm. 1305 women were randomised to either a single IORT treatment, or EBRT. In the IORT arm, 87% of patients had tumours 2 cm or less in size, 81% had ductal histology and 80% had grade 1 or 2 tumours. Median follow-up overall was 5.8 years.

Local recurrence rate at five years was 0.4% in the EBRT arm and 4.4 % in the IORT arm. The absolute difference in local recurrence was within the predetermined limit of 7.5% but the relative risk of recurrence in the IORT group was significantly greater at 9.3 (95% CI: 3.3–26.3) times that in the EBRT treated patients.[27]

Survival did not differ between the two arms and mortality did not differ significantly between breast cancer and non-breast cancer causes.[27] Significantly fewer skin side-effects were noted in the IORT

group than in those in the EBRT group for those patients where data was available, with 8.0% having any skin toxicity in the EBRT groups and 2.7% in the IORT group.

5.2 IORT as additional therapy

5.2.1 Breast cancer

There is a substantial body of evidence for planned use IORT in conjunction with EBRT, sometimes called 'boost IORT'.[37] The largest source of data is the International Society of Intraoperative Radiotherapy (ISIORT) Europe Pooled Analysis. A median intraoperative radiotherapy with electrons (IOERT) dose of 10Gy was applied before EBRT with 50–54Gy (single doses 1.7–2Gy) to 1109 unselected patients of any risk group and of all ages, of whom 60% had at least one adverse prognostic factor for local recurrence. Follow-up at 73.3 months showed in-breast tumour control rate of 99.2%. One comparison of patients who received boost IOERT with those who received a boost EBRT found that:[37]

- at 10-year follow-up, the recurrence rate was 1.6% in the IOERT group and 7.2% in the EBRT group
- treatment-related mortality and excess acute local morbidity did not differ
- cosmetic results were similar, but inferior if time intervals between IORT and EBRT was less than 30 days.

The TARGIT-A trial included a subgroup of 253 patients who received both IORT and EBRT. 219 of these were patients who had been randomised prepathology and 20 postpathology to receive IORT alone, but at surgery were found to meet high risk criteria to also receive EBRT. A further 14 patients randomised to EBRT alone, eight prepathology and six postpathology, also received both IORT and EBRT. No explanation is given of why patients randomised to EBRT received IORT. Only results for the 219 randomised prepathology to IORT but receiving both treatments are reported. They showed a substantially higher rate of breast cancer mortality than the other patients at 8%, but these patients are a high-risk, poor-prognosis sub-group and this result cannot validly be compared with the fatality rates in the TARGIT (2.6%) and EBRT (1.9%) alone groups. However, local recurrence was low in that group (0·9%, CI: 0·1–6·1), and did not differ from those who received TARGIT alone.[30]

5.2.2 Gastric cancer

The addition of IORT in treatment of gastric cancer provides minimal effectiveness in increasing survival and is associated with a high complication rate.[1, 12, 38, 39] There may be reduced local progression.[40]

5.2.3 Pancreatic cancer

The evidence shows the addition of IORT provides minimal or no benefit for patients with localised pancreatic cancer disease, and the evidence is inconsistent.[12, 38] A systematic review of studies published up to 2008 on the use of IORT in treatment of pancreatic cancer concluded that it did not improve effectiveness when used in addition to other treatment modalities including surgery. Its use

in localised disease showed limited improvement in survival time. There were no randomised studies.[41] The balance of studies published since the systematic review show no benefit.[1]

5.2.4 Soft tissue sarcoma

There is potential benefit for IORT used as an addition to multi-modal approach to retroperitoneal tumours. IORT may reduce risk to structures adjacent to the tumour site compared with EBRT. One study of adding IORT to ERBT post-surgery compared with EBRT alone reported reduced tumour recurrence of retroperitoneal sarcomas, but with no change in survival;[38] whereas others found the addition of IORT or EBRT produced no change in local control.[12] For other soft tissue sarcoma, the addition of IORT may have favourable impact on control and survival.[12] Toxicity seems to be similar to EBRT treatment.[1]

5.2.5 Gynaecological cancer

No systematic reviews were identified for IORT used for gynaecological cancers.[38]

There is some evidence for IORT in combination with surgery for patients with locally recurrent disease of the cervix or uterus for whom surgery alone might not be curative.[1] A phase 2 trial of IORT in conjunction with radical surgery performed after pre-operative chemotherapy and EBRT in patients with locally advanced cervical cancer concluded that the regimen was effective for a subgroup of patients and has a role in the treatment of locally advanced cervical cancer. Authors of a case series concluded that IORT is a valuable boosting technique in the management of advanced but resectable cervical cancer.[38]

5.2.6 Head and neck cancer

Initial research shows a potential role for IORT in locally advanced head and neck cancer.[12, 38, 42] In patients with recurrent or persistent disease, IORT appears to improve local control and survival. However, there are no RCTs assessing the role of IORT in head and neck cancer.[1]

5.2.7 Prostate cancer

The feasibility of IORT as an addition to radical prostatectomy for localised prostate cancer has been investigated in a phase I-II trial. The authors considered that feasibility of IORT in prostate cancer was shown, but comparative effectiveness was not reported.[12]

5.2.8 Colorectal cancer

The role of IORT for primary advanced and locally recurrent colorectal disease was examined in a systematic review and meta-analysis.[43] It found that IORT appears to be used more frequently for rectal cancer than colon cancer, and that IORT improved five-year local control, disease free survival and overall survival. However, the two RCTs included in the meta-analysis assessing IORT for primary advanced disease failed to show additional benefit over surgery alone. One of the RCTs was limited by its sample size and a relatively low risk patient group. In the other RCT, the control group showed high local control and it was thought that complete resection was achieved, suggesting no benefit

from the addition of IORT in the setting of complete surgical resection. For locally recurrent disease there were three comparative studies but data on possible confounding was not available.[43]

Further studies since the systematic review was published include a study of patients with localised recurrent disease, which showed benefit of IORT for local control although not overall survival.[44] A retrospective study comparing IORT and EBRT in rectal cancer with local spread treated with surgery and post-op chemo therapy showed equivalent outcomes.[45]

Other reviews, based on case series of patients with advanced or recurrent disease, have reported that for patients with locally advanced disease, the addition of IORT to standard therapy appears to improve local disease control and survival,[12, 38] and that IORT offers an option when there is limited opportunity to increase the radiation dose or re-irradiate.[1] However, a recent systematic review suggests that the improvements found are likely to reflect better patient selection and better optimised treatment in the trial groups rather than the benefit of IORT as an intervention.[46]

