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McGill University  
Health Centre

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

**Magnetic resonance imaging-guided  
radiotherapy for cancer patients undergoing  
radiotherapy at the MUHC**

**Report number: 87**

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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 Committee of the TAU on 18 November, 2021**

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- Dr. Tarek Hijal, Director of the Radiation Oncology Division, McGill University Health Centre
- Dr. William Parker, Clinical Chief of the Department of Medical Physics, McGill University Health Centre.

## REPORT REQUESTOR

This report was requested by Dr. Tarek Hijal of the Radiation Oncology Division, on July 12, 2021. The completed evaluation will be presented to Dr. Ewa Sidorowicz, Director of Professional Services at the MUHC.

## TYPES OF RECOMMENDATIONS ISSUED BY THE TAU COMMITTEE

Type of recommendation	Explanation
<b>Approved</b>	<ul style="list-style-type: none"> <li>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</li> </ul>
<b>Approved for evaluation</b>	<ul style="list-style-type: none"> <li>There is a reasonable <i>probability</i> 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.</li> <li>The evidence is sufficiently strong to recommend a <i>temporary</i> approval in a restricted population for the purposes of evaluation, funded through the institutional operating budget.</li> </ul>
<b>Not approved</b>	<ul style="list-style-type: none"> <li>There is insufficient evidence for the relevant decision criteria, including efficacy, safety, and cost;</li> <li>The costs of any use of the technology (e.g. for research purposes) should not normally be covered by the institutional budget.</li> </ul>

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## TABLE OF CONTENTS

Acknowledgements.....	i
Report Requestor.....	i
Types of Recommendations Issued by the TAU committee.....	ii
Disclaimer.....	ii
Table of Contents.....	iii
List of Tables .....	v
List of Figures .....	vi
Abstract.....	vii
Résumé.....	ix
Executive Summary.....	xi
Sommaire .....	xvii
List of Abbreviations .....	xxiv
1. Background.....	1
1.1 Currently available MRgRT systems.....	1
1.2 Reason for HTA Request .....	2
2. Policy and Evaluation Questions .....	3
2.1 Policy question.....	3
2.2 Evaluation questions (Objective of this report).....	3
3. Methods.....	3
3.1 Literature search and quality assessment .....	3
3.2 MUHC experience .....	4
3.3 Cost analysis.....	4
4. Results.....	4
4.1 Results of the literature search.....	4
4.2 Patients characteristics and disease sites.....	5
4.3 Effectiveness & Safety.....	5
4.4 Patient Tolerance .....	8
4.5 Economic Evaluations .....	8
5. Guidelines and HTAs.....	10

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5.1	Recommendations by the European Society for Therapeutic Radiology and Oncology (ESTRO) Advisory Committee for Radiation Oncology Practice (ACROP).....	10
5.2	CADTH and INESSS HTAs .....	11
5.3	MR-linac Consortium .....	12
6.	Cost analyses .....	12
7.	IGRT at the MUHC and elsewhere .....	13
7.1	MRgRT in Quebec.....	13
7.2	MRgRT in other Canadian and US centres.....	13
8.	Discussion .....	15
8.1	Summary of the efficacy/safety results and concerns with the evidence .....	15
8.2	Applicability of MRI-Linac at the MUHC .....	16
9.	Conclusions.....	17
10.	Recommendations.....	18
	Figures.....	19
	Tables .....	22
	References .....	38
	Appendices.....	42
	Appendix A: Cost Analysis.....	42

**LIST OF TABLES**

Table 1. Observational Studies and trials assessing the clinical outcomes of MRI-linac treatment.....	22
Table 2. Observational Studies assessing patient’s reported outcomes of MRgRT on a low-field hybrid MRI-linac.....	36
Table 3: Cost analysis (costs presented in USD) .....	37
Table A-1: Difference in Assumptions between CTgRT and MRgRT* [34] .....	42
Table A-2: Projected cost for standard linac vs. MRI-linac [4].....	42

**LIST OF FIGURES**

Figure 1: Flowchart of the literature search .....	19
Figure 2: MRgRT workflow recommended by ESTRO-ACROP (1).....	20
Figure 3. The average number of fractions per patient per fiscal year .....	20
Figure 4. Proportion of fractions administered through 2D/3D, SBRT or IMRT per fiscal year .....	21
Figure 5. Average number of patients treated per linac unit per fiscal year .....	21
Figure A-1: Side-effect reduction thresholds according to the added cost of MRgRT .....	43



**ABSTRACT**

- Image-guided radiotherapy (IGRT) relies on 3-D imaging scans to analyze the treatment area and plan the most precise dose and treatment path possible for patients undergoing radiotherapy treatments for cancer. Imaging scans processed by a computer program are used both for treatment planning before radiotherapy and also during radiotherapy sessions.
- The current standard of practice for IGRT uses computed tomography (CT) imaging (CTgRT). Magnetic resonance-guided radiotherapy (MRgRT) involves a new hybrid technology that combines magnetic resonance (for imaging) and linear accelerator (for radiotherapy delivery) functions in a single machine; these devices are therefore called MRI-Linac machines.
- Dosimetry studies have demonstrated that hybrid MRI-Linac systems enabled more precise and higher dose delivery to the tumour. Health Canada approved MRI-Linac delivery systems in 2017 on the basis of these dosimetry studies, but reports by INESSS and CADTH in 2019 concluded that the high cost and lack of clinical efficacy data did not justify routine use of the device. Nonetheless, MRI-Linac was adopted by some Canadian centres.
- The MUHC Division of Radiology will need to replace their conventional linear accelerators in 2024; there is an interest to replace 1 of their 7 conventional accelerators with an MRI-linac system.
- The objective of this report is to evaluate new evidence on the safety, effectiveness and cost of MRgRT vs. CTgRT in terms of toxicity, local control and survival.
- We identified 20 published observational studies and 6 trials that evaluated the clinical effectiveness and/or patient tolerance of MRI-Linac. However, almost all were small and uncontrolled, leaving us unable to directly compare MRgRT with CTgRT. No studies reported the occurrence of grade  $\geq 4$  toxicity. Ongoing clinical trials will allow us to better evaluate comparative effectiveness in the future.
- In indirect comparisons, the reported toxicity and survival rates for MRgRT compared well with that of other modalities. The largest single-arm trial of MRgRT in prostate cancer treatment (n=101) reported toxicity and a biochemical relapse-free survival at 1-year that were comparable to results from a systematic review and meta-analysis of prospective studies evaluating modalities other than MRI-Linac in more than 6000 prostate cancer patients.
- Patient-reported outcome studies showed MRgRT is generally safe and well tolerated by patients.
- Published cost impact analyses indicate that MRgRT is more expensive than CTgRT due to its acquisition, infrastructure and maintenance costs, as well as longer treatment times. A UK study modelled MRI-Linac demand based on 6 disease sites

(i.e., prostate, central nervous system, head and neck, non-small cell lung cancer, oesophagus and pancreas) and found that MR-Linac could cover 16% of the country's fraction burden (number of treatment sessions required to deliver the total prescribed dose).

- Interviews with users of the technology suggest that MRgRT creates opportunities to treat patients who otherwise would be difficult to treat with standard radiation therapy technology.
- In conclusion, MRgRT has several functional advantages over CTgRT: (1) better volumetric soft tissue imaging of tumours and organs at risk prior and during treatment, which improves delineation of treatment margins and avoids the placement of fiducial markers, (2) gating system (i.e., movement-tracking of the tumour and organs at risk and hence, radiation is only delivered when the tumour is in the treatment field), (3) adaptive planning by real-time imaging to re-plan treatment while the patient is on the table. Although long-term comparative effectiveness data are not yet available, indirect comparisons indicate that downstream outcomes are not expected to be worse than those with CTgRT. However, uncertainty about cost remains; MRgRT may be cost-effective relative to CTgRT depending on reductions in toxicity from increased precision, and the need for fewer treatment sessions.

**RÉSUMÉ**

## La radiothérapie guidée par imagerie par résonance magnétique pour les patients cancéreux traités par radiothérapie au CUSM

- La radiothérapie guidée par l'imagerie (RTgI) s'appuie sur les images détaillées en 3D pour analyser la zone à traiter et planifier la dose et la trajectoire de traitement les plus précises possibles pour les patients cancéreux traités par radiothérapie. Les images analysées par un logiciel sont utilisées pour la planification du traitement avant et pendant les séances de radiothérapie.
- La norme actuelle de pratique pour la RTgI utilise la tomodensitométrie (TDM) (RTgI par TDM). La radiothérapie guidée par résonance magnétique (RTgIRM), quant à elle, utilise une nouvelle technologie hybride qui combine les fonctions de résonance magnétique (pour l'imagerie) et d'accélérateur linéaire (pour l'administration de la radiothérapie) dans un seul dispositif, appelé appareil IRM-linac.
- Des études dosimétriques ont démontré que les systèmes hybrides IRM-linac permettent d'administrer une dose plus précise et plus élevée à la tumeur. Santé Canada a homologué des appareils IRM-linac en 2017 sur la base de ces études dosimétriques, mais des rapports de l'INESSS et de l'ACMTS de 2019 ont conclu que le coût élevé et l'absence de données sur l'efficacité clinique ne justifiaient pas leur utilisation systématique. Néanmoins, certains centres canadiens de cancérologie ont adopté l'IRM-linac.
- Le département de radiologie du CUSM devra remplacer ses accélérateurs linéaires conventionnels en 2024; il y a un intérêt pour le remplacement d'un des sept accélérateurs conventionnels par un appareil IRM-linac.
- Ce rapport a pour objectif d'évaluer de nouvelles preuves sur la sécurité, l'efficacité et le coût de la RTgIRM par rapport à la RTgI par TDM en matière de toxicité, de contrôle tumoral local et de survie.
- Nous avons répertorié 20 études observationnelles publiées et 6 essais qui ont évalué l'efficacité clinique ou la tolérance des patients à l'IRM-linac. Toutefois, presque tous étaient de petite taille et sans groupes témoins, ce qui nous empêche de faire une comparaison directe entre la RTgIRM et la RTgI par TDM. Aucune étude n'a rapporté de toxicité de grade  $\geq 4$ . Les essais cliniques en cours nous permettront de mieux comparer l'efficacité à l'avenir.
- Dans des comparaisons indirectes, la toxicité et les taux de survie rapportés pour la RTgIRM sont comparables à ceux d'autres modalités. La plus grande étude à une seule branche sur la RTgIRM pour le traitement du cancer de la prostate (n=101) a rapporté une toxicité et une survie sans rechute biochimique après un an qui étaient comparables aux résultats d'une revue systématique et d'une méta-analyse d'études prospectives évaluant les modalités autres que l'IRM-linac chez plus de 6 000 patients atteints du cancer de la prostate.

- Les études sur les résultats déclarés par les patients montrent que la RTgIRM est généralement sûre et bien tolérée par les patients.
- Les analyses d'effet de coûts publiées indiquent que la RTgIRM est plus coûteuse que la RTgl par TDM en raison des coûts d'acquisition, d'infrastructure et d'entretien, ainsi que de la durée de traitement plus longue. Une étude britannique a modélisé la demande d'IRM-linac selon six sites de maladie (c.-à-d. prostate, système nerveux central, tête et cou, cancer du poumon non à petites cellules, œsophage et pancréas) et a trouvé que l'IRM-linac pourrait remplir 16 % des obligations en matière de fractions du pays (nombre de séances de traitement requises pour administrer la dose totale prescrite).
- Les entretiens avec les utilisateurs de la technologie suggèrent que la RTgIRM offre des possibilités de traiter des patients qui seraient difficilement traitables avec la technologie de radiothérapie normale.
- En conclusion, la RTgIRM a plusieurs avantages fonctionnels sur la RTgl par TDM : (1) meilleure imagerie volumétrique des tissus mous des tumeurs et des organes à risque avant et pendant le traitement, ce qui améliore la délimitation des contours pour le traitement et évite le placement de repères radio-opaques; (2) système de synchronisation (*gating*) (c.-à-d. suivi des mouvements de la tumeur et des organes à risque qui permet l'administration de radiation uniquement lorsque la tumeur est dans le champ d'irradiation); (3) planification adaptative par imagerie en temps réel pour réviser le traitement pendant que le patient est sur la table. Même s'il n'y a pas encore de données à long terme sur l'efficacité comparative, des comparaisons indirectes indiquent que les résultats en aval ne devraient pas être moins bons que ceux obtenus avec la RTgl par TDM. Cependant, l'incertitude demeure quant aux coûts; la RTgIRM peut être rentable par rapport à la RTgl par TDM en fonction des réductions de toxicité dues à l'augmentation de la précision et au moins grand nombre de traitements requis.

## EXECUTIVE SUMMARY

### BACKGROUND

Image-guided radiotherapy (IGRT) uses imaging during radiation treatment to improve precision and accuracy. IGRT may use CT-scan, magnetic resonance imaging (MRI), fiducial markers (metal objects implanted near the tumour to pinpoint its location), ultrasound, or 3D-body surface mapping as imaging modalities. IGRT has been proven to reduce radiation treatment-related morbidity as a result of better visualization of tumour location and surrounding organs at risk (OAR). Stereotactic body radiotherapy (SBRT), a modality of hypofractionation where a patient receives fewer treatments but a higher radiation dose at each treatment, used along with IGRT would allow for significantly reducing treatment duration compared with conventional fractionation, and thus treating a greater volume of patients in a much shorter period.

While computed tomography-guided radiotherapy (CTgRT) is the current standard of care, there is growing evidence that magnetic resonance-guided radiotherapy (MRgRT) could improve radiation treatment due to high contrast visualization of soft tissue. MRgRT delivery systems combine a linear accelerator (linac) system for delivery of radiotherapy, and a magnetic resonance imaging (MRI) scanner for visualizing the treatment area and are thus called MRI-Linac machines.

Dosimetry studies have demonstrated that MRgRT offers several advantages including:

- better visibility of soft tissue, which improves delineation of tumour margins;
- adaptive planning by real-time imaging to re-plan treatment while the patient is on the table;
- a gating system i.e. movement-tracking of the tumour and OAR and hence, radiation is only delivered when the tumour is in the treatment field. This is especially important for cancers in the abdomen, pelvis, and central thorax, which are challenging to target due to respiratory and bowel movement;
- No need for use of fiducial markers (metal objects implanted with needle by interventional radiologists to pinpoint tumour location) before treatment of liver and prostate tumours, in contrast to CTgRT.

