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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: An Update

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

by

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Update of TAU report #63: Single-dose Intraoperative Radiotherapy Using Intrabeam® for Early-stage Breast cancer: A Health Technology Assessment

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REPORT REQUESTOR

This report is an update of TAU report #63 "*Single-dose Intraoperative Radiotherapy Using Intrabeam® for Early-stage Breast cancer: A Health Technology Assessment"* which was requested by the former Administrative Director of the Surgical Mission, Mr. Gary Stoopler. The new report will be presented to the current Administrative Director, Neuroscience Mission, Ms. Teresa Mack.

TABLE OF CONTENTS

LIST OF TABLES

ABSTRACT

- Intrabeam® intraoperative radiotherapy treatment for breast cancer avoids the unnecessary irradiation of vital organs such as the heart and lungs, and reduces the burden on the patient of frequent hospital visits.

- Evidence of the efficacy of Intrabeam® in preventing local breast cancer recurrences in comparison with conventional whole breast external beam radiotherapy is derived from a single randomized controlled trial, TARGIT-A, which recently updated its 4-year results with 5-year follow-up data.

- Serious concerns have been raised about the analysis and presentation of these 5-year results, undermining the authors' claims of establishing non-inferiority of Intrabeam® compared with whole breast radiotherapy.

- The TARGIT-A trial authors' omission of 95% confidence intervals for the absolute difference in risk of local recurrence prevents readers from assessing non-inferiority of Intrabeam®. 95% confidence intervals calculated by TAU indicate that the pre-determined non-inferiority margin of 2.5% set by the authors was indeed exceeded, demonstrating failure to establish non-inferiority of the Intrabeam® technology.

- Based on TARGIT-A's earlier 4-year results which were suggestive of non-inferiority of Intrabeam®, TAU had recommended that Intrabeam® be approved temporarily at the MUHC, conditional on participation in research trials with informed consent from all participants. TARGIT-A's most recent results, which are inconclusive with respect to the non-inferiority of Intrabeam® when compared to external beam radiotherapy, do not allow us to make a recommendation of permanent approval of this technology.

- Thus, TAU's previous recommendation that Intrabeam® not be used other than in the context of a research study, with stringent patient selection criteria and strict research protocols, still stands.

- Since October 2013, 16 women have received Intrabeam® at the MUHC under a research protocol, with no local recurrences detected to date.

RÉSUMÉ

- Le traitement de radiothérapie Intrabeam® peropératoire lors de cancers du sein permet d'éviter l'irradiation superflue d'organes vitaux tels le coeur et les poumons et allège le fardeau des visites fréquentes des patientes à l'hôpital.

- Les preuves de l'efficacité du traitement Intrabeam® pour prévenir les récidives du cancer du sein local par comparaison avec le traitement conventionnel par radiothérapie externe du sein entier, découlent d'une seule étude randomisée, soit l'étude TARGIT-A, dont on a récemment mis à jour les 4 années de résultats suite à un suivi de 5 ans.

- De sérieuses interrogations ont été formulées concernant l'analyse et la présentation des résultats de ces 5 années de suivi, ébranlant les revendications des auteurs voulant établir la non-infériorité de l'Intrabeam® comparativement à la radiothérapie externe du sein entier.

- L'omission de l'intervalle de confiance de 95% par les auteurs de l'étude TARGIT-A concernant la différence absolue des risques de récidives locales, empêche les lecteurs de reconnaître la non-infériorité du traitement Intrabeam®. Les intervalles de confiance de 95% calculés par les intervenants du TAU (Technology Assessment Unit) indiquent que la marge prédéterminée de non-infériorité de 2.5% fixée par les auteurs était effectivement dépassée, démontrant l'incapacité de prouver la non-infériorité de la technologie Intrabeam®.

- En se basant sur les résultats antérieurs de 4 ans de l'étude TARGIT-A qui laissaient entrevoir une non-infériorité de la technologie Intrabeam®, le TAU avait recommandé que l'Intrabeam® soit approuvée temporairement au CUSM (Centre hospitalier de santé McGill), à la condition de participer à des recherches cliniques avec le consentement éclairé de tous les participantes. Les résultats les plus récents de l'étude TARGIT-A, qui ne sont pas concluants en regard de la non-infériorité de la technique Intrabeam® lorsque comparée à la radiothérapie externe, ne nous permettent pas de recommander cette technologie sur une base permanente.

- Par conséquent, la recommandation précédente du TAU à l'effet que l'Intrabeam® ne soit utilisée que dans le contexte d'une étude de recherche comportant des critères de sélection très stricts et des protocoles de recherche rigoureux, est maintenue.

- Depuis le mois d'octobre 2013, 16 femmes ont été traitées par Intrabeam® au CUSM selon un protocole de recherche, sans aucune récidive locale détectée à ce jour.

LIST OF ABBREVIATIONS

APBI	Accelerated partial breast irradiation
ASTRO	American Society for Radiation Oncology
BCS	Breast-conserving surgery
CI	Confidence interval
DCIS	Ductal carcinoma in situ
EBRT	External beam radiotherapy
EIC	Extensive intraductal component
GEC-ESTRO	Groupe Européen de Curiethérapie of the European Society of Therapeutic Radiology and Oncology
Gy	Gray, SI unit of ionizing radiation dose
HER2	Human epidermal growth factor receptor 2
HR positive	Hormone receptor (estrogen receptor or progesterone receptor) positive
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
IORT	Intra-operative radiotherapy
INESSS	Institut National d'Excellence en Santé et en Service Sociaux
K-M	Kaplan-Meier
LR	Local recurrences of breast cancer
LVSI	Lymph-vascular space invasion
MUHC	McGill University Health Centre
NICE	National Institutes for Health and Clinical Excellence
RCT	Randomized controlled trial
RTOG toxicity score	Radiation therapy oncology toxicity score ranges from 0 (no toxicity) to 5 (death directly related to radiation)
TARGIT-A	Targeted intra-operative radiotherapy trial
TAU	MUHC Technology Assessment Unit

EXECUTIVE SUMMARY

Background

Intraoperative radiotherapy (IORT) is one of the modalities 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, resulting in a cumulative dose of 45-50 Gy over 5-7 weeks, intraoperative therapy is delivered directly to the tumour bed during breast conserving surgery, and is given in a single higher dose. 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. In IORT with Intrabeam®, low-energy x-rays are directly delivered to the tumour bed in a procedure lasting 25-30 minutes, attaining a maximum dose of 20 Gy at the surface of the tumour bed.

Efficacy of Intrabeam® has only been evaluated in a single non-inferiority trial, the TARGIT-A trial. Based on TARGIT-A's 4-year follow-up results which were suggestive of the non-inferiority of Intrabeam® to EBRT in terms of local breast cancer recurrences, TAU did not recommended use of this technology in 2012, except in the context of a research study. In 2014, 5-year results of the TARGIT-A trial were published, necessitating an update of our earlier report.

Objectives

The objectives of this report were to update our previous report on the efficacy and safety of the Intrabeam® intraoperative device in preventing local breast cancer recurrences when compared with external beam radiotherapy, among women with early-stage breast cancer.

Methods

A systematic literature search was conducted since the last literature review in November 2012, to identify all relevant randomized controlled trials (RCT), observational studies, systematic reviews or health technology assessment (HTA) reports that

specifically assessed the Intrabeam® device. We also summarized the MUHC experience to date with the Intrabeam® device in terms of patient selection and clinical outcomes.

Results

We identified one RCT, the TARGIT-A non-inferiority trial, which assessed the efficacy of Intrabeam® compared to EBRT in preventing local breast cancer recurrences. The same group has recently published 5-year follow-up results. The TARGIT-A trial pre-determined the non-inferiority margin as an absolute difference of 2.5% between Intrabeam® and EBRT in the primary endpoint of local recurrence risk, based on the assumption that the background 5-year local recurrence rate was 6%. 3,451 women with early stage breast cancer and low risk of recurrence were randomized to receive either IORT or EBRT; median follow-up time was 2.4 years. However, there are serious concerns regarding the presentation and analysis of these data which undermine the authors' claims of having established non-inferiority of Intrabeam®.

The trial reported an increased risk of local recurrence in the IORT group of 2% (log-rank p-value: 0.042). 95% confidence intervals(CI) around this risk difference are necessary to evaluate non-inferiority because an upper confidence limit exceeding 2.5% indicates failure to establish non-inferiority. The authors failed to provide this information. A 95% CI estimated by us for the 2% risk difference was (0.21, 3.80), i.e. the upper limit exceeded the non-inferiority margin of 2.5%. We thus cannot conclude that Intrabeam® is non-inferior to EBRT in preventing local recurrences based on the current evidence.

A further concern is that the follow-up time (median of 2.4 years) was too short to capture the peak in local breast recurrence rates. This is particularly problematic given that almost all trial participants had hormone receptor-positive breast cancer, which has a longer time to recurrence, and that the majority of women received adjuvant hormone therapy, which may delay breast cancer recurrence.

The difference in breast cancer-related mortality (secondary endpoint) between the IORT and EBRT groups (2.6% vs. 1.9%; log-rank p-value: 0.56) was not statistically significant. The TARGIT-A authors reported a significantly lower risk of non-breast cancer deaths in the IORT- vs. EBRT-treated women (1.4% vs. 3.5%; log-rank p-value: 0.009), which they attribute to a greater number of radiation toxicity-related deaths in the EBRT arm. However, this assertion is arguable because of the long latency period (10-20 years) for radiation-related morbidity and mortality. Furthermore, our calculated 95% CI for

the difference in non-breast cancer mortality between IORT and EBRT (-3.81, -0.39) was wide and approached 0, suggesting the evidence regarding the effect of EBRT vs IORT on non-breast cancer deaths is also inconclusive.

