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SUMMARY WITH CRITICAL APPRAISAL

Magnetic Resonance Imaging-Guided Radiotherapy Delivery Systems for Cancer Treatment: A Review of Clinical Effectiveness, Cost- Effectiveness and Guidelines

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Abbreviations

| | |
|--------|--|
| CRD | Centre for Reviews and Dissemination |
| CT | computed tomography |
| Gy | Gray unit |
| HU | Hounsfield unit |
| LINAC | linear accelerator |
| MRgRT | magnetic resonance imaging-guided radiotherapy |
| MRI | stereotactic ablative radiotherapy |
| OAR | organs at risk |
| PRISMA | Preferred Reporting Items for Systematic Reviews and Meta-Analyses |
| SABR | stereotactic ablative radiotherapy |

Context and Policy Issues

In Canada, cancer is the leading cause of death, comprising 30% of all death events.¹ Radiation therapy is a common treatment option used in approximately two-thirds of all cancer patients,² and can be used on its own or in combination with chemotherapy and/or surgery.^{1,3} Image-guided radiotherapy facilitates tracking the location of the tumour and surrounding organs, and may result in less radiation treatment-related morbidity for patients compared those without image-guided radiotherapy.⁴ While using computed tomography (CT) for image-guided radiotherapy is the current standard of care, the field of radiation oncology is constantly evolving with the emergence of new technologies for cancer treatment.^{5,6}

In 2017, the first magnetic resonance imaging-guided radiotherapy (MRgRT) delivery system was approved by Health Canada.⁷ MRgRT delivery systems combine a linear accelerator system and a magnetic resonance imaging (MRI) scanner into one therapeutic device.^{6,8} MRgRT delivery systems enable “cross-sectional, beam-on imaging,”(p.1058) which aids in monitoring motion of the tumour and organs at risk (OAR) while delivering radiotherapy treatment.⁶ Compared to CT, MRI has superior tissue contrast resolution providing improved visibility of soft issues and has less motion blurring issues because a slice of MR data can be acquired in a fraction of a second.^{6,9} This is particularly important for target areas susceptible to respiratory motion and bowel motility.⁶

Given that MRgRT requires significant health care resources (e.g., financial, physical space to house the delivery system),¹⁰ there is a need to determine whether MRgRT may offer a more clinical and cost-effective form of treatment for purchasing decisions by health care decision-makers. Ultimately, the feasibility of novel MRgRT delivery systems as a standard of care for patients with cancer will depend on its clinical and cost-effectiveness compared to other cancer treatments.

The aim of this report is to summarize the evidence regarding the clinical and cost-effectiveness, as well as guidelines for the use of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy.

Research Questions

1. What is the clinical effectiveness of magnetic resonance imaging-guided radiotherapy delivery systems for the treatment of patients with cancer requiring radiotherapy?
2. What is the cost-effectiveness of magnetic resonance imaging-guided radiotherapy delivery systems for the treatment of patients with cancer requiring radiotherapy?
3. What are the evidence-based guidelines regarding the use of magnetic resonance imaging-guided radiotherapy delivery systems for the treatment of patients with cancer requiring radiotherapy?

Key Findings

One relevant non-randomized, retrospective cohort study was identified comparing the clinical effectiveness of a magnetic resonance imaging-guided radiotherapy (MRgRT) delivery system to a linear accelerator delivery system for the treatment of lung cancer patients with cancer requiring radiotherapy. This study examined mean lung density changes after treatment as an approach to examine early radiological lung damage. Evidence of limited quality from this study found no significant differences in mean lung density changes for patients who had lung stereotactic ablative radiotherapy using a MRgRT delivery system (i.e., tri-⁶⁰Co MRgRT) versus a linear accelerator delivery system.

No evidence regarding the cost-effectiveness of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy were identified.

No relevant evidence-based guidelines were identified for the use of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy.

Given the limited availability and low quality of evidence, the effectiveness and utility of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy remains uncertain.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Medline, 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. Two separate searches were conducted. The first search, on specific technology, used no filters. A second search, on the broader technology, applied methodological filters to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic studies and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2014 and February 25, 2019.

