www.breastcancer.org.nz

Submission to the Health Select Committee 2018

Re: Intro-operative Radiation Therapy

To: The Health Select Committee

From: Breast Cancer Aotearoa Coalition (BCAC)

Date: 31 August 2018

Contents

1. About Breast Cancer Aotearoa Coalition

Breast Cancer Aotearoa Coalition (BCAC) is a charitable incorporated society representing more than 30 New Zealand breast cancer organisations as well as many individual members around the country. BCAC provides an evidence-based voice for people with breast cancer and works to ensure that those diagnosed in New Zealand have timely access to world-class detection, treatment and care for breast cancer.

2. Introduction

We write in favour of the immediate introduction of intraoperative radiotherapy (IORT) by Intrabeam to the public health system in New Zealand. IORT is a highly effective treatment option for New Zealand women in selected cases of early-stage breast cancer.

Compared with conventional radiation options, it offers substantial advantages for New Zealand women (including better outcomes and less intervention), together with significant cost savings ($8 million per annum), reduction in waiting times, and improved resource use.

IORT provides a safe and effective single dose of radiation during the surgical phase of treatment. This means women can complete their entire radiation treatment at the time of their operation, with lower toxicities and reduced time spent away from family and whanau, and work commitments.

We note that for the Ministry of Health to provide public funding for new treatments, those treatments must be desirable, feasible and viable. We consider that the evidence demonstrates that IORT clearly meets each of these criteria.

Accordingly, we believe the option of targeted IORT should be available for oncologists to provide, with appropriate informed consent, to women who meet eligibility criteria. The criteria should be as outlined by the international TARGIT-A trial, which will be explained further in this submission.

IORT is already being used in more than 300 treatment centres around the world and is publicly funded in Australia and the UK. More than 20,000 women have been treated worldwide with IORT.

We were pleased to see the introduction of IORT with Intrabeam into New Zealand at a private Auckland clinic in 2013 and hope to see this important treatment option adopted and funded in the public health system as soon as possible.

3. Intraoperative radiotherapy benefits

IORT via Intrabeam treatment consists of a single dose of radiation delivered at the time of the surgery to remove the breast cancer tumour. IORT is delivered directly to the tumour bed, the most common site of breast cancer recurrence. We recommend that the therapy is used at the time of initial surgery, as this appears to achieve the best result in disease-free survival.

IORT is appropriate for approximately 30% of breast cancer patients who are at an early stage, amounting to approximately 1,000 women in New Zealand per year. The provision of a single treatment of radiotherapy intraoperatively provides an extremely efficient, convenient and safe option for patients with low risk early breast cancer.

The currently used method of external beam radiation therapy (EBRT) requires an intensive, extended regime of daily treatment over 3 to 6 weeks. This is often stressful and disruptive to the lives of patients, and can create practical difficulties and financial hardship for many women, especially those living in rural areas and at significant distance from radiation oncology treatment facilities.

This drives some women to make treatment choices that are less than optimal, with a number refusing radiation therapy altogether. Declining recommended treatment leads to greater breast cancer recurrence, with poorer patient outcomes and a higher cost to the public health sector.

Rural and remote women are often required to spend up to six weeks away from home, which carries with it a cost many women and families cannot afford. Travel commitments may also have an impact on partners or carers who may be required to take extended time off work, placing even greater strain on family and whānau budgets.

BCAC is aware that there is a 50% higher mastectomy rate in women who live away from a radiation centre. The negative physical and psychological impacts of mastectomy versus breast conserving surgery are well documented.

The availability of the single treatment option offered by IORT would allow some women to choose less disfiguring surgery, save on travelling and treatment times and have fewer breast-related quality of life issues in the long term, without any reduction in the benefits of radiotherapy (prevention of local recurrence of breast cancer and mortality). They would also potentially be at less risk of death from cardiovascular issues or other cancers.