These advantages could improve safety and, when used in conjunction with SBRT, could reduce the treatment period by allowing delivery of higher dose per fraction (a proportion of the total prescribed dose delivered at each treatment session) and substantially reducing the number of fractions while at the same time preserving the surrounding OAR.

Currently, there are two commercial MRgRT delivery systems approved by the Food and Drug Administration (FDA): MRIdian Linac (ViewRay Inc., Ohio, US) with **low** magnetic field (0.35 Tesla) and The Unity (Elekta, Ltd., Stockholm, Sweden) with **high** magnetic field (1.5 Tesla). MRIdian was approved by Health Canada in 2017, followed by the Unity in 2019, on the basis of dosimetry studies.

Although MRI and linear accelerators have been used routinely as separate modalities, evidence for the clinical and cost effectiveness of the hybrid MRI-Linac device compared to CTgRT have yet to be evaluated. CADTH released their report in March 2019 and INESSS in September 2019 with the same conclusion that it was too early to evaluate the efficacy of MRgRT given the lack of clinical evidence at the time of the reports and the high acquisition and operational costs.

The radio-oncologists at the MUHC will need to replace their conventional linear accelerators in 2024 and are interested in replacing 1 of their 7 linear accelerators with an MRI-linac device. At the MUHC, there are 50-500 estimated patients who would be affected annually. Two centres in Sunnybrook and Princess Margaret Hospital (PMH) have been using the Unity Elekta for MRgRT and are part of Elekta's collaborating centres. The Centre Hospitalier de l'Université de Québec (CHUQ) and the Tom Baker center in Alberta have acquired the device, while the Centre Hospitalier de l'Université de Montréal (CHUM) in Quebec has a pending agreement with Elekta.

## OBJECTIVES

The objectives of this report are to

- assess new evidence on the safety and efficacy of MRI-Linac for MRgRT when compared with CTgRT in terms of toxicity, local control and survival rates;
- evaluate new evidence on the cost or cost-effectiveness of MRgRT.

## METHODS

INESSS conducted a scoping review including studies published up to 2018. Our review therefore included studies on MRgRT published between 2019/1/1 - 2021/9/30 by searching PubMed, ClinicalTrials.gov and the health technology assessment (HTA) databases (CADTH and INESSS). The most recent search was conducted on October 14, 2021. We also identified relevant HTAs and clinical guidelines assessing the use of MRI-Linac. We conducted interviews with users of the technology from US and Canadian centres.

## RESULTS

We identified 26 studies (20 observational and 6 trials) for our analysis. Most observational studies and trials had no comparison and short follow up time (ranged between 5 weeks to 29 months). There are 26 ongoing clinical trials registered at the ClinicalTrials.gov expected to finish in 2-3 years; 7 of them have parallel assignments with sample sizes ranging from 70-1000 participants. There is also an international registry with currently 1000+ patients around the world.

### Effectiveness outcomes:

- Fourteen studies found that MRgRT did not cause grade  $\geq 3$  toxicity as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events v4.0. The only controlled study compared 0.35T Tri-60-Co hybrid unit (MRgRT ViewRay) vs. standard linac in locally advanced cervical cancer patients (n=18) and reported a reduction in risk of gastrointestinal toxicity in the MRgRT arm of 22.2% (95% confidence interval (CI): -20.3, 55.5) and genitourinary toxicity of 11.1% (95% CI: -27.8, 46.2); the high uncertainty is due to the very small sample size (n=9 in each arm). Pathologic responses were comparable between the two arms.
- The largest single-arm trial of MRgRT in prostate cancer treatment (n=101) reported no early or 1-year grade 3 genitourinary or gastrointestinal toxicity and a biochemical relapse-free survival at 1-year of 98%. These were comparable to results from a meta-analysis of prospective studies evaluating SBRT, delivered via conventional linac, in more than 6000 prostate cancer patients with a median follow up of 30 months (range 12-115). It reported a biochemical relapse-free survival rate at 1-year of 98.4%. The overall late grade  $\geq 3$  genitourinary toxicity was 2.0% (95% CI 1.4%-2.8%) and 1.1% (95% CI 0.6%-2.0%) for gastrointestinal toxicity. Nonetheless, larger controlled studies are needed to evaluate its effectiveness relative to CTgRT.
- Studies also showed that MRgRT was overall well tolerated and patients appreciated their active role in respiratory gating during the treatment. Coldness, paraesthesia, anxiety, and disturbing noise sensations were most reported and should be considered for future improvement.

### Economic evaluations:

- A time-driven activity-based costing (TDABC) study compared the cost of treatment on linear accelerators between CTgRT and low magnetic field MRgRT in treating localized unresectable hepatocellular carcinoma. Although MRgRT offers real-time image guidance, avoidance of fiducial placement, and ability to

use adaptive treatments, its use increased the direct clinical cost by \$1,316 (18%) and each adaptive treatment would cost \$529. Nevertheless, increased MRgRT costs could be diminished by omitting CT simulation (\$322 saved) or shortening treatment to 3 fractions (\$1,815 saved).

- Another TDABC evaluation for treatment of prostate cancer with low magnetic field MRgRT and CTgRT showed that a 7% reduction in gastrointestinal and/or genitourinary grade  $\geq 2$  toxicity is required for MRgRT using 5-fraction SBRT to be cost-effective at a threshold of \$100,000 USD (\$123,730 CAD) per quality adjusted life years (QALY); a 14% reduction in toxicity is required at a threshold of \$50,000 USD (\$61,865 CAD) per QALY.
- A study that evaluated the cost of high magnetic field MR-Linac in 5 fractions for prostate cancer found the latter would cost €62,500 (\$89,681 CAD) per patient when side effects, including gastrointestinal, genitourinary, and sexual complications, are reduced to no complications compared to 5 fractions of external beam radiotherapy with conventional linac.
- To simulate the number of cancer patients potentially available for treatment with MRgRT, a recent study in the UK modelled the MRI-Linac demand in the country. For the simulation, they used the initial clinical indications recommended by the MRI-Linac consortium (i.e., prostate, central nervous system, head and neck, non-small cell lung cancer, oesophagus and pancreas) which covers 23 types of cancers, and all would be treated with the same numbers of conventional fractions. They found that MR-Linac could cover 16% of the country's fraction burden.

#### EXPERIENCE AT THE MUHC AND ELSEWHERE

MRI-Linac has not been used at any centres in Quebec, but data from the Ministère de la Santé et des Services Sociaux for 2016/2017 until 2020/2021 fiscal years showed that the MUHC has the one of lowest number of treatment sessions (i.e., average number of fractions) per patient relative to other centres. According to Dr. Hijal, this could be explained by the use of SBRT, i.e. hypofractionated radiotherapy, at the MUHC. Hence, acquisition of an MRI-Linac may further reduce this average, but not as much as for other centres. In terms of patient volume, the number of patients treated per linear accelerator unit at the MUHC is comparable to, if not higher than, other centres.

Interviews with users of the technology suggest that MRgRT creates opportunities to treat people who otherwise would be difficult to treat with the standard radiation technology. It would be particularly useful to:

- Treat prostate and liver tumours, which are difficult to visualize with CTgRT;



- Treat pancreatic tumours because of the need to reduce irradiation of structures around the pancreas;
- Avoid the use of fiducial markers (implanted with needle by interventional radiologists) before treatment with CTgRT. MRI can improve imaging precision and can avoid this invasive technique thus reducing additional visits and risk of infection;
- Reduce the number of treatment sessions for prostate cancer patients to five sessions over a period of 1 – 2 weeks because MRI-Linac allows greater precision to deliver higher doses safely over fewer treatment sessions. Fewer treatments will benefit patients and increase hospital's capacity to treat other patients.

## COSTS

In the Quebec setting, INESSS conducted a probabilistic analysis of the cost of using the standard linac vs. the two commercially available MRI-Linac devices. They took into consideration the acquisition, construction, maintenance and utilisation costs. Their probabilistic analysis indicated that, over a 10-year horizon, there is an 80% probability that the incremental cost of an MRI-Linac device compared to a conventional linac would vary between \$11.7M and \$20.1M CAD for the Elekta Unity system and from \$12.7M to \$18.4M CAD for the MRIdian system.

The acquisition cost for the Elekta Unity system has since decreased from \$11M to \$8M CAD. Moreover, there is an opportunity to reduce service costs because increased precision would mean fewer fractions for patients treated with MRgRT.

## CONCLUSIONS

- The current standard of care for radiotherapy is CT-guided SBRT. SBRT delivered in 5 fractions, a modality of hypofractionation where a patient receives fewer treatments but a higher radiation dose at each treatment, allows for significantly reducing treatment duration compared with conventional fractionation, and thus treating a greater volume of patients in a much shorter period.
- Both MRI and linear accelerators are modalities that are part of standard practice, and the combination of these two modalities offers considerable advantages including (1) better volumetric soft tissue imaging of tumours and organs at risk prior and during treatment, which improves delineation of treatment margins and avoids the placement of fiducial markers, (2) gating system (i.e., movement-tracking of the tumour and organs at risk and hence, radiation is only delivered when the tumour is in the treatment field), (3) adaptive planning by real-time imaging to re-plan treatment while the patient is on the table.

- Uncontrolled studies of MRgRT have shown it to be generally safe and well tolerated by patients, with good short-term local control and overall survival. The largest single-arm trial of MRgRT in prostate cancer treatment showed a high biochemical relapse-free survival rate (98%), no grade  $\geq 3$  toxicities, and good patient-reported outcomes at 1-year follow up. These findings were comparable to a systematic review and meta-analysis of prospective studies evaluating other radiotherapy modalities. However, data from controlled studies are not yet available that show long-term reductions in toxicity and improvements in survival relative to CTgRT. Nonetheless, downstream outcomes are not expected to be worse than those with CTgRT. Ongoing clinical trials will allow us to better evaluate comparative effectiveness in the future.
- Uncertainty about the cost impact remains due to uncertainty surrounding acquisition and operational costs, and costs associated with potential reductions in toxicity.

## RECOMMENDATIONS

- The TAU Policy Committee, comprised of stakeholders from across the McGill University Health Centre, reviewed the evidence and issued the following recommendation: [Approved for evaluation](#)
- This recommendation was reached based on the following:
  - MRgRT offers functional advantages over CTgRT including real-time image guidance with better soft tissue contrast, avoidance of fiducial placement, and ability to perform adaptive treatments;
  - More precise delivery of high-dose radiotherapy in fewer treatment sessions would increase patient convenience and increase the hospital's capacity to treat other patients;
  - High quality comparative-effectiveness evidence for downstream outcomes is still needed, but these outcomes are not expected to be worse than those with CTgRT;
  - Given the high acquisition and operating costs, acquisition of one MRI-Linac device is conditional on approval from the Ministère de la Santé et des Services Sociaux.
- Upon acquisition, it is necessary that data be systematically collected, including data on patient selection criteria and downstream clinical outcomes;
- This recommendation should be reviewed in 2 years when new evidence from the clinical trials becomes available.

## SOMMAIRE

### CONTEXTE

La radiothérapie guidée par l'imagerie (RTgI) utilise l'imagerie pendant le traitement de radiothérapie pour améliorer la précision et l'exactitude. La RTgI peut utiliser la tomodensitométrie, l'imagerie par résonance magnétique, des marqueurs radio-opaques (objets métalliques implantés près de la tumeur pour en localiser l'emplacement), les ultrasons ou la modélisation 3D comme modalités d'imagerie. Il est prouvé que la RTgI réduit la morbidité liée aux traitements de radiothérapie grâce à une meilleure visualisation de la localisation de la tumeur et des organes à risques (OAR) à proximité. La radiothérapie stéréotaxique corporelle (RSC), une modalité d'hypofractionnement où le patient reçoit un plus petit nombre de traitements avec une dose de radiation plus forte chaque fois, combinée avec la RTgI permettrait une réduction importante de la durée de traitement par rapport au fractionnement conventionnel. Par conséquent, il est possible de traiter un plus grand volume de patients en une période beaucoup plus courte.

Même si la radiothérapie guidée par la tomodensitométrie (RTgI par TDM) est la norme actuelle pour les soins, la preuve est de plus en plus grande que la radiothérapie guidée par résonance magnétique (RTgIRM) pourrait améliorer les traitements de radiothérapie grâce à une visualisation à contraste élevé des tissus mous. Les systèmes d'administration de RTgIRM combinent un accélérateur linéaire (linac) pour l'administration de radiothérapie et un appareil d'imagerie par résonance magnétique (IRM) pour visualiser la zone de traitement. Ils sont donc appelés appareils IRM-linac.

Des études dosimétriques ont démontré que la RTgIRM offre plusieurs avantages :

- meilleure visibilité des tissus mous, ce qui améliore la délimitation des contours de la tumeur;
- planification adaptative par imagerie en temps réel pour réviser le traitement pendant que le patient est sur la table;
- système de synchronisation, c.-à-d. le suivi des mouvements de la tumeur et des OAR, qui permet l'administration de radiation uniquement lorsque la tumeur est dans le champ d'irradiation. Cet élément est particulièrement important pour les cancers de l'abdomen, du bassin et de la partie centrale du thorax, qui sont difficiles à cibler en raison des mouvements respiratoires et intestinaux;
- marqueurs radio-opaques (objets métalliques implantés avec une aiguille par un radiologiste interventionnel pour délimiter la tumeur) non requis avant le traitement des tumeurs au foie ou à la prostate, contrairement à la RTgI par TDM.

Ces avantages peuvent améliorer la sécurité et, conjointement avec la RSC, réduire la période de traitement en permettant l'administration de doses plus fortes par fraction (une portion de la dose totale prescrite administrée à chaque traitement) et en

réduisant de façon substantielle le nombre de fractions tout en préservant les OAR à proximité.

Actuellement, il y a deux systèmes commercialisés de RTgIRM homologués par la Food and Drug Administration (FDA) : MRIdian Linac (ViewRay Inc., Ohio, États-Unis) à **faible** champ magnétique (0,35 tesla) et Unity (Elekta, Ltd., Stockholm, Suède) à **haut** champ magnétique (1,5 tesla). MRIdian a été homologué par Santé Canada en 2017, suivi de Unity en 2019, sur la base d'études dosimétriques.

Même si l'IRM et les accélérateurs linéaires sont couramment utilisés en tant que modalités distinctes, la preuve de l'efficacité clinique et de l'efficacité d'un appareil hybride IRM-linac comparé à la RTgl par TDM reste à faire. L'ACMTS a publié son rapport en mars 2019 et l'INESSS en septembre 2019, avec la même conclusion : il était trop tôt pour évaluer l'efficacité de la RTgIRM étant donné le manque de données cliniques probantes au moment des rapports et les coûts d'acquisition et d'exploitation élevés.