Complication rates were not reported for the 5-year follow-up study. Results from the 4-year follow-up study showed that IORT-treated women had a significantly increased risk of seroma and a significantly decreased risk of radiation toxicity grade of 3 or 4 compared to EBRT-treated women.

Intrabeam® at the MUHC

16 women have been treated with Intrabeam® since November 2013, and were selected based on having low risk factors for breast cancer recurrence. Of the 12 women with available follow-up data, 5 (45%) received further treatment with EBRT due to high risk factors at presentation or after ascertaining tumour pathology. None developed a local recurrence. With respect to complications, 6 (50%) developed a seroma, 2 (16%) developed a hematoma, and one woman (8%) had a radiation toxicity score of grade 3.

Costs

We estimated the cost per procedure of treatment with Intrabeam® to be $5,434 and $3,668 if 15 and 30 procedures, respectively, are performed annually, after accounting for the increased operation room time, the assumption that 20% of women also receive EBRT therapy, and that the capital cost of the equipment was borne by a donor. Given the estimated cost of EBRT treatment of $4,667, performing 30 Intrabeam® procedures per year would result in estimated annual savings of approximately $30,000 ($4,667-$3668)*30] from the point of view of the MUHC. If in the future, the capital cost is to be covered by the MUHC, the per-patient costs given above would increase to $12,132 and $7,017 for 15 and 30 procedures, respectively.

CONCLUSIONS

- **The TARGIT-A trial remains the sole trial comparing intraoperative radiation therapy using Intrabeam® to conventional external beam radiation therapy. Given the serious concerns with the results, the current evidence fails to conclusively establish the non-inferiority of Intrabeam® to external beam radiation.**
- **The short median follow-up time of 2.4 years in the TARGIT-A trial is particularly problematic if hormone receptor-positive women, who constituted the majority of trial participants, are more likely to have recurrences later in follow-up.**
- **A longer follow-up may indeed establish non-inferiority of Intrabeam®, but until such convincing evidence is available, Intrabeam® should only be considered an experimental procedure to be delivered under strict research protocols. Guidelines established by the radiation oncology societies as well as the selection criteria used in TARGIT-A may serve in selecting appropriate low-risk patients in such research settings.**

RECOMMENDATIONS

- **The current evidence does not warrant a change in the recommendation previously accorded this technology which was a <u>temporary</u> approval, conditional on participation in research studies. Presently, Intrabeam® should not be approved for use in the MUHC except in the context of the ongoing MUHC-funded research study with:**
    - **continued adherence to a strict protocol and stringent collection of follow-up data on clinical outcomes, patient satisfaction and quality of life;**
    - **informed consent obtained from all patients agreeing to receive Intrabeam®, who would be informed in a clear and accessible way, of the lack of conclusive evidence regarding the efficacy of Intrabeam® in preventing recurrences.**

- **In light of the numerous trials of Intrabeam® currently underway, the evidence should be reviewed in 5 years or when sufficient evidence has accrued about the 5-year recurrence rate.**

SOMMAIRE

Contexte

La radiothérapie peropératoire (RTPO) est une des modalités d'irradiation partielle et accélérée du sein (IPAS) qui fut introduite en se basant sur l'argument selon lequel la majorité des récidives locales réapparaissent à l'intérieur du site de la tumeur primaire. Contrairement à la radiothérapie par faisceau externe (RTFE) qui irradie entièrement le sein touché à l'aide de doses journalières de 1.8 à 2.0 Gy, résultant en une dose cumulative de 45 à 50 Gy sur une période de 5-7 semaines, la thérapie peropératoire irradie directement le lit tumoral durant la chirurgie conservatrice du sein et consiste en une dose unique de plus forte intensité. La thérapie peropératoire évite ainsi l'irradiation inutile d'organes vitaux tels le coeur et les poumons et allège le fardeau des visites fréquentes des patientes à l'hôpital. Lors de la RTPO par Intrabeam®, des rayons X de faible énergie irradient directement le lit tumoral lors d'une procédure d'une durée de 25-30 minutes, permettant d'atteindre une dose maximale de 20 Gy à la surface du lit tumoral.

L'efficacité de l'Intrabeam® a seulement été évaluée lors d'une étude unique de non-infériorité, soit l'étude TARGIT-A. En se basant sur les résultats du suivi de 4 ans de l'étude TARGIT-A qui laissaient entrevoir la non-infériorité de la technique Intrabeam®par rapport à la RTFE en termes de récidives du cancer du sein localisé, le TAU (Technology Assessment Unit) n'avait pas recommandé l'utilisation de cette technologie en 2012, sauf dans le contexte d'une étude de recherche. En 2014, les résultats d'un suivi de 5 ans de l'étude TARGIT-A furent publiés, nécessitant ainsi une mise à jour de notre rapport antérieur.

Objectifs

Les objectifs de ce rapport consistaient en la mise à jour de notre rapport précédent sur l'efficacité et l'innocuité de la technique peropératoire Intrabeam® pour la prévention des récidives du cancer du sein localisé, par comparaison à la radiothérapie par faisceau externe chez les femmes présentant un cancer du sein au stade précoce.

Méthodologie

Une recherche systématique de la littérature fut menée depuis la dernière revue de la littérature datant de novembre 2012, pour identifier toutes les études randomisées pertinentes, les études observationnelles, les revues systématiques ou les rapports d'évaluation des technologies évaluant spécifiquement le dispositif Intrabeam®. Nous avons de même résumé l'expérience de l'utilisation du dispositif Intrabeam® au CUSM à ce jour, en termes de la sélection des patients et des résultats cliniques.

Résultats

Nous avons identifié une étude randomisée, soit l'étude de non-infériorité TARGIT-A, qui évaluait l'efficacité de l'Intrabeam® par rapport à la RTFE dans la prévention des récidives du cancer du sein localisé. Le même groupe a récemment publié les résultats d'un suivi de 5 ans. L'étude TARGIT-A déterminait à l'avance que la marge de non-infériorité correspondait à une différence absolue de 2.5% du critère principal d'évaluation du risque de récidive locale entre l'Intrabeam® et la RTFE, en supposant que le taux de récidive locale du suivi de 5 ans était de 6%. 3,451 femmes avec un cancer précoce du sein et un faible risque de récidive furent randomisées pour être traitées par RTPO ou RTFE; la durée médiane du suivi était de 2.4 ans. Cependant, il persiste de sérieuses interrogations concernant la présentation et l'analyse de ces données, ébranlant les revendications des auteurs qui mentionnent avoir établi la non-infériorité de l'Intrabeam®.

L'étude rapportait une augmentation du risque de récidive locale dans le groupe RTPO de 2% (p=0.042, test de log-rank). Des intervalles de confiance (IC) de 95% sont nécessaires de part et d'autre de cette différence de risque pour évaluer la non-infériorité car une limite supérieure de confiance excédant 2.5% dénote un échec pour établir la non-infériorité. Les auteurs ont omis de fournir cette information. Nous avons calculé que des intervalles de confiance de 95% pour une différence de risque de 2% était de 0.21 et 3.80, soulignant que la limite supérieure excédait la marge de non-infériorité de 2.5%. Nous ne pouvons donc pas conclure de la non-infériorité de l'Intrabeam® par rapport à la RTFE pour prévenir les récidives locales en se basant sur les preuves actuelles.

Une autre interrogation concerne la durée du suivi (durée médiane de 2.4 ans) qui était trop courte pour enregistrer le maximum des taux de récidives du cancer du sein localisé. Ceci est plutôt problématique car la majorité des participantes à l'étude avaient des récepteurs hormonaux positifs du cancer du sein associés à un temps plus long avant une récidive, et la majorité des femmes avaient reçu un traitement hormonal adjuvant pouvant retarder la récidive d'un cancer du sein.

La différence du taux de mortalité du cancer du sein (critère secondaire) entre les groupes RTPO et RTFE (2.6% vs 1.9%; p=0.56, test de log-rank) n'était pas statistiquement significative. Les auteurs de l'étude TARGIT-A rapportaient un risque significativement plus faible de décès non reliés au cancer du sein chez les femmes traitées par RTPO vs RTFE (1.4% vs 3.5%; p=0.009, test de log-rank), attribué à un nombre plus élevé de décès reliés à une toxicité par radiation chez le groupe RTFE. Cependant, cette assertion est discutable étant donné la période de latence importante (10-20 ans) en regard de la morbidité et de la mortalité liées à la radiation. De plus, notre calcul pour l'intervalle de confiance de 95% pour la différence de mortalité non reliée au cancer du sein entre RTPO et RTFE (-3.81, -0.39) était grande et approchait 0, suggérant que les preuves en regard des effets de la RTFE vs la RTPO sur les décès non reliés au cancer du sein sont peu concluantes.

Les taux de complication n'ont pas été rapportés pour l'étude du suivi de 5 ans. Les résultats pour l'étude du suivi de 4 ans montraient que les femmes traitées par RTPO avaient un risque significativement plus élevé de développer un sérome et un risque significativement plus faible de toxicité par radiation de grade 3 ou 4, par rapport aux femmes traitées par RTFE.

Intrabeam® au CUSM

Seize femmes ont été traitées par Intrabeam® depuis le mois de novembre 2013 et furent choisies parce qu'elles avaient de faibles facteurs de risque relatifs à la récidive du cancer du sein. Parmi les 12 femmes ayant des données d'un suivi, 5 (45%) reçurent un traitement de RTFE supplémentaire étant donné les facteurs de risque élevés à première vue ou après vérification de la pathologie tumorale. Aucune ne développa une récidive locale. Concernant les complications, 6 (50%) développèrent un sérome, 2 (16%) développèrent un hématome et une femme (8%) eut une toxicité par radiation de grade 3.

