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

Hydrogel Spacer to reduce rectal toxicity in prostate cancer radiotherapy: a health technology assessment

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

by

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REPORT REQUESTOR

This report was requested by Dr. Tarek Hijal, Department of Oncology, Head of Radiation Oncology, at the MUHC in May 2017.

TYPES OF RECOMMENDATIONS ISSUED BY THE TAU COMMITTEE

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

DISCLAIMER

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ABSTRACT

- SpaceOAR is an injectable polyethylene-glycol hydrogel intended to decrease the amount of radiation received by the rectum in patients with prostate cancer who are treated with external beam radiotherapy (EBRT).
- The objective of this report is to review the evidence in terms of efficacy (rectal toxicity and quality of life), safety and cost-effectiveness of SpaceOAR; and to undertake a budget impact analysis in case of adoption of this technology at the MUHC.
- We identified one RCT and five non-randomized studies that evaluated the effectiveness of SpaceOAR in reducing amount of radiation to the rectum, rectal toxicity or improving quality of life.
- Whereas there was evidence that SpaceOAR use does result in lower rectal radiation exposure, this did not translate into an important reduction in rectal toxicity.
- 4 studies (1 RCT and 3 observational) evaluated quality of life (QoL) with no major differences found between the SpaceOAR and control groups within the first year of follow-up. However, longer-term follow-up results are inconsistent across studies. Results from the RCT showed at least moderate decline in quality of life in 15% vs. 20% of patients at one year for the SpaceOAR and the control group, respectively. At 36 months, 5% of SpaceOAR vs. 21% of control group patients had at least a moderate decline in QoL.
- The cost of SpaceOAR is $2800 per patient. We found that the overall cost of treating a patient for prostate cancer with or without SpaceOAR was $5,543.08 and $2,712.88, respectively. The budget impact of treating 70 prostate cancer patients with SpaceOAR is estimated to be $198,114.34 annually ($388,015.60 with SpaceOAR and $189,901.26 without Spacer).
- Assuming a reduction of 1.5% in Grade 2 or higher rectal toxicity with the use of SpaceOAR, it would cost $191,230.06 to avoid one additional case of ≥Grade 2 rectal toxicity.

RÉSUMÉ

- L'hydrogel injectable SpaceOAR, à base de polyéthylène glycol, a pour but de diminuer la quantité de radiation irradiant le rectum des patients avec un cancer de la prostate, qui sont traités par radiothérapie externe (RE).
- L'objectif de ce rapport est de revoir les preuves de l'efficacité (toxicité rectale et qualité de vie), de l'innocuité et du coût-efficacité de l'hydrogel SpaceOAR et de même, faire une analyse de l'impact budgétaire de l'adoption possible de cette technologie au CUSM (Centre Universitaire de Santé McGill).
- Nous avons identifié une étude randomisée (RCT) et cinq études non randomisées qui ont évalué l'efficacité de l'hydrogel SpaceOAR pour réduire la quantité de radiation au rectum et la toxicité rectale, ou pour améliorer de la qualité de vie.
- Bien qu'il existe des preuves à l'effet que l'utilisation de l'hydrogel SpaceOAR réduit l'exposition du rectum aux radiations, ceci ne s'est pas traduit par une réduction importante de la toxicité rectale.
- Quatre études (1 étude randomisée et 3 études observationnelles) ont évalué la qualité de vie (QoL) et n'ont trouvé aucune différence majeure entre les groupes SpaceOAR et les groupes contrôles au cours de la première année de suivi. Cependant, les résultats des suivis à long terme sont incohérents parmi les études. Les résultats de l'étude randomisée montrèrent, à tout le moins, une réduction modérée de la qualité de vie chez 15% vs 20% des patients après un an, chez le groupe SpaceOAR et le groupe contrôle, respectivement. Après un suivi de 36 mois, 5% des patients du groupe SpaceOAR vs 21% des patients du groupe contrôle avaient, à tout le moins, une réduction modérée de la qualité de vie.
- Le coût de l'hydrogel SpaceOAR est de 2 800 $ par patient. Nous avons déterminé que le coût total pour traiter un patient avec un cancer de la prostate avec et sans l'hydrogel Space OAR était de 5 543,08 $ et 2 712,88 $, respectivement. L'impact budgétaire pour traiter 70 patients présentant un cancer de la prostate avec l'hydrogel Space OAR est évalué à 198 114,34 $ par année (388 015,60 $ avec l'hydrogel SpaceOAR et

  189 901,26 $ sans l'hydrogel SpaceOAR).
- En supposant une réduction de 1,5% de la toxicité rectale de Grade 2 ou supérieur suite à l'utilisation de l'hydrogel SpaceOAR, il en coûterait 191 230,06 $ pour éviter un cas supplémentaire de toxicité rectale de Grade 2 ou supérieur.

LIST OF ABBREVIATIONS

ADP	Androgen deprivation therapy
CI	Confidence interval
CTCAE	Common Terminology Criteria for Adverse Events, a standardized classification of the adverse events arising from cancer treatment
EBRT	External beam radiotherapy
EPIC	Expanded Prostate Cancer Index Composite
Gy	Gray, unit used to measure the total radiation a patient is exposed to
HTA	Health technology assessment
ICER	Incremental cost effectiveness ratio; In this report ICER is the ratio of the incremental cost associated with the prevention of one additional Grade 2 or more case of rectal toxicity.
IMRT	Intensity modulated radiation therapy
INESSS	Institut National d'Excellence en Santé et en Service Sociaux
MUHC	McGill University Health Centre
NICE	National Institutes for Health and Clinical Excellence
NNT	Number needed to treat, a measure intended to indicate the effectiveness of a treatment. Defined as the number of patients needed to be treated with the intervention to prevent one outcome.
PSA	Prostate Specific Antigen, serum protein associated with prostate cancer
QoL	Quality of life
RD	Risk difference
RCT	Randomized controlled trial
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group criteria, a scoring schema for radiation toxicity
rV	Volume of rectal tissue receiving a particular dose of radiation. E.g. rv70 is the volume of rectum receiving a dose of 70 Gy
SBRT	Stereotactic body radiation therapy
TAU	MUHC Technology Assessment Unit
TNM	Tumor Node Metastasis- Cancer classification
VMAT	Volumetric modulated arc therapy

EXECUTIVE SUMMARY

Background

SpaceOAR is an injectable polyethylene-glycol hydrogel intended to increase the distance between the prostate and rectal wall in patients undergoing radiotherapy for prostate cancer, thus decreasing the amount of radiation received by the rectum. Prostate cancer patients are conventionally treated with external beam radiotherapy (EBRT). Hypofractionated radiotherapy is an alternative technique for delivering the same overall radiation dose as EBRT but in fewer daily treatments; patients thus receive a larger daily dose of radiation (>2 Gy) in comparison with conventional EBRT. While both radiotherapy techniques have similar survival outcomes, there is interest in spacing devices which would allow the use of hypo fractionation or dose escalation to shorten treatment time, while sparing adjacent organs from increased radiation doses and subsequent radiation toxicity.

Objectives

The objectives of this report are to:

- Review the evidence on short and long-term efficacy and effectiveness of SpaceOAR in reducing radiation to the rectum, reducing rectal toxicity and improving quality of life;
- Review the evidence on safety of SpaceOAR;
- Review the evidence on the cost-effectiveness of SpaceOAR;
- Undertake a budget impact analysis in case of adoption of this technology at the MUHC;

Methods

We performed a systematic review to identify randomized or non-randomized controlled studies, meta-analyses and HTA reports evaluating the efficacy, effectiveness, safety or cost-effectiveness of SpaceOAR in reducing rectal toxicity and improving quality of life. We described the MUHC experience with using hypofractionated radiotherapy, and performed a cost and budget impact analysis to evaluate the impact of the integration of SpaceOAR at the MUHC.

Results: Literature review

We identified one randomized controlled trial (RCT) and five non-randomized studies that evaluated SpaceOAR in terms of its effectiveness in reducing the amount of radiation to the rectum, rectal toxicity or improving quality of life.

- Rectal dose-volume (rV): Four studies evaluating the amount of radiation received by the rectum after placement of SpaceOAR found that it does result in lower rectal radiation exposure.

- Rectal toxicity: Two studies (based on one RCT) and two non-randomized studies evaluated acute rectal toxicity (up to 3 months after radiotherapy) and late rectal toxicity (beyond 3 months post-radiotherapy) using the Common Terminology Criteria for Adverse Events (CTCAE), or the modified Radiation Therapy Oncology Group (RTOG) criteria. Following these criteria, toxicity may be classified as Grade 0 (normal) to Grade 5 (severe complications). Grade 2 and above are considered clinically meaningful requiring intervention. None of these studies found important differences between the SpaceOAR and control group for rectal toxicity. The RCT reported acute rectal toxicity of Grade ≥2 in 4.1% vs. 4.2% [risk difference (RD): 0.1%; 95% confidence interval (CI): -5.0% to 8.0%], and late Grade ≥2 rectal toxicity in 0% and 1.4% [RD: 1.4%; 95% CI: -1.3% to 7.6%] of the SpaceOAR and control groups, respectively. Furthermore, no studies reported Grade 4 or 5 toxicity, even among controls.

- Quality of life: Two studies (based on one RCT) and three non-randomized studies assessed patient-reported quality of life (QoL) which was assessed according to the function and bother score of the Expanded Prostate Cancer Index Composite (EPIC). All studies reported no major differences between the SpaceOAR and control groups within the first year of follow-up and long-term results differ considerably across the studies. Results from the RCT showed at least moderate decline in quality of life in 15% vs. 20% (RD: 5%; 95% CI: -5.4% to 16.0%) of patients at one year for the SpaceOAR and the control group, respectively. In the RCT, at 36 months, 5% of SpaceOAR vs. 21% (RD: 16%; 95% CI: 4.9% to 30.0%) of control group patients had at least a moderate decline in QoL. However, these long-term results are hard to interpret due to the high drop-out rate (37% in both groups) and unblinded trial design.