Les radio-oncologues du CUSM devront remplacer les accélérateurs linéaires conventionnels en 2024 et s'intéressent au remplacement d'un des sept accélérateurs linéaires par un appareil IRM-linac. Au CUSM, on estime que de 50 à 500 patients seraient touchés chaque année. Deux centres hospitaliers, Sunnybrook et l'Hôpital Princess Margaret, utilisent l'appareil Unity d'Elekta pour la RTgIRM et font partie des centres de collaboration d'Elekta. Le Centre Hospitalier de l'Université de Québec (CHUQ) et le centre Tom Baker en Alberta ont fait l'acquisition de l'appareil, alors que le Centre Hospitalier de l'Université de Montréal (CHUM), au Québec, est dans l'attente d'un accord avec Elekta.

## OBJECTIFS

Les objectifs du présent rapport sont les suivants :

- évaluer de nouvelles données probantes sur la sécurité et l'efficacité de l'IRM-linac pour la RTgIRM par rapport à la RTgl par TDM en matière de toxicité, de contrôle tumoral local et de taux de survie;
- évaluer de nouvelles données probantes sur les coûts et le coût-efficacité de la RTgIRM.

## MÉTHODES

L'INESSS a mené une étude de portée comprenant des études publiées jusqu'en 2018. Notre examen a donc porté sur des études sur la RTgIRM publiées entre le 1er janvier 2019 et le 30 septembre 2021 et trouvées en interrogeant PubMed, ClinicalTrials.gov et les bases de données d'évaluation des technologies et des modes d'interventions de la santé (ÉTMIS) (ACMTS et INESSS). La plus récente recherche a été effectuée le 14 octobre 2021. Nous avons également identifié les ÉTMIS pertinentes et

les directives cliniques évaluant l'utilisation d'IRM-linac. Nous nous sommes entretenus avec des utilisateurs de la technologie de centres hospitaliers américains et canadiens.

## RÉSULTATS

Nous avons répertorié 26 études (20 études observationnelles et 6 essais) pour notre analyse. La plupart des études observationnelles et des essais n'étaient pas comparatifs et avaient une durée de suivi courte (entre 5 semaines et 29 mois). Il y a 26 essais cliniques en cours enregistrés sur le site ClinicalTrials.gov qui doivent se terminer d'ici deux à trois ans; sept d'entre eux sont des études en parallèle avec des échantillons variant de 70 à 1 000 participants. Il existe également un registre international qui compte actuellement plus de 1 000 patients dans le monde.

### Résultats en matière d'efficacité :

- Quatorze études ont trouvé que la RTgIRM ne cause pas de toxicité de grade  $\geq 3$ , telle que définie par le National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Le seul essai comparatif a examiné l'unité hybride à 3 sources de  $^{60}\text{Co}$  à 0,35 T (RTgIRM de ViewRay) comparativement à un linac standard pour le traitement de patients atteints de cancer localement avancé du col de l'utérus (n=18) et a noté une réduction du risque de toxicité gastro-intestinale dans le groupe de la RTgIRM de 22,2 % (intervalle de confiance (IC) de 95 % : -20,3, 55,5) et de toxicité génito-urinaire de 11,1 % (IC de 95 % : -27,8, 46,2); l'incertitude élevée est due à la très petite taille de l'échantillon (n=9 dans chaque groupe). Les réponses pathologiques étaient semblables dans les deux branches.
- La plus grande étude à une seule branche sur la RTgIRM pour le traitement du cancer de la prostate (n=101) n'a rapporté aucune toxicité génito-urinaire ou gastro-intestinale précoce de grade 3 à 1 an et une survie sans rechute biochimique à 1 an de 98 %. Ces résultats sont comparables à ceux d'une méta-analyse d'études prospectives d'évaluation de la RSC, administrée par linac conventionnel, chez plus de 6 000 patients atteints du cancer de la prostate avec un suivi médian jusqu'à 30 mois (entre 12 et 115 mois). Elle a rapporté un taux de survie sans rechute biochimique à 1 an de 98,4 %. La toxicité génito-urinaire tardive globale de grade  $\geq 3$  était de 2,0 % (IC de 95 % : 1,4 % à 2,8 %) et de 1,1 % (IC de 95 % : 0,6 % à 2,0 %) pour la toxicité gastro-intestinale. Néanmoins, des études comparatives de plus grande envergure sont nécessaires pour évaluer l'efficacité relative par rapport à la RTgl par TDM.
- Des études ont montré que la RTgIRM était généralement bien tolérée par les patients et qu'ils aimaient jouer un rôle actif dans la synchronisation respiratoire pendant le traitement. Les sensations les plus rapportées étaient le froid, les paresthésies, l'anxiété et le bruit inquiétant. Elles devraient être prises en compte pour améliorer le traitement à l'avenir.

### Évaluations économiques :

- Une étude de comptabilité par activité (CPA) en fonction des délais a comparé le coût de traitement par accélérateurs linéaires entre la RTgl par TDM et la RTgIRM à faible champ magnétique pour le traitement de carcinomes hépatocellulaires localisés inopérables. Même si la RTgIRM offre un guidage par imagerie en temps réel, évite l'installation de repères radio-opaques et permet l'utilisation de traitements adaptatifs, son utilisation augmente les coûts cliniques directs de 1 316 \$ (18 %) et chaque traitement adaptatif coûterait 529 \$. Néanmoins, l'augmentation des coûts de la RTgIRM pourrait être diminuée en omettant la simulation (économie de 322 \$) ou en ramenant le traitement à trois fractions (économie de 1 815 \$).
- Une autre évaluation de la CPA en fonction des délais pour le traitement du cancer de la prostate par RTgIRM à faible champ magnétique et RTgl par TDM montre qu'une réduction de 7 % de la toxicité gastro-intestinale ou génito-urinaire de grade  $\geq 2$  est nécessaire pour que la RTgIRM qui utilise cinq fractions de RSC soit rentable à un seuil de 100 000 \$ US (123 730 \$ CA) par année de vie pondérée par la qualité (AVPQ); une réduction de 14 % est nécessaire en utilisant un seuil de 50 000 \$ US (61 865 \$ CA) par AVPQ.
- Une étude qui a évalué le coût de l'IRM-linac à haut champ magnétique en cinq fractions pour le traitement du cancer de la prostate a déterminé qu'il en coûterait 62 500 € (89 681 \$ CA) par patient, alors que les effets secondaires, y compris les complications gastro-intestinales, génito-urinaires et sexuelles, sont éliminés comparativement à cinq fractions de radiothérapie externe avec un linac conventionnel.
- Pour simuler le nombre de patients atteints de cancer potentiellement admissibles à un traitement par RTgIRM, une étude britannique récente a modélisé la demande d'IRM-linac au pays. Pour la simulation, les chercheurs ont utilisé les indications cliniques initiales recommandées par le consortium IRM-linac (c.-à-d. prostate, système nerveux central, tête et cou, cancer du poumon non à petites cellules, œsophage et pancréas), ce qui recoupe 23 types de cancer. Tous les patients seraient traités avec le même nombre de fractions conventionnelles. Les chercheurs ont trouvé que l'IRM-linac pourrait couvrir 16 % des obligations en matière de fractions du pays.

### EXPÉRIENCE AU CUSM ET AILLEURS

Aucun centre hospitalier québécois n'a utilisé d'IRM-linac, mais des données du ministère de la Santé et des Services sociaux pour les exercices financiers 2016–2017 jusqu'à 2020–2021 ont montré que le CUSM a l'un des plus bas nombres de séances de traitement par patient (c.-à-d. nombre moyen de fractions) comparativement aux autres centres. Selon le Dr Hijal, cela pourrait s'expliquer par l'utilisation de la RSC, c.-à-d. la radiothérapie hypofractionnée, au CUSM. L'acquisition d'une IRM-linac peut donc réduire encore cette moyenne, mais pas autant que pour les autres centres. Pour ce qui

est du volume de patients, le nombre de personnes traitées par accélérateur linéaire au CUSM est comparable aux autres centres, sinon plus élevé.

Les entretiens avec les utilisateurs de la technologie suggèrent que la RTgIRM offre des occasions pour soigner des personnes qui seraient difficilement traitables avec la technologie de radiothérapie normale. L'approche serait particulièrement utile pour les cas suivants :

- traitement de tumeurs de la prostate et du foie, qui sont difficiles à visualiser avec la RTgl par TDM;
- traitement de tumeurs pancréatiques en raison de la nécessité de réduire l'irradiation des structures à proximité du pancréas;
- marqueurs radio-opaques (implantés avec une aiguille par un radiologiste interventionnel) non requis avant le traitement, contrairement à la RTgl par TDM. L'IRM peut améliorer la précision de l'imagerie et éviter cette technique invasive, réduisant ainsi les visites supplémentaires et le risque d'infection;
- pour les patients atteints du cancer de la prostate, réduction du nombre de séances de traitement à cinq sur une période d'une à deux semaines, car l'IRM-linac permet une plus grande précision pour administrer des doses plus fortes de façon sécuritaire en moins de séances de traitement. La réduction du nombre de traitements profitera aux patients et augmentera la capacité de l'hôpital à traiter d'autres patients.

## Coûts

Dans le contexte québécois, l'INESSS a effectué une analyse probabiliste des coûts d'utilisation d'un linac standard comparativement aux deux appareils IRM-linac sur le marché. Elle a tenu compte des coûts d'acquisition, de construction, d'entretien et d'utilisation. Son analyse probabiliste indique que, sur un horizon de 10 ans, il y a une probabilité de 80 % que le coût différentiel d'un appareil IRM-linac par rapport à un linac conventionnel varie entre 11,7 M\$ CA et 20,1 M\$ CA pour le système Unity d'Elekta et entre 12,7 M\$ CA et 18,4 M\$ CA pour le système MRIdian.

Le coût d'acquisition du système Unity d'Elekta est depuis passé de 11 millions de dollars à 8 millions de dollars canadiens. De plus, il existe une possibilité de réduire les coûts de services, car une précision accrue signifierait moins de fractions pour les patients traités par RTgIRM.

## CONCLUSION

- La RSC guidée par TDM représente la norme actuelle de soins en radiothérapie. La RSC en cinq fractions, une modalité d'hypofractionnement où le patient reçoit un plus petit nombre de traitements avec une dose de radiation plus forte chaque fois, permet une réduction importante de la durée de traitement par rapport au



fractionnement conventionnel. Par conséquent, il est possible de traiter un plus grand volume de patients en une période beaucoup plus courte.

- L'IRM et les accélérateurs linéaires font partie de la pratique normale et la combinaison des deux modalités offre des avantages considérables, notamment : (1) meilleure imagerie volumétrique des tissus mous des tumeurs et des organes à risque avant et pendant le traitement, ce qui améliore la délimitation des contours pour le traitement et évite le placement de repères radio-opaques; (2) système de synchronisation (c.-à-d. suivi des mouvements de la tumeur et des organes à risque qui permet l'administration de radiation uniquement lorsque la tumeur est dans le champ d'irradiation); (3) planification adaptative par imagerie en temps réel pour réviser le traitement pendant que le patient est sur la table.
- Des essais non comparatifs sur la RTgIRM ont montré qu'elle est généralement sûre et bien tolérée par les patients, avec un bon contrôle tumoral local et une bonne survie globale à court terme. La plus grande étude à une seule branche sur la RTgIRM pour le traitement du cancer de la prostate a rapporté un taux élevé de survie sans rechute biochimique (98 %), aucune toxicité de grade  $\geq 3$  et de bons résultats déclarés par les patients au suivi après un an. Ces résultats étaient comparables à une revue systématique et méta-analyse d'études prospectives évaluant les autres modalités de radiothérapie. Toutefois, il n'y a pas encore de données d'essais comparatifs qui montrent une réduction à long terme de la toxicité et une amélioration de la survie par rapport à la RTgl par TDM. Néanmoins, les résultats en aval ne devraient pas être moins bons que ceux obtenus avec la RTgl par TDM. Les essais cliniques en cours nous permettront de mieux comparer l'efficacité à l'avenir.
- L'incertitude à propos de l'effet des coûts demeure en raison de l'imprévisibilité des coûts d'acquisition et d'exploitation, et des coûts liés aux réductions potentielles de toxicité.

## RECOMMANDATIONS

- Le comité consultatif de l'Unité d'évaluation des technologies de la santé (TAU), composé de parties prenantes de tout le Centre universitaire de santé McGill, a examiné les données probantes et formulé la recommandation suivante : [Approuvé pour l'évaluation](#)
- Le comité est parvenu à cette recommandation sur la base des éléments suivants :
  - la RTgIRM offre des avantages fonctionnels par rapport à la RTgl par TDM, notamment le guidage par imagerie en temps réel avec un meilleur contraste des tissus mous, l'élimination des repères radio-opaques et la possibilité de donner des traitements adaptatifs;
  - l'administration plus précise d'une forte dose de radiothérapie en moins de séances de traitement serait plus commode pour les patients et augmenterait la capacité de l'hôpital à traiter d'autres patients;
  - des preuves d'efficacité comparative de haute qualité pour les résultats en aval sont encore nécessaires, mais ces résultats ne devraient pas être moins bons que ceux obtenus avec la RTgl par TDM;



- compte tenu des coûts d'acquisition et d'exploitation élevés, l'acquisition d'un appareil IRM-linac est conditionnelle à l'approbation du ministère de la Santé et des Services sociaux.
- Lors de l'acquisition, il est nécessaire de colliger systématiquement les données, y compris celles sur les critères de sélection des patients et les résultats cliniques en aval;

La présente recommandation devrait être revue dans deux ans lorsque de nouvelles données issues d'essais cliniques seront accessibles.

