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Guideline 21-2 Version 2

A Quality Initiative of the Program in Evidence-Based Care (PEBC), Cancer Care Ontario (CCO)

Three-Dimensional MR-Guided Intracavitary and Interstitial Brachytherapy for Cervical Cancer

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An assessment conducted in March 2024 deferred the review of Guideline 21-2 Version 2. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 21-2v2 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/57316

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DEFINITIONS

The following definitions are used throughout this review and align with those in the CCO recommendation report *Imaging Strategies for Definitive Intracavitary Brachytherapy of Cervical Cancer*. For the purpose of this practice guideline, **MR-guided BT refers to MR-adaptive BT or MR-informed BT**:

- MR-adaptive BT — Brachytherapy guided by MR imaging obtained after each intracavitary applicator and/or needle insertion with treatment plan adaptation and optimization based on GEC-ESTRO and ICRU 89 recommendations.
- MR-informed BT — Brachytherapy informed by MR imaging obtained after the first intracavitary applicator and/or needle insertion, with CT after subsequent insertions, and treatment plan adaptation and optimization based on GEC-ESTRO and ICRU 89 recommendations.
- MR-hybrid BT — Brachytherapy informed by MR imaging obtained at most one week prior to the brachytherapy procedure (at diagnosis and/or near the end of external beam radiotherapy) and CT imaging obtained after each insertion. MR-hybrid BT may incorporate treatment plan adaptation and optimization based on GEC-ESTRO and ICRU 89 recommendations.
- CT-guided BT — Brachytherapy informed by CT imaging obtained after each applicator insertion. CT-guided BT may incorporate treatment plan adaptation and optimization based on GEC-ESTRO and ICRU 89 recommendations. Alternatively, a conventional point-A prescription may be used.
- 2D BT — Brachytherapy informed by orthogonal x-rays obtained after each applicator insertion and based on a conventional point-A dose prescription as outlined in ICRU 89.
- 3D BT — Brachytherapy informed by volumetric CT or MR imaging obtained after each applicator insertion. 3D BT encompasses CT-guided BT, MR-adaptive BT, MR-informed BT and MR-hybrid BT.
- IC BT — Intracavitary brachytherapy using an intracavitary applicator (intrauterine tandem with an intravaginal ring or intravaginal ovoids) **without** interstitial needles
- ICIS BT — Intracavitary and Interstitial brachytherapy using an intracavitary applicator (intrauterine tandem with an intravaginal ring or intravaginal ovoids) **with** interstitial needles.

Three-Dimensional MR-Guided Intracavitary and Interstitial Brachytherapy for Cervical Cancer
Section 1: Recommendations

GUIDELINE OBJECTIVES

To assess the added clinical value of magnetic resonance (MR)-guided intracavitary (IC) or MR-guided intracavitary/interstitial (ICIS) brachytherapy (BT), compared with two-dimensional (2D) BT and computed tomography (CT)-guided BT.

TARGET POPULATION

Women with potentially curable, non-operable, locally advanced cervical cancer receiving external beam radiation (with or without chemotherapy) and BT.

INTENDED USERS

Intended users include radiation and gynecologic oncologists, physicists, dosimetrists and radiation therapists for the purpose of MR-guided IC and ICIS BT for patients with cervical cancer. Administrators and policy makers will also use the guideline for programmatic planning.

QUALITY OF STUDIES USED TO INFORM RECOMMENDATIONS

All studies used to inform the recommendations received a rating of moderate for overall risk of bias and a rating of moderate for risk of bias on the domain of 'confounding', since none were randomized. Quality assessments for studies informing each recommendation are listed below. More details regarding quality assessment ratings are available in Section 4 (Study Quality) and Appendix 4.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1
MR-guided (either MR-adaptive or MR-informed) IC or ICIS BT is the preferred method of practice for cervical cancer patients in Ontario and is recommended over 2D BT.
Qualifying Statements for Recommendation 1
• There is evidence to indicate improved tumour control and reduced toxicity with MR-guided BT compared with 2D BT. • Although definitive comparative studies are lacking, in our expert opinion, MR-adaptive BT and MR-informed BT yield comparable results. • Although definitive comparative studies are lacking, in our expert opinion, MR-adaptive BT and MR-informed BT are superior to MR-hybrid BT (with MR before applicator insertion) because of the marked changes in tumour and normal tissue anatomy that can result from applicator insertion, diminishing the relevance of MR images obtained earlier in the course of treatment. • Best-practice MR-guided BT includes the use of IS needles in a proportion of patients to achieve optimal tumour and normal tissue dosimetry.

Recommendation 2

There is a clear benefit of MR-guided BT over CT-guided BT alone in terms of tumour delineation, plan adaptation/optimization, and improved local control. Thus, MR-guided BT is preferred over CT-guided BT.

Qualifying Statements for Recommendation 2

- MR-guided (either MR-adaptive or MR-informed) BT is superior to CT-guided BT because of better tumour visualization, which translates to greater confidence in treatment plan adaptation and optimization, a higher likelihood of achieving optimal tumour and normal tissue dosimetry and a higher expectation of tumour control without toxicity.
- CT-guided BT may provide adequate visualization of normal tissues for treatment planning. However, without also having unambiguous visualization of the tumour with the applicator and/or needles in place, flexibility in plan optimization to assure adequate tumour coverage and normal tissue sparing is likely to be constrained.

Recommendation 3

MR-guided ICIS BT (with the use of IS needles) should be considered for patients with asymmetrical or large residual tumours at the time of BT, and in patients with small or large tumours at the time of BT where there is unfavourable normal tissue geometry or dosimetry and a high likelihood of excessive toxicity.

Qualifying Statements for Recommendation 3

- Evidence suggests greater planning flexibility and better tumour coverage without overdosing normal tissues with MR-guided ICIS BT, resulting in a higher likelihood of tumour control without toxicity.

Three-Dimensional MR-Guided Intracavitary and Interstitial Brachytherapy for Cervical Cancer
Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To assess the added clinical value of magnetic resonance (MR)-guided intracavitary (IC) or MR-guided intracavitary/interstitial (ICIS) brachytherapy (BT), compared with two-dimensional (2D) BT and computed tomography (CT)-guided BT.

TARGET POPULATION

Women with potentially curable, non-operable, locally advanced cervical cancer receiving external beam radiation (with or without chemotherapy) and BT.

INTENDED USERS

Intended users include radiation and gynecologic oncologists, physicists, dosimetrists and radiation therapists for the purpose of MR-guided IC and ICIS BT for patients with cervical cancer. Administrators and policy makers will also use the guideline for programmatic planning.

QUALITY OF STUDIES USED TO INFORM RECOMMENDATIONS

All studies used to inform the recommendations received a rating of moderate for overall risk of bias and a rating of moderate for risk of bias on the domain of 'confounding', since none were randomized. Quality assessments for studies informing each recommendation are listed below. More details regarding quality assessment ratings are available in Section 4 (Study Quality) and Appendix 4.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1

MR-guided (either MR-adaptive or MR-informed) IC or ICIS BT is the preferred method of practice for cervical cancer patients in Ontario and is recommended over 2D BT.

Qualifying Statements for Recommendation 1

- There is evidence to indicate improved tumour control and reduced toxicity with MR-guided BT compared with 2D BT.
- Although definitive comparative studies are lacking, in our expert opinion, MR-adaptive BT and MR-informed BT yield comparable results.
- Although definitive comparative studies are lacking, in our expert opinion, MR-adaptive BT and MR-informed BT are superior to MR-hybrid BT (with MR before applicator insertion) because of the marked changes in tumour and normal tissue anatomy that can result from applicator insertion, diminishing the relevance of MR images obtained earlier in the course of treatment.
- Best-practice MR-guided BT includes the use of IS needles in a proportion of patients to achieve optimal tumour and normal tissue dosimetry.

Key Evidence for Recommendation 1

- In a 2012 study by Charra-Brunaud et al. (STIC study), 24-month local relapse-free survival was significantly improved for patients treated with MR-guided or CT-guided BT compared with 2D BT: 78.5% versus 73.9% for those with more advanced tumours treated with 2D BT (p=0.003). Likewise, 24-month loco-regional relapse-free survival was significantly

improved for patients treated with 3D BT compared with 2D BT (69.6% vs. 61.2%; p=0.001) [1].
- Lindegaard et al. found a significant improvements in cause-specific (87% vs. 68%; p=0.001) and overall (79% vs. 63%; p=0.005) survival comparing MR-guided BT with 2D BT [2].
- Nomden et al. found increased three-year pelvic control (84% vs. 76%) and overall survival (OS) (65% vs. 54%) in an MR-guided BT group compared with a previously treated (historical cohort) x-ray group [3].
- Rijkmans et al. reported significantly improved local control (93% vs. 69%; p=0.01), pelvic recurrence (7% vs. 32%; p<0.001), disease-free survival (DFS) (83% vs. 49%; p<0.001)) and OS (86% vs. 51%; p=0.03) among patients treated with MR-guided BT, compared with those treated with 2D BT [4].
- Significantly less grade 3/4 gastrointestinal (GI) or genitourinary (GU) toxicity was seen with MR-guided BT compared with 2D BT in two studies [1,4].
- The quality assessment of the above studies resulted in the assignment of a moderate rating on the domain of risk of bias due to 'measurement of outcomes' for all four studies. Two were rated at moderate risk of bias for 'classification of intervention' [2,4]. For three of the above noted studies [2-4] it was unclear as to the how some of the participants were selected for participation into the study and, for all four, it was unclear whether the results were selectively reported. (For more detail see Section 4 'Study Quality' and Appendix 4.)

Interpretation of Evidence for Recommendation 1

Given the benefits of improved local control and reduced toxicity, MR-guided (either MR-adaptive of MR-informed) BT should be used when treating women with cervical cancer.

Recommendation 2

There is a clear benefit of MR-guided BT over CT-guided BT alone in terms of tumour delineation, plan adaptation/optimization, and improved local control. Thus, MR-guided BT is preferred over CT-guided BT.

Qualifying Statements for Recommendation 2

- MR-guided (either MR-adaptive or MR-informed) BT is superior to CT-guided BT because of better tumour visualization, which translates to greater confidence in treatment plan adaptation and optimization, a higher likelihood of achieving optimal tumour and normal tissue dosimetry and a higher expectation of tumour control without toxicity.
- CT-guided BT may provide adequate visualization of normal tissues for treatment planning. However, without also having unambiguous visualization of the tumour with the applicator and/or needles in place, flexibility in plan optimization to assure adequate tumour coverage and normal tissue sparing is likely to be constrained.

Key Evidence for Recommendation 2

- Kamran et al. found improved OS for patients receiving MR-guided BT compared with individuals receiving CT-guided BT on univariate analysis; however, the difference was not significant in a multivariate model [5].
- According to Potter et al., improved local control in tumours >5 cm in maximal size at diagnosis translated to improved three-year cause-specific survival in serial cohorts of patients spanning the period from 1993 to 2008 (70%/57%/40% for 2001-2008/1998-2000/1993-1997) [6,7]. There was no difference in tumours 2–5 cm in size at diagnosis.
- One of the two studies comparing MR-guided BT to CT-guided BT demonstrated a reduction in major morbidity with MR [8] while the second study showed no difference [5]. The two

studies comparing MR-guided BT to MR-hybrid BT found comparable late toxicity rates [9,10].
- Both of the studies noted above received a moderate rating on the domain of risk of bias due to 'measurement of outcomes'. Kamran et al. was rated at moderate risk of bias for 'departure from intended intervention' and unclear for selectively reporting results [5].

Interpretation of Evidence for Recommendation 2

Given improved tumour visualization with MR, which translates to greater flexibility and confidence in treatment plan adaptation and optimization, a higher likelihood of achieving optimal tumour and normal tissue dosimetry and a higher expectation of tumour control without toxicity, MR-guided (either MR-adaptive of MR-informed) BT is preferred over CT-guided BT.

Recommendation 3

MR-guided ICIS BT (with the use of IS needles) should be considered for patients with asymmetrical or large residual tumours at the time of BT, and in patients with small or large tumours at the time of BT where there is unfavourable normal tissue geometry or dosimetry and a high likelihood of excessive toxicity.

Qualifying Statements for Recommendation 3

- Evidence suggests greater planning flexibility and better tumour coverage without overdosing normal tissues with MR-guided ICIS BT, resulting in a higher likelihood of tumour control without toxicity.

Key Evidence for Recommendation 3

- The evidence base for Question 2 is derived from both clinical and dosimetric studies. The dosimetric data are grounded in strong dose-response relationships between tumour dose and long-term tumour control and between normal tissue doses and the development of serious side effects.
- Tanderup et al. evaluated the dosimetric outcomes for optimized MR-guided BT plans and compared the results to what could be achieved with 2D BT. They showed that patients with large residual tumours (high-risk clinical target volume [CTV_{HR}] >30 cm^3) at the time of BT were more likely to have favorable tumour and normal tissue dosimetry when IS needles were included in the treatment plan [11].
- Fokdal et al. (RetroEMBRACE) found the three-year local control rate in patients having a tumour volume at the time of BT (CTV_{HR}) ≥30 cm^3 to be 10% higher in the MR-guided ICIS BT group compared with IC BT alone. No difference was found for tumours that were <30 cm^3 at the time of BT. No significant difference in late morbidity was found between the two groups [12].
- In the RetroEMBRACE cohort, the improvement in pelvic control in the MR-guided BT group (compared with historical cohorts) was larger in patients with advanced-stage disease: absolute improvements were 4% to 10% in stage I/IIA patients, 7% to 12% in IIB, 8% to 24% in IIIB, and 59% in IVA. IS needles were used in 23% of patients. The authors argued that there was further room for treatment plan adaptation and more strategic use of IS needles in patients with advanced-stage disease, to facilitate greater dose escalation and a higher likelihood of pelvic control [13].
- In the Vienna study reported by Potter et al., a cohort treated between 1998 and 2003 was split into two groups: one treated between 1998 to 2000 when MR-guided BT was being used but the GEC-ESTRO guidelines were not fully optimized, and the other treated between 2001 and 2003 after guideline optimization. Overall, 44% of patients were treated with IS needles. The authors reported a 20% improvement in local control and a 30%

improvement in OS in patients with large (>5 cm) tumours at diagnosis treated in the latter period compared with the earlier period. Grade 3/4 late GU or GI toxicity was reduced from 10% to 2% [6].

- All four of the studies noted above received a moderate rating on the domain of risk of bias due to 'measurement of outcomes'. Three of the studies [12,13] were rated at moderate risk of bias for 'classification of intervention' and it was unclear in one of the studies whether results were selectively reported.

Interpretation of Evidence for Recommendation 3

The improved tumour visualization provided by MR facilitates treatment plan optimization and adaption. With these new tools, it is evident that planning dose constraints cannot be achieved (lower than required dose to the tumour and/or high doses to normal tissues) in some patients with MR-guided IC BT alone, placing these patients at high risk of cancer recurrence or toxicity. Strong consideration should then be given to the use of MR-guided ICIS BT (with the addition of IS needles) to improve the therapeutic ratio. The proportion of patients benefiting from the addition of IS needles is not well defined. However, current prospective treatment protocols such as EMBRACE II anticipate that a minimum of 40% to 50% of patients in any individual centre be treated with IS needles.

FURTHER QUALIFYING STATEMENTS AND IMPLEMENTATION CONSIDERATIONS

MR-guided BT (either MR-adaptive BT or MR-informed BT) with the use of IS needles when necessary should be the standard of care for patients with locally advanced cervical cancer in Ontario. However, MR-guided BT is considerably more demanding of resources and optimized, efficient, safe processes are of paramount importance in achieving the best possible outcomes. Barriers to implementation include the availability of MR for each BT fraction, initial and continuing education of all staff, the high cost of MR-compatible ICIS applicators, and the added time necessary for applicator insertion, imaging, planning, and treatment. **It is imperative that all members of the multidisciplinary team (radiation oncologists, medical physicists, and radiation therapists) are appropriately educated about best-practice MR-guided ICIS BT before undertaking procedures and that continuing professional education is available.** Furthermore, each centre and each practitioner must treat a sufficient number of patients with MR-guided ICIS BT annually to maintain clinical and technical competency. The required number of patients is not known. Previous studies in the 2D BT and CT-guided BT era suggested a minimum of 10 patients per year, although more patients may be needed to maintain competency with MR-guided ICIS BT given greater complexity at every step of the treatment planning and delivery process [14] .

The transition to MR-guided ICIS BT in Ontario should include the measurement of key quality indicators of programmatic and provincial performance to drive quality and system performance improvement. The indicators and benchmarks should be developed by consensus among practitioners, program leaders, and provincial leaders considering national and international guidelines balanced against local practicalities, including cost. Key quality indicators may include: 1) Patient wait times from referral to consultation with a radiation oncologist, and 'ready to' treat' with radiotherapy until the start of treatment; 2) Total treatment duration from the first fraction of external beam radiotherapy to the end of BT; 3) The number of patients treated annually; 4) The proportion of patients treated with high-quality MR-adaptive or MR-informed BT; and 5) The proportion of patients treated with IS needles. In addition, systematic prospective collection of physician-evaluated and patient-reported outcomes should be undertaken to evaluate efficacy (local tumour control, progression-free survival [PFS], and OS) and toxicity in a real-world clinical environment.

Three-Dimensional MR-Guided Intracavitary and Interstitial Brachytherapy for Cervical Cancer
Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-Based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

JUSTIFICATION FOR GUIDELINE

The CCO's PEBC recently re-assessed a previously published guideline (Guideline 21-2) "The Delivery of Brachytherapy for Cervix Cancer" (2009). The outcome of the assessment was that the document, which is based on 2D planning, should be updated to reflect rapidly evolving practices of BT.

GUIDELINE DEVELOPERS

This guideline was developed by the CCO MR-guided BT Working Group, which was convened at the request of the Radiation Treatment Program Gynaecological Community of Practice (GYN CoP) (Appendix 1).

The project was led by a small Working Group of the CCO GYN CoP, which was responsible for reviewing the evidence base, drafting the guideline recommendations and responding to comments received during the document review process. The Working Group had expertise in radiation oncology. Other members of the GYN CoP served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendix 1 and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [15]. This process includes a systematic review, interpretation of the evidence by the Working Group and draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [16] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

As a first step in developing this guideline, a search for existing guidelines was undertaken to determine whether an existing guideline could be adapted or endorsed. To this end, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: the Standards and Guidelines Evidence Directory of Cancer Guidelines (SAGE), Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse, and the Canadian Medical Association Infobase.
- Guideline developer websites: National Institute for Health and Care Excellence (NICE), Scottish Intercollegiate Guidelines Network (SIGN), American Society of Clinical Oncology (ASCO), and National Health and Medical Research Council - Australia.

Since no recent guidelines or systematic reviews were found, the literature was searched using MEDLINE (2005 through March 1, 2018), EMBASE (2005 through March 1, 2018), the Cochrane Central Register of Controlled Trials (OVID CCTR: March 2018), and the Database of Abstracts of Reviews of Effects (OVID DARE: 1st quarter 2018).

GUIDELINE REVIEW AND APPROVAL

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

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- Melissa Brouwers, Sheila McNair, Xiaomei Yao, Bill Evans and Donna Maziak, Laurie Elite and Kara Schnarr for providing feedback on draft versions.
- Kristyn Yiu, Sarah Deshpande, and Katelyn Beaulne for conducting a data audit.
- Sara Miller for copy editing.

Three-Dimensional MR-Guided Intracavitary and Interstitial Brachytherapy for Cervical Cancer
Section 4: Systematic Review

INTRODUCTION

Patients with cervical cancer often present with locally advanced, inoperable disease that has extended beyond the cervix to adjacent tissues and organs or spread to pelvic or para-aortic lymph nodes. Despite this high burden of disease, these patients can be cured with external beam radiotherapy and concurrent cisplatin chemotherapy followed by BT. BT is essential in the curative treatment of cervical cancer, with population-based studies showing substantially worse survival when BT is not used [17]. Historically, BT was delivered using a 'one size fits all' approach where the same treatment was provided to every patient regardless of individual tumour or patient characteristics. 2D planning was based on dose prescription points derived from orthogonal x-ray images as surrogates for the doses to tumour and normal tissues. This was effective but associated with suboptimal tumour control in some patients and an unacceptably high risk of serious treatment complications in others. It is now acknowledged that 3D, volumetric imaging, and optimized dosimetry can be used to personalize and adapt BT, thereby improving tumour control and reducing toxicity for patients.

The GEC-ESTRO has led the development of 3D image-based BT, standardizing the concepts, language, and protocols around this advanced technique [18-21]. These have been incorporated into a recent revision of the International Commission on Radiation Units and Measurements (ICRU) report 89 *Prescribing, Recording and Reporting Brachytherapy for Cancer of the Cervix*. The benefits of 3D image-based BT are derived from the use of optimal soft tissue imaging to visualize tumour and relevant, adjacent normal tissues with confidence **and** the ability to adapt BT using this imaging in a manner that optimally treats the tumour and minimizes the risk of toxicity. It is acknowledged that MR is the best-practice method of imaging the cervix for cancer diagnosis, staging, tumour response assessment, and BT planning [22] by virtue of providing greater soft tissue resolution and discrimination than CT. Although MR imaging facilitates volumetric dosimetry, plan optimization and adaptation may be limited with standard IC applicators. The addition of IS needles can overcome this limitation by allowing more freedom during treatment planning. This increases the likelihood of achieving optimal dose distributions that are 'sculpted' to treat the tumour and avoid normal tissues. Although IS BT has been available for decades, high toxicity rates were reported with 2D planning techniques, which substantially limited widespread uptake. It is now recognized that, with 3D imaging and planning, ICIS BT is safe and may offer advantages in specific clinical circumstances, such as in the treatment of large, advanced cervical tumours and/or in patients at high risk of toxicity. This evolution toward MR imaging as an enabler of advanced, adaptive BT in cervical cancer is reflected in a CCO recommendation report entitled, *Imaging Strategies for Definitive Intracavitary Brachytherapy of Cervical Cancer*, which was previously endorsed by the GYN CoP.

Given the momentum toward the use of MR-guided BT in cervical cancer, CCO's PEBC recently re-assessed a previously published guideline (Guideline 21-2), "The Delivery of BT for Cervix Cancer" (2009). The outcome of the assessment was that the document, which was based on 2D planning, should be updated to reflect rapidly evolving BT practice.

This systematic review summarizes published reports on 3D image-based IC and ICIS BT for cervical cancer. The data provide the foundation for recommendations about the use of MR-guided BT for cervical cancer patients in Ontario.

RESEARCH QUESTIONS

Q1. Does MR-guided IC BT, with or without IS needles and including treatment plan adaptation and optimization, improve tumour control and/or survival and/or reduce harmful side effects compared with conventional 2D-guided BT or CT-guided BT in patients with cervical cancer?

Q2. Which patients with cervical cancer benefit from the use of MR-guided ICIS BT compared with MR-guided IC BT alone?

STUDY SCOPE

The scope of this evidence review was limited to evaluating the clinical benefit of MR-guided BT compared with 2D BT or CT-guided BT (Q1) and identifying patient populations that benefit from MR-guided BT with the addition of IS needles (Q2). The latter question is particularly relevant in Ontario at present because MR-guided ICIS BT is offered in only a limited number of centres and scaled up or new models of care will be needed to make it available to all who can benefit. The review did not directly address the benefits of MR imaging over CT or other modalities in the diagnosis, staging, and management of cervical cancer, the strengths and limitations of different cervical cancer BT applicators, procedural issues relating to applicator and/or needles implantation (including the use of intra-operative ultrasound or other imaging), or the technical aspects of applicator reconstruction and treatment plan optimization.