Other benefits:

- IORT is less expensive than EBRT (between $5,000-$8,000 less per treatment).
- Women treated with IORT avoid the potential side-effects of EBRT including burns to the skin and potential damage to heart and lungs.
- No difference in breast cancer-related mortality after IORT or EBRT.
- Significantly fewer women die of causes other than breast cancer (other cancers and cardiovascular events) with IORT compared with EBRT. This is probably because IORT's more focused irradiation avoids other organs and the iatrogenic injury that can result from EBRT.
- The low energy radiation means IORT can be used in a standard operating theatre, freeing up traditional radiation facilities (linear accelerators for which NZ is under commissioned for future growth) and expanding the number of centres in which IORT may ultimately be available. By freeing up the linear accelerators, there will be additional capacity for treatment of other tumour types.
- IORT can also be used in other cancer streams such as colorectal, skin, head and neck, gynaecological and spine.
- IORT can contribute significantly to saving patients time, cost, fuel and CO_2 emissions (Coombs *et al*. 2016).
- IORT patients report significantly better long- term breast-related quality of life (fewer breast symptoms, fewer arm concerns, more sexual enjoyment) than those receiving EBRT (Corica *et al*., 2016).

Benefits for Māori and Pasifika women

Māori and Pasifika women are disproportionately affected by breast cancer, with exceptionally high mortality rates that need to be addressed with better screening and treatment including radiation treatment. Introduction of IORT could improve treatment access and survival outcomes, thus helping to address inequities in care.

- Important research released by the University of Waikato in June 2018 (Tin Tin *et al*. 2018; Brown *et al*. 2017; Lawrenson *et al*. 2016; 2017a; 2017b) shows the following:

- Māori women diagnosed with breast cancer are 76% more likely to die from the disease after five years than New Zealand European women. They are less likely to be diagnosed through mammographic screening, or receive chemotherapy, Herceptin or surgery.

- Māori women with breast cancer are more likely to experience delay in receiving treatment, less likely to receive radiotherapy, more likely to be treated with a mastectomy, and less likely to adhere to long-term endocrine therapy than non-Māori women.

- Pasifika women diagnosed with breast cancer are twice as likely to die after five years than New Zealand European women. They are diagnosed with breast cancer younger than other groups, and the cancer is almost twice as likely to be an aggressive form.

These appalling statistics highlight the importance and urgency of introducing a range of measures to make screening and treatment including radiation more accessible.

4. Evidence in support of IORT

The evidence in support of IORT is well established. A clinical trial, TARGIT-A*, demonstrated that for appropriately selected women, a single dose of IORT with Intrabeam will offer protection against local breast cancer recurrence, similar to that offered by 15-25 treatments of EBRT (Vaidya *et al*. 2010; 2014; 2016a).

The evidence provided from the TARGIT-A trial demonstrates that IORT is a safe and effective treatment when delivered to appropriately selected patients (according to the criteria used in the TARGIT-A trial) during surgery to remove the breast cancer tumour.

The trial was conducted as an international randomised controlled trial and recruited 3,451 patients. It was designed to test for non-inferiority, i.e. that patients receiving IORT would have similar outcomes to those receiving EBRT. Local recurrence of breast cancer in the same breast, mortality from breast cancer and mortality from other causes were the main outcomes measured. Complications such as skin breakdown and delayed healing were also recorded and a cost-utility analysis performed.

Five-year analysis showed no difference in the risks of local recurrence, and similar breast cancer mortality with IORT or EBRT. There were significantly fewer non-breast-cancer deaths with IORT than with EBRT, attributable to fewer deaths from cardiovascular causes and other cancers. Radiotherapy toxicity and skin complications were significantly lower in patients receiving IORT. Wound-related complications were similar in both groups. Health economic analyses showed that IORT was less costly, and produced slightly more quality-adjusted life-

years than EBRT. Sub-studies of the trial have shown that patients receiving IORT have better breast-related quality of life, and save time, cost and travel.