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

| | |
|----------------------|--|
| Population | Patients with a diagnosis of cancer who require radiotherapy |
| Intervention | Magnetic resonance imaging-guided radiotherapy (MRgRT) delivery systems such as MR-Linac (i.e., MRI combined with a radiotherapy linear accelerator, such as Elekta, Viewray MRIdian, Viewray MRIdian LINAC) or any other magnetic resonance-guided radiation therapy (MRgRT) hybrid delivery system |
| Comparator | Q1 and 2: Other image-guided (e.g., CT or X-ray or other imaging modality guided) hybrid radiotherapy interventions; Image-guided (non-hybrid) therapy (e.g., MRI Simulator, non-hybrid MRgRT, other image-guided radiotherapy approaches); Before-and-after treatment comparisons Q3: No comparator |
| Outcomes | Q1: Clinical effectiveness outcomes (e.g., therapeutic benefit [overall survival, progression free survival, mortality], quality of life, tissue sparing, treatment duration); Harms (e.g., acute toxicity, adverse events resulting from contraindications to MRI [pacemakers, neurostimulators], adverse events resulting from metallic objects acting as projectiles in magnetic field) Q2: Cost-effectiveness outcomes (e.g., incremental cost per quality adjusted life year or health benefit) Q3: Evidence-based guideline recommendations regarding appropriate indications, appropriate use, etc. |
| Study Designs | Q1: Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies Q2: Economic evaluations Q3: Evidence-based guidelines |

CT = computed tomography; MRgRT = magnetic resonance imaging-guided radiotherapy; MRI = magnetic resonance imaging

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 2014. Guidelines with unclear methodology were also excluded.

Critical Appraisal of Individual Studies

The included clinical study was critically appraised using Downs and Black Checklist.¹¹ 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 1,191 citations were identified in the literature search. Following screening of titles and abstracts, 1,138 citations were excluded and 53 potentially relevant reports from the electronic search were retrieved for full-text review. Four potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 56 publications were excluded for various reasons, and one non-randomized study met the inclusion criteria and was included in this report. Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Study Design

One relevant clinical study was identified from the literature search i.e., a non-randomized, retrospective, matched-comparison cohort study published in 2018.¹²

Country of Origin

The included clinical study was conducted in the Republic of Korea.¹²

Patient Population

The population of the included study was comprised of patients who received stereotactic ablative radiotherapy (SABR) for lung cancer within one institution between 2015 and 2016.¹² Patients were excluded if they had previously received radiotherapy in their thorax or showed locoregional recurrence during the follow-up period.¹² The MRgRT system group was comprised of eight patients (intervention; mean age of 73 years). The investigators matched the intervention patients at a 1:1 ratio with eight patients who received SABR via a linear accelerator (control; mean age of 71 years). Patients were matched according to dose/fractionation, tumour size, tumour location, and age.¹²

Interventions and Comparators

The intervention of interest for the included study was a tri-⁶⁰Co magnetic-resonance image (MRI) guided system called MRIdian™ (tri-⁶⁰Co SABR; manufacturer: ViewRay Inc., Cleveland, United States) for radiation treatment of patients with cancer.¹² The comparator of interest was a linear accelerator (LINAC SABR; manufacturer: Varian Medical Systems, United States) for radiation treatment of patients with cancer.¹² For both groups, prescription doses were 52 Gray units (Gy) or 60 Gy in four fractions.¹²

Outcomes

From the included study, the main outcomes of interest were paired differences between lung density changes in patients receiving tri-⁶⁰Co SABR versus LINAC SABR based on the first and second follow-up computed tomography (CT) scans.¹² Study investigators acquired outcome data by co-registering the first two follow-up CT scans with the planning (baseline) CT through deformable registration software (MIMTM version 5.4). Investigators reported changes in lung density in Hounsfield units (HU).¹² Authors estimated the minimum detectable difference in lung density changes as 100 HU.¹²

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

Summary of Critical Appraisal

The included study had a number of strengths and limitations. The authors clearly described the objectives, intervention, comparator, and main outcomes. The patient characteristics and main findings were adequately reported. Actual probability values (*P* values) reported for the main outcomes and the estimates of the random variability were provided as 95% confidence intervals. However, these 95% confidence intervals were presented as error bars in a figure making it difficult to determine explicit values. The authors disclosed their funding sources, and published an erratum which acknowledged one missing funding source.¹³ When examining the external validity of the findings, it is unclear whether the patients were representative of the source population, and whether the staff, places, and facilities where the patients were treated are representative of the treatment the majority of the patients receive. Due to the retrospective cohort design, the included study has certain inherent threats to its internal validity. For example, patients

were not blinded to the intervention nor were they randomized. Moreover, the study authors did not mention if the evaluators were blinded when ascertaining outcome data and they did not mention whether the outcome measured (i.e., lung density change) was the gold standard for assessing radiation-induced lung damage. Though the authors provide the median time intervals between the end date of radiotherapy (i.e., treatment) and the follow-up CT scans (i.e., outcome ascertainment), the authors do not describe if the time period between treatment and outcome ascertainment were the same for both groups. However, patients in both groups came from the same institution and were treated during same period of time (i.e., 2015 – 2016), which reduces the threat of selection bias, a component of internal validity. Finally, the authors did conduct a power calculation to determine the required sample size for their investigation was 16 patients (eight patients per group) to achieve 80% power to detect a difference.