The evidence base for Q1 and Q2 was grounded in studies that reported clinical outcomes for patients receiving MR-guided BT with or without IS needles compared with 2D BT or CT-guided BT. Additional evidence to inform Q2 was derived from studies that reported differences in tumour or normal tissue dosimetry with the addition of IS needle compared with IC treatment alone. In general, advances in radiation treatment planning and delivery that increase the dose to the tumour and reduce the dose to adjacent normal tissue have the potential to improve local control and reduce side effects. Strong cervical cancer MR-guided BT dose-response relationships have been reported for both tumour control and normal tissue toxicity [12,13,23-27], supporting the use of dosimetric surrogates of outcome in this review.

METHODS

This evidence review was conducted in two planned stages, including a search for existing guidelines and systematic reviews followed by a search for primary literature where guidelines and reviews do not exist. These stages are described in subsequent sections.

Search for Existing Systematic Reviews and Guidelines

MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews were searched for existing systematic reviews published since 2005. Relevant articles were identified by searches of MEDLINE (2005 – April 2017 week 10), EMBASE (2005 – 2016 week 10), and the Cochrane Library (2017). The reference lists of eligible trials were searched for relevant articles, and the National Guidelines Clearinghouse (http://www.guideline.gov/index.asp) was searched for existing evidence-based practice guidelines. Expert colleagues were also asked to identify any relevant unpublished or published trials not otherwise identified. The complete MEDLINE and EMBASE search strategies are detailed in Appendix 2.

Search for Primary Literature

Since no recent guidelines or systematic reviews were found, the literature was searched using MEDLINE (2005 through March 1, 2018), EMBASE (2005 through March 1, 2018), the Cochrane Central Register of Controlled Trials (OVID CCTR: March 2018), and the Database of Abstracts of Reviews of Effects (OVID DARE: 1st quarter 2018). In addition, the proceedings

of the meetings of the ASCO (2009 to 2018), the American Society of Therapeutic Radiology and Oncology (2009 to 2018), the American Brachytherapy Society (2009-2018), the Canadian Association of Radiation Oncology (2009-2018) and the European Society for Radiotherapy and Oncology (ESTRO: 2009 to 2018) were searched for relevant abstracts. Reference lists of studies deemed eligible for inclusion were scanned for additional citations. The literature search of the electronic databases combined disease-specific terms (cervix cancer, cervical carcinoma, etc.) along with disease stage-specific terms (potentially curable, non-operable, locally advanced) and treatment-specific terms (brachytherapy, MR-guided, intracavitary, interstitial, etc.) for all study designs (Appendix 2).

Study Selection Criteria and Process

Articles were eligible for inclusion in the systematic review if they met the following criteria:

- They were cohort, case-control, or historically controlled comparative studies (since it was determined that no randomized controlled trials exist),
- They included women with potentially curable, non-operable, locally advanced cervical cancer receiving external beam radiation and BT,
- (Q1) They included an intervention group receiving MR-guided ICIS BT, with control groups receiving conventional 2D BT or CT-guided BT,
- (Q2) They included an intervention group receiving MR-guided ICIS BT in relevant subgroups: volume of disease at diagnosis and/or at BT,
- They reported on at least one the following outcomes: local control, pelvic control, OS, cancer-specific survival (CSS), PFS, DFS, or lower GI and GU toxicity. Dosimetric surrogates for tumour control and toxicity were also included.

Studies were excluded if they:

- Reported only on the technical aspects of MR-guided IC or ICIS BT,
- Were case reports, commentaries, or editorials,
- Included cervical cancer patients' post-treatment,
- Had a sample size of fewer than 30 per group,
- Reported only on dosimetric surrogates as outcomes (Q1 only).

Data Extraction and Assessment of Study Quality and Potential for Bias

All relevant papers identified by the literature search were assessed against the above selection criteria independently by one of the authors (JB) (see Appendix 1 for a list of authors of this report). Discrepancies regarding eligibility were resolved by consensus of all the authors. The methodological quality of eligible studies was assessed using "ROBINS-I", a tool for assessing the risk of bias in non-randomized studies of interventions [27]; the following seven risk of bias criteria were considered: 1) Bias due to confounding, 2) Bias in selection of participants into the study, 3) Bias in classification of interventions, 4) Bias due to departures from intended interventions, 5) Bias due to missing data, 6) Bias in measurement of outcomes, and 7) Bias in selection of the reported results.

Data extraction was performed by one of the authors (JB), while a second reviewer acted as an independent auditor to verify the accuracy of the data extraction.

Synthesizing the Evidence

A quantitative analysis of the trial data was planned for the outcomes of interest if the authors deemed it appropriate (i.e., clinical homogeneity of the treatment regimens and patient populations). When data were available from two or more trials, a meta-analysis would be performed using Review Manager (RevMan 5.3.1) [28] provided by the Cochrane

Collaboration. The hazard ratio (HR) is the preferred statistic for pooling time-to-event outcomes because it incorporates data from the entire Kaplan-Meier curve and allows for censoring. When available, the HR would be extracted directly from the most recently reported trial results. The variances of the HR estimates would be calculated from the reported confidence intervals (CIs) or p-values using the methods described by Parmar et al. [29]. Qualitative assessment of the data, along with consideration of implementation issues with MR, also informed the recommendations.

RESULTS

Literature Search Results

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram summarizing this information is provided in Appendix 3.

Articles were retrieved from the MEDLINE (n=1550) and EMBASE (n=400) databases, and additional records identified through other sources (n=422). After duplicates were removed from the combined search results, 1338 articles were assessed by title and abstract for possible inclusion in the evidence summary. Of these, 1178 articles were rejected at the title level and the remaining 160 were assessed at the level of full text.

Fifty-six articles were included, with the most recent publication used where duplicate reports existed [1-6,8-13,23-26,30-69]. Table 4-1 shows the characteristics of these studies, including the MR vs. CT vs. 2D treatment group(s) and the proportion of patients with IS needles. Many of the included articles were based on data from two large, MR-guided cervical cancer databases (EMBRACE and RetroEMBRACE - prospective and retrospective, respectively) that together comprise over 2000 patients with comprehensive documentation of pre-treatment tumour characteristics, radiation treatment details, BT dosimetry according to GEC-ESTRO/ICRU 89 and long-term clinical outcomes, including local control, survival, and toxicity.

Study Characteristics

Eight studies addressed Q1 [1-5,8-10]. One study was a matched-pair case control study [62] and the remaining studies were cohort designs. Three of these followed patients prospectively [1,5,9], three followed patients retrospectively [3,4,10], and two used a combination of retrospective and prospective designs to follow patents contemporaneously compared with historical cohorts [2,8]. Three studies compared 3D MR with 2D technologies [1,3,4], three compared MR with CT [2,8,10], and two compared MR with a hybrid CT/MR technique [9,10]. The median follow-up periods ranged from 18 [5] to 41 months [9] and the median age of the cohorts ranged from 42 [9] to 58 years [8]. Sample sizes ranged from 56 [5] to 750 [1] (Table 4-1).

Six [3,12,35,42,55,69] of the 56 studies compared MR-guided ICIS BT to IC BT alone, addressing Q2. All six were cohort studies, with one following patients prospectively [35], and five following patients retrospectively [3,12,42,55,69]. The median follow-up periods ranged from three months [35] to five years [12] and the median age of the cohorts ranged from 50 [3] to 61 years [69]. Sample sizes ranged from 58 [35] to 610 [12] (sTable 4-1).

The remaining 42 articles reported primarily on MR-guided BT without a 2D BT or CT-guided BT comparison group and were examined for sub-group comparisons and dosimetric surrogates of outcomes. All were cohort studies, with 11 following patients prospectively [1,2,5,8,23,26,35,41,49,55,59,64,65] and one not indicating study design [43]; the remaining studies used a retrospective data collection method. The median follow-up periods ranged from seven weeks [56] to 60 months [26] and the median age of the cohorts ranged from 42 [9] to 61 years [69]. Sample sizes ranged from 33 [42] to 960 [26] (Table 4-1).

Study Quality

Appendix 4 shows the risks of bias using ROBINS-I [70]. Ten [9,31,32,34,42-44,64,65] of the 56 studies were assigned a serious rating on overall risk of bias and the remaining were assessed at a moderate overall risk of bias.

All studies received a moderate risk of bias rating on the domain of 'confounding' since none were randomized and thus confounding due to local and regional accessibility of MR technology, among other things, could not be ruled out.

It was unclear in 11 studies as to how at least one of the cohorts was selected for inclusion in the study [2-4,40,42,47,48,58,62,64,69]. The remaining studies received a low risk of bias rating on the domain of 'bias in selection of participants' since their selection process was consecutive, using incident cases.

Thirty-six studies [2,4,5,9-11,13,25,30-32,34-36,38-40,42,45-48,50-55,57,58,60-63,67,69] were rated as moderate for risk of bias on the domain of 'classification of interventions' since data were collected retrospectively and thus characteristics of the intervention was not recorded at the time of the intervention itself. While MR-guided BT was used for most of the patients in most of the studies, CT-guided BT was the predominate strategy in one study [1]. Two studies were rated as being unclear about classification of intervention [43,44]. The remaining studies were rated low on this domain.

Most studies were rated as low risk of bias due to 'departure from intended intervention' since choice of MR, etc. was usually based on availability. However, two studies [30,51] were rated as moderate on this domain because some patients refused CT. Likewise five studies [9,42-44,64] were rated as serious on risk of bias on this domain due to various departures from intended study interventions. The remaining studies were rated as being at low risk of bias on the domain of 'departures from intended intervention'.

Most studies scored at low risk of bias on the domain of 'missing data'. However, in 10 studies [2,34,42-44,57,58,64-66] it was unclear as to whether there were missing data.

Four studies were assessed at serious risk on the domain of 'bias in measurement of outcomes' due to, among other things, CTV_{HR} surrogate measurements being used with retrospectively collected data [31,32] and inadequate follow-up [1,65]. Only one study [26] was assigned a low rating due to the assessment that measurement error was unlikely. The remaining studies were assigned a moderate rating on the domain of risk of 'bias due to measurement of outcomes', since, among other things, their retrospective data collection process necessitated surrogate measurement for some or all of the outcomes.

Finally, for most of the studies, it was unclear as to whether there was potential risk of bias due to 'selection of the reported results'. However, 17 studies [12,13,23,25,26,33,35,41,45,46,56,68] had very well-described study methodologies and were rated as low risk of bias on this domain.

Table 4-1. Study Characteristics

Study	Population	FIGO risk groups	Treatment groups and % needles	Follow-up, predictors and outcomes
1. Castelnau-Marchand, 2015 [30]; **2.** Mazeron, 2015a [51] **3.** Mazeron, 2015b [54] **4.** Mazeron, 2014 [53] Villejuif, France (2006-2011)	Retrospective data from 225 consecutive patients with histologically proven stage IB-IVA cervical cancer treated with curative intent in a single institution (mean 48.53 yrs. [±11.42]).	IB-IVA (IB1 2.7%, IB2 24.9%, IIA 8.0%, IIB 48.9%, IIIA 1.8%, IIIB 10.7%, IVA 3.1%)	PDR MR (89.3%) or CT (10.7%) (primarily MR-CT if refused MR)/IC 97.8%, ICIS 2.2%	Med. 39.0 mos. (Castelnau) 6-8 wks./LC, DFS, OS, patterns of relapse, toxicity, dosimetry (Castelnau) dosimetric only (Mazeron)
5. Chargari, 2009 [31] Villejuif, France (2004-2006)	Retrospective data from 45 consecutive patients with primary locally advanced cervix carcinoma treated in a single institution (med. 50 yrs. [31-74]).	IB-IVA (IB 31%, II 51%, III-IVA 18%)	PDR MR (100%)/100% IC	26 mos./DVHP, relapse, toxicity
6. Chargari, 2016 [32] Villejuif, France (2007-2012)	Retrospective review of 109 patients treated with PDR BT at a single institution (med. 44 yrs. [26-69]).	IB-IVA (IB1 4.6%, IB2 37.6%, IIA 8.3%, IIB 43.1%, IIIA 0%, IIIB 5.5%, IVA 0.9%)	PDR IGBT (MR 91.7%, CT 8.3%)/IC 92.7% vs. ICIS 7.3%	39 mos./patterns of relapse, dosimetry
7. Charra-Brunaud 2012 [1] Q1 (3D [MR, CT]) vs. 2D STIC (2005-2012)	A French multi-centered (20) non-randomized prospective study of patients (n=705) treated for cervix carcinoma from 2005-2007 (mean age 56.1 3 and 53.4).	IBI-IIIB (IB1 28%, IB2 IIA IIB 58%, IIIA IIIB 14%)/NR	3D (CT [n=302] or MR [n=67]) 2D (orthogonal x-rays) <u>Treatment sub-groups</u> Group 3 (n=117,118): more advanced tumours treated with EBRT (+chemotherapy) and BT w/o surgery (primarily MR)/IC vs. ICIS not reported	Med. 24.34 (5.3 - 49.5) mos./LC, pelvic control, regional control, toxicity
8. Choong, 2016 [9] Q1 (MR vs. hybrid) Leeds, UK (2008-2012)	76 patients with at least one MR with applicator in place prospectively followed from 2008-2012 (med. age 42 yrs. [21-78]) Note: UK EMBRACE recruitment centre with 17 patients coming from the centre's EMBRACE cohort and the remaining not.	IB1-IVA (IB1 1%, IB2 14%, IIA 4%, IIB 72%, IIIA 3%, IIIB 1%, IVA 1%)	3-fraction conformal MR over 3 wks. (n=27 – 17 included in EMBRACE) Hybrid CT/MR (only at first treatment – standard treatment at institution) (n=49)/MR only IC 81.5%, ICIS 18.5%	Med 41 (23-71 mos.)/dosimetry, LC, other relapse and control, OS
9. Dimopoulos, 2009a [33]; **10.** Dimopoulos 2009b [23]; **11.** Potter, 2007 [6];	141 patients with cervical cancer from the population of 145 reported by Potter et al. (Stages	IB-IVA (I 9%, II 62%, III 25%, IV 5%)	All MR - 2-5cmDIAG 46%, >5cmDIAG 54%, (>5cmDIAG.2-5cmBT	Med. 51 mos./LR Rectum, sigmoid, bladder

Table 4-1. Study Characteristics

Study	Population	FIGO risk groups	Treatment groups and % needles	Follow-up, predictors and outcomes
12. Georg, 2011 [37]; **13.** Georg, 2012 [24] Vienna Group (1998-2003)	IB–IVA) treated in 1998–2003 (med. age 60 yrs. [26-92]).		59%, >5cmDIAG.>5cmBT 41%)/IC 79.4%, ICIS 20.6%	
14. Dyk, 2014 [34] Missouri (2009-2011)	Retrospectively collected data on 134 consecutive patients with newly diagnosed cervical cancer treated with MR-guided ICBT and IMRT (Med. 49 yrs. [25-85]).	IB-IVB (IB1 13.4%, IB2 17.9%, IIA 1.5%, IIB 40.3%, IIIA 2.2%, IIIB 22.4%, IVA 1.5%, IVB 0.7%)	MR-guided HDR and IMRT (100%)/IC 100%	Med/ 29 mos./DVP predicting GTV
15. Fokdal, 2013 [35] (Q2) EMBRACE (2001-2011) – 1 centre (Aarhus, Denmark)	58 consecutive patients prospectively accrued in the EMBRACE study from 2008-2011 (age NR).	IIB-IV (IB2-IIA 12%, IIB 64%, III-IV 24%)	Group 1: Combined ICIS implant at BT1 and BT2 (n=24 – 41.4%); Group 2: IC BT only (n=34 - 58.6%)	3 mos./toxicity, TVP
16. Fokdal, 2016 [12] (Q2) ; **17.** Sturzda, 2016 [13] RetroEMBRACE (1998-2012) – 12 centres	Data from 610 patients from 12 institutions retrospectively collected 1998-2012 (med. age 52 yrs. [23-91]).	IB-IVB (IB 19%, 2A 7%, 2B 48%, 3A 3%, 3B 19%, 4A + 4B 4%)	Group 1: MR/CT guided ICIS(n=300) Group 2: MR/CT guided IC (n=310)	Med. 45 mos./ 3yr LC overall 5yr LC
18. Gill, 2015 [10] Q1 (MR vs. hybrid) Pittsburgh (2007-2013)	128 patients in a single institution retrospectively followed 2007-2013 (median age 52 yrs. [28-91]).	IB-IVA (IB/IIA 25%, HR IIB/IIIA 59%, HR IIIB/IVA 16%)	Group 1: HDR MR (n=62) with each application Group 2: Hybrid (CT and MR) (n=66)/100% IC	3yr./ dosimetry, LC, DFS, OS, toxicity
19. Georg 2013 [36]; **20.** Majercakova, 2015 [50] Vienna (1998-2008)	Retrospectively collected data from 225 consecutive cervical cancer patients from a single institution (mean 58 yrs. [26-92]).	I 11%, II 61%, III 24% IV 4%	MR-based BT was performed using tandem ring applicators ± IS needles, and/or combination of tandem and vaginal cylinders ±IS needles/IC 66%, ICIS 34%	44 mos./Late rectal and urinary bladder, dosimetry
21. Haie-Meder, 2009 [38] (FIGO IB1-IIB); **22.** Haie-Meder, 2010 [39] (FIGO IB2-IVB) Villejuif, France (2000-2004)	Haie-Meder 2009 Retrospective study of 39 patients with early cervical cancer who were treated with preoperative LDR BT followed by surgery in single institution (med. 46 yrs. [31-71]). Haie-Meder 2010 84 patients with primary locally advanced cervix carcinoma were treated in our institution with LDR BT after initial concomitant chemotherapy in single institution (med. 46.5 yrs. [25-82]).	Haie-Meder 2009 (IB-IIB) IB1 94.9%, IIA 2.6%, IIB 2.6% Haie-Meder 2010 IIB2-IVB (IB2 23.8%, IIA 5.9%, IIB 38.1, IIIA 2.4%, IIIB 23.8%, IVA 4.8%, IVB 1.2%)	MR-based LDR BT consisting of IC uterovaginal BT with a prescribed dose of 60 Gy to the 100% of the intermediate-risk CTV given in one fraction at a dose rate of 0.6 Gy/100% IC	4.4 yrs./DVHP, toxicity, patterns of failure and survival, dosimetry

Table 4-1. Study Characteristics

Study	Population	FIGO risk groups	Treatment groups and % needles	Follow-up, predictors and outcomes
23. Hannoun-Levi, 2013 [40] Nice France (2007-2011)	Retrospectively collected data on 103 patients with a histologically proven invasive cervical cancer with high risk of local recurrence (size 2 cm, adenocarcinoma type, perineural and/or lymphovascular invasion) (med. 51 yrs. [28-73]).	1B2-IV (69%)	(all MR) preoperative HDRB, which delivered a total dose of 39 Gy in nine fractions over 5 days/100% ICIS	Med. 24 mos./DVHP, pathologic response
24. Jastaniyah, 2016 [41]; **25.** Yoshida, 2015 [68] EMBRACE (2008-2013) – 22 centers	Prospective data from 626 patients with FIGO stage IIB and IIIB cervical cancer accrued into the EMBRACE trial between July 2008 and November 2013 (med. age 50 yrs. [24-91]).	IIB-IIIB (IIB 71%, IIIB 29%)	All MR - G1: IB1-like tumours n= 55, G2: tumours with good response and any size n=78, G3 small tumours with moderate response n=123, G4 large tumours with moderate response n=147, G5 tumours with poor response n=75/IC 55%, ICIS 45%	?/Dosimetric only
26. Kamran, 2017 [5] Q1 (MR vs. CT) Boston (2005-2015)	56 patients with biopsy-proven locally advanced cervical cancer, prospectively followed, who were treated with HDR IS BT between 2005 and 2015 (med age 55.0 yrs. [26.9-77.5]).	I-IVA (I 5%, II 20%, III 45%, IVA 30%)	HDR MR (n=29) vs. CT (n=27)/ IC 100%	Med. 18.6 Mos. (1.2-92.8)/ dosimetry, local recurrence, OS, toxicity
27. Karlsson, 2017 [42] (Q2) Sweden (2012-2015)	Retrospectively collected data from 33 patients (71 fractions), where 25 fractions were without and 46 were with IS needles in a single institution (age NR).	NR	MR/CT intra-fractional longitudinal tandem applicator shift between imaging and dose delivery in cervix BT and its estimated dosimetric impact on the target, CTV_{HR} for patients with (Group 1) and without needles (Group 2)/IC 35.2%, ICIS 64.8%	NR/dosimetry

Table 4-1. Study Characteristics

Study	Population	FIGO risk groups	Treatment groups and % needles	Follow-up, predictors and outcomes
28. Kim, 2017 [43]; **29.** Kim, 2016 [44] Korea (2008-2013)	135 consecutive patients received high-dose-rate MR-guided BT with curative intent (mean 53 yrs. [27-84]) (note: could not assess whether prospective or retrospective design)	IB- IVB (IB1-IVB (IB1 8.6%, IB2 9.5, IIA1 7.8%, IIA2 7.0%, IIB 39.8%,IIIA 2.3%, IIIB 6.3%, IVA 4.7%, IVB (positive PAN) 14.1%))	high-dose-rate MR-guided BT of 5 Gy in 6 fractions (100%)/IC 100%	44 mos./DVP, toxicities, LRFS, RRFS, DMFS, DFS, CSS, OS
30. Kirchheiner, 2016 [45]; **31.** Kirchheiner, 2014 [46] EMBRACE (2008-2013) – 19 centres	Prospective data from 630 previously untreated, biopsy proven squamous-, adeno- or adenosquamous carcinoma of the uterine cervix (med. 49 yrs. [22-89]).	IB-4B (IB 17%, 2A 5%, 2B 54%, 3A <1%, 3B 19%, 4A 4%, 4B 1%)	PDR or HDR, with MR with the applicator in situ performed for at least the first BT fraction (100%)/IC 99.3%, ICIS .07%	Med 24 mos./vaginal stenosis, early, late vaginal morbidity
32. Lakosi, 2015 [47] Belgium (2007-2014)	Retrospective data on 85 patients with FIGO stage 1B1 N+ or ≥ 1B2 cervical cancer treated in a single institution (med. 50 yrs. [26-78]).	IB-IVA (IB 22.3%, IIA 17.6%, IIB 40.0%, IIIA 2.4%, IIIB 15.3%, IVA 2.4%)	MR-guided PDR BT was performed in all cases. IC-BT was delivered using initially a titanium tandem-ovoid applicator which was replaced by a plastic tandem ring applicator from 2012/IC 88.3%, ICIS 11.7%	36 mos. (6 – 94)/ toxicity, PFS, LC, PFS pelvic (PC), PFS overall, CSS, OS
33. Lee, 2017 [48]	Retrospective data from patients with histologically confirmed squamous cell carcinoma of the cervix, staged as FIGO Ib2-IVa on initial pelvic MR (n=225)	FIGO Ib2-IVa	Initial pelvic MR and -CRT MR was performed median 35 days after the beginning of CRT and before BT/ICIS 0%	3 yrs./CSS, RFS
34. Lindegaard, 2013 [2] Q1 (MR vs. CT) NOCECA study (2005-2011)	Prospective data (with historical comparison) from 140 patients accrued from February 1994 to March 2000 to the NOCECA study and 140 consecutive patients treated with BT from November 2005 to February 2011 (mean age BT 56 yrs. [27-84], NOCECA 61 [28-80]).	IB-IVA (IB/IIA 14%, HR IIB/IIIA 62%, HR IIIB/IVA 24%)	MI-guided BT (N=140) 2005-2011 (IC & ICIS) NOCECA cohort CT-based, some x-ray (n=99) 1994-2000 (all IC)/57% IC, 43% ICIS	3 yrs./DVH parameters, toxicity
35. Mahantshetty, 2017 [49] EMBRACE (single center - India)	LACC patients enrolled in a prospective (EMBRACE) study (n=94)	IIB 33%, IIIB 58.5%, IVA 8.5%	All MR 2 (BT applications once weekly and 2 treatments 12 to 15 hours apart per application, with a planning aim of 4	39 mos./LCR, PFS, DSS, toxicity

