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McGill University Health Centre

Technology Assessment Unit of the McGill University Health Centre (MUHC)

Update of TAU Reports #63 and #76: Single-dose Intraoperative Radiotherapy Using Intrabeam® for Early-stage Breast cancer

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Brief Report

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Report prepared for the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC)

by

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Approved by the TAU Policy Committee via an online poll

Mission Statement

The MUHC Health Technology Assessment Unit (TAU) advises hospital administrators and clinical teams in difficult resource allocation decisions. Using an approach based on independent, critical evaluations of the available scientific evidence and a transparent, fair decision-making process, novel and existing medical equipment, drugs and procedures used by healthcare professionals are prioritized on a continuous basis ensuring the best care for life with the best use of resources.

Brief Reports

Brief reports are prepared in response to urgent requests for information or to update previous reports with new evidence; in such cases an in-depth evaluation is either not possible or is unnecessary. Brief reports are reviewed by the Manager of TAU and the Chair of the Policy Committee, and only submitted for approval to the Policy Committee when recommendations are updated.

Declaration of Conflicts of Interest

Members of TAU's research staff and policy committee declare no conflicts of interest.

Suggested Citation

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- Melissa Charbonneau, the Clinical Research Coordinator of the Cedars Cancer Centre, MUHC for providing data and reviewing the final draft of this report

REPORT REQUESTOR

The original reports were requested by Dr. Tarek Hijal of the Radiation Oncology Division, and published in November 2012 and June 2015.

TYPES OF RECOMMENDATIONS ISSUED BY THE TAU COMMITTEE

Type of recommendation	Explanation
Approved	• Evidence for relevant decision criteria, including efficacy, safety, and cost, as well as context-specific factors such as feasibility, is sufficiently strong to justify a recommendation that the technology be accepted, used and funded through the institutional operating budget
Approved for evaluation	• There is a reasonable *probability* that relevant decision criteria, including efficacy, safety, and cost, as well as context-specific factors such as feasibility, are favorable but the evidence is not yet sufficiently strong to support a recommendation for permanent and routine approval. • The evidence is sufficiently strong to recommend a *temporary* approval in a restricted population for the purposes of evaluation, funded through the institutional operating budget.
Not approved	• There is insufficient evidence for the relevant decision criteria, including efficacy, safety, and cost; • The costs of any use of the technology (e.g. for research purposes) should not normally be covered by the institutional budget.

DISCLAIMER

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SUMMARY

BACKGROUND

Intraoperative radiotherapy (IORT), a modality of accelerated partial breast irradiation (APBI), which was introduced based on the rationale that the vast majority of local breast cancers recur within the primary tumour site. Unlike external beam radiation therapy (EBRT),which irradiates the entire affected breast in daily doses of 1.8-2.0 Gy over 5-7 weeks, IORT with Intrabeam® delivers a single higher dose directly to the tumour bed during breast conserving surgery. Intraoperative therapy thus avoids the unnecessary irradiation of vital organs such as the heart and lungs, and reduces the burden on the patient of frequent hospital visits.

Efficacy of Intrabeam® has only been evaluated in a single non-inferiority trial, the TARGIT-A trial. Based on the relatively short follow-up time (median 2.4 years) of this study and some missing information in the results to evaluate the non-inferiority of Intrabeam® to EBRT, the TAU policy committee did not recommend use of this technology in 2012 and 2015, except in the context of a research study.

Between 2016 and 2021, some articles reporting longer follow-up results from the same trial were published, necessitating an update of our recommendations.

OBJECTIVES

The objectives of this report are to assess:

- any new evidence on local recurrence, survival and complication rates of IORT vs. EBRT;
- local evidence on the use of Intrabeam® at the MUHC

FINDINGS

New evidence:

Long-term follow-up (median 8.6 years) results from the TARGIT-A trial (n=2234) showed that the 5-year Kaplan-Meier (K-M) risk of local recurrence was 2.23% vs. 1.02 % for IORT vs. EBRT, resulting in an absolute risk difference of 1.21% (90% CI: 0.47, 1.95). The binomial proportions of 5-year local recurrence were 2.11% (24/1140) and 0.95% (11/1158) for IORT vs. EBRT, respectively. The resulting absolute risk difference was 1.16% (90% CI: 0.32, 1.99). Therefore, the results for both the difference in Kaplan-Meier

risk and the difference in binomial proportions were within the pre-defined non-inferiority margin of 2.5%.

The authors reported no statistically significant differences between IORT and EBRT for local recurrence-free survival (hazard ratio (HR) 1.13; 95% confidence interval (95%CI) 0.91 to 1.41); mastectomy-free survival (HR: 0.96; 95% CI: 0.78 to 1.19); distant disease-free survival (HR: 0.88; 0.69 to 1.12); overall survival (HR: 0.82; 0.63 to 1.05); and breast cancer mortality (HR: 1.12; 0.78 to 1.60). Mortality from other causes was significantly lower (HR: 0.59; 0.40 to 0.86).

A cost-utility analysis comparing IORT and EBRT for treating early breast cancer treatment in the UK showed that IORT appeared to be $1,386 CAD less costly than EBRT ($14,480 vs. $15,866 CAD, respectively). IORT also produced better quality-adjusted life-years: discounted QALYs gained were 8.15 for IORT vs. 7.97 for EBRT (i.e., IORT gained 0.18 incremental QALY).