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Clinical Effectiveness of Magnetic Resonance Imaging-Guided Radiotherapy Delivery Systems for the Treatment of Patients with Cancer Requiring Radiotherapy

After the first and second follow-up CT scans, no significant differences were identified between the intervention and control groups for mean lung density changes for all reported dose regions ($P > 0.05$ for all investigations).¹² This suggests that there was no significant difference in early radiological lung damage between tri-⁶⁰Co SABR and LINAC SABR.¹²

Cost-Effectiveness of Magnetic Resonance Imaging-Guided Radiotherapy Delivery Systems for the Treatment of Patients with Cancer Requiring Radiotherapy

No relevant cost-effectiveness literature regarding the use of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy was identified; therefore, no summary can be provided.

Guidelines

No relevant evidence-based guidelines regarding the use of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy was identified; therefore, no summary can be provided.

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

Limitations

There are certain limitations to consider when reviewing this report.

No systematic reviews or randomized controlled trials met the eligibility criteria; the one included study is a retrospective cohort study,¹² which is inherently more susceptible to bias due to its design. Randomized controlled trials allow for random allocation of participants to either the intervention group or control group with the goal of reducing bias when testing an intervention. Without this, it is difficult to be certain of the true effects of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy. The lack of eligible studies may be due to MRgRT being a novel technology. In addition, the included study

primarily examined change in lung density (essentially, a surrogate marker for clinical effectiveness) in patients with lung cancer treated with SABR. Not only is additional and higher quality research required to discern the true clinical effects of MRgRT for radiation-induced lung damage among patients who receive radiotherapy, we require studies examining other clinical outcomes (e.g., overall survival, progression free survival, mortality, quality of life, and harms) and additional cancer populations who are candidates for radiation therapy. Finally, the one eligible study included in this report was not conducted in Canada; therefore, it is unclear how generalizable the results are to the Canadian context (e.g., available treatments, patient characteristics). With the limited number of eligible studies describing clinical effectiveness, as well as the lack of relevant cost-effectiveness studies or evidence-based guidelines, there is limited evidence to inform decision-making for the use of MRgRT delivery systems in the treatment of patients with cancer requiring radiotherapy.

Conclusions and Implications for Decision or Policy Making

One relevant, non-randomized study regarding the clinical effectiveness of MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy was identified in the search. This study provided some evidence that the use of a MRgRT delivery system may not result in early radiological lung damage compared to a linear accelerator delivery system for lung stereotactic ablative radiotherapy. To reduce uncertainty of the clinical effectiveness of MRgRT delivery systems, outcomes to consider for future research may include: overall survival, progression free survival, mortality, quality of life, and harms (e.g., acute toxicity).