## LIST OF ABBREVIATIONS

CI	Confidence interval
bRFS	Biochemical recurrence-free survival
CADTH	Canadian Agency for Drugs and Technologies in Health
CTgRT	Computed tomography for image-guided radiotherapy
CHUM	Centre Hospitalier de l'Université de Montréal
CHUQ	Centre Hospitalier de l'Université de Québec
EBRT	External beam radiotherapy
FDA	Food and Drug Administration
Gy	Gray, unit used to measure the total radiation a patient is exposed to
HTA	Health technology assessment
IGRT	Image-guided radiotherapy
INESSS	Institut National d'Excellence en Santé et en Service Sociaux
MRgRT	Magnetic resonance imaging-guided radiotherapy
MRgSBRT	Magnetic resonance imaging-guided stereotactic body radiotherapy
MSSS	Ministère de la Santé et des Services sociaux, MSSS
MUHC	McGill University Health Centre
OAR	Organs at risk
PMH	Princess Margaret Hospital
QoL	Quality of life
RCT	Randomized controlled trial
SBRT	Stereotactic body radiotherapy
SMART	Stereotactic MRI Guided Online Adaptive Radiotherapy
TAU	MUHC Technology Assessment Unit

# MAGNETIC RESONANCE IMAGING-GUIDED RADIOTHERAPY USING MRI-LINAC FOR CANCER PATIENTS UNDERGOING RADIOTHERAPY AT THE MUHC

## 1. BACKGROUND

Radiotherapy is commonly used on its own or in combination with chemotherapy and/or surgery to treat cancer patients. Image-guided radiotherapy (IGRT) has proven to reduce radiation treatment-related morbidity as a result of better visualization of the location of the tumour and surrounding organs. While the use of computed tomography for image-guided radiotherapy (CTgRT) is the current standard of care, there is growing evidence that magnetic resonance imaging-guided radiotherapy (MRgRT) could provide additional advantages. In principle, MRgRT delivery systems are a hybrid of a linear accelerator (linac) system that delivers radiotherapy and a magnetic resonance imaging (MRI) scanner to visualize the treatment area, and are hence called MRI-linac devices. This combination allows real-time non-ionizing imaging, better visibility of the soft tissues, and tracking of the movement of the tumour and organs at risk (OAR). These advantages are important for cancers in the abdomen, pelvis, and central thorax, which are challenging to target due to respiratory and bowel movement. Thus, real-time tumour tracking could reduce the adverse effect of radiotherapy on OAR. Hybrid MRI-linac is a ground-breaking modality in radiotherapy because it enables online imaging and adaptive treatment planning to be done during treatment delivery.

### 1.1 CURRENTLY AVAILABLE MRGRT SYSTEMS

Currently, there are two commercial MRgRT delivery systems approved by the Food and Drug Administration (FDA). MRIdian Linac (ViewRay Inc., Ohio, US) was the first one approved in 2012. The first version had a three-headed cobalt source system with a **low field magnet** (0.35 T). In the second version, the three-headed cobalt source was replaced with a 6 megavoltage (MV) linear accelerator. It was approved by the FDA in February 2017. To date, there are 34 MRIdian systems in 13 countries around the world that have treated more than 10,000 cancer patients. Twenty international MRIdian users formed a multicentre group called Clinical Co-operative Think Tank (C2 T2) to share clinical data and collaborate in MRgRT research and evaluation.(2)

The Unity (Elekta, Ltd., Stockholm, Sweden), the second MRgRT delivery system, was approved by the FDA in December 2018. It has a **high magnetic field** strength of 1.5 T and a 7 MV linear accelerator. To date, there are 16 Unity systems in 11 countries around the world that have treated more than 1,000 cancer patients. Seven research

centers from the United Kingdom, Europe, and the United States collaborated and formed an international consortium.(2)

In Canada, MRIdian was approved by Health Canada in 2017, followed by the Unity in 2019. Although to date only phase I or II clinical trials of MRI-Linac have been published, an extensive system bench testing and a comprehensive software verification and validation testing have been done to determine that both MRI and the radiation treatment delivery subsystems operate safely and effectively. This evidence became the basis of Health Canada's approval (Class III, Medical Device License) for MRI-Linac systems for precision radiotherapy.

CADTH released their health technology assessment report in March 2019 and INESSS in September 2019 with the same conclusion that it was too early to evaluate the efficacy of MRgRT given the lack of clinical evidence at the time the reports were released to support the use of these new MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy (3, 4). INESSS recommended that the use of MRI-linac should be restricted to a research context. (4) Odette Cancer Centre at Sunnybrook Health Sciences Centre and Princess Margaret Cancer Centre in Ontario have been involved in developing and evaluating Elekta Unity and are part of the Multiple Outcome Evaluation of Radiation Therapy Using the MR-Linac Study (MOMENTUM) study. MOMENTUM is a prospective multi-institutional registry for evaluating patterns of care, tolerability, and safety of the first cohort of patients treated with Elekta MRgRT system (NCT04075305).

The Centre Hospitalier de l'Université de Québec (CHUQ) and the Tomb Baker center in Alberta are in the process of installing the Elekta Unity. The Centre Hospitalier de l'Université de Montréal (CHUM) in Quebec has a planned/pending agreement with Elekta.

A team from the Cross Cancer Institute in Alberta led by Dr. Gino Fallone created the Alberta Linac-MR P3 system. It has received approval from the Canadian Nuclear Safety Commission and ethics approval from the Cross Cancer Institute, but it is not yet approved by Health Canada. In fact, they just started the Northern LIGHTs – 1 (NCT04358913) clinical trial to evaluate if their MRI-Linac can achieve its capabilities.

## **1.2 REASON FOR HTA REQUEST**

The radio-oncologists at the MUHC are interested in the acquisition of an MRI-linac system to replace their linear accelerators in 2024. They believe MRI-linac would improve targeting to decrease treatment margins and reduce the need of daily

replanning capabilities. MRI-linac has not been used at any centers in Quebec. It is estimated that 50-500 patients would be affected annually (personal communication, Dr. Hijal). Although MRI or linac have been used as separate modalities, the evidence of effectiveness for the hybrid MRI-linac is unknown. Likewise, there is a growing interest among patients regarding the use of MRI-Linac, but evidence on patient-centred outcome measures following a change in practice is unknown.

Therefore, this evaluation 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. POLICY AND EVALUATION QUESTIONS

### 2.1 Policy question

Should the Radiation Oncology Division of the MUHC acquire an MRI-linac system for magnetic resonance-guided radiotherapy (MRgRT) to treat cancer patients?

### 2.2 Evaluation questions (Objective of this report)

- What is the new evidence on the safety and efficacy of MRI-Linac for MRgRT when compared with CTgRT? Specifically, does MRgRT result in similar toxicity, local control and survival rates compared to CTgRT?
- What is the new evidence on the cost or cost-effectiveness of MRI-Linac?

## 3. METHODS

### 3.1 Literature search and quality assessment

We conducted a literature search on MRgRT by searching PubMed, ClinicalTrials.gov and the health technology assessment (HTA) databases (CADTH and INESSS). The most recent search was conducted on October 14, 2021. The following key words were used: (MRgRT OR "MR-guided radiotherapy" OR "magnetic resonance guided radiotherapy") OR (SBRT OR "stereotactic body radiotherapy")) AND ("linear accelerator" OR linac). Filters applied: clinical Trial, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Meta-Analysis, Multicentre Study, Observational Study, Randomized Controlled Trial, Review, Systematic Review, from 2019/1/1 - 2021/9/30.

Thus, case reports and studies or reviews evaluating image-guided radiotherapy other than linac were excluded. We also identified relevant HTAs and clinical guidelines assessing the use of MRI-linac.

### 3.2 MUHC experience

We obtained information from Dr. Tarek Hijal and Mr. William Parker on current use of IGRT and the expected impact of MRgRT on patients and services at the MUHC. We also used data from the Ministry of Social and Health Services (Ministère de la Santé et des Services sociaux, MSSS) for 2016/2017 until 2020/2021 fiscal years to calculate the proportions of different modalities used in radiotherapy, the average number of fractions per patient, and the number of patients treated per linac unit at the MUHC compared to other centres across Quebec.

### 3.3 Cost analysis

We did not conduct a budget impact analysis because INESSS recently conducted one in the Quebec setting. However, it is possible that acquisition costs of MRI-Linac have decreased since the publication of their report.

## 4. RESULTS

### 4.1 Results of the literature search

We screened 186 articles and excluded 129 that were not trials, observational studies or systematic reviews/meta-analyses. Subsequently 35 studies including dosimetry or feasibility studies that did not report clinical outcomes or patient's tolerance were excluded, leaving 26 studies for our analysis ([Figure 1](#)). Most observational studies and trials had no comparison and short follow up time (ranged between 5 weeks to 29 months). There were 33 studies registered at the ClinicalTrials.gov: 29 are clinical trials and 4 observational studies. All studies are ongoing except 3 that were withdrawn, terminated, or completed without any results. Seven trials have parallel assignments with sample size 70-1000 subjects and are expected to finish in 2-3 years. There are five ongoing trials at Sunnybrook and PMH centers and one large cohort study at PMH.

## 4.2 Patients characteristics and disease sites

Henke and colleagues (5) reported a single institution experience treating 642 patients with the first version of MRIdian tricobalt-60. The median age was 64 years (range: 64–90). Of 666 unique treatment courses, the most frequent disease sites were the abdomen (41.2%), breast (31.4%), pelvis (13.2%), and thorax in 11.6%. The mean number of fractions was 12 (range 1–44) with a median dose per fraction of 4.5 Gy (range 1.2–20.0 Gy). MRgRT indications were the need for cine MRI gating (i.e., a type of MRI sequence to capture motion) (57.5%); adaptive radiotherapy (ART) (28.5%); and improved soft-tissue visualisation (14%). More than 80% of ART were done for abdominal malignancies with an increasing proportion over time (23% in 2014 vs. 75% in 2018).

Sahin and colleagues (6) reported the feasibility of the first 500 fractions using MRI-Linac MRIdian in 72 patients with 84 tumor sites in Turkey. The median age was 66 years (range: 28-83 years). The most frequent disease sites were upper abdominal (43%) and pelvic (34%). The most common diagnosis was prostate cancer (14%). The median number of fractions was 5 (range, 3-28) with a median dose of 36.25 Gy (range: 24-70 Gy). On-table adaptive radiation therapy (oART) was used in 93.2% patients and breath-hold with patient visual feedback in 43.1% patients. The mean total treatment time was 47 min (range: 21-125 min) and mean beam-on time was 16.7 min (range: 6-62 min).

The MOMENTUM Study (7) reported characteristics of 702 patients treated with MRI-Linac Unity who completed baseline data. Most of the patients were males (79%) with a median age of 68 years (range: 22-93). The most frequent indications were prostate (40%), oligometastatic lymph node (17%), brain (12%), and rectal (10%) cancers. The median number of fractions was 5 (range, 1-35) with a median dose of 53.2 Gy (range: 14-71 Gy). Six patients discontinued MR-Linac treatments, but none was caused by an inability to tolerate repeated high-field MRI.

## 4.3 Effectiveness & Safety

We identified 17 observational studies that evaluated clinical outcomes of MRI-Linac with median follow up time ranging from 3 to 25 months (7-23). Only one of these studies had a control group. We also identified six single-arm phase I or II trials (24-29) ([Table 1](#)).

### 4.3.1 Toxicity

Fourteen studies reported that there were no occurrences of grade  $\geq 3$  toxicity according to National Cancer Institute Common Terminology Criteria for Adverse Events v4.0 ([Table 1](#)) (9-16, 21). Nine showed low percentages of grade 3 toxicities, but none reported grade  $\geq 4$  toxicity (7, 17-19).

Only one small study (n=18) had a control group: Boldrini and colleagues compared 0.35T Tri-60-Co hybrid unit (MRgRT ViewRay) vs. CTgRT in conventional treatment for locally advanced cervical cancer (8). Pathologic responses were comparable between the two arms. Comparison with CTgRT showed that acute grade  $\leq 2$  gastrointestinal and genitourinary toxicities were lower in MRgRT than standard linac patients (55.5% vs. 33.3% and 33.3% vs. 22.2%, respectively) (8). The risk difference for gastrointestinal toxicity was 22.2% (95% confidence interval [CI]: -20.3, 55.5) and for genitourinary toxicity 11.1% (95% CI: -27.8, 46.2); the high uncertainty is due to the very small sample size (n=9 in each arm). Treatment was discontinued in 2 cases (1 per arm) due to neutropenia. Pathologic responses were comparable between the two arms.

The biggest trial involving 101 patients with clinical stage T1-3bN0M0 prostate cancer showed no early grade 3 genitourinary or gastrointestinal toxicity (28). At 1-year follow up, no grade  $\geq 3$  toxicity was reported. This was confirmed by the patient-reported outcome: the mean International Prostate Symptom Score (IPSS) was 7.4 (mild) at baseline, peaked to 12.9 (moderate) at the end of MRgRT and gradually returned to baseline at 12-month (29).

### 4.3.2 Local control

Local control rates at 1 year were 95.2% for renal cell cancer (14); for 76% for cholangiocarcinoma (11); 87.8% for pancreas cancer (17); 90% for hepatocellular carcinoma (16); and 95.6% for high-risk lung tumor (10) ([Table 1](#)). A small trial in four patients show stereotactic MRgRT (SMART) in ultracentral thorax malignancies resulted in 100% local control at 3 and 6-month (24). SBRT with MRgRT in liver tumor patients (n=23) showed 79.6% local control (26). Ten abdominal tumor patients who underwent SBRT with MRgRT showed no local progression with a median follow up of 7.2 months.(23)

### 4.3.3 Survival

In small observational studies, the overall survival rates at 1 year ranged from 58.9% for pancreas cancer (17); 69% for a mixed primary liver tumor and metastasis lesions (18); 85.6% for cholangiocarcinoma (11); 88.0% for high-risk lung tumor (10); 91.2% for renal



cell cancer (14); to 93.3% for liver metastases in oligometastatic patients (21). No distant recurrences or cancer-related deaths were observed among hormone sensitive stage 0-I breast cancer who received single-fraction at a median of 25 months post high-gradient partial-breast irradiation (SFHGPI) with MRgRT (27). SBRT with MRgRT in liver tumor patients showed 50.7% overall survival at 2-year (26). A study of MRgRT on a low field magnet comparing high dose (biologically effective dose [BED10 ] >70) vs. standard dose (BED10 ≤70) in inoperable pancreatic cancer patients (19) shows 2-year overall survival of 49% vs 30% (P=0.03) and freedom from distant failure 77% vs 57% (P= 0.15) ([Table 1](#)).

The SMART trial in 10 ovarian cancer patients yielded a median Kaplan-Meier estimated systemic-therapy-free survival of 11.5 month following radiation completion (25). The biggest trial in prostate cancer patients showed that the biochemical relapse-free survival (bRFS) or biochemical no evidence of disease (bNED) at 1-year was 98% and at 2-year was 96.7% (29).