- Safety: One RCT and one non-randomized study reported no procedural complications or adverse events with the use of SpaceOAR. These data taken in

combination with the evidence for rectal toxicity, which showed no important differences between the SpaceOAR and control groups, indicate that the use of SpaceOAR in prostate cancer patients does not result in any additional adverse events.

In summary, although the use of SpaceOAR is effective in reducing the amount of radiation to the rectum, it remains unclear whether such reductions translate into lower rectal toxicity and improved Qol compared with patients not treated with SpaceOAR.

All studies reviewed in this report had serious limitations, in particular with selection and confounding bias.

Experience at the MUHC

SpaceOAR is not yet in use at the MUHC. The MUHC introduced the use of conformal hypofractionated external beam radiotherapy in 2002 to shorten treatment times. Patients with localized prostate cancer with low, moderate and occasionally high risk are treated with hypofractionated doses of 60 Gy in 20 sessions, i.e. 3 Gy radiation dose per session. In two papers describing outcomes in patients treated with this procedure over median follow-up times of 51 months and 80 months, respectively, the authors report that survival outcomes were similar to other radiotherapy modalities. They evaluated gastrointestinal toxicity using the CTCAE, and while they did not report results at specific time-points post-radiotherapy, they state that cumulative incidence of Grade ≥2 GI toxicity at median follow-up times of 51 and 80 months was 18% and 20%, respectively. In comparison, the RCT reported a cumulative incidence of Grade ≥2 rectal toxicity at a median of 37 months of 6%.

Costs

We estimated the additional cost associated with treating 70 prostate cancer patients with SpaceOAR, accounting for device, procedure and complication costs. We found that the cost of treating 70 prostate cancer patients with and without SpaceOAR was $388,015.60 and $189,901.26, respectively, or $5,543.08 and $2,712.88 per patient, respectively. Given the costs associated with this procedure, and assuming a reduction of 1.5% in Grade 2 or higher rectal toxicity with the use of SpaceOAR, the cost of each additional Grade ≥2 toxicity avoided, when compared with no SpaceOAR would be of $191,230.06.

CONCLUSIONS

- SpaceOAR is a device intended to increase the distance between the prostate and rectal wall, and thus decrease the amount of radiation received by the rectum during prostate cancer radiotherapy. While the evidence indicates that the use of SpaceOAR is effective for this purpose, it remains unclear whether the reduction in rectal dose-volume results in reduced rectal toxicity and improved quality of life.

- We identified one RCT and five non-randomized studies, none of which found important differences between the SpaceOAR and control groups for rectal toxicity and long-term quality of life. Furthermore, all of these studies had serious limitations. The estimated risk difference between the SpaceOAR and control group in terms of the risk of Grade 2 or greater toxicity at 3-15 months was 1.5%, implying that it would require treating 68 people in order to avoid one Grade 2 or greater event of rectal toxicity.

- We estimated that the use of SpaceOAR in 70 prostate cancer patients at the MUHC would result in an additional cost of $198,114.34, which is considerable given the equivocal effectiveness outcomes. Assuming a risk reduction of 1.5% in Grade ≥2 rectal toxicity with the use of SpaceOAR, it would cost $191,230.06 to avoid one additional case of Grade 2 or higher rectal toxicity. The data are too unreliable to permit calculations of cost utility metrics such as QALYs.

RECOMMENDATIONS

Given the limited and inconclusive evidence of the clinical benefit of SpaceOAR, and the high costs associated with its use at the MUHC:

- Routine use of SpaceOAR in prostate cancer patients receiving radiotherapy is not-approved. This recommendation is subject to re-evaluation as and when new evidence becomes available.

SOMMAIRE

Contexte

L'hydrogel injectable SpaceOAR, à base de polyéthylène glycol, a pour but d'augmenter l'espace entre la prostate et le mur rectal chez les patients traités par radiothérapie pour un cancer de la prostate, diminuant ainsi la quantité de radiation reçue par le rectum. Les patients présentant un cancer de la prostate sont classiquement traités par radiothérapie externe (RE). La radiothérapie hypofractionnée est une technique alternative pour délivrer la même dose de rayonnement globale que la RE, mais au cours de moins de traitements quotidiens ; les patients reçoivent ainsi une dose quotidienne plus importante de radiation (>2 Gy), par comparaison à la RE conventionnelle. Bien que ces deux techniques de radiothérapie présentent des résultats de survie identiques, il existe un intérêt pour des techniques d'espacement qui permettraient l'utilisation de l'hypofractionnement ou de l'escalade de doses pour raccourcir la durée des traitements, tout en épargnant les organes adjacents d'une augmentation des doses de radiation et d'une toxicité rectale subséquente.

Objectifs

Les objectifs de ce rapport sont les suivants :

- Revoir les preuves de l'efficacité et de l'efficience à court et à long terme de l'hydrogel SpaceOAR pour réduire la radiation au rectum et la toxicité rectale, et pour améliorer la qualité de vie ;
- Revoir les preuves de l'innocuité de l'hydrogel SpaceOAR ;
- Revoir les preuves du coût-efficacité de l'hydrogel SpaceOAR ;
- Réaliser une analyse de l'impact budgétaire advenant l'adoption de cette technologie par le CUSM (Centre Universitaire de Santé McGill).

Méthodologie

Nous avons réalisé une revue systématique pour identifier les études randomisées et non randomisées, les méta-analyses et les rapports d'évaluation des technologies (HTA) évaluant l'efficacité, l'efficience, l'innocuité ou le coût-efficacité de l'hydrogel SpaceOAR pour réduire la toxicité rectale et améliorer la qualité de vie. Nous avons décrit l'expérience du CUSM avec la radiothérapie hypofractionnée et avons réalisé une

analyse des coûts et de l'impact budgétaire pour évaluer l'impact de l'adoption de l'hydrogel SpaceOAR au CUSM.

Résultats : Revue de la littérature

Nous avons identifié une étude randomisée (RCT) et cinq études non randomisées qui évaluaient l'hydrogel SpaceOAR en termes de son efficacité pour réduire la quantité de radiation au rectum, la toxicité rectale ou pour améliorer la qualité de vie.

- Dose-volume rectale (rV) : Quatre études évaluant la quantité de radiation reçue par le rectum après le positionnement de l'hydrogel SpaceOAR montrèrent que l'exposition à la radiation rectale était plus faible.

- Toxicité rectale : Deux études (basées sur l'étude randomisée) et deux études non randomisées évaluèrent la toxicité rectale aigue (jusqu'à 3 mois après la radiothérapie) à partir des critères du "Common Terminology Criteria for Adverse Events" (CTCAE) ou des critères modifiés du "Radiation Therapy Oncology Group" (RTOG). Selon ces critères, la toxicité peut être classifiée selon le Grade 0 (normale) jusqu'au Grade 5 (complications sévères). Les Grades 2 et supérieurs sont considérés comme cliniquement significatifs, requérant une intervention. Aucune de ces études ne trouva de différences importantes concernant la toxicité rectale entre le groupe SpaceOAR et le groupe contrôle. L'étude randomisée rapporta une toxicité rectale aigue de Grade ≥ 2 dans 4.1% vs 4.2% des cas (différence de risque (RD): 0.1% ; 95% intervalle de confiance (CI): -5% à 8.0%), et pour une toxicité rectale tardive de Grade ≥ 2 dans 0% et 1.4% des cas (RD: 1.4% ; 95% CI: -1.3% à 7.6%) pour les groupes SpaceOAR et les groupes contrôles, respectivement. De plus, aucune étude ne rapporta une toxicité de Grade 4 ou 5, même chez les groupes contrôles.

- Qualité de vie : Deux études (basées sur une étude randomisée) et trois études non randomisées ont évalué la qualité de vie rapportée par les patients (QoL), qui fut estimée selon un pointage de fonctionnalité et de conséquences négatives du "Expanded Prostate Cancer Index Composite" (EPIC). Toutes les études n'ont rapporté aucune différence majeure entre les groupes SpaceOAR et les groupes contrôles pendant la première année de suivi, mais les résultats à long terme diffèrent considérablement parmi les études. Les résultats de l'étude randomisée montrèrent, à tout le moins, une diminution modérée de la qualité de vie des patients dans 15% vs 20% des cas (RD: 5% ; 95% CI: -5.4% à 16%) après un an pour les groupes SpaceOAR et les groupes contrôles, respectivement. Dans l'étude randomisée, après 36 mois, 5% des patients du groupe SpaceOAR vs 21% des patients du groupe contrôle (RD: 16% ; 95% CI:

4.9% à 30.0%) avaient, à tout le moins, une diminution modérée de la qualité de vie. Cependant, ces résultats à long terme sont difficiles à interpréter, étant donné le taux d'abandon élevé (37% chez les deux groupes) et le protocole d'essais cliniques non masqués.

- Innocuité : Une étude randomisée et une étude non randomisée n'ont rapporté aucune complication liée aux procédures ni d'effets indésirables lors de l'utilisation de l'hydrogel SpaceOAR. Ces données recueillies lors de toxicité rectale évidente et qui ne montraient aucune différence importante entre les groupes SpaceOAR et les groupes contrôles, soulignent que l'utilisation de l'hydrogel SpaceOAR chez les patients avec un cancer de la prostate n'entraîne aucun effet indésirable additionnel.

En résumé, même si l'utilisation de l'hydrogel SpaceOAR est efficace pour réduire la quantité de radiation au rectum, il n'est pas certain que de tels réductions se traduisent par une toxicité rectale plus faible et une qualité de vie améliorée, par comparaison avec les patients non traités avec l'hydrogel SpaceOAR.

Toutes les études révisées dans ce rapport avaient de sérieuses lacunes, tout particulièrement avec les biais liés à la sélection et à la confusion des données.

