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Technology Assessment Unit

of the McGill University Health Centre (MUHC)

Single-dose Intraoperative Radiotherapy Using Intrabeam® for Early-stage Breast cancer: A Health Technology Assessment

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- Proof of the non-inferiority of the intrabeam approach compared to conventional external beam irradiation rests on a single trial which has several weaknesses.
- Until evidence of long-term efficacy becomes available use of this technology at the MUHC should only be considered in the context of a clinical trial with informed consent.

List of abbreviations

CI	Confidence Interval
EAC	Equivalent Annual Cost
HTA	Health Technology Assessment
IORT	Intraoperative Radiotherapy
ITT	Intention To Treat
MGH	Montreal General Hospital
MUHC	McGill University Health Centre
OR	Operating Room
PP	Per-Protocol
QoL	Quality of Life
RCT	Randomized Clinical Trial
RTOG	Radiation Therapy Oncology Group

EXECUTIVE SUMMARY

Background

Postoperative whole-breast external beam radiotherapy, usually delivering a dose of 42.56-50 Gy in 16-25 fractions over 4-5 weeks, reduces the risk of tumour recurrence and improves survival of breast cancer patients managed with breast-sparing surgery. Using a proposed newer treatment, single dose intraoperative radiotherapy (IORT), radiation is delivered to the tumour bed at the time of surgical excision without postoperative whole-breast external beam radiotherapy and boost for the selected patients with early-stage breast cancer. The objectives of the present report are to evaluate the effectiveness and safety of Intrabeam® radiotherapy for early-stage breast cancer and to estimate the budget impact of using this technology at the MUHC.

Method

Literature search

A systematic literature search was carried out. We limited our literature search to randomized clinical trials (RCTs), observational studies and systematic reviews where the full-text article was published in a peer-reviewed journal or to health technology assessment (HTA) reports from public agencies.

Cost analysis

We estimated the procedure costs of radiotherapy when using either Intrabeam® radiotherapy or whole breast external beam radiotherapy. Estimates of usage and cost of the two treatment approaches were mainly provided by Dr. Tarek Hijal. The costs analysis was conducted from the perspective of the MUHC, and all costs were expressed in Canadian dollars in 2012.

Results: Literature review

We were able to find no previous HTA reports, systematic reviews or case series describing the use of Intrabeam® that met our inclusion criteria.

We identified 1 non-inferiority RCT that compared single dose Intrabeam® radiotherapy with conventional whole breast external beam radiotherapy (active control), in a total of 2,232 patients from 28 centres. The women were relatively low-risk, and the median follow up time was only 2 years (a total of 739 and 420 patients were followed to end of 3 years and 4 years, respectively), and, 23.3% of 1,113 patients originally randomized to the Intrabeam® arm did not receive the assigned therapy.

At 4 years follow-up, 6 (1.2%) local recurrences were identified in the Intrabeam® group compared to 5 (0.95%) in the external beam group, with no statistically significant difference between the two groups (log rank test: $p>0.05$). The difference

in recurrence rates between the 2 groups was 0.25% (95%Cl, -1.04 to 1.54%), thus falling within the pre-defined inferiority margin, 2.5%.

Complication rates between the Intrabeam® group and the external beam group did not differ significantly except that patients in the Intrabeam® group were significantly less likely to experience toxicity (6 (0.5%) versus 23 (2.1%)) and significantly more likely to develop a seroma needing more than three aspirations (23 (2.1%) versus 9 (0.8%)).

Estimated Costs to the MUHC

With amortisation of capital costs the estimated cost per treatment will vary with the number of treatments given. Thus, the unit cost, for Intrabeam® treatments at MUHC would be $3,204 or $6,670 (taxes included) for 100 or for 30 Intrabeam® treatments per year, respectively. The estimated cost of conventional external beam therapy is about $4,667 (Range, $3,556-$5,556). Thus, for 100 patients per year the budget impact of replacing conventional external beam therapy by Intrabeam® would be a saving of $146,300. However 30 Intrabeam® treatments yearly would result in a budget increase of $60,090.

