

CADTH RAPID RESPONSE REPORT:  
SUMMARY WITH CRITICAL APPRAISAL

# Magnetic Resonance Imaging Simulators for Simulation and Treatment for Patients Requiring Radiation Therapy: A Review of the Clinical Effectiveness, Cost- Effectiveness, and Guidelines

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## Abbreviations

CRD	Centre for Reviews and Dissemination
CT	computed tomography
MRI	magnetic resonance imaging
PET	positron emission tomography
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial

## Context and Policy Issues

Radiation therapy is a common type of local therapy used to treat cancer, and can be used alone or in combination with chemotherapy, surgery, or both.<sup>1,2</sup> Approximately 470,000 patients receive radiation therapy each year in the United States of America.<sup>3</sup> In Canada, great progress has been made in cancer control which can be attributed to improvements in prevention, screening, early detection, and treatment options for patients with cancer.<sup>2</sup> This progress has translated into decreased rates of cancer death within Canada over the last three decades (17% in females, 32% in males).<sup>2</sup> In part, this has enabled the field of radiation oncology to investigate other important health outcomes in addition to mortality, such as patient's quality of life and adverse effects associated with radiation therapy.<sup>1</sup>

Accurate treatment planning (e.g., tumor volume, organs at risk) before patients undergo radiation therapy is one way to reduce unnecessary treatment.<sup>4</sup> Computed tomography (CT) simulation is the current gold standard for radiation therapy treatment planning.<sup>5,6</sup> Radiation treatment planning using CT typically involves obtaining a set of CT images while the patient is immobilized in an adequate position for radiation therapy.<sup>1</sup> These CT images can be used to define the extent of the tumor (i.e., target delineation) and plan treatment delivery (e.g., dose calculation).<sup>1</sup> More recently, magnetic resonance imaging (MRI) has also been used for radiation therapy planning due to its superior soft tissue contrast compared with CT;<sup>7</sup> improved soft tissue contrast may provide more precisely targeted treatment sparing healthy organs at risk of developing comorbidities from radiation.<sup>8</sup> To truly discern whether MRI simulation improves health outcomes and, thus, should be considered for treatment planning for patients who require radiation therapy, a synthesis of the currently available literature is required.

The current report aims to summarize evidence regarding the clinical and cost-effectiveness, as well as guidelines for the use of MRI simulators for simulation and treatment planning for patients requiring radiation therapy.

## Research Questions

1. What is the clinical effectiveness of the use of magnetic resonance imaging simulators for simulation and treatment planning for patients requiring radiation therapy?
2. What is the cost-effectiveness of the use of magnetic resonance imaging simulators for simulation and treatment planning for patients requiring radiation therapy?
3. What are the evidence-based guidelines regarding the use of magnetic resonance imaging simulators in the simulation and treatment of patients requiring radiation therapy?

## Key Findings

Clinical evidence of limited quality from one retrospective cohort study of patients with prostate cancer suggested that the use of magnetic resonance imaging simulation in conjunction with computed tomography simulation for treatment planning may reduce acute genitourinary toxicity compared with computed tomography simulation only. Magnetic resonance imaging use had no identified benefit for reduced acute gastrointestinal (rectal) toxicity.

No relevant cost-effectiveness studies were identified on the use of magnetic resonance imaging simulators for simulation and treatment planning for patients requiring radiation therapy.

No relevant evidence-based guidelines were identified for the use of magnetic resonance imaging simulators in the simulation and treatment of patients requiring radiation therapy.

Given the limited availability and low quality of evidence, the effectiveness and use of magnetic resonance imaging simulators for simulation and treatment planning for patients requiring radiation therapy remains uncertain.

## Methods

### Literature Search Methods

A limited literature search was conducted on key resources including Medline and Embase via Ovid, PubMed, the Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2013 and December 12, 2018.

### Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Patients with a diagnosis of cancer who require radiation therapy treatment (e.g., cervical, prostate, all sarcoma, head and neck cancer)
<b>Intervention</b>	Magnetic resonance imaging simulator
<b>Comparator</b>	Q1 & Q2: Computed tomography simulator, other treatment planning methods Q3: No comparator required
<b>Outcomes</b>	Q1: Treatment localization (i.e., focusing treatment on a smaller tissue volume), adverse events, quality of life, tissue sparing for non-affected tissues, organs at risk, customized treatment for patients Q2: Cost-Effectiveness Q3: Guidelines
<b>Study Designs</b>	Q1: Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies Q2: Economic evaluations Q3: Guidelines

### Exclusion Criteria

Articles were excluded if they: (i) did not meet the selection criteria outlined in Table 1; (ii) were duplicate publications; (iii) were non-English publications; or (iv) were published prior to 2013. Clinical studies using a within-subject design to examine different health outcomes were excluded. For example, studies where *all patients* received MRI simulation/MR-generated synthetic CT and another treatment planning method, such as CT simulation or positron emission tomography [PET] simulation were excluded.