Expérience au CUSM

L'hydrogel SpaceOAR n'est pas encore en utilisation au CUSM. Le CUSM a introduit l'utilisation de la radiothérapie externe hypofractionnée en 2002 pour raccourcir les temps de traitement. Les patients avec un cancer prostatique localisé présentant un risque faible, modéré et occasionnellement élevé, sont traités avec des doses hypofractionnées de 60 Gy lors de 20 séances, i.e. une dose de radiation de 3 Gy par séance. Dans deux publications décrivant les résultats chez les patients traités avec cette procédure, avec des suivis de durées médianes de 51 mois et de 80 mois, respectivement, les auteurs mentionnent que les résultats en termes de survie étaient identiques aux autres modalités de radiothérapie. Ils ont évalué la toxicité gastrointestinale à partir du CTCAE et bien qu'ils n'aient pas rapporté les résultats selon un agenda post-radiothérapie précis, ils indiquent que l'incidence cumulative d'une toxicité gastrointestinale de Grade ≥ 2 à des temps de suivi médians de 51 et de 80 mois était de 18% et de 20%, respectivement. Par comparaison, l'étude randomisée montrait une incidence cumulative de la toxicité rectale de Grade ≥ 2 de 6%, à un temps médian de suivi de 37 mois.

Coûts

Nous avons estimé le coût additionnel associé au traitement de 70 patients avec un cancer de la prostate avec l'hydrogel SpaceOAR en tenant compte du matériel, des coûts de la procédure et des complications. Nous avons déterminé que les coûts pour traiter 70 patients atteints d'un cancer de la prostate, avec et sans l'hydrogel SpaceOAR, étaient de 388,015.60 $ et de 189,901.26 $, respectivement, ou 5,543.08 $ et 2,712.88 $, respectivement, par patient. Étant donné les coûts associés à cette procédure et en supposant une diminution de la toxicité de 1.5% de Grade 2 ou supérieur suite à l'utilisation de l'hydrogel SpaceOAR, le coût de chaque toxicité de grade ≥ 2 évitée, par comparaison au traitement sans hydrogel SpaceOAR, serait de 191,230.06 $.

CONCLUSIONS

- L'hydrogel SpaceOAR est une substance ayant pour but d'augmenter l'espace entre la prostate et le mur rectal de façon à diminuer la quantité de radiation que reçoit le rectum lors d'une séance de radiothérapie pour le cancer de la prostate. Bien que les preuves soulignent que l'utilisation de l'hydrogel SpaceOAR est efficace dans ce but, il n'est pas certain que la diminution de la dose-volume rectale se traduise par une toxicité rectale plus faible et une amélioration de la qualité de vie.

- Nous avons identifié une étude randomisée et cinq études non randomisées et aucune étude n'a trouvé de différences importantes entre les groupes SpaceOAR et les groupes contrôles en regard de la toxicité rectale et la qualité de vie à long terme. De plus, toutes ces études avaient de sérieuses lacunes. La différence de risque estimée entre les groupes SpaceOAR et les groupes contrôles en termes de toxicité de risque de Grade 2 ou supérieur, à 3-15 mois, était 1.5%, impliquant qu'il faudrait traiter 68 patients de façon à éviter un cas de toxicité rectale de Grade 2 ou supérieur.

- Nous avons estimé que l'utilisation au CUSM de l'hydrogel SpaceOAR chez 70 patients avec un cancer de la prostate se traduirait par un coût supplémentaire de 198,114.34 $, ce qui est considérable étant donné les résultats équivoques d'efficacité. Si l'on présume une diminution du risque de toxicité rectale de 1.5% de Grade ≥ 2 suite à l'utilisation de l'hydrogel SpaceOAR, il en coûterait 191,230.06 $ pour éviter un cas supplémentaire de toxicité rectale de Grade 2 ou

supérieur. Les données sont trop peu fiables pour permettre le calcul de variables coût-utilité tel que le facteur QALY (Quality-Adjusted Life-Years).

RECOMMANDATIONS

Étant donné les preuves limitées et non-concluantes du bénéfice clinique de l'hydrogel SpaceOAR et des coûts élevés associés à sa mise œuvre au CUSM :

- L'utilisation systématique de l'hydrogel SpaceOAR chez les patients atteints de cancer de la prostate recevant une radiothérapie n'est pas approuvée. Cette recommandation est sujette à une réévaluation au fur et à mesure que de nouvelles preuves deviennent disponibles.

Hydrogel Spacer to reduce rectal toxicity in prostate cancer radiotherapy: a health technology assessment

1. BACKGROUND

Prostate cancer is the most common cancer among Canadian men, accounting for 21% of all male cancers and affecting one in seven men during their lifetime.[1] Treatment options depend on the risk classification assigned by the clinician according to the clinical and pathological results of the tumor node metastasis (TNM) classification, PSA level and Gleason score.

External beam radiation therapy (EBRT) techniques such as intensity modulated radiotherapy (IMRT) or stereotactic body radiation therapy (SBRT) are considered a curative option for patients with localized prostate cancer with low to intermediate risk. Hypofractionated radiotherapy delivers the conventional radiation dose of EBRT in fewer daily treatments. Hence, a larger daily dose of radiation (>2 Gy) is delivered in comparison with conventional EBRT. Hypofractionation or dose-escalation seeks to achieve more accurate targeting of the tumor while simultaneously increasing the dose of radiation.[2-4] However, as the rectum is adjacent to the prostate, it receives a substantial amount of radiation; hence sparing the rectal wall is desired to ensure safer treatment, especially in overall doses above 70.[5-7] SpaceOAR (Augmenix®) is a polyethylene-glycol hydrogel that is injected via a transperineal approach under transrectal ultrasound guidance, with local or general anesthesia, into the Denonvillier's space, resulting in an approximately 10 mm separation of the prostate from the rectum (Figure 1). This separation is believed to permit a higher dose of prostate radiation without necessarily increasing rectal toxicity[8] i.e. rectal complications associated with radiotherapy (including high frequency of rectal urgency, diarrhea, bleeding and pain). SpaceOAR was approved for use in the US in 2015, and in Canada in 2016, based on the results of a single RCT.[4]

The Department of Radiation Oncology at the McGill University Health Centre (MUHC) is interested in evaluating the adoption of SpaceOAR as part of their hypofractionated stereotactic body radiation therapy (SBRT) protocol in order to improve quality of life of patients with prostate cancer. The Technology Assessment Unit (TAU) of the MUHC was requested to carry out a health technology assessment of the SpaceOAR hydrogel in patients with localized prostate cancer who are candidates for external beam radiotherapy.

2. OBJECTIVES

The objectives of this report are to:

- Review the evidence on short and long-term efficacy and effectiveness of SpaceOAR in reducing rectal toxicity and improving quality of life
- Review the evidence on safety of SpaceOAR
- Review the evidence on the cost-effectiveness of SpaceOAR
- Undertake a budget impact analysis in case of adoption of this technology at the MUHC.

3. METHODS

3.1 Literature search and quality assessment

We conducted a systematic review of polyethylene-glycol hydrogel spacers by searching PubMed and the health technology assessment (HTA) database of the Centre for Reviews and Dissemination. The most recent search was conducted on October 4th, 2017. Several other spacers besides SpaceOAR have been described in the literature; however, they are either not available or are not approved as spacers in Canada and hence will not be part of this report.

Our literature search included randomized controlled trials (RCT) or non-randomized studies provided they included a control group, systematic reviews, meta-analyses, economic evaluations and health technology assessment reports focusing on the population of interest (Table 1). The first author selected the studies, first by title and abstract and then by applying the exclusion criteria to the full text of the remaining papers. A risk of bias assessment of the individual research studies was undertaken using the checklists published by the Cochrane Collaboration according to the type of study appraised (non-randomized or RCT) by all three co-authors. We considered that consensus was reached when at least two of the reviewers agreed in each of the domains evaluated.

We calculated confidence intervals for a number of results when they were not reported by the original studies, such as the 95% confidence intervals for mean rectal toxicity values and for mean change in quality of life before vs. after radiotherapy. We repeated

the Fisher exact test comparing rectal toxicity in the SpaceOAR group vs. the control group and reported the p-value. We also calculated the number needed to treat (NNT) for rectal toxicity and quality of life outcomes, based on the results of the RCT.

3.2 MUHC experience

To gather local data on the frequency of rectal toxicity at the MUHC, we reviewed two publications by the division of radiation oncology of the MUHC.[9,10]

3.3 Cost analysis

A budget impact analysis was performed to estimate the financial impact of integrating SpaceOAR at the MUHC. Costs were calculated from the perspective of the MUHC; hence, physician costs were omitted. The time horizon was 15 months and only direct costs were considered. Procedure costs were obtained from the Department of Finance of the MUHC. Probabilities of the incidence of rectal toxicity were obtained from the RCT by Mariados et al.[4]

We assumed that, in the absence of adverse events, the follow-up costs would be limited to the cost of the prostate-specific antigen (PSA) test. We assumed that Grade 1 toxicity would result in an emergency room (ER) visit for 50% of patients and would be diagnosed as part of routine follow-up for 50% of patients.

Though the magnitude of effectiveness of SpaceOAR in preventing Grade 2 or greater toxicity was not statistically significant, we carried out a cost-effectiveness analysis for the purposes of illustration. The cost-effectiveness was estimated in terms of the incremental cost effectiveness ratio (ICER), which is the ratio of the incremental cost to the incremental number of cases of rectal toxicity of Grade 2 or more that are avoided. A multivariate sensitivity analysis was performed in an attempt to capture the uncertainty in the ICER due to the uncertainty in the effectiveness of SpaceOAR. To do this we assumed that the risk of toxicity in the control group remained fixed, and applied the limits of the 95% confidence interval of the risk difference from the RCT to determine the most optimistic and pessimistic estimates for the toxicity in the SpaceOAR group.

4. RESULTS

4.1 Results of literature search

A total of 85 research studies were screened, 10 of which were included in this review (Appendix A). The main reasons for excluding studies were: usage of a different radiation technique, e.g. proton or brachytherapy, usage of a different dose of radiation, lack of reporting of clinical outcomes and lack of a control group.