Coûts

Nous avons évalué que le coût d'un traitement par Intrabeam® est de 5 434$ et de 3 668$ si 15 et 30 traitements, respectivement, sont donnés annuellement en tenant compte du temps opératoire augmenté, de l'hypothèse selon laquelle 20% des femmes recevront aussi un traitement RTFE et que le coût d'acquisition de l'équipement est supporté par un donateur. Étant donné que le coût estimé d'un traitement RTFE est de 4 667$, 30 traitements Intrabeam® réalisés par année entraîneraient des économies annuelles d'environ 30 000$ ((4 667$ - 3 668$) x 30) pour le CUSM. Si, éventuellement, les coûts d'acquisition devaient être supportés par le CUSM, les coûts par patient augmenteraient à 12 132$ et 7 017$ pour 15 et 30 traitements, respectivement.

CONCLUSIONS

- **L'étude TARGIT-A demeure la seule étude comparant la thérapie peropératoire par Intrabeam®à la thérapie conventionnelle par radiation externe. Étant donné les sérieuses interrogations concernant les résultats, les preuves actuelles ne parviennent pas à établir de façon concluante la non-infériorité de l'Intrabeam®face à la radiation externe.**

- **La courte durée médiane du suivi de 2.4 années dans l'étude TARGIT-A est particulièrement problématique si les femmes ayant des récepteurs hormonaux positifs et qui constituent la majorité des participantes à l'étude, sont plus susceptibles d'avoir une récidive lors d'un suivi ultérieur.**

- **Un suivi d'une durée plus longue peut en effet établir la non-infériorité de l'Intrabeam®, mais avant que de telles preuves ne soient disponibles, l'Intrabeam® devrait seulement être considérée comme un traitement expérimental pouvant être administré sous des protocoles de recherche rigoureux. Les lignes directrices émises par les sociétés de radio-oncologie ainsi que les critères de sélection utilisés dans l'étude TARGIT-A peuvent aider dans le choix des patients présentant de faibles risques pour de telles recherches.**

RECOMMANDATIONS

- **Les preuves actuelles ne justifient pas un changement au niveau de la recommandation précédemment attibuée à cette technologie qui était une appropation temporaire, conditionnellement à la participation à des études de recherche. Présentement, l'utilisation de l'Intrabeam® ne devrait pas être approuvée au CUSM, sauf dans le contexte d'études de recherche en cours et supportées par le CUSM avec:**
    - **un engagement continu à suivre un protocole rigoureux et une collecte serrée des données de suivi sur les résultats cliniques, la satisfaction des patients et la qualité de vie;**
    - **un consentement éclairé obtenu de toutes les patientes qui acceptent de recevoir le traitement Intrabeam® et qui seraient informés d'une manière claire et franche du manque de preuves concluantes en regard de l'efficacité de l'Intrabeam® pour prévenir les récidives.**
- **À la lumière des nombreuses études sur la technologie Intrabeam® actuellement en cours, les preuves devraient être revues dans 5 ans ou lorsque des preuves suffisantes auraient été accumulées concernant le taux de récidive après 5 ans.**

Single-dose Intraoperative Radiotherapy Using Intrabeam® for Early-stage Breast cancer: An Update

1. BACKGROUND

The treatment for early breast cancer changed radically in the mid-eighties with the publication of two landmark trials that ushered the transition from mastectomy to breast-conserving therapy.[1,2] This latter treatment typically involves breast-conserving surgery (BCS) such as lumpectomy or quadrantectomy followed by partial or whole breast radiation therapy. The treatment for breast cancer has continued to evolve with advances in technology and an improved understanding of cancer biology.

The standard-of-care for early breast cancer is post-operative whole breast external beam radiation therapy (EBRT), which consists of high-energy x-rays delivered to the entire breast and affected axillary nodes. Treatment is typically given several weeks after surgery to allow the surgical wound to heal, and is administered over 5-7 weeks in daily doses of 1.8-2.0 Gy, resulting in cumulative whole breast doses of 45-50 Gy.

Studies have suggested that the intensive nature of EBRT, which requires women to return for daily treatment, may result in poor adherence to radiation therapy, particularly among geographically-isolated and elderly patients,[3-5] with some women opting for mastectomies over breast-conserving therapy.[6,7] This prompted an increased interest in accelerated courses of radiation therapy, in which the overall dose of radiation is delivered over a shorter course of treatment and at higher doses (hypofractionation), thus shortening the duration of treatment.

Accelerated *partial* breast irradiation (APBI), which includes modalities such as interstitial brachytherapy; intracavitary brachytherapy, three-dimensional conformal radiotherapy (3D-CRT), stereotactic body radiation therapy and intraoperative radiotherapy (IORT) were introduced with the rationale that over 90% of local breast cancer recurrences occur near the primary tumour site.[8,9] Thus, sparing the unaffected portion of the breast would also reduce radiation exposure to neighbouring structures such as the heart and lungs, potentially reducing radiation toxicity. Critically, because the dose is administered in a single fraction at the time of surgery, intraoperative radiotherapy reduces the burden on women of frequent hospital visits. Other advantages of IORT include the absence of treatment delay between surgery and radiation therapy, and visualization of the tumour bed immediately before radiation,

thus enabling targeted therapy. Some disadvantages include the longer operating times, the expensive devices, and the unavailability of pathological results at the time of radiation therapy.[10]

This report will focus on IORT with Intrabeam®, the APBI technology currently available at the McGill University Health Centre as part of an ongoing research study. There are several different methods of delivering IORT: low-energy X-ray systems,[11] electron beam radiation therapy,[12] high-dose-rate afterloaders[13] or specific balloon devices.[14] IORT with Intrabeam® (Carl Zeiss, Germany) uses a device with a miniature electron beam-driven X-ray source to deliver low-energy x-rays (50KV) directly to the tumour bed.[11] This therapy is administered immediately following lumpectomy in a procedure lasting 25-30 minutes. The tumour bed receives a radiation dose of 20 Gy, with the dose attenuating to 5-7 Gy at greater tissue depths.

The targeted intraoperative radiotherapy (TARGIT-A) non-inferiority clinical trial, launched in 2000, was the first trial to specifically investigate the efficacy of IORT using Intrabeam® in preventing local breast cancer recurrence when compared with whole breast EBRT.[15] A non-inferiority trial was conducted with the premise that Intrabeam® offers specific advantages over EBRT such as increased convenience and lower radiation doses, while not significantly increasing the risk of local breast cancer recurrence. TARGIT-A initially randomized 2,232 women with early-stage breast cancer to receive either IORT or EBRT. The 4-year risk of local breast cancer recurrence was 1.20% (95% CI: 0.53, 2.71) *vs.* 0·95% (0·39–2·31) in the IORT and EBRT groups, respectively. The risk difference and its 95% CIs (0·25%;–1·04 to 1·54) established that the non-inferiority margin of 2.5% was not exceeded. Based on these results, TAU recommended that the technology not be approved except for use within a research setting. The same group recently published 5-year follow-up results of their trial,[16] necessitating an update of our previous report.

This report is an update of TAU report #63[17] which assessed the safety and efficacy of single-dose intraoperative radiotherapy using Intrabeam® in women with early stage breast cancer, and which was requested by the former Administrative Director, Surgical Mission, Mr. Gary Stoopler. The new report, which will be presented to the current Administrative Director, Neuroscience mission, Ms. Teresa Mack, summarizes the newly published results as well as data collected at the MUHC on IORT procedures performed since November 2013.

2. OBJECTIVES

The objectives of this report are to re-evaluate the safety and efficacy of intraoperative radiation therapy using Intrabeam®, in light of newly published data. Specifically, the objectives are to:

- Assess the risk of local breast cancer recurrence and complications associated with the use of intraoperative radiation therapy (IORT) using Intrabeam® compared with whole breast external beam radiation therapy (EBRT) among women with early stage breast cancer who were eligible for breast-conservation surgery.
- Evaluate the costs and budget impact of using Intrabeam® at the MUHC.
- Report on the MUHC experience in terms of patient selection factors, clinical outcomes, and the budget impact of using Intrabeam®.

3. METHODS

3.1 Literature search and quality assessment

We searched Pubmed, the Cochrane library and the health technology assessment (HTA) database of the Centre for Reviews and Dissemination to identify pertinent studies and reports on the use of single-dose intraoperative radiotherapy using Intrabeam® for early-stage breast cancer, published since the last literature search conducted on November 5th, 2012. The current literature search was conducted on March 27th, 2015.

Our literature search was limited to studies that specifically evaluated Intrabeam® such as RCTs that assessed efficacy and safety, and any cohort studies that evaluated safety.

3.2 MUHC experience

Descriptive statistics were used to summarize data on the clinical characteristics and outcomes of the small group of women treated so far with Intrabeam® at the MUHC.

3.3 Cost analysis

We estimated procedure costs per patient associated with performing 15-30 procedures with Intrabeam® at the MUHC. Cost of Intrabeam® and EBRT were obtained from Dr.

Tarek Hijal and Mr. W. Parker of the Radiation Oncology and Medical Physics Departments at the Montreal General Hospital (MGH). As the Intrabeam® machine was donated to the MUHC, we report cost estimates that included and excluded the capital cost of the machine. The cost analysis also included material costs, cost of operation room use, and costs associated with Intrabeam®-treated women requiring additional EBRT therapy; physician fees were not included.