#### 4.3.4 Indirect comparisons of MRgRT versus other modalities

To evaluate the effectiveness of MRgRT compared to other modalities, we looked at a systematic review and meta-analysis of 6,116 localized prostate cancer patients who underwent SBRT with modalities other than MRI-Linac (a mixed of standard linac and CyberKnife). Of 38 prospective studies, 92% included low-risk, 78% included intermediate-risk, and 38% included high-risk patients. The median of follow up time was 39 months (range, 12-115 months). The biochemical relapse-free survival rate at 5-year was 95.3% (95%CI 91.3%-97.5%). The estimated rate for late ≥3 genitourinary toxicity was 2.0% (95% CI 1.4%-2.8%) and 1.1% (95% CI 0.6%-2.0%) for gastrointestinal toxicity. The urinary and bowel domain scores on the Expanded Prostate Cancer Index returned to baseline 2 years post-SBRT (30).

These results compare well with the largest trial of MRgRT in prostate cancer patients (n=101) which reported no early or 1-year grade 3 genitourinary or gastrointestinal toxicity and a biochemical relapse-free survival at 1-year of 98% (29).

#### 4.3.5 Summary of effectiveness results

- All but one of the studies we identified on the clinical effectiveness and safety of MRgRT were uncontrolled. The small (n=19) controlled study showed a reduction in toxicity rates for MRgRT vs CTgRT, but with a high degree of uncertainty.

- The largest single-arm trial of MRgRT in prostate cancer treatment (n=101) showed a high biochemical relapse-free survival rate (98%), no grade  $\geq 3$  toxicities, and good patient-reported outcomes at 1-year follow up, which compare well with rates reported from a large review of other modalities in prostate cancer patients.
- Given that the use of MRI and linear accelerator (linac) devices are well-established in clinical practice, we could hypothesize that a device combining these 2 modalities (MRI-Linac) would not result in worse outcomes than the current standard of practice i.e. CTgRT. Nonetheless, long-term controlled studies are needed to confirm this hypothesis.

## 4.4 Patient Tolerance

### 4.4.1 Cosmesis and patient tolerance

Three observational studies by Kluter (31), Sayan (32), and Tetar (33), which included between 43 and 89 patients with various types of cancers, showed that MRgRT was overall well-tolerated ([Table 2](#)). Patients appreciated their active role in respiratory gating during the treatment. Coldness, paraesthesia, anxiety, and disturbing noise sensations were most reported and should be considered for future improvement. Patients and physicians reported good cosmesis post MRgRT in low risk breast cancer patients (27).

## 4.5 Economic Evaluations

We identified four studies that estimated the cost of using MRgRT. Three studies (26, 34, 35) used high-magnetic field and one (36) used low magnetic field MRI-linac. Two studies conducted a time-driven activity-based costing (TDABC) analysis to compare the cost of treatment on linear accelerators between CTgRT and MRgRT in treating localized unresectable hepatocellular carcinoma (34) and prostate cancers (35) in the US. Assumptions between the two modalities are summarized in the [Table A-1](#) of the Appendix.

In the TDABC analysis in prostate cancer, Schumacher et al. (35) estimated the cost for each step of patient care (i.e., consultation, simulation, planning, treatment, on-treatment visits, and follow-up visits) for over 15 years. Subsequently, the sum of the costs was divided by the estimated total number of unique patients treated during the same period and compared between the two modalities to obtain the additional treatment cost with MR-IGRT. Second, they calculated the side effect reduction (%SER)

needed to warrant the added costs of MRgRT over CTgRT. Literature values and cost accounting from University of Miami and H. Lee Moffitt Cancer Center Radiation Oncology Departments were used for cost comparison.

The authors (35) used Markov modeling to determine the savings per patient for every 1% relative reduction in acute and chronic toxicities by MRgRT over 15 years. The added cost of MRgRT was \$1,459 per course of SBRT and \$10,129 per course of conventionally fractionated radiotherapy. A 7% reduction in grade  $\geq 2$  genitourinary and/or gastrointestinal toxicity is required for MRgRT using 5-fractions of SBRT to be cost-effective using a threshold of \$100,000 USD (\$123,730 CAD) per quality adjusted life years (QALY) and a 14% reduction using \$50,000 USD (\$61,865 CAD) per QALY. Very high toxicity reductions (50% for \$100,000 USD per QALY and 94% for \$50,000 USD per QALY) are needed for MRgRT to be cost-effective if using 39 conventional fractions ([Table 3](#)). Side effect reduction thresholds for a range of added costs of MRgRT are illustrated in Appendix [Figure A-1](#).

A Dutch study by Hehakaya and colleagues (36) reported that, if MRI-linac were to cost €6460 (\$9262 CAD) per patient, no reduction of complications over the assumed baseline of 28% for grade  $\geq 2$  urinary and 5% for grade  $\geq 2$  bowel toxicity were needed for 5-fraction high magnetic field MR-Linac to be cost-effective at €80,000 per QALY compared to 20 and 39 fractionation schedules of conventional linac in patients with low and intermediate risk localized prostate cancer. However, in comparison to 5-fraction conventional linac or 5-fraction low-dose-rate brachytherapy (internal radiotherapy), 5-fraction MRI-linac was only cost-effective if complications were reduced by 54% and 66%, respectively. Therefore, the cost per patient would be €62,500 (\$89,681 CAD) if complications were reduced to no complications compared to standard linac. The results were in concordance with the Schumacher study, but they demanded bigger side-effect reductions to be cost effective since they also took into account sexual complications, which have been shown to be an important outcome.

Parikh and colleagues (34) demonstrated that although MRgRT offers real-time image guidance, avoidance of fiducial placement, and ability to use adaptive treatments; it resulted in an increase in the direct clinical cost by \$1,316 (18%) compared to CTgRT and each adaptive treatment would cost \$529 ([Table 3](#)). Nevertheless, increased MRgRT costs could be diminished by omitting CT simulation (\$322 saved) or shortening treatment to 3 fractions (\$1,815 saved). Difference in assumptions between CTgRT and MRgRT are displayed in [Table A-1](#).

Van Dams (26) compared the treatment plans for 5 fractions SBRT using CTgRT vs. MRgRT in liver tumour patients. Simulation with CTgRT costs \$662 more than MRgRT

mostly because of the fiducial marker placement. The actual treatment with MRgRT, however, costs \$1,730 more than CRgRT mostly for space/equipment and personnel due to longer treatment times on the machine [Table 3](#).

## 5. GUIDELINES AND HTAS

### 5.1 Recommendations by the European Society for Therapeutic Radiology and Oncology (ESTRO) Advisory Committee for Radiation Oncology Practice (ACROP)

ESTRO-ACROP (1) recently published their recommendations, which highlight aspects to be considered for the implementation of hybrid MR-linac systems for online adaptive MRgRT (oMRgRT) and did not focus on the current evidence for the clinical efficacy of MRgRT. In general, they recommend that all treatments should be prospectively evaluated according to the principles of evidence-based medicine and health technology assessment for cost-benefit analysis.

#### 5.1.1 Workflow

As shown in [Figure 2](#), MR-linac workflows involve a team of radiation technologists or therapists (RTT), a radio-oncologist, and a medical physicist. Training prior to the implementation of oMRgRT should include: (1) MR safety training for all professionals including the cleaning staff; (2) vendor specific training to learn the online workflow including alternative workflows in case of system errors, and to be able to make the required choices for safe online adaptive treatments; (3) training specific to each role in the workflow. The latter, includes training for RTT and radiation oncologists to use the online contouring tools and algorithms; and training for medical physicists or dosimetrists specialized who will be responsible for the online treatment planning process. Time for (re-)contouring is limited during online adaptive procedures and should not be extended without need because the patient is in treatment position.

#### 5.1.2 Patient selection criteria

Characteristics of the patients and target volume should be considered in patient selection and indications for MR-linac.

##### Patient characteristics:

- All patients should be carefully screened for MRI compatibility

- Treatment time for online adaptive treatments using full online replanning are significantly longer than on conventional Linacs and can last up to 60 minutes. Therefore, the radiation oncologists should carefully evaluate the general clinical status of the patient, especially related to the required degree of compliance and in consideration of the clinical benefits expected from the use of oMRgRT.
- Elderly age and frailty are not direct exclusion criteria, and specific scoring systems can be used as decisional support systems.

#### Target volume characteristics:

- The ideal target volume for oMRgRT involves soft tissues where MR-based imaging is superior to CT-based imaging in identifying the therapy volumes (i.e. lung, pancreatic, liver, head-and-neck, prostate, breast, pelvic lymph nodes cancers or other oligometastases, kidney and adrenal gland metastases).
- Moving targets are managed very well with oMRgRT, especially if they are particularly close to sensitive OAR. The online adaptive approaches with motion management and automated gating systems allow safe high precision radiotherapy with optimal sparing of healthy tissues.

#### **5.1.3 Technical challenges**

- Adaptive MRgRT requires approving of re-contoured target- and OAR contours and adapted plans for each separate fraction, either at the treatment console or remotely. Therefore, rapid availability of radiation oncologists and/or physicists for each treatment fraction is crucial. (1)
- Since most RT centres only have one active treatment unit due to the complexity and costs of MRgRT systems, support agreements with nearby centres equipped with the same technology is recommended to ensure the continuity of the therapy in the event of a machine failure. (1)

#### **5.2 CADTH and INESSS HTAs**

In 2019, both CADTH and INESSS evaluated MRgRT. At the time of their reports, no clinical studies on the effectiveness and safety of the MRI-linac systems were available (3, 4). Based on their cost analyses and lack of clinical efficacy data, INESSS concluded that it was not justified to replace the conventional systems with MRI-linac. They recommended that the use of MRI-linac should be restricted to a research context. “The purchase of these devices should be limited to a small number because the low volume of patients for whom a potential benefit is anticipated at this time; include a commitment on the part of the facilities concerned to participate in generating evidence to help define the role of MRI-linac in radiation oncology’s therapeutic arsenal; and

involve an agreement with the manufacturer to limit the financial risk and share the burden of generating evidence” (4).

### 5.3 MR-Linac Consortium

In 2012, seven international institutes that use the clinical prototypes of Elekta's MR-linac formed the MR-linac consortium, which is composed of radiation oncologists, physicists, technologists, engineers, dosimetrists, radiation therapists, researchers, epidemiologists, radiographers and statisticians. Six disease sites (prostate, central nervous system, head and neck, non-small cell lung cancer, oesophagus and pancreas) were selected as the MRI-linac indications based on expected clinical benefits, such as increased local control, decreased toxicity and a better quality of life (37).

The indications for use (IFU) of the MRIdian Linac system of the ViewRay states that it is intended for radiotherapy for a broad spectrum of lesions, tumours, and conditions anywhere in the body in patients who are compatible for MRI. Nonetheless, the treatment has been focused on oligometastatic, liver, prostate, pancreatic, breast, and lung cancers.

## 6. COST ANALYSES

In the Quebec setting, INESSS compared the projected cost over a 10-year period for radiation therapy using the standard linac vs. the two commercially available MRI-linac devices. They took into consideration the acquisition, construction, maintenance and utilisation costs. Subsequently they calculated the cost/fraction and cost/1-hour treatment in the 1st year ([Table A-2](#)) (4).

Their probabilistic analysis indicated that, over a 10-year horizon, there is an 80% probability that the incremental cost of an MRI-linac device compared to a conventional linac would vary between \$11.7M and \$20.1M CAD for the Elekta Unity system and from \$12.7M to \$18.4M CAD for the MRIdian system. Given the high cost and lack of clinical efficacy data at the time of the report in 2019, they concluded that it was not justified to replace the conventional systems with MRI-linac.

The acquisition cost for the Elekta Unity system has since decreased \$11M to \$8M CAD. Moreover, there is an opportunity to reduce service costs with MRgRT due to its increased precision and subsequent fewer treatment sessions.

## 7. MRGRT AT THE MUHC AND ELSEWHERE

### 7.1 MRgRT in Quebec

MRI-Linac has not been used at the MUHC nor at other centers in Quebec. The use of MRI-Linac is not expected to generate cost savings, nor would it impact the budget of other departments. However, it is unknown if it would generate cost expenditures nor increase hospital efficiency (costs avoided). Currently the MUHC has 7 units of Linac, which are due to be replaced in 2024. There is a potential source of external funding from the MUHC Foundation for acquiring MRI-Linac. MUHC radiation oncology already operates a 3T MRI system autonomously. Moreover, the MUHC has the necessary radiotherapy team to adopt the MRI-Linac (i.e. radio-oncologists, physicist, and radio-therapists) with adequate training.

The adoption of MRI-Linac is believed to increase the potential for cross collaboration between departments and institutions locally and internationally. It will also increase the attractiveness of the MUHC to patients, hospital professionals and researchers. There is no particular ethical or legal consideration to be aware of.

Based on the MSSS data for 2016/2017 until 2020/2021 fiscal years, the MUHC has the one of lowest average number of fractions per patient relative to other centres ([Figure 3](#)). According to Dr. Hijal, this could be explained by the use of SBRT and hypofractionation at the MUHC. Hence, acquisition of an MRI-Linac may further reduce this average, but not as much as for other centres. Lower number of fractions per patient is beneficial for the patients as long as toxicity is not increased.

The Centre Hospitalier de l'Université de Québec and the Centre Hospitalier de l'Université de Montréal (CHUM) appear to have moved exclusively towards IGRT over 2D/3D RT over the years ([Figure 4](#)). The MUHC is aiming to do the same because it is more conformal and reduces further dose to adjacent organs. In terms of patient volume, the number of patients treated per linac unit at the MUHC is comparable to if not higher than other centres ([Figure 5](#)).

### 7.2 MRgRT in other Canadian and US centres

We interviewed Gino Fallone, PhD, who created Alberta Linac-MR P3 system; Nawaid Usmani, MD, the principal investigator of the Northern LIGHTs – 1 clinical trial; Stephen Rosenberg, MD, Director of MRI Guided Radiation Therapy, Dept. of Radiation Oncology, Moffitt Cancer Center; Raymond Mak, MD from Brigham and Women's Hospital, Dana Farber Cancer Institute; and Dr. Brian Keller a radiation physicist at Sunnybrook Hospital,



Odette Cancer Centre Toronto. We also attended presentations by ViewRay and Elekta researchers.

Our consultants agreed that MRgRT creates opportunities to treat people who otherwise would be difficult to treat with the standard radiation technology. In particular, MRgRT is particularly useful to:

- Treat prostate and liver tumors, which are difficult to visualize with CTgRT;
- Treat pancreatic tumours because of the need to reduce irradiation of structures around the pancreas;
- Reduce the need for fiducial markers (implanted with needle by interventional radiologists) before treatment with CTgRT. MRI can improve imaging precision and can avoid this invasive technique;
- Enhance visualization of the tumor and healthy tissue around them, and thus enable greater precision to deliver high dose radiation.