CONCLUSIONS

- **Proof of the non-inferiority of the Intrabeam® approach compared to conventional external beam irradiation rests on a single trial which has several weaknesses, including insufficient follow-up. None the less, the rates of local recurrence of breast cancer and rates of major complications appear to be comparable in the two arms of the trial.**
- **From the perspective of MUHC, use of single dose Intrabeam® radiotherapy would slightly reduce or increase budget expenditure depending on turnover.**
- **Its use would reduce the workload of the Radiation Oncology Department. From the perspective of patients, it would greatly reduce the inconvenience associated with weekly external beam radiation, and would reduce the waiting time for radiotherapy patients.**
- **Use of this technology would cause an increased load on the Operating Room with the potential of increasing wait times for surgery.**

RECOMMENDATIONS

- **The currently available evidence supporting the use of Intrabeam® radiotherapy is not yet adequate to justify its permanent approval.**
- **Acquisition of this technology should be conditional on the department's participation in research studies designed to determine local recurrence, mortality rates, and patient satisfaction following Intrabeam® over a longer term period.**

- **The use of this technology should be reviewed annually in the light of evidence reported in the literature and the recurrence, mortality, and complication rates at the MUHC.**
- **Permanent approval of this technology for routine use should only be made when robust evidence supports this decision.**
- **All patients offered management by Intrabeam® should be informed in writing of the paucity of robust evidence of its long-term effectiveness, by a member of the medical team.**

SOMMAIRE

Contexte

La radiothérapie post-opératoire du sein entier à partir d'un faisceau externe libérant une dose de 42,59 à 50 Gy, fractionnée en 16-25 parties sur une période de 4-5 semaines, réduit la récurrence d'une tumeur et améliore la survie des patientes souffrant d'un cancer du sein et ayant subi une chirurgie mammaire conservatrice. Un nouveau traitement, soit la radiothérapie peropératoire à dose unique, permet une irradiation du lit tumoral pendant l'excision de la tumeur sans radiothérapie post-opératoire classique, et est suggérée aux patientes ayant un cancer du sein à un stade précoce. Les objectifs du présent rapport sont d'évaluer l'efficacité et l'innocuité de la radiothérapie Intrabeam® lors d'un cancer du sein à un stade précoce et d'évaluer l'impact budgétaire de cette technologie au CUSM (Centre universitaire de santé McGill).

Méthodologie

Revue de la littérature

Une revue systématique de la littérature fut menée et nous avons limité cette revue aux essais cliniques randomisés, aux études d'observation, aux revues systématiques publiées dans des revues avec révision du texte intégral par des pairs, ou aux rapports d'évaluation des technologies d'organismes publics.

Analyse des coûts

Nous avons estimé le coût des traitements de radiothérapie par Intrabeam® ou par radiothérapie avec faisceau externe pour le sein complet. Les estimés de l'utilisation et des coûts de ces deux traitements nous ont été fournis par le D^{r} Tarek Hijal. L'analyse des coûts fut faite du point de vue du CUSM et tous les coûts ont été exprimés en dollars canadiens (2012).

Résultats. Revue de la littérature

Nous n'avons trouvé aucun rapport d'évaluation des technologies ou revue systématique ou série de cas en regard de l'utilisation de l'Intrabeam® qui répondaient à nos critères d'inclusion. Par contre, nous avons identifié une seule étude randomisée comparant la radiothérapie à dose unique Intrabeam® et la radiothérapie avec faisceau externe pour le sein complet (contrôle) pour un total de 2,232 patientes provenant de 28 centres. Les patientes présentaient un risque faible et la durée médiane du suivi n'était que de 2 ans. Un total de 739 et 420 patientes ont été suivies pour une durée de 3 ans et 4 ans, respectivement, et 23,3% des 1,113 patientes choisies de façon randomisée pour recevoir le traitement Intrabeam® ne l'ont pas reçu.

Après un suivi de 4 ans, 6 (1,2%) récurrences locales furent identifiées dans le groupe Intrabeam®**,** comparativement à 5 (0,95%) récurrences dans le groupe faisceau externe, sans différence statistique significative entre ces deux groupes (p**>**0,05). La

différence du taux de récurrence entre ces 2 groupes était de 0,25% (95% CI; -1,04 à 1,54%), se situant ainsi à l'intérieur de la marge inférieure prédéfinie de 2,5%.

Les taux de complication entre le groupe Intrabeam® et le groupe faisceau externe n'étaient pas différents de façon significative, sauf que les patientes du groupe Intrabeam® étaient moins susceptibles de façon significative de démontrer une toxicité (6 (0,5%) versus 23 (2,1%)) et plus susceptibles de façon significative de développer un sérome nécessitant plus de trois aspirations (23 (2,1) versus 9 (0,8%)).