MUHC experience:

Until July 2018, there were 2 (5.6%) recurrences among 36 women treated at the MUHC over a mean follow up of 5.05 years as part of a clinical trial. There was no acute Radiation Therapy Oncology Group **(**RTOG) toxicity score ≥3, while late RTOG toxicity score ≥3 was found in 1 (3.0%) patient. These rates are within the range found in the TARGIT-A trial. Since August 2018, IORT using Intrabeam® has been used as routine treatment in 35 patients: 26 with breast cancer and 9 with brain cancer. No local recurrence was found at follow-up.

CONCLUSIONS

- The most recent evidence indicates that intraoperative radiotherapy (IORT) using Intrabeam® during lumpectomy is non-inferior to whole breast external beam radiation therapy (EBRT) for 5-year local recurrences and overall mortality. Moreover, there were no statistically significant differences for local recurrence-free survival, mastectomy-free survival, distant disease-free survival, overall survival, and breast cancer mortality. Mortality from other causes was significantly lower in the TARGIT-IORT group.
- Local recurrence rates for women treated with Intrabeam® as part of a research study at the MUHC were low.
- We conclude that IORT using Intrabeam® is a feasible and safe method of treatment for carefully selected breast cancer patients.

UPDATED RECOMMENDATIONS

- We conclude that IORT using Intrabeam® may be used in a restricted population of carefully selected breast cancer patients at the MUHC. This would correspond to a recommendation of: Approved for evaluation
- This recommendation was updated based on the following:
    - The new long-term follow-up evidence of non-inferiority
    - Local data from MUHC indicating low recurrence rates
- It is necessary that data be systematically collected, including data on patient selection criteria and downstream clinical outcomes;
- This recommendation should be reviewed should any further evidence become available.

SOMMAIRE

Contexte

La radiothérapie peropératoire (RTPO), une modalité d'irradiation partielle accélérée du sein (IPAS), a été introduite en se basant sur le fait que la grande majorité des cancers du sein locaux récidivent dans le site de la tumeur primaire. Contrairement à la radiothérapie externe (RTE), qui irradie l'ensemble du sein affecté à des doses quotidiennes de 1,8 à 2,0 Gy pendant 5 à 7 semaines, le RTPO avec Intrabeam® délivre une seule dose plus élevée directement sur le lit tumoral pendant la chirurgie conservatrice du sein. La radiothérapie peropératoire évite ainsi l'irradiation inutile d'organes vitaux, tels que le cœur et les poumons, et réduit le fardeau du patient en diminuant la fréquence des visites à l'hôpital.

L'efficacité d'Intrabeam® a été évaluée seulement dans un essai clinique de non-infériorité, l'essai TARGIT-A. Étant donné la durée de suivi relativement courte (médiane de 2,4 ans) de cette étude et de certaines informations manquantes dans les résultats pour évaluer la non-infériorité d'Intrabeam® par rapport à la RTE, le comité de politique du TAU n'a pas recommandé l'utilisation de cette technologie en 2012 et 2015, sauf dans le cadre d'une étude de recherche.

Certains articles publiés entre 2016 et 2021 ont rapporté des résultats de suivi plus long provenant du même essai clinique, nécessitant ainsi une mise à jour de nos recommandations.

Objectifs

Les objectifs de ce rapport sont d'évaluer :

- toutes les nouvelles preuves sur le taux de récidive locale, de survie et de complications de la RTPO par rapport à la RTE;
- les données probantes locales sur l'utilisation d'Intrabeam® au CUSM

Résultats

Nouvelle preuve:

Les résultats du suivi à long terme (médiane de 8,6 ans) de l'essai TARGIT-A (n = 2234) ont montré que le risque de récidive locale à 5 ans de Kaplan-Meier (KM) était de 2,23% contre 1,02% pour la RTPO contre la RTE, entraînant une différence de risque absolu de 1,21% (IC à 90% : 0,47, 1,95). Les proportions binomiales de récidive locale à 5 ans

étaient de 2,11% (24/1140) et de 0,95% (11/1158) pour la RTPO et la RTE, respectivement. Ainsi, la différence de risque absolue était de 1,16% (IC à 90% : 0,32, 1,99). Par conséquent, les résultats pour la différence de risque de Kaplan-Meier et la différence de proportions binomiales se situaient dans la marge de non-infériorité prédéfinie de 2,5%.

Les auteurs ont rapporté qu'il y avait aucune différence statistiquement significative entre la RTPO et la RTE pour la survie sans récidive locale (rapport de risque instantané (HR) 1,13; intervalle de confiance à 95% (IC à 95%) 0,91 à 1,41); la survie sans mastectomie (HR: 0,96; IC 95%: 0,78 à 1,19); la survie sans maladie à distance (HR: 0,88; 0,69 à 1,12); la survie globale (HR: 0,82; 0,63 à 1,05); et la mortalité par cancer du sein (HR: 1,12; 0,78 à 1,60). La mortalité due aux autres causes était significativement plus faible (HR: 0,59; 0,40 à 0,86).

Une analyse du coût-utilité comparant la RTPO et la RTE pour le traitement du cancer du sein précoce au Royaume-Uni a montré que la RTPO semblait coûter 1 386 $ CA de moins que la RTE (14 480 $ contre 15 866 $ CA, respectivement). LA RTPO a également donnée un meilleur coût par années de vie pondérées par la qualité: les gains QALY étaient de 8,15 pour la RTPO contre 7,97 pour la RTE (c'est-à-dire que la RTPO a gagné 0,18 QALY supplémentaires).