4.2 Effectiveness of SpaceOAR

Six of the included studies reported on the efficacy and effectiveness of SpaceOAR: five observational studies [3,11-14] and one RCT (which resulted in two different publications, [4,15] one for early and one for late results) (Table 2). Three studies [4,12,13,15] considered rectal toxicity as an outcome of interest, while four [3,4,11,14,15] of them reported on quality of life from the patient perspective as an outcome of interest. In all studies, patients had localized prostate cancer of grade T1-T3, and were treated with conventionally fractionated external beam radiotherapy in a dose of 78 - 80 Gy (Table 2). These regimens are considered to be comparable in survival outcomes to the hypofractionated radiotherapy regimen currently used at the MUHC.[16,17]

4.2.1 Reduction in rectal dose-volume

One RCT and three observational studies evaluated the reduction in rectal volume between baseline and post-procedure. Rectal dose-volume (rV) is defined as the volume of rectal tissue receiving a particular radiation dose, and is correlated with the risk of gastrointestinal toxicity.

One of the primary endpoints of the RCT by **Mariados et al.** was the proportion of SpaceOAR patients who achieved ≥25% reduction in rectal volume receiving a dose of 70Gy (rV70). Before placement of the spacer, the rV70 of SpaceOAR patients was 12.4%, which was the same in control patients. Following treatment with the spacer, the rV70 was reduced to 3.3%, while it was 11.7% in controls ($p<0.0001$). 97.3% of SpaceOAR patients achieved ≥25% reduction in rV70 after spacer placement.

Pinkawa et al. in 2012 reported that rV70 in SpaceOAR vs. control patients post-treatment was 6% and 8% respectively. **Whalley et al.** found that rectal doses were significantly lower in the SpaceOAR group for all dose-volume end-points (rV30 to rV82); rectal volume receiving a dose of 75 Gy (rV75) was 2.2% vs. 9.5% in the SpaceOAR vs.

control patients, respectively. Similarly, **te Velde et al.** also reported significant differences in rectal dose volume (rV35 to rV75) between the study groups; rV75 was 2% vs. 11% in SpaceOAR and control patients, respectively.

4.2.2 Rectal toxicity

In all studies, acute (up to 3 months after radiotherapy) and late (beyond 3 months post-radiotherapy) rectal toxicity and its severity were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE),[18] or the modified Radiation Therapy Oncology Group (RTOG)[19] criteria (see Appendix B for a more detailed interpretation). In brief, the grade of rectal toxicity can be interpreted as follows:

Grade 0: no symptom or complication was present;
Grade 1: mild symptoms are present but no intervention is required;
Grade 2: a moderate event affecting daily activities, intervention is required;
Grade 3: a severe event that requires hospitalization;
Grade 4: a life-threatening event; and
Grade 5: death

Acute rectal toxicity

Results from the only RCT we identified were first published by **Mariados et al**.[4] in 2015, who reported no important differences between the SpaceOAR and control groups for acute rectal toxicity (Table 3). During the 3-month post-radiotherapy period, they reported Grade 1 rectal toxicity in 23% vs. 28% of the SpaceOAR and control groups, respectively [risk difference (RD): 5%; 95% confidence interval (CI): -7%, 17%]; and Grade 2 or greater rectal toxicity in 4.1% vs. 4.2% [RD: 0.1%; 95% CI: -5.0% ,8.0%]. Other than a single Grade 3 case among the controls, no cases of Grade 3 or Grade 4 rectal toxicity were reported.

Similarly, a study by **Whalley et al.**[12] in 2016 comparing a small prospective cohort with historical controls, also reported no differences in acute toxicity between study groups (Table 3). Grade 1 rectal toxicity was 43% in the SpaceOAR group vs. 50.6% in the controls (RD: 7.6%; 95% CI: -8%, 29%) and Grade 2 toxicity was 0% vs 4.5%, respectively (RD 4.5%; 95% CI: -7%, 10%).

In 2017, **te Velde et al**.[13] performed a retrospective analysis of the use of SpaceOAR in 65 patients vs. 60 controls (Table 3). During the 9-week period of radiotherapy, the only difference between the two groups was for Grade 1 (mild) toxicity for diarrhea, with

13.8% in the SpaceOAR group vs. 31.7% in the controls (RD: 17.9%; 95% CI: 3.1%, 31.9%). No differences were found for fecal incontinence, proctitis, or hemorrhoids.

Late toxicity

The RCT by **Mariados et al.**[4] assessed toxicity 3 to 15 months post-radiotherapy, and found only small differences in Grade 1 rectal toxicity of 2.0% vs. 5.6% (RD: 3.6%; 95% CI: -1.5%, 11.3%); and Grade ≥2 rectal toxicity of 0% vs. 1.4% [RD: 1.4%; 95% CI: -1.3%, 7.6%] in the SpaceOAR vs. control group, respectively. No cases of Grade 3 or Grade 4 toxicity were reported, other than a single Grade 3 case in the controls.

In a subsequent publication in 2017, **Hamstra et al.**[15] published results of an extended follow up of 3 years, also reported no important differences between the two groups with no Grade 2 toxicity events in both groups and one event (2.2%) of Grade 3 in the control group. Grade 1 toxicity was 2.0% vs. 6.8% (RD: 4.8%; 95% CI: -0.5, - 13.1%) in the SpaceOAR and control group, respectively. It should be noted that at 3 years follow-up, there was about 37% loss-to-follow-up compared to the original study. This trial also studied genitourinary toxicity but did not find any important differences between the two groups.

te Velde et al.[13] evaluated rectal toxicity 12 weeks after radiotherapy and reported that results were similar between the two groups except for Grade 1 hemorrhoids which were more frequent in the SpaceOAR group (11.7% vs. 3.1%; RD: -8.6%; 95% CI: -19.4%, - 1%). (Note: Numbers in the tables of the original publication appear to be inverted when compared to conclusions in the text).

In the small non-randomized study by **Whalley et al.**,[12] late Grade 1 rectal toxicity was significantly different between the two groups (16.6% for the SpaceOAR group vs. 41.8% for the control group; RD: 25.2%; 95% CI: 6.1%, 38.4%), though late Grade 2 toxicity was comparable in both groups (3.3% vs. 3.6%; RD: 0.3%; 95% CI: -13.2%, 6.3% for SpaceOAR vs. control group, respectively).

4.2.3 Quality of life

Patient-reported quality of life (QoL) was evaluated in one RCT (two articles) and three observational studies. QoL was assessed according to the function and bother score of the Expanded Prostate cancer Index Composite (EPIC),[20] and classified as follows:

- changes of 5 points or less on EPIC, when comparing pre- vs. post-radiation therapy, are considered not clinically significant;
- changes between 5–10 points are considered “small”;
- changes between 10-20 points are “moderate”; and
- changes greater than 20 are “big”.[21,22]

A positive score change implies a decreasing quality of life.

QoL outcomes from the RCT, reported by **Mariados et al.** in 2015 and later **Hamstra et al.**[4,15] in 2017, were evaluated at baseline and at 3, 6, 9, 12, 15 and 36 months after radiotherapy. In these papers, the EPIC bowel bother score was presented as the percentage of patients who had small or moderate declines (Table 4). At 6 months, changes of more than 10 points (moderate) were seen in 12% vs. 19% in the SpaceOAR vs. control group, respectively (RD: 7.0%; 95% CI: -2.5%, 18.4%); and at 12 months, moderate changes were seen in 15% vs. 20% (RD: 5.0%; 95% CI: -4.3%, 17.4%). Nonetheless, at 3 years follow up (Hamstra 2017), there was a significant difference between the two groups in the percentage of patients who had at least moderate declines: 5% vs. 21% (RD: 16.0%; 95% CI: 4.9%, 30.0%) of patients in the SpaceOAR vs. the control group, respectively. However, these results should be interpreted with caution due to the high percentage of loss to follow-up (37%) in both groups and the time elapsed since the intervention.

In 2012, **Pinkawa et al**.[11] published the results of a small matched analysis evaluating patient-reported QoL pre- and post-radiotherapy in patients with T1-3N0M0 prostate cancer. QoL was assessed in three cohorts (with apparently 28 patients in each group as per the abstract, though this is not clear from the text of the paper): one treated with intensity-modulated radiotherapy (IMRT) at 78 Gy using SpaceOAR; a control group treated with IMRT alone; and a second control group treated with conventional three-dimensional conformal radiotherapy (3DCRT) at 70.2 Gy. Results were collected at baseline, at the end of radiotherapy and at 3 months post-radiotherapy for urinary, bowel, sexual, and hormonal function and bother score. Although significant differences in scores were observed in all three study groups between baseline and end of radiotherapy, these differences disappeared 3 months post-radiotherapy, except for the bowel bother score (Table 5). For the latter score, small declines of 6 and 8 points were observed in the IMRT non-SpaceOAR group and the 3DCRT group, respectively, and a clinically non-significant decline of 2 points in the SpaceOAR group. However, there was no difference in the percentage of patients reporting moderate or big changes in bowel bother scores between the three time points for any of the study groups.

Pinkawa et al.[3] published two more studies, assessing QoL at later time points. In 2017, the authors reported on a study evaluating QoL in the 2 years post-radiotherapy in 101 SpaceOAR patients and 66 controls. Data was collected at baseline, at the end of radiotherapy, and at a median time of two months and 17 months post-radiotherapy. The authors report a significant difference in the two groups in the bowel function score at >1-year post-radiotherapy (5-point decrease in the control group vs. 0-point decrease in SpaceOAR patients; p<0.01) [Table 5]. They also report that, at >1-year post radiotherapy, a greater percentage of control patients had moderate (29% vs. 11%; RD: 18%; 95% CI: 6%, 31%) or big declines (7% vs. 1%; RD: 6%; 95% CI: 0.4%, 16%) in bowel function scores; and moderate (31% vs. 15%; RD: 16%; 95% CI: 4%, 30%) or big declines (16% vs. 3%; RD: 13%; 95% CI: 5%, 25%) in bowel bother scores.

In 2017, **Pinkawa et al.**[14] published the results of a 5-year follow-up in 114 patients with localized prostate cancer (54 of whom received SpaceOAR) [Table 5].(It appears that these patients are a sub-set of those followed in the previous study). QoL was assessed at baseline, end of radiotherapy, and at a median time of 2 months, 17 months, and 63 months. In concordance with their earlier study, the authors report that a greater percentage of control patients had moderate declines in the bowel bother score at 17 months (32% vs. 6%; RD: 26%; 95% CI: 12%, 39%) in comparison to SpaceOAR patients; however, these differences disappeared at 63 months (14% vs. 5%; RD: 9%; 95% CI: -4%, 19%).