Table 4-1. Study Characteristics

Study	Population	FIGO risk groups	Treatment groups and % needles	Follow-up, predictors and outcomes
			fractions of 7 Gy)/ICIS unclear.	
36. Mazeron, 2016 [26] EMBRACE (2008-?) all 24 centers	Prospectively collected data from 960 patients from the EMBRACE study (med. 50.5±13.1 yrs)	IA-IVA (IA 0.1%, IB 19.2%, IIA 5.5%, IIB 53.1%, IIIA 0.6%, IIIB 17.1%, IVA 3.0%, unknown 1.3%)	All MR - HDR or PDR BT/IC 65.6%, ICIS 34.4%	60 mos./late rectal morbidity
37. Mazeron, 2014 [53] Villejuif, France (2008-?)	Prospective data from 229 consecutive patients treated for locally advanced cervical cancer in a single institution (age NR)	1B1-IVA (% NR)	MR- or CT-guided uterovaginal BT/ IC 100%	NR/dosimetry only
38. Mohamed, 2015 [55] Q2 Aarthus, Denmark (2008-2011) note: data based on 23 patients who later received IC – IS BT compared with simulated treatment with IC))	Retrospective data from 51 consecutive patients with locally advanced cervical cancer with parametrial involvement at diagnosis (age NR).	IIIB, IIIB, IV (IIB 43%, IIIB-IV 57%)	MR – ICIS BT (n=23 – 45.1%) combined intrauterine tandem and a ring with a cap for needle insertion MR – IC BT + EBRT PB (n=28 – 54.9%)	7 wks./dosimetry only
39. Mohamed, 2016 [56] EMBRACE (2008-?) 3 centres	Prospective data from 50 consecutive locally advanced cervical cancer patients without lower or middle vaginal involvement at diagnosis (Age NR).	IB-IVB (IB 24%, IIA 4%, IIB 56%, IIIB, 14%, and IVB 2%)	Vaginal dose de-escalation (VDD) and non-VDD/IC 74%, ICIS 26%	NR/dosimetry only
40. Murofushi, 2017 [57] Conference Abstract	Retrospective analysis of consecutive patients with locally advanced cervical cancer treated with radical radiotherapy (n=146).	Ib2 n=6, II n=67, III n= 64, IVA n=9	All MR (standard IC BT was principally administered for patients with 4 cm or smaller mass and symmetrical location on interim MR)/ICIS 0%	3 yrs./complete response, OS, DFS, LC, DMFS, dosimetry
41. Nomden, 2013 [3] Q1 (MR vs. 2D) also Q2 The Netherlands (2006-2008)	Retrospective data on 46 patients treated in a single institution between 2006 and 2008 and 54 historical cohorts (med. 50 yrs. [29-86])	IB-IVB (IB/IIA 30% HR IIB/IIIA 50%) HR IIIB/IVA 20% FICO stage IB 13%, IIA 17%, IIB 48%, IIIA 2%, IIIB 15%, IVA 2%, IVB 2%; IB, IIA, IIB 78%, IIIA, IIIB, IVA, IVB 22%)	chemo-radiation and MR-image guided adaptive BT (MR-BT) using tandem-ovoid applicators for IC or combined ICIS approaches. Historical cohort with a previous treated with chemo-radiation and x-ray-	3yrs./LC, PFC, OS, late morbidity

Table 4-1. Study Characteristics

Study	Population	FIGO risk groups	Treatment groups and % needles	Follow-up, predictors and outcomes
			based BT between 1999 and 2004/69.6 IC, ICIS 30.4%	
42. O'Steen, 2017 [58] Conference Abstract	Retrospective review of patients with FIGO stage I-IV cervical cancer who underwent MR-guided HDR tandem and ring (T&R) BT (n=43)	56% were FIGO stage IIB	MR with at least the first BT insertion (CT was performed for non-MR insertions) and completed at least 4 fractions of BT.	5 yrs./ LC, DFS, OS, freedom from DM, toxicity
43. Petit, 2016 [59] Villejuif, France (2009-2014)	Prospective data from 115 patients treated with curative intent and followed prospectively in a single institution (Med. 47.5 yrs. [26.9-79.8]).	IB1-IVA (IB2 33.9%, IIA 4.3%, IIB 51.3%, IIIB 6.1%, IVA 4.3%)	Evaluated by small bowel morbidity (grade 0,1,2,3)/IC 100%	2 yrs./late morbidity, dosimetry
44. Potter, 2011 [8] Q1 (MR protocol period vs. CT vs. MR learning) Vienna (2001-2008)	Prospective cohort (with historical comparison) of patients (n=156 Vienna 2001-2008) from a single institution with stage IB1 to IVA disease, who underwent the complete definitive RT and who did not have a previous history of malignancy (med. age 58 yrs.).	IA-IVA (IA 1%, IB 13.4%, IIA 1.9%, IIB 56.4%, IIIA 3.1%, IIIB 20.5%, IVA 3.7%)	Vienna 2001-2008 MR-BT –protocol period EBRT with 45-50.4 By ± concomitant CBT CT plus 4 × 7 Gy HDR BT (n=156 – 69/156 ICIS) Historical Vienna 1998-2000 (n=73) MR-BT –learning period; Vienna 1993-1997 (n=189) CT-BT – learning period/IC/56%, ICIS 44%	Med. 35.6 mos./dose volume adaptation, dose escalation, disease control, Toxicity
45. Ribeiro, 2016 [60] Belgium (2002-2012)	Retrospectively collected data from 170 consecutive patients with cervical cancer without metastases beyond the para-aortic nodal region treated in single institution (Med. 55 yrs. [16-88]).	IB–IVB (IB 11.8%, IB2 10%, IIA 6.5%, IIB 41.2%, IIIIA 2.4%, IIIB 15.3%, IVA 5.9%, IVB 17.1%)	MR (%?) or CT (%?) (dose optimization for first 16 patients done manually by adjusting dwell positions and dwell times in a trial and error procedure, continuously checking the effect on the dose distribution] vs. not optimized)/IC 84%, ICIS 16%	Med. 37 mos./LC, OS, relapse, late toxicity, DVH parameters

Table 4-1. Study Characteristics

Study	Population	FIGO risk groups	Treatment groups and % needles	Follow-up, predictors and outcomes
46. Rijkmans, 2014 [4]Q1 (3D [MR&CT] vs 2D historical) The Netherlands (2000-2012)	Retrospective cohort (n= 126) of patients from a single centre treated with primary radiation therapy between 2000 and 2012 (mean age 56 yrs. [26-92).	IB-IVA (IB/IIA 35%, HR IIB/IIIA 45%, HR IIIB/IVA 21%)	3D IGBT (n=83) Historical conventional (2D) BT (n=43) EBRT and BT, mostly combined with CT (wkly. CBT, 5-6 cycles of 40 mg/m^2 i.v.) and in a minority of cases with deep hyperthermia (5 sessions, once per wk. concurrent with RT)/80% IC/20% ICIS	3y/Pelvic tumour control, OS, dosimetry, pari-aortic nodal recurrence, distant metastases, adverse events.
47. Schmid, 2014 [61]; **48.** Schmid, 2013 [63] Vienna (1998-2009)	Retrospective data from 189 patients with cervical cancer treated with definitive radiotherapy in a single institution (mean 57 yrs. [26-80]).	1B-IVA (IB 13%, IIA 4%, IIB 58%, IIIIA 2%, IIIB 18%, IVA 4%)	All MR - Various high and low risk groups based on FIGO stage, tumour size, lymph node status, histology, grade, age and OTT/ICIS NR	Med. 54 mos./distant metastasis free survival, patterns of distant failure
49. Schmid, 2011 [62] Athens, Greece (1998-2009)	Retrospectively collect (matched-pair case control) data on 265 patients treated with definitive EBRT ± chemotherapy and image- guided BT at a single institution (mean age 52 yrs. [33-90]).	IB-IVA (IB 0%, IIA 5%, IIB 38%, IIIB 48%, IVA 10%)	LR vs. matched pairs CCLR according to FIGO stage, histology, lymph node status, tumour size and chemo/IC 73.8, ICIS 26.2%	Med. 17 mos./patterns of failure, dose analysis
50. Sharma, 2011 New Delhi, India (2005-2007)	Prospective data from 42 patients with locally advanced cervix carcinoma in a single institution (med. 49 yrs. [25-67])	IIB-IVA (IIB 24%, IIIB 64%, IVA 12%)	HDR CT (%?) and MR (%?)/ICIS 100%	Med. 23 mos./toxicity, OS, LC
51. Tanderup, 2016 [25]; RetroEMBRACE (sub-cohort – 7 centers)	Retrospective data from 488 patients from 7 institutions consecutive (6 centres) or represented all patients who were treated with MR-guided BT (1 centre) between 1998-2009 (med. age 54 yrs. [23-91])	IB-IVB (IB 19%, IIA 7%, IIB 50%, IIIA 3%, IIIB 18%, IVA 0%, IVB 3%).	All MR/ICIS NR	Med 46 mos./LF, LC
52. Tanderup, 2010 [11] Aarhus, Denmark (2005-2009)	Retrospective data from 72 consecutive patients treated in a single institution (age NR)	IB-IVB (IB 8%, IIA 4%, IIB 46%, IIIA 8%, IIIB 25%, IVA 1%, IVB 7%).	All MR/IC 62.5%, ICIS 37.5%	NR/dosimetry

Table 4-1. Study Characteristics

Study	Population	FIGO risk groups	Treatment groups and % needles	Follow-up, predictors and outcomes
53. Tharavichitkul, 2013 [65] Thailand (2008-2011)	Prospective data from 47 patients with carcinoma of cervix uteri treated in a single institution (Mean age 52.4 yrs. [36-63])	IIB-IIIB (IIB 68%, IIIB 32%)	CT (68%) or MR (32%)/IC 100%	Med. 26 mos./LC, DFS, OS, toxicity, dosimetry
54. Tinkle, 2015 [66] San Francisco (2003-2009)	Retrospective data from 111 consecutively accrued patients with locoregionally advanced cervical cancer treated at a single institution (med. Age 51.9 yrs. ([28.2-85.3])	IB1-IVB (IB1 5%, IB2 12%, IIA 3%, IIB 23%, IIIA 5%, IIIB 34%, IVA 3%, IVB 15%)	CT (60%) or MR (40%) planning/ICIS 100%	Med. 42 mos./rate of recurrence, LC, DFS, OS, toxicity
55. Ujaimi, 2017 [67]	Retrospectively data for women with Stage IB - IVA cervical cancer treated consecutively with MR-guided BT between 2008 and 2013	1B 56%, 2A/2VB 39%, 3A/3B 6%	All MR	44 mos./toxicity
56. Yoshida, 2013 [69] Q2 Japan (1993-2011)	Retrospectively included 100 patients with vaginal cancers (90% cervical) treated between 1993 and 2011 at a single institution (med. age 61 yrs. [33-88])	I0-IV (1%, IA 0%, IB 6%, IIA 7%, IIB 31%, IIIA 7%, IIIB 47%, IIIIA 1%)	IC BT (n=37) ICIS BT (n=63)	NR/toxicity

BT = brachytherapy; CBT = cisplatin; CCLR = continuous complete remission; CSS = cancer specific survival; CT = computer tomography; CBT = conventional brachytherapy; DFS = disease-free survival; DMFS = distant metastasis-free survival; DVHP = dose-volume histogram parameters; DVP = dose volume parameters; EBRT = external beam radiation therapy; GTV = Gross tumour Volume; HDR = High dose rate; IC = intracavitary BT; ICIS = Interstitial and IC BT; IGBT = image guided brachytherapy; IMRT = intensity-modulated radiation therapy; LACC = locally advanced cervical cancer; LC = local control; LDR = low dose rate; LF = local failure; LRFS = local relapse-free survival; LR = local recurrence; OS = overall survival; OTT = overall treatment time; PC = pelvic control; PDR = pulsed dose rate; RRFS = regional recurrence-free survival; RT = radiotherapy; TVP = tumour volume parameters

Question 1:

Does MR-guided IC BT, with or without IS needles and including treatment plan adaption and optimization, improve tumour control and/or survival and/or reduce harmful side effects compared with conventional 2D BT or CT-guided BT in patients with cervical cancer?

It is broadly accepted that MR is the best-practice method of imaging the cervix and adjacent pelvic tissues for BT treatment planning because it provides greater soft tissue definition and discrimination than other imaging modalities, including CT [71]. However, the use of MR alone may not necessarily improve clinical outcomes. MR facilitates improved tumour delineation, 3D dosimetry, and treatment plan adaptation. However, even with MR imaging and treatment plan optimization, the use of IC applicators alone may impose significant constraints in some patients that limit the benefits. The addition of IS needles can overcome this by allowing more freedom during treatment planning, thereby increasing the likelihood of achieving optimal dose distributions that are 'sculpted' to treat the tumour, while avoiding normal tissues. Question 1 evaluates the literature comparing best-practice MR-guided BT with IS needles when needed to 2D BT and CT-guided BT. The eight clinical studies with tumour control outcomes relevant to Q1 are summarized in Table 4-2. Appendix 5 provides more detailed information about relevant tumour control and survival outcomes.

In a 2012 study by Charra-Brunaud et al. (STIC), two-year local relapse-free survival was significantly improved for patients treated with 3D BT, compared with 2D BT (78.5% vs. 73.9% for Group 3 patients treated with external beam radiation therapy and BT without surgery, p=0.003). Likewise, two-year loco-regional relapse-free survival was significantly improved for patients treated with 3D BT compared with 2D BT (69.6% vs. 61.2%, p=0.001). There were no differences in DFS or OS [1]. Only approximately 20% of patients in this study were treated using MR-guided BT, with the majority receiving CT-guided BT. Furthermore, the proportion of patients treated with IS needles was not stated. Therefore, this study, while showing a benefit of 3D imaging and treatment planning compared with conventional 2D BT, does not represent best-practice MR-guided BT.

Lindegaard et al. demonstrated a trend toward improved pelvic control (85% vs. 76%) and significant improvements in cause-specific (87% vs. 68%; p=0.001) and overall (79% vs. 63%; p=0.005) survival comparing MR-guided BT to 2D BT [2]. Nomsden et al. found improved three-year pelvic control (84% vs. 76%) and OS (65% vs. 54%) in the MR-guided BT group compared with a previous (historical cohort) 2D BT group [3]. Likewise, Rijkmans et al. reported significantly improved local control (p=0.01), pelvic control (p=0.001), DFS (p<0.01), and OS (p<0.01) among patients treated with MR-guided BT, compared with those treated with 2D BT [4] (Table 4-2). IS needles were used in 43%, 30%, and 13% of patients in these three studies respectively.

Comparing MR-guided BT with CT-guided BT, Kamran et al. found significantly better OS among patients treated with MR-guided ICIS BT relative to those treated with CT-guided ICIS BT on univariate analysis; however, the difference was not significant in a multivariate model [5]. According to Potter et al., improved local control in tumours >5 cm in maximal size at diagnosis translated to improved three-year cause-specific survival in serial cohorts of patients spanning the period from 1993 to 2008 (70%/57%/40% for 2001-2008/1998-2000/1993-1997) [6,7]. There was no difference in tumours 2–5 cm in size at diagnosis.

In examination of MR-hybrid BT techniques, Choong et al. showed very comparable three-year local control, PFS, and OS results of 92.2%, 66.3%, and 69.6%, respectively, using MR-guided BT and 92.6%, 78.8%, and 77.7%, respectively, with MR-hybrid BT [9]. Likewise, Gill et al. estimated two-year local control, DFS, and cause-specific survival rates to be 91.6%, 81.8%, and 87.6%, respectively, with no significant differences between the MR-guided BT group

and the MR-hybrid BT group [10]. IS needles were used in only a minority (<10%) of patients in these two studies.

Table 4-2. Studies with Tumour Control Outcomes Relevant to Q1

Study	Control	Survival
MR-guided or CT-guided BT vs. 2D BT		
Charra-Brunaud, 2012 3D (MR/CT) vs. 2D BT *(Note: Only group 3 focused on patients treated with RT alone)*	2yr RLRFS: G3: 69.6% vs. 61.2% (p=0.001) 2yr LFRS: G3 78.5% vs. 73.9% (p=0.003)	2yr OS: G3 74% vs. 65% (p=0.27); 2yr DFS: G3 60.3% vs. 55.2% (p=0.086)
Lindegaard, 2013 MR-guided BT vs. NOCECA 2D BT	3 yr LC: 91% vs. NR 3 yr pelvic control: 85% vs. 76%, HR 1.6 (0.9-2.8), p=0.12.	3 yr OS: 79% vs. 63%, HR 1.8 (1.2-2.8), p=0.005; 3 yr OS: IIB-IV 77% vs. 63%, HR 1.7 (1.1-2.6), p=0.01 3 yr CSS: 87% vs. 68%, HR 5.0 (2.8-8.9), p=0.001.
Nomden, 2013 3D MR vs. 2D BT	3 yr Pelvic control: 84% vs. 76% 3 yr LRFR: 93% vs. NR 3 yr PFS: 71% vs. 53%	3 yr OS: 65% vs. 54%
Rijkmans 2014 2D vs. 3D MR	3-yr LC: 69% vs. 93%; HR=0.2(0.1-0.7) p=0.01 3-yr pelvic recurrence: 32% vs. 7%; p < 0.001 3-yr PAO recurrence: 16% vs. 8%; p=0.07 Distant metastasis: 38% vs. 12%; p<0.01 Any disease recurrence: 49% vs. 15%; p<0.01	3-yr OS: 51%; vs. 86% HR=0.5 (0.2-0.9) p=0.03 3-yr DFS: 49% vs. 83%; p<0.01
MR-guided BT vs. CT-guided BT		
Kamran, 2017 MR vs CT	3 yr LC (MR vs. CT): 96% vs. 87%, HR 0.65 (0.08-4.13), p=0.64 (univariate) 3 yr DFI (MR vs. CT): 73% vs. 65%, HR 0.92 (0.36-2.41), p=0.87 (univariate)	3 yr OS (MR vs. CT): 84% vs. 56%, HR 0.27 (0.06-0.90), p=0.03 (univariate); note: on multivariate analysis MR vs. CT HR 0.35 (0.08-1.18) – squamous cell histology only significant factor HR 0.23 (0.07-0.72)
Potter, 2011 MR-guided BT (learning period) vs. MR-BT (protocol period) vs. CT-guided BT	3yr PFS: IB 100% IIB 87% IIIB 69% IVA 60% vs. IB 95% IIB 92% IIIB 67% IVA 70% vs. IB 94% IIB 96% IIIB 75% IVA 75% 3-yr $PFS_{(overall)}$: TV 2-5cm 95%, TV >5cm 90% MR-BT (protocol period) alone (n=156) 3-yr LC: all 95%, TV 2-5cm 98%, TV >5cm 92%, IB 100%, IIB 96%, IIIB 86% 3-yr PC: TV 2-5cm 95%, TV >5cm 90% 3-yr DFF: All 82%; TV 2-5cm 87%, TV >5cm 78%, IB 88%, IIB 85%, IIIB 69%, IVA 60%	3yr OS: IB 62% IIB 70% IIIB 46% IVA 40% vs. IB 80% IIB 61% IIIB 12% IVA 25% vs. IB 74% IIB 79% IIIB 45% IVA 33% 3yr CSS: IB 77% IIB 78% IIIB 59% IVA 53% vs. IB 80% IIB 71% IIIB 28% IVA 25% vs. IB 83% IIB 84% IIIB 52% IVA 40% MR-BT (protocol period) alone (n=156) 3-yr CSS: All 74%, TV 2-5cm 83%, TV >5cm 70%, IB 83%, IIB 84%, IIIB 52% 3-yr OS: All 68%, TV 2-5cm 72%, TV >5cm 65%, IB 74%, IIB 79%, IIIB 45%
MR-guided BT vs. MR-hybrid BT		
Choong, 2016 3 Fraction conformal - MR vs. hybrid (MR/CT)	3yr PFS LC: 92.2% vs. 92.6%, p>0.05 3yr PFS overall: 66.3% vs. 78.8%	3yr OS: 69.6% vs. 77.7%
Gill, 2015 MR vs hybrid (CT/MR)	3yr LC: P=0.89	2 yr OS: P=0.36; 2 yr DFS: P=0.21, CSS p=0.622; 2 yr CSS: p=0.62
BT = brachytherapy; CSS = cancer-specific survival; CT = computed tomography; DFI = disease-free interval; DFS = disease-free survival; DFF = distant failure free; HR = hazard ratio; LC = local control; LRFS= local free relapse survival; MR = magnetic resonance; PAO = peri-aortic lymph nodes, PFS = progression-free survival; RLRFS = loco-regional relapse-free survival; OFF = overall failure free; OS = overall survival; PC = pelvic control; RC = regional control; TV = tumour volume		

Table 4-3 shows the toxicity outcomes for the eight studies that compared MR-guided BT with 2D BT, CT-guided BT, or MR-hybrid BT. Appendix 6 provides more detailed information about relevant toxicity outcomes. Three studies reported substantially lower grade 3/4 GI and GU toxicity with MR-guided BT relative to 2D BT [1,2,4]. For example, Lindegaard et al. reported a significant reduction in overall grade 3 toxicity from 15% with 2D BT to 7% with MR-guided BT [2]; IS needles were used in 43% of the patients treated in the MR-guided BT arm of this study, which can aid in both tumour coverage and normal tissue sparing and may in part explain the reduction in morbidity. One of the two studies comparing MR-guided BT to CT-guided BT demonstrated a large reduction in major morbidity with MR [8] while the second study showed no difference [5]. The two studies comparing MR-guided BT with MR-hybrid BT found comparable late toxicity rates with these treatment approaches [9,10].