Expérience au CUSM:

Jusqu'en juillet 2018, il y a eu 2 (5,6%) récidives chez 36 femmes traitées au CUSM au cours d'un suivi moyen de 5,05 ans dans le cadre d'un essai clinique. Il n'y avait pas de score de toxicité aiguë Radiation Therapy Oncology Group (RTOG) ≥ 3, tandis qu'un score de toxicité tardif RTOG ≥ 3 a été rapporté chez 1 patient (3,0 %). Ces taux se situent dans la fourchette trouvée dans l'essai TARGIT-A. Depuis août 2018, la RTPO avec Intrabeam® a été utilisée comme traitement de routine chez 35 patients : 26 atteints d'un cancer du sein et 9 d'un cancer du cerveau. Il y a eu aucune récidive locale lors du suivi.

CONCLUSIONS

- Les preuves probantes les plus récentes indiquent que la radiothérapie peropératoire (RTPO) utilisant Intrabeam® pendant la tumorectomie est non inférieure à la radiothérapie externe (RTE) du sein entier pour les récidives locales à 5 ans et la mortalité globale. De plus, il n'y avait pas de différences statistiquement significatives pour la survie sans récidive locale, la survie sans mastectomie, la survie

sans maladie à distance, la survie globale et la mortalité par cancer du sein. La mortalité due à d'autres causes était significativement plus faible dans le groupe TARGIT-IORT.

- Les taux de récidive locale chez les femmes traitées avec Intrabeam® dans le cadre d'une étude de recherche au CUSM étaient faibles.
- Nous concluons que la RTPO utilisant Intrabeam® est une méthode de traitement faisable et sécuritaire pour des patientes atteintes d'un cancer du sein soigneusement sélectionnées.

RECOMMANDATIONS

- Nous concluons que la RTPO utilisant Intrabeam® peut être utilisée dans une population restreinte de patientes atteintes d'un cancer du sein soigneusement sélectionnées au CUSM. Cela correspondrait à une recommandation de : Approuvé pour évaluation
- Cette recommandation a été mise à jour sur la base des éléments suivants :
    - La nouvelle preuve de suivi à long terme de non-infériorité
    - Données locales du CUSM indiquant de faibles taux de récidive
- Il est nécessaire que les données soient systématiquement collectées, y compris les données sur les critères de sélection des patientes et les événements cliniques en aval;
- Cette recommandation devrait être réexaminée si d'autres éléments de preuve devenaient disponibles.

LIST OF ABBREVIATIONS

APBI	Accelerated partial breast irradiation
CI	Confidence interval
EBRT	External beam radiotherapy
Gy	Gray, unit used to measure the total radiation a patient is exposed to
HR	Hazard ratio
IORT	Intra-operative radiotherapy
K-M	Kaplan-Meier
MUHC	McGill University Health Centre
QoL	Quality of life
RCT	Randomized controlled trial
RTOG	Toxicity criteria of the Radiation Therapy Oncology Group
TAU	MUHC Technology Assessment Unit

UPDATE OF TAU REPORTS #63 AND #76: SINGLE-DOSE INTRAOPERATIVE RADIOTHERAPY USING INTRABEAM® FOR EARLY-STAGE BREAST CANCER

1. BACKGROUND

Postoperative whole-breast external beam radiotherapy (EBRT), usually delivering a total dose of 45-50 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. Intra-operative radiotherapy (IORT) with Intrabeam® was conceived to deliver a single dose of radiation directly to the tumour bed during surgery for lumpectomy, thus avoiding postoperative whole-breast radiotherapy for selected patients with early-stage breast cancer. IORT was proposed based on the results of a single non-inferiority trial, the TARGIT-A trial [1]. TARGIT-A was a pragmatic, non-blinded, randomized clinical trial that compared patients who were treated with IORT with Intrabeam® vs. EBRT for early breast cancer. Some of the hypothesized advantages of using Intrabeam® over whole breast EBRT were that IORT would: avoid unnecessary irradiation of vital organs such as the heart and lungs; reduce the frequency of patient hospital visits; shorten the waiting time for radiotherapy patients; and lower the workload of the Radiation Oncology Department.

TARGIT-A first published their early results in 2010 where only 13% of patients had a median follow-up time of 5 years [1]. This study reported acute complications and formed the basis for TAU's evaluation published in November 2012. In 2014, TARGIT-A published updated results on long-term complications for 35% of participants who had a median follow-up time of 5 years [2]. These results were evaluated in a second TAU report published in June 2015.

1.1 Reason for Brief Report

This brief report is to update the recommendations issued in TAU reports #63 (November 2012) [3] and #76 (June 2015) [4], which evaluated the effectiveness and safety of Intrabeam® for selected patients with early-stage breast cancer. TAU's last evaluation (report #76) concluded that the available evidence supporting the use of Intrabeam®, based on the relatively short follow-up time (median 2.4 years) and inconsistencies in the TARGIT-A results to allow proper evaluation of non-inferiority, was not yet adequate to justify its approval for routine use. Hence, the TAU policy

committee did not recommend routine use of this technology; rather they recommended that that the acquisition of Intrabeam® 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.

Longer term follow-up results have recently been published by the TARGIT-A trial authors. Therefore, an update was requested by Dr. Tarek Hijal, Director of the Division of Radiation Oncology at the McGill University Health Centre (MUHC) on July 12, 2021.

2. OBJECTIVES

- What is the new evidence on local recurrence, survival and complication rates of IORT vs. EBRT?
- What is the local evidence on the use of Intrabeam® at the MUHC?