Coûts

Estimation des coûts pour le CUSM

En tenant compte de l'amortissement des coûts en capital, le coût estimé par traitement variera selon le nombre de traitements. Ainsi, le coût d'un traitement par Intrabeam® serait de 3 204$ ou 6 670$ (incluant les taxes) pour 100 ou 30 traitements par année, respectivement. Le coût estimé d'un traitement de radiothérapie par faisceau externe est environ 4 667$ (de 3 556$ à 5 556$). Ainsi, pour un achalandage de 100 patientes par année, l'impact budgétaire pour remplacer la radiothérapie classique par faisceau externe par la radiothérapie Intrabeam® se traduirait par des économies de 146 300$. Cependant, 30 traitements Intrabeam® par année entraineraient une augmentation budgétaire de 60 090$.

CONCLUSIONS

- La preuve de la supériorité de l'approche par Intrabeam®**,** comparée à l'irradiation classique par faisceau externe, repose sur un seul essai qui comporte plusieurs faiblesses, incluant un suivi insuffisant. Néanmoins, les taux de récidive locale du cancer du sein et les taux de complications majeures semblent comparables dans les deux bras de l'étude.
- Du point de vue du CUSM, l'utilisation de la radiothérapie à dose unique Intrabeam® pourrait légèrement réduire ou augmenter le budget des dépenses, selon l'achalandage.
- Son utilisation permettrait de réduire la charge de travail du département de radio-oncologie. Du point de vue des patientes, cette approche réduirait de façon importante les inconvénients associés aux séances hebdomadaires de radiothérapie par faisceau externe et réduirait le temps d'attente pour les patientes en radiothérapie.
- L'utilisation de cette technologie augmenterait la charge de travail sur le bloc opératoire, avec un impact possible sur les temps d'attente en chirurgie.

RECOMMANDATIONS

- Les preuves actuelles disponibles pour supporter la radiothérapie Intrabeam® ne sont toujours pas suffisantes pour justifier une autorisation permanente.
- L'acquisition de cette technologie devrait être conditionnelle à la participation du département de radio-oncologie à des études portant sur la récurrence locale, les taux de mortalité et la satisfaction des patientes suite aux traitements Intrabeam® et ce, sur une longue période.

- L'utilisation de cette technologie devrait être revue sur une base annuelle à la lumière des preuves publiées dans la littérature ainsi que des données du CUSM en regard de la récurrence, de la mortalité et des taux de complications.
- L'autorisation permanente de cette technologie pour une utilisation de routine devrait être donnée uniquement lorsque des preuves solides supporteront cette décision.
- Toutes les patientes qui se verraient offrir un traitement par Intrabeam® devraient être informées par écrit de l'absence de preuves robustes sur son efficacité à long terme par un membre de l'équipe médicale.

Single-dose Targeted Intraoperative Radiotherapy Using Intrabeam® for Early-stage Breast cancer: A Health Technology Assessment

1. BACKGROUND

Postoperative whole-breast external beam radiotherapy reduces the risk of tumour recurrence and improves survival of breast cancer patients[1;2]. Typically, when treated by external beam radiation therapy a woman would receive 42.56-50 Gy of radiation in 16-25 fractions over 4-5 weeks. Most women also receive an additional boost of 10-16 Gy in 4-8 fractions[3;4]. Though the risk of recurrence has fallen sharply over the years, 80-90% of recurrences occur at the site of the original tumour, regardless of whether the patient had radiotherapy[4;5]. Newer treatment strategies have aimed to increase the precision with which radiation is delivered. This is typically achieved by reducing the volume of tissue irradiated from whole breast to partial breast. Such a strategy also decreases the treatment duration.

Intraoperative radiotherapy (IORT) using Intrabeam® is one of several options for partial breast irradiation[4]. IORT is delivered to the tumour bed at the time of surgical excision. Typically, IORT takes 20-35 minutes, and the radiation dose is about 20 Gy at the surface of the tumour bed, and 5-7 Gy for the surrounding tissues.

In phase 2 studies of this technique, patients received regular postoperative whole-breast external beam radiotherapy, but without boost therapy, in addition to intraoperative radiotherapy[5;6]. The resulting 5-year ipsilateral recurrence rate was low, namely 1.73%[7]. More recently, in a phase 3 study, Vaidya et al 2010[3] applied a single dose intraoperative radiotherapy using Intrabeam® without postoperative whole-breast external beam radiotherapy and boost for selected patients with early-stage breast cancer.