5.3 Organisational positions on IORT

5.3.1 National Institute of Clinical Care and Excellence (NICE UK)

NICE in the UK has recently provisionally recommended the use of Intrabeam in the management of breast cancer as an option for treatment. Publication of the final recommendation following consultation will be November 2014.[47] In taking their position, they noted the following:

- patients should be fully informed of the risks and benefits; in particular that less is known of the long-term outcomes and that local recurrence rates are higher for Intrabeam than conventional radiotherapy
- all patients treated should be included in a national register to gather further data on patient characteristics and clinical outcomes
- longer follow-up of patients in TARGIT-A would be helpful to provide more long-term data
- the non-inferiority of Intrabeam compared with EBRT in terms of local recurrence has not been established, because the criterion for non-inferiority in TARGIT-A was not appropriately defined and the results in terms of local recurrence could not be considered sufficiently robust. However, NICE acknowledged that the reported recurrence rates could be considered low in absolute terms and not out of line with current recurrence rates with EBRT in the National Health Service
- it was not possible to confirm that there was an overall survival benefit from Intrabeam compared to EBRT in early breast cancer
- some patients were willing to accept a slightly higher risk of local recurrence as long as the absolute risk remained low and the treatment had other benefits which they considered important. There were benefits for patients of Intrabeam, particularly associated with length of treatment and quality of life.

5.3.2 Blue Cross and Blue Shield Association (US healthcare insurers)

The Blue Cross and Blue Shield Association (BCBS) have evidence-based guidelines which indicate accepted clinical indications and clinical conditions where the use of IORT is not considered effective.

BCBS indicate a limited number of cancer conditions for which IORT may be considered effective. They consider IORT may be appropriate in the treatment of rectal cancer patients in which the surgical margins are close or positive and lesions are at a stage T4 or disease is recurrent.[(2) (38)] Use of IORT is otherwise considered 'investigational'[(38)], meaning it is a technology which is in a developmental stage or has not been proven to improve health outcomes such as length of life, quality of life, and functional ability. Specifically, the use of IORT in breast cancer is considered investigational.[(24)]

5.3.3 Aetna (US healthcare insurers)

Aetna considers IORT medically necessary under certain clinical conditions for cervical, uterine, colorectal and soft tissue sarcoma. The benefit in other cancers is considered to have not been established.[(12)]

5.3.4 Cancer Treatment Advisory Group (CTAG) and Radiation Oncology Work Group (ROWG)

The CTAG provides clinical advice on cancer treatment to the Cancer Control Steering Group which itself provides governance for the Cancer Control Programme, which is a national programme that covers Ministry of Health, District Health Boards (DHBs), and regional cancer networks activity to implement the New Zealand Cancer Control Strategy and New Zealand Cancer Control Strategy Action Plan. Among the membership of the CTAG are the national clinical director of the cancer programme, the clinical directors of the regional cancer networks, a radiation oncologist, a medical oncologist, a paediatric oncologist, a haematologist, a surgeon, an oncology nurse and primary care clinician. Clinicians are nominated by relevant clinical colleges or professional bodies. The CTAG establishes and co-ordinates work groups to provide advice on specialist areas within cancer control, one of which is the Radiation Oncology Working Group.[(48)]

The CTAG forwarded its position to the National Health Committee without a formal request. The CTAG sought advice from the ROWG who provided the following advice on whether IORT should be publically funded for patients with breast cancer.[1] The ROWG:

- do not believe that IORT for women with early breast cancer is currently an appropriate addition to treatments
- do not believe that IORT should currently be offered in the public health system
- believe that the TARGIT-A trial needs longer follow-up
- believe that the only place for IORT in New Zealand currently would be in the form of participation of an Ethics Committee approved trial
- propose that the data be re-evaluated two-yearly or earlier if significant new data is released

[1] Personal Communication

- recognised that delivering a single treatment instead of multiple treatments is attractive to both patients and the health sector
- observed that subgroups of the TARGIT-A trial showed similar outcomes to standard external beam radiation but that the follow-up was short in the breast cancer context. Longer follow-up could lead to significant changes in outcomes.

The CTAG endorsed this advice from the ROWG, with the additional comment that patients have the right to make an informed choice regarding their treatment options. Patients who understand the uncertainty about the long term outcome of IORT have the right to choose that treatment option, but the CTAG felt that public investment in the technology and infrastructure to allow for IORT would be premature given that this could potentially become obsolete if long term outcomes from IORT show poorer outcomes. The CTAG further advises that the position on IORT can be reconsidered when new evidence becomes available.

5.3.5 Northern Regional Clinical Practice Committee

The National Health Committee did not formally request the position of the Northern Regional Clinical Practice Committee (NRCRC).

The NRCRC has recently produced a technology brief on IORT and early breast cancer.[1] This expressed the view that the issue of non-inferiority should be comprehensively addressed before widespread adoption of IORT for early stage breast cancer patients. It considered that a longer follow-up interval is required to establish such a claim for IORT.

5.4 Clinical advice

5.4.1 The Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists (the Faculty)

The Faculty provided its position on IORT in response to direct communication from the NHC Executive. The Faculty considers that IORT should not yet be used in the treatment of breast cancer or other cancers outside of a clinical trial. The Faculty's response included reservations about the Intrabeam trial:

- the trial median reported follow-up of 2.4 years is currently too short and 10 years of follow up is preferred. A number of local recurrences could present later because the trial participants are of low risk.
- based on known evidence of radiation dose and cardiac mortality, the Faculty does not accept the attribution of non-cancer deaths to whole breast irradiation and consider the deaths may be due to chance given the small number of events and non-stratification of patients by underlying cardiac risk.

With respect to economic considerations in the use of IORT in early breast cancer, the Faculty considers that possibly only between 10–16% of new breast cancer patients may be suitable

candidates for IORT, and notes that low risk patients receiving EBRT would be treated with 15–19 radiation fractions rather than the standard 25 sessions.

In relation to the potential role of IORT in patients who do not take up radiotherapy after breast-conserving surgery, the Faculty considers that the underlying issues impacting the decision not to not take up radiotherapy should be addressed rather than IORT being considered as an option.