4.2.4 Summary of the evidence on effectiveness

From the results of four studies evaluating reductions in rectal dose-volume, it appears that placement of a SpaceOAR between the prostrate and rectum does result in reductions in rectal volumes receiving a particular radiation dose.

However, the evidence for whether these reductions translate into lower rectal toxicity and improved QoL is less conclusive. Four studies (two based on the same RCT) that assessed rectal toxicity found no important differences in the short or long term with the use of SpaceOAR. Interestingly, no studies reported symptoms more severe than Grade 2, even in control patients.

With respect to QoL, five studies (three by the same author) reported no major differences between the SpaceOAR and control groups. Although differences in QoL between baseline and immediately following radiotherapy were observed between the groups, these differences disappeared over longer follow-up periods of up to 5 years.

Table 6 provides the NNT, i.e. the number of patients who need to receive SpaceOAR to avoid one additional case of rectal toxicity or a moderate decline in QoL. The NNT to prevent one event of Grade 2 or more rectal toxicity was 67. The wide confidence interval around this figure shows that there is no conclusive proof of benefit of SpaceOAR and there is also a probability that it is worse than the control. The NNT required to avoid any grade of toxicity was 10, as was the NNT to avoid a 10-point decline in their QoL. In both cases, the confidence intervals were very wide.

4.3 Risk of bias assessment

The risk of bias assessment is summarized in Appendix C. For the RCT, it was unclear if the randomization was adequately concealed from the clinician as the treatment group information was kept in an "opened envelope". Also, though it is mentioned that patients were blinded at randomization, it is unclear if they remained blinded throughout the follow-up period. If not, this could potentially affect the results on subjective outcomes such as the EPIC score. The long-term follow-up study at 3 years reported an attrition of 35%, though this was comparable in the SpaceOAR and control groups. It should be noted that the RCT was supported by Augmenix Inc, the company that manufactures SpaceOAR; and two of the main authors are shareholders.

As expected, all non-randomized studies were vulnerable to selection and confounding bias. None of the studies adjusted for these biases by undertaking suitable statistical analyses. In all studies, intervention was offered by the clinician to those patients previously selected as "candidates", and in one study, only patients with private insurance accepted to undergo the procedure.[13] It is possible that this results in a selection of patients with better overall health in the SpaceOAR group. Lack of blinding in all the studies raises the risk of detection bias, particularly for recording of subjective outcomes. Additionally, with respect to the three studies by Pinkawa et al., in one of them[14] all authors reported grants from the manufacture as well as support for the cost of SpaceOAR used. In the second one[11], the authors declared that the company provided the hydrogel for the study but do not mention if grants of financial support were received. Finally, in the third one, the study institution also participated in the original clinical trial by Mariados,[4] and part of the spacer material was provided.[3]

4.4 Economic evaluations

We identified three economic evaluations that estimated the cost effectiveness of SpaceOAR in patients treated with external beam radiation therapy.

In 2015, **Vanneste et al.** [23] conducted a cost-utility analysis using a five-year horizon. Rates and assumptions were extracted from multiple sources and differ with the outcomes observed at the MUHC[10] and the selected literature in this report. The total cost for treatment and follow-up (including costs for treatment of genitourinary toxicity) was estimated to be €3,144 in the SpaceOAR group (including €1,700 for the SpaceOAR) vs. €1,604 in the group without SpaceOAR. The incremental cost effectiveness ratio (ICER) was estimated to be €55,800 per quality-adjusted life year (QALY) gained (or $ 82,223.59 CAD/QALY at the current rate). The authors estimated that there was a 77% chance of SpaceOAR being a cost-effective intervention, considering an explicit threshold of €80,000.

Hutchinson et al. in 2016 aimed to determine the cost effectiveness of SpaceOAR with the aid of a decision model. The base case was standard of care for a patient with prostate cancer stage T1-T2c. Rates of adverse events were estimated based on the literature, and costs were based on the data from one institution in the United States. The complication rates assumed by this analysis were much higher and differed significantly from those reported by studies included in our systematic review or by the MUHC radiation oncology department.[10] The authors included both direct and indirect costs (productivity) in their economic analysis. Over a time-horizon of 10 years, the authors estimated that the average incremental cost was $518 ($3,428 control vs. $3,946 with SpaceOAR). This result varied according to the dose or radiation and the assumed complications rates.

In 2017, **Van Wijk et al.** [24] developed a prediction model to identify patients most likely to benefit from SpaceOAR, given that it has not been associated with significant benefits for all patients and is a costly and invasive technique. The model included a group with real spacers implanted (8 patients with hydrogel spacer and 15 with rectal balloon implant), and a group with virtual spacers (8 hydrogel and 8 balloon spacers) created using computed tomography scans of patients with rectal balloon implants. Cost-effectiveness was estimated using a published Markov model,[23] comparing gains in quality of life versus increases in cost. For a defined threshold of €80,000, the hydrogel spacer resulted in a cost-effective intervention in 2 out of 8 patients. The authors conclude that these devices are not cost-effective for all patients, and that more individual-patient information is needed.

4.5 Health technology assessments

In 2017, the National Institute for Clinical Excellence (NICE)[25], the national health technology assessment body in the United Kingdom (UK), carried out a rapid review

aiming to appraise the efficacy and safety of the insertion of *any* biodegradable spacers for prostate-rectum separation (including intra rectal balloons, hydrogel spacers and hyaluronic acid) following different radiotherapy techniques (radiotherapy and brachytherapy). Their inclusion criteria as well as the interventions appraised were broader than those considered in this report. The report included four articles evaluating SpaceOAR in external beam radiotherapy – the RCT by Mariados et al.,[4] the non-randomized study by Whalley et al., [12] and two case series. NICE concluded that the evidence on efficacy and safety was adequate to "support the use of this procedure provided that standard arrangements are in place for clinical governance, consent and audit".

4.6 Safety and procedure-related complications

The RCT by **Mariados et al.**[4] defined the primary safety endpoint as the proportion of patients experiencing Grade 1 or greater rectal or procedural complications in the first 6 months. These rates were 34.2% vs. 31.5% (RD: 2.7%; CI -10.8, 15.1) for the SpaceOAR and the control group respectively. There were no rectal perforations, serious rectal bleeding or rectal infections in either group. There were no device-related adverse events.

Whalley et al.[12] reported that 6 of 30 (20%) patients in the SpaceOAR group had some kind of postoperative complication: in one case the intervention failed (it was injected in the rectal lumen), one patient reported moderate tenesmus, two mild bowel frequencies, one had rectal bleeding and one had constipation. All of them were symptom free at the one-week follow-up and no allergies or infections were seen.

The other studies included in this report either did not attempt to report procedure-related complications or they stated that there were no device-related adverse events, allergies or infections. Nevertheless, in the literature [3,25] some serious, rare SpaceOAR-related complications such as focal rectal necrosis/ulceration or urinary retentions have been seen.

In the 2017 NICE report, a total of four studies and one FDA adverse event report accounting for 262 patients with prostate cancer treated with SpaceOAR and external beam radiotherapy were selected for the evaluation of safety and procedure related complications. One case of intravascular injection of the hydrogel was reported by the FDA in 2015 without further complications. Also, an inadvertent rectal wall infection that resulted in a focal mucosal necrosis and bladder perforation was reported by Uhl et al. [26] in 2014 in a case series of 52 patients; this resolved without sequelae. The overall

opinion (*for all evaluated spacers* in the NICE report) was that there are no major concerns regarding the safety of this procedure that suggest it is not appropriate for routine use.

In summary, these data taken in combination with the evidence for rectal toxicity, which showed no important differences between the SpaceOAR and control groups, indicate that the use of SpaceOAR in prostate cancer patients does not result in any additional adverse events.

5. SPACEOAR AT THE MUHC

5.1 Current treatment policy and risk of rectal toxicity

Patients with localized prostate cancer with low, moderate and occasionally high risk are currently treated at the MUHC with hypofractionated external beam radiotherapy of 60 Gy in 20 sessions, i.e. 3 Gy radiation dose per session. This modality allows clinicians to treat patients with fewer sessions by increasing the radiation dose, thus increasing efficiency. It has been shown to be equivalent to the standard fractionated radiation protocol in terms of survival outcomes. [16,17]

Faria et al. described the MUHC experience with treating moderate-risk prostate cancer patients with conformal hypofractionated radiotherapy in two articles. [10] The first one reported outcomes in 80 patients at a median follow-up of 51 months, and the second one for 100 patients at a median follow-up of 80 months. The overall and cancer-specific survival rate at 8 years was 84% and 96%, respectively. Gastrointestinal (GI) toxicity was measured according to the common terminology criteria for adverse events ([18])[18] from three months post-radiotherapy. While the authors did not report results at specific time-points post-radiotherapy, they state that cumulative incidence of Grade ≥2 GI toxicity from 3 months post-radiotherapy to median follow-up times of 51 (range: 7-95 months) and 80 (range: 7-195 months) months was 18% and 20%, respectively. In comparison, the RCT by **Mariados et al.** reported that the cumulative incidence of Grade ≥2 rectal toxicity at a median of 37 months was 6%. However, **Faria et al.**[10] report that at the last follow-up visit, at a median of 80 months, the incidence of Grade 1 and Grade 2/3 GI toxicity was 10% and 2%, respectively, indicating that the majority of rectal toxicity cases resolve over time. No cases of Grade 4 or 5 GI toxicity were observed.

SpaceOAR has not yet been used at the MUHC. In 2016, 156 patients were treated for prostate cancer with curative intent; 50% of these patients would have been candidates

for this technology. Therefore, the radiation oncology department estimates that around 70 SpaceOAR devices could be implanted in the first year of use.