Table 4-3. Studies with Toxicity Outcomes Relevant to Q1

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
MR-guided or CT-guided BT vs. 2D BT				
Charra-Brunaud, 2012 2D vs. 3D	Grade 3-4 G3 9% vs. %, p=0.17 Grade 2-4 G3 18.7% vs. 15.2%, p=0.45	Grade 3-4 G3 9.2% vs. 1.2%, p=0.02 Grade 2-4 G3 23.1% vs. 13.7%, p=0.03 Grade 3-4 G3 13.8% vs. 1.2%, p=0.027	Grade 3-4 G3 15.4% vs. 1.4%, p=0.01 Grade 2-4 G3 35.7% vs. 19.4%, p=0.125	Grade 3-4 G3 22.7% vs. 2.6%, p=0.002 Grade 2-4 G3 53.4% vs. 42.4%, p=0.028
Lindegaard 2013 MR-guided vs. NOCECA cohort CT-based	Grade 2 18% vs. 35%, HR 2.9 (1.6 – 5.2) p<0.001 Grade 3 3% vs. 8% HR 3.8 (0.9 – 15.5), p=0.08	Grade 2 17% vs. 18%, HR 1.4 (0.7 – 2.7), p=0.29 Grade 3 1% vs. 2% HR 3.6 (0.5-26.0), p=0.23	Grade 2 33% vs. 87% 4.8 (2.7-8.4), p<0.001 Grade 3 4% vs. 9%, HR 2.8 (0.9-8.7), p=0.08	Grade 2 55% vs. 90%, HR 4.3 (2.9 – 6.4), p< 0.001 Grade 3 7% vs. 15%, HR 3.0 (1.2 – 7.3) p=0.02
Nomden, 2013 3D vs. 2D	Grade 3-4 9.5% vs. NR		GRADE 3-5 Renal/genitourinary 2.2% vs. NR Sexual/reproductive 4.3% vs. NR	GRADE 3-5 9.5% vs. NR
Rijkmans, 2014 MR-guided BT vs. 2D BT	Grade 3-4 Rectum 4.8% vs. 3.7%; Small bowel 0% vs. 1.2%; Sigmoid 7.1% vs. 1.2%	Grade 3-4 Bladder 2.4 vs. 0% Ureter 4.8% vs. 0%	Grade 3-4 Vaginal 4.8% vs. 0%	Grade 3-4 21.4% vs. 7.3%, p=0.04; median mos. to GR3-4 12.6 (1.0-77.2) vs. 9.5 (2.1-23.7); 3yr rate 15.4% vs. 8.4%, p=0.06
MR-guided BT vs. CT-guided BT				
Kamran, 2017 MR vs CT	Rectal Grade 1 3% vs. 5%, p=0.38 Rectal Grade 2 4% vs. 1%, p=0.17 Rectal Grade 3 3% vs. 4%, p=0.61	Grade 1 6% vs. 4%, p=0.57 Grade 2 3% vs. 3%, p=0.93 Grade 3 3% vs. 1%, p=0.32		
Potter, 2011 CT BT vs. MR BT practice vs. MR BT protocol	3Yr-Grade 3/4 Bowel/rectum 10% vs. 5% vs. 4%	3Yr-Grade 3/4 Bladder 3% vs. 3% vs. 2%	3Yr-Grade 3/4 Vagina 31% vs. 7% vs. 1%	
MR-guided BT vs. MR-hybrid BT				
Choong, 2016 3 Fraction conformal -MR vs. hybrid	Late toxicity Rectum 0% vs. 2%; small bowel 3.7% vs. 8.2;	Late toxicity Bladder 0% vs. 6.1%		

Table 4-3. Studies with Toxicity Outcomes Relevant to Q1

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
Gil 2015 MR vs hybrid (CT & MR)				Grade ≥3 Toxicity p=0.24

2D = two-dimensional; 3D = three-dimensional; BT = brachytherapy; CT = computed tomography, IGABT = image-guided adaptive brachytherapy; MR = magnetic resonance imaging; NR = not reported

Question 2:

Which patients with cervical cancer benefit from the use of MR-guided intracavitary BT with the addition of IS needles compared with MR-guided intracavitary BT alone?

The evidence base for Q2 included both clinical and dosimetric studies. The dosimetric data are grounded in strong dose-response relationships between tumour dose and long-term tumour control and between normal tissue doses and the development of serious side effects that have emerged from the RetroEMBRACE and EMBRACE studies [12,13,23-27]. There is a trade-off during BT treatment planning between the tumour and the normal tissues; the objective is to use treatment geometry with IC applicators and IS needles when necessary to achieve tumour doses that have a high likelihood of curing the cancer while at the same time limiting the normal tissue doses and the risk of side effects.

Several studies have addressed the dosimetric advantages of MR-guided ICIS BT vs. MR-guided IC BT [3,35,55,69]. Appendix 7 provides additional detailed information about tumour and normal tissue dosimetry, with and without the use of IS needles, from several relevant MR-guided BT studies.

Tanderup et al. evaluated the dosimetric outcomes for optimized MR-guided BT plans and compared the results to what could be achieved with 2D BT [11] (Figure 4-1).

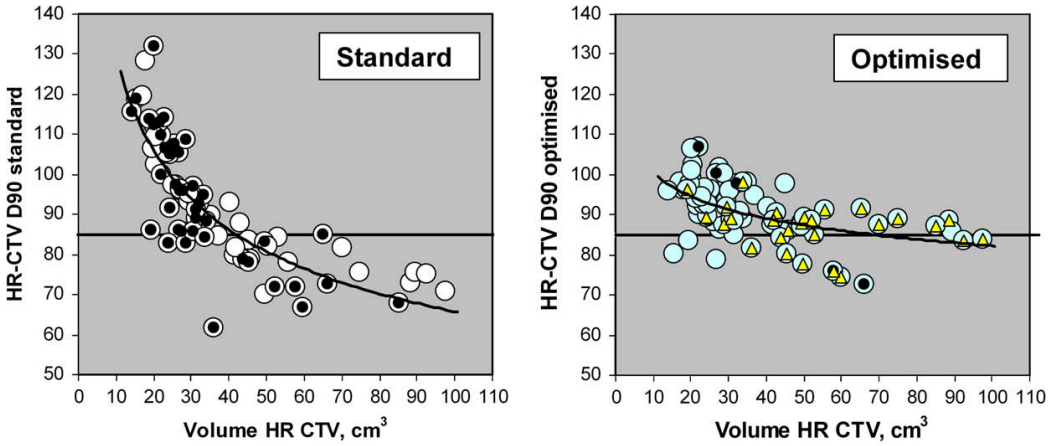

Figure 4-1. Volume dependence of tumour CTV_{HR} D90 for standard 2D BT (left) and optimized (right) MR-guided BT plans. The 85 Gy tumour planning target is indicated by the black horizontal lines. Black circles indicate patients in whom the normal tissue dose constraints were exceeded. The yellow triangles indicate patients in whom interstitial needles were used. Adapted from Tanderup et al. 2010 [11]

The graph on the left shows what is achievable dosimetrically with 2D IC BT. Most (94%) of the smaller tumours (CTV_{HR} <30 cm^3 at the time of BT) received doses above the planning target of 85 Gy, which is associated with at least an 80% likelihood of long-term tumour control [25,33,53]. However, excessive normal tissue doses were seen in 72% of these patients (black circles), placing them at high risk of serious complications [24,26]. The graph on the right shows the improvement with MR-guided BT and the strategic use of needles (yellow triangles). The distribution of tumour doses was more uniform around the 85 Gy planning target and normal tissue dose constraints were exceeded in only a minority (6%) of patients. Most patients (64%) with tumours >30 cm^3 benefited from the addition of needles, compared with only 11% of patients with smaller tumours. These data provide evidence in support of the value of MR-guided BT with IS needles when needed compared with 2D BT (Q1), and evidence to indicate

that patients with large residual tumours (CTV_{HR} >30 cm^3) at the time of BT are more likely to benefit from the addition of needles (Q2) (Figure 4-1).

Table 4-4 summarizes tumour control outcomes for the one study that directly compared patients treated using MR-guided BT, with and without IS needles. Fokdal et al. (RetroEMBRACE), found the three-year local control rate in patients having a tumour volume at the time of BT (CTV_{HR}) ≥30 cm^3 to be 92% in the MR-guided ICIS BT group and 82% in the MR-guided IC BT group (p=0.02). This benefit was sustained at five years (91% vs. 80% respectively, p=0.02). No difference was found for tumours that were <30 cm^3 at the time of BT (p=0.50). No significant difference in late morbidity was found between the two groups.

Table 4-4. Studies with Tumour Control Outcomes Relevant to Q2

Study	Local Control
Fokdal, 2016	3yr LC: 94% vs. 89%; 5yr LC: 91% vs. 86% (p=0.06) CTV_{HR} ≥30cm 3yr LC: 92% vs. 82%; 5yr LC: 87% vs. 80% (p=0.02) CTV_{HR} <30cm 3yr LC: 97% vs. 96%, 5yr LC: 97% vs. 93% (p=0.50)
CTV_{HR} = high-risk clinical target volume; LC = local control survival	

Table 4-5 shows the toxicity outcomes for the studies that directly compared MR-guided BT with and without IS needles. Patients exhibited milder but similar late mucosal morbidity following MR-guided ICIS BT compared with MR-guided IC BT. There was a suggestion of more severe vaginal stenosis with MR-guided ICIS BT in one study [69] and a higher rate of acute, minor (grade 2) GI morbidity in another study [35].

Table 4-5. Studies with Toxicity Outcomes Relevant to Q2

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
Fokdal 2013 Q2 MR-guided ICIS BT vs. MR-guided IC BT	Grade 2 Pain and bleeding requiring transfusion 1.7 vs. 4%			
Fokdal 2016 Q2 MR-guided ICIS BT vs. MR-guided IC BT	Gastro-intestinal Grade 2-5 NS, Grade 3-4 NS	Urinary bladder Grade 2-5 NS, Grade 3-4 NS	Vaginal morbidity Actuarial Grade 2-5 NS, Grade 3-4 NS	
Yoshida, 2013 MR-guided IS BT vs. MR-guided IC BT	Grade 1 Bleeding type 6% vs. 3%, NS Bleeding severity 11% vs. 5%, NS Discharge frequency 6% vs. 0%, NS		Late vaginal reaction discharge type 6% vs. 0%, NS	Grade 1 Stenosis 49% vs. 46%, Pallor 33% vs. 43%, Grade 2 Stenosis 46% vs. 24%, Pallor 37% vs. 41%, Grade 3 Stenosis 0% vs. 5%, p=0.003 Pallor 25% vs. 3%, p=0.006 Grade 1 Erythema 29% vs. 35%, NS Ulcer 3% vs. 8%, NS Telangiectasia 62% vs. 59%, NS Grade2 Erythema 6% vs. 3%, NS Ulcer 0% vs. 0%, NS Telangiectasia 13% vs. 11%, NS
BT = brachytherapy; MR = magnetic resonance imaging; IC = intracavitary; IS = interstitial; NS = not significant				

Appendix 5 and 6 show additional clinical and toxicity outcomes, respectively, and Appendix 7 shows dosimetric outcomes. Although not directly comparing MR-guided ICIS BT with MR-guided IC BT, several studies provided indirect evidence to indicate that patients with smaller tumours may be less likely to benefit from MR-guided BT with IS needles in terms of tumour control but more likely to benefit from reduced toxicity; patients with larger tumours may benefit in terms of both improved tumour control and reduced toxicity.

In the RetroEMBRACE cohort, the improvement in pelvic control in the MR-guided BT group (compared with historical cohorts) was larger in patients with advanced-stage disease: absolute improvements were 4% to 10% in stage I/IIA patients, 7% to 12% in IIB, 8% to 24% in IIIB, and 59% in IVA. IS needles were used in 23% of patients. The mean dose to 90% of the residual tumour volume (D_{90}) at the time of BT (CTV_{HR}) was 87 Gy, although it varied substantially with disease stage; it was 93 Gy in stage IB patients, 88 Gy in IIB, and 83 Gy in stage IIIB. The authors argued that there was further room for treatment plan adaptation and more strategic use of IS needles in patients with advanced-stage disease to facilitate greater dose escalation and a higher likelihood of pelvic control [13].

In the Vienna study, a cohort treated between 1998 and 2003 was split into two groups: one treated from 1998 to 2000 when MR-guided BT was being used but the GEC-ESTRO guidelines were not fully optimized and the other treated between 2001 and 2003 after guideline optimization. Overall, 44% of patients were treated with IS needles. The authors reported a 20% improvement in local control and a 30% improvement in OS in patients with tumours >5 cm in maximal size at diagnosis treated in the latter period compared with the earlier period. Grade 3/4 late GU or GI toxicity was reduced from 10% to 2% [6]. The incidence of local relapse for the total 1998-2003 cohort was 4% for patients who achieved a tumour D_{90} >87 Gy, compared with 20% for D_{90} <87 Gy, which was significant for patients with tumour size > 5 cm (see Appendices 5 and 7) [33].

DISCUSSION

The present review examined the evidence supporting improved tumour control and reduced toxicity with MR-guided BT compared with 2D BT or CT-guided BT in patients with cervical cancer undergoing potentially curative treatment with radiotherapy (Q1). Furthermore, it examined the evidence supporting the use of MR-guided ICIS BT (with the addition of IS needles) in specific patient cohorts (Q2).

Question 1

There is evidence of improved outcomes and reduced toxicities with MR-guided BT over 2D BT. The literature review identified studies that showed significantly improved local relapse-free survival [1], loco-regional relapse-free survival [1], pelvic control [2,3], and DFS and OS [2,3] among patients receiving MR-guided BT compared with those receiving 2D-based techniques. Along with significantly improved local control with MR-guided BT, less grade 3/4 GI or GU toxicity was noted in two studies [1,4]. **Given these benefits of improved local control and reduced toxicity, MR-guided ICIS BT is the preferred method of practice for cervical cancer patients in Ontario and is recommended over 2D BT (Recommendation 1).**

The standard treatment paradigm for cervical cancer BT has evolved significantly since the dissemination of the 2005 GEC-ESTRO recommendations [18-21]. The enhanced soft tissue contrast afforded by MR imaging makes it the modality of choice to visualize the tumour and to distinguish it from the adjacent normal tissues. The ability to accurately differentiate between these structures enables patient-specific cervical cancer BT that delivers conformal dose distributions to the tumour while sparing normal tissues. However, implementation of a cervical cancer MR-guided BT program is resource intensive, requiring appropriate investment in infrastructure, equipment, and training.

With the use of MR at the time of BT, the response of the tumour to external beam radiotherapy can be assessed. This includes tumour regression and changes in tumour topography. This imaging information presents new clinical challenges and often reveals the inadequacies of conventional 2D BT treatments plans that use a standard, 'one-size-fits-all' pear-shaped dose distribution and a point dose prescription [25]. For smaller tumours, a standard pear-shaped dose distribution, while adequately covering the tumour, may treat a larger volume of normal tissues to a higher than necessary dose resulting in an unacceptably high risk of toxicity. On the other hand, large unresponsive tumours may be undertreated. MR-guided BT has opened the door to providing personalized medicine based on the specifics of the residual disease on MR and the patient's anatomy. By employing this individualized approach, the therapeutic ratio between tumour and normal tissue doses is expanded leading to improved patient outcomes.

The evidence also showed a benefit of MR-guided BT over CT-guided BT. **There is a clear benefit of MR-guided BT over CT-guided BT alone in terms of tumour delineation, plan adaptation/optimization, and improved local control. Thus, MR-guided BT is preferred over CT-guided BT (Recommendation 2)**. MR-guided (either MR-adaptive or MR-informed) BT is superior to CT-guided BT because of better tumour visualization, which translates to greater confidence in treatment plan adaptation and optimization, a higher likelihood of achieving optimal tumour and normal tissue dosimetry, and a higher expectation of tumour control without toxicity. CT-guided BT may provide adequate visualization of normal tissues for treatment planning. However, without also having unambiguous visualization of the tumour with the applicator and/or needles in place, flexibility in plan optimization to assure adequate tumour coverage and normal tissue sparing is likely to be constrained.

Question 2

The evidence also showed that **MR-guided ICIS BT (with the use of IS needles) should be considered for patients with asymmetrical or large residual tumours at the time of BT, and in patients with small or large tumours at the time of BT where there is unfavourable normal tissue geometry or dosimetry and a high likelihood of excessive toxicity (Recommendation 3)**. The evidence base for Q2 was derived from both clinical and dosimetric studies. These suggest that patients with smaller tumours may be less likely to benefit from MR-guided ICIS BT compared with MR-guided IC BT in terms of tumour control but more likely to benefit from reduced toxicity; patients with larger tumours may benefit in terms of both improved tumour control and reduced toxicity. In cases where planning dose constraints cannot be achieved (lower than required dose to the tumour and/or high doses to normal tissues) with MR-guided IC BT alone, strong consideration should then be given to the use of MR-guided ICIS BT to improve the therapeutic ratio. The proportion of patients benefiting from the addition of IS needles is not well defined. However, current prospective treatment protocols such as EMBRACE II require that at least 40% to 50% of patients in any individual centre be treated with IS needles.

The radiation therapy technique used to treat each patient should be tailored to her individual anatomy in order to maintain the desired dosimetric coverage of the tumour and sparing of normal tissue. Conventional IC applicators include an intrauterine tandem in combination with an intravaginal ring or intravaginal ovoids. MR-guided ICIS BT uses special MR-compatible applicators, including intravaginal rings or ovoids that can accommodate the addition of IS needles, or trans-perineal template-based applicators.

With the adoption of high-resolution MR imaging and consensus about contouring definitions and treatment planning [18], robust correlations between dosimetric parameters and clinical outcomes are emerging from the RetroEMBRACE and EMBRACE studies [12,13,23-27]. Armed with these data, the trade-offs between tumour coverage and normal tissue sparing

can be quantified and balanced to achieve an optimal radiotherapy treatment plan for each patient. From the current body of literature, it is evident that planning goals for cervical cancer BT should aim to achieve a combined (external beam radiotherapy plus BT) isoeffective dose to 90% of the tumour volume (CTV_{HR} D_{90}) of 90 to 95 Gy in equivalent 2 Gy fractions, while limiting the doses to critical adjacent structures such as rectum, sigmoid, and bladder (combined isoeffective doses to the maximally irradiated contiguously 2 cm^3 volumes (D_{2cm3}) of 65 Gy, 70 Gy, and 80 Gy, respectively, in equivalent 2 Gy fractions.

Challenges of Implementing MR-guided BT in Ontario

The current body of evidence alludes to three clinical scenarios where MR-guided BT may improve the outcomes of patients with locally advanced cervical cancer. In any individual patient, the decision about the BT technique and applicator choice is based on clinical, technical, and dosimetric considerations, including the size and extent of disease at diagnosis (CTV_{IR}), the amount of regression during external beam radiotherapy, the size and extent of the residual disease at the time of BT (CTV_{HR}), and the anatomical relationships between the tumour and adjacent normal tissues.

Small symmetrical tumours

Small tumours (<5 cm in largest dimension at diagnosis and <2 cm at the time of BT with CTV_{HR} <30 cm^3) that are symmetrically distributed around the applicator can often be treated using MR-guided IC BT alone without IS needles. For tumours with this morphology, CTV_{HR} D_{90} values in excess of 85 Gy can be achieved using standard pear-shaped distributions. MR image guidance in this clinical context is unlikely to yield significant benefits in terms of local control [11,25]. However, this same body of evidence has demonstrated that the use of MR guidance in this cohort of patients results in lower treatment-related morbidity. MR image guidance enables the accurate distinction between the tumour and the surrounding normal tissues. This allows standard pear-shaped dose distributions to be optimized to ensure that an adequate tumour dose is delivered while simultaneously limiting normal tissue doses to safe levels.

It is important to note that tumours with such favourable, symmetrical geometry may be relatively uncommon. Only approximately 20% of patients enrolled to date in the prospective EMBRACE II protocol, which includes clearly specified tumour and normal tissue planning dose constraints, have been treated with an IC applicator alone; 80% of patients have required IS needles to ensure that all planning dose constraints are met (K. Tanderup, personal communication, April 2018). An example of a frequently encountered scenario is a small tumour that appears elliptical on axial MR images, making it challenging to adequately encompass the lateral parametrial extensions using MR-guided IC BT alone without exceeding rectal, sigmoid, and/or bladder dose constraints. These patients may benefit from the addition of lateral IS needles to enable treatment plan adaption and optimization.

From a practical perspective, it is often difficult to anticipate at diagnosis which patients can safely be treated with MR-guided IC BT alone and which patients will benefit from the addition of IS needles. This is best determined using MR imaging near the end of external beam radiotherapy to evaluate tumour response. This implies the need for a rapid triage and referral system if MR-guided ICIS BT is not available in all treatment centres, since overall treatment time (including external beam radiotherapy and BT) should be limited to <8 weeks for optimal outcomes [72].

Large tumours

Large tumours at the time of BT often cannot be treated adequately with MR-guided IC BT alone and require the addition of IS needles to ensure tumour coverage without exceeding normal tissue dose constraints. These patients often have large, advanced-stage tumours at

diagnosis and the need for MR-guided ICIS BT can be anticipated earlier in the course of treatment.

Asymmetric tumours and/or tumours with vaginal extension and/or challenging anatomy

The dose distribution around IC applicators is cylindrically symmetrical and, as such, IC applicators alone are unable to effectively treat asymmetric disease. The addition of IS needles can overcome this limitation by allowing more degrees of freedom during treatment planning, thereby facilitating optimal dose distributions that are 'sculpted' to treat the tumour and avoid nearby normal tissues. Specially designed, MR-compatible intravaginal rings or ovoids are available that can accommodate IS needles. These hybrid ICIS applicators offer several advantages, including easy insertion of parametrial needles with minimal trauma, needle geometry that is parallel to the intrauterine tandem, and rapid and accurate applicator reconstruction for treatment planning. However, while adequate for the treatment of most tumours with asymmetrical parametrial extension, hybrid ICIS applicators do not help with tumours that extend to the mid or lower vagina. Furthermore, they cannot be used in patients with an upper vagina that is too small to accommodate the ring or ovoids. In these circumstances, a Syed-Neblett-type trans-perineal approach offers greater flexibility to ensure that the tumour is adequately treated without exceeding normal tissue dose limits.

Clinical implementation and best-practice quality indicators

MR-guided ICIS BT represents a paradigm shift in the treatment of patients with locally advanced cervical cancer, yielding improved tumour control and reduced side effects. However, MR-guided BT is considerably more demanding of resources. Optimized, efficient, and safe processes are of paramount importance in achieving the best possible outcomes. Barriers to implementation include the availability of MR for each BT fraction, initial and continuing education of all staff, the cost of MR-compatible ICIS applicators, and the added time necessary for applicator insertion, imaging, planning, and treatment. It is imperative that all members of the multidisciplinary team (radiation oncologists, medical physicists, and radiation therapists) are appropriately educated about best-practice MR-guided ICIS BT before undertaking procedures and that continuing professional education is available. Furthermore, each centre and each practitioner must treat a sufficient number of patients with MR-guided ICIS BT annually to maintain clinical and technical competency. The required number of patients is not known. Previous studies in the 2D BT and CT-guided BT era suggested a minimum of 10 patients per year, although more patients may be needed to maintain competency with MR-guided ICIS BT given the greater complexity at every step of the treatment planning and delivery process.

The transition to MR-guided ICIS BT in Ontario should include the measurement of key quality indicators of programmatic and provincial performance to drive quality and system performance improvement. The indicators and benchmarks should be developed by consensus among practitioners, program leaders, and provincial leaders considering national and international guidelines balanced against local practicalities, including cost. Key quality indicators may include: 1) Patient wait times from referral to consultation with a radiation oncologist, and 'ready to' treat' with radiotherapy until the start of treatment; 2) Total treatment duration from the first fraction of external beam radiotherapy to the end of BT; 3) The number of patients treated annually; 4) The proportion of patients treated with MR-adaptive or MR-informed BT; and 5) The proportion of patients treated with IS needles. In addition, systematic prospective collection of physician-evaluated and patient-reported outcomes should be undertaken to evaluate efficacy (local tumour control, PFS, and OS) and toxicity in a real-world clinical environment.

CONCLUSIONS

The use of MR-guided BT for potentially curable, non-operable, locally advanced cervical cancer requires a trained multidisciplinary team with access to appropriate imaging technologies to allow optimal treatment planning and delivery. MR is the preferred imaging modality for planning as it allows visualization of both the tumour and normal tissues, the strategic use of IS needles when necessary, and optimized treatment planning that together maximize the likelihood of long-term tumour control without side effects. CT-guided BT alone, while inferior to MR-guided BT because the tumour cannot be visualized as well, is adequate for the identification of adjacent normal tissues including bowel and bladder and may facilitate reduction doses to these structures compared with 2D BT. However, the degree of normal tissue sparing, and the corresponding reduction in normal tissue toxicity, is likely to be limited in some cases by poor tumour visualization and concern about inadvertently under-dosing tumour. Both MR and CT require a greater investment of time and resources than conventional techniques, including the availability of compatible applicators and staff experience. **MR-guided BT (either MR-adaptive BT or MR-informed BT) with the use of IS needles when necessary should be the standard of care for patients with locally advanced cervical cancer in Ontario.**

ONGOING, UNPUBLISHED, OR INCOMPLETE STUDIES

Table 4-6 includes ongoing studies and studies that have reported an interim analysis, but are not yet complete. Studies that have closed, but have not yet been published, are also included.