Responses of radiation oncologists that were received by the Faculty after the deadline were forwarded to the NHC executive. These responses considered that:

- Intrabeam was considered to have demonstrated 'non-inferiority' to EBRT
- the use in New Zealand should be on appropriately selected patients with the collection of prospective data
- potential benefit of IORT is promoted in terms of patient convenience and improved quality of life
- reduction in mastectomy is expected as the current need for EBRT acts as a disincentive to breast-conserving surgery
- potential of IORT to treat patients who are considered unlikely to initiate or complete a course of EBRT was supported
- IORT enhances quality of life, cosmetic results, patient preference regarding convenience and the support of consumer groups.

5.4.2 Breast Surgeons Society of Australia and New Zealand Inc (BSSANZ)

The BSSANZ gave its position on IORT in early breast cancer management in response to the request of the NHC executive. They consider that the role of IORT in early breast cancer is still being established as there are limited long-term data. The society felt it is an appropriate option to consider for low risk patients that meet the TARGIT selection criteria.

5.4.3 Royal Australasian College of Surgeons (RACS)

The NHC Executive requested advice from the New Zealand Board of the RACS on the uses of IORT in cancers other than breast cancer. The college reported that IORT has a complementary role in the treatment of locally advanced and recurrent rectal cancer. The supportive evidence for this indication is based on case series. IORT is not considered to have a role in urological, plastic or head and neck surgery cancer management but may have a place in the management of retroperitoneal sarcomas and pelvic rhabdomyosarcoma.

Advice has not been formally requested by the Executive from any other body.

Overall, there is little high-quality evidence available on the use of IORT in the treatment of cancers. Evidence for IORT as an adjunct therapy in any of the described cancer groups is based on low quality studies. Current evidence for the use of IORT in addition to EBRT in:

- prostate cancer is at an early stage
- gastric and pancreatic cancers indicates no benefit

- locally advanced cervical cancer, locally advanced head and neck cancers, and locally advanced or recurrent colorectal cancer is inconclusive but suggests IORT may have a role.

Clinical stakeholders have not identified use of IORT in other cancers as appropriate. Identified commissioning bodies have considered cervical, uterine, colorectal and soft tissue sarcoma as appropriate indications under certain conditions.

Evidence for IORT in early breast cancer as a substitute for EBRT is of better quality. It is unclear whether Intrabeam in early stage breast cancer has been adequately demonstrated as non-inferior to EBRT. Some clinical stakeholders consider that IORT for the treatment of early breast cancer is not currently supported as the evidence is immature and longer follow-up is needed; whereas others have noted the potential benefit of IORT for some patients in overcoming barriers to access to radiotherapy, and the potential improved quality of life that IORT offers in comparison to standard radiotherapy. It has been proposed that IORT should be provided for breast cancer treatment and patients should be in a position to make informed choices about treatment with the knowledge of its benefits and risks.

6 Materiality

6.1 Current configuration of cancer services impacted by IORT

New Zealand currently operates six cancer centres (Auckland, Waikato, Mid-Central, Capital and Coast, Canterbury and Southern DHBs) which offer a variety of cancer therapies. International opinion suggests that 45–52% of people with cancer would benefit from radiation therapy.[49] IORT is currently only suggested for use in the treatment of a subset of cancers which would otherwise be treated by EBRT alone.

EBRT, currently provided by Linear Accelerators (Linacs), is a well-established treatment for selected cancers, often used in conjunction with surgery and chemotherapy. There are 31 Linacs currently operating in New Zealand: 23 in the public sector across the six cancer centres, and eight in the private sector.

Hypofractionated radiotherapy is an alternative to standard whole breast irradiation for delivering radiotherapy. Accelerated radiotherapy involves providing fewer, higher-dose EBRT sessions, often 15 sessions over three weeks as opposed to 25 sessions over five weeks.

In New Zealand in 2012, 11,878 publically funded radiation therapy courses were delivered by both public and private providers. 7346 of these were first course radiation therapies. There were 176,047 attendances for treatment, an average of 14.8 attendances per course. There were 448 courses per Linac per year, indicating an average of 6600 attendances per Linac per year. It is predicted that between 8 and 20 additional Linacs will be needed in the 10 years from 2013. The base scenario is dependent on the increase in cancer registrations and the higher scenarios on increases in the rate of treatment of cancers by radiotherapy.[49]

6.1.1 Volume materiality

Cancer as a group of diseases represents a large portion of hospital admissions and is the largest contributor of DALYs in New Zealand. As shown in Table 2 below, in 2010 there were 21,235 new cancer registrations in New Zealand. However, IORT would only be relevant to a subset of these cancers, being dependant on the indications for different stages of disease.

Table 2 New Zealand cancer registrations by site 2010

Site	ICD-10	Registrations	% total
Breast	C 50	2812	13.2%
Colorectal	C 18–21	2988	14.1%
Non-rectal	C 18,19,21	2268	10.7%
Rectal	C 20	720	3.4%
Prostate	C 61	2988	14.1%
Head and neck	C 7–14, 32, 33	248	1.2%
Gynaecological	C 51–58	1086	5.1%

Soft tissue sarcoma	C 49	123	0.6%
Pancreatic	C 25	493	2.3%
Gastric	C 16	369	1.7%
Others		7140	33.6%
Total registrations 2010		**21,235**	**100.0%**

Source: Cancer: New registrations and deaths 2010, Ministry of Health 2013

6.1.2 Breast cancer management post diagnosis

Early breast cancer is subdivided into two major categories: in situ disease, mainly in the form of ductal carcinoma in situ (DCIS), and invasive cancer. DCIS is predominantly detected by breast screening as microcalcifications on mammography and is not commonly palpable. DCIS, by definition, has not spread outside the boundaries of the normal structures of the breast. Invasive breast cancer infiltrates into the breast stroma and has the potential to spread to lympho-vascular spaces and to metastasise. Not all invasive breast cancers are the same; some are more aggressive and some may spread earlier to distant sites.

There are a variety of methods for classifying invasive breast cancer. An important one is histological grading, which identifies tumours as being of histological grade 1 (least aggressive), grade 2 or grade 3 (most aggressive). Assessment of lymph nodes in the axilla, which requires surgical excision and microscopic examination, is crucial to staging and prognosis of patients with operable breast cancer.