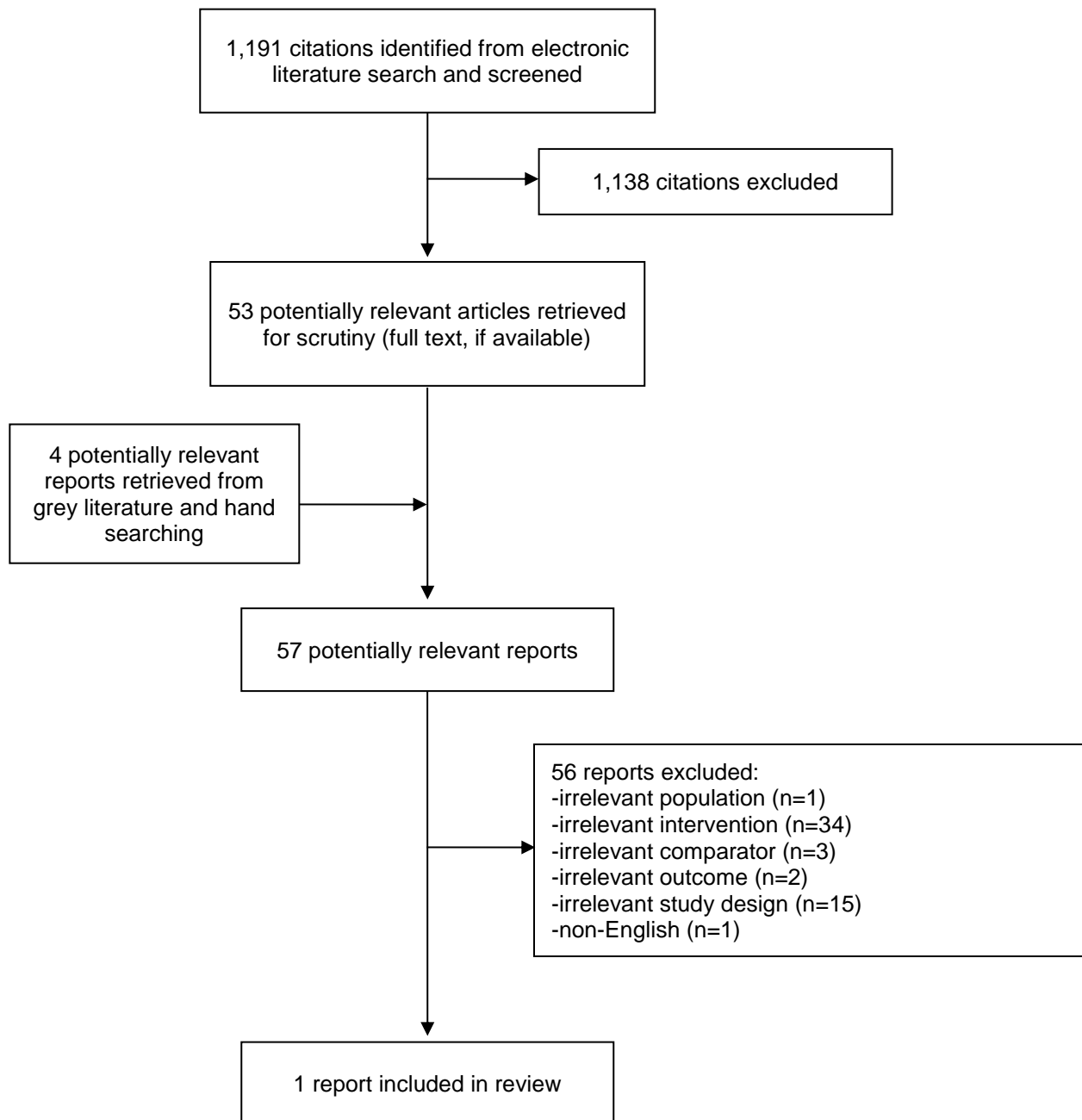
No relevant cost-effectiveness studies or evidence-based guidelines were identified. Therefore, no conclusions regarding the cost-effectiveness or recommended use can be provided.

The limited amount and quality of evidence indicates that additional clinical and cost-effectiveness studies comparing MRgRT delivery systems for the treatment of patients with cancer requiring radiotherapy to other cancer treatments are required to inform decision-making regarding its place in the care pathway for cancer patients.

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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 and Comparator(s) | Clinical Outcomes, Length of Follow-Up |
|---|--|---|---|---|
| Kim, 2018, ¹² Republic of Korea | Non-randomized, retrospective, matched-comparison cohort study | n = 16 patients who received lung SABR for lung cancer Intervention: 8 patients, mean age 73 (SD ± 7) years; 4 men, 4 women Control: 8 patients, mean age 71 (SD ± 9) years; 6 men, 2 women | Intervention: tri- ⁶⁰ Co magnetic-resonance image guided system, MRIdian™ (tri- ⁶⁰ Co SABR; manufacturer: ViewRay Inc., Cleveland, United States) Comparator: linear accelerator (LINAC SABR; manufacturer: Varian Medical Systems, United States) | Changes in radiological lung density 2 follow-up periods: 1) after first follow-up CT scan (median interval from end date of radiotherapy to CT scan for all patients = 5.5 weeks, range 4-7 weeks) 2) after first follow-up CT scan (median interval from end date of radiotherapy to CT scan for all patients = 20.5 weeks, range 16-31 weeks) |

CT = computed tomography; LINAC = linear accelerator; SABR = stereotactic ablative radiotherapy; SD = standard deviation; tri-⁶⁰Co = tri-⁶⁰Co magnetic-resonance image guided system