Table 4-6. Ongoing Studies

Protocol ID(s)	Title and details of study
NCT03210428 EMBRACE II (substudy)	**Official title:** Quantitative MR Imaging in Locally Advanced Cervical Cancer Sub-study Under the EMBRACE II Protocol **Study type:** Interventional (randomized) phase NR **Treatment groups:** MR-based BT **Estimated enrolment:** 320 **Start date:** Sep., 2017 **Date trial summary last modified:** Jul. 4, 2017 **Estimated primary completion date:** Sep. 2021 **Status:** not yet open for participant recruitment **Primary results reported:** none
NCT03005743	**Official title:** Conventional Radiography Based Intracavitary Brachytherapy (Standard Arm) Versus Magnetic Resonance Image Based Brachytherapy (Study Arm) in Locally Advanced Cervical Cancers: A Phase III Randomized Controlled Trial (COMBAT - Cervix Trial) **Study type:** Interventional (randomized) phase 3 **Treatment groups:** MR-based BT vs. Conventional BT (radiotherapy-based BT) **Estimated enrolment:** 1050 **Start date:** Dec. 2016 **Date trial summary last modified:** Dec. 25, 2016 **Estimated primary completion date:** Dec. 2021 **Status:** currently recruiting patients **Primary results reported:** none
NCT01399658	**Official title:** A Clinical Trial to Evaluate Image-Guided Gynecologic Brachytherapy in the Advanced Multimodality Image-Guided Operating Suite (AMIGO) **Study type:** Interventional (single group assignment) phase2 **Treatment groups:** Image-guided BT vs. standard CT-guided BT **Estimated enrolment:** 93 **Start date:** Sep. 2011 **Date trial summary last modified:** Aug. 9, 2016 **Estimated primary completion date:** Feb. 2017 **Status:** ongoing but not recruiting patients **Primary results reported:** none
NCT02993900	**Official title:** A Clinical Trial To Evaluate Image-Guided Gynecologic Brachytherapy In The MR Simulator Suite **Study type:** Interventional (single group assignment) phase2 **Treatment groups:** Image-guided BT vs. standard CT-guided BT **Estimated enrolment:** 54 **Start date:** Sep. 2016 **Date trial summary last modified:** Dec. 14, 2016 **Estimated primary completion date:** Sep. 2021 **Status:** currently recruiting patients Primary results reported: none
NCT01706705	**Official title:** 3D Image-guided Intracavitary Brachytherapy Treatment Planning for Cervical Cancer Using a Novel Shielded Applicator **Study type:** Interventional (single group assignment) **Treatment groups**: Image-guided BT vs. standard CT-guided BT vs. 2D **Estimated enrolment:** 57 **Start date:** Oct. 2012 **Date trial summary last modified:** Feb. 17, 2017 **Estimated primary completion date:** Oct. 2018 **Status:** ongoing but not recruiting patients **Primary results reported:** none

Three-Dimensional MR-Guided Intracavitary and Interstitial Brachytherapy for Cervical Cancer
Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the Expert Panel, comprising the CCO GYN CoP and the PEBC RAP (Appendix 1). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 30 eligible (37 – 2 votes but no COI, 5 no vote no COI) members of the CCO GYN CoP (Expert Panel), 27 members cast votes and three did not vote (but returned COI), for a total of 90% (27/30) response from those eligible to vote in May 2018. All 27 members casting votes approved the document (100%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
1. Some rewording was suggested for Recommendation 1	We have changed the recommendation wording as stated in sections 1 and 2.
2. Some rewording was suggested for Recommendation 2	We have changed the recommendation wording as stated in sections 1 and 2.
3. Some rewording was suggested for Recommendation 3	We have changed the recommendation wording as stated in sections 1 and 2.
4. Recommendation 1: My impression of the summary of evidence provided suggests the following change be considered: Given the benefits of improved local control and reduced toxicity**, 3D guided/informed or MR/CT hybrid** ICIS BT should be used when treating women with cervical cancer.	MR/CT guided hybrid BT is mentioned in Recommendation 2.
5. Recommendation 1: My impression of the summary of evidence provided suggests the following change be considered: **3D guided (preferably MR-guided**) BT is the preferred method of practice for cervical cancer patients in Ontario and is recommended over 2D-guided BT.	The changes have been made to the phrasing of Recommendation 1

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in May 2018. The RAP conditionally approved the document in May 2018. Overall, the RAP members commented that it was a well-written, focused, and clearly stated guideline and that the evidence was clearly stated and supports the recommendations formulated. The main comments from the RAP that needed attention and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
Reviewer 1	
1. The limitations are discussed in Section 4, but briefly	We have included a discussion on the quality of evidence in the recommendations and systematic review sections of the document.
Reviewer 2	
2. The title of the guideline suggest that the guideline is about BT when in fact it is really about the imaging techniques used to plan IC and IS BT. The guideline objectives as stated at the top of page 2 are quite clear but I think the research questions could be restated more clearly on page 2 and page 6. I have suggested possible wording that I think makes it clear that the question to be answered has to do with the type of imaging used in the planning of IC and IS BT.	We have reworded the guidelines as suggested.
3. There is no section 3 in this guideline that I could find so it is not clear how the recommendations were arrived at by the guideline drafting committee. However, the discussion that follows the presentation of the evidence related to each of the questions is quite clear as to how you arrived at the recommendations. It is just not clear how this information was vetted with the authors of the guideline to arrive at each of the three recommendations.	This section has been added to the report.
4. Section 2 is reasonably clear in its summary of the key evidence supporting each of the three recommendations although it would be strengthened by some additional information and rewording. I have made some suggestions for edits to the text of the guideline for consideration. A specific example would be to cite data in support of the statement in the fourth bullet of the key evidence for Recommendation 1	We have reworded the guidelines as suggested and corrected some references.
5. The first recommendation is in fact ambiguous as it begins by stating "it is recommended…" And then indicates that 3D MR-guided BT "may be" the preferred method… The data appear to me to be robust enough to say that BT "is" the preferred method	We have removed the phrase "may be" and inserted "is" as suggested.
6. Please review bullet number 1 in the key evidence for recommendation 1 section page on 3. The evidence indicates ''that the 24-month local relapse-free survival was significantly improved for patients treated with 3D brachytherapy compared with 2D'' but the percentages are reversed. The same is true for the next statement about loco-regional relapse-free survival.	Thank you. These modifications have been incorporated

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Nine targeted peer reviewers from Ontario, Quebec, British Columbia, and around the world who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Two agreed (both from Ontario) to be the reviewers (Appendix A). Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.	0	0	0	2 (100%)	0
2. Rate the guideline presentation.	0	0	0	1 (50%)	1 (50%)
3. Rate the guideline recommendations.	0	1 (50%)	0	0	1 (50%)
4. Rate the completeness of reporting.	0	0	0	1 (50%)	1 (50%)
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?	0	1 (50%)	0	0	1 (50%)
6. What are the barriers or enablers to the implementation of this guideline report?	• Barriers to implementation are accessibility to MRI imaging and interstitial program development. However, I do believe that this is becoming standard of care and therefore the barriers must be overcome. • Does this technology exist at RT centres in Ontario? Are health care providers appropriately trained? What ongoing quality control initiative is in place to validate patients are not harmed? If the randomized controlled trials show no benefit or indeed harm of implementing this guideline, what action will be taken?				
	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
7. Rate the overall quality of the guideline report.	0	0	1 (50%)	0	1 (50%)
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
8. I would make use of this guideline in my professional decisions.	NA	NA	NA	NA	1 (50%)
9. I would recommend this guideline for use in practice.	0	1(50%)	0	0	1 (50%)

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
Q1 comments	
• Overall, the guidelines were very well done. My only concern with the extrapolation of evidence is the wording of Recommendation 2 'There is a clear benefit of MR-guided BT over CT-guided BT'. I believe the document showed solid evidence to support 3D BT over 2D BT, but the evidence to compare MRI to CT is not as strong. The evidence that is used to support this claim consists of one study that found an OS benefit for MRI use on univariate analysis but not multivariate analysis, and the studies outlining improvement in late toxicity were also mixed. The quality of the evidence may not be strong enough to claim 'a clear benefit'. I still agree	We agree that the evidence comparing MRI and CT-guided therapy is not as compelling as the evidence comparing 3D MRI with 2D. However, we are not making a strong recommendation of one technology over the other; rather, we are asserting that we believe that MRI-guided BT is superior to CT-guided BT. Our qualifying statements connected to Recommendation 2 represent our expert opinion and general consensus in the field.

with the recommendation, but wonder if the statement comes more as an expert opinion than from conclusive evidence.	
Q3 comment	
• I understand the decision for the recommendations but the quality of the research informing this decision is not good. Approving this document is a lost opportunity for the Ontario Gyn RT group to actually prove one technology superior to another or participate in on-going randomized controlled trials (RCTs) to this end. If this guideline was about an expensive medication, it is unlikely it would be approved without RCT to show benefit over standard of care. Why is RT different? In positron emission tomography scanning (another expensive technology), demonstration projects (RCTs) were required to develop standards, optimize skill sets and show effectiveness.	We agree. Although we advocate for the need for RCTs in the area, our role in this document is to evaluate the best evidence available, taking into consideration our experience in the field.
Q5 comment	
• This guideline is making a recommendation using retrospective and in some cases prospective case series or cohort data with moderate levels of bias. Could we actually harm patients by approving this guideline without the results from a RCT?	Again, although we advocate for the need for RCTs in the area, our role in this document is to evaluate the best evidence available, taking into consideration our experience in the field. We believe denying patients MRI-guided BT would be harmful at this time.
Q6 comment	
• Barriers to implementation are accessibility to MRI imaging and interstitial program development. However, I do believe that this is becoming standard of care and therefore the barriers must be overcome.	We agree. That you for your comment.
• Does this technology exist at RT centres in Ontario? Are healthcare providers appropriately trained? What ongoing quality control initiative is in place to validate patients are not harmed? If the RCTs show no benefit or indeed harm of implementing this guideline, what action will be taken?	These are all very important questions and we have added a discussion regarding the need for more availability in the use of MR-guided **BT** for c**ancer in Ontario;** requiring a trained multidisciplinary team with access to appropriate imaging technologies to allow optimal treatment planning and delivery.
Q9 comment	
• It is interesting to see a guideline mix both evidence and recommendations on a treatment strategy with standards for developing competency. This speaks to the lack of process in Ontario for standards, i.e., aspects about what a facility must have in terms of technologies, training for health care professionals, etc. • I would recommend participation in a high-quality RCT or at least prospective Canadian study that evaluates patient outcomes and practitioner capacity to perform the application appropriately.	We agree with these points.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All physicians with an interest in BT for cervical cancer in the PEBC database were contacted by email to inform them of the survey. A total of 132 individuals were contacted in Canada, all of whom practice within Ontario. Twelve (9%) responses were received. None of the non-participants gave reasons why they were unavailable to review this guideline at the time. The results of the feedback survey from 12 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	reviewer rating n=7(%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.	0	0	0	6 (50%)	6 (50%)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.			1 (8%)	3 (25%)	8 (67%)
3. I would recommend this guideline for use in practice.	0	0	0	3 (25%)	9 (75%)
4. What are the barriers or enablers to the implementation of this guideline report?	• At my centre it would the lack of expertise and resources to perform IS BT. • Timely access to MRI or centres with MR-BT capabilities. • Barriers: resources including human, monetary, and equipment. Learning curve to insert interstitial needles. Enablers: Expertise in department re physics, oncology, and therapy regarding gynecological BT. • Resource limitations with access to a dedicated MRI. • Enablers: evidence to support Rad Onc planning and treatment with enhanced outcomes. Barriers: limited end-users; need to consider nursing education as an enabler to support patient education. • Time, cost, resource issues for MR-BT and training required for this. • Expertise. • Barriers are costs and education for all staff to implement IS. Although it states to use IS when necessary, it implies that one would not know the size and shape beforehand; therefore, IS would need to be used for all patients to ensure one it getting best practice. MR is necessary. • As a general OBGYN it is difficult to advocate for MR-guided therapy, but this could mitigate sexual dysfunctions. More				

	evidence is needed from a survivorship perspective. • Lack of MRIs and IS (+expertise) BT programs in some centres.

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. Would caution the statements/ recommendations. Most of the recommendations seem reasonable for technical and imaging benefits; however, the recommendation for clinical benefit should be mitigated by the fact that there are no prospective comparative studies, and the data are retrospective, which comes along with inherent bias.	Although definitive comparative studies are lacking, in our expert opinion, MR-adaptive BT and MR-informed BT yield comparable results. Also, in our expert opinion, MR-adaptive BT and MR-informed BT are superior to MR-hybrid BT (with MR before applicator insertion) because of the marked changes in tumour and normal tissue anatomy that can result from applicator insertion, diminishing the relevance of MR images obtained earlier in the course of treatment.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the Working Group and approved by the GYN CoP and the PEBC RAP.

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Appendix 1: Affiliations and Conflict of Interest Declarations

Name	Affiliation	Declarations of interest
Working Group		
Judy Brown	McMaster University, Department of Oncology, Program in Evidence-based Care, Hamilton	None declared
David D'Souza	London Regional Cancer Program London	PI for RTOG 1174 which uses MR based cervix brachytherapy
Sarah Ferguson	University Health Network and Princes Margaret Cancer Centre, Toronto	None declared
Eric Leung	Sunnybrook Hospital and Odette Cancer Centre, Toronto	None declared
Michael Milosevic	University Health Network and Princes Margaret Cancer Centre, Toronto	None declared
Ananth Ravi	Sunnybrook Hospital and Odette Cancer Centre, Toronto	None declared
Radiation Treatment Program Gynaecological Community of Practice (Expert Panel)		
Allison Ashworth	The Cancer Centre of Southeastern Ontario, Kingston	None declared
Margaret Anthes	Thunder Bay Regional Cancer Centre	None declared
Quinn Benwell	London Regional Cancer Centre	None declared
Ekaterina Borodina	R.S.McLaughlin Durham Regional Cancer Centre, Oshawa	None declared
Julie Bowen	Northeastern Ontario Regional Cancer Centre, Sudbury	None declared
Paule Charland	Grand River Regional Cancer Centre, Kitchener	None declared
Clair Copp	Windsor Regional Cancer Centre	None declared
Jennifer Croke	Princess Margaret Hospital, Toronto	None declared
Joana Cygler	Ottawa Hospital Regional Cancer Centre	None declared
Laura D'Alimonte	Odette Cancer Centre, Toronto	None declared
Anthony Fyles	Princess Margaret Hospital, Toronto	None declared
Robert Hunter	Princess Margaret Hospital, Toronto	None declared
Chandra Joshi	The Cancer Centre of Southeastern Ontario, Kingston	None declared
Sofya Kobeleva	Grand River Regional Cancer Centre, Kitchener	None declared
Iwa Kong	Princess Margaret Hospital, Toronto	None declared
Audrey Li	R.S.McLaughlin Durham Regional Cancer Centre, Oshawa	None declared
Krystine Lupe	Ottawa Hospital Regional Cancer Centre	None declared
Dasaben Patel	R.S.McLaughlin Durham Regional Cancer Centre (Oshawa)	None declared
Patrick Rapley	Thunder Bay Regional Cancer Centre	None declared
Alexandra Rink	Princess Margaret Hospital, Toronto	None declared
Raxa Sankreacha	Carlo Fidani Peel Regional Cancer Centre, Mississauga	None declared
Ken Schneider	Windsor Regional Cancer Centre	None declared
Kathleen Surrey	London Regional Cancer Centre	None declared
Vikram Velker	London Regional Cancer Centre	None declared

Angele Vendette	Northeastern Ontario Regional Cancer Centre, Sudbury	None declared
Mary Westerland	The Cancer Centre of Southeastern Ontario, Kingston	None declared
Lauren Yesovitch	Royal Victoria Regional Health Centre, Simcoe Muskoka, Barrie	None declared
Report Approval Panel		
Bill Evans	Oncosynthesis Consulting Inc, Hamilton	None declared
Donna Maziak	Ottawa General Hospital	None declared
Targeted Peer Review		
Laurie Elite	Juravinski Cancer Centre, Hamilton	None declared
Kara Schnarr	Department of Oncology, McMaster University, Hamilton	None declared

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors, Radiation Treatment Program Gynaecological Community of Practice members, and internal and external reviewers were asked to disclose potential conflicts of interest. The authors, members, and reviewers reported that they had no conflicts of interest.

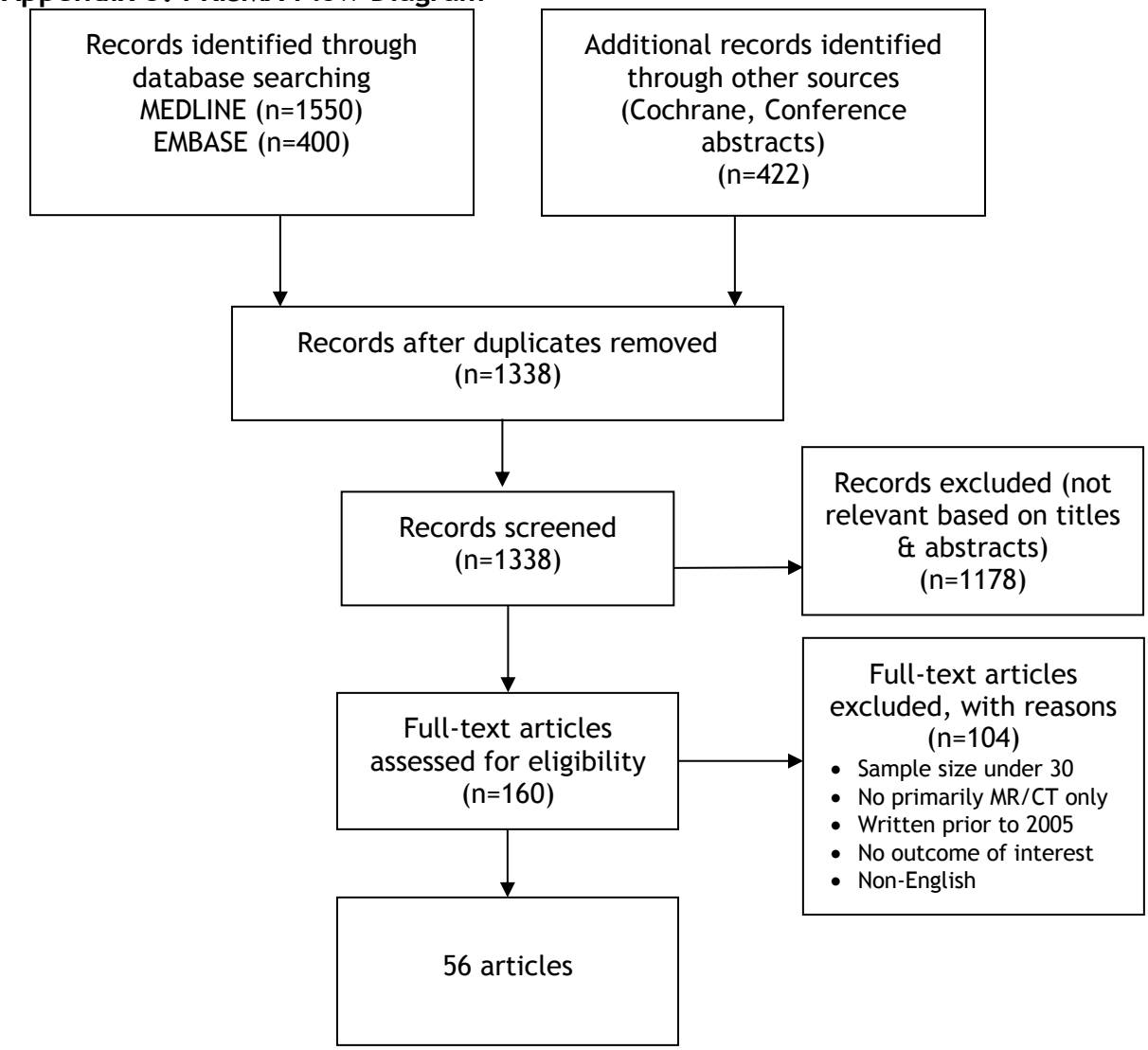
Appendix 2: Literature Search Strategy

SEARCH STRATEGY: MEDLINE	
Methods Terms	1. letter.pt.
	2. comment.pt.
	3. editorial.pt.
	4. or/1-3
Cancer Terms	5. exp cervix neoplasms/
	6. (cervi: cancer or cervi: carcinoma or cervi: tumo?r: or cervi: malignan:).ti,tw.
	7. *cervix neoplasms/dt
	8. exp Uterine Cervix Neoplasms/ or exp Cervix Intraepithelial Neoplasia/
	9. (cerv* adj4 (cancer* or tumo?r* or neoplas* or malignan* or dysplas*)).ti,ab.
	10. or/5-9
Brachytherapy	11. Brachytherapy/
	12. Brachytherapy.ab,ti.
	13. brachytherap$.ti,ab.
	14. brachytherap$.mp.
	15. (internal radiotherap$ or sealed source radiotherap$ or ((permanent or seed) adj4 implant$) or curietherap$ or endocurietherap$).mp.
	16. exp Brachytherapy/ or exp Magnetic Resonance Imaging/ or exp Imaging, Three-Dimensional/ or image guided brachytherapy.mp. or exp Radiotherapy, Image-Guided/
	17. intracavitary brachytherapy.mp.
	18. interstitial brachytherapy.mp.
Limiting Terms	19. or/11-18
	20. 10 and 19
	21. 20 not 4
	22. limit 21 to yr="2000 -Current"
	23. limit 22 to english language
	24. limit 23 to human

SEARCH STRATEGY: EMBASE	
Methods Terms	1. letter.pt.
	2. editorial.pt.
	3. or/1-2
Cancer Terms	4. (cervi: cancer or cervi: carcinoma or cervi: tumo?r: or cervi: malignan:).ti,tw.
	5. exp Uterine Cervix Neoplasms/ or exp Cervix Intraepithelial Neoplasia/
	6. (cerv* adj4 (cancer* or tumo?r* or neoplas* or malignan* or dysplas*)).ti,ab.
	7. or/4-6

Brachytherapy Terms	8. Brachytherapy/
	9. Brachytherapy.ab,ti.
	10. brachytherap$.ti,ab.
	11. brachytherap$.mp.
	12. (internal radiotherap$ or sealed source radiotherap$ or ((permanent or seed) adj4 implant$) or curietherap$ or endocurietherap$).mp.
	13. image guided brachytherapy.mp.
	14. intracavitary brachytherapy.mp.
	15. interstitial brachytherapy.mp.
Limiting Terms	16. or/8-15
	17. 7 and 16
	18. 17 not 3
	19. limit 18 to yr="2000 -Current"
	20. limit 19 to english language
	21. limit 20 to human

Appendix 3: PRISMA Flow Diagram



Appendix 4: Risk of Bias, ROBINS-1

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
Castelnau-Marchand, P. (2015) **Villejuif, France**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Moderate** (some refused CT	**Low** (missing data not likely to be different between groups)	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**
Chargari, C. (2009) **Villejuif, France**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Serious** (retrospective data & CTV_{HR} measurement surrogates used)	**Unclear**	**Serious**
Chargari, C. (2016) **Villejuif, France**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Serious** (retrospective data & CTV_{HR} measurement surrogates used)	**Unclear**	**Serious**
Charra-Brunaud, C. (2012) **STIC (2005-12)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Choong, E. S. (2016) **Leeds, UK (2008-12)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Serious** (only given hybrid at first BT)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Unclear**	**Serious**
Dimopoulos, J. C. (2009) **Vienna Group (1998-03)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Low (**1 centre from EMBRACE with clear protocol)	**Moderate**
Dimopoulos, J. C. (2009) **Vienna Group (1998-03)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Low (**1 centre from EMBRACE with clear protocol)	**Moderate**