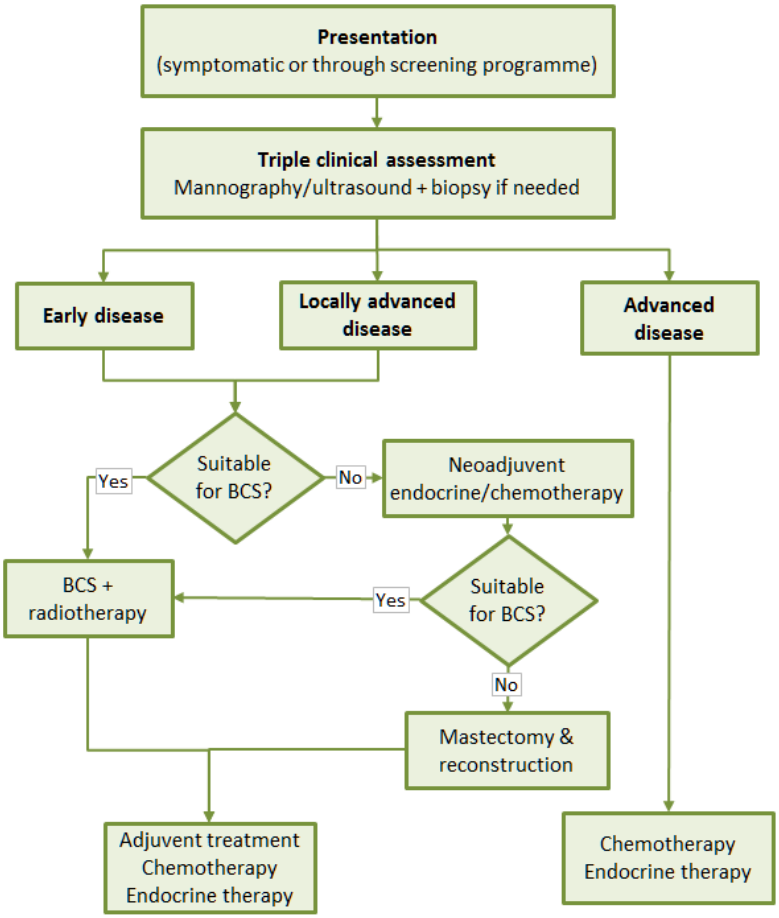
Early breast cancer is defined by its stage at diagnosis. Surgery may be considered in stage I disease, where the cancer is confined to the breast or there are only micro-deposits of tumour spread to the axilla; and stage II disease where the tumour is in the axilla and the lymph nodes are mobile. Some sub-classes of stage III may also be considered suitable for surgery, where the nodes are fixed or matted or numerous and affecting other lymph node regions.

Surgical management aims to excise invasive and non-invasive cancer with clear margins. Mastectomy, without the need for radiotherapy, may be recommended when breast conserving surgery is not possible owing to tumour size, multifocal disease, aesthetically unfavourable ratio of breast size to tumour volume or at the patient's request. Axillary lymph node dissection is performed on those with clinically positive nodes pre-operatively and a positive result to sentinel lymph node biopsy at operation. Clinical assessment includes hormonal and genetic status of the tumour to inform the use of adjuvant systemic therapy.[50] Survival after breast conserving surgery followed by radiotherapy is equivalent to that after mastectomy.[51, 52]

Figure 2 illustrates a simplified potential flow for patients presenting with breast cancer. Presentation can be symptomatic or via detection by screening. Diagnosis is initially with mammography and/or ultrasound. If needed, a sample of tissue is obtained by fine needle cytology or core biopsy. Treatment options depend on stage and tumour characteristics, including hormone receptor and tumour gene expression. In early breast cancer where tumour size initially prevents

consideration of BCS, neoadjuvant therapy can be used. This therapy is also used in locally advanced disease to reduce facilitate BCS. Treatment of patients with advanced disease includes hormone therapy and chemotherapy.[53, 54]

Figure 2: Simplified breast cancer patient flow



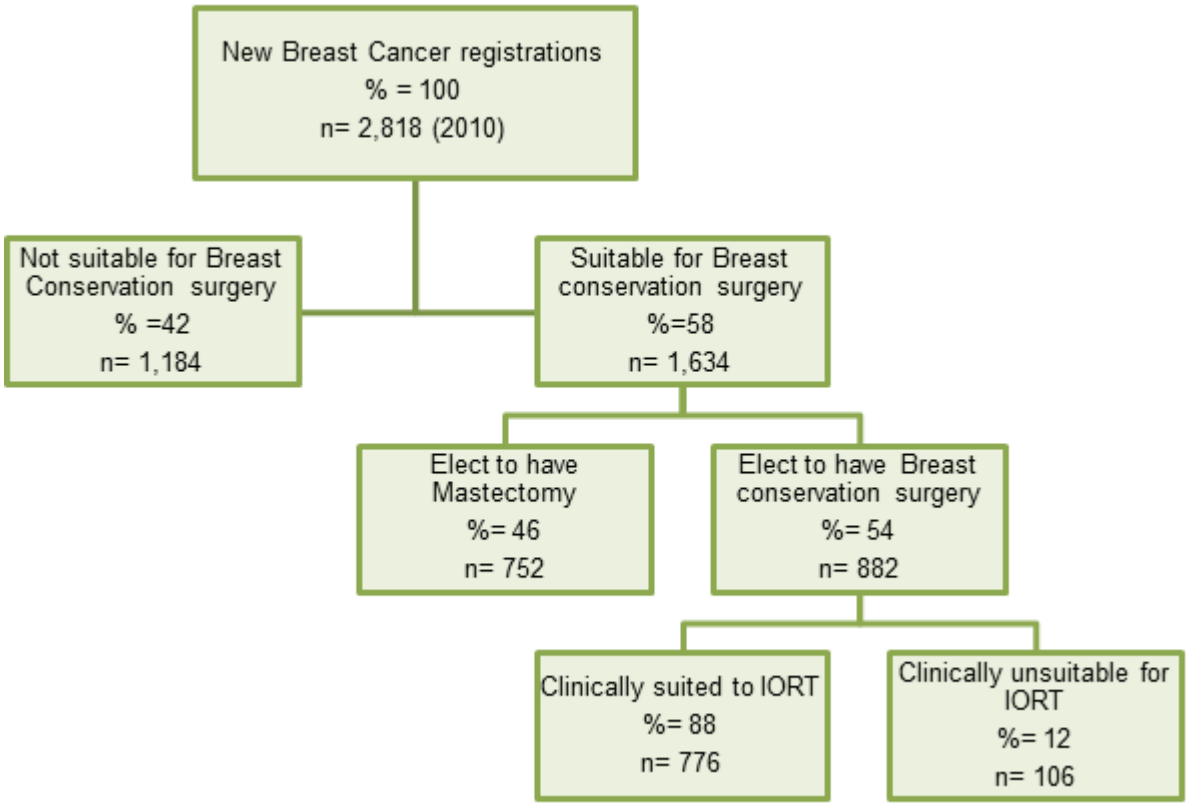
Source: National Health Committee Executive using sources[53, 54]