5.2 Costs and budget impact estimates

SpaceOAR is a one-time intervention injected during radiotherapy, and is then reabsorbed by the body. The cost of the device is estimated at CAD $2800 (Table 7). Assumptions used for the probabilities of rectal toxicity are explained in Table 8**.** Our budget impact analysis for 2018, which accounted for device, procedure, and complication costs, found that the cost of treating 70 patients with and without SpaceOAR was $388,015.60 and $189,901.26 respectively ($5,543 and 2,712 per patient), resulting in an additional cost associated with the use of SpaceOAR of $198,114.34 [Table 7]. Furthermore, we calculated the incremental cost-effectiveness ratio (ICER) for avoiding one additional case of Grade ≥2 rectal toxicity at $191,230.06.

Additionally, we performed a multivariate sensitivity analysis considering the maximum and minimum probabilities of rectal toxicity based on the confidence limits obtained from the RCT by **Mariados et al.** This resulted in the total cost for the 70 patients decreasing to $387,213.05 ($5,531 per patient) for the most optimistic scenario (i.e. lowest toxicity rates using SpaceOAR) and increasing to $411,514.57 ($5,878 per patient) for the worst-case scenario for SpaceOAR. Correspondingly, the ICER was $73,789.00 to avoid one additional case of Grade ≥2 rectal toxicity for the most optimistic scenario. In the worst-case scenario, the SpaceOAR arm resulted dominated, being more expensive and less effective in preventing complications than the base case without the SpaceOAR. These results are explained by the potentially large difference in cost (more than double) for a very small absolute risk reduction of rectal toxicity.

6. DISCUSSION

Current therapeutic options for patients with localized prostate cancer vary considerably with regards to the preferred technique, the radiation dose used, and the length of treatment. However, given the similar survival outcomes with the different radiotherapy modalities, there is interest in identifying techniques that reduce treatment time and improve quality of life in prostate cancer patients. External beam radiotherapy has evolved to allow radiation oncologists the ability to treat and sometimes cure patients faster with higher radiation protocols. However, this potentially increases the risk of exposing healthy tissue to the risks of radiation and producing adverse events in

adjacent areas. SpaceOAR is a health technology that has elicited interest among clinicians who wish to reduce the risk of radiation to the rectum during the process of treating prostate cancer with radiotherapy.

While the evidence shows a clear reduction in the amount of radiation to the rectum with the use of SpaceOAR, it remains unclear whether this reduction results in improved clinical and patient-reported outcomes. The studies we identified generally showed a small magnitude of benefit of SpaceOAR for reducing relatively mild symptoms, classified as Grade 1 toxicity not requiring intervention. Furthermore, studies of quality of life were not conclusive and the evidence was weak. The only RCT suggests a greater improvement in quality of life over longer periods of follow-up, but this RCT was beset with numerous limitations including a large loss to follow-up. These results were not reproduced in the observational study evaluating quality of life up to five years

These equivocal findings for effectiveness do not appear to justify the additional cost of $2,830 per patient (budget impact of extra $198,114.34 for 70 patients) associated with the use of SpaceOAR. Given the high costs associated with this procedure, and assuming an absolute risk reduction of 1.5% in Grade 2 or higher rectal toxicity with the use of SpaceOAR, the cost of each additional Grade ≥2 toxicity avoided, would be $191,230.06.

Multiple limitations were found in the evidence reviewed. There was only one RCT, and this study was weakened by the possibility of unblinding of patient assignment, and attrition bias during long term follow-up. There was concern for confounding and selection bias in the non-randomized studies. Another concern with all studies is whether outcomes measured during the long-term can be attributed to SpaceOAR.

Though it was not the focus of our report, it is worth noting that SpaceOAR could be a promising technology in a context where the dose of radiation per fraction is much higher than the current regimen used at the MUHC. Such a regimen would reduce the cost of radiotherapy treatment and be more convenient for patients as it would result in a decrease in the number of fractions requiring fewer visits to the hospital. Appropriately designed research studies are needed to evaluate the efficacy and safety of such radiotherapy regimens as well as the efficacy and safety of SpaceOAR as part of such regimens.

7. CONCLUSIONS

- SpaceOAR is a device intended to increase the distance between the prostate and rectal wall, and thus decrease the amount of radiation received by the rectum during prostate cancer radiotherapy. While the evidence indicates that the use of SpaceOAR is effective for this purpose, it remains unclear whether the reduction in rectal dose-volume results in reduced rectal toxicity and improved quality of life.

- We identified one RCT and five non-randomized studies, none of which found important differences between the SpaceOAR and control groups for rectal toxicity and long-term quality of life. Furthermore, all of these studies had serious limitations. The estimated risk difference between the SpaceOAR and control group in terms of the risk of Grade 2 or greater toxicity at 3-15 months was 1.5%, implying that it would require treating 68 people in order to avoid one Grade 2 or greater event of rectal toxicity.

- We estimated that the use of SpaceOAR in 70 prostate cancer patients at the MUHC would result in an additional cost of $198,114.34, which is considerable given the equivocal effectiveness outcomes. Assuming a risk reduction of 1.5% in Grade ≥2 rectal toxicity with the use of SpaceOAR, it would cost $191,230.06 to avoid one additional case of Grade 2 or higher rectal toxicity. The data are too unreliable to permit calculations of cost utility metrics such as QALYs.

8. RECOMMENDATIONS

Given the limited and inconclusive evidence of the clinical benefit of SpaceOAR, and the high costs associated with its use at the MUHC:

- Routine use of SpaceOAR in prostate cancer patients receiving radiotherapy is not-approved. This recommendation is subject to re-evaluation as and when new evidence becomes available.

FIGURES

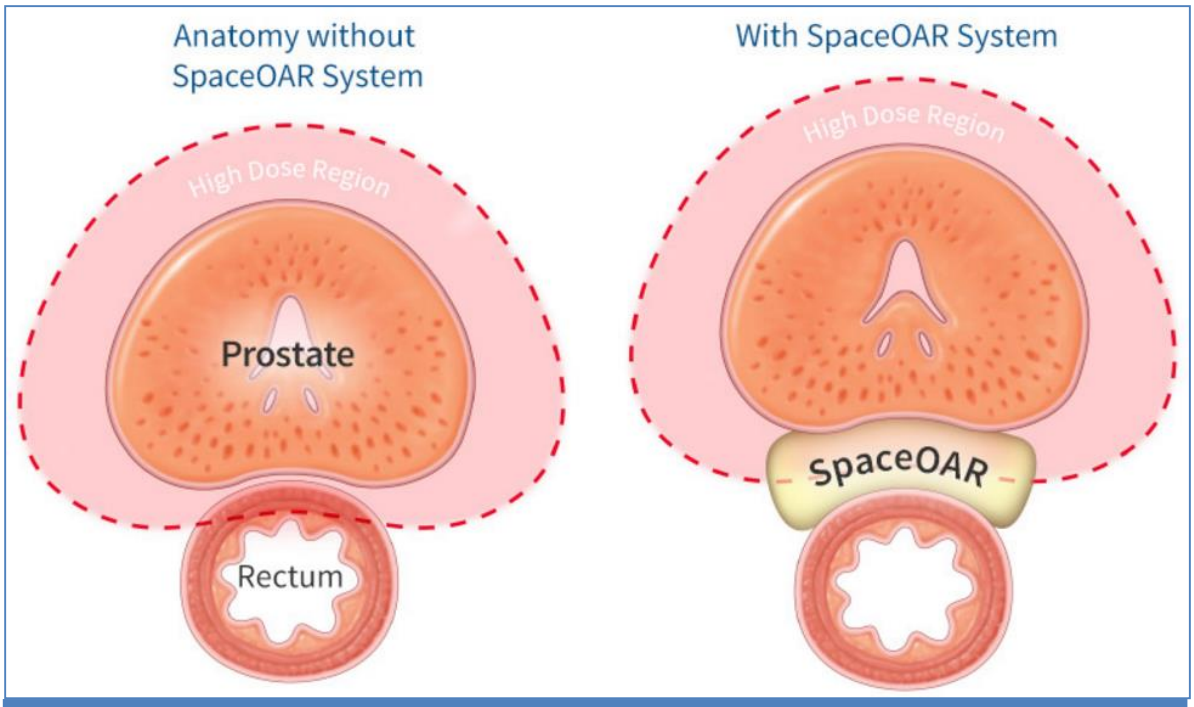


Figure 1. Illustration of SpaceOAR positioning

TABLES

Table 1. Systematic review inclusion and exclusion criteria summarized according to PICOS (Population, Intervention, Control, Outcome, Settings) criteria

	INCLUSION CRITERIA	EXCLUSION CRITERIA
P	Patients with prostate cancer T1-3 Low to High Risk.	Extended prostate cancer. Studies with exclusively T3 and or high risk patients.
I	Spacer	Other devices not approved by Health Canada.
C	vs. No spacer	
O	Clinical rectal toxicity and QoL	Studies evaluating exclusively dosimetry levels. Proton or brachytherapy studies
S	Conventional or Hypo fractionated External beam RT: SBRT, VMAT, IMRT	
Literature	English, French, RCTs, Observational study.	Full text not available, methodology not described. Lack of control group.