### Critical Appraisal of Individual Studies

The included clinical study was critically appraised using Downs and Black checklist.<sup>9</sup> A summary score was not calculated for the included study; rather, a review of the strengths and limitations was described narratively.

### Summary of Evidence

#### Quantity of Research Available

A total of 584 citations were identified in the literature search. Following screening of titles and abstracts, 531 citations were excluded and 53 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 54 publications were excluded for various reasons, and one publication met the inclusion criteria and was included in this report. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)<sup>10</sup> flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

#### Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

### *Study Design*

One relevant clinical study was identified from the literature search.<sup>11</sup> This study was a retrospective cohort study published in 2013.<sup>11</sup>

### *Country of Origin*

The included study was conducted in the United States of America.<sup>11</sup>

### *Patient Population*

The population of the included study comprised of patients with and treated for prostate cancer within one institution between the years of 2004 and 2008.<sup>11</sup> Patients were excluded if they previously received definitive treatment (e.g., surgery, cryotherapy, high-intensity focused ultrasound) or a combination of intensity modulated radiation therapy and brachytherapy. For patients in the CT-MRI simulation group (n = 28 patients), the median age of patients was 71 years. For patients in the CT simulation group (n = 53 patients), the median age of patients was 67 years.<sup>11</sup>

### *Intervention and Comparator*

The intervention of interest for the included study was CT and MRI simulation for radiation treatment planning for patients with prostate cancer.<sup>11</sup> Generally, the MRI scan was performed within one week of the CT scan. The comparator was CT simulation for radiation treatment planning for patients with prostate cancer.<sup>11</sup>

### *Outcomes*

From the included study, relevant outcomes included acute genitourinary toxicity and acute gastrointestinal (rectal) toxicity.<sup>11</sup> Investigators assessed toxicity using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0. This information was available by retrospectively tabulating data from a continuing prostate database.<sup>11</sup>

## Summary of Critical Appraisal

Additional detail regarding the strengths and limitations of included publication is provided in Appendix 3.

The included study had a number of strengths and limitations. The authors clearly described the objectives, intervention, comparator, and main outcomes. The main findings were adequately reported. The authors provided estimates of the random for univariate and multivariate analyses as 95% confidence intervals (Table 6 of manuscript), but were not provided for comparisons of acute genitourinary and gastrointestinal (rectal) toxicity rates for CT-MRI and CT-based plans (Table 4 and 5 of manuscript).<sup>11</sup> When examining the external validity of the findings, it is unclear whether the participants were representative of the source population, and whether the staff, places, and facilities where the patients were treated were representative of the treatment the majority of the patients receive. When interpreting the internal validity of the study, one important factor to consider is blinding. In this case, blinding participants to the type(s) of simulation or blinding investigators responsible for analyzing the study was not described. If blinding was not performed in any capacity, the authors could have included this as a limitation in the discussion for improved transparency. Both intervention and control groups were followed for two years; however, it is not clear if the investigators excluded patients in situations where patients did not survive two years post-radiation treatment. More details regarding how lost to follow-up was

handled when determining each patient's eligibility for this study would improve the understanding of the included patient population and of the study's findings. In addition, all patients were from the same 4-year cohort (2004 through 2008), but it is unclear whether the number of patients between both groups was balanced within each year of inclusion. MRI simulation for treatment planning is a more recent clinical method; therefore, it would be important to know if the institution was using MRI simulation as early as 2004 and whether CT simulation alone was still being used for treatment planning after CT-MRI was introduced at this institution. These details would also be important in discerning whether patient demographic and treatment data characteristics were balanced, ultimately assisting with the interpretation of results. The authors did not describe sample size calculations to determine statistical power; however, they did mention that the number of patients included in the study precludes an adequately powered statistical analysis.

## Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions.