6.1.3 Estimation of role of IORT for breast cancer treatment in New Zealand

There are approximately 2,900 new diagnoses of breast cancer annually in New Zealand. Figure 3 uses a UK estimate that 58% of new diagnoses of breast cancer are early breast cancer eligible for breast conservation therapy.[55] Currently in New Zealand, 46% of women with early breast cancer elect to have a mastectomy and 54% elect to have breast-conserving surgery.[56] A minimum of about 12% of women with early breast cancer would not be suitable for Intrabeam because of tumour size alone.[56] Other additional clinical factors could limit the eligible population further.

Figure 3 illustrates these percentages using the 2010 figures, when there were 2818 breast cancer registrations.

Figure 3: Estimated proportion of patients with breast cancer suitable for IORT



Source: NHC Executive analysis[55, 56]

Figure 3 shows that 1634 (58%) of the 2818 breast cancer registrations were suitable for breast conservation surgery. Subsequently, an estimated 882 (54%) elect to have breast conservation surgery, while an estimated 752 elect to have a mastectomy. Of those who elect breast conservation surgery, an estimated 776 (88%) were suitable for IORT.

This suggests that IORT could have been provided for between 750 and 800 (27%) out of 2818 of breast cancer registrations in 2010. Estimates provided to the NHC by the Breast Cancer Aotearoa Coalition (BCAC) suggest that 30% of these new diagnoses could be suitable for IORT, very similar to the number calculated above. However, the Faculty of Radiation Oncology of the Royal Australian and New Zealand College of Radiologists were of the opinion that only between 10–16% of patients with breast cancer would be suitable for IORT although they provided no basis for this estimate.

The role of IORT will also depend on uptake and the impact on traditional EBRT service. About 8% of early breast cancer patients are not prescribed radiotherapy post breast-conserving surgery.[56] The reasons for non-prescription may include clinical circumstances or a decision to not accept treatment because of difficulties accessing the treatment. A small study on patient preference regarding IORT and EBRT suggests that 64% of patients would be willing to receive IORT with some additional risks compared with EBRT.[57] Patients who elect to receive IORT would be given therapy during their breast conservation surgery with no subsequent EBRT planned. However, the TARGIT-A trial

suggests that about 22% would also require EBRT post IORT because of the cancer histological type, only identifiable post-surgery and IORT delivery.

In the US, an estimated 13% of patients do not complete EBRT.[58] We are not aware of data for non-completion for New Zealand. If patients who are unlikely to complete EBRT could be identified prior to surgery, then they could be suitable for targeting for IORT. If an estimated 13% of EBRT patients do not fully complete their prescribed EBRT therapy with an average of 10 sessions each; and 87% complete their prescribed EBRT therapy with an average of 20 sessions each, there is an average of 18.7 EBRT sessions per patient.

Figure 4 shows four potential scenarios of IORT provision. Scenario A assumes all suitable individuals receive IORT; B assumes that patients can select freely between IORT and EBRT; C assumes perfect targeting is used to select only patients who will not complete their EBRT therapy; and D models the use of EBRT alone.

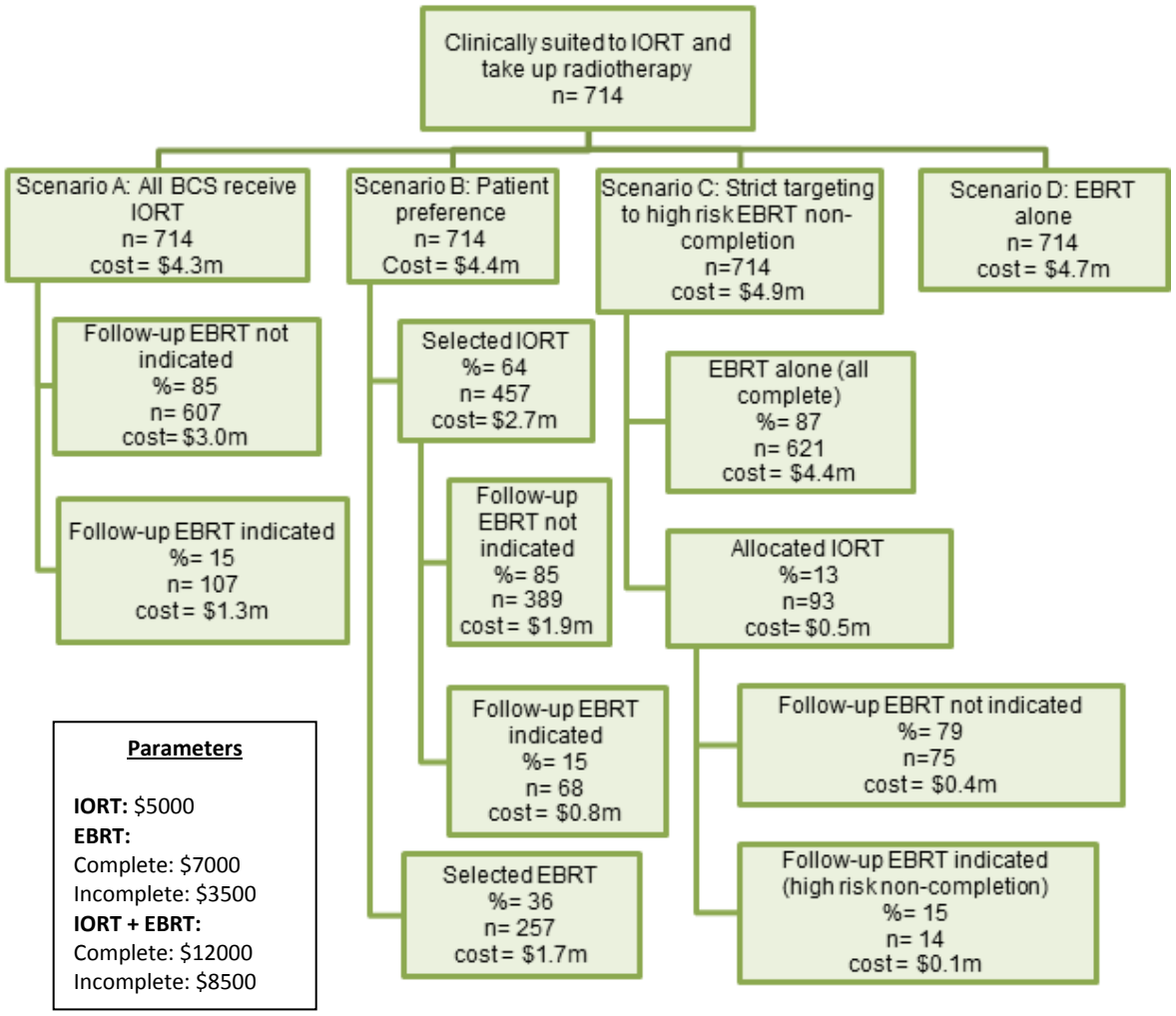
In all scenarios the following assumptions are made:

- 15% of women who receive IORT require follow-up EBRT (as was found in the TARGIT-A trial)
- 87% of patients that are prescribed EBRT complete treatment and have 20 sessions
- those who do not complete are assumed to receive 50% of full treatment or 10 sessions
- in scenario C all who receive EBRT complete treatment.

A cost has been calculated for each scenario. The costs used are $350 per EBRT session[2] giving a cost of $6,545 for an average 18.7 sessions completed. The cost of IORT is estimated at $5,000 based on the costing of IORT and EBRT sessions in the economic analysis in the NICE assessment.

[2] National Collections purchase units M50024 and M50025.

Figure 4: Estimated impact of IORT under four scenarios



Source: NHC Executive analysis

As Figure 4 shows there are around 720 patients suitable for IORT who currently take up radiotherapy (excluding the 8% who do not have radiotherapy prescribed). IORT could reduce costs by up to $0.4 million per annum if provided to all women who receive breast conserving surgery, and $0.3 million when patients are allowed to select between IORT and EBRT. This cost reduction is due to reduced need for EBRT sessions, which for a course of 20 sessions is estimated to cost $2,000 more per patient than IORT. Strict patient targeting (scenario C) resulted in increased costs compared to EBRT, though it is assumed with improved health outcomes with increased access to treatment.

This analysis suggests that there may be the opportunity for material savings from using IORT as a substitute for traditional EBRT. In 2012, 10,841 publically funded radiation therapy courses were delivered in New Zealand, with an estimated cost of $103 million. IORT could therefore deliver a very modest reduction to the cost of EBRT if used only in breast cancer. However, the material savings would need to be balanced against any increase in clinical risk (of increased local recurrence and future breast cancer related mortality) from IORT when compared to EBRT.

Figures 3 and 4 do not model the possible substitution of breast conservation surgery for mastectomy. Substitution would not increase procedure cost (both were estimated at $7,000). But it would increase subsequent IORT/EBRT volumes as post-mastectomy management for early breast cancer does not include radiotherapy. A US study estimated that 44% of women living within 25 miles of a EBRT facility elected mastectomy compared to 53% of women living more than 25 miles from a facility. Assuming distance was the only factor, this suggests that 9% of women may be electing a mastectomy over breast conservation surgery due to the need for EBRT sessions. In New Zealand, 56% of the population lives in a main urban area with EBRT facilities, and 44% do not. Applying the US experience to New Zealand, in Figure 3 44% of the women electing mastectomy live outside of a main urban area. If 9% of these chose to have mastectomy due to distance from EBRT facility, then 4% (30 in 2010) of women having mastectomies may switch to breast conservation surgery.

There are other non-clinical factors that may influence the decision to undertake mastectomy over breast conservation surgery, such as convenience, work commitments and childcare. The size of the influence of these factors is currently unknown, but may be affected by reduced need for EBRT.

The cost of treating any change in local recurrence was not modelled explicitly in Figure 4. However if IORT has a 2% higher local recurrence rate compared to EBRT(the central estimate from the TARGIT-A trial),[(26)] and between 79 and 600 women receive IORT alone, then between 2 and 12 additional local recurrences could be expected from an annual cohort within five years. The treatment for local recurrence is mastectomy, with an estimated cost of $7,000 per procedure, resulting in additional costs of between $84,000 and $14,000.

Colorectal cancer is the only other cancer with an evidence base for which IORT may provide benefit as an adjunct therapy. The evidence is more extensive for rectal than colon cancer. There were 2988 colorectal cancers registered in New Zealand in 2010, and 720 of these (24%) were rectal cancers. About 40% of incident cases of rectal cancer have locally invasive disease or regional node involvement[3] for which IORT in addition to the current therapeutic regimen could be applied, suggesting 288 rectal cancers may have benefited from complementary IORT in 2010. This suggests that scope for between 1064 selected breast and rectal procedures annually in New Zealand if IORT was offered as a complement or substitute to EBRT.

6.1.4 Fiscal materiality

The number of interventions which can be provided per machine is assumed by the manufacturer to be 100 interventions per machine per year, while the economic evaluation performed for the NICE assessed it as between 100 and 126 per year.[(47)] If the number of interventions is 100 per year, it would equate to about two interventions per week, which may be consistent with the provision of operating sessions in a single site. This means about seven devices would be required to meet demand for the substitution for EBRT in treating selected women with breast cancer, and an additional three devices would be needed to treat the patients who receive IORT complementary to EBRT, about 10 devices needed in total to treat both groups.

[3] Source: National Health Committee using data from the Cancer Registry, Ministry of Health.

The estimated cost of an IORT machine is $1.2 million, with an annual maintenance cost of $100,000 per annum. If 10 machines were purchased, extending IORT to both groups, $12 million in capital expenditure may be required to acquire the devices and $1.0 million in running costs per year. There are also other costs including staff training and overheads (e.g. electricity). These capital and running costs would be reduced if greater use could be made of each machine. This could be achieved by using the machines across multiple sites. The device stand and control cart are not portable but other components feasibly are using appropriate equipment. The non-portable equipment account for about 50% of the overall system costs according to the manufacturer. The ongoing development of a new technology can lead to obsolescence of machines with loss of use before the end of their expected lifespan.