Apart from recurrence rates, the Intrabeam® therapy has the potential advantage of eliminating postoperative visits to the hospital for radiotherapy. However, the Intrabeam® therapy must be delivered in an operating room, thus placing increased pressure on that resource. Further, this technology is associated with a high capital cost of $550,000.

The Technology Assessment Unit was asked by Mr. Gary Stoopler, Administrative Director, Surgical Mission, to evaluate single-dose intraoperative radiotherapy using Intrabeam® technology (Intrabeam® radiotherapy for short). The following report will focus on this application.

2. OBJECTIVES

The objectives of the present health technology assessment are to:

- Evaluate the effectiveness and safety of Intrabeam® radiotherapy for early-stage breast cancer.
- Estimate the budget impact of using this technology at the MUHC.

3. METHODS

3.1. Literature search

A systematic literature search was carried out using Pubmed, the Cochrane library and the health technology assessment (HTA) database of the Centre for Reviews and Dissemination[8] to identify randomized clinical trials (RCT), observational studies, systematic reviews and HTA reports of single-dose intraoperative radiotherapy using Intrabeam® for early-stage breast cancer, with no limits on language. A further search was conducted by tracking references in publications identified.

We limited our literature search to studies where the full-text article was published in a peer-reviewed journal or to HTA reports from public agencies. For the observational studies or case series, we required that the sample size was greater than 100 and that the median follow up time was not less than 3 years. The first author carried out the literature search, and the eligible articles were reviewed by all co-authors. The last literature search was conducted on November 5th 2012.

3.2. Cost analysis

We estimated the procedure costs of radiotherapy when using either Intrabeam® radiotherapy or whole breast external beam radiotherapy (the current treatment approach at MUHC) for early-stage breast cancer, and the purchase and maintenance cost of the Intrabeam® system, the cost of disposable components and the cost of additional operating room (OR) use. Estimates of usage and cost of various components within the two treatment approaches were mainly provided by Dr. T Hijal and Mr. W. Parker of the Radiation Oncology and Medical Physics Departments, Montreal General Hospital (MGH). We used MUHC surveillance data from the Department of Finance for the estimate of the cost of the OR (primarily personnel cost and supplies)[9]. We estimated the budget impact based on the expected number of eligible patients at the MUHC. The cost analysis was conducted from the perspective of MUHC, thus excluding the physician fee. All costs were expressed in Canadian dollars in 2012[10].

4. LITERATURE REVIEW: EFFECTIVENESS

After reviewing all abstracts and selected full-texts, we identified 1 RCT[3] that compared Intrabeam® radiotherapy with conventional whole breast external beam radiotherapy. There were no HTA reports, systematic reviews or observational studies concerning use of Intrabeam®. We summarize the lone RCT below.

Study design and patient selection: Vaidya et al 2010[3] carried out a multicenter, randomized, controlled, non-inferiority phase 3 trial to evaluate single-dose intraoperative Intrabeam® radiotherapy versus conventional whole breast external beam radiotherapy in patients who had breast-conserving surgery. Women, aged 45 or older, with operable early-stage breast cancer were eligible for enrolment. Patients with lobular carcinoma were excluded[11].

Eligible patients were recruited into the trial at one of three possible points in the course of their treatment for breast cancer: i) pre-pathology entry: these patients were recruited into the trial before undergoing breast conserving surgery, ii) post-pathology entry: these patients were recruited provided that tumour margins were cleared (by re-excision if necessary), and that they did not have extensive intraductal disease or other adverse prognostic features (site-dependent), iii) history of contralateral breast cancer: these patients had a previous history of cancer in the contralateral breast but otherwise met the eligibility criteria for the trial.

After randomization, neither investigators nor patients were masked to the treatment. The primary outcome was pathologically confirmed local recurrence in the conserved breast; and the secondary outcomes included local and generalised complications. Patients were assessed at entry, 3 months, 6 months, thereafter are every 6 months up to 5 years, and then yearly to 10 years.