### *Clinical Effectiveness of Magnetic Resonance Imaging Simulator versus Other Treatment Planning Methods*

#### Acute genitourinary toxicity

The authors of the included study found an absolute reduction in acute grade 2 genitourinary toxicity of approximately 22% for CT-MRI versus CT-based treatment plans.<sup>11</sup> Of the grade 2 symptom subcategories, dysuria (painful or difficult urination) and urinary frequency were different between CT-MRI patients and CT patients. When focusing on patients without lymph nodes treated, there were no statistical differences found between CT-MRI and CT-based treatment plans.

Univariate regression for the entire database revealed MRI use (i.e., MRI-delineated prostate) had significant benefit in terms of improved acute genitourinary toxicity. When analyzing those patients who had fiducial markers used for simulations, MRI use did not affect acute genitourinary toxicity.

Multivariate regression revealed MRI use had a significant effect for reducing genitourinary toxicity when analyzing the entire database and those patients who had fiducial markers used for simulations.<sup>11</sup>

#### Acute gastrointestinal (rectal) toxicity

For the included study, MRI use had no significant effect for acute gastrointestinal (rectal) toxicity for all analyses.<sup>11</sup>

### *Cost-Effectiveness of Magnetic Resonance Imaging Simulator to Other Treatment Planning Methods*

No relevant evidence regarding the use of MRI simulators for simulation and treatment planning for patients requiring radiation therapy was identified; therefore, no summary can be provided.

#### *Guidelines*

No relevant guidelines regarding the use of magnetic resonance imaging simulators in the simulation and treatment of patients requiring radiation therapy was identified; therefore, no summary can be provided.

## Limitations

There are certain limitations to consider when reviewing the report.

The included study is a retrospective cohort study<sup>11</sup> and no randomized controlled trials were identified. Without randomized controlled trials, it is difficult to be certain of the true effects and the magnitude of benefit of MRI simulators for simulation and treatment planning for patients requiring radiation therapy. Moreover, the included study focused solely on acute toxicity in patients with prostate cancer treated with intensity modulated radiation therapy. Not only is more, higher quality research required to discern true clinical effects of MRI simulation for reduced toxicity among patients with prostate cancer, we require studies examining other clinical outcomes and investigating additional cancer populations who use radiation therapy as a treatment option.

Since no relevant cost-effectiveness studies or evidence-based guidelines were identified, there is limited evidence to inform decision-making for the use of MRI simulators for simulation and treatment planning.

## Conclusions and Implications for Decision or Policy Making

One relevant clinical study was identified in the search. This retrospective cohort study provided some evidence that supports the use of MRI simulation in conjunction with CT simulation for radiation treatment planning in that it may reduce acute genitourinary toxicity compared with CT simulation only. This same study did not find evidence to support the use of MRI for reducing gastrointestinal (rectal) toxicity. To reduce uncertainty of the clinical effectiveness of MRI simulators, important outcomes to consider for future research include: treatment localization, quality of life, tissue sparing for non-affected tissues, organs at risk, customized treatment for patients, and other adverse events.

No relevant cost-effectiveness studies or evidence-based guidelines were identified. Therefore, no conclusions regarding the cost-effectiveness or recommended use can be provided.