3. METHODS

3.1 Literature search and quality assessment

When TAU's report #76 was released in June 2015, there were nine ongoing studies evaluating local recurrence, survival and complication rates of IORT. We updated our search on PubMed and ClinicalTrials.gov on January 24, 2022.

3.2 MUHC experience

We obtained information from Dr. Tarek Hijal and the Radiation Oncology Clinical Research team of the Cedar Cancer Center on current use of Intrabeam® at the MUHC.

4. RESULTS

4.1 Results of the literature search

We found 13 studies registered at the ClinicalTrials.gov: 9 are clinical trials and 4 observational studies (Appendix A:). All studies are ongoing except TARGIT-A trial that has completed and published their results, and a study by the University of Southern California that was terminated due to lack of funding.

4.2 New evidence from the TARGIT-A trial

The TARGIT-A trial was a non-inferiority trial that included 3451 women ≥ 45 years with early-stage breast cancer (with unifocal invasive ductal carcinoma preferably ≤ 3.5 cm in size) from 33 centers in 11 countries.

A non-inferiority trial tests whether the experimental treatment is not worse than the control treatment by more than a pre-specified non-inferiority margin. The TARGIT-A trial defined their non-inferiority margin as an absolute difference of 2.5% in the binomial proportions (number of recurrences/number of patients) of the 5-year local recurrence rate between the two radiotherapy treatment groups. Thus, the trial protocol specified that IORT would be considered non-inferior to EBRT if the upper limit of the 90% CI of the treatment difference between the two groups did not exceed 2.5%.

TARGIT-A included two parallel cohorts of women, categorized as pre-pathology or post-pathology. Their first publication reported short-term follow-up (median: 2.4 years) results for both groups. The post-pathology group included women (n=1153) who had already undergone breast-conserving surgery, and subsequently received IORT as a second procedure after surgery (delayed TARGIT-IORT). As the intended use of IORT is delivery *during* surgery, our evaluation will only focus on the pre-pathology stratum (n=2298) where women were randomized before surgical removal of the tumour. These women completed their 5-year follow up in 2016 [5] and new evidence at long-term follow-up (median: 8.6 years) [6] was recently available.

4.2.1 Short-term follow-up results

TARGIT-A's short-term follow-up results showed that the 5-year Kaplan-Meier (K-M) risk of local recurrence for the pre-pathology group (n=2234) was 2.1% (95% confidence interval (CI): 1.1, 4.2) vs. 1.1 % (95% CI: 0.5, 2.5) for IORT vs. EBRT, resulting in an absolute risk difference of 2% (no 95% CI provided) for IORT vs. EBRT respectively. The 95% CI calculated by the authors of the TAU report for the difference in K-M recurrence rates (cumulative incidence rates) found that the upper CI exceeded the 2.5% non-inferiority margin. However, for the difference in binomial proportions (number of recurrences divided by the number of patients), the 90% CI reported in the study were within the 2.5% non-inferiority margin (Table 1).

4.2.2 Long-term follow-up results

Long-term follow-up (median 8.6 years, maximum 18.90 years, interquartile range 7.0-10.6) results of women in the pre-pathology stratum (n=2234) showed that the 5-year Kaplan-Meier (K-M) risk of local recurrence was 2.23% vs. 1.02 % for IORT vs. EBRT, resulting in an absolute risk difference of 1.21% (90% CI: 0.47, 1.95). The binomial proportions of 5-year local recurrence were 2.11% (24/1140) and 0.95% (11/1158) for IORT vs. EBRT, respectively. The resulting absolute risk difference was 1.16% (90% CI: 0.32, 1.99) [Table 1]. Therefore, the results for both the difference in Kaplan-Meier risk and the difference in binomial proportions were within the 2.5% threshold [6].

The authors reported no statistically significant differences between IORT and EBRT for local recurrence-free survival (hazard ratio (HR) and 95% CI: 1.13; 0.91, 1.41), mastectomy-free survival (HR: 0.96; 0.78, 1.19), distant disease-free survival (HR: 0.88; 0.69, 1.12), overall survival (HR: 0.82; 0.63, 1.05), and breast cancer mortality (HR: 1.12; 0.78, 1.60). Mortality from other causes was significantly lower for IORT vs. EBRT (HR: 0.59; 0.40, 0.86) [6].

4.2.3 Cost Utility Analysis

A cost-utility analysis comparing IORT and EBRT for treating early breast cancer treatment in the UK was done using decision analytic modelling by a Markov model for a time horizon of 10 years. The decision analytic model was constructed based on outcome probabilities from the published TARGIT-A trial data (817 patients randomised in the 'earliest cohort' in the pre-pathology stratum); costs from the INTRABEAM manufacturer and UK National Health Service cost data; and utility values from the published literature [9]. Uncertainty was tackled by performing one-way and probabilistic sensitivity analyses. Future costs and effects were discounted at the rate of 3.5%. IORT appeared to be $1,386 CAD less costly than EBRT ($14,480 vs. $15,866 CAD, respectively). IORT also produced better quality-adjusted life-years: discounted QALYs gained were 8.15 for IORT vs. 7.97 for EBRT (i.e., IORT gained 0.18 incremental QALY).