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
Dyk, P. (2014) **Missouri (2009-11)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Moderate** (intervention not GEC-ESTRO prescribed)	**Unclear**	**Serious** (some surrogate measures likely and short follow-up)	**Unclear**	**Serious**
Fokdal, L. (2016) **EMBRACE (2001-11) – 1 centre (Aarhus, Denmark)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (CTV_{HR} measurement surrogates used)	**Low** (EMBRACE study well described)	**Moderate**
Fokdal, L. (2013) **RetroEMBRACE (1998-12) – 12 centres**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (CTV_{HR} measurement surrogates used)	**Low** (RetroEMBRACE study well described)	**Moderate**
Georg, P. (2013) **Vienna Group (1998-08)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Georg, P. (2011) **Vienna Group (1998-03)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Low (**1 centre from EMBRACE with clear protocol)	**Moderate**
Georg, P. (2012) **Vienna Group (1998-03)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Low (**1 centre from EMBRACE with clear protocol)	**Moderate**
Gill, B. S. (2015) **Pittsburgh (2007-13)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Haie-Meder, C. (2009) **Villejuif, France (2000-04)**	**Moderate** (non-randomized)	**Low** (consecutive	**Moderate** (intervention	**Low** (departure from	**Low** (missing data not likely to be different	**Moderate** (some surrogate	**Unclear**	**Moderate**

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
		and incident cases used)	determined retrospectively)	intervention not likely)	between groups)	measures likely)		
Haie-Meder, C. (2010) **Villejuif, France (2000-04)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Hannoun-Levi, J. M. (2013) **Nice, France (2007-11)**	**Moderate** (non-randomized)	**Unclear** (can't tell if patients consecutive)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Jastaniyah, N. (2016) **EMBRACE (2008-13) 22 centres**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (CTV_{HR} measurement surrogates used)	**Low** (EMBRACE study well described)	**Moderate**
Kamran, S. C. (2017) **Boston (2005-15)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**
Karlsson, L. (2017) **Sweden (2012-15)**	**Moderate** (non-randomized)	**Unclear** (can't tell if patients consecutive)	**Moderate** (intervention determined retrospectively)	**Serious** (only fractions based on CT images used)	**Unclear**	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Serious**
Kim, Y. (2017) **Korea (2008-13)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Unclear** (could not assess whether data prospective or retrospective	**Serious** (MR not at each treatment section)	**Unclear**	**Moderate** (some surrogate measures likely)	**Unclear**	**Serious**
Kim, Y. J. (2016) **Korea (2008-13)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Unclear** (could not assess whether data prospective or retrospective	**Serious** (MR not at each treatment section)	**Unclear**	**Moderate** (some surrogate measures likely)	**Unclear**	**Serious**
Kirchheiner, K. (2016) **EMBRACE (2008-13) - 19 centres**	**Moderate** (non-randomized)	**Low** (consecutive	**Moderate** (intervention	**Low** (departure from	**Low** (missing data not likely to be different	**Moderate** (CTV_{HR} measurement	**Low** (EMBRACE study well described)	**Moderate**

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
		and incident cases used)	determined retrospectively)	intervention not likely)	between groups	surrogates used)		
Kirchheiner, K. (2014) **EMBRACE (2008-13) – 19 centres**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (CTV_{HR} measurement surrogates used)	**Low** (EMBRACE study well described)	**Moderate**
Lakosi, F. (2015) **Belgium (2007-14)**	**Moderate** (non-randomized)	**Unclear** (can't tell if patients consecutive)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**
Lee, SW (2017)	**Moderate** (non-randomized)	**Unclear** (can't tell if patients consecutive)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**
Lindegaard, J. C. (2013) **NOCECA study (2005-11)**	**Moderate** (non-randomized)	**Unclear** (consecutive and incident cases used, but not sure how historical cohort sampled)	**Moderate** (data prospectively collected, but historical cohort)	**Low** (departure from intervention not likely)	**Unclear**	**Moderate** (prospective but retrospective cohort)	**Unclear**	**Moderate**
Mahantshetty U. (2017)	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Low** (measurement error unlikely)	**Low** (EMBRACE study well described)	**Moderate**
Majercakova, K. (2015) **Vienna Group (1998-08)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Mazeron, R. (2015) **Villejuif, France**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Moderate** (some refused CT	**Low** (missing data not likely to be different	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
					between groups)			
Mazeron, R. (2016) **(EMBRACE)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Low** (measurement error unlikely)	**Low** (EMBRACE study well described)	**Moderate**
Mazeron, R. (2013) **Villejuif, France**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Mazeron, R. (2014) **Villejuif, France**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Moderate** (some refused CT	**Low** (missing data not likely to be different between groups)	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**
Mazeron, R. (2015) **Villejuif, France**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Moderate** (some refused CT	**Low** (missing data not likely to be different between groups)	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**
Mohamed, S. (2015) Aarthus, Denmark (2008-11)	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**
Mohamed, S. (2016) **EMBRACE (2008-?) - 3 centres**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Low** (EMBRACE study well described)	**Moderate**
Murofushi, K.N. (2017)	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**unclear**	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
Nomden, C. N. (2013) **The Netherlands (2006-08)**	**Moderate** (non-randomized)	**Unclear** (consecutive and incident cases used, but not sure how historical cohort sampled)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (retrospective data, blinding unclear)	**Unclear**	**Moderate**
O'Steen, L. (2017)	**Moderate** (non-randomized)	**Unclear** (unclear if patients consecutive)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Unclear**	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Petit, C. (2016) **Villejuif, France (2009-14)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Potter, R. (2007) **Vienna Group (1998-03)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups)	**Moderate** (some surrogate measures likely)	**Low (**1 centre from EMBRACE with clear protocol)	**Moderate**
Potter, R. (2011) **Vienna Group (2001-08)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Low (**1 centre from EMBRACE with clear protocol)	**Moderate**
Ribeiro, I. (2016) **Belgium (2002-12)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Rijkmans, E. C. (2014) **The Netherlands (2000-12)**	**Moderate** (non-randomized)	**Unclear** (unclear if patients consecutive)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
Schmid, M. P. (2014) **Vienna Group (2001-09)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Schmid, M. P. (2011) **Athens, Greece (1998-09)**	**Moderate** (non-randomized)	**Unclear** (unclear if patients consecutive)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Schmid, M. P. (2013) **Vienna Group (2001-09)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Sharma, D. N. (2011) **New Delhi, India (2005-07)**	**Moderate** (non-randomized)	**Unclear** (unclear if patients consecutive)	**Low** (data prospectively collected)	**Serious** (groups not defined)	**Unclear**	**Moderate** (some surrogate measures likely)	**Unclear**	**Serious**
Sturdza, A. (2016) **RetroEMBRACE (1998-12) – 12 centres**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (CTV_{HR} measurement surrogates used)	**Low** (RetroEMBRACE study well described)	**Moderate**
Tanderup, K. (2016) **RetroEMBRACE (sub-cohort) – 7 centres**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (CTV_{HR} measurement surrogates used)	**Low** (RetroEMBRACE study well described)	**Moderate**
Tanderup, K. (2010) **Aarhus, Denmark (2005-09)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (CTV_{HR} measurement surrogates used)	**Unclear**	**Moderate**
Tharavichitkul, E. (2013) **Thailand (2008-11)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from	**Unclear**	**Serious** (short follow-up)	**Unclear**	**Serious**

Studies	Bias due to confounding	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Overall risk of bias judgement
				intervention not likely)				
Tinkle, C. L. (2015) **San Francisco (2003-09)**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Unclear**	**Moderate** (surrogates used)	**Unclear**	**Moderate**
Ujama (2017)	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (some surrogate measures likely)	**Unclear**	**Moderate**
Yoshida, K. (2015) **EMBRACE (2008-13) 22 centres**	**Moderate** (non-randomized)	**Low** (consecutive and incident cases used)	**Low** (data prospectively collected)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Moderate** (CTV_{HR} measurement surrogates used)	**Low** (EMBRACE study well described)	**Moderate**
Yoshida, K. (2013) **Japan (1993-11)**	**Moderate** (non-randomized)	**Unclear** (unclear if patients consecutive)	**Moderate** (intervention determined retrospectively)	**Low** (departure from intervention not likely)	**Low** (missing data not likely to be different between groups	**Serious** (some surrogate measures likely, follow-up unclear)	**Unclear**	**Serious**

As determined using ROBINS (Risk of Bias in Non-randomized Studies-Interventions) tool [70].
BT = brachytherapy; CT = computed tomography; CTV_{HR} = High risk clinical target volume

Appendix 5. Additional Study outcomes (subgroups)

Study	Sub-groups	Volume/Dose	Control	Survival
Castelnau-marchand, 2015 Needles NR	All		2-yr LC 87.5% 2-yr PC 85.1% 2-yr RC 81.6% 5-yr LC 85.5% 5-yr PC 81.7% 5-yr RC 76.1%	2-yr DFS 77.0% 2-yr OS 95.5% 3-yr DFS 71.6% 3-yr OS 76.1%
	B1	D_{90} CTV_{HR} 88.9±11.3; D_{90} CTV_{IR} 76.0±11.2	3-yr LC 100%; PC 100%; RC 100%	3-yr OS 100%
	IB2	D_{90} CTV_{HR} 84.3±9.5; D_{90} CTV_{IR} 68.5±5.2	3-yr LC 90.5% ;PC 88.7%; RC 85.0%	3-yr OS 76.4%
	IIA	D_{90} CTV_{HR} 78.4 ±7.1; D_{90} CTV_{IR} 67.5±3.8	3-yr LC 100%; PC 94.1%; RC 94.1%	3-yr OS 93%
	IIB	D_{90} CTV_{HR} 79.7 ±9.8; D_{90} CTV_{IR} 67.5±5.6	3-yr LC 85.8%;PC 84%; RC 79.4%	3-yr OS 70.8%
	IIIA	D_{90} CTV_{HR} 71.3 ±11.2; D_{90} CTV_{IR} 62.2±7.1	3-yr LC 50%;PC 50%; RC 50%	3-yr OS 100%
	IIIB	D_{90} CTV_{HR} 73.4 ±7.1; D_{90} CTV_{IR} 64.1±5.3	3-yr LC 77.1%; PC 72.8%; RC 64.9%	3-yr OS 75.4%
	IVA	D_{90} CTV_{HR} 65.4±5.8; D_{90} CTV_{IR} 59.6±4.6	3-yr LC 66.7%;PC 66.7%; RC 44.4%	3-yr OS 100%
	D_{90} pf CTV_{HR} ≥85 Gy vs. bet. 80-85 vs. <80 Gy		3 yr-LC 95.6% vs. 88.8% vs. 80% (p=0.018)	
	All	D_{90} CTV_{HR} 80.4 ±10.3; D_{90} I CTV_{IR} 67.7±6.1	LC 86.4%;PC 84.1%; RC 79.6%	OS 76.1%
Chargari, 2009 0% needles	All			2-yr OS 78% 2-yr DFS 73%
	IB			FRS (PO) 0/14, FRS (PN+DM) 0/14, FRS (PAN) 1/14, FRS (DM) 1/14, FRS (PAN+DM) 0/14 FRS (unkn) 0/14, FRS (TR) 2/14
	II			FRS (PO) 0/23 FRS (PN+DM) 1/23, FRS (PAN) 0/23, FRS (DM) 3/23, FRS (PAN+DM) 4/23, FRS (unkn) 0/23, FRS (TR) 8/23
	III-IVA			FRS (PO) 0/8, FRS (PN+DM) 1/8, FRS (PAN) 1/8, FRS (DM) 1/8, FRS (PAN+DM) 0/8, FRS (unkn) 1/8, FRS (TR) 4/8
	All			FRS (PO) 0/45, FRS (PN+DM) 2/45, FRS (PAN) 2/45, FRS (DM) 5/45, FRS (PAN+DM) 4/45,

Study	Sub-groups	Volume/Dose	Control	Survival
				FRS (unkn.) 1/45, FRS (TR) 14/45
Chargari, 2016 7.3% needles	CTV_{HR} volume<40cm^3		3 yr LFFS: 93% (88-99)	
	CTV_{HR} volume≥40cm^3		3-yr LFFS: 74% (52-96)	
	D_{90} CTV_{HR} <85Gy (LF patients removed)		3 yr non-LF: 98% (96-100)	
	D_{90} CTV_{HR} ≥85Gy (LF patients removed)		3 yr non-LF: 84% (79-89)	
	CTV_{HR} volume<40cm^3		3-yr non-LF 91% (88-94)	
	CTV_{HR} volume≥40cm^3		3-yr non-LF: 82% (81-83)	
	All		Factors tested for local failure D_{90} CTV_{HR} ≥85Gy NS, OTT ≥ 49dys NS, Stage IV vs III NS, Tumour width >50 mm NS, CTV_{HR} *volume ≥ 40cm^3 p=0.025*, Presence of pelvic nodes NS, hemoglobin level NS. Factors tested for non-local failure (patients with LF excluded) *D_{90} CTV_{HR} ≥85Gy p=0.002*, Stage IV vs III NS, Tumour width >50 mm NS, CTV_{HR} *volume ≥ 40cm^3 p=0.035*, Presence of pelvic nodes NS, hemoglobin level NS.	
Dimopoulos, 2009 [33] Vienna cohort 20.6% needles	All		LR 14/141	
	All	GTV V (cm^3) GTV D_{100} (Gy) GTV D_{90} (Gy) CTV_{HR} V (cm^3) CTV_{HR} D_{100} (Gy) CTV_{HR} D_{90} (Gy) CTV_{IR} V (cm^3) CTV_{IR} D_{100} (Gy) CTV_{IR} D_{90} (Gy)	LR 13±10, No-LR 11±13, p>0.05 LR 82±13, No LR 91±24, p>0.05 LR 113±23, No-LR, 124±36, p>0.05 LR 50±24, No-LR 34±23, p<0.05 LR 60±7, No LR 66±10, p<0.05 LR 113±23, No-LR, 124±36, p>0.05 LR 118±45, No-LR 88±41, p<0.05 LR 53±4, No LR 53±7, p>0.05 LR 62±6, No-LR, 66±9, p>0.05	

Study	Sub-groups	Volume/Dose	Control	Survival
	1; 2-5cmDIAG	GTV – D_{100} (Gy) GTV – D_{90} (Gy) CTV_{HR} - D_{100} (Gy) CTV_{HR} - D_{90} (Gy) CTV_{IR} D_{100} (Gy) CTV_{IR} D_{90} (Gy)	*LR* 92±13, *No LR* 95±27, p>0.05 *LR* 124±19, *No LR* 131± 39, p>0.05 *LR* 69±1, *No LR* 65±12, p>0.05 *LR* 92±3, *No LR* 89±17, p>0.05 *LR* 53±1, *No LR* 51±8, p>0.05 *LR* 69±1, *No LR* 65±10, p>0.05	
	2; >5cmDIAG	GTV – D_{100} (Gy) GTV – D_{90} (Gy) CTV_{HR} - D_{100} (Gy) CTV_{HR} - D_{90} (Gy) CTV_{IR} D_{100} (Gy) CTV_{IR} D_{90} (Gy) LR - D_{90} CTV_{HR} LR D_{100} CTV_{HR}	*LR* 80±12, *No LR* 87±20, p>0.05 *LR* 111±24, *No LR 117*±31, p>0.05 *LR* 59±6, *No LR* 66±8, p<0.05 *LR* 73±11, *No LR* 86±15, p<0.05 *LR* 53±5, *No LR* 56±4, p<0.05 *LR* 61±6, *No LR* 67±8, p<0.05 <87Gy 33% ≥87Gy 3% <66Gy 32%, ≥66Gy 6%	
	2a; >5cmDIAG - 2-5cmBT	GTV – D_{100} (Gy) GTV – D_{90} (Gy) CTV_{HR} - D_{100} (Gy) CTV_{HR} - D_{90} (Gy) CTV_{IR} D_{100} (Gy) CTV_{IR} D_{90} (Gy) LR - D_{90} CTV_{HR} LR D_{100} CTV_{HR}	*LR* 90±15, *No LR* 90±22, p>0.05 *LR* 134±29, *No LR 121*±33, p>0.05 *LR* 62±4, *No LR* 68±8, p>0.05 *LR* 83±7, *No LR* 88±15, p>0.05 *LR* 52±7, *No LR* 56±4, p>0.05 *LR* 64±4, *No LR* 68±7, p>0.05 <87Gy 19% ≥87Gy 4% <66Gy 19%, ≥66Gy 4%	
	2b; >5cmDIAG - >5cmBT	GTV – D_{100} (Gy) GTV – D_{90} (Gy) CTV_{HR} - D_{100} (Gy) CTV_{HR} - D_{90} (Gy) CTV_{IR} D_{100} (Gy) CTV_{IR} D_{90} (Gy) LR - D_{90} CTV_{HR} LR D_{100} CTV_{HR}	*LR* 76±9, *No LR* 81±17, p>0.05 *LR* 101±12, *No LR 109*±25, p>0.05 *LR* 57±7, *No LR* 64±7, p<0.05 *LR* 69±9, *No LR* 81±13, p<0.05 *LR* 53±4, *No LR* 56±5, p>0.05 *LR* 60±6, *No LR* 65±8, p>0.05 <87Gy 46% ≥87Gy 0% <66Gy 43%, ≥66Gy 13%	
	>5cmDIAG	D_{90} CTV_{HR} <87 D_{90} CTV_{HR} ≥87 D_{100} CTV_{HR} <66 D_{100} CTV_{HR} ≥66	33% 3% 32% 6%	
	>5cmDIAG ● - 5cmBT	D_{90} CTV_{HR} <87 D_{90} CTV_{HR} ≥87 D_{100} CTV_{HR} <66 D_{100} CTV_{HR} ≥66	19% 4% 19% 4%	

Study	Sub-groups	Volume/Dose	Control	Survival
	>5cmDIAG● >5cmBT	D_{90} CTV_{HR} <87 D_{90} CTV_{HR} ≥87 D_{100} CTV_{HR} <66 D_{100} CTV_{HR} ≥66	46% 0% 43% 13%	
	All	D_{90} CTV_{HR} <87 D_{90} CTV_{HR} ≥87 $D1_{00}$ CTV_{HR} <66 D_{100} CTV_{HR} ≥66	20% 4% 17% 7%	
Dimopoulos, 2009 [23] 20.6% needles	1	D_{90} CTV_{HR} 89±17, D_{100} CTV_{HR} 65±11	% LR: 3.1	
	2	D_{90} CTV_{HR} 83±15, D_{100} CTV_{HR} 65±8	% LR: 20.8	
	2a	D_{90} CTV_{HR} 88±15, D_{100} CTV_{HR} 67±8	% LR: 10.9	
	2b	D_{90} CTV_{HR} 77±13, D_{100} CTV_{HR} 61±8	% LR: 35.5	
	All	D_{90} CTV_{HR} 86±12, D_{100} CTV_{HR} 65±10	% LR: 12.8	
Dyk, 2014 0% needles	All		Total recurrences 43.3% (Pelvis only 17%, Distant only 17%, Pelvic and distant 9%, cervix only 6.7%); Median time to recurrence mos. (range) 8 (0-36) Median time to cervix recurrence, mos. (range) 5.5 (0.27)	
	All	Median D_{90}, EQD2, Gy (range)	LF 57.8 (2.2-132.6), LC 98.9 (38.5-533.5), p <0.001	
	Patients who completed radiation	Median D_{90}, EQD2, Gy (range)	LF 65.4 (30.2-132.6), LC 98.9 (38.5-533.5). p <0.001	
	All	Median D_{100}, EQD2, Gy (range)	LF 41.2 (1.3-100.6) LC 67.4 (26.2-255.3) p<0.001	
	Patients who completed radiation	Median D_{100}, EQD2, Gy (range)	LF 43.4 (21.6-100.6), LC 67.4 (26.2-255.3), p<0.001	
	All	Median Dmean, EQD2, Gy (range)	LF 135.8 (6.9-363.0) LC 235.6 (83.6-2086.8) p<0.001;	
	Patients who completed radiation	Median Dmean, EQD2, Gy (range)	LF 156.1 (81.4-362.9) LC 235.6 (83.6-2086.8) p<0.001	
Gill, 2015 0% needles	All		1-yr LC 92.5% (90.1-94.9) 2-yr LC 91.6% (89.0-94.2) 3-yr LC 91.6 (89.0-94.2)	1-yr DFS 85.1% (81.9-88.3) 2-yr DFS 81.8% (78.1-85.5) 3-yr DFS 80.0% (76.0-84.0) 1-yr CSS 93.1% (90.6-95.6)

Study	Sub-groups	Volume/Dose	Control	Survival
				2-yr CSS 87.6% (84.0-91.2) 3-yr CSS 85.4% (81.3-89.5) 1-yr OS 93.1% (90.6-95.6) 2-yr OS 85.0% (81.5-88.5) 3-yr OS 76.6% (71.8-81.4)
	IB1 IB2 IIA1 IIA2 IIB IIIB			2 yr DFS 100% 2 yr DFS 92.3% 2 yr DFS 100% 2 yr DFS 0% 2 yr DFS 83.6% 2 yr DFS 60.0% for IIIB; p=.01
	(tumour size≥6 cm[vs. other])			2 yr DFS 66.8% vs 90.3%, p<0.01 2 yr CSS 71.2% vs 94.4%, p<0.01
	(incomplete clinical response at first foll-up [vs. other])		2 yr LC 42.9% vs. 94.5%, p<0.01	2 yr DFS 14.3% vs 85.7%, p<0.01 2 yr CSS 0.0% vs 92.5%, p<0.01 2 yr OS 60.0% vs 89.7%, p<0.01
	(treatment time >52 dys [vs. other])			2 yr CSS 80.5% vs 93.9%, P<0.01 2 yr OS 80.1% vs 89.1%, p<0.01
	patients with adenocarcinomas, CTV_{HR} D_{90} EQD2≥84 2 [vs. other])		2 yr LC 100% vs 54.5%, p=0.03	
	Adenocarc. histology [vs. other])		2-yr LC 74.7% vs. 95.0%, p<0.01	2-yr DFS 74.7% vs 83.3%, p=0.07).
	Older age			2-yr OS P<0.01
Haie-Meder, 2009 (n=39) 0% needles	All		Local relapse 1, Pelvic node 2, Para-aortic node 0, Distant metastasis 3, Local and distant 2, Total relapse 4	2-yr LRFS 94% (95%CI 86-100) 4-yr LRFS 91% (95%CI 81-100) 4-yr OS 94% (95%CI 82-98) 4-yr DFS 86% (95%CI 67-95)
Haie-Meder, 2010	All		2-yr LC 89.2%	3-yr OS 67% (56-77) 4-yr OS 57% (43-69)