Appendix 3: Critical Appraisal of Included Publication

Table 3: Strengths and Limitations of Clinical Study using Downs and Black Checklist¹¹

| Strengths | Limitations |
|--|--|
| Kim, 2018 ¹² | |
| <ul style="list-style-type: none"> • Objectives, intervention, comparator, and main outcomes of the study clearly described • Patients in both groups from the same institution and recruited from same period of time • Characteristics of the patients included in the study clearly described • Appropriate statistical tests used to assess outcomes • Main findings adequately described • Estimates of the random variability provided as 95% confidence intervals • Actual probability values (<i>P</i> values) reported for main outcomes • Funding stated, including an erratum published to acknowledge one missing funding source.¹³ • Authors declared no competing interests • Sample size for statistical power calculated, indicating 80% power to detect a difference | <ul style="list-style-type: none"> • Due to the type of study design used, no attempt made to blind study participants to the intervention • Due to the type of study design used, no randomization of patients performed • No mention of blinding evaluators who ascertained outcome data • It is unclear if the time period between intervention and outcome ascertainment were the same for the intervention and control groups • It is unclear if outcome measures used are the gold standard (i.e., valid, reliable) • It is unclear whether the participants were representative of the source population • It is unclear if the staff, places, and facilities where the patients were treated are representative of the treatment the majority of the patients receive |

Appendix 4: Main Study Findings and Authors' Conclusions

Table 4: Summary of Findings of Included Primary Clinical Study

| Main Study Findings | Authors' Conclusion |
|---|--|
| Kim, 2018 ¹² | |
| <p><u>Mean lung density changes after first follow-up CT scan</u></p> <ul style="list-style-type: none"> Intervention: mean density lung changes in area above 48 Gy were -37.79 HU, 95% CI, - 78.38 to 2.8 Control: mean density lung changes in area above 48 Gy were 10.98 HU, 95% CI, -34.65 to 56.61 A non-significant difference between intervention and control group, with $P > 0.05$ <p><u>Mean lung density changes after second follow-up CT scan</u></p> <ul style="list-style-type: none"> Intervention: mean density lung changes "(HU) in 6 ± 12 Gy, 12 ± 18 Gy, 18 ± 24 Gy, 24 ± 36 Gy, 36 ± 48 Gy, and > 48 Gy were 25.6, 38.5, 69.9, 122.4, 167.1, and 154.2, respectively (p = 0.036, 0.012, 0.012, 0.012, 0.012, and 0.025, respectively)" (p. 6) Control: mean lung density changes "(HU) in 6 ± 12 Gy, 12 ± 18 Gy, 18 ± 24 Gy, 24 ± 36 Gy, 36 ± 48 Gy, and > 48 Gy were 23.6, 45.4, 74.5, 92.7, 91.8, and 100.8, respectively (P = 0.013, 0.003, 0.003, 0.002, 0.001, and 0.012, respectively)" (p. 6) A non-significant difference between intervention and control group for "all dose regions (0.5 ± 3 Gy, P = 0.859; 3 ± 6 Gy, P = 0.961; 6 ± 12 Gy, P = 0.871; 12 ± 18 Gy, P = 0.999; 18 ± 24 Gy, P = 0.982; 24 ± 36 Gy, P = 0.978; 36 ± 48 Gy, P = 0.545; > 48 Gy, p = 0.665)" (p. 6) | <p><i>"In conclusion, the difference in early lung density changes between tri-⁶⁰Co system SABR and LINAC SABR did not reach statistical significance. Although the lung dosimetric parameters of tri-⁶⁰Co plans were poor compared to those of the LINAC plans, our results suggest that tri-⁶⁰Co SABR could be performed safely. Moreover, the advantage of tri-⁶⁰Co system's ability to monitor tumor movement can reduce the planning target volume and it seems important to patients with limited lung function. However, further follow-up and more experience are needed to assess late lung damage."</i> (p. 8)</p> |

95% CI = 95% confidence interval; CT = computed tomography; Gy = Gray unit; HU = Hounsfield unit; LINAC = linear accelerator; SABR = stereotactic ablative radiotherapy; tri-⁶⁰Co = tri-⁶⁰Co magnetic-resonance image guided system

Appendix 5: Additional Reference of Potential Interest

Non-English Report

Jossart C. La radiothérapie guidée à l'aide de l'imagerie par résonance magnétique (IRM) en temps réel. [Real-time magnetic resonance imaging (MRI)-guided radiation therapy] Montréal (QC): Institut national d'excellence en santé et services sociaux (INESSS). 2014 https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Oncologie/INESSS_radiotherapie_guidee_IRM.pdf. Accessed 2019 Mar 14.

Ongoing clinical trials with no published results

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