5. INTRABEAM AT THE MUHC

5.1 MUHC experience with Intrabeam

Between October 29, 2013, and July 31, 2018, 39 breast cancer patients were treated with IORT using Intrabeam® in the context of a clinical research, but four withdrew from

the trial leaving 36 patients for the analysis. Of the four who withdrew, one refused EBRT during follow up, one was off protocol due technical issues with the machine, and two withdrew prior to IORT**.** Two-quarters of patients had a grade-2 tumour and a third had a grade-1 tumour (Table 2). Two (5.6%) patients required adjuvant chemotherapy, 22 (61.1%) received adjuvant hormonal therapy, and 15 (41.7%) had EBRT following IORT. With a mean follow up time of 5.05 years (Standard error (SE): 0.84), local recurrence was found in two (5.6%) patients (Table 3). There was no acute RTOG toxicity score (Toxicity criteria of the Radiation Therapy Oncology Group) ≥3, while late RTOG toxicity score ≥3 was found in 1 (3.0%) patient. These rates are within the range found in the TARGIT-A trial. (1) Seroma was the most common complication (27.8%).

5.2 Current treatment policy

Considering evidence from the recent studies supporting the non-inferiority of IORT compared to EBRT, Intrabeam® has been used in a non-research setting in carefully selected patients at the MUHC since August 2018. Between August 2018 and May 21, 35 patients received the treatment: 26 with breast cancer and 9 with brain cancer. No local recurrence was found at follow-up. Post-pathology IORT has never been done at the MUHC.

6. DISCUSSION

TARGIT-A's short-term follow-up results were suggestive of non-inferiority of IORT over EBRT. However, the relatively short follow-up time (median: 2.4 years) and crossing of the 2.5% non-inferiority margin for the 95% CI for Kaplan-Meir 5-year local recurrence rates lead to a recommendation to not approve Intrabeam® for routine use at the MUHC in 2015.

Long-term follow up (median 8.6 years) from the TARGIT-A trial were reassuring and indicated that IORT during lumpectomy was non-inferior to EBRT for 5-year local recurrences, as defined by the trial protocol. Furthermore, this study found that there were no statistically significant differences between IORT and EBRT for local recurrence-free survival, mastectomy-free survival, distant disease-free survival, overall survival, and breast cancer mortality. Mortality from other causes was significantly lower in the IORT group. Moreover, a UK cost utility analysis showed that IORT appeared to be less costly and produced better quality-adjusted life-years than EBRT.

Results from local data from 36 women treated with IORT as part of a clinical trial at the MUHC over an average of 5 years showed that local recurrence rates and grade≥3 toxicity rates were within the range found in the TARGIT-A trial.

7. CONCLUSIONS

- The most recent evidence from the TARGIT-A trial, which includes long-term follow-up, showed non-inferiority of TARGIT-IORT delivered during lumpectomy to EBRT for 5-year local recurrences, as well as no statistically significant differences for local recurrence-free survival, mastectomy-free survival, distant disease-free survival, overall survival, and breast cancer mortality. Mortality from other causes was significantly lower in the IORT group.
- Until July 2018, there were 2 (5.6%) recurrences among 36 women treated at the MUHC over a mean follow up of 5.05 years as part of a clinical trial. There was no acute RTOG toxicity score ≥3, while late RTOG toxicity score ≥3 was found in 1 (3.0%) patient. These rates are within the range found in the TARGIT-A trial.
- Since August 2018, IORT using Intrabeam® has been used to treat 35 patients: 26 with breast cancer and 9 with brain cancer. No local recurrence was found at follow-up.
- We conclude that IORT using Intrabeam® is a feasible and safe method of treatment for carefully selected breast cancer patients.

8. RECOMMENDATIONS

- We conclude that IORT using Intrabeam® may be used in a restricted population of carefully selected breast cancer patients at the MUHC. This would correspond to a recommendation of: Approved for evaluation
- This recommendation was updated based on the following:
    - The new long-term follow-up evidence of non-inferiority ;
    - Local data from MUHC indicating low recurrence rates
- It is necessary that data be systematically collected, including data on patient selection criteria and downstream clinical outcomes;
- This recommendation should be reviewed should any further evidence become available.

TABLES

Table 1. Results of TARGIT-A trial follow-up: 5-year risk of local recurrence and mortality in the pre-pathology strata

	Median follow-up	5-year risk of local recurrence and mortality						Absolute difference	
		Intrabeam®			EBRT			K-M¥	Binomial§
		No. of patients	No. of events	K-M % (95%CI)ǂ	No. of patients	No. of events	K-M % (95%CIǂ)	% (95% CI)*	% (90%CI)
Pre-pathology, short-term follow-up									
Local recurrence (n=2234)	2.4 years	1107	10	2.1 (1.1, 4.2)	1127	6	1.1 (0.5, 2.5)	1.0 (-0.89, 2.89)	0.4 (-0.2, 1.0)
Overall mortality (n=2298)			29	4.6 (1.8, 6.0)		42	6.9 (4.3, 9.6)	-2.3 (-5.05, 0.45)	
Breast cancer deaths		1140	17	3.3 (1.9, 5.8)	1158	15	2.7 (1.5, 4.6)	0.6 (-1.96, 3.16)	
Non-breast cancer deaths			12	1.3 (0.7, 2.8)		27	4.4 (2.8, 6.9)	-3.1 (-5.50, -0.70)	
Pre-pathology, long-term follow-up									
Local recurrence (n=2298)	8.6 years	1140	24	2.23	1158	11	1.02	1.21 (0.33, 2.09)	1.16 (0.32, 1.99)
Overall mortality (n=2298)									
Breast cancer deaths		1140	42		1158	56			1.15 (-0.52, 2.84)

ǂ Kaplan-Meier estimate of 5-year local recurrence risk and 95% confidence intervals
¥ Absolute difference in Kaplan-Meier estimates of 5-year local recurrence
§ Absolute difference in binomial proportions of local recurrence
* These 95% CIs were not provided by the TARGIT-A trial authors, but calculated by TAU report authors (see Appendix for calculation).