MRgRT can also improve patient convenience and safety by reducing the overall number of treatments. For example, prostate cancer patients used to be treated with 44 fractions over 9 weeks while liver cancer patients used to have 6 weeks of treatment. Since MRI-Linac can deliver more precise radiation, the number of sessions can be safely reduced to five sessions (over a period of 1 – 2 weeks). The overall patient experience has been positive.

The consultants agreed that the future of MRI-Linac is promising as it enables them to treat with better precision, and to treat tumors that currently cannot be treated. While they hope it will also lead to improved local control and overall survival, those data are not yet available.

The consultants emphasized that all the relevant MRI safety training must be in place, in addition to the usual radiation safety training. The centre needs to establish safety protocols and the relevant MRI zones. In addition, the fact that the radiation beam rotates beneath the floor needs to be considered in radiation safety calculations. Consideration must be given to adjacent linear accelerators during installation of the MRI-linac machine, because stray magnetic fields can affect the bending magnet specifications of adjacent linacs.

Our physician consultant does not foresee any ethical issues, but selection of patients might be an issue when the machine is limited in number.



## 8. DISCUSSION

### 8.1 Summary of the efficacy/safety results and concerns with the evidence

MRgRT offers real-time image guidance with better soft tissue visibility, avoidance of fiducial placement, and ability to use adaptive treatments. It creates opportunities to treat people who otherwise would be difficult to treat with the standard radiation technology. The better visualization with MRI-Linac allows for precise delivery of high dose radiation while preserving the surrounding organs. The use of MR-guided SBRT, which would reduce the number of treatments, would be an improvement over CT-guided SBRT due to the ability to deliver better targeted radiotherapy.

Recent studies of MRgRT in various disease sites reported none or low grade 3 toxicities, and most importantly, none reported grade  $\geq 4$  toxicity. High percentages of local control were reported by these studies. However, most of them are small, single arm, and have short follow up time. The only study that compared MRgRT vs. CTgRT was done in 18 patients (8).

In an indirect comparison of MRgRT relative to other modalities in prostate cancer patients, the reported toxicity and survival rates for MRgRT compared well with that of other modalities. The largest single-arm trial of MRgRT in prostate cancer treatment (n=101) showed a biochemical relapse-free survival rate, toxicity, and patient-reported outcomes at 1-year follow up that were comparable to results from a systematic review and meta-analysis of prospective studies evaluating SBRT with other modalities in more than 6000 patients. Moreover, this study showed higher dose of SBRT with other modalities was associated with better biochemical control, but on the other hand related to higher late grade  $\geq 3$  GU toxicity (30). Use of MRI-Linac allows for better visualization of the tumour and healthy tissue around them, and thus greater precision to deliver high dose radiation.

Side effect reduction analysis by Schumacher and colleagues (35) demonstrated that a small toxicity reduction by using MRgRT compared to CTgRT is required for 5-fractions of SBRT to be cost-effective (7-14% using a threshold of \$100,000 to \$50,000 per QALY, respectively). A study by Boldrini and colleagues (8) suggested that this reduction rate is feasible: they found 11-22% reduction of acute grade  $\leq 2$  gastrointestinal and genitourinary toxicities with 5-fraction SBRT via MRgRT than CTgRT. Nonetheless, the differences were not statistically significant due to small sample size.

## 8.2 Applicability of MRI-Linac at the MUHC

A cost-analysis study (34) showed that MRgRT would cost 18% more than CTgRT in upfront costs, but there are cost mitigating factors such as eliminating CT simulation cost and reducing the number of fractionation. Currently, the MUHC has the one of lowest average number of fractions per patient relative to other centres by implementing CT-guided SBRT and hypofractionation. The acquisition of an MRI-Linac can further reduce number of fractions for all abdominal/pelvic cases. For gynecologic cases, the number of fractions could be reduced by 15% (from 8 to 7 fractions). The majority of 2D/3D cases are breast or emergency cases that require immediate treatment. Breast cases are moving targets so patients eligible for ablation therapy (like SBRT for breast) would benefit MRI-linac.

A recent study in the UK modelled MRI-linac demand in the country. For the simulation, they used the initial clinical indications recommended by the MRI-linac consortium (i.e., prostate, central nervous system, head and neck, non-small cell lung cancer, oesophagus and pancreas) which covers 23 types of cancers, and all would be treated with the same numbers of conventional fractions. They found that MR-linac could cover 16% of the country's fraction burden (38). Currently the MUHC has 7 conventional CTgRT linear accelerators, which are due to be replaced in 2024. Based on the UK simulation, acquisition of one MRI-linac device for the MUHC is justified.

Another critical aspect is the treatment time. As acknowledged by the users, the challenge with MRI-Linac is to keep the treatment time as short as possible since registration and contouring take a lot of time. Currently at the MUHC one fraction of SBRT with standard linac takes 45 minutes, which is a good representation of how long an MRgRT treatment with MRI-linac takes. Moreover, a reduction in interventional techniques for placements of fiducial markers is important for reducing complexity of patient care due to coordination between departments, reducing additional visits, and reducing the risk of infection following invasive techniques. Fewer treatments would improve patient convenience due to fewer visits to the hospital, but also important for the hospital as this adds capacity to treat other patients.

When it comes to comparison between the available commercial delivery systems, Crockett and colleagues (2) highlighted some technical issues. Elekta Unity has a high magnetic field, which offers high quality images. On the other hand, high magnetic field may cause bigger electron return effect (ERE). With the effect of the magnetic field (Lorentz force) on secondary electrons, the higher the magnetic field, the higher the accumulation of secondary electrons at air-tissue interfaces, which in turn can cause increased doses. Although ERE can be managed with the Monaco plan optimisation,

MRIdian system has the advantage of a lesser amount of ERE because it has a low magnetic field strength. (2) (39) The second technical issue relates to the effects of cardiac and respiratory motion. “The use of breath-hold imaging, respiratory gating, and 4D MRI are additional functions that would be beneficial in MRgRT for thoracic tumors. While both Unity and MRIdian can monitor target movement (2-dimensionally) during treatment delivery, only the MRIdian can currently utilize real-time tumor imaging to modulate beam-on time during respiration. On the other hand, 4D MRI is not currently possible on either system and this could create a challenge for multi-target treatment.” (2)

## 9. CONCLUSIONS

- The current standard of care for radiotherapy is CT-guided SBRT. SBRT delivered in 5 fractions, a modality of hypofractionation where a patient receives fewer treatments but a higher radiation dose at each treatment, allows for significantly reducing treatment duration compared with conventional fractionation, and thus treating a greater volume of patients in a much shorter period.
- Both MRI and linear accelerators are modalities that are part of standard practice, and the combination of these two modalities offers considerable advantages including (1) better volumetric soft tissue imaging of tumours, other target volumes, and organs at risk prior and during treatment, which improves delineation of treatment margins and avoids the placement of fiducial markers, (2) gating system (i.e., movement-tracking of the tumour and organs at risk and hence, radiation is only delivered when the tumour is in the treatment field), (3) adaptive planning by real-time imaging to re-plan treatment while the patient is on the table.
- Uncontrolled studies of MRgRT have shown it to be generally safe and well tolerated by patients, with good short-term local control and overall survival. The largest single-arm trial of MRgRT in prostate cancer treatment showed a high biochemical relapse-free survival rate (98%), no grade  $\geq 3$  toxicities, and good patient-reported outcomes at 1-year follow up. These findings were comparable to a systematic review and meta-analysis of prospective studies evaluating other radiotherapy modalities. However, data from controlled studies are not yet available that show long-term reductions in toxicity and improvements in survival relative to CTgRT. Nonetheless, downstream outcomes are not expected to be worse than those with CTgRT.

- Uncertainty about the cost impact remains due to uncertainty surrounding acquisition and operational costs and costs associated with potential reductions in toxicity.

## 10. RECOMMENDATIONS

- The TAU Policy Committee, comprised of stakeholders from across the McGill University Health Centre, reviewed the evidence and issued the following recommendation: [Approved for evaluation](#)
- This recommendation was reached based on the following:
  - MRgRT offers advantages over CTgRT including real-time image guidance with better soft tissue contrast, avoidance of fiducial placement, and ability to perform adaptive treatments;
  - More precise delivery of high-dose radiotherapy in fewer treatments sessions would increase patient convenience and increase the hospital's capacity to treat other patients;
  - Given the high acquisition and operating costs, acquisition of one MRI-Linac device is conditional on approval from the Ministère de la Santé et des Services Sociaux.
- Upon acquisition, it is necessary that data be systematically collected, including data on patient selection criteria and downstream clinical outcomes;
- This recommendation should be reviewed in 2 years when new evidence from the clinical trials becomes available.

## FIGURES

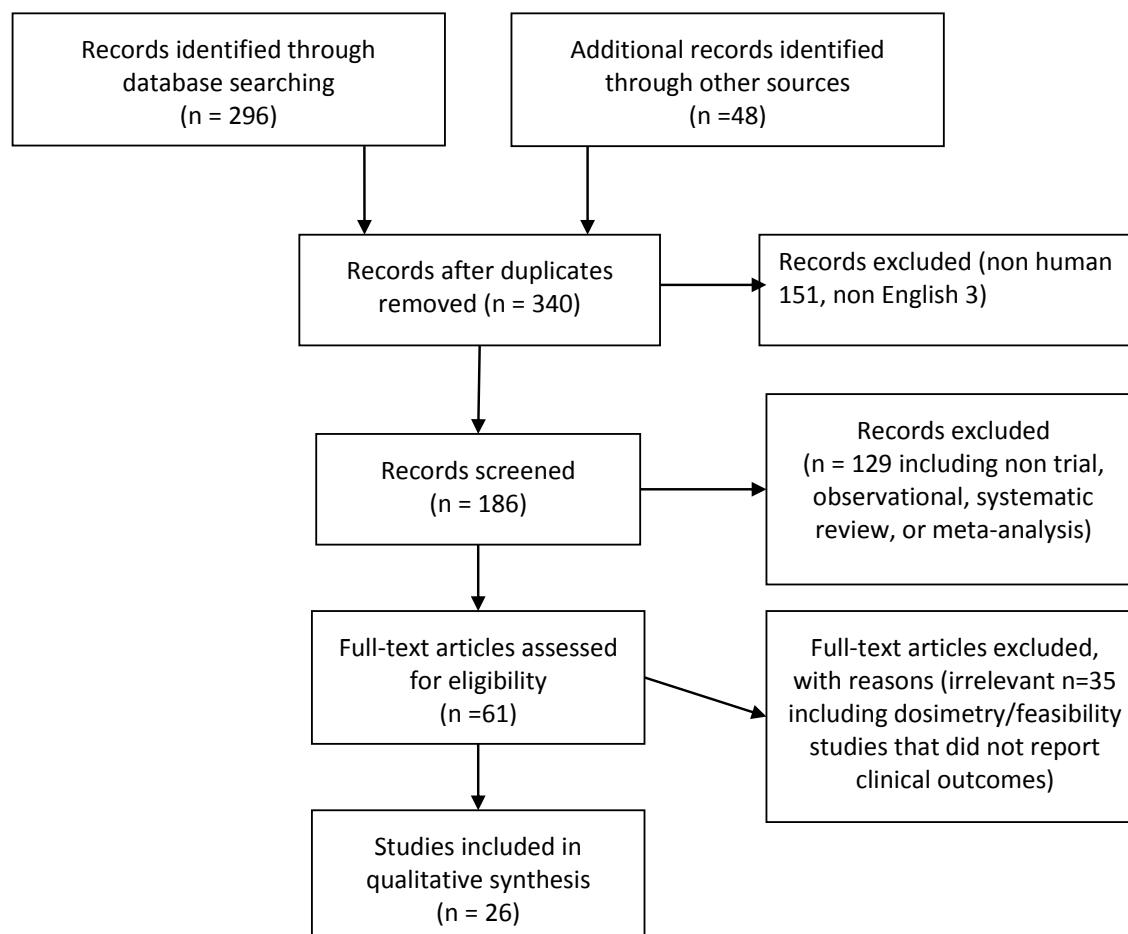


Figure 1: Flowchart of the literature search

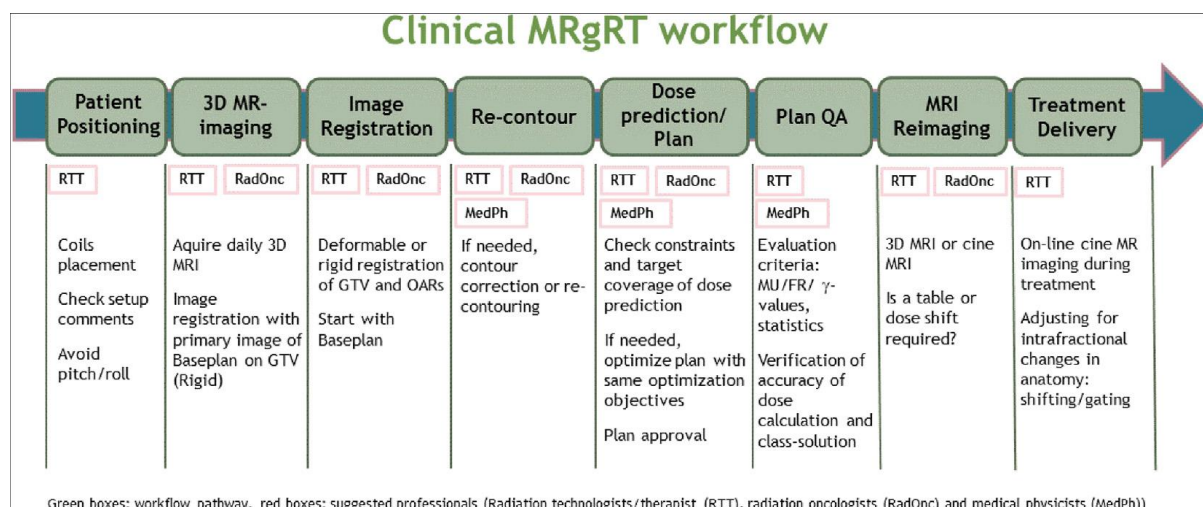


Figure 2: MRgRT workflow recommended by ESTRO-ACROP (1)