4. LITERATURE REVIEW

We identified 1 RCT, which was a longer follow-up of the TARGIT-A trial reviewed in our earlier TAU report (report #63).[17] We also identified 2 HTA reports: one under development at NICE,[18] which provisionally supported Intrabeam® for patients with early breast cancer, pending further information from the TARGIT-A trial authors; and one written by INESSS that evaluated the efficacy of intraoperative radiotherapy for various cancers.[19] INESSS concluded that, given the serious concerns raised by numerous critics with respect to the TARGIT-A trial results and analysis,[20-25] the current evidence is insufficient to recommend Intrabeam® as standard practice, outside of rigorously monitored institutional protocols. The information requested by NICE seeks to address these concerns in order to complete their evaluation of Intrabeam®. These issues, relating to the short median follow-up time and missing information, are further elaborated upon in the Discussion section of this report. We identified several clinical trials in progress assessing the use of Intrabeam® in various sub-populations of women with breast cancer (Appendix Table A1). Below, we summarize the single completed RCT to date on the efficacy of Intrabeam® in women with early-stage breast cancer.

The TARGIT-A Trial (Vaidya et al. 2010; 2014)[15,16]

The TARGIT-A trial was a non-inferiority trial launched in 2000 in 33 centres across 11 countries. It aimed to evaluate whether a single dose of targeted intra-operative radiotherapy administered directly to the tumour bed during surgery was not substantially inferior to post-operative EBRT in preventing local breast cancer recurrence. 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 local recurrence risk between the two radiotherapy treatment groups. 2.5% was chosen as a clinically relevant increase or decrease in recurrence risk based on a 5-year

local recurrence rate of 6.0% in low-risk women receiving EBRT versus those not receiving any radiotherapy.[26] Thus, IORT would be considered non-inferior to EBRT if the upper limit of the 95% CI of the treatment difference between the two groups did not exceed 2.5%.

Patient selection and randomization: Women ≥ 45 years, with unifocal invasive ductal carcinoma and a tumour size of ≤3.5 cm were eligible to participate in the trial. Table 1 lists the other inclusion and exclusion criteria. The first study published in 2010 reported that 2232 women had been randomized, and this number increased to 3451 at the time of publication of the second study in 2014, with 1721 and 1730 women randomized to IORT and EBRT, respectively. 1571 (91.3%) in the IORT arm and 1590 (91.9%) in the EBRT arm received the allocated treatment, and an intention-to-treat analysis was performed on all randomized patients. Patients, surgeons, study investigators and outcome adjudicators were all unblinded to the treatment received.

Although IORT was developed as a procedure to be administered during surgery, the TARGIT-A trial also included women who had already undergone breast-conserving surgery (post-pathology group). Women in the pre-pathology stratum (n=2298) were randomized before surgical removal of the tumour while those in the post-pathology stratum (n=1153) were randomized *after* surgical excision of the lesion. Thus, women in the post-pathology stratum constituted a lower-risk group because their inclusion into the trial was based on not having any adverse criteria present in the histo-pathological analysis of the excised tumour. However, these women required a second surgery in order to receive IORT, and had to be randomized within 30 days of the initial breast-conserving surgery (median length of time from BCS to IORT was 37 days). Women randomized to IORT were eligible to receive a full course of EBRT after IORT if unfavourable features were detected after surgery, such as positive tumour margins, extensive in-situ component, or invasive lobular carcinoma. 15.2% (239 of 1571) of the IORT-treated women received EBRT.[16]

Patient follow-up: Patients were assessed at entry, 3 months, 6 months and thereafter, every 6 months for 5 years, and then annually for up to 10 years. In the study published in 2014, authors present results for three overlapping cohorts based on their median length of follow-up: the whole cohort (n=3451) with a median follow up of 2 years and 5 months; the mature cohort consisting of the original 2232 patients with a median follow-up of 3 years and 8 months; and the earliest cohort (n=1222) with a median follow-up of 5 years.

Local recurrence: The primary outcome was the risk of pathologically confirmed local recurrence (recurrence in the index quadrant of the breast) or loco-regional recurrence (recurrence in the ipsilateral breast or the axilla). 3375 of the 3451 randomized women were included in recurrence analyses because the remainder (n=76) had mastectomies. The 5-year Kaplan-Meier (K-M) risk of local recurrence was 3.3% (95% CI:2.1, 5.1) and 1.3% (95% CI:0.7, 2.5) in the IORT and EBRT groups, respectively, resulting in an absolute difference of 2% (no 95% CI provided) [Table 2]. The absolute difference in the 5-year risk of local recurrence was 1.0% in the pre-pathology stratum, and 3.7% in the post-pathology stratum, exceeding the non-inferiority margin in the latter case. The authors also report the absolute difference in the binomial proportions of local recurrence (number of recurrences/number of patients) and corresponding 90% CIs for the three different cohorts of women based on their length of follow-up (Table 2). The earliest cohort (n=1222) had the longest median follow-up of 5 years, and had an absolute difference in the binomial proportions of local recurrence between EBRT and IORT of 1.14% (90 % CI: -0.1, 2.4) [pre-pathology: 0.76% (-0.4, 2.0); post-pathology: 1.8% (-1.2. 4.8)].

Mortality: The authors report no difference in overall mortality at 5 years between the IORT and EBRT groups [K-M estimates: 3.9% (2.7, 5.8) vs. 5.3% (3.9, 7.3)] [Table 2]. They did, however, find a significantly lower risk of non-breast cancer deaths in the IORT arm at 5-years compared with the EBRT arm [1.4% (0.8, 2.5) vs. 3.5% (2.3, 5.2)]. The authors attribute the lower number of non-breast cancer deaths in the IORT-treated women to the fewer number of deaths due to cardiovascular causes (2 vs. 11) and other cancers (8 vs. 16) compared with the EBRT group.

Complications: Secondary outcomes included risk of seroma, hematoma, wound infection, and RTOG toxicity grade. In the most recent study, rates of complications at 5 years were not reported; instead authors only report complication rates at 6 months after randomization. Hence the only data on complications from the TARGIT-A trial remain the 4-year rates reported in the 2010 study, which found a significantly increased risk of seroma and a significantly lower risk of RTOG toxicity grade 3 or 4 in IORT- vs. EBRT-treated women (Table 3).

5. RADIOTHERAPY FOR EARLY BREAST CANCER AT THE MUHC

5.1 Current treatment policy

The standard of care for early breast cancer treatment at the MUHC remains whole breast external beam radiotherapy which is delivered after breast-conserving surgery. Approximately 80% of women, typically those at high risk of recurrence, also receive a tumour bed boost dose of EBRT (treatment targeted at the tumour bed and given at higher doses than regular EBRT). Treatment consists of 16 to 25 sessions of EBRT followed by 4 to 8 booster sessions delivered within 5 to 6 weeks post-surgery or post-chemotherapy. Each session lasts about 15 minutes (10 minutes for preparation and 5 minutes for treatment delivery) [Dr. Tarek Hijal].

5.2 MUHC experience with Intrabeam®

The MUHC treats approximately 600 breast cancer patients a year; however, only 100-150 of these patients have new cancer and are at low-risk of recurrence. Furthermore, only 30-40% of these low-risk women receive breast-conserving surgery at the MUHC, with the remainder operated elsewhere and hence ineligible to be treated with intraoperative therapy at the MUHC. Thus, approximately 30-40 women per year are eligible for Intrabeam® therapy at the MUHC.

Since November 2013, 18 patients at the MUHC agreed to receive IORT using Intrabeam® under the aegis of an uncontrolled non-randomized clinical trial with the objective of assessing the efficacy and safety of Intrabeam® in a local setting. Women could receive Intrabeam® therapy alone, or Intrabeam® plus EBRT (Intrabeam® boost) for those with risk factors for local recurrence. Two women withdrew before receiving treatment. In general, women were eligible to receive treatment if they were ≥ 60 years of age, were hormone receptor (HR) positive, presenting with unifocal invasive ductal carcinoma, a tumour of <2 cm in size, and a tumour grade of 1 or 2. Women were ineligible if they had invasive lobular carcinoma (ILC) or carcinoma of mixed histology, had previous cancer in the ipsilateral breast, were HER2 positive, or had lymphovascular space invasion (LVSI).

We summarize patient characteristics of the 16 women who received Intrabeam® in Table 4. Two women with high risk factors (one with age <60 years, and another with LVSI) were selected to receive Intrabeam + EBRT. A further three women received EBRT after pathology reports showed close tumour margins; thus, 5 (42%) women received EBRT, approximately 2 months after Intrabeam® therapy, 3 of whom were unplanned

(i.e. 19% of EBRT procedures were unplanned). Data on clinical outcomes were available for 12 women at the time of writing this report (Table 5). No local breast cancer recurrences occurred in any of the women. None received adjuvant chemotherapy and 8 (67%) received hormone therapy. With respect to complications after treatment, 6 (50%) of the 12 women developed a seroma, 2 (16%) developed a hematoma, and one woman (8%) had an RTOG toxicity score of grade 3 (dermatitis).

5.3 Cost and budget impact estimates

Table 6 shows the breakdown of costs and the total cost associated with using Intrabeam® at the MUHC, which demonstrates that the cost per procedure will decrease with an increasing number of procedures per year. The cost per procedure if 15 and 30 procedures are performed annually is $5,434 and $3,668, respectively. These cost calculations take into account that the initial capital cost of $550,000 for the Intrabeam® machine was borne by a donor, and that the procedure takes an additional 60 minutes of operation room time. The estimates also assume that 20% of Intrabeam®-treated women receive further treatment with EBRT. If, instead, 30% of women treated with Intrabeam® received EBRT, the cost per procedure for 30 annual procedures would rise to $4,134. If in the future, the capital cost is to be covered by the MUHC, the per-patient costs given above would increase to $12,132 and $7017 for 15 and 30 procedures, respectively.