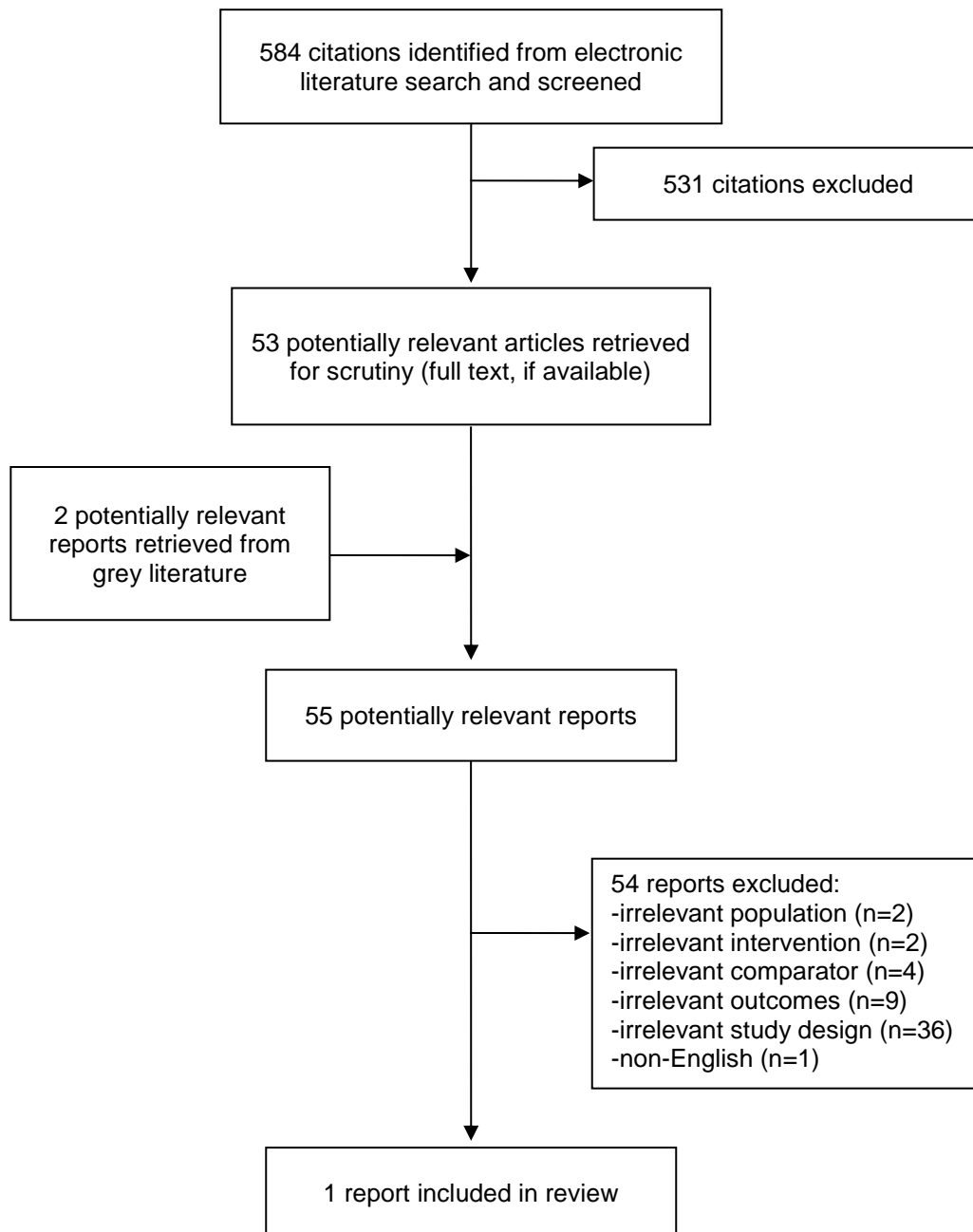
The limited evidence indicates that further research comparing MRI simulation to other treatment planning methods is needed in order to determine its place in treatment planning for radiation therapy.



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## Appendix 1: Selection of Included Studies



## Appendix 2: Characteristics of Included Publication

**Table 2: Characteristics of Included Primary Clinical Study**

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention	Comparator	Clinical Outcomes, Length of Follow-Up
Ali, 2013, <sup>11</sup> USA	Retrospective cohort study	n = 81 patients diagnosed with prostate cancer  Intervention: 28 patients, median age 71 years  Control: 53 patients, median age 67 years	MRI and CT used for radiation treatment planning	CT used for radiation treatment planning	Acute genitourinary toxicity and acute gastrointestinal (rectal) toxicity, both graded based on National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0  2-year follow-up

CT = computed tomography; MRI = magnetic resonance imaging; USA = United States of America