Table 2. Characteristics of the six studies included in this report evaluating the effectiveness of SpaceOAR

Author / Year	EBRT type	Total Radiation Dose - Gy.	Radiation Dose - Gy per session.	Type of Evidence	N (spacer vs. control)	Months of Follow up	Moment of toxicity assessment *	Moment of QoL assessment*	Toxicity - QoL assessment Scale
Te Velde 2017	IMRT	81	1.8	Observ	65 vs. 60	4	Dur - aft	NA	CTCAE
Pinkawa 2017	IMRT	76 - 80	2.0	Observ	66 vs. 101	12	NA	Dur - Aft	EPIC
Pinkawa 2017. 5 yrs	IMRT	76 - 78	2.0	Observ	54 vs. 60	72	NA	Be-Dur-Aft	EPIC
Whalley 2016	IMRT	80	2.0	Observ	30 vs. 110	28	Dur - aft	NA	RTOG
Pinkawa 2012	IMRT	78 vs. 76 vs. 70	2.0 vs 2.0 vs 1.8	Observ	28 vs. 28 vs. 28	3	NA	Be-Dur-Aft	EPIC
Mar-Ham 2015/17	IMRT	79.2	1.8	RCT	149 vs. 73	36	Be-Dur-Aft	Be-Dur-Aft	CTCAE - EPIC

** In relation with radiotherapy*
Be=Before, Dur= during, Aft=after.
EBRT: External beam radiation therapy

Table 3. Acute and late rectal toxicity outcomes reported by the included studies

Author, year (n, SpaceOAR vs Control)	Outcome	Toxicity Grade	Radiation induced rectal toxicities (%)								
			During RT and 3 months post RT			3 months up to 15 months post RT			*Cumulative incidence* from *3* months up to 3 years after RT		
			SpaceOAR	Control	*p-value*	SpaceOAR	Control	*p-value*	SpaceOAR	Control	*p-value*
te Velde 2017[1] (65 vs. 60)[3]	Diarrhea	Grade 0	86.2	68.3	0.02	95.4	95	1			
		Grade 1	13.8	31.7		4.6	5				
		Grade 2	0	0		0	0				
	Faecal incontinence	Grade 0	96.9	96.7	1	100	98.3	0.5			
		Grade 1	3.1	3.3		0	1.7				
		Grade 2	0	0		0	0				
	Proctitis	Grade 0	86.2	85	0.6	98.5	95	0.3			
		Grade 1	9.2	13.3		1.5	5				
		Grade 2	4.6	1.7		0	0				
	Haemorrhoids	Grade 0	72.3	76.7	0.8	96.9	88.3	0.09			
		Grade 1	23.1	20		11.7	3.1	0.09			
		Grade 2	4.6	3.3		0	0	1			
Whalley 2016[2] Observational (30 vs. 110)	Rectal Toxicity	Grade 0	57	44.9	0.8	80.1	54.6	0.02			
		Grade 1	43	50.6		16.6	41.8				
		Grade 2	0	4.5		3.3	3.6				
Mariados 2015[1] RCT (148 vs. 72)[4]	Rectal Toxicity	Grade 0	73	68	0.53	98	93	0.04			
		Grade 1	23	27.8		2	5.6				
		Grade 2	4.1	2.8		0	0				
		Grade 3	0	1.4		0	1.4				
Hamstra 2017 RCT[5] (94 vs. 46)	Rectal Toxicity	Grade 0							98	91	0.14
		Grade ≥1							2	9	
		Grade ≥2							0	6	

[1] Based on the Common Terminology Criteria for Adverse Events (CTCAE)
[2] Based on the modified Radiation Therapy Oncology Group (RTOG) criteria for acute and late effects
[3] The number of patients evaluated at follow up was not provided
[4] The sample size in the control group was 71 for late toxicity
[5] Results of long-term follow-up of the RCT by Mariados et al.

Table 4. Quality of life outcomes from RCTs studies evaluating SpaceOAR

Study	Follow-up length	Threshold for minimal clinically detectable bowel function score changes (EPIC) at follow-up vs baseline	Proportion of patients with changes in bowel function score		Difference between SpaceOAR and Control
			SpaceOAR	Control	
Mariados 2015 (148 SpaceOAR vs 72 Control)	3 months	5-point	49%	47%	Not significant
		10-point	32%	31%	Not significant
	6 months	5-point	24%	32%	Not reported
		10-point	12%	19%	
	12 months	5-point	24%	32%	
		10-point	15%	20%	
	15 months	5-point	25%	34%	
		10-point	12%	21%	p=0.09
Hamstra 2017 (94 SpaceOAR vs 46 Control)	36 months	5-point	14%	41%	p=0.009
		10-point	5%	21%	p=0.14

EPIC (Expanded Prostate Cancer Index Composite). QoL changes of below 5 points can be defined as clinically not significant, 5–10 as “little”, 10–20 as “moderate” and >20 as “very much”. Positive score changes correspond to decreasing QoL

Table 5. Quality of life outcomes from observational studies evaluating SpaceOAR

Author, Year	Sample size *SpaceOAR vs. Control*	Mean bowel function or bother score before RT (0 – 100)		Mean QoL function or bowel bother score changes[1]							
				End of RT		2 - 4 months post RT		17 months post RT		63 months post RT	
		SpaceOAR	Control	SpaceOAR	Control	SpaceOAR	Control	SpaceOAR	Control	SpaceOAR	Control
Pinkawa 2012[A]	28 vs. 28 vs. 28	96	96;96[2]	16	14;17[2]	2	8;6[2]	NR	NR		
Pinkawa 2017[B]	101 vs. 66	93	93	11	14	4	5	0	5		
Pinkawa 2017[A]	54 vs. 60	100	96	10-15	21	NR	8	-1	7	1	6

[1] Based on the EPIC (Expanded Prostate Cancer Index Composite). QoL changes of below 5 points can be defined as clinically not significant, 5–10 as “little”, 10–20 as “moderate” and >20 as “very much”. Positive score changes correspond to decreasing QoL;
[2] Two control groups without spacer;
A= Bother score, B= Function score
NR Not reported

Table 6. Number needed to treat (NNT) with SpaceOAR in order to avoid one toxicity event or a moderate decline in QoL

Outcomes	Spacer (n=148)		Control (n=72)		RD (95% CI)	NNT (95% CI)
	No. of events	**Risk of events**	**No. of events**	**Risk of events**		
3-15 months						
Grade ≥1 toxicity	43	29%	28	39%	10% (-3.2, 23.2)	***10*** *(4.3, -31.5)*
Grade ≥2 toxicity	6	4%	4	5.50%	1.5% (-4.1, 9.7)	***67*** *(10.3, -24.2)*
10-pt decline in bowel QoL	Np	11.60%	Np	21.40%	9.8% (-0.1, 21.5)	***10.2*** *(4.7, -1000)*
Up to 36 months	***Spacer (n=94)***		***Control (n=46)***			
10-pt decline in bowel QoL	Np	5.00%	Np	21.00%	16.0% (4.9, 30.6)	***6.3*** *(3.3, 20.4)*

Np = Not provided

Table 7. Cost analysis of average resource use over a one-year period in a cohort of 70 patients treated with SpaceOAR

Item	Base Case with SpaceOAR				Base Case with No SpaceOAR			
	Unit cost	Resource use	Probability of outcome	Cost	Unit cost	Resource use	Probability of outcome	Cost
	a	b	c	a*b*c	a	b	c	a*b*c
Device cost								
Cost of SpaceOAR				$ 2,800.00				NA
Procedure costs								
Cost of SpaceOAR insertion	$ 48.22	1.6 UTP		$ 77.15				NA
Cost of 22 RT sessions	$ 48.22	34 UTP + 20 sessions		$ 2,603.88	$48.22	34 UTP + 20 sessions		$ 2,603.88
Cost of follow-up No AEs visit (PSA test)	$ 5.54	3 visits		$ 16.63	$ 5.54	3 visits		$ 16.63
Cost of complications								
Acute Grade 1 rectal toxicity			0.23				0.28	
Out-patient visit	$ 5.54	50% of patients		$ 0.64	$ 5.54	50% of patients		$ 0.78
ER visit	$264.16	50% of patients		$ 30.38	$264.16	50% of patients		$ 36.98
Late Grade 1 rectal toxicity			0.02				0.056	
Out-patient visit	$ 5.54	50% of patients		$ 0.06	$ 5.54	50% of patients		$ 0.16
ER visit	$264.16	50% of patients		$ 2.64	$264.16	50% of patients		$ 7.40
Acute Grade 2 rectal toxicity			0.041				0.028	
ER visit	$264.16	100% of patients		$ 10.83	$264.16	100% of patients		$ 7.40
Medications (diarrhea, pain)	$ 21.28	100% of patients		$ 0.87	$ 45.88	100% of patients		$ 1.28
Late Grade 2 rectal toxicity			0				0	
ER visit	$264.16	100% of patients		$ -	$264.16	100% of patients		-
Medications	$ 21.28	100% of patients		$ -	$ 21.28	100% of patients		-
Acute Grade 3 rectal toxicity			0				0.0138	
ER visit	$264.16	100% of patients		$ -	$264.16	100% of patients		$ 3.65
Medications and 2 days hospitalization (Int. Med)	$759.92	100% of patients		$ -	$759.92	100% of patients		$ 10.49
Argon plasma coagulation / sigmoidoscopy (device +nursing costs)	$356.20	100% of patients		$ -	$356.20	100% of patients		$ 4.92
Late Grade 3 rectal toxicity			0				0.014	
ER visit	$264.16	100% of patients		$ -	$264.16	100% of patients		$ 3.70
Medications and 2 days hospitalization (Int. Med)	$759.92	100% of patients		$ -	$759.92	100% of patients		$ 10.64
Argon plasma coagulation / sigmoidoscopy (device +nursing costs)	$356.20	100% of patients		$ -	$356.20	100% of patients		$ 4.99
Total cost per patient				$ 5,543.08				$ 2,712.88
Cost for 70 patients				***$ 388,015.60***				***$ 189,901.26***
Δ								***$ 198,114.34***

[1] Unité technique;
[2] 34 unités techniques for planning + 22 unités techniques for each session;
[3] Procedure and nursing costs;
[4] See Table 8 for sources and assumptions for probabilities