Table 2. Characteristics of the trial participants who received Intrabeam® IORT at the MUHC until July 2018

Patient characteristics	
Age, years, mean (min, max)	68.5 (50.0; 80.0)
Tumour size, cm, mean (min, max)	1.2 (0.4; 5.0)
Follow up time, years, median	5.1
Histology, N (%)	
Ductal	30 (83.3)
Mammary	2 (5.6)
Mixed (lobular-mammary; ductal-papilloma)	2 (5.6)
Other (mucinous)	2 (5.6)
Tumour stage, N (%)	
T1	36 (100)
N0	36 (100)
Tumour grade, N (%)	
1	12 (33.4)
1 to 2	1 (2.8)
2	22 (61.1)
2 to 3	1 (2.8)
DCIS present, N (%)	25 (69.4)
Extensive intraductal component, N (%)	1 (2.8)
Lympho-vascular invasion, N (%)	2 (5.6)
Unifocal tumour, N (%)	34 (94.4)
Hormone receptor status (ER/PR), N (%)	36 (100)
Human epidermal growth factor 2 status	
Positive	0 (0)
Negative	34 (94.4)
Equivocal	2 (5.6)

Table 3. Outcomes of the trial participants who received Intrabeam® IORT at the MUHC until July 2018

Outcome	N (%)
Local recurrence	2 (5.6)
Adjuvant therapy	
Chemotherapy	2 (5.6)
Hormone therapy	22 (61.1)
Received EBRT after IORT	
Planned	15 (41.6)
Complications	
Seroma	10 (27.8)
Acute RTOG toxicity score ≥3	0 (0)
Late RTOG toxicity score ≥3	1 (3.0)

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APPENDIX

APPENDIX A: LIST OF STUDIES EVALUATING INTRABEAM® IORT REGISTERED AT CLINICALTRIALS.GOV

	NCT Number	Title	Other Names	Status	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Funder Type	Dates	Locations
1	NCT03637738	Medico Economic Study, Comparing Intrabeam® on Surgical Resection Bed to Conventional Surgery + EBRT, in Breast Cancer Study Documents:	Title Acronym: RIOP-SEIN Other Ids: ICO-2012-03	Active, not recruiting	•Menopausal Patients •Low-risk Breast Cancer	•Radiation: RIOP-Intrabeam® system •Radiation: conventional surgery +RTE	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Actual cost •Local-regional recurrence rate •Complication rates •Esthetic result •quality of life after surgery and radiotherapy	Enrollment: 246 Age: 55 Years and older (Adult, Older Adult) Sex: Female	•Institut Cancerologie de l'Ouest	•Other	Study Start: June 2012 Primary Completion: August 2014 Study Completion: May 2024 First Posted: August 20, 2018 Results First Posted: No Results Posted Last Update Posted: August 20, 2018	•Institut Bergonié, Bordeaux, France •Chu Morvan, Brest, France •Centre G F Leclerc, Dijon, France •Centre Léon Berard, Lyon, France •Institut Paoli Calmette, Marseille, France •INSTITUT REGIONAL DU CANCER MONTPELLIER - Val D'Aurelle, Montpellier, France •Hôpital Saint Louis, Paris, France •Centre René Gauducheau, Saint Herblain, France
2	NCT01440010	TARGeted Intraoperative radioTherapy With INTRABEAM as a Boost for Breast Cancer - A Quality Control Registry Study Documents:	Title Acronym: TARGIT_BQR Other Ids: TARGIT BQR	Completed	•Breast Cancer	•Radiation: IORT with 50 kV x-rays, 20 Gy	Study Type: Observational Phase: Study Design: •Observational Model: Ecologic or Community •Time Perspective: Prospective Outcome Measures: •Local recurrence rate •Toxicity, Overall survival	Enrollment: 1135 Age: 18 Years to 85 Years (Adult, Older Adult) Sex: Female	•Universitätsmediz Mannheim	•Other	Study Start: September 1, 2011 Primary Completion: December 31, 2020 Study Completion: December 31, 2020 First Posted: September 23, 2011 Results First Posted: No Results Posted Last Update Posted: May 20, 2021	•University Medical Center Mannheim, Mannheim, Germany

	NCT Number	Title	Other Names	Status	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Funder Type	Dates	Locations
3	NCT02389686	Intra-operative Radiotherapy For Breast Cancer Women After NSM Study Documents:	Title Acronym: Other Ids: GGHBCRG-IORT-NSM	Recruiting	•Breast Neoplasms	•Device: INTRABEAM (Carl Zeiss, Oberkochen, Germany)	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Ipsilateral breast tumor recurrence rate after surgery within five years •Disease free survival after surgery within five years •Overall survival after surgery within ten years	Enrollment: 110 Age: 17 Years to 80 Years (Child, Adult, Older Adult) Sex: Female	•Liao Ning •Guangdong Academy of Medical Sciences	•Other	Study Start: October 2014 Primary Completion: October 2019 Study Completion: October 2024 First Posted: March 17, 2015 Results First Posted: No Results Posted Last Update Posted: March 17, 2015	•Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, China
4	NCT02213991	Intraoperative Radiotherapy for Korean Patients With Breast Cancer Study Documents:	Title Acronym: Other Ids: K-IORT	Unknown status	•Breast Cancer	•Device: Intraoperative radiotherapy using Intrabeam®	Study Type: Interventional Phase: Phase 2 Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Acute local toxicity in breast receiving IORT •Delayed local toxicity •Cosmesis •Local tumor recurrence in ipsillateral breast •Dosimetray	Enrollment: 215 Age: 18 Years and older (Adult, Older Adult) Sex: Female	•Gangnam Severance Hospital	•Other	Study Start: August 2014 Primary Completion: October 2017 Study Completion: March 2020 First Posted: August 12, 2014 Results First Posted: No Results Posted Last Update Posted: February 15, 2018	•Gangnam Severance Hospital, Seoul, Korea, Republic of