Study	Sub-groups	Volume/Dose	Control	Survival
0% needles				3-yr DFS 63% (52-73) 4-yr DFS 52% (40-64)
Hannoun-Levi, 2013 100% needles	All		Local or distant recurrence 0%	
Kim, 2016 0% needles	All			5 yr LRFS: 94% (predictors: none) 5 yr RRFS: 92% (predictors: pathology p=0.016, tumour size p=0.009) 5 yr DMFS: 74% (predictors: pathology p=0.002, pelvic LN p=0.005) 5 yr DFS: 73% (predictors: pathology p=0.0001, pelvic LN p=0.02) 5 yr CSS: 89% (predictors: pathology p=0.04) 5 yr OS: 85% (predictors: pelvic LN p=0.04, GTV D_{90} >110 Gy EQD2 p=0.05, treatment duration ≤ 56 dys, p=0.03)
Lakosi, 2015 11.7% needles	All		3-yr PFSlocal/LC: 94% 3-yr PFSpelvic/PC: 90%	3-yr PFS overall: 74% 3-yr CSS: 85% 3-yr OS: 81%
	Node negative vs. node positive			3-yr OS: 92% vs. 72%, p=0.016 3-yr CSS: 100% vs. 72%, p=0.01
Lee, 2017	*All*		3 yr LRR 14.3% 3 yr PAR 8.3% 3 yr DR 19.2%	
	0, Ib2 II, III IVa			3-yr CSS: 93.2% 3-yr CSS: 80.3% 3-yr CSS: 61.2% 3-yr CSS: 35.4% 16.1%

Study	Sub-groups	Volume/Dose	Control	Survival
Mazeron, 2015 [51] 54.9% needles	*IB-IIA* IIB III-IVA	85 GY to D_{90} CTV_{HR} 85 GY to D_{90} CTV_{HR} 85 GY to D_{90} CTV_{HR}	LC: 94.5% (80/225, 35.6%) 88.5% (110/225, 48.9%) 85% (35/225, 15.5%); p=0.005	
	Tumour width at Diag. ≥50mm vs. <50mm	Gy required to warrant 90%	LC: (50.2%) 93 Gy, vs. 73.9Gy	
	CTV_{HR} *volume ≥30cm³ vs. <30cm³*	Gy required to warrant 90%	% LC: *(33.3%) 92Gy vs. (66.7%) 73.9Gy*	
	All		Prognostic factors for LC (univariate): Stage III-IV vs I-II (p=0.012), CTWdiag >45 (p=0.006), OTT days >55 (p<0.006), D_{90} CTV_{HR} <85 Gy (p=0.008), D_{90} CTV_{IR} <65 Gy (p=0.031), TRAK cGy/m²) <1.8 (p=0.025), CTV_{HR} volume (cm³) ≥30 (p<0.0001) Prognostic factors for LC (multivariate): OTT days >55 (p=0.047), RR=2.2 (1.0-4.5); CTV_{HR} volume (cm³) ≥30 (p<0.048); RR= 2.5(1.007-6.25)	
Mahantshetty, 2017	All		39 mos. LCR: 90.1%±3.4% 39 mos. OPRS: 72.1%±4.8%	
	IIB, IVA IIIB		39 mos. LCR: 100% 39 mos. LCR: 85%, p=0.013	
Murofushi, 2017			3 yr LC: 90.1%	3 yr OS84.2%, 3 yr DFS 75.6%,
Nomden, 2013 30.4% needles	All		3-yr LC 93%	3-yr PFS: 71% 3-yr OS: 65% 3-yr DMFS: 81.8%
	Node negative vs. node positive			3-yr PFS 85% vs. 53% p=0.013 3-yr OS 77% vs. 50% p=0.032
	Node negative vs. node positive for FIGO stages IB-IIB			3-yr PFS 87% vs. 42% p=0.002 3-yr OS 83% vs. 46% p=0.007
	I-IIB vs. III-IVA			3 yr OS: 69.4% vs. 50%, p=0.262
O'Steen, 2017	All		5-yr LC: 98% 5-yr RCR: 84% Freedom from distant metastases: 90%	5-yr DFS: 73% 5-yr CSS: 78% 5-yr OS: 57%

Study	Sub-groups	Volume/Dose	Control	Survival
Ribeiro, 2016 16% needles	All		LC: 96%, LC 3/5 yrs – 95% RC: 81%, RC 3-yrs – 80%, RC 5-yrs – 77% SC: 73%, SC 3-yrs – 76%, SC 5-yrs – 70%	3-yr OS:73% 5-yr OS: 65%
	All FIGO stages except IVB			3-yr OS:76% 5-yr OS: 66%
Schmid, 2011 (matched-pair analyses) 26.2% needles	All		Central recurrence: 8/21 MPD [Gy_{ab10} {mean (st. dev.)] 69.5 (±9.9); true central 83.3 (±9.3); whole small pelvis 65.0 (±4.5) Non-central recurrence: 13/21 MPD [Gy_{ab10} {mean (st. dev.)}] 73.5 (±14.8) ; ipsilateral 65.6 (±9.2); contralateral 91.2 (±7.1)	
	IB		LR 0/21; CCLR 1/21, p=0.32	
	IIA		LR 1/21; CCLR 0/21, p=0.32	
	IIB		LR 8/21; CCLR 9/21, p=0.76	
	IIIB		LR 10/21; CCLR 9/21, p=0.76	
	IVA		LR 2/21; CCLR 2/21, p=1.00	
	Sq. cell carcinoma Adenocarcinoma Others		LR 17/21; CCLR 18/21, p=0.69 LR 3/21; CCLR 3/21, p=1.00 LR 1/21; CCLR 0/21, p=0.32	
	Tumour size width <5 vs. ≥ 5cm		LR 3/21; CCLR 3/21, p=100 LR 18/21; CCLR 18/21, p=100	
	Regional lymph node involvement		LR 7/21; CCLR 17/21	
	Concurrent chemo		LR 12/21; CCLR 15/21	
	All	Doses to CTV_{HR} Gyab10 mean (st. dev.) MPD D_{100} D_{98} D_{90} D_{50}	 LR 72 (±13); CCLR 99 (±20) p<0.001 LR 61 (±7); CCLR 71 (±7) p<0.001 LR 67 (±8); CCLR 80 (±8) p <0.001 LR 77 (±12); CCLR 95 (±10) p <0.001 LR 121 (±30); CCLR 146 (±20) p <0.001	
	All	Doses to CTV_{IR} Gyab10 mean (st. dev.) MPD D_{100} D_{98} D_{90} D_{50}	 LR 58 (±6); CCLR 73 (±6) p <0.001 LR 54 (±4); CCLR 60 (±5) p <0.001 LR 57 (±5); CCLR 66 (±6) p <0.001 LR 64 (±6); CCLR 76 (±6) p <0.001 LR 95 (±17); CCLR 115 (±13) p <0.001	
	All	Mean D_{90} CTV_{HR}	LR 77 Gy, CCLR 95 Gy	
	All	Mean D_{100} CTV_{HR}	LR 61 Gy, CCLR 71 Gy, p<0.01	

Study	Sub-groups	Volume/Dose	Control	Survival
	All	D_{90} for CTV_{HR} ≥87 Gy [n]: MPD for CTV_{HR} ≥87 Gy [n]:	LR 7; CCLR 17 p – LR 3; CCLR 17 p –	
Schmid, 2013, Schmid 2014 Needles NR	All			3-yr DMFS 78% (72-84) 5-yr DMFS 73% (67-80) Positive predictors of DMFS FIGO stage (p=0.000), Lymph node status (p=0.003), treatment time (p=.001), size of CTV_{HR} (p=0.000), CTV_{HR} CTV90 (p=0.007), tumour regression (p=0.026)
	Low vs. high risk groups			5-yr DMFS 91% vs. 60%
Sturdza, 2016 retroEMBRACE – 12 centres 50% needles	All		LC 3/5 yr 91%/89% PC 3/5 yr 87%/84%	CSS 3/5 yr 79%/73% OS 3/5 yr 74%/65%
	IB IIB IIIB		LC 3/5 yr 98%/98%; PC 3/5 yr 96%/96% LC 3/5 yr 93%/91%; PC 3/5 yr 89%/87% LC 3/5 yr 79%/75%; PC 3/5 yr 73%/67%	
	Tumour ≥ 5cm vs. <5 cm			OS 3/5 yr 66%/57% vs. 81/74%, p<0.001
	Mod negative vs. node positive			OS 3/5 yr 78%/71% vs. 67/57%, p=0.006
	581 patients treated with MR-based IGBT		3/5 yr LC tumour < 5cm 95%/94% vs. ≥ 5cm 85%/81%	
	IA	Mean D_{90} CTV_{HR} in Gy -	LC 3/5 yr 100% PC 3/5 yr 100%	OS 3/5 yr 100% CSS 3/5 yr IA 100%
	IB	Mean D_{90} CTV_{HR} in Gy 93±17	LC 3/5 yr 98%/98% PC 3/5 yr 96%/96%	OS 3/5 yr 88%/83% CSS 3/5 yr 93%/90%
	2A	Mean D_{90} CTV_{HR} in Gy 89±16	LC 3/5 yr 97%/94% PC 3/5 yr 95%/92%	OS 3/5 yr 83%/80% CSS 3/5 yr 87%/84%
	2B	Mean D_{90} CTV_{HR} in Gy 88±14	LC 3/5 yr 93%/91% PC 3/5 yr 89%/87%	OS 3/5 yr 78%/70% CSS 3/5 yr 83%/77%
	3A	Mean D_{90} CTV_{HR} in Gy 83±12	LC 3/5 yr 71%/71% PC 3/5 yr 66%/66%	OS 3/5 yr 54%/42% CSS 3/5 yr 54%/48%
	3B	Mean D_{90} CTV_{HR} in Gy 83±13	LC 3/5 yr 79%/75% PC 3/5 yr 73%/67%	OS 3/5 yr 56%/42% CSS 3/5 yr 65%/53%
	4A	Mean D_{90} CTV_{HR} in Gy (±SD) 78±13	LC 3/5 yr 76%/76% PC 3/5 yr 76%/76%	OS 3/5 yr 43%/32% CSS 3/5 yr 53%/40%

Study	Sub-groups	Volume/Dose	Control	Survival
	4B	Mean D_{90} CTV_{HR} in Gy 78±2	LC 3/5 yr 4B - PC 3/5 yr -	OS 3/5 yr - CSS 3/5 yr -
	All	Mean D_{90} CTV_{HR} in Gy 87±15	LC 3/5 yr 91%/89% PC 3/5 yr 87%/84%	OS 3/5 yr 74%/65% CSS 3/5 79%/73%
Sharma, 2011 100% needles	IIB		PR 20%, DM 1/42, TR 30%, PC 80%	3-yr RFS: 67%
	IIIB		PR 37%, DM 2/42, TR 344%, PC 63%	3-yr RFS: 34%
	IVA		PR 80%, DM 0/42, TR 80%, PC 20%	3-yr RFS: 20%
	All			3-yr OS: 47%
Tanderup, 2016 retroEMBRACE (sub-cohort – 7 centres) Needles NR	IB	CTV_{HR} volume 25±15 cm^3, CTV_{HR} D_{90} 9±13 Gy, 101±27 Gy, CTV_{IR} D_{90} 71±7 Gy	%LF: 1.5%	
	IIA-IIIB	CTV_{HR} volume 33±19 cm^3, CTV_{HR} D_{90} 87±11 Gy, GTV D_{100} 93±18 Gy, CTV_{IR} D_{90} 69±6 Gy	%LF: 7.5%	
	IIIA+IIIB + IV	CTV_{HR} volume 47±27 cm^3, CTV_{HR} D_{90} 3±12 Gy, GTV D_{100} 88±18 Gy, CTV_{IR} D_{90} 66±7 Gy	%LF: 14.9%	
	All	CTV_{HR} volume 36±22 cm^3, CTV_{HR} D_{90} 86±12 Gy, GTV D_{100} 92±19 Gy, CTV_{IR} D_{90} 68±7 Gy	%LF: 8.8%	
	All		LC (predictors): stage I (ref.) p=0.046, Stage II HR 0.118 (0.015-0.903), Stage III HR 0.538 (0.271-1.068), CTV_{HR} volume HR 1.017 per cm^3 (1.005 – 1.029) p=0.004; CTV_{HR} D_{90} HR 0.967 per Gy (0.940 – 0.995) p=0.022, OTT HR 1.023 (1.007-1.039)	
Tharavichitkul, 2013 0% needles	All		LC: 97.9%	DFS: 85.1% OS: 93.6%
	IIB		LC: 96.9%	DFS: 87.5%, OS: 96.9%
	IIIB		LC: 100%	DFS: 80% OS: 86.7%
Tinkle, 2015 100% needles	All		4 yr LC: 94.0% (87.1-97.3) 4 yr LRC: 91.9% (84.4-95.9) 4 yr DC: 69.1% (58.7-77.4)	4 yr OS: 64.3% (54.1-72.8) 4 yr DFS: 61.0% (51.0-69.6) 4 yr OS (MO at diag.): 69.2 (58.2-77.8) 4 yr DFS (MO at diag.): 66.2 (55.4-74.9)
	No distant metastasis at diag.			4-yr OS 69.2% (58.2-77.8) 4-yr DFS 66.2% (55.4-74.9)

CCLR = continuous complete local remission; CSS = cancer-specific survival; CTV_{HR} = high-risk clinical target volume; CTV_{IR} = intermediate-risk clinical target volume; D_{90} = 90% of the residual tumour volume; DC = distant control; DMFS = distant metastasis-free survival; DFS = disease-free survival; DM = distant metastases, DR = distant recurrence; EQD2 = Doses converted to the equivalent dose in 2 Gy; FRS = first relapse site; GTV = gross tumour volume;

Study	Sub-groups	Volume/Dose	Control	Survival
LC = local control LFFS = local failure free survival; LRFS – local relapse-free survival; LRFS= local free-relapse survival; LRC = local regional control; MPD = minimum point dose; NED = no evidence of disease; PC = pelvic control; RR = regional recurrence; RRFS = regional recurrence-free survival; RLRFS = loco-regional relapse-free survival; OS = overall survival; PC = pelvic control; PAN = para-aortic node; PN = pelvic node; PR = pelvic recurrence; PO = pelvis only; RC = regional control; SC = systemic control; TR = total recurrence/relapse.				

Appendix 6. Toxicity Outcomes

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
Castelnau-Marchand, 2015	Diarrhea: Grade 0 125 (55.6%) Grade 1 86 (38.2%) Grade 2 14 (6.2%) Grade 3 0 Grade 4 0 Grade 3-4 0 Incontinence: Grade 0 199 (88.4%) Grade 1 21 (9.3%) Grade 2 5 (2.2%) Grade 3 0 Grade 4 0 Grade 3-4 0 Proctitis: Grade 0 212 (94.2%) Grade 1 12 (5.3%) Grade 2 1 (0.4%) Grade 3 0 Grade 4 0 Grade 3-4 0 Bleeding: Grade 0 195 (86.7%) Grade 1 20 (8.9%) Grade 2 9 (4.0%) Grade 3 1 (0.04%) Grade 4 0 Grade 3-4 1 (0.4%) Stenosis: Grade 0 211 (93.8%) Grade 1 1 (0.4%) Grade 2 3 (1.3%) Grade 3 4 (1.8%) Grade 4 2 (0.9%) Grade 3-4 6 (2.7%) Fistula: Grade 0 223 (99.1%) Grade 1 0 Grade 2 0 Grade 3 2 (0.9%) Grade 4 0 Grade 3-4 2 (0.9%)	Frequency: Grade 0 160 (71.1%) Grade 1 51 (22.7%) Grade 2 12 (5.3%) Grade 3 2 (0.9%) Grade 4 – Grade 3-4 2 (0.9%) Incontinence: Grade 0 171 (76.0%) Grade 1 35 (15.6%) Grade 2 17 (7.6%) Grade 3 2 (0.9%) Grade 4 – Grade 3-4 2 (0.9%) Cystitis: Grade 0 197 (87.6%) Grade 1 17 (7.6%) Grade 2 11 (4.9%) Grade 30 Grade 4 0 Grade 3-4 0 Bleeding: Grade 0 215 (95.6%) Grade 1 6 (2.7%) Grade 2 4 (1.8%) Grade 30 Grade 4 0 Grade 3-4 0 Stenosis: Grade 0 220 (97.8%) Grade 11 (0.4%) Grade 2 2 (0.9%) Grade 3 2 (0.9%) Grade 4 0 Grade 3-4 2 (0.9%) Fistula: Grade 0 222 (98.7) Grade 1 0 Grade 2 0 Grade 3 3 (1.3%) Grade 4 0 Grade 3-4 3 (1.3%)	Sexuality: Grade 0 129 (57.3%) Grade 161 (27.1%) Grade 2 29 (12.9%) Grade 3 6 (2.7%) Grade 4 – Grade 3-4 6 (2.7%) Pelvic fibrosis: Grade 0 158 (70.2%) Grade1 49 (21.8%) Grade 2 13 (5.8%) Grade 3 5 (2.2%) Grade 4 – Grade 3-4 5 (2.2%)	
Chargari, 2009	Acute Diarrhea Grade1 16, Grade2 0, Grade3 0. Delayed complications Rectitis Grade 1 2, Grade 2 0, Grade 3 0; Fistula Grade 1 0, Grade 2 0, Grade 3 1.	Acute Cystitis Grade1 2, Grade2 0, Grade3 0. Delayed complications Cystitis Grade1 5, Grade2 3, Grade3 0.	Acute Vulvitis Grade1 9, Grade2 6, Grade3 2; Vaginal epithelitis Grade1 0, Grade2 1, Grade3 1. Delayed complications Vagina Grade1 3, Grade2 1, Grade3 0; Perineal pain Grade 1 1, Grade 2 0, Grade 3 0; Pelvic fibrosis Grade1 5, Grade2 3, Grade3 0	Acute Dermatitis Grade1 4, Grade2 1, Grade3 1. Delayed complications Lymphedema Grade1 1, Grade2 1, Grade3 0; Dyspareunia Grade1 2, Grade2 3, Grade3 0.
Georg, 2011 Vienna Cohort	Group 1 (G0) vs. Group 2 (G1-G4)			

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
	Bladder: DICRU 71±15 vs. 76±16 p=0.144; D2cc 94±20 vs. 101±29 p=0.197; D1cc 107±28 vs. 117±42 p=0.159; D0.1cc 158±65 vs. 182±116 p=0.168. Rectum: DICRU 66±12 vs. 80±19 p=0.002; D2cc 64±12 vs. 75±13 p=0.003; D1cc 69±14 vs. 80±16 p=0.007; D0.1cc 84±26 vs.103±31 p=0.022. Sigmoid: DICRU NA vs. NA; D2cc 62±12 vs. 77±11 p=0.028; D1cc 66±14 vs. 84±14 p=0.037; D0.1cc 83±33 vs. 104±24 p=0.279. <u>Group 3 (G0-G1) vs. Group 4 (G2-G4)</u> Bladder: DICRU 71±15 vs. 78±15 p=0.133; D2cc 94±20 vs. 108±33 p=0.021; D1cc 106±28 vs. 126±48 p=0.019; D0.1cc 157±63 vs. 208±140 p=0.016. Rectum: DICRU 66±12 vs. 83±22 p=0.001; D2cc 64±12 vs. 75±15 p=0.014; D1cc 69±14 vs. 80±18 p=0.030; D0.1cc 85±26 vs.100±30 p=0.122. Sigmoid: DICRU NA vs. NA; D2cc 62±12 vs. 77±11 p=0.028; D1cc 66±14 vs. 84±14 p=0.037; D0.1cc 83±33 vs. 104±24 p=0.279.			
Georg, 2013	LSE Rectum G1 4.4%, G2 6.2%, G3, 1.8%, G4 1.3%, total 13.8%	LSE Bladder G1 9.8%, G2 8.9%, G3, 2.2%, G4 0.9%, total 21.88%		
Haie-Meder, 2009	Rectal (late complications) 1/39 Small bowel (late complications) 1/39	Bladder (late complications) 10/39 Ureteral (late complications) 3/39	Vaginal (late complications) 1/39	Total late complications 13/39 (4 grade 2, 9 Grade 1) Pelvic fibrosis (late complications) 1/39 Peripheral nerve (late complications) 1/39

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
				Other complications (not specified) 2/39
Haie-Meder, 2010	Rectal (late complications) 7/84 Small bowel (late complications) 5/84 Colic (late complications) 3/84	Bladder (late complications) 13/84 Ureteral (late complications) 4/84	Vaginal (late complications) 2/84	Total late complications 39/84 (4 Grade 3, 6 grade 2, 29 Grade 1) Pelvic fibrosis (late complications) 1/84 Other complications (not specified) 4/84
Hannoun-Levi, 2013	Grade 1 diarrhea 15/32	Grade 1 urinary frequency 13/32 Grade 1 urinary urgency 13/32	Dyspareunia (late complication) 4/24 (followed for 24 mos.)	
Kim, 2017 (n=35)	<u>Rectum Group1 and Group 2 (Acute Toxicty)</u> D_{ICRU} Mean (median) SD: *Total* 73.8 (69.8) 17.4; *Group1* 73.1 (69.0) 15.6; *Group2* 74.0 (69.8) 17.8; p=0.470. $D_{0.1cc}$ Mean (median) SD: *Total* 84.4 (83.9) 15.0; *Group1* 82.1 (80.2) 18.3; *Group2* 84.9 (84.3) 14.1; p=0.066. D_{1cc} Mean (median) SD: *Total* 74.1 (73.7) 11.2; *Group1* 72.4 (72.6) 13.4; *Group2* 74.6 (73.9) 10.5; p=0.087. D_{2cc} Mean (median) SD: *Total* 70.3 (69.3) 9.9; *Group1* 68.5 (69.1) 11.4; *Group2* 70.7 (70.5) 9.5; p=0.073. D_{5cc} Mean (median) SD: *Total* 64.7 (64.1) 8.1; *Group1* 62.7 (62.7) 8.6; *Group2* 65.2 (64.8) 8.0; p=0.046 <u>Rectum Group3 and Group 4 (Acute Toxicty)</u> D_{ICRU} Mean (median) SD: *Total* 73.8 (69.8) 17.4; *Group1* 73.9	<u>Bladder Group1 and Group 2 (Acute Toxicty)</u> D_{ICRU} Mean (median) SD: *Total* 77.2 (73.9) 23.1; *Group1* 73.1 (69.0) 15.6; *Group2* 77.9 (75.5) 19.0; p=0.375. $D_{0.1cc}$ Mean (median) SD: *Total* 120.7 (110.2) 64.7; *Group1* 119.8 (109.4) 68.0; *Group2* 126.6 (117.9) 37.4; p=0.163. D_{1cc} Mean (median) SD: *Total* 100.4 (95.6) 30.0; *Group1* 99.4 (94.8) 30.6; *Group2* 106.8 (105.2) 25.7; p=0.097. D_{2cc} Mean (median) SD: *Total* 93.9 (90.7) 22.7; *Group1* 93.0 (90.4) 22.7; *Group2* 99.4 (96.7) 22.6; p=0.135. D_{5cc} Mean (median) SD: *Total* 84.1 (81.9) 16.2; *Group1* 83.3 (81.9) 15.7; *Group2* 89.0 (83.1) 19.1; p=0.157 <u>Bladder Group3 and Group 4 (Acute Toxicty)</u> D_{ICRU} Mean (median) SD: *Total* 77.2 (73.9) 23.1; *Group1* 77.2		