An absolute difference of 2.5% of primary endpoint between the two radiotherapeutic approaches was defined as the non-inferiority margin, based on the assumption that the background 5-year local recurrence rate was 6%. This means that if the upper limit of the 95% confidence interval (CI) of local absolute recurrence in the Intrabeam® arm compared to the external beam arm was less than 2.5%, authors would reject the null hypothesis and conclude that Intrabeam® therapy is not inferior to external beam therapy. It should be noted that both the article and study protocols did not report the statistical method used to estimate the 95% confidence interval of the absolute difference in recurrence rate[3;11]. An intention-to-treat analysis was conducted for all randomized patients.

Patient recruitment and patient characteristics: A total of 2,232 patients from 28 centres in 9 countries were randomly allocated into two groups: 1,113 in the Intrabeam® arm and 1,119 in the conventional radiotherapy arm. In all, 1,482 patients were recruited in the pre-pathology stratum, 672 in the post-pathology stratum and 78 in the contralateral stratum. In the Intrabeam® arm, 996 (89.5%) patients received the allocated treatment, including 142 (14%) patients who were

treated by both Intrabeam® radiotherapy and external beam radiotherapy. In the conventional radiotherapy arm, 1,025 (91.6%) patients received the allocated treatment. Patients in the Intrabeam® group received external beam therapy in addition if the pathological examination of the excised lesion revealed unfavourable features. Patients were followed for a similar duration in the two groups. The median follow up time was 2 years. A total of 739 and 420 patients were followed to end of 3 years and 4 years, respectively.

The patient characteristics were very similar in the two groups (See Table 1). Overall, this trial recruited a relatively low-risk sample of women.

The clinical outcomes: The authors presented results over 4 years of follow-up because less than 20% of patients were followed beyond that point. At 4 years follow-up, 6 (1.2%) local recurrences were identified in the Intrabeam® group compared to 5 (0.95%) in the external beam group, with no statistically significant difference between the two groups (log rank test: $p>0.05$). It should be noted that these recurrence rates were much lower than the rate of 6% on which the study was designed. The difference in recurrence rates between the 2 groups was 0.25% (95%Cl, -1.04 to 1.54%), thus falling within the pre-defined inferiority margin.

The complications: The number of patients with any complications in the Intrabeam® group was slightly higher than the external beam group (196 (17.6%) versus 174 (15.5%)), though this difference was not statistically significant. Clinically significant complications were similar (haematoma needing surgical evacuation, infection needing intravenous antibiotics or surgical intervention, and skin breakdown or delayed wound healing). However, the Intrabeam® group was significantly less likely to experience toxicity (i.e. a toxicity score[3] of 3 or 4 as defined by the radiation therapy oncology group (RTOG) 6 (0.5%) versus 23 (2.1%)) and significantly more likely to experience seroma needing more than three aspirations (23 (2.1%) versus 9 (0.8%)).

5. RADIOTHERAPY FOR BREAST CANCER AT THE MUHC

5.1. Overview of the current practice

Number of target patients: The Radiation Oncology Department of MGH treats about 600 breast cancer patients per year. Roughly 75% (or 450) of these 600 patients are new patients. The rest have experienced metastases. Of the new patients, two thirds (approximately 300) receive treatment of the breast alone, while for the other one third treatment involves both the breast and lymph nodes. Of the 300 patients who need radiotherapy of the breast alone, at least 100-150 are considered low risk and therefore eligible for Intrabeam® radiotherapy. However,

largely because of the shortage of operating room time, the initial intention is to treat approximately 30 patients per year [Dr. Tarek Hijal].

Present treatment policy: Whole breast external beam radiotherapy followed by tumour bed boost is delivered after breast surgery (or surgery + chemotherapy, if patients are candidates for chemotherapy). About 16 to 25 sessions of treatment and 4 to 8 sessions of boosting are scheduled within the 5 to 6 weeks period following surgery or chemotherapy. An estimated 80% of patients (typically patients considered at high risk including those with age < 70 or a grade III tumor) receive the boost. Each treatment takes about 15 minutes (10 minutes for the preparation and 5 minutes for delivering the treatment)[Dr. Tarek Hijal].

Waiting time: The Montreal General Hospital (MGH) currently has 6 linear accelerators and offers radiotherapy from 7:30 am to 6:00 pm on working days, mainly in 15 minute segments. Almost all service time has been booked. Dr. Hijal estimated that the waiting time for patients with breast cancer is around 3 to 4 weeks currently. He also guessed that the demand for radiotherapy will continue to increase in the future given the aging population, the longer survival of cancer patients now than in the past, and the increasing use of radiotherapy in common tumour types. According to government statistics cited by Dr Hijal, there will be a 3% increase in demand per year. The government has opened two new centres in the Montreal area in the past 2 years, with no further openings planned. Our numbers have probably decreased by about 5% -10% because of these openings. We now expect the numbers to restart their natural increase by 3% per year.