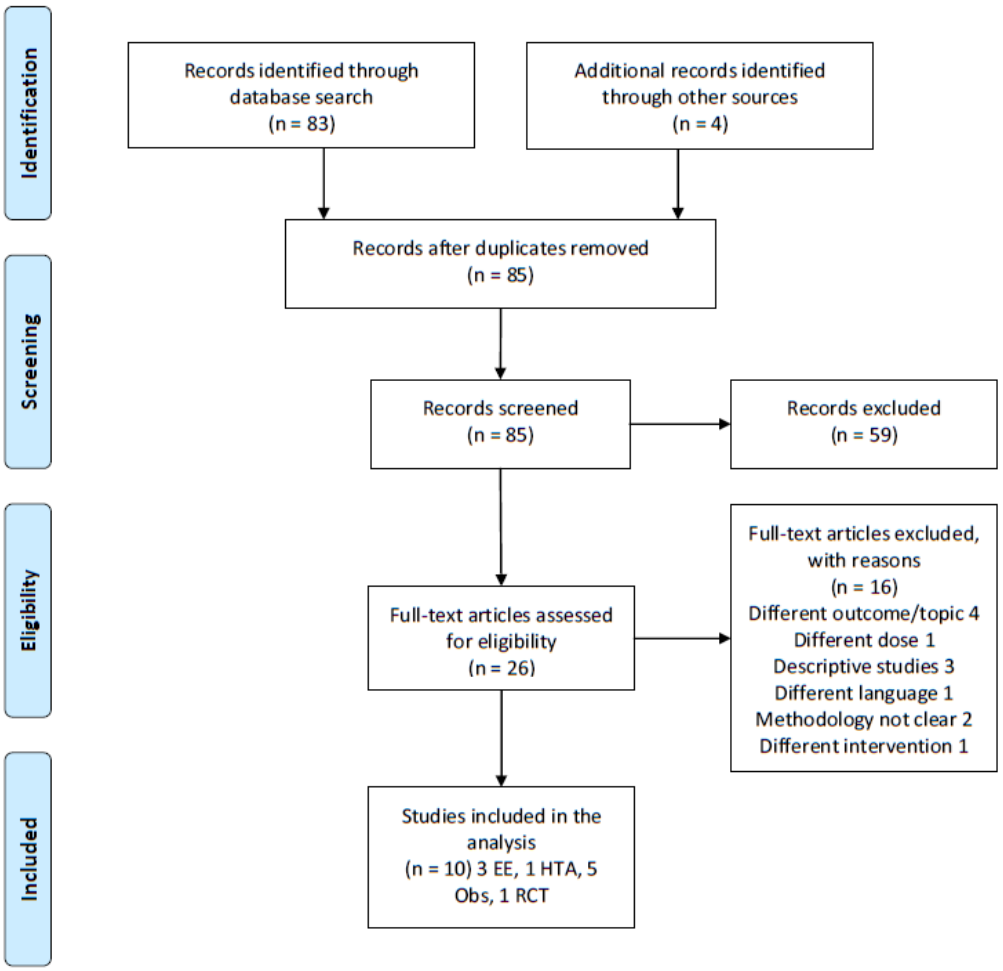
Table 8. Sources for costs and probabilities used in cost and sensitivity analysis

Item	Base case SpaceOAR		Base Case No SpaceOAR		Best Case Sens. Analysis		Worst Case Sens. Analysis		Reference	Reference
	Unit cost	Probability of outcome	Unit cost	Probability of outcome	Unit cost	Probability of outcome	Unit cost	Probability of outcome	Base case	Sensitivity Analysis
Device cost									-	
Cost of SpaceOAR									Dr. Fabio Cury	
Procedure costs									-	
Cost of SpaceOAR insertion †	$48.22				$48.22		$48.22		MUHC Dept. of Finance	
Cost of 22 RT sessions†	$48.22		$48.22		$48.22		$48.22		MUHC Dept. of Finance	
Cost of follow-up (PSA test)	$ 5.54		$ 5.54		$ 5.54		$ 5.54		MUHC Dept. of Finance	
Cost of complications									-	
Acute Grade 1 rectal toxicity		0.23		0.28		0.2113		0.4559	Mariados	CI (-0.0687 - 0.1759)
Out-patient visit	$ 5.54		$ 5.54		$ 5.54		$ 5.54		MUHC Dept. of Finance	
ER visit	$264.16		$264.16		$264.16		$264.16		MUHC Dept. of Finance	
Late Grade 1 rectal toxicity		0.02		0.056		0		0.204	Mariados	CI (-0.056 - 0.148)
Out-patient visit	$ 5.54		$ 5.54		$ 5.54		$ 5.54		MUHC Dept. of Finance	
ER visit	$264.16		$264.16		$264.16		$264.16		MUHC Dept. of Finance	
Acute Grade 2 rectal toxicity		0.041		0.028		0.0176		0.1031	Mariados	CI (-0.0586 - 0.0621)
ER visit	$264.16		$264.16		$264.16		$264.16		MUHC Dept. of Finance	
Medications (diarrhea, pain)	$ 21.28		$ 45.88		$ 45.88		$ 45.88		Hakkaart-van Roijen L.	
Late Grade 2 rectal toxicity		0		0		0		0.0507	Mariados	CI (-0.0253 - 0.0507)
ER visit	$264.16		$264.16		$264.16		$264.16		MUHC Dept. of Finance	
Medications	$ 21.28		$ 21.28		$ 21.28		$ 21.28		Hakkaart-van Roijen L.	
Acute Grade 3 rectal toxicity		0		0.0138		0		0.0884	Mariados	CI (-0.0139 - 0.0746)
ER visit	$264.16		$264.16		$264.16		$264.16		MUHC Dept. of Finance	
Medications and 2 days hospitalization (Int. Med)	$759.92		$759.92		$759.92		$759.92		MUHC Dept. of Finance	
Argon plasma coagulation / sigmoidoscopy (device +nursing costs)	$356.20		$356.20		$356.20		$356.20		MUHC Dept. of Finance	
Late Grade 3 rectal toxicity		0		0.014		0		0.0896	Mariados	CI (-0.0137 - 0.0756)
ER visit	$264.16		$264.16		$264.16		$264.16		MUHC Dept. of Finance	
Medications and 2 days hospitalization (Int. Med)	$759.92		$759.92		$759.92		$759.92		MUHC Dept. of Finance	
Argon plasma coagulation / sigmoidoscopy	$356.20		$356.20		$356.20		$356.20		MUHC Dept. of Finance	

†Detailed explanation in table 5.

APPENDICES

APPENDIX A: PRISMA DIAGRAM OF THE LITERATURE REVIEW



APPENDIX B: SCALES TO ASSESS RADIATION TOXICITY

Table B-1. RTOG and CTCAE Radiation Toxicity Scales

Scale	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
CTCAE	Mild • Asymptomatic or mild symptoms; • Clinical or diagnostic observations only; • Intervention not indicated	Moderate • Minimal, local or non-invasive • Intervention indicated; • Limiting age appropriate daily life activities.	Severe or medically significant but not immediately life-threatening • Hospitalization indicated; • Disabling; • Limiting self-care and daily life activities.	Life-threatening consequences • Urgent intervention indicated	Death related to AE
RTOG	• Able to eat with some nausea, • One vomit episode in 24 hrs, • Increase 2-3 stools per day. • Painless ulcers, erythema or mild soreness	• Intake significantly reduced, • 2-5 vomit episodes in 24 hrs, • Increase 4-6 stools per day, • Painful erythema, edema or ulcers	• No significant intake, • 6-10 vomit episodes in 24 hrs, • Increase 7-9 Stools per day or incontinence or severe cramping • Painful erythema, edema or ulcers and cannot eat	• >10 episodes in 24 hrs or requiring parenteral support, • Increase of >=10 stools/day or grossly bloody diarrhea, or need for parenteral support.	N/A

APPENDIX C: RISK OF BIAS ASSESSMENT

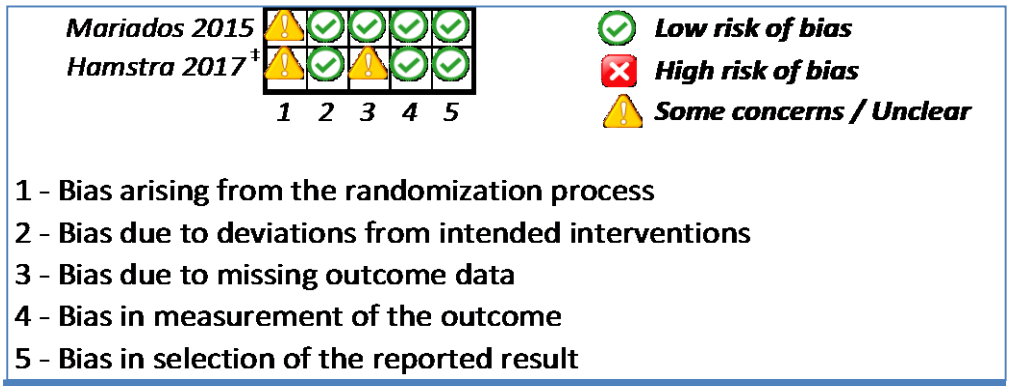


Figure C-1. Risk of bias assessment of the RCTs

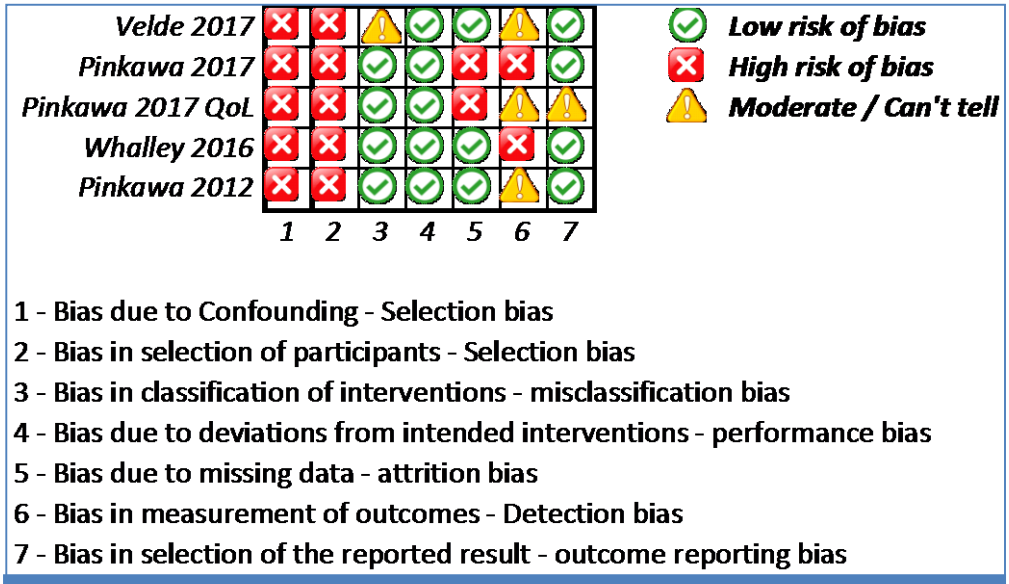


Figure C-2. Risk of bias assessment of the observational studies

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