The cost per patient of treatment with EBRT has previously been estimated by The Department of Radiation Oncology to be $4,667.[17] On the basis of this estimate, the net cost of using Intrabeam® instead of EBRT would be approximately -$1,000 ($3,668-$4,667) per patient (assuming 30 Intrabeam® treatments per year of whom 20% would also receive EBRT). From the point of view of the MUHC, use of Intrabeam® instead of external beam radiation would then result in anticipated savings of $30,000 ($3,668-$4,667)*30] per year.

6. DISCUSSION

The TARGIT-A trial remains the sole source of evidence regarding the efficacy of targeted intra-operative radiation therapy using Intrabeam® for the treatment of early breast cancer; however, several trials in different countries and sub-populations are currently underway and their results may strengthen the current evidence. Although the authors of the TARGIT-A trial purport that Intrabeam® remains non-inferior to EBRT at the 5-year

follow-up, numerous concerns about the trial results have been raised,[20-23,25] and we summarize them below.

6.1 Concerns with the TARGIT-A trial

Non-inferiority criterion:

In order to properly evaluate whether a new treatment is indeed non-inferior to the control treatment, it is imperative to report 95% CIs around the estimate of the treatment difference.[27] The TARGIT-A trial authors fail to provide 95% CIs for the absolute difference in K-M estimates of 5-year local recurrence.[16] Assuming the authors used the log-log transformation method (which is the default method in the SAS statistical software used by the authors) to calculate CIs of the K-M estimate, we were able to back-calculate the standard error and 95% CIs of the absolute difference in local recurrence risk (see Appendix B). Thus, for the whole cohort, for which a risk difference in 5-year local recurrence of 2% had been reported, we found a 95% CI of (0.21, **3.80**), with the upper confidence limit exceeding the non-inferiority margin of 2.5%. For the pre- and post-pathology strata, our calculated 95% CIs for the local recurrence risk difference between IORT and EBRT were (-0.89, **2.89**) and (-0.40, **7.80**), with upper limits again exceeding the 2.5% margin.

We were also able to calculate the 95% CI of the K-M risk difference for the pre-pathology group from Figure 4 presented in the publication which shows the risk difference in 5-year K-M estimates of local recurrence between IORT and EBRT and their corresponding standard errors.[16] Using the standard error from the figure of approximately 0.8% for the whole cohort, we calculated the 95% upper limit as [1.0% (risk difference in pre-pathology group) +1.96*0.80%] = 2.57%, which once again exceeds the non-inferiority margin.

Confusingly, in addition to differences in K-M risk estimates, the authors also present differences in binomial proportions of local recurrence risk, for which they provide 90% CIs. It is unclear why the authors choose to present 90% instead of 95% CIs. Although these 90% CIs show that none of the upper limits exceed 2.5%, the use of binomial proportions to estimate 5-year risk is inappropriate when not all patients have been followed for 5 years, even in the earliest cohort whose median follow-up was 5 years. In the whole cohort, only 18% (611 of 3451) of patients were at risk at 5 years.

Thus, based on the above information, we cannot conclude that IORT with Intrabeam® is non-inferior to EBRT, and can instead only conclude that the results of the trial are

inconclusive (see Appendix C). Although it is possible that the true treatment difference may be less than 2.5%, our calculated 95% confidence intervals for the whole cohort show that IORT is significantly worse than EBRT in preventing local breast cancer recurrence.

Length of follow-up:

The median length of follow-up for all patients included in the trial was 2.4 years, which other researchers have contended is too short to ascertain local breast cancer recurrence risk. The TARGIT-A trial authors did present results for women with longer follow-up times, such as the earliest cohort that had a median follow-up of 5 years. However, K-M estimates of risk difference were only provided for the pre-pathology group (without 95% CIs). Instead, differences in binomial proportions, with 90% CIs, were presented for the entire cohort.

Despite the immaturity of the cohort, the authors argue in favour of presenting their current results based on findings that the hazard rate of first breast cancer recurrence peaks at 2-3 years after diagnosis, with a smaller peak at around 5 years.[28,29] However, Silverstein et al. pointed out that the vast majority of women (>90%) included in the TARGIT-A trial had ER-positive tumours, who do not have the same hazard rates of recurrence as women with ER-negative tumours.[24] The hazard rates of ER-positive women are lower than those of ER-negative women in the first 5 years, and higher from 5 to 12 years after diagnosis.[30] Furthermore, approximately 65% of women received adjuvant hormone therapy which is known to delay recurrences in ER-positive women.[31] Thus, as these women may have a longer median time to recurrence, a median follow-up length of 2.4 years may be too short to capture the majority of cancer recurrences.

Non-breast cancer deaths:

The TARGIT-A trial found that while there were no significant differences in overall mortality between the IORT and EBRT groups, there were significantly more non-breast cancer deaths in the EBRT group (35 vs. 17), which the authors suggested may be attributable to radiotherapy-related toxicity. However, other researchers have argued that cardiac toxicity from radiotherapy would only become apparent after 10-14 years, and hence it is premature to attribute the increased number of cardiac deaths in the EBRT group (8 vs. 2) to radiation therapy.[21,23] Furthermore, our estimated 95% CI for the difference in non-breast cancer mortality between IORT and EBRT (-3.81, -0.39) was wide and approached 0, suggesting the evidence regarding the effect of EBRT vs. IORT on non-breast cancer deaths is also inconclusive.

Statistical methods:

The TARGIT-A trial should have ideally been analyzed using a competing risks approach, which would take into account that each patient was at risk of both recurrence or death at any given time. In a naive Kaplan-Meier analysis of recurrence, there would be no distinction between censoring due to loss to follow-up or death. This would bias the results of the analysis by increasing the estimated risk of recurrence. The authors mention that using a competing risks approach did not change their results, but they do not present any data to support this. The TARGIT-A trial was a multi-centre trial, yet no effort seems to have been made to adjust for between-centre heterogeneity, which would have been considerable given the great latitude allowed in patient selection at each centre. This would have the impact of widening the reported confidence intervals, requiring more data to accrue before a definitive conclusion can be made.

Potential conflict of interest:

26 of the 29 authors, including the principal author, declare receiving funding from Carl Zeiss, the manufacturer of Intrabeam®, either in the form of research grants, honoraria or travel and accommodation funds to attend data monitoring and international steering committee meetings.

6.2 Applicability of TARGIT-A results to the MUHC setting

At the MUHC, IORT with Intrabeam® will be offered at the time of breast-conserving surgery, and hence the results from the pre-pathology group of the TARGIT-A trial are most applicable to the MUHC setting. Although the difference in 5-year risk of local and loco-regional breast cancer recurrence between IORT and EBRT was smaller in the pre-pathology group than in the overall cohort, the upper 95% confidence limits exceeded 2.5% (Table 2), and hence we cannot conclusively say that IORT is non-inferior to EBRT in this group. Patients deemed to be at low risk for local breast cancer recurrences based on the guidelines presented below, as well as using the TARGIT-A trial's inclusion criteria, may be considered for IORT with Intrabeam® within a research setting.

6.3 Guidelines for the use of accelerated partial breast irradiation (APBI)

Guidelines for the selection of patients for treatment with APBI were set out by the American Society for Radiation Oncology (ASTRO) and Groupe Européen de Curiethérapie of the European Society of Therapeutic Radiology and Oncology (GEC-ESTRO) in 2009 and 2010, respectively. The ASTRO guidelines classified treatment as

suitable, cautionary or unsuitable, while the GEC-ESTRO guidelines similarly classified treatment as good, possible, or contraindicated based on several clinical characteristics (Table 1). However, these guidelines are not specific to the use of IORT, and the two societies' guidelines differ on several selection criteria including age, tumour size and tumour stage. In general, the GEC-ESTRO guidelines are less stringent, recommending that younger-aged women with larger tumours could be good candidates for APBI.

Guidelines specific to IORT use have not yet been established, and a generally conservative approach is used in patient selection, where women at low risk of local recurrence ('suitable' or 'good' according to ASTRO and GEC-ESTRO) are considered the best candidates for such treatment. A recent study in women who had undergone BCS and EBRT wherein women were categorized as eligible or ineligible for IORT based on the TARGIT-A trial's inclusion (Table 1) criteria found a significantly higher 5-year recurrence-free survival among women deemed eligible based on these criteria.[32] These results indicate that women selected using the TARGIT-A trial's inclusion factors are indeed at lower risk of local recurrences, and IORT with Intrabeam® is only appropriate in women who fit these criteria.