5.2. Cost and budget impact estimates

Cost of external beam radiotherapy: Based on a study carried out by the Radiation Oncology Department [W. Parker], it is estimated that the average cost per patient for postoperative whole-breast external beam radiation would be $4,667 (Range, $3,556-$5,556). (See Appendix 1.)

Cost of Intrabeam®: Intraoperative radiotherapy using Intrabeam® takes an additional 45 minutes in the operating room (OR). It is expected that about 80% of patients who receive treatment with Intrabeam® will not need additional whole breast radiotherapy. The capital cost for Intrabeam® is $550,000 before tax, including installation, training, etc. We assumed that its service life is 7 years. The maintenance cost is about $50,000 per year. The cost of the reusable applicator is about $5,832. It will need to be replaced roughly every 100 treatments. The other consumables include sterile drapes and radiation shields [Dr T Hijal].The estimated procedure costs of radiotherapy using Intrabeam® are summarized in Table 2. In summary, assuming 100 Intrabeam® treatments per year the procedure cost (including annualised capital cost) would be $3,204 (taxes included). Thus, from the

point of view of the MUHC for each case treated by Intrabeam® instead of external beam radiation there would be an anticipated saving $1,463 ($4,667 - $3,204).

However, If only 30 Intrabeam® procedures were carried out each year the procedure cost would be $6,670, or $2003 ($6,670 - $4,667) more than external beam radiation.

Sensitivity Analysis: We also conducted a series of sensitivity analysis to explore the uncertainties (see Table 3). The volume of Intrabeam® treatment is the main factor impacting the procedure costs. Briefly, if more than 50 Intrabeam® procedures were conducted annually, the single dose Intrabeam therapy would result in cost savings, compared with conventional external beam therapy. Otherwise, Intrabeam® treatment would be more costly.

Budget impact: If 100 Intrabeam® treatments were to be carried out annually, there would be a budget saving of $146,300 (($4,667 - $3,204)*100). If only 30 patients were treated by Intrabeam® yearly, it would result in a budget increase of $60,090 (($6,670 - $4,667)*30).

6. DISCUSSION

Proof of the non-inferiority of the Intrabeam® approach compared to conventional external beam irradiation rests on a single randomized controlled trial with a relatively short follow-up time of 4 years, whereas the evidence of efficacy and safety of the conventional external beam therapy is based on 10-20 or more years of follow up[1;4]. It is therefore important that the strengths and weaknesses of this study be fully appreciated.

Concerns with the RCT of Vaidya et al.

Intention to treat rather than per protocol analysis

The results of this study [3] were analysed using only an Intention to Treat (ITT) approach. ITT analysis includes all patients randomized, according to the initial treatment assigned, regardless of whether they received and/or completed the treatment. By contrast per-protocol (PP) analysis, includes only those patients who complete the entire treatment assigned[12]. Thus ITT analysis tends to minimize the differences between experimental and control groups, whereas the PP analysis tends to reflect the maximum possible difference between the two groups. When the hypothesis being considered is "non-inferiority" of one treatment compared to a standard treatment it would be desirable to analyse results using both approaches, in spite of the recognised problems associated with PP analysis. In this study[3] given the fact that 23.3% of 1,113 patients originally randomized to the Intrabeam® arm did not receive the assigned therapy (17 (1.5%) dropped out, 100 (9%) did not receive Intrabeam® therapy and 142 (12.8%) received both Intrabeam® and external

beam radiotherapy), the absence of a significant difference in a per-protocol analysis would have provided stronger assurance of non-inferiority.

Adjuvant therapy

It should also be noted that in this study[3] many patients received additional adjuvant therapies. Overall, 66% of patients received hormone therapy and and 12% patients received additional chemotherapy, (in approximately equal numbers in each arm) Since both are associated with reduced risks of local recurrences[13]. It should be noted that the intended comparison of Intrabeam® versus external beam is in fact a comparison of Intrabeam® plus hormone versus external beam plus hormone.