## Appendix 3: Critical Appraisal of Included Publication

**Table 3: Strengths and Limitations of Clinical Study using Downs and Black checklist<sup>9</sup>**

Strengths	Limitations
Ali, 2013 <sup>11</sup>	
<ul style="list-style-type: none"> <li>• Objectives, intervention, comparator, and main outcomes of the study clearly described</li> <li>• Outcomes of interest graded using a recognized scale (i.e., National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0)</li> <li>• Same length of follow-up for both groups (i.e., 2-years)</li> <li>• Patients in both groups from the same institution</li> <li>• Appropriate statistical tests used to assess outcomes</li> <li>• Characteristics of the study population clearly described</li> <li>• Main findings of the study adequately described</li> <li>• Distributions of potential confounders described; adjustment for confounders performed in analysis</li> <li>• Estimates of the random variability provided for univariate and multivariate analyses as 95% confidence intervals (i.e., Table 6 of manuscript)</li> <li>• Actual probability values (<i>P</i> values) reported for main outcomes</li> <li>• Due to the type of outcome being assessed (i.e., toxicity), adverse events reported</li> <li>• Funding for the study clearly stated and authors declared no conflicts of interest</li> </ul>	<ul style="list-style-type: none"> <li>• Estimates of the random variability not provided for comparisons of acute rectal and genitourinary toxicity rates for CT-MRI and CT-based plans (i.e., Table 4 and 5 of manuscript)</li> <li>• No mention of blinding evaluators who ascertained outcome data</li> <li>• Due to the type of study design, randomization and blinding of participants not possible</li> <li>• It is unclear whether the participants were representative of the source population</li> <li>• It is unclear if the staff, places, and facilities where the patients were treated were representative of the treatment the majority of the patients receive</li> <li>• It is unclear if patients were included over the same period of time; for example, it is possible that patients who had CT simulation versus CT-MRI CT simulation were included from different time periods within the years 2004 and 2008, especially if the incorporation of MRI simulation is a more recent clinical method</li> <li>• Sample size for statistical power not calculated</li> </ul>

CT = computed tomography; MRI = magnetic resonance imaging

## Appendix 4: Main Study Findings and Authors' Conclusions

**Table 4: Summary of Findings of Included Primary Clinical Study**

Main Study Findings	Authors' Conclusion
Ali, 2013 <sup>11</sup>	
<p><u>Acute genitourinary toxicity (CT-MRI use versus CT use)</u>  <i>Entire database</i></p> <ul style="list-style-type: none"> <li>Mantel-Haenzel chi-squared test: <math>P = 0.024</math>; grade 2 symptom subcategories different between CT-MRI patients and CT patients were dysuria (<math>P = 0.019</math>) or and urinary frequency (<math>P = 0.011</math>).</li> <li>univariate regression: <sup>a</sup> -1.030; 95% CI, -1.958 to -0.102*</li> <li>multivariate regression: <sup>a</sup> -1.772; 95% CI, -3.306 to -0.239*</li> </ul> <p><i>Only patients with fiducial use</i></p> <ul style="list-style-type: none"> <li>univariate regression: NS</li> <li>multivariate regression: <sup>a</sup> -2.256; 95% CI, -4.354 to -0.158*</li> </ul> <p><i>For those patients without lymph nodes treated</i></p> <ul style="list-style-type: none"> <li>Mantel-Haenzel chi-squared test: NS</li> </ul> <p><u>Acute gastrointestinal/rectal toxicity (CT-MRI use versus CT)</u>  <i>Entire database</i></p> <ul style="list-style-type: none"> <li>Mantel-Haenzel chi-squared test: NS</li> <li>univariate regression: NS</li> <li>multivariate regression: NS</li> </ul> <p><i>Only patients with fiducial use</i></p> <ul style="list-style-type: none"> <li>univariate regression: NS</li> <li>multivariate regression: NS</li> </ul> <p><i>For those patients without lymph nodes treated</i></p> <ul style="list-style-type: none"> <li>Mantel-Haenzel chi-squared test: NS</li> </ul>	<p><i>“This study demonstrates a statistically significant reduction in clinical acute GU [genitourinary] toxicity with the clinical implementation of MRI in the treatment planning process.” p. e8<sup>11</sup></i></p> <p><i>“A clinical prostate database review of patients treated with CT-MRI and CT only based treatment plans was performed and found a statistically significant reduction in genitourinary acute toxicity with the clinical use of MRI. This investigation represents findings providing the foundation for larger prospective studies exploring MRI use in the multi-institution or cooperative group setting.” p. e8<sup>11</sup></i></p>

CT = computed tomography; MRI = magnetic resonance imaging; NS = not significant

<sup>a</sup> Presented as coefficient, 95% confidence intervals

\*  $P < 0.05$

## Appendix 5: Additional References of Potential Interest

### MRI simulation/MR-generated synthetic CT versus other treatment planning methods – within subject design

Christensen M, Kamson DO, Snyder M, et al. Tryptophan PET-defined gross tumor volume offers better coverage of initial progression than standard MRI-based planning in glioblastoma patients. *Journal of Radiation Oncology*. 2014;3(2):131-138. (outcome: gross tumor volume for delineation of glioblastoma)

Doemer A, Chetty IJ, Glide-Hurst C, et al. Evaluating organ delineation, dose calculation and daily localization in an open-MRI simulation workflow for prostate cancer patients. *Radiation Oncology*. 2015;10:37. (outcomes: organ delineation, dose calculation, daily localization)