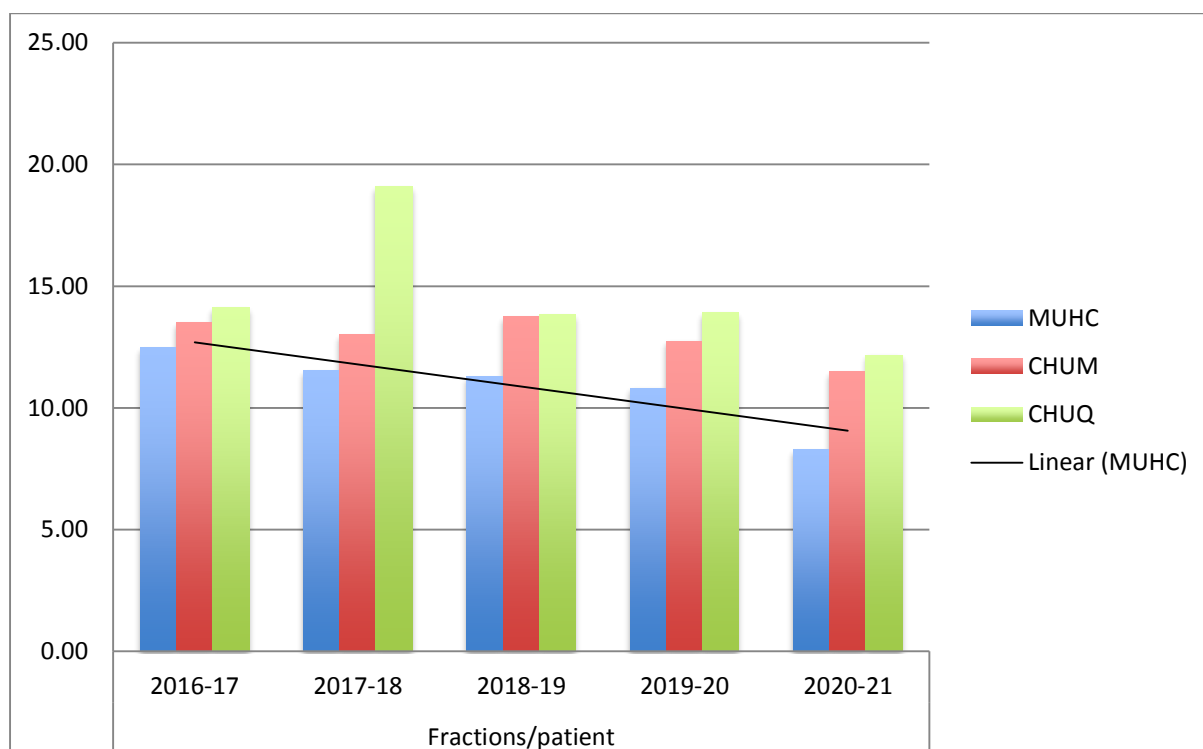
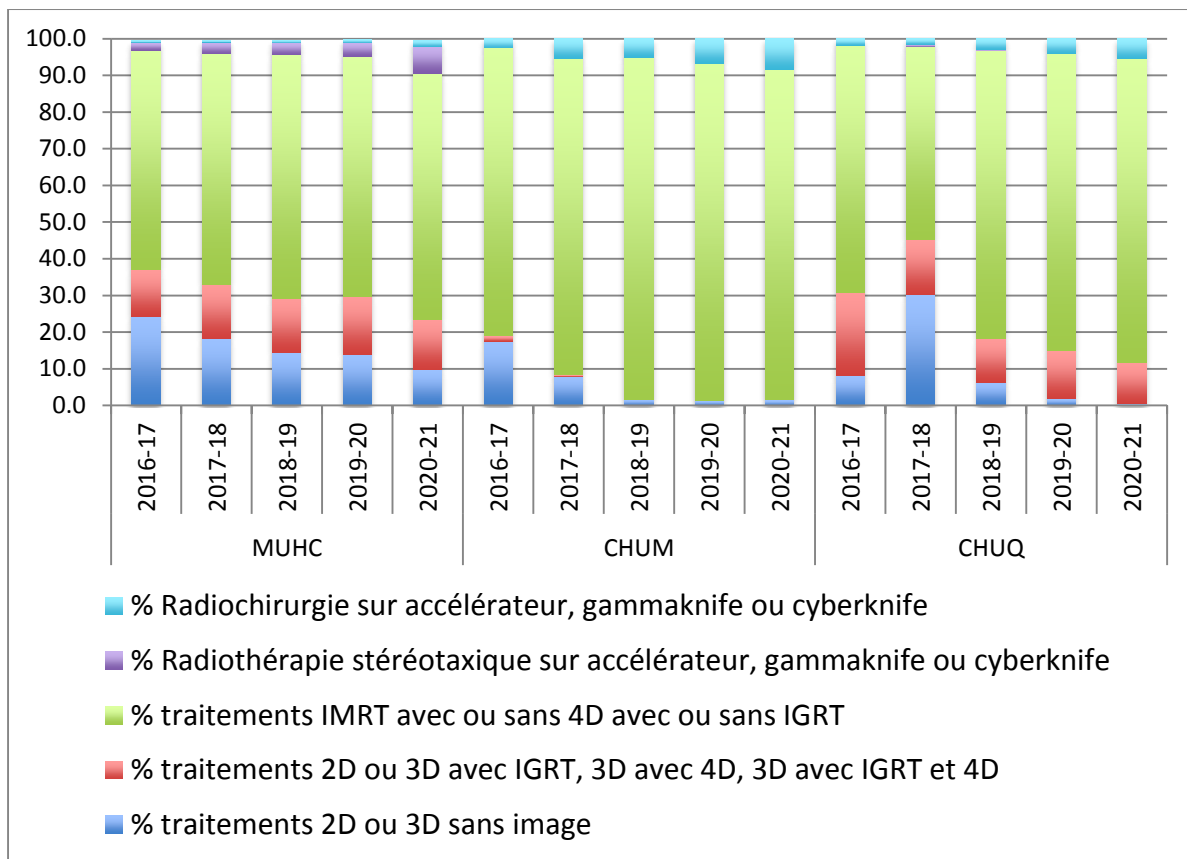
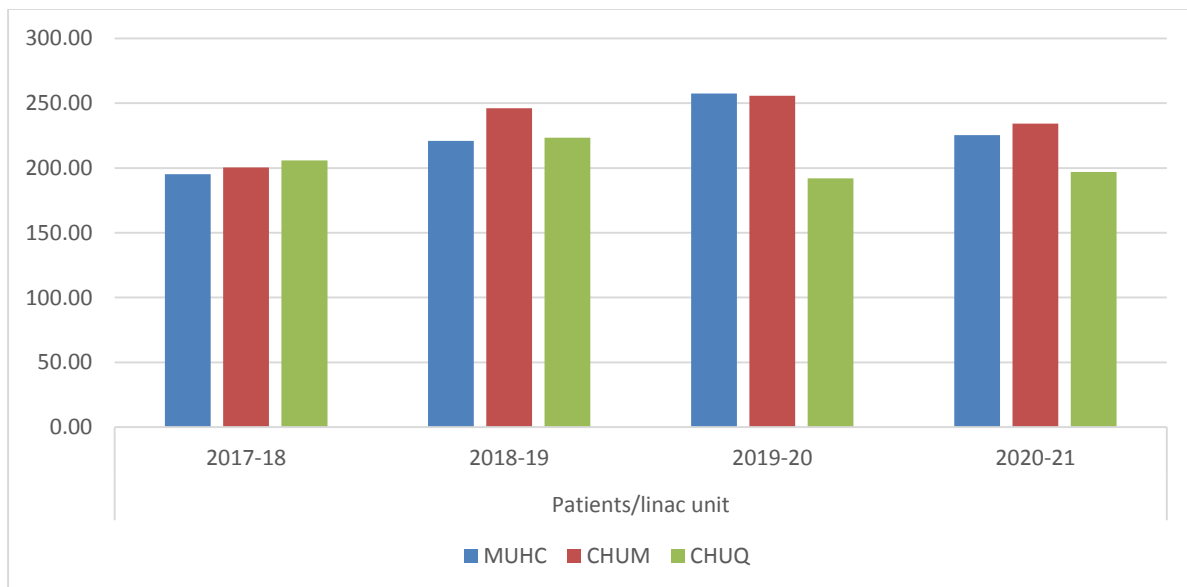


Figure 3. The average number of fractions per patient per fiscal year



**Figure 4. Proportion of fractions administered through 2D/3D, SBRT or IMRT per fiscal year**



**Figure 5. Average number of patients treated per linac unit per fiscal year**

## TABLES

**Table 1. Observational Studies and trials assessing the clinical outcomes of MRI-linac treatment**

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
Alongi	2020	Observational, Prospective	Localized prostate cancers patients (n=25)	SBRT consisted of a 35 Gy schedule delivered in 5 fractions within 2 weeks.				No G <sub>≥</sub> 3 toxicity. 12% reported acute G2 GU toxicity, while only one patient reported mild rectal pain.	No relevant deteriorations were reported in PROMs.
Finazzi	2020	Observational, Prospective	Primary lung cancer (n=29) or lung metastases (n=21) patients.	All but 1 patient completed the planned SMART schedule. BED ≥100 Gy with daily plan adaptation.	Median 21.7 months (95% confidence interval, 19.9-28.1).		1-year local control, overall, and disease-free survival rates were 95.6%, 88.0%, and 63.6%.	G2 and G3 toxicities were 30% and 8%, respectively. No G4 or G5 toxicity.	



Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
Hall	2020	Observational, Prospective	Abdominal tumours (n=10). Tumour types included liver metastatic lesions from melanoma and sarcoma, primary liver hepatocellular carcinoma (HCC), pancreatic metastatic lesions from renal cell carcinoma (RCC), and recurrent pancreatic cancer.	Dose ranged from 30 Gy in 6 fractions and 60 Gy in 3 fractions	Median approximately 7.2 months		No local recurrences or progression.	Acute G2 skin toxicities: 20%. No acute G $\geq$ 3 during the treatment course. Late G3 toxicity: 10%.	
Luterstein	2020	Observational, Prospective	Unresectable locally advanced cholangiocarcinoma (n=17): 12 had extrahepatic cholangiocarcinoma and 5 had intrahepatic tumours.	MRgRT-based SABR was administered at a median dose of 40 Gy/5 fractions.	2 years		Local control and overall survival rates were 76% and 85.6% at 1-year; and 46.1% and 73.3% at 2-year.	Acute G1 toxicity 70.5%; no G2 toxicity.	

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
Mazzola	2021	Observational, Prospective	Castration sensitive oligorecurrent prostate cancer patients (n=20)	SBRT schedule consisted of 35 Gy delivered in 5 fractions.				No acute G $\geq$ 2 toxicity.	Radiotherapy treatment was safe and well tolerated according to the PROMs.
Mazzola	2020	Observational, Prospective	Localized prostate cancer or abdominal-pelvic oligometastases (n=40)	SBRT schedule consisted of 35 Gy delivered in 5 fractions.		No difference between the pre- and post-SBRT QoL in all patients, except for the fatigue item that declined after SBRT		No G $\geq$ 3 GI toxicity.	
Sandoval	2021	Observational, Prospective	Prostate cancer (n=35): favourable intermediate risk (43%), unfavourable intermediate risk	Each patient received 36.25 Gy/5 fractions over 2 weeks with urethral sparing	Median 11.97 months (range 4.37-19.80).			No G $\geq$ 3 GI toxicity.	Statistically significant decreased PSA between pre-treatment and

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
			(54%), and only one had low-risk prostate cancer.	to a maximal dose of 35 Gy.					at first follow-up ( $p < 0.005$ ).
Tetar	2020	Observational, Prospective	Renal cell cancer patients (n=36)	MRgRT in 40 Gy/5 fractions. All patients completed MRgRT with an average fraction duration of 45 min.	1 year		1-year local control and overall survival rates were 95.2% and 91.2%.	No G3 toxicity.	
Ugurluer	2021	Observational, Prospective	Prostate cancer patients (n=50). The median age was 73.5 years (range 50-84 years)	SBRT consisted of 36.25 Gy in 5 fractions with a 7.25 Gy fraction size.	Median 10 months (range 3-29 months).			Acute GU toxicity: G1 28% and G2 36%. Acute GI toxicity: G1 6%; no G2 GI toxicity. Late G1 GU toxicity 24%; G2 GU toxicity 2%; G2 GI toxicity	Due to the short follow-up, PSA nadir has not been reached yet in our cohort.

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
								6%.	
de Mol	2021	Observational, Prospective (international registry)	Patients participated in the MOMENTUM Study (n= 702). The most frequent indications were prostate (40%), oligometastatic lymph node (17%), brain (12%), and rectal (10%) cancers		3 months			Of 415 complete data on acute toxicity, acute G3 toxicity 4%. No G4 or G5 toxicity.	
Boldrini	2020	Observational, Retrospective	Locally advanced cervical cancer undergoing neoadjuvant chemoradiotherapy (CRT) on MRgRT (n=9) vs. standard linac (n=9)	Total prescribed dose 50.6 Gy (2.3 Gy/fraction) with MRgRT Tri-60-Co hybrid unit (n=9)	Median 25 months			Acute G1-G2 GI toxicities: 33.3% vs. 55.5% of MRgRT vs. linac; acute G1-G2 GU toxicities in 22.2% and 33.3%,	No differences were observed in pathologic response between the 2 groups.

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
								respectively. No G3 toxicity except neutropenia in 2 patients.	
Boldrini	2021	Observational, Retrospective	Patients with hepatocellular carcinoma (n=10)	A total BED > 100 Gy/5 consecutive fractions	Median 6.5 months (range 1-25) after SBRT.		Local control 90% at the time of analysis	Acute G2 toxicity 20%.	
Chuong	2021	Observational, Retrospective	Pancreatic cancer patients (n=35). Most had locally advanced disease (80%) and received induction chemotherapy (91.4%) for a median 3.9 months before stereotactic body radiation therapy	SMART with a median total dose of 50 Gy/5 fractions (BED (10) 100 Gy (10)). Elective nodal irradiation was delivered to 20 (57.1%) patients. No patient had fiducial markers placed	Median 10.3 months		1-year local control, distant metastasis-free survival, progression-free survival, cause-specific survival, and overall survival were 87.8%, 63.1%, 52.4%, 77.6%,	G3 toxicities: acute 2.9% and late 2.9%.	

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
							and 58.9%.		
Rosenberg	2019	Observational, Retrospective	Patients with primary liver tumours or metastatic lesions (n=26): 6 hepatocellular carcinomas, 2 cholangiocarcinomas, and 18 metastatic liver lesions (44% colorectal metastasis)	The median dose delivered was 50 Gy at 10 Gy/fraction.	Median 21.2 months.		The 1-year and 2-year overall survival were 69% and 60%. Freedom from local progression for patients with hepatocellular carcinomas, colorectal metastasis, and all other lesions were 100%, 75%, and 83%, respectively.	No G <sub>≥4</sub> GI toxicity.	