Choice of magnitude of non-inferiority margin and reporting of results over time

Vaidya et al defined an absolute difference of 2.5% in local recurrence as the non-inferiority margin. This margin was selected assuming the 5-year recurrence rate following conventional radiotherapy is 6%. However, the observed 4-year local recurrence rate was only 0.95% in this group[3], or roughly 16% of the assumed value. Whether this fixed margin of 2.5% is still appropriate given the much lower than expected background risk of 0.95% is questionable.

Moreover, for the time-to-event data, the absolute difference of primary endpoints changes over time. Thus, it would have been more appropriate to examine non-inferiority over time and not only at 1 single point.

The length of follow up time

The median follow up time was about 2 years, and only 420 (20%) patients had 4 years or longer follow up. The aim of breast radiotherapy is to prevent, not only delay, the recurrence over 10-year or 20-year[14] after surgery. The present treatment of external beam radiotherapy has been proven to be an effective approach to reach this goal. The median time to local recurrences is between 40 months and 65 months following conventional radiotherapy[13]. An adequate number of patients would have to complete at least this length of follow-up before a definitive conclusion on the value of Intrabeam® can be drawn from this study.

In summary, the strength of the evidence supporting the efficacy and safety of Intrabeam® is still relatively insubstantial.

Quality of life following Intrabeam® radiotherapy

Welzel et al. conducted a matched-pair study (N=69) to evaluate the health-related quality of life (QoL) following three types of radiotherapy: i), Intrabeam® radiotherapy alone, ii) Intrabeam® and conventional radiotherapy, and iii) conventional radiotherapy alone[15]. Overall, patients in all 3 groups showed similar results. Using the self-assessment questionnaires for general cancer-specific QoL (QLQ-C30)[16], the Intrabeam® and conventional therapy arms had the same quality of life. However, while using breast cancer-specific QoL (QLQ-BR23)[17], the Intrabeam® arm showed less breast symptoms, compared with the conventional radiotherapy arm. Furthermore, compared with those on conventional radiotherapy, patients in the

Intrabeam® plus conventional therapy group had a lower satisfaction rate, more pain and reduced QoL.

Resource usage

Cost-analysis shows that from the MUHC's perspective, the average per-patient cost of treatment with Intrabeam® would, depending on the volume, cost slightly more or slightly less than conventional therapy. In addition, Intrabeam® radiotherapy can substantially decrease the workload of healthcare staff. Every breast cancer patient treated by Intrabeam® rather than by routine external beam radiotherapy would release on average 20 fractions for use by other patients. It is not surprising that Vaidya et al. reported that Intrabeam® shortened the waiting time at oncology departments in the United Kingdom[3]. Furthermore, from the patients' perspective, Intrabeam® radiotherapy would save on average 20 half day visits to the hospital.

On the other hand each treatment increases the load on the operating room, extending operating time by approximately 45 minutes, a factor that in some hospitals, such as the MUHC, would be an important disadvantage.

7. CONCLUSIONS

- **Proof of the non-inferiority of the Intrabeam® approach compared to conventional external beam irradiation rests on a single trial which has several weaknesses, including insufficient follow-up. None the less, the rates of local recurrence of breast cancer and rates of major complications appear to be comparable in the two arms.**
- **From the perspective of MUHC, use of single dose Intrabeam® radiotherapy would slightly reduce or increase budget expenditure depending on turnover.**
- **Its use would reduce the workload of the Radiation Oncology Department. From the perspective of patients, it would greatly reduce the inconvenience associated with weekly external beam radiation, and would reduce the waiting time for radiotherapy patients.**
- **Use of this technology would cause an increased load on the Operating Room with the potential of increasing wait times for surgery.**

8. RECOMMENDATIONS

- **The currently available evidence supporting the use of Intrabeam® radiotherapy is not yet adequate to justify its permanent approval.**
- **Acquisition of this technology should be conditional on the department's participation in research studies designed to**

determine local recurrence, mortality rates, and patient satisfaction following Intrabeam® over a longer term period.