7. CONCLUSIONS

- **The TARGIT-A trial remains the sole trial comparing intraoperative radiation therapy using Intrabeam® to conventional external beam radiation therapy. Given the serious concerns with the results, the current evidence fails to conclusively establish the non-inferiority of Intrabeam® to external beam radiation.**
- **The short median follow-up time of 2.4 years in the TARGIT-A trial is particularly problematic if hormone receptor-positive women, who constituted the majority of trial participants, are more likely to have recurrences later in follow-up.**
- **A longer follow-up may indeed establish non-inferiority of Intrabeam®, but until such convincing evidence is available, Intrabeam® can only be considered an experimental procedure to be delivered under strict research protocols. Guidelines established by the radiation oncology societies as well as the selection criteria used in TARGIT-A may serve in selecting appropriate low-risk patients in such research settings.**

8. RECOMMENDATIONS

- **The current evidence does not warrant a change in the recommendation previously accorded this technology which was a <u>temporary</u> approval, conditional on participation in research studies. Presently, Intrabeam® should not be approved for use in the MUHC except in the context of the ongoing MUHC-funded research study with:**
    - **continued adherence to a strict protocol and stringent collection of follow-up data on clinical outcomes, patient satisfaction and quality of life;**
    - **informed consent obtained from all patients agreeing to receive Intrabeam®, who would be informed in a clear and accessible way, of the lack of conclusive evidence regarding the efficacy of Intrabeam® in preventing recurrences.**
- **In light of the numerous trials of Intrabeam® currently underway, the evidence should be reviewed in 5 years or when sufficient evidence has accrued about the 5-year recurrence rate.**

TABLES

Table 1. Selection criteria for treating women with APBI according to the American and European radiation oncology societies, and the TARGIT-A trial's inclusion criteria

Criterion	ASTRO*	GEC-ESTRO	ASTRO*	GEC-ESTRO	ASTRO*	GEC-ESTRO	TARGIT-A§
	Suitable	Low-risk	Cautionary	Intermediate risk	Unsuitable	High risk	
Age	≥60 years	>50 years	50-59 years	40-50 years	< 50 years	≤40 years	≥45 years
Tumour size	≤2.0 cm	≤3.0 cm	2.1-3.0 cm	≤3.0 cm	≥3.0 cm	>3 cm	≤3.5 cm
T stage	T1	pT1-T2 (≤3.0 cm)	T0 or T2	pT1-T2(≤3.0 cm)	T3-T4	pT2(>3.0cm), pT3, pT4	T1 and small T2
Surgical margins	Negative (≥ 2.0 mm)	Negative (≥ 2.0 mm)	Close (<2.0 mm)	Close (<2.0 mm)	Positive	Positive	Positive margins allowed
Pure DCIS	Not allowed	Not allowed	≤3.0 cm	Allowed	>3.0 cm	-	Not allowed
Invasive lobular carcinoma (ILC)		Not allowed	Allowed	Allowed		-	Not allowed
Lymph-vascular space invasion (LVSI)	No	Not allowed	Local	Not allowed	Extensive	Present	Criterion not used
Estrogen receptor (ER) status	Positive	Any	Negative	Any	-	-	Criterion not used
Multicentricity	Unicentric	Unicentric	-	Unicentric	Multicentric	Multicentric	-
Multifocality	Clinically unifocal with total size ≤2.0cm	Unifocal	Clinically unifocal with total size 2.1-3.0cm	Multifocal within 2cm of index lesion	Microscopically multifocal with total size >3.0cm or clinically multifocal	Multifocal >2cm from index lesion	Unifocal
Extensive intraductal component (EIC)	Not allowed	Not allowed	≤3.0 cm	Not allowed	>3.0 cm	Present	Not allowed
Nodal status	pN0	pN0	-	pN1	pN1, pN2, pN3	pNx; ≥pN2	N0-N1

Neoadjuvant chemotherapy	Not allowed	Not allowed	-	Not allowed	If used	If used	Not allowed

* ASTRO(American Society for Radiation Oncology) guidelines recommend that treatment with APBI is 'suitable' if **all** factors in the green column are present, and 'cautionary' or 'unsuitable' if **any** of the factors in the yellow or red columns, respectively, are present.

 GEC-ESTRO (Groupe Européen de Curiethérapie of the European Society of Therapeutic Radiology and Oncology) guidelines recommend that women be considered 'good' candidates if **all** factors in the green column are present, and 'possible' or 'poor' candidates for APBI if **any** criteria in the yellow or red columns, respectively, are present.

§ Inclusion criteria for participants in the TARGIT-A randomized clinical trial.

Table 2.Results of TARGIT-A trial 5-year follow-up: 5-year risk of local recurrence and mortality in all patients, and in the pre-pathology and post-pathology strata[16]

	Median follow-up	5-year risk				Absolute difference	
		Intrabeam®		EBRT		K-M¥	Binomial§
		No. of events	K-M % (95%CI)	No. of events	K-M % (95%CI)	% (95% CI)*	% (90%CI)
All patients							
Local recurrence, whole cohort (n=3375)	2.4 years	23	3.3 (2.1, 5.1)	11	1.3 (0.7, 2.5)	2.0 (0.21, 3.80)	0.7 (0.2, 1.3)
Local recurrence, mature cohort (n=2232)	3.6 years					1.0	1.1 (0.3, 2.0)
Local recurrence, earliest cohort (n=1222)	5 years					0.9	1.1 (-0.1, 2.4)
Loco-regional recurrence (n=3375)			4.2 (2.8, 6.1)		2.0 (1.1, 3.5)	2.2 (0.14, 4.26)	
Overall mortality (n=3451)		37	3.9 (2.7, 5.8)	51	5.3 (2.9, 7.3)	-1.4 (-3.84, 1.04)	
Breast cancer deaths		20	2.6 (1.5, 4.3)	16	1.9 (1.1, 3.2)	0.7 (-1.06, 2.46)	
Non-breast cancer deaths		17	1.4 (0.8, 2.5)	35	3.5 (2.3, 5.2)	-2.1 (-3.81, -0.39)	
Pre-pathology							
Local recurrence, whole cohort (n=2234)	2.4 years	10	2.1 (1.1, 4.2)	6	1.1 (0.5, 2.5)	1.0 (-0.89, 2.89)	0.4 (-0.2, 1.0)
Local recurrence, mature cohort (n=1450)	3.7 years					1.0 (-0.57, 2.57)**	0.6 (-0.3, 1.5)
Local recurrence, earliest cohort (n=817)	5 years					0.9 (-0.86, 2.66)**	0.8 (-0.4, 2.0)
Loco-regional recurrence (n=3375)			3.1 (1.8, 5.2)		2.0 (1.0, 4.0)	1.1 (-1.21, 3.41)	
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		17	3.3 (1.9, 5.8)	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)	

Post-pathology							
Local recurrence (n=1141)	2.4 years	13	5.4 (3.0, 9.7)	5	1.7 (0.6, 4.9)	3.7 (-0.40, 7.80)	1.4 (0.2, 2.6)
Local recurrence, mature cohort (n=782)	3.6 years						2.0 (0.3, 3.8)
Local recurrence, earliest cohort (n=405)	5 years						1.8 (-1.2, 4.8)
Loco-regional recurrence (n=3375)			6.2 (3.6, 10.6)		2.0 (0.8, 5.2)	4.2 (-0.09, 8.49)	
Overall mortality (n=1153)		8	2.8 (1.3, 5.9)	9	2.3 (1.0, 5.2)	0.5 (-2.65, 3.65)	
Breast cancer deaths		3	1.2 (0.4, 4.2)	1	0.5 (0.1, 3.5)	0.7 (-1.44, 2.84)	
Non-breast cancer deaths		5	1.6 (0.6, 4.0)	8	1.8 (0.7, 4.4)	-0.2 (-2.66, 2.26)	

 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 us (see Appendix for calculation).

** These K-M estimates and 95% CIs were calculated from Figure 4 in Vaidya et al. *The Lancet* 2014;383:603-613. doi:10.1016/S0140-6736(13)61950-9

Table 3. Rates of complications reported in the TARGIT-A trial 4-year follow-up[15]

Complication	Intrabeam® (n=1113)	EBRT (n=1119)	p-value
Hematoma needing surgical intervention	11 (1.0%)	7 (0.6%)	0.34
Seroma needing more than 3 aspirations	23 (2.1%)	9 (0.8%)	0.01
Infection needing IV antibiotics/surgical intervention	20 (1.8%)	14	0.29
Skin breakdown or delayed wound healing	31 (2.8%)	21 (1.9%)	0.16
RTOG toxicity grade 3 or 4	6 (0.5%)	23 (2.1%)	0.002
Major toxicity	37 (3.3%)	44 (3.9%)	0.44

Table 4. Characteristics of the 16 women who received Intrabeam® IORT at the MUHC since November 2013

Patient characteristic	
	Mean (range)
Age, years	68.4 (50-80)
Tumour size, cm	1.05 (0.55-1.80)
	N (%)
Histology	
Ductal	13 (81.3)
Lobular	1 (6.3)
Mixed (Mammary carcinoma)	1 (6.3)
Other (encapsulated papillary)	1 (6.3)
Tumour stage	
T1	16 (100)
pN0	16 (100)
Tumour grade	
1	8 (50.0)
2	8 (50.0)
3	0 (0)
DCIS present	13 (81.3)
Extensive intraductal component	0 (0)
LVSI	1 (6.3)
Unifocal tumour	15 (93.8)
Hormone receptor positive	16 (100)
HER2 positive	15 (93.8)(1 equivocal)
Menopausal	
Yes	12 (75.0)
No	0 (0)
Unknown	4 (25.0)

Table 5. Clinical outcomes among the women who received Intrabeam® IORT at the MUHC since November 2013

Clinical outcomes	N=12
	N (%)
Local recurrence	0
Adjuvant therapy	
Chemotherapy	0
Hormone therapy	8 (66.6)
Received EBRT after IORT	5 (41.7)
Planned	2
Unplanned	3 (25.0)
Complications	
Seroma	6 (50.0)
Hematoma	2 (16.6)
Infection	0 (0)
RTOG toxicity score 3 or 4	1 (8.3)
Other(breast pain)	1 (8.3)

Table 6: Estimated costs of using Intrabeam® at the MUHC

	Breakdown of costs (CAD)	Estimated cost per procedure, including taxes		Estimated cost per procedure, including capital cost and taxes	
		15 procedures	30 procedures	15 procedures	30 procedures
Capital cost	550,000				
Equivalent annual cost (EAC)**	95,051	0 §	0 §	6697.9 □	3349.0 □
Maintenance cost	50,000/ year	3523.3 □	1761.7 □	3523.3 □	1761.7 □
Operating room use for an additional hour	869 per hour *1 hour	869.0	869.0	869.0	869.0
Post-operation EBRT (20% patients)¥	4,667*0.20	933.4	933.4	933.4	1400.1
Applicator	5,832 for 100 treatments	61.6 □	61.6 □	61.6 □	61.6 □
Sterile drapes	176 for 5 drapes	37.2 □	37.2 □	37.2 □	37.2 □
Radiation shield (reused for each procedure)	1,316 for 10 shields	9.3 □	4.6 □	9.3 □	4.6 □
Total		**5433.9**	**3667.6**	**12131.8**	**7016.5**

§ Capital cost of Intrabeam® was borne by a donor.