*** See Appendix 1 for further details of the TARGIT-A clinical trial**

5. The IORT consideration process to date in New Zealand

Despite strong evidence in support of IORT and support from the previous National Health Committee (NHC), the process for enabling public funded access to IORT did not proceed under the last Government.

- The National Health Committee completed a Tier 2 assessment for IORT in May 2015 concluding that "...the current evidence of clinical effectiveness of [IORT] is sufficient to consider further analysis across other decision domains".

- A Tier 3 Project Plan was approved on 2 September 2015 and commenced on 29 September 2015. The planned end date was April 2016.

- In March 2016, the NHC was disbanded (at a point where the Tier 3 assessment was near complete) and incorporated into the Ministry of Health.

- Subsequently, progress on IORT slowed. In July 2016, a Ministry manager advised that its cancer team, as the new owners of IORT assessment and information, did not have the required technology assessment expertise or resource.

- In October 2016, the Ministry referred the matter to Deloitte to undertake a medical and economic assessment of IORT, in which they would "assess if IORT is superior, inferior or equivalent" to EBRT based on a literature review. We understand that Deloitte was never provided with the results of the Tier 3 assessment. The report concluded in December 2016 that investing in IORT would likely present cost savings for the New Zealand health system. It assumed clinical equivalence for the purposes of the report, considering this was an appropriate assumption on the basis of clinical evidence and the literature reviewed.

- In December 2016, the Ministry advised all DHBs that the Ministry had concluded "there is insufficient evidence to introduce IORT in the New Zealand public health system at this time" because "clinical equivalency between IORT and EBRT has not yet been established". The letter noted that further clinical trials are underway internationally with results expected after 2020.

- In June 2017, the Ministry Chief Medical Officer advised that the Tier 3 project plan was draft only and the assessment did not proceed. Information obtained under the Official information Act (OIA) shows the Tier 3 project plan was finalised and assessment well progressed.

- Documents released under the OIA demonstrate that the Ministry appeared to place inappropriate weight on submissions from organisations and individuals that were likely conflicted. It also appeared to place no proper weight on the NHC assessment, international evidence, and submissions from organisations such as BCAC and NZBCF.

6. Conclusion

We consider there is a strong basis of evidence for the the immediate introduction of funded intraoperative radiotherapy (IORT) by Intrabeam to the public health system in New Zealand.

The benefits to women with breast cancer, their families and whānau, the public health system including budgets and people with other cancer types are undeniable. There will also be a step forward in better treatment of Māori and Pasifika women who experience inequities in breast cancer screening, care and mortality rates in New Zealand.

We would like to work with the Ministry to develop an effective process for implementing access to IORT for New Zealand women, and look forward to this effective treatment being introduced to New Zealand.

Appendix 1: TARGIT-A clinical trial

For the TARGIT-A (Targeted Intra-operative Radiotherapy) clinical trial, 33 centres in 10 countries recruited patients. The trial randomised patients to receive either whole breast EBRT or IORT using Intrabeam, with updated results recently published in *The Lancet* and elsewhere (Vaidya *et al*. 2010; 2014; 2016a). The trial began recruiting patients in 2000 and closed after the enrolment of 3,451 women. The 3,451 patients have had a median follow-up of two years and five months, while four-year follow-up is available for 2,020 patients and five-year follow-up for 1,222 patients.

Some patients were randomised before their first surgery (pre-pathology group, n=2,298) and others after their surgery (post-pathology group, n=1,153). This meant that the post-pathology patients allocated to the IORT arm received IORT to the tumour bed during a second surgical procedure (not a preferred option). The local recurrence rate for the pre-pathology IORT group of 2.1% (1.1 – 4.2) was not significantly different from that in the standard EBRT treatment arm of 1.1% (0.5 – 2.5) (p= 0.31)). The recurrence rate was somewhat higher in the post-pathology group.