Gong G, Kong X, Wang X, Zheng C, Guo Y, Yin Y. Finding of dose evaluation for organs at risk in intensity-modulated radiation therapy for nasopharyngeal carcinoma using magnetic resonance imaging. *Precision Radiation Oncology*. 2017;1(1):7-12. (outcome: dose evaluation feature of organs at risk)

Gustafsson C, Nordstrom F, Persson E, Brynolfsson J, Olsson LE. Assessment of dosimetric impact of system specific geometric distortion in an MRI only based radiotherapy workflow for prostate. *Phys Med Biol*. 2017;62(8):2976-2989. (outcomes: planned dose distribution, delineated structures)

Hoogcarspel SJ, Van der Velden JM, Lagendijk JJ, van Vulpen M, Raaymakers BW. The feasibility of utilizing pseudo CT-data for online MRI based treatment plan adaptation for a stereotactic radiotherapy treatment of spinal bone metastases. *Phys Med Biol*. 2014;59(23):7383-7391. (outcome: dosimetric accuracy)

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Huang F, Ma C, Wang R, Gong G, Shang D, Yin Y. Defining the individual internal gross tumor volume of hepatocellular carcinoma using 4DCT and T2-weighted MRI images by deformable registration. *Translational Cancer Research*. 2018;7(1):151-157 (outcome: gross tumor volume)

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Lim Joon D, Lim A, Schneider M, et al. Prostate cancer post-prostatectomy radiotherapy: CT vs MRI for vesico-urethral anastomosis target delineation. *Radiother Oncol.* 2017;125(1):113-117. (outcome: spatial differences in vesico-urethral anastomosis and its impact on clinical target volume)

Maspero M, Savenije MHF, Dinkla AM, et al. Dose evaluation of fast synthetic-CT generation using a generative adversarial network for general pelvis MR-only radiotherapy. *Phys Med Biol.* 2018;63(18):185001. (outcome: dose calculation)

Paradis E, Cao Y, Lawrence TS, et al. Assessing the Dosimetric Accuracy of Magnetic Resonance-Generated Synthetic CT Images for Focal Brain VMAT Radiation Therapy. *Int J Radiat Oncol Biol Phys.* 2015;93(5):1154-1161 (outcome: dosimetric accuracy)

Tyagi N, Fontenla S, Zhang J, et al. Dosimetric and workflow evaluation of first commercial synthetic CT software for clinical use in pelvis. *Phys Med Biol.* 2017;62(8):2961-2975. (outcomes: dosimetric comparison, accuracy of localization at the treatment machine)

Veera J, Lim K, Dowling JA, O'Connor C, Holloway LC, Vinod SK. Dedicated MRI simulation for cervical cancer radiation treatment planning: Assessing the impact on clinical target volume delineation. *J Med Imaging Radiat Oncol.* 2018. (outcome: clinical target volume)

Yang DS, Yoon WS, Lee JA, et al. The effectiveness of gadolinium MRI to improve target delineation for radiotherapy in hepatocellular carcinoma: a comparative study of rigid image registration techniques. *Phys Med.* 2014;30(6):676-681 (outcome: gross target volume).

Young T, Thwaites D, Holloway L. Assessment of electron density effects on dose calculation and optimisation accuracy for nasopharynx, for MRI only treatment planning. *Australas Phys Eng Sci Med.* 2018;41(4). (outcomes: dose calculation, optimisation accuracy)

Walker A, Metcalfe P, Liney G, et al. MRI geometric distortion: Impact on tangential whole-breast IMRT. *J Appl Clin Med Phys.* 2016;17(5):7-19. (outcome: geometric distortions for target delineation and planning)

Wang H, Du K, Qu J, Chandarana H, Das IJ. Dosimetric evaluation of magnetic resonance-generated synthetic CT for radiation treatment of rectal cancer. *PLoS ONE [Electronic Resource].* 2018;13(1):e0190883. (outcomes: planning target volume, organs at risk, gamma analysis of dose distributions)

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### **MRI, PET/CT, and CT with intravenous contrast simulation - within-subject design**

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### **Non-English recommendations regarding the indication of MRI for the investigation and planning of breast cancer treatment**

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[https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/IRM\\_sein/IRM\\_Cancer-du-sein\\_EN\\_VF.pdf?sword=list%5B0%5D=mri&no\\_cache=1](https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/IRM_sein/IRM_Cancer-du-sein_EN_VF.pdf?sword=list%5B0%5D=mri&no_cache=1)