	NCT Number	Title	Other Names	Status	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Funder Type	Dates	Locations
5	NCT02977468	Effects of MK-3475 (Pembrolizumab) on the Breast Tumor Microenvironment in Triple Negative Breast Cancer Study Documents:	Title Acronym: Pembro/IORT Other Ids: AAAQ7863	Recruiting	•Triple Negative Breast Cancer	•Drug: Merck 3475 Pembrolizumab •Radiation: Intraoperative radiation therapy (IORT)	Study Type: Interventional Phase: Phase 1 Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: Number of subjects with significant mean percent change in TILs	Enrollment: 15 Age: 21 Years to 80 Years (Adult, Older Adult) Sex: Female	•Eileen Connolly •Merck Sharp & Dohme Corp. •Columbia University	•Other •Industry	Study Start: October 25, 2017 Primary Completion: December 31, 2022 Study Completion: December 31, 2024 First Posted: November 30, 2016 Results First Posted: No Results Posted Last Update Posted: August 23, 2021	•Columbia University Irving Medical Center, New York, New York, United States
6	NCT00983684	Comparison of Intra-operative Radiotherapy With Post-operative Radiotherapy for Women With Early Breast Cancer Study Documents:	Title Acronym: TARGIT Other Ids: •ISRCTN 34086741 •MREC No. 99/0307 •UKCRN ID 7265	Completed	•Invasive Breast Cancer •Breast Cancer	•Device: Intrabeam •Radiation: Post-operative radiotherapy	Study Type: Interventional Phase: Phase 3 Study Design: •Allocation: Randomized •Intervention Model: Parallel Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Local relapse within the treated breast. •Site of relapse within the breast •Relapse-free survival and overall survival •Local toxicity/morbidity	Enrollment: 3451 Age: 45 Years and older (Adult, Older Adult) Sex: Female	•University College, London •National Institute for Health Research, United Kingdom	•Other	Study Start: March 2000 Primary Completion: June 2012 Study Completion: June 2012 First Posted: September 24, 2009 Results First Posted: No Results Posted Last Update Posted: December 5, 2014	•Clinical Trials Group, London, United Kingdom

	NCT Number	Title	Other Names	Status	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Funder Type	Dates	Locations
7	NCT01792726	A Comparison of Intra-operative Radiotherapy Boost With External Beam Radiotherapy Boost in Early Breast Cancer. Study Documents:	Title Acronym: TARGIT-B Other Ids: • TARGIT Boost • NHS NIHR HTA	Recruiting	• Early Breast Cancer	• Radiation: Boost to the tumour bed	Study Type: Interventional Phase: Not Applicable Study Design: • Allocation: Randomized • Intervention Model: Parallel Assignment • Masking: None (Open Label) • Primary Purpose: Treatment Outcome Measures: • Local tumour control (defined as no recurrent tumour in the ipsilateral breast). • Site of relapse within the treated breast • Relapse-free survival • Overall survival • Adverse events related to the primary treatment of the breast cancer. • Quality of life assessed by patient completed validated questionnaires.	Enrollment: 1796 Age: Child, Adult, Older Adult Sex: Female	• University College, London • National Institute for Health Research, United Kingdom	• Other	Study Start: June 2013 Primary Completion: January 2022 Study Completion: April 2022 First Posted: February 15, 2013 Results First Posted: No Results Posted Last Update Posted: July 12, 2019	• Helen Rey Breast Cancer Research Foundation, Los Angeles, California, United States • Memorial Health University Medical Center, Savannah, Georgia, United States • Beaumont Health - Royal Oak, Detroit, Michigan, United States • Lakeland Regional Health System, Saint Joseph, Michigan, United States • Ashikari Breast Center, Dobbs Ferry, New York, United States • Cleveland Clinic, Cleveland, Ohio, United States • West Virginia University, Morgantown, West Virginia, United States • Aurora Breast Center, Green Bay, Wisconsin, United States • Beijing Cancer Hospital, Beijing, China • Institut Bergonié, Bordeaux, France • and 24 more