Breast cancer mortality did not differ between the combined pre- and post-pathology IORT groups at 2.6% (1.5 – 4.3) and the EBRT group at 1.9% (1.1 – 3.2) (p=0.56). However, there were significantly fewer non-breast-cancer deaths with IORT at 1.4% (0.8 – 2.5) compared to 3.5% (2.3 – 5.2) for EBRT (p=0.0086). This was due to fewer cardiovascular deaths (2 vs 10) and fewer deaths from cancers other than breast (8 vs 16). In the pre-pathology group, at five years (n=2,298), there were 29 deaths in those receiving IORT and 42 in those receiving EBRT. Overall 5-year mortality was 3.9% (2.7 – 5.8) (37 deaths) for the combined IORT group vs 5.3 (3.9 – 7.3) (52 deaths) for EBRT (p=0.099) (n = 3,451).

Meta-analysis of TARGIT-A and other trials using partial breast irradiation techniques confirm non-inferiority of these techniques to whole breast irradiation in terms of local recurrence and breast-cancer-related mortality, and superiority in non-breast-cancer-related mortality (Vaidya *et al*. 2016b).

There were fewer grade 3 or 4 radiotherapy-related skin complications with TARGIT than with EBRT (four of 1,721 vs 13 of 1,730, p=0·029). Skin burns following EBRT cause severe pain and discomfort to the women who experience this, making it all the more difficult to put breast cancer behind them during post-treatment recovery. Reducing toxicity and damage to skin and other breast tissue would be an additional advantage of Intrabeam IORT.

We suggest that patient selection criteria for the use of Intrabeam IORT in New Zealand be set to be the same as those used for the TARGIT trial. We further suggest that every effort be made to use the therapy at the time of initial surgery, as this appears to achieve the best result in disease-free survival.

We note that IORT using Intrabeam has gained rapid and wide uptake around the world (Small *et al*. 2017).

Appendix 2: About BCAC

The Breast Cancer Aotearoa Coalition (BCAC) is an incorporated charitable society established in 2004 to provide a unified, evidence-based voice for the New Zealand breast cancer sector. Our membership comprises more than 30 breast cancer-related groups from around New Zealand, as well as many individual members (www.breastcancer.org.nz/About-Us/our-member-groups).

BCAC is run by a committee of women who have experienced breast cancer. We work as volunteers to make world class detection, treatment and care accessible to all those affected by breast cancer in New Zealand. By virtue of our experience and knowledge of this disease, as well as our networks across breast cancer patients, groups and clinicians around the country we are able to provide unique insights into improvements that can be made in the provision of breast cancer services.

BCAC provides direct support to those diagnosed with breast cancer and information for decision makers through:

- providing support and evidence-based information for women with breast cancer
- informing women and their families about the latest in breast cancer news and research through our comprehensive and regularly-updated website – www.breastcancer.org.nz
- supporting women with information and resources via our *Step by Step* publication distributed free of charge via BCAC's website and through a nationwide network of breast and cancer clinics, hospitals, and support organisations
- helping to develop the Guidelines for the Management of Early Breast Cancer and the Standards of Service Provision for Breast Cancer Patients in New Zealand
- providing a consumer voice to many expert clinical groups and international scientific meetings
- ensuring our knowledge of breast cancer science and clinical practice remains current by attending conferences and meetings including the San Antonio Breast Cancer Symposium, the Annual Scientific Meeting of Breast Cancer Trials (Australia and New Zealand), NZ Society for Oncology conferences, meetings of Breast Special Interest Group (NZ specialists), and by regularly consulting clinical experts on particular issues
- engaging with PHARMAC, Ministers and the Ministry of Health over the public funding of a range of breast cancer medicines including taxanes, aromatase inhibitors, CDK4/6 inhibitors and HER2-targeted molecules

- engaging with people via our Facebook and Twitter pages at www.facebook.com/breastcanceraotearoacoalition and www.twitter.com/BCACNZ

- providing a Facebook support group for New Zealanders with advanced breast cancer (www.facebook.com/groups/metavivorsnz)

- creating and sharing a series of web videos for those with primary breast cancer and advanced breast cancer (www.youtube.com/nzbreastcancer).