The economic assessment performed as part of the NICE assessment indicates that Intrabeam would be cost saving with lost quality of life; £1596 saved for each quality-adjusted life year (QALY) lost. An alternative way of presenting this is that if Intrabeam was standard care and then it would only cost £1596 to gain an additional QALY by introducing EBRT, which would be considered a cost-effective treatment. The manufacturer's submission indicated greater savings and QALY gain. The NICE assessment noted that some of the manufacturer's assumptions (including a greater number of EBRT sessions) were not in line with UK clinical practice .[7]

As indicated in Figure 4, the use of IORT in early breast cancer could reduce costs. It is not known how the complementary use of IORT in rectal cancer will affect costs.

6.2 Feasibility of adoption

If IORT is decided to be a safe, effective, cost-effective and appropriate way to treat selected patients, then it is likely to be technically feasible to adopt the technology into the New Zealand public health system. Feasibility is assessed here in terms of impact on the sector (hospital, workforce), population (access, ethical considerations) and fiscal feasibility.

The introduction of IORT for selected women with breast cancer is likely to result in some reduction in the demand for EBRT services. IORT may therefore reduce waiting times for EBRT sessions, and reduce growth in EBRT services, relieving pressure from current workforce shortages and capital investment programs. The portability and reduction/removal of operating theatre shielding requirements compared with other radiological interventions mean that the treatment could potentially be provided in all locations currently providing surgical cancer treatments. The trade-off between increased theatre utilisation and reduced EBRT sessions will need to be considered and feasibility will depend in part on the relative capacities of these resources. There is also the possibility of moving the core device between centres which possess only Intrabeam 'arms' and consoles to reduce the number of devices required.

IORT would impact on the time taken to conduct surgery, with an estimated 45–60 minutes of additional theatre time required to provide the IORT during the surgical procedure. It is unlikely that other activities could be performed by staff during this time. Careful consideration should be made as to the impact of this additional theatre time and labour requirement for staff involved will impact on theatre bookings and surgical volumes.

Currently breast surgery is performed widely across New Zealand hospitals. If IORT was offered it may be concentrated in a restricted number of centres so that the improved convenience in terms of access to radiation treatment would be relative for some women. Possibly this would mean that for surgery patients would spend two to three days at a regional centre rather than their local centre, but would not need to spend five to six weeks at a regional centre for radiation therapy. If patients move to another centre for surgery in order to receive IORT this will have implications for resources at the referral centres. There may also be implications for the range of surgery offered at the referring centres. These issues may be overcome by portability of IORT equipment.

The feasibility of IORT for patients will depend on patient willingness to undertake a more convenient procedure, while accepting a reduction in effectiveness within a known limit for local recurrence that translates into a predictable increase in later mortality. To allow patients to make this trade off, the provision of complete information for patients around the safety and effectiveness of the procedure will be important so that patients can make a fully informed choice as to the treatment they choose, and maintaining the option to undertake traditional EBRT, with proven safety and effectiveness, remains an important consideration should IORT be adopted. Formal inclusion and exclusion criteria for IORT treatment would need to be considered and any impact on equity of access. Adoption would require configuration of these to New Zealand.

While the cost of IORT may be offset by reductions in the growth of EBRT services, avoiding the need to purchase new EBRT equipment and reducing labour force growth in this area, the savings will not be accrued until several years after IORT capital is purchased. In the case of early breast cancer and of all eligible patients opting for IORT about 600 patients (Figure 4) would solely have IORT delivered. This would avoid about 11,200 EBRT attendances, equivalent to the utilisation of 1.7 Linacs or 1.1 Linacs for the scenario determined by patient preference.

As IORT is not yet well established in the clinical literature, there is also the risk that the machines may become obsolete, or only of use in combination with traditional EBRT, meaning that the savings may not be realised to offset the capital expenditure. A private hospital in New Zealand has begun providing IORT for treating breast cancer, with a facility recently established in Auckland by Focus Radiotherapy that operates through Southern Cross North Harbour Hospital. This facility uses the Intrabeam machine. A procedure is priced at approximately $8,600.[59]

6.3 Future research

A superiority trial in patients with early breast cancer receiving EBRT has been registered at the clinical trials database but is yet to start recruiting. The trial is to compare Intrabeam at time of surgery versus usual tumour bed boost therapy given after EBRT.[60] A phase 1 RCT is currently recruiting patients with operable rectal cancer to alternative doses of photon IORT. A study of the Xoft Axxent IORT system in breast cancer is recruiting currently. A phase 2 trial is currently recruiting patients with resectable retroperitoneal sarcoma to assess the effect of IORT with surgery after pre-operative radiotherapy.[61]

NICE noted that research currently in progress is to assess the effectiveness of EBRT delivered over one week and whether some women with breast cancer at very low risk of recurrence could have radiotherapy omitted. In due course, results from these trials could have an impact on the postulated place of IORT in the management of early breast cancer.

6.4 Societal and ethical considerations

A NICE assessment of the equality impact of IORT did not identify any equity issues around the provision of IORT.[62] Any further assessment into IORT should include some assessment of geographical access to IORT facilities, distribution of cancers which could be treated by key socio-economic characteristics and expenditure on these cancer services relative to other cancers may be required to assess the societal and ethical impact. Should IORT be provided under trial conditions then this should be subject to ethics approval.

As IORT is conducted during surgery, and removes the need for EBRT sessions over several weeks, there is also a societal savings to patients. This will include transportation costs to and from sessions, the opportunity cost of the time taken (including lost wages or childcare costs) and the accommodation costs for patients who do not live near facilities that can provide EBRT. It may also result in improved return to work times, reduced sick leave and greater productivity amongst patients.

With specific regard to IORT in breast cancer, there is indication that some women choose mastectomy over EBRT due to the costs, inconvenience and side effects which are reduced or removed with IORT, and there may be substitution from mastectomies to breast conserving surgery with IORT which may have a societal benefit. Distance from radiotherapy has been shown to be associated with reduced uptake of EBRT[63] and increased mastectomy in early stage breast cancer.[64] In a US study, 87% of participants completed full EBRT therapy, and non-completion was associated with higher risk of local recurrence.[58]

Although the evidence for Intrabeam does not appear to satisfactorily demonstrate 'non-inferiority' compared to EBRT it could be considered to have a potential role where standard therapy cannot be completed. It would be necessary to be able to reliably identify patients who are at risk of not completing their ERBT course prior to the commencement of treatment, which may be difficult to achieve.