	NCT Number	Title	Other Names	Status	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Funder Type	Dates	Locations
8	NCT00556907	Targeted Intra-Operative Radiotherapy for the Management of Ductal Carcinoma In-Situ of the Breast Study Documents:	Title Acronym: Other Ids: 1B-06-9	Terminated	•Breast Cancer	•Radiation: Intraoperative radiotherapy •Device: Intraoperative radiotherapy	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Feasibility. The primary efficacy endpoint will be reoperation (re-excision or mastectomy) rates following WLE or IORT •Safety endpoints: The overall serious adverse event rate will be assessed for all patients at stated follow-up periods. Complications associated with each of the following setting will be documented and reported separately	Enrollment: 22 Age: 40 Years and older (Adult, Older Adult) Sex: Female	•University of Southern California	•Other	Study Start: October 2007 Primary Completion: March 2015 Study Completion: November 2016 First Posted: November 12, 2007 Results First Posted: No Results Posted Last Update Posted: July 11, 2017	•USC/Norris Comprehensive Cancer Center, Los Angeles, California, United States
9	NCT02386371	Intraoperative Radiotherapy After Local Recurrence in Breast Cancer Study Documents:	Title Acronym: RE-IORT01 Other Ids: ICM-URC2014/07	Active, not recruiting	•Breast Carcinoma	•Procedure: tumorectomy •Radiation: Intra Operative Radiotherapy	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Tolerance of intra operative radiation as assessed by acute and late toxicities •Cosmetic outcome evaluated by photography	Enrollment: 66 Age: 50 Years and older (Adult, Older Adult) Sex: Female	•Institut du Cancer de Montpellier - Val d'Aurelle	•Other	Study Start: March 2014 Primary Completion: June 12, 2020 Study Completion: April 2023 First Posted: March 11, 2015 Results First Posted: No Results Posted Last Update Posted: December 21, 2021	•Institut Bergonié, Bordeaux, France •Chu Brest, Brest, France •Centre George Francois Leclerc, Dijon, France •Centre Léon Bérard, Lyon, France •CHU La TIMONE, Marseille, France •Institut Paoli Calmette, Marseille, France •CRLC Val d'Aurelle, Montpellier, France •Institut de Cancérologie de l'Ouest, Nantes, France

	NCT Number	Title	Other Names	Status	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Funder Type	Dates	Locations
10	NCT04994067	Intra-Operative Radiation Registry Study Documents:	Title Acronym: Other Ids: 2018-9409	Recruiting	•Breast Cancer		Study Type: Observational Phase: Study Design: •Observational Model: Cohort •Time Perspective: Prospective Outcome Measures: •Number of patients with locally controlled disease •Number of patients with regionally controlled disease •Number of patients with grade 2 or higher toxicities	Enrollment: 250 Age: 18 Years and older (Adult, Older Adult) Sex: Female	•Albert Einstein College of Medicine	•Other	Study Start: August 9, 2018 Primary Completion: August 9, 2023 Study Completion: August 9, 2024 First Posted: August 6, 2021 Results First Posted: No Results Posted Last Update Posted: August 6, 2021	•Montefiore Medical Center - Moses Campus, Bronx, New York, United States
11	NCT03536897	IORT Following Breast Conserving Surgery for Early Stage Breast Cancer Registry Study Documents:	Title Acronym: Other Ids: 180212-1	Recruiting	•Breast Cancer	•Radiation: IORT	Study Type: Observational Phase: Study Design: •Observational Model: Cohort •Time Perspective: Prospective Outcome Measures: •In-Breast Tumor Recurrence (IBTR) •Late Toxicity •Acute Toxicity •Disease Free Survival •Overall Survival	Enrollment: 168 Age: 65 Years and older (Older Adult) Sex: Female	•Mount Carmel Health System	•Other	Study Start: February 27, 2018 Primary Completion: February 27, 2028 Study Completion: February 27, 2028 First Posted: May 25, 2018 Results First Posted: No Results Posted Last Update Posted: July 2, 2021	•Mount Carmel West Hospital, Columbus, Ohio, United States

	NCT Number	Title	Other Names	Status	Conditions	Interventions	Characteristics	Population	Sponsor/ Collaborators	Funder Type	Dates	Locations
12	NCT02290782	TARGIT-C(Consolidation) Prospective Phase IV Study of IORT in Patients With Small Breast Cancer Study Documents:	Title Acronym: TARGIT-C Other Ids: TARGIT C	Active, not recruiting	•Breast Cancer	•Radiation: Intraoperative radiotherapy (IORT)	Study Type: Interventional Phase: Not Applicable Study Design: •Allocation: N/A •Intervention Model: Single Group Assignment •Masking: None (Open Label) •Primary Purpose: Treatment Outcome Measures: •Local relapse •Ipsi- or contralateral breast cancer •Survival •Toxicity (CTC, LENT SOMA) •General QoL and breast specific QoL (EORTC QLQ C30 + BR23)	Enrollment: 387 Age: 50 Years and older (Adult, Older Adult) Sex: Female	•Universitätsmediz Mannheim	•Other	Study Start: October 2014 Primary Completion: December 2026 Study Completion: December 2026 First Posted: November 14, 2014 Results First Posted: No Results Posted Last Update Posted: November 3, 2021	•Institut régional du Cancer de Montpellier, Montpellier, France •IUCT, Toulouse, Toulouse, France •Klinikum Kassel, Kassel, Germany •Department of Radiotherapy University Hospital Mannheim, Mannheim, Germany
13	NCT02114086	IORT-Boost-Study, Prospective Observational Study for Intraoperative Radiotherapy of the Breast as a Boost Study Documents:	Title Acronym: Other Ids: •ROKSM 01/12 •KMünsterlingen	Active, not recruiting	•Adverse Effect of Radiation Therapy		Study Type: Observational Phase: Study Design: •Observational Model: Case-Control •Time Perspective: Prospective Outcome Measures: •number of Participants with local recurrence histologically proven •observation of acute and late effects of Radiotherapy •Overall survival •Quality of life •Cosmesis	Enrollment: 163 Age: Child, Adult, Older Adult Sex: Female	•Kantonsspital Münsterlingen	•Other	Study Start: January 2013 Primary Completion: December 31, 2019 Study Completion: August 31, 2025 First Posted: April 15, 2014 Results First Posted: No Results Posted Last Update Posted: March 4, 2021	•KMünsterlingen, Münsterlingen, Thurgau, Switzerland