** EAC= $\frac{Capital\ cost}{\frac{1-(\frac{1}{1+r})^t}{r}}$, where t is the service life of Intrabeam® =7 years, and r is the annual discount rate=5%, and capital cost of Intrabeam®=CAD550,000

□ Medical services and devices tax of 5.7% was added to the cost estimate.

¥ Assuming 20% of patients receiving Intrabeam® also receive EBRT

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APPENDICES

Appendix A. Clinical trials of Intrabeam® in progress

Table A1: Clinical trials of IORT with Intrabeam® completed or in progress since 2012

Trial Name (Identifier)	Principal Investigator	Country	Intervention	Control	Outcome	Estimated sample size	Estimated completion of data collection
TARGIT-B (NCT01792726)	Jayant S Vaidya	US, UK, France, Italy	IORT boost targeted to the tissues at the highest risk of local recurrence in women undergoing BCS who have a higher risk of local recurrence	Standard post-operative external beam radiotherapy boost	• Local recurrence rate • Site of relapse • Relapse-free survival • Overall survival • Adverse events • Toxicity and morbidity • Quality of life	1796	2022
TARGIT-C (NCT02290782)	Frederik Wenz	Germany	IORT in patients ≥ 50 years with small, low-risk breast cancer (cT1 and small cT2 (< 3.5 cm), cN0, cM0), followed by EBRT only in the presence of risk factors	None (single-arm trial)	• Local recurrence rate • Ipsi- or contralateral breast cancer • Relapse-free survival • Overall survival • Cosmetic outcome • Quality of life	387	Mar 2016

TARGIT-E (NCT01299987)	Frederik Wenz	Germany	IORT in elderly low risk patients (≥ 70 years, cT1, cN0, cM0, invasive-ductal), followed by EBRT only in the presence of risk factors	None (single-arm trial)	• Local recurrence rate • Ipsi- or contralateral breast cancer • Overall survival • Cosmetic outcome • Quality of life • Toxicity	265	Nov 2015
IORT for Korean Patients With Breast Cancer (NCT02213991)	Joon Jeong	Republic of Korea	BCS + IORT	Unclear	• Acute local toxicity • Delayed local toxicity • Cosmesis • Local recurrence rate • Dosimetry	215	Mar 2017
IORT after local recurrence in breast cancer (NCT02386371)	Jacques Domergue	France	Tumourectomy and re-irradiation with IORT after local recurrence	None (single-arm trial)	• Acute local toxicity • Delayed local toxicity • Cosmesis	51	Mar 2016
IORT for breast cancer after NSM (NCT02389686)	Liao Ning	China	Nipple-sparing mastectomy and IORT	Only nipple-sparing mastectomy	• Local recurrence rate within 5 years after surgery • Relapse-free survival • Overall survival	110	Oct 2019
IORT for women with	Liao Ning	China	BCS + IORT	Only BCS	• Ipsilateral breast tumour recurrence	222	Jun 2019

ductal carcinoma in situ breast cancer (NCT02389673)					• Relapse-free survival • Overall survival		
Comparison of IORT with post-operative radiotherapy for women with ductal carcinoma in situ (NCT02389699)	Liao Ning	China	BCS + IORT boost +EBRT	BCS + EBRT	• Ipsilateral breast tumour recurrence • Relapse-free survival • Overall survival	74	Jun 2019
IORT in early stage breast cancer (IORT Breast) (NCT02266602	Janie Grumley	US	BCS + IORT	None (single arm)	• Local recurrence rate • Toxicity and morbidity • Relapse-free survival • Overall survival • Total cost associated with treatment	500	Feb 2017

Appendix B. Back-calculation of standard errors and 95% confidence intervals of the K-M risk difference

We assumed the TARGIT-A trial authors used the log-log transformation method[33] to estimate 95% confidence intervals of the Kaplan-Meier estimate of 5-year local recurrence.

Let S(t) be the K-M estimate of 5-year local recurrence, which is given by $\prod_{t_i \le t}(1 - \frac{d_i}{n_i})$, where t_i is the observed time interval, n_i is the number at risk at the start of the interval, and d_i are the number of observed events in that time interval.

The standard error, SE of S(t) = $S(t)\sqrt{\sum_{t_i \le t} \frac{d_i}{n_i\,(n_i - d_i)}}$

The log-log transformation of S(t) = S(t)' = ln (-ln S(t)), and

The standard error of S(t)' = SE' = $\frac{1}{\ln S(t)}\sqrt{\sum_{t_i \le t} \frac{d_i}{n_i(n_i - d_i)}}$ = $\frac{SE}{S(t) * \ln S(t)}$

Thus, the 95% CI of the risk estimate S(t) is:

$$S(t)^{e^{\pm 1.96 * SE}}$$

Then, for the IORT group with $S(t)_{IORT}$=0.033 and upper confidence limit=0.051,

$$0.051 = 0.033^{e^{-1.96 * SE'}}$$

SE'_{IORT}= $\frac{\ln[\frac{\ln(0.051)}{\ln(0.033)}]}{-1.96}$ =0.070, and

SE_{IORT} of $S(t)_{IORT}$ = SE'_{IORT} * $S(t)_{IORT}$ * ln($S(t)_{IORT}$)= 0.070 * 0.033 * ln(0.033) = -0.008

Similarly, for the EBRT group with $S(t)_{EBRT}$ =0.013 and upper confidence limit=0.025:

$SE_{EBRT=}$ $\frac{\ln[\frac{ln(0.025)}{ln(0.013)}]}{-1.96} * 0.013 * ln(0.013)$ = -0.005

The SE of the absolute difference in risk estimates between IORT and EBRT is given by:

$\sqrt{SE_{IORT}{}^2 + SE_{EBRT}{}^2} = \sqrt{(-0.008)^2 + (-0.005)^2} = 0.009$

Then the 95% upper confidence limit of the risk difference of 2% between IORT and EBRT = 0.02 + 1.96*0.009 = 0.038,

and the 95% lower confidence limit of the risk difference = 0.02 - 1.96*0.009 = 0.002

Appendix C. Interpreting non-inferiority trials

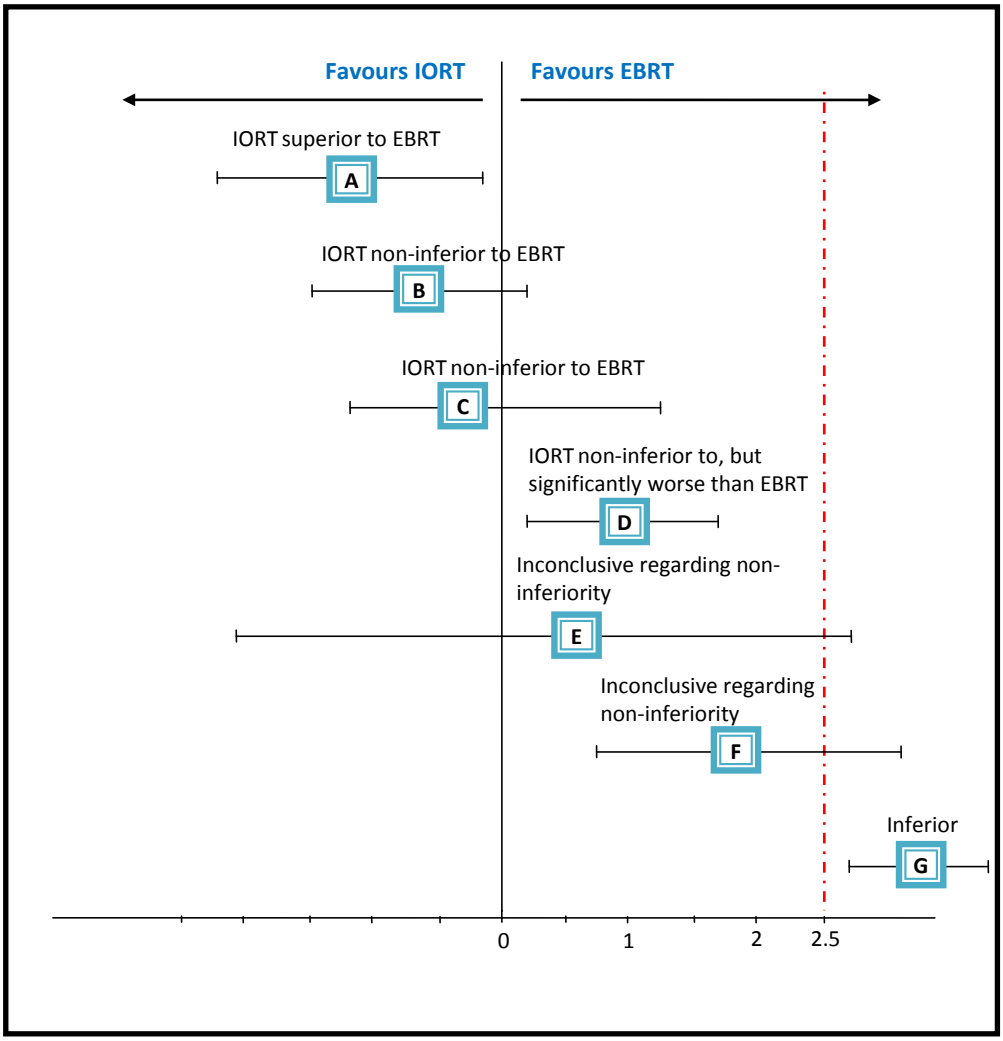

Figure 1: Graphical representation of the various possible scenarios and interpretations of treatment differences in non-inferiority trials. The red dashed line delineates the non-inferiority margin of 2.5% set by the TARGIT-A trial authors. Error bars indicate 95% confidence intervals (CI). Figure adapted from Piaggio et al.[27]