References

Brown C, Lao C, Lawrenson R, Tin Tin S, Schaaf M, Kidd J, Allan-Moetaua A, Herman J, Raamsaroop R, Campbell I, Elwood M. 2017. Characteristics of and differences between Pasifika women and New Zealand European women diagnosed with breast cancer in New Zealand. *NZMJ* 15 December 2017 **130**: (1467) 50-61. www.nzma.org.nz/journal

Coombs NJ, Coombs JM, Vaidya UJ, Singer J, Bulsara M, *et al*. 2016. Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. *BMJ Open* **6**: e010703. DOI 10.1136/bmjopen-2015-010703

Corica T, Nowak AK, Saunders C, Bulsara M, *et al*. 2016. Cosmesis and breast-related quality of life outcomes after intraoperative radiation therapy for early breast cancer: a substudy of the TARGIT-A trial. *International Journal of Radiation Oncology Biology Physics* **96**: (1) 55-64. DOI 10.1016/j.ijrobp.2016.04.024

Lawrenson R, Seneviratne S, Scott N, Peni T, Brown C, Campbell I. 2016. Breast cancer inequities between Māori and non- Māori women in Aotearoa/New Zealand. *European J Cancer Care* **25**: 225-230. DOI 10.1111/ccc.12473

Lawrenson R, Lao C, Campbell I, Harvey V, Brown C, Seneviratne S, Edwards M, Elwood M, Kuper-Hommel M. 2017a. The use of trastuzumab in New Zealand women with breast cancer. *Asia-Pac J Clin Oncol* 2017: 1-9. DOI 10.1111/ajco.1276

Lawrenson R, Lao C, Campbell I, Harvey V, Brown C, Seneviratne S, Edwards M, Elwood M, Scott N, Kidd J, Sarfati D, Kuper-Hommel M. 2017b. Treatment and survival disparities by ethnicity in New Zealand women with stage I–III breast cancer tumour subtype. *Cancer Causes Control* **28**: 1417-1427. DOI 10.1007/s10552-017-0969-9

Small W, Thomas TO, Alvarado M, Baum M, *et al*. 2017. Commentary on "Accelerated partial breast irradiation consensus statement: Update of an ASTRO Evidence-Based Consensus Statement". *Practical Radiation Oncology* **7**: e159-e163.

Tin Tin S, Elwood J M, Brown C, Sarfati D, Campbell I, Scott N, Raamsaroop R, Seneviratne S, Harvey V, Lawrenson R. 2018. Ethnic disparities in breast cancer survival in New Zealand: which factors contribute? *BMC Cancer* **18**: 58. DOI 10.1186/s12885-017-3797-0

Vaidya JS, Joseph DJ, Tobias JS, Bulsara M, Wenz F, Saunders C, *et al.* 2010. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* **376**: 91-102. DOI 10.1016/S0140-6736(10)60837-9

Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, *et al*. 2014. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* **383**: 603-613. DOI 10.1016/S0140-6736(13)61950-9

Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Saunders C, *et al.* 2016a. An international randomised controlled trial to compare TARGeted Intraoperative radioTherapy (TARGIT) with conventional postoperative radiotherapy after breast-conserving surgery for women with early-stage breast cancer (the TARGIT-A trial). *Health Technology Assessment* **20**: (73) DOI 10.3310/hta20730

Vaidya JS, Bulsara M, Wenz F, Coombs N, Singer J, et al. 2016b. Reduced mortality with partial-breast irradiation for early breast cancer: a meta-analysis of randomized trials. *International Journal of Radiation Oncology Biology Physics* **96**: (2) 259-265. DOI 10.1016/j.ijrobp.2016.05.008