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
Rudra	2019	Observational, Retrospective	Inoperable pancreatic cancer (n=44)	Conventional fractionation, hypofractionation, and SBRT. High-dose (BED10 >70) (n = 24, 55%) vs. standard dose (BED10 ≤70 (n = 20, 45%)	Median 17 months		High vs. standard dose: 2-year overall survival 49% vs 30% (P=0.03); freedom from distant failure 77% vs 57% (P 0.15)	G≥3 GI toxicity 12.5% in the standard-dose group and none in the high-dose group.	
Sim	2020	Observational, Retrospective	Patients with cardiac metastases (4 intracardiac and 1 pericardial)	MRgSBRT; median PTV prescribed dose 40 Gy (range 40-50 Gy) and delivered in five fractions on non-consecutive days.	Median 4.7 months (range 0.9-12.3).		Two patients exhibited stable disease, two had a partial response and one exhibited a complete response.	No acute adverse events. One patient without prior cardiac disease developed atrial fibrillation 6 months after treatment.	All symptomatic patients experienced some relief.

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
								Two patients died of causes unrelated to cardiac MRgSBRT.	
Ugurluer	2021	Observational, Retrospective	Patients with liver metastasis (n=24 lesions)	SMART; median total dose 50 Gy (range 40-60 Gy); with a median 5 fractions (range 3-8 fractions) and the median fraction dose was 10 Gy (range, 7.5 to 18 Gy).	Median 11.6 months (range 2.2-24.6 months).		1-year overall survival 93.3%. Intrahepatic and extrahepatic progression-free survival was 89.7% and 73.5% at 1 year, respectively	No acute or late G $\geq$ 3 toxicity.	
Henke	2019	Prospective phase 1 trial	Patients with oligometastatic (n = 4) or unresectable primary (n = 1) ultracentral thorax	SMART; initial plans prescribed 50 Gy/5 fractions	Up to 6 months after treatment		Local control was 100% at 3 and 6 months.	No G $\geq$ 3 acute toxicity.	



Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
			malignancies.						
Henke	2021	Prospective phase 1 trial	Patients with recurrent oligometastatic ovarian cancer (n=10).	SMART; initial plans prescribed 35 Gy/5 fractions with dose escalation permitted subject to strict OAR constraints. Daily adaptive planning was used.	Up to 6 months after treatment	QoL improved concomitant to systemic-therapy-free survival	Local control at 3 months was 94%; median progression-free survival was 10.9 months. Median Kaplan-Meier estimated systemic-therapy-free survival following radiation completion was 11.5 month.	A single G $\geq$ 3 acute (within 6 months of SMART) treatment-related toxicity (duodenal ulcer) was observed	

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
van Dams	2021	Prospective phase 1 trial	Patients with liver tumours (n=23)	SBRT to a median dose of 54 Gy (range 11.5-60) in a median of 3 fractions (range 1-5) with a MRI-guided tri-(60)Co. <b>Treatment plan</b> was compared with CTgRT	Median 18.9 months		the 1- and 2-year estimate of local control were 94.7% and 79.6%, respectively. The 2-year estimate of overall survival was 50.7% with a median of 29 months.	No acute G $\geq$ 3 toxicities. There was one late G3/4 toxicity from a single patient whose plan exceeded an unrecognized dose constraint at the time.	
Kennedy	2020	Prospective phase 1/2 Clinical Trial	Patients with low-risk, hormone-sensitive breast cancer (n=50)	Single-fraction, high-gradient partial-breast irradiation (SFHGPBI: 20 Gy to the surgical bed and 5 Gy to the breast tissue within 1 cm of the	Median 25 months	QoL did not decline other than temporarily in the systemic therapy effects and hair loss	No distant recurrences or cancer-related deaths. There was 1 non-invasive in-breast recurrence in	No G3+ toxicity. G1 erythema 34%.	Good-to-excellent pre-treatment cosmesis in 100% per physicians and 98% per patients, and did not

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
				surgical bed simultaneously in 1 fraction using external beam) 2 to 8 weeks after lumpectomy for node-negative, invasive, or in situ breast cancer.		domains, both of which returned to pre-treatment values.	an untreated quadrant 18 months post-SFHGPBI and 1 isolated axillary recurrence 30 months post-SFHGPBI.		change post-SFHGPBI.
Bruynzeel	2019	Prospective phase 2 trial	Patients with clinical stage T1-3bN0M0 prostate cancer (n=101)	MRgRT was delivered in 5 fractions of 7.25 Gy to the target volume using daily plan adaptation with simultaneous relative sparing of the urethra to a dose of 6.5 Gy per fraction	Up to 3 months after treatment			Early G $\geq$ 2 GU toxicity 23.8% and GI toxicity 5.0%. No early G3 GI toxicity. Early G3 GU toxicity was 0% and 5.9% according to CTCAE and RTOG. GU G $\geq$ 2 toxicity peaked to	The low incidence of early GI toxicity was confirmed by patient-reported outcome data.

Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
								19.8% at the end of MRgRT and returned to the baseline score at 3-month follow-up.	
Tetar	2021	Prospective phase 2 trial	Patients with clinical stage T1-3bN0M0 prostate cancer (n=101)	All patients received 36.25 Gy/5 fractions of MRgRT delivered within 2 weeks.	1 year	The biochemical relapse-free survival (biochemical no evidence of disease [bNED]) at 1-year was 98% and at 2-year was 96.7%		No G $\geq$ 3 toxicity.	Only 2.2% of patients reported a relevant impact on daily activities due to bowel problems at 1 yr. Urinary and bowel symptoms peaked in the first 6 week of follow-up and returned to

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Study	Year	Design	Population, disease sites (n)	Treatment	Median follow-up (months)	QoL	Local control, survival	Toxicity	Other outcome parameters
									baseline values at 12 mo.

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BED: biologically effective dose; G: grade; GI: gastrointestinal; GU: genitourinary; MRgSBRT: magnetic resonance imaging-guided stereotactic body radiotherapy; QoL: Quality-of-life; SBRT: stereotactic body radiotherapy; SMART: Stereotactic MRI Guided Online Adaptive Radiotherapy

**Table 2. Observational Studies assessing patient's reported outcomes of MRgRT on a low-field hybrid MRI-linac**

Study	Year	Design	Population, disease sites (n)	Treatment	Methods	Patient's reported outcomes
Klüter	2020	Observational, Prospective	Various sites (n=43), the most common were nodal metastases and liver lesions	SBRT was done in 20 patients (47%). Total applied doses ranged 4-66 Gy, with single doses ranging 2-15 Gy. The mean number of fractions per patient was 9 (range 2–33)	Patients completed an in-house developed PRO-Q after the first fraction, weekly during the treatment, and last fraction of MRgRT.	Overall, patients scored positive or at least tolerable. 65% patients complained mainly concerning coldness, paresthesia, and uncomfortable positioning. All patients satisfied with their active role in breath-hold delivery.
Sayan	2020	Observational, Prospective	Various sites (n=90); the most treated anatomic sites were the abdomen (47%), pelvis (33%) and thorax (20%).	Mean dose 43.34 Gy (range, 24–70 Gy); median number of fractions 5 (range, 3–28). Respiratory gating was utilized in 62% of the patients. Median treatment delivery time 45 min (range 42–64 min).	PRO-Q was administered after the first and last fraction of MRgRT.	MRgRT was well-tolerated. The most common complaints were the coldness (61%), paresthesias (57%), anxiety (45%), and disturbing noise (43%). All patients appreciated their active role during the treatment.
Tetar	2019	Observational, Prospective	Localized prostate cancer (n=140, but only 89 patients completed PRO-Q.	Online adapted plan was used in 97% of fractions. The average duration of an uneventful fraction was 45min.	PRO-Q was administered after the first and last fraction of MRgRT.	MRgRT was generally well tolerated; disturbing noise was the most commonly reported complaint.

MRgRT: magnetic resonance imaging-guided radiotherapy; PRO-Q: patient reported outcome questionnaire; SBRT: stereotactic body radiotherapy

**Table 3: Cost analysis (costs presented in USD)**

	CTgRT	MRgRT
Direct clinical cost for treating localized unresectable hepatocellular carcinoma (34)	\$7,306	\$8,622
• Personnel cost	\$3,752	\$3,603
• Space and equipment cost	\$2,912	\$4,769
• Material cost	\$642	\$250
Total		+\$1,316 (18%)
% side effect reduction (SER) <sup>d</sup> to be cost effective (35)		
• 39 conventional fractions <sup>b</sup>		7% using \$100K per QALY 14% using \$50K per QALY
• 5 SBRT fractions <sup>c</sup>		50% using \$100K per QALY 94% using \$50K per QALY
5 fractions of SBRT in liver tumor treatment (26)		
- Simulation	\$2,090	\$1,428
- Actual treatment	\$2,757	\$4,487

<sup>a</sup> Based on estimation of 20 min treatments for CTgRT and 30 min treatments and 60 min MRI simulations for MRgRT. Both machines were assumed to be operated for 8 h/day, 5 days/week, for 15 years with 10 operational days/year subtracted for holidays and maintenance. Fiducial markers were assumed to be used with CTgRT-based SBRT, but not with conventional fractionation or MRgRT.

<sup>b</sup> CTgRT could perform 24 treatments per day. MRgRT was required to divide operational time between treatments (15.2/day) and simulations (0.4/day)

<sup>c</sup> CTgRT could perform 24 treatments per day and MR-IGRT decreased to 11.4 treatments per day to accommodate more simulations (2.3/day)

<sup>d</sup> %SER =  $\text{Cost of MR IGRT} / \text{Cost of CT IGRT} \times \text{IQQ} \times \text{ACWP} + \text{ICS}$

ACWP, added cost willing to pay (\$ per QALY, analyzed at \$50,000/QALY and \$100,000/QALY thresholds); ICS, incremental cost savings (\$ per 1% side-effect reduction); IQG.

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## APPENDICES

### APPENDIX A: COST ANALYSIS

Table A-1: Difference in Assumptions between CTgRT and MRgRT\* (34)

Assumption	LINAC SBRT	
	CT-Guided	MR-Guided
Machine (manufacturer)	TrueBeam STx (Varian); ExacTrac (BrainLAB)	MRIdian LINAC (ViewRay)
Real-time imaging of soft tissue	No	Yes
Type of simulation required	CT simulation	CT and MR simulation
Technique	VMAT	Fixed-gantry, step-and-shoot IMRT
No. of arcs or beams	2 arcs	10 beams
Fiducials placed	Yes	No
Beam-on time per fraction, without gating, minutes	5	8.16
Annual time spent on machine QA, minutes	8,760	15,660
Construction costs for LINAC vault, \$/sq ft	1,000	1,363
List price of machine, \$	4,750,000	7,800,000
Annual maintenance costs for machine, \$	417,500	550,000
Space required for LINAC vault, sq ft	686	1,134

Abbreviations: CT, computed tomography; CTgRT, computed tomography-guided radiation therapy; IMRT, intensity-modulated radiation therapy; LINAC, linear accelerator; MR, magnetic resonance; MRgRT magnetic resonance-guided radiation therapy; QA, quality assurance; SBRT, stereotactic body radiotherapy; VMAT, volumetric arc therapy.

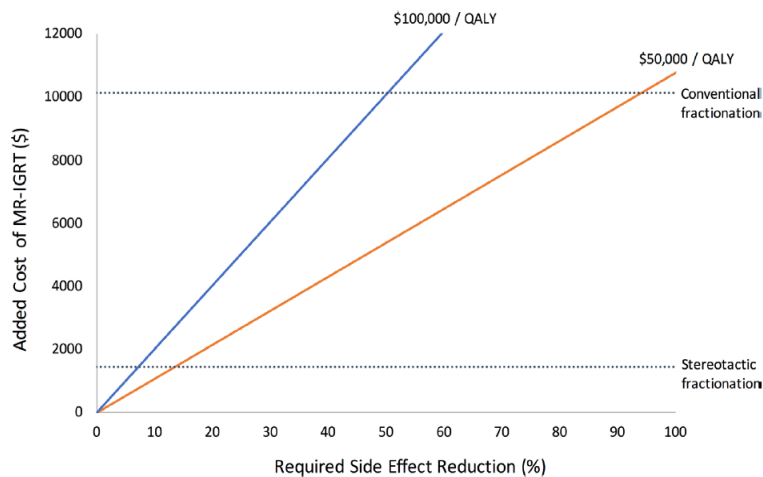
\* List price of the machine 5.88M CAD for CTgRT and 9.65M CAD for MRgRT

Annual maintenance costs for machine 516,580 CAD for CTgRT and 680,525 CAD for MRgRT

Table A-2: Projected cost for standard linac vs. MRI-linac (4)

Cost (in CAD dollars)	Linac	Unity, Elekta	MRIdian Linac, ViewRay
<b>Projected cost over 10-year period</b>			
Acquisition	2,850,000	11,000,000	14,000,000
Constructions	336,000	3,023,775	1,344,915
Maintenance	1,778,786	6,865,489	5,731,396
Utilisation	5,441,574	5,409,797	5,409,797
Total cost	10,406,360	26,299,061	26,486,108
<b>Estimated annual cost</b>			
Acquisition	365,305	1,409,951	1,794,482
Construction	43,068	387,579	172,388
Maintenance	114,000 to 380,000	660,000 to 1.1M	735,000
<b>Estimated cost in the first year</b>			
Cost/fraction	249	1,470	1,481
Cost/1 hour treatment	499	1,260	1,269

Figure 2. Side-effect reduction thresholds for a range of added costs of MR-IGRT. The two solid cost/QALY lines demonstrate the direct relationships between added cost of MR-IGRT and side-effect reduction needed to be cost-effective. As added costs of MR-IGRT increases, more side-effect reduction is needed to justify its use. The dotted lines represent the added costs of the two fractionation schedules determined by the cost assessment. SBRT's added cost is \$1,459 per patient and conventionally fractionated radiotherapy added cost is \$10,129 per patient. The points where the dotted lines intersect the solid lines represent the minimum side-effect reductions MR-IGRT need to achieve to be cost-effective. For SBRT, the thresholds are 14% using \$50,000/QALY and 7% using \$100,000/QALY. For conventional fractionation, the thresholds are 94% using \$50,000/QALY and 50% using \$100,000/QALY. MR-IGRT, MRI-guided radiotherapy; QALY, quality adjusted life year; SBRT, stereotactic body radiotherapy.



**Figure A-1: Side-effect reduction thresholds according to the added cost of MRgRT**