A. The upper CI lies to the left of 0, indicating that IORT is superior to EBRT
B, C. The upper CI crosses 0, but lies to the left of the non-inferiority margin, indicating that IORT is not superior to EBRT, but remains non-inferior to EBRT
D. The CI lies entirely to the right of 0 but to the left of the non-inferiority margin, indicating that IORT is significantly worse that EBRT, but remains non-inferior to EBRT
E. The CI crosses 0 and the non-inferiority margin, indicating that IORT is not significantly different from EBRT, but no conclusion can be drawn regarding non-inferiority
F. IORT is significantly worse than EBRT, but result is inconclusive regarding non-inferiority
G. CI lies wholly to the right of the non-inferiority margin, and hence IORT is inferior to EBRT

Appendix D. Glossary of terms

Adjuvant therapy

Additional therapy, including hormone, radiation, biological or chemotherapy given after breast-conserving surgery

Breast cancer recurrences

Local: A local recurrence is defined as reappearance of cancer in the ipsilateral preserved breast.

Regional recurrence: A recurrence of a tumour involving the regional lymph nodes, usually ipsilateral axillary or supraclavicular, less commonly infraclavicular and/or internal mammary.

Locoregional recurrence: is used to indicate a recurrence in either the breast or regional nodes.

Distant recurrence: A distant (metastatic) recurrence means the cancer has traveled to distant parts of the body, most commonly the bones, liver and lungs.

Breast cancer tumour grade (Elston-Ellis modification of the Scarff-Bloom-Richardson grading system)

Grade 1: Low grade or well differentiated; (Total score = 3–5)

Grade 2: Intermediate grade or moderately differentiated; (Total score = 6–7)

Grade 3: High grade or poorly differentiated; (Total score = 8–9)

Breast cancer tumour morphology

Invasive ductal carcinoma (IDC): The most common type of invasive breast cancer, accounting for 70-80% of invasive tumours, and typically arises in the milk ducts.

- Tubular: A subtype of IDC in which the tumours are made up of tube-shaped structures or 'tubules'. 1.5% of tumours
- Medullary: A subtype of IDC where the tumour resembles the medulla of the brain due to its soft, fleshy appearance. 1.2% of tumours
- Papillary: A subtype of IDC that derives its name from the finger-like projections or papules on the tumour cells. 1% of tumours

Invasive lobular carcinoma (ILC): 8% of tumours, which typically begin in the mammary lobules.

Ductal/lobular (Invasive mammary carcinoma): 7% of tumours, where the tumour originates at the junction of the milk duct and the lobule.

Mucinous (colloid): 2.4% of tumours. The tumour is made up of cancer cells surrounded by mucin. A less aggressive type of tumour that responds well to treatment.

Encapsulated papillary: Traditionally considered a variant of DCIS, but some consider to be invasive. 0.5-1% of tumours

DCIS (Ductal carcinoma in situ)

A pre-cancer wherein the cells lining the ducts in the breast have changed to look like cancer cells, but there is no evidence of invasion into surrounding tissue.

Pure: Not accompanied by invasive tumours

Accompanying IDC: a variable amount of DCIS is present along with IDC

Extensive intraductal component (EIC)

When ≥25% of the tumour is intraductal

Lymphovascular space invasion (LVSI)

Spread of cancer to the blood vessels or lymphatic vessels

HER2-positive

Women with human epidermal growth factor receptor 2 (HER2)-positive breast cancer

Hormone Receptor (HR) positive

A tumour is estrogen- or progesterone-positive if it has receptors for estrogen or progesterone. 66% of cancers are hormone positive, and are likely to respond to hormone therapy.

Intention-to-treat analysis

Analysis where results are analyzed based on the initial treatment assignment and not on treatment actually received, in order to preserve the integrity of randomization.

Multicentric tumour

There is more than one area carcinoma in different quadrants of the breast.

Multifocal tumour

There is more than one area of carcinoma within the same quadrant of the breast.

Neoadjuvant therapy

Treatment, such as chemo or hormone therapy given before surgery, normally to shrink the tumour

Non-inferiority trial

Unlike superiority trials which seek to determine if one intervention is significantly better than another, non-inferiority trials aim to establish that an intervention is not significantly worse than a control intervention by more than an acceptable amount. This amount, the non-inferiority margin, is set *a priori*, and is based on outcome rates in the published literature. Conventionally, the margin is set to the size of the effect that is considered clinically relevant. Non-inferiority trials are typically conducted to establish that a new treatment has some added advantage over the standard treatment, such as increased convenience or decreased invasiveness. Thus, the new treatment can be recommended if the difference in the primary endpoint does not exceed the non-inferiority margin.

Quadrantectomy vs. lumpectomy

In a lumpectomy, only the 'lump' or tumour and a small area of tissue around the tumour are removed. In a quadrantectomy, also known as a partial or segmental mastectomy, a quarter of breast tissue and chest wall muscle within a 2-3 cm radius of the tumour are removed.

RTOG Toxicity scale

Radiation Therapy Oncology toxicity score which ranges from 0 (none) to 5 (death directly related to radiation).

Seroma

A build-up of clear serous fluid that develops in the body after surgery. The larger the surgical intervention, the greater the risk of developing a seroma.

Unifocal tumour

One area of carcinoma contained within the same quadrant of the breast.

TNM (Tumour Node Metastasis) Staging system[34]

Primary tumour (T)		Regional lymph nodes (N)				Metastasis (M)	
		Clinical		Pathological			
TX	Primary tumour cannot be assessed	NX	Regional lymph nodes cannot be assessed (eg, previously removed)	pNX	Regional lymph nodes cannot be assessed (eg, previously removed, or not removed for pathologic study)	M0	No clinical or radiographic evidence of distant metastases
T0	No evidence of primary tumour	N0	No regional lymph node metastases	pN0	No regional lymph node metastasis identified histologically	cM0(i+)	No clinical or radiographic evidence of distant metastases
Tis	Carcinoma in situ	N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)	pN0(i-)	No regional lymph node metastases histologically, negative immunohistochemistry (IHC)	M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven larger than 0.2 mm
Tis(DCIS)	Ductal carcinoma in situ	N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted; or in clinically detected ipsilateral internal mammary nodes in the absence of clinically evident axillary lymph node metastases	pN0(i+)	Malignant cells in regional lymph node(s) no greater than 0.2 mm		
Tis (LCIS)	Lobular carcinoma in situ	N2a	Metastases in ipsilateral level I, II axillary lymph	pN0(mol-)	No regional lymph node metastases histologically,		

			nodes fixed to one another (matted) or to other structures		negative molecular findings (RT-PCR)
Tis (Paget's)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma in situ (DCIS and/or LCIS) in the underlying breast parenchyma.	N2b	Metastases only in clinically detected ipsilateral internal mammary nodes and in the absence of clinically evident level I, II axillary lymph node metastases	pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
T1	Tumour ≤20 mm in greatest dimension	N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement; or in clinically detected ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases; or metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement	pN1	Micrometastases; or metastases in 1-3 axillary lymph nodes; and/or in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected

T1mi	Tumour ≤1 mm in greatest dimension	N3a	Metastases in ipsilateral infraclavicular lymph node(s)	pN1mi	Micrometastases (greater than 0.2 mm and/or more than 200 cells, but none greater than 2.0 mm)
T1a	Tumour>1 mm but ≤5 mm in greatest dimension	N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)	pN1a	Metastases in 1-3 axillary lymph nodes, at least one metastasis greater than 2.0 mm
T1b	Tumour>5 mm but ≤10 mm in greatest dimension	N3c	Metastases in ipsilateral supraclavicular lymph node(s)	pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
T1c	Tumour>10 mm but ≤20 mm in greatest dimension			pN1c	Metastases in 1-3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
T2	Tumour>20 mm but ≤50 mm in greatest dimension			pN2	Metastases in 4-9 axillary lymph nodes; or in clinically detected internal mammary lymph nodes in the absence of axillary lymph node metastases
T3	Tumour>50 mm in			pN2a	Metastases in 4-9 axillary

	greatest dimension		lymph nodes (at least one tumor deposit greater than 2.0 mm)
T4	Tumour of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)	pN2b	Metastases in clinically detected◊◊ internal mammary lymph nodes in the absence of axillary lymph node metastases
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion	pN3	Metastases in ten or more axillary lymph nodes; or in infraclavicular (level III axillary) lymph nodes; or in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive level I, II axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected; or in ipsilateral supraclavicular lymph nodes
T4b	Ulceration and/or ipsilateral satellite nodules and/or	pN3a	Metastases in ten or more axillary lymph nodes (at least one tumor deposit greater

	edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma		than 2.0 mm); or metastases to the infraclavicular (level III axillary lymph) nodes
T4c	Both T4a and T4b	pN3b	Metastases in clinically detected ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected
T4d	Inflammatory carcinoma	pN3c	Metastases in ipsilateral supraclavicular lymph nodes