- **The use of this technology should be reviewed annually in the light of evidence reported in the literature and the recurrence, mortality, and complication rates at the MUHC.**
- **Permanent approval of this technology for routine use should only be made when robust evidence supports this decision.**
- **All patients offered management by Intrabeam® should be informed in writing of the paucity of robust evidence of its long-term effectiveness, by a member of the medical team.**

TABLES

Table 1 Patient and tumour characteristics in Vaidya et al 2010

	Intrabeam® (n=1,113)	External beam (n=1,119)
Age (years)		
<45	17/1113 (2%)	10/1119 (1%)
45–54	212/1113 (19%)	167/1119 (15%)
55–64	443/1113 (40%)	464/1119 (41%)
65–74	355/1113 (32%)	381/1119 (34%)
>74	86/1113 (8%)	97/1119 (9%)
Pathological tumour size (cm)		
<1	381/1056 (36%)	388/1061 (37%)
1–2	531/1056 (50%)	519/1061 (49%)
>2	144/1056 (14%)	154/1061 (15%)
Unknown	57/1113 (5%)	58/1119 (5%)
Tumour type		
Invasive ductal carcinoma	1012/1070 (95%)	1018/1079 (94%)
Invasive lobular carcinoma	47/1070 (4%)	45/1079 (4%)
Mixed	32/1070 (3%)	35/1079 (3%)
Unknown	43/1113 (4%)	40/1119 (4%)
Tumour grade		
1	341/1040 (33%)	374/1048 (36%)
2	540/1040 (52%)	514/1048 (49%)
3	159/1040 (15%)	160/1048 (15%)
Unknown	73/1113 (7%)	71/1119 (6%)
Lymphovascular invasion		
Absent	881/1022 (86%)	894/1026 (87%)
Present	141/1022 (14%)	132/1026 (13%)
Unknown	91/1113 (8%)	93/1119 (8%)
Ductal carcinoma in situ		
Present	529/1063 (50%)	547/1069 (51%)
Absent	534/1063 (50%)	522/1069 (49%)
Unknown	50/1113 (4%)	50/1119 (4%)
Nodes involved		
0	866/1059 (82%)	898/1070 (84%)
1–3	155/1059 (15%)	149/1070 (14%)
>3	38/1059 (4%)	23/1070 (2%)
Unknown	54/1113 (5%)	49/1119 (4%)

Table 2 The estimated procedure cost of radiotherapy using Intrabeam®

	Breakdown of costs ¶ ($)	**Estimated cost per procedure, including taxes @ ($)**	
		100 procedures /year	**30 procedures /year**
Intrabeam® system	Capital cost: 550,000; Equivalent annual cost (EAC)#: 90,525	956.85 @	3189.49 @
Maintenance cost	50,000 per year	528.5 @	1761.67 @
Additional operating room use	869 per hour * 0.75	652	652
Post operation whole breast external beam radiotherapy (20% patients)	4,667*0.2	933.4	933.4
Applicator	5,832 for 100 treatments	61.64 @	61.64 @
Sterile drapes	176 for 5 drapes	37.21 @	37.21 @
Radiation shield (25% patients)	1,316 for 10 shields * 0.25	34.78 @	34.78 @
Total		**3,204**	**6,670**

¶: These prices are before discounts from the manufacturer.
@: The 5.7% tax was included in the cost estimates. MUHC pays 5.7% tax for medical devices and services.
#: We assumed that the service life of Intrabeam® system is 7 years. The annual discount rate of 5% is used in the calculation of equivalent annual cost (EAC).

Table 3 Sensitivity Analyses of the procedure cost of radiotherapy using Intrabeam®

Scenario	Estimated procedure cost, including taxes ($)
150 Intrabeam® procedures per year	2,709
120 Intrabeam® procedures per year	2,956
100 Intrabeam® procedures per year	3,204
70 Intrabeam® procedures per year	3,841
50 Intrabeam® procedures per year	4,689
30 Intrabeam® procedures per year	6,670
The following analyses based on an assumed 100 Intrabeam® procedures per year	
10 years service life of Intrabeam® system	2,964
Half hour of operating room use for Intrabeam® treatment	2,987
15% patients receiving post operation whole breast external beam radiotherapy	2,971
30% patients receiving post operation whole breast external beam radiotherapy	3,671

APPENDIX 1: Cost of routine postoperative whole-breast external beam radiotherapy at MUHC

Estimates carried out within the Radiation Oncology Department indicate the following:

Total costs per year = approximately $8million (Includes: Capital equipment replacement, expendables and all salaries including radio physics. Excludes: Radiotherapists (MDs) fees)

Total number of fractions administered 2010-2011: 36,000

Average cost per fraction = $222.22 (Assuming all fractions are equal)

Number of fractions per breast cancer patient = Average 21 (range 16-25)

Average cost per patient for external beam radiation = $4,667 ($3,556-$5,556)

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