Table 3: Summary of value of IORT interventions and assessment criteria

Intervention description	Population	Clinical safety and effectiveness	Societal and ethical	Economic	Feasibility of adoption	Other considerations	Value of NHC HTA
IORT instead of EBRT	Women with early stage breast cancer	Survival: ELIOT = no difference;[27] TARGIT-A = breast cancer mortality equivalent; mortality from other causes significantly lower in IORT.[26] 5-year recurrence equivalent – ELIOT within the 7.5% margin;[27] TARGIT-A = within 2.5% margin.[26] Relative risk of 5-year recurrence: ELIOT RR of = 9.3;[27] TARGIT-A hazard ratio = 2.56.[33] Significantly fewer skin side-effects from IORT.[30]	IORT more convenient; may be of particular benefit to those who are at risk of not completing standard radiotherapy. Increased risks may warrant choice rather than total substitution. Increased risks means patients would need to be fully informed. NICE found Intrabeam cost savings entailed lost quality of life. Already being offered privately in New Zealand.	IORT could reduce costs by up to $0.4 million per annum if provided to all women who receive breast conserving surgery, and $0.3 million if patients are allowed to choose between IORT and EBRT. Could be cost-savings through substitute for projected investment in EBRT machines. NICE found Intrabeam cost savings of £1,596 for each QALY lost. Wider availability may reduce elective mastectomy in favour of breast conservation.	Technically feasible to adopt. Mobility of devices and lack of need for shielding will aide adoption. Feasibility depends on the trade-off between increased theatre utilisation and reduced EBRT sessions.	Evidence base includes two large RCTs of non-inferiority and equivalence design and a broader body of case series and lower level evidence. Effectiveness data is from the ELIOT trial using NOVAC 7 system and TARGIT-A RCT using Intrabeam. 'Equivalence' and 'non-inferiority' margins and whether recurrence is within them is debated. TARGIT-A referred some women randomised to IORT for EBRT following surgery.	**High**
IORT in addition to EBRT	Women with breast cancer	IORT prior to EBRT consistently and significantly improves local control rates across all risk subgroups.[37] Cosmetic results are similar at 10-year follow-up.[37] Treatment-related mortality and morbidity are not significantly different.[37]			Technically feasible to adopt. Mobility of devices and lack of need for shielding will aid adoption.	Evidence base is relatively mature, including a large pooled dataset, case series and lower level evidence. The TARGIT-B[36] trial currently recruiting compares IORT boost to EBRT boost. Already mooted as standard treatment overseas. Some public awareness and demand.	**Moderate**

Intervention description	Population	Clinical safety and effectiveness	Societal and ethical	Economic	Feasibility of adoption	Other considerations	Value of NHC HTA
IORT added to treatment	People with primary advanced colorectal cancer	Systematic review found improved 5-year local control, disease free survival and overall survival.[43] RCT evidence failed to show additional benefit over surgery alone.[43]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Appears to be used more frequently for rectal cancer than colon cancer. Evidence base immature and probably not yet sufficient for meaningful analysis.	**Moderate**
IORT added to treatment	People with locally recurrent colorectal cancer	Benefit for local control but not overall survival.[44] Appears to improve local disease control and survival.[12, 38] May offer an option when there is limited opportunity to increase the radiation dose or re-irradiate.[1]		Added to standard treatment so increased costs. 2010 figures show 288 people may have benefited from adding IORT. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Improvements may reflect better patient selection and better optimised treatment in the trial groups rather than the benefit of IORT as an intervention.[46]	**Moderate**
IORT instead of EBRT	People with locally recurrent rectal cancer	Equivalent outcomes compared with surgery and post-op chemotherapy.[45]	IORT more convenient and may be of particular benefit to those who do not complete standard radiotherapy.	Insufficient evidence of adequate standard to calculate.	Technically feasible to adopt but not examined in detail.	Evidence base immature.	**Moderate**
IORT added to treatment	People with gastric cancer	Minimal increase in survival.[1, 12, 38, 39] High complication rate.[1, 12, 38, 39] Possible reduced local progression.[40]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Evidence base immature and probably not yet sufficient for meaningful analysis.	**Low**
IORT added to treatment	People with pancreatic cancer	Inconsistent evidence of minimal or no benefit for patients with disease.[12, 38] Systematic review (SR) concluded no improvement in effectiveness when used in addition to other treatment modalities including surgery.[41]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Evidence base immature and without consistent benefits.	**Low**

Intervention description	Population	Clinical safety and effectiveness	Societal and ethical	Economic	Feasibility of adoption	Other considerations	Value of NHC HTA
IORT added to treatment	People with *localised* pancreatic cancer	Lower-quality evidence pre-2008 shows limited survival time improvement.[41] Studies published since 2008 show no benefit.[1]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Evidence base immature and without consistent benefits.	**Low**
IORT added to treatment	People with retroperitoneal tumours	One study reported reduced tumour recurrence but no change in survival compared with EBRT alone.[38] Other studies found no change in local control.[12]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Evidence base immature and without consistent benefits.	**Low**
IORT added to treatment	People with soft tissue sarcoma other than retro-peritoneal tumours	May be some improvement in control and survival.[12] Toxicity similar to EBRT treatment.[1]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Evidence base immature and probably not yet sufficient for meaningful analysis.	**Low**
IORT added to treatment	Women with gynaecological cancer	Some evidence of effectiveness for some patients with advanced but resectable cervical cancer.[1, 38]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Evidence base immature and probably not yet sufficient for meaningful analysis.	**Low**
IORT added to treatment	People with locally advanced head and neck cancer	Low-level evidence of improving local control and survival.[12, 38, 42]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Evidence base immature and probably not yet sufficient for meaningful analysis.	**Low**

Intervention description	Population	Clinical safety and effectiveness	Societal and ethical	Economic	Feasibility of adoption	Other considerations	Value of NHC HTA
IORT added to treatment	Men with prostate Cancer	Some evidence for clinical feasibility but none found for effectiveness.[12]		Added to standard treatment so increased costs. Insufficient evidence of adequate standard to calculate detail.	Technically feasible to adopt but not examined in detail.	Evidence base immature and probably not yet sufficient for meaningful analysis.	**Low**

Appendix: Search strategy

Medical literature databases and general internet were searched for relevant literature on the clinical use or IORT.

The Cochrane library was searched using the term ‘intraoperative radiotherapy’ in the title, abstract and keyword. Medline was searched using the term ‘intraoperative radiotherapy’ in the title and results were limited to English, reviews and from 2005 onwards. The NICE website search function was searched for ‘intraoperative radiotherapy’. Google was searched for ‘guidelines for intraoperative radiotherapy’.

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