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
	(69.1) 18.0; *Group2* 84.2 (83.5) 12.1; p=0.399. $D_{0.1cc}$ Mean (median) SD: *Total* 84.4 (83.9) 15.0; *Group1* 74.2 (73.5) 12.2; *Group2* 74.1 (75.4) 8.5; p=0.442. D_{1cc} Mean (median) SD: *Total* 74.1 (73.7) 11.2; *Group1* 72.4 (72.6) 13.4; *Group2* 74.6 (73.9) 10.5; p=0.374. D_{2cc} Mean (median) SD: *Total* 70.3 (69.3) 9.9; *Group1* 70.3 (69.1) 10.9; *Group2* 70.2 (71.5) 7.3; p=0.388. D_{5cc} Mean (median) SD: *Total* 64.7 (64.1) 8.1; *Group1* 64.8 (64.0) 9.0; *Group2* 64.6 (64.9) 5.8; p=0.450 <u>Rectum Group1 and Group 2 (Late Toxicty)</u> D_{ICRU} Mean (median) SD: *Group1* 71.9 (69.1) 17.0; *Group2* 77.1 (71.6) 17.7; p=0.016. $D_{0.1cc}$ Mean (median) SD: *Group1* 82.7 (82.1) 16.1; *Group2* 84.9 (84.3) 14.1; p=0.066. D_{1cc} Mean (median) SD: *Group1* 72.8 (72.6) 11.7; *Group2* 76.4 (76.3) 9.8; p=0.022. D_{2cc} Mean (median) SD: *Group1* 69.1 (69.0) 10.2; *Group2* 72.4 (71.7) 9.05; p=0.035. D_{5cc} Mean (median) SD: *Group1* 63.7 (63.3) 8.2; *Group2* 66.5 (65.1) 7.9; p=0.054 <u>Rectum Group3 and Group 4 (Late Toxicty)</u> D_{ICRU} Mean (median) SD: *Group1* 72.6 (68.9) 16.9; *Group2* 79.1 (74.5) 18.7; p=0.039.	(73.9) 23.0; *Group2* 78.0 (75.6) 27.60; p=0.408. $D_{0.1cc}$ Mean (median) SD: *Total* 120.6 (109.8) 65.5; *Group1* 119.8 (109.4) 68.0; *Group2* 123.6 (111.5) 46.2; p=0.484. D_{1cc} Mean (median) SD: *Total* 100.4 (95.6) 30.0; *Group1* 100.3 (95.3) 30.0; *Group2* 104.1 (105.2) 34.1; p=0.369. D_{2cc} Mean (median) SD: *Total* 93.9 (90.7) 22.7; *Group1* 93.8 (90.6) 22.5; *Group2* 96.1 (92.2) 30.2; p=0.489. D_{5cc} Mean (median) SD: *Total* 84.1 (81.9) 16.2; *Group1* 84.1 (82.0) 15.9; *Group2* 84.8 (76.5) 24.8; p=0.413 <u>Bladder Group1 and Group 2 (Late Toxicty)</u> D_{ICRU} Mean (median) SD: *Group1* 76.6 (73.6) 23.8; *Group2* 79.4 (75.9) 20.4; p=0.203 $D_{0.1cc}$ Mean (median) SD: *Group1* 119.7 (107.5) 70.9; *Group2* 124.5 (113.1) 34.7; p=0.049 D_{1cc} Mean (median) SD: *Group1* 99.0 (94.3) 31.5; *Group2* 105.6 (102.3) 23.2; p=0.027. D_{2cc} Mean (median) SD: *Group1* 92.6 (89.2) 23.5; *Group2* 98.3 (96.4) 19.4; p=0.038. D_{5cc} Mean (median) SD: *Group1* 83.2 (81.6) 16.6; *Group2* 87.2 (86.5) 14.7; p=0.077 <u>Bladder Group3 and Group 4 (Late Toxicty)</u> D_{ICRU} Mean (median) SD: *Group1* 76.4 (73.6) 23.5; *Group2* 83.1 (85.1) 19.1; p=0.043		

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
	$D_{0.1cc}$ Mean (median) SD: *Group1* 83.4 (83.0) 15.1; *Group2* 84.9 (84.3) 14.1; p=0.066. D_{1cc} Mean (median) SD: *Group1* 73.4 (72.6) 11.1; *Group2* 77.5 (76.9) 11.2; p=0.047. D_{2cc} Mean (median) SD: *Group1* 69.6 (69.1) 9.7; *Group2* 73.3 (72.0) 10.3; p=0.072. D_{5cc} Mean (median) SD: *Group1* 64.2 (63.9) 7.9; *Group2* 67.1 (65.2) 9.0; p=0.0130 <u>Sigmoid Group1 and Group 2 (Late Toxicty)</u> D_{ICRU} Mean (median) SD: *NR* $D_{0.1cc}$ Mean (median) SD: *Group1* 71.1 (80.0) 13.6; *Group2* 84.9 (84.3) 14.1; p=0.066. D_{1cc} Mean (median) SD: *Group1* 72.6 (72.1) 10.3; *Group2* 69.7 (69.6) 10.8; p=0.324. D_{2cc} Mean (median) SD: *Group1* 69.2 (68.6) 9.1; *Group2* 66.8 (66.7) 9.4; p=0.306. D_{5cc} Mean (median) SD: *Group1* 64.1 (63.7) 7.6; *Group2* 62.3 (61.8) 7.3; p=0.324 <u>sigmoid Group3 and Group 4 (Late Toxicty)</u> D_{ICRU} Mean (median) SD: *NR* $D_{0.1cc}$ Mean (median) SD: *Group1* 81.1 (80.0) 13.6; *Group2* 75.5 (75.2) 13.6; p=0.263. D_{1cc} Mean (median) SD: *Group1* 72.6 (72.1) 10.3; *Group2* 69.7 (69.6) 10.8; p=0.324 D_{2cc} Mean (median) SD: *Group1* 69.2 (68.6) 9.1; *Group2* 66.8 (66.7) 9.4; p=0.306.	$D_{0.1cc}$ Mean (median) SD: *Group1* 120.6 (108.5) 68.4; *Group2* 121.9 (113.1) 29.9; p=0.115. D_{1cc} Mean (median) SD: *Group1* 99.5 (94.5) 31.0; *Group2* 106.3 (102.7) 20.9; p=0.035 D_{2cc} Mean (median) SD: *Group1* 93.0 (89.2) 23.3; *Group2* 99.8 (98.6) 17.7; p=0.027. D_{5cc} Mean (median) SD: *Group1* 83.4 (81.5) 16.5; *Group2* 89.2 (87.4) 13.5; p=0.3031		

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
	D_{5cc} Mean (median) SD: *Group1* 64.1 (63.7) 7.6; *Group2* 62.3 (61.8) 7.3; p=0.324			
Kirchheiner 2014, Kirchheiner 2016			Vaginal stenosis: G0 41%; G1 43%, G2 15%, G3 1%. Vaginal dryness: G0 53%; G1 42%, G2 5%. Vaginal mucositis: G0 71%; G1 25%, G2 4%. Vaginal bleeding: G0 69%; G1 30%, G2 1% Vaginal fistual: G0 99%, G3 1% Other vaginal symptoms: G0 89%; G1 8%, G2 2%, G3 1% Overall vaginal morbidity: G0 26%; G1 53%, G2 19%, G3 2%. EQD2 (continuous) p=0.3.	
Lakosi, 2015	≥ Grade 3 5 (5.8) ≥3-yr Grade 3 8 (5)	≥ Grade 3 5 (5.8) ≥3-yr Grade 3 5 (3)	≥ Vaginal Grade 3 5 (5.8) ≥ Vaginal Grade 3 8 (5)	

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
Mahantshetty, 2017	ICRU rectum point Grade 0, (Gy10) 69.7 ± 7.8 Grade 1, (Gy10) 64.89±2.3 Grade 2, (Gy10) 72.43 ± 2.3 Grade 3, (Gy10) 75.9 ±16.9 Rectum 0.1 cm^3 Grade 0, (Gy10) 77.7 ± 11.4 Grade 1, (Gy10) 82±21.6 Grade 2, (Gy10) 91.5 ± 12.83 Grade 3, (Gy10) 84.9 ±11.4 Rectum 2 cm^3 Grade 0, (Gy10) 64.7 ± 6.9 Grade 1, (Gy10) 66.9±11.1 Grade 2, (Gy10) 70 ± 6 Grade 3, (Gy10) 70 ±7 Sigmoid 0.1 cm^3 Grade 0, (Gy10) 83.2± 613 Grade 1, (Gy10) 78.5±13.2 Grade 2, (Gy10) 80 ± 4 Grade 3, (Gy10) 82 ±14.5 Sigmoid 2 cm^3 Grade 0, (Gy10) 67.1 ± 9.1 Grade 1, (Gy10) 64.7±7.8 Grade 2, (Gy10) 767.1 ± 5.2 Grade 3, (Gy10) 66.5 ± 8.6			
Mazeron, 2016	Grade 0 Proctitis 81.5%, bleeding 83.8%, stenosis 98.9%, fistula 99.1%, all 72.3%; Grade 1 Proctitis 14.1%, bleeding 12.0%, stenosis 0.5%, fistula 0%, all 20.1%; Grade 2 Proctitis 4.1%, bleeding 3.2%, stenosis 0.6%, fistula 0.5%, all 6.0%; Grade 3 Proctitis 0.4%, bleeding 1.0%, stenosis 0%, fistula 0.3%, all 1.6%; Grade 4			

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
	Proctitis 0%, bleeding 100%, stenosis 00%, fistula 0.1%, all 0.1%;			
Murofushi, 2017	Grade 2 or 3 late rectal complications 6 pts (4.2%)			
O'Steen, 2017				Late grade 3 and higher 14% late grade 2 or higher 28%
Petit, 2016	Grade 1 (small bowel) Diarrhea 57.4%, flatulence 55.7%, bleeding, 0%, obstruction, 1.7%, fistula 0%, pain 18.3% total 65.2%; Grade 2 (small bowel) Diarrhea 10.4%, flatulence 13.0%, bleeding, 0%, obstruction, 0%, fistula 0%, pain 1.7% total 17.4%; Grade 3 (small bowel) Diarrhea .9%, flatulence 0%, bleeding, 0%, obstruction, .9%, fistula .9%, pain 0% total 2.6. Small bowel $D_{0.1cm^3}$% (mean±SD[Gy]): G0 79.5±21.3,G1 84.7±27.6, G2 93.7±55.4, G3 100.4±20.0, p=0.515. Small bowel D_{2cm^3}% (mean±SD[Gy]): G0 66.5±12.9,G1 68.3±12.3, G2 70.4±18.5, G3 78.1 ±10.3, p=0.472. Small bowel $D_{0.1cm^3}$% (mean±SD[Gy]): G0 83.7±26.4, G2 94.5±51.9, p=0.520. Small bowel D_{2cm^3}% (mean±SD[Gy]): G0 68.0±12.3, G2 71.4±17.7, p=0.688.			
Ribeiro, 2016	Grade 3 Rectal 9/161 Grade 3-4 Sigmoid 3/161	Grade 3-4 10/161		
Sharma, 2011	Grade 3-3: Proctitis 1/42	Grade 3: Cystitis 1/42	Grade 3-4: Vesico vaginal fistula 1/42	3 yr cummulative delayed toxicity (Grade III-IV) 9%

Study	Gastrointestinal	Urinary	Sexual/Gynecological	Overall toxicity/other
	bowel obstruction 1/42			
Tharavichitkul, 2013	Grade 1-2 13% Grade 3-4 2%		Grade 1-2 2% Grade 3-4 2%	Grade 1-2 Skin 0%, subcutaneous tissue 4%, Grade 3-4 Skin 0%, subcutaneous tissue 0%,
Tinkle, 2015	Grade 3 Acute 0/108 late 4/105		Grade 3 Acute 0/108 late 2/105	Grade 3 constitutional Acute 1/108 late 0/105 Grade 3 Hematologic Acute 1/108 late 0/105
Ujama, 2017	Any rectal toxicity G0 69 (65), G1 7 (7), G2 17 (16), G3 13 (12) Fecal incontinence G0 99 (93) G1 6 (6) G2 (1) G3 0 (0) Bleeding G0 72 (68) G1 15 (14) G2 13 (12) G3 6 (6) Proctitis G0 70 (66) G1 7 (7) G2 17 (16) G3 12 (11)	Any bladder toxicity G0 65 (61) G1 18 (17) G2 14 (13) G3 9 (8) Incontinence G0 92 (87) G1 10 (9) G2 3 (3) G3 3 (3) Lower ureteric obstruction G0 103 (97) G1 0 (0) G2 0 (0) G3 3 (3) Vesicovaginal fistula G0 105 (99) G1 0 (0) G2 0 (0) G3 1 (1) Cystitis G0 69 (65) G1 18 (17) G2 11 (10) G3 8 (8) Hematuria G0 93 (88) G1 1 (1) G2 5 (5) G3 (7)		
DICRU = International Commission on Radiation Units and Measurements point doses				

Appendix 7. Dosimetric Parameters

Study	
Castelnau-Marchand, 2015	**Dosimetric parameters**
CTV_{HR} Mean volume (cm^3)	32.6±21.8
Mean D_{100} (Gy)	63.8±7.3
Mean D_{90} (Gy)	80.4±10.3
CTV_{IR} Mean D_{100} (Gy)	56.7±4.6
Mean D_{90} (Gy)	67.7±6.1
Bladder Mean $D2cm^3$ (Gy)	71.1± 8.7
Rectum Mean $D2cm^3$ (Gy)	62.1±6.7
Sigmoid colon Mean $D2cm^3$ (Gy)	60.0±5.7
TRAK Mean cGy/m^2	1.94±0.3
Point A Mean (Gy)	66.1±5.5
Chargari, 2009	
Point A dose (Gya/b10)	71.4±6;
CTV_{HR}	
Volume (cm^3)	36.3±35
$D_{100}(Gy_{a/b10})$	61.66±7
D_{90} ($Gy_{a/b10}$)	74.85±10;
Bladder	
$D_{0.1cc}$ ($Gy_{a/b3}$)	87.6±12
D_{1cc} ($Gy_{a/b3}$)	75.9±12
D_{2cc} ($Gy_{a/b3}$)	71.7±6
ICRU ($Gy_{a/b3}$)	63.7±9;
Rectum	
$D_{0.1cc}$ ($Gy_{a/b3}$)	70.6±11
D_{1cc} ($Gy_{a/b3}$)	63.3±7
D_{2cc} ($Gy_{a/b3}$)	60.5±6
ICRU ($Gy_{a/b3}$)	67.3±8
Sigmoid	
$D_{0.1cc}$ ($Gy_{a/b3}$)	72.7±18
D_{1cc} ($Gy_{a/b3}$)	63.6±7
D_{2cc} ($Gy_{a/b3}$)	60.5±6
Chargari, 2016	**Treatment characteristics**
Median CTV_{HR}	21 (6-76)
volume in cm^3 (range)	
Median D_{90} CTV_{HR} in Gy (range)	83 (53-108)
Number of patients with an CTV_{HR} volume ≥ 40 cm^3	16 (14.7)
Median D_{90} CTV_{IR} in Gy (range)	69 (51-82)
Charra-Brunaud, 2012	**Dosimetric data comparison (Group 3)**
Duration of treatment(h)	46 (16.5) vs. 41.3 (13.7), p<0.001
Dose to point A (Gy)	70.8 (9.6) vs. 68.5 (7.8), p=0.66
60Gy isodose volume (cc)	205 (112) vs. 165 (111), p=0.54
Total Reference Air Kerma Trak ($Gy.cm^2.h^{-1}$)	184 (105) vs. 200 (133), p=0.16
Bladder ICRU dose (Gy)	65.9 (10.8) vs. 63.9 (7.4), p=0.001
Rectum ICRU dose (Gy)	67.2 (12.9) vs. 65.3 (6.2), p=0.27
Dosimetric data in 3D arm Group 3 (n=117)	
Number of pulses	44.6 (17)
Duration of pulse (min)	23 (11)
Dose to Point A ($Gy_{a/b3}$)	70.3 (9.6)
CTV_{HR}	
Mean volume (cc)	35.2 (26.7)

Study	
V85 (%)	58.6 (925)
D_{90} ($Gy_{a/b3}$)	73.1 (11.3)
CTV_{IR}	
Mean volume (cc)	98.6 (56.1)
V60 (%)	86 (20)
D_{90} ($Gy_{a/b3}$)	61.7 (6.9)
Bladder	
Mean volume (cc)	110 (65)
V60 (cc)	17.7 (27.4)
Dose to ICRU point ($Gy_{a/b3}$)	64.2 (11.9)
D_{2cc} ($Gy_{a/b3}$)	69.5 (12.3)
$D_{0.1cc}$ ($Gy_{a/b3}$)	86.4 (23.4)
Rectum	
Mean volume (cc)	67.4 (33)
V60 (cc)	6.8 (8.5)
Dose to ICRU point ($Gy_{a/b3}$)	67.2 (20)
D_{2cc} ($Gy_{a/b3}$)	61 (9.3)
$D_{0.1cc}$ ($Gy_{a/b3}$)	70.7 (16.3)
Sigmoid	
Mean volume (cc)	50.8 (57)
V60 (cc)	4.9 (6.7)
D_{2cc} ($Gy_{a/b3}$)	58.1 (8.9)
$D_{0.1cc}$ ($Gy_{a/b3}$)	69.9 (28.9)
Choong, 2016	
MRI vs. hybrid	**Dosimetric data**
CTV_{HR} (cm^3)	23±14 vs. 21±14, NA
D_{90} (EQD2) (Gya/b10)	96±6 vs. 97±11, p=0.730
V_{100} (%)	99±2 vs. 98±3, NA
Bladder D_{2cc} (EQD2) (Gya/b3)	76±9 vs. 83±9, p=0.002
Rectum D_{2cc} (EQD2) (Gya/b3)	64±7 vs. 64±6, p=0.858
Sigmoid D_{2cc} (EQD2) (Gya/b3)	61±6 vs. 66±8, p=0.006
Small bowel D_{2cc} (EQD2) (Gya/b3)	57±6 vs. 59±8, p=0.214
Dimopoulos, 2009	
GTV v(cm^3)	12±13
GTV D_{100} (Gy)	90±23
GTV D_{90} (Gy)	123±35
CTV_{HR} v(cm^3)	36±23
CTV_{HR} D_{100} (Gy)	65±10
CTV_{HR} D_{90} (Gy)	86±16
CTV_{IR} v(cm^3)	92±42
CTV_{IR} D_{100} (Gy)	53±7
CTV_{IR} D_{90} (Gy)	66±9
Fokdal, 2013 (Q2) C/IS vs. IC	
Tumour volume at diagnosis(MRI) cm^3	ICIS 76±48 vs. IC 46±35, P=0.01
CTV_{HR} volume	
BT0 (week 5) cm^3	ICIS 46±26, IC 33±19
BT1 (week 6) cm^3	ICIS 46±24, IC 29±15
BT2 (week 7) cm^3	ICIS 39±18, IC 27±12
Patients treated with combined ICIS pre-plans (BTO) with ICIS pre-plan (BTO and actual ICIS plans)	Dose Gy (EQD2) *pre-plan IC mean/ pre-plan ICIS mean,(Adif., P)/ BT1 + BT2 mean (Adif., P)*
CTV_{HR} D_{90}	85.1±9.0/ 89.6±5.0 (4.5±8.4, 0.02)/ 90.0±3.7 (4.9±9.0, <0.01)
CTV_{HR} D_{100}	66.2±7.3/ 72.6±5.7 (6.4±8.5 0.01)/ 72.6±5.(1 6.3±8.0 <0.01)
CTV_{IR}	D_{90} 65.9±5.0/ 66.4±3.7 (0.5±5.1 0.65)/ 66.3±2.7 (0.4±5.3 0.70)
Bladder	D2cc 74.7±9.5/73.9±8.7 (-0.9±8.9 0.64/ 72.1±4.9 (-2.6±8.7 0.15)
Rectum	D2cc 65.6±6.4/ 64.0±5.8 (-1.7±5.8 0.17/ 64.1±5.2 (-1.6±6.1 0.21)

Study	
Sigmoid	D2cc 67.6±7.8/ 65.6±6.6 (-2.0±5.1 0.03/ 62.8±5.3 (-4.8±7.0 <0.01)
Bowel	D2cc 64.3±13.2/ 60.9±9.3 (-3.4±6.3 <0.01/ 59.6±6.8 (-4.7±9.9 0.04)
Fokdal, 2016 (Q2) ICIS vs. IC	
Volume CTV_{HR} (Gy)	All: 36±24 ICIS: 39±25, IC: 33±24, p<0.01
CTV_{HR} D_{90} (Gy)	All: 88±14 ICIS: 92±13, IC: 83±14 , p<0.01
D2CC Bladder (Gy)	All: 81±22 ICIS: 79±12, IC: 83±29, p=0.07
D2CC Rectum (Gy)	All: 64±8 ICIS: 65±7, IC: 64±10, p=0.12
ICRU Rectum (Gy)	All: 69±13 ICIS: 69±13, IC: 69±15, p=0.84
D2CC Sigmoid (Gy)	All: 65±10 ICIS: 65±7, IC: 66±12, p=0.38
Gill, 2015	
Volume or organ parameter	
Ring & Tandem (n=121)	BT dosimetry for target volumes & OAR
HRCT	Median (range)
Volume (cc)	31.0 (15.3-75.0)
D_{90} EQD2 (Gy)	82.6 (74.8-93.3)
Point A	
D_{90} EQD2 (Gy)	75.5 (61.8-93.5)
Bladder	
D_{2cc} EQD2 (Gy)	76.5 (61.0-86.6)
Rectum	
D_{2cc} EQD2 (Gy)	55.8 (43.2-71.0)
Sigmoid	
D_{2cc} EQD2 (Gy)	65.1 (49.2-80.0)
Vienna applicator (n=7)	
HRCT	
Volume (cc)	46.0 (31.0-60.0)
D_{90} EQD2 (Gy)	84.3 (78.3-85.7)
Point A	
D_{90} EQD2 (Gy)	84.3 (71.4-140.5)
Bladder	
D_{2cc} EQD2 (Gy)	76.7 (72.0-83.6)
Rectum	
D_{2cc} EQD2 (Gy)	56.0 (51.9-64.0)
Sigmoid	
D_{2cc} EQD2 (Gy)	64.8 (54.6-69.0)
Haie-Meder, 2010	
CTV_{HR}	**DVP related to CTV and critical organs**
Volume (cm^3)	17 (3–107)
D_{100} ($Gy_{a/b10}$)	67 (47–119)
D_{90} ($Gy_{a/b10}$)	79 (53–122)
CTV_{IR}	
Volume (cm^3)	54.5 (16–207)
D_{100} ($Gy_{a/b10}$)	56.5 (37–83)
D_{90} ($Gy_{a/b10}$)	69 (52–113)
Bladder	
$D_{0.1cc}$ ($Gy_{a/b3}$)	94 (63–193)
D_{1cc} ($G_{ya/b3}$)	82 (60–145)
D_{2cc} ($G_{ya/b3}$)	77 (59–132)
ICRU ($G_{ya/b3}$)	63.5 (51–80)
Rectum	
$D_{0.1cc}$ ($Gy_{a/b3}$)	71 (54–148)
D_{1cc} ($G_{ya/b3}$)	65 (53–118)
D_{2cc} ($G_{ya/b3}$)	63 (52–108)
ICRU ($G_{ya/b3}$)	70.5 (50–108)
Sigmoid	
$D_{0.1cc}$ ($Gy_{a/b3}$)	69 (49–114)
D_{1cc} ($G_{ya/b3}$)	63 (48–97)

Study	
D_{2cc} ($Gy_{a/b3}$)	60 (48–90)
Vagina	
$D_{0.1cc}$ ($Gy_{a/b3}$)	632 (125–4650)
D_{1cc} ($Gy_{a/b3}$)	186 (95–1753)
D_{2cc} ($Gy_{a/b3}$)	141 (61–915)
Hannoun-Levi, 2013	
CTV (cc)	50 (42-74) - NR
V_{100} (cc; %)	49 (42-50) 98 (85-99)
V_{150} (cc; %)	27 (16-35) 55 (33-70)
V_{200} (cc; %)	12 (6-20) 25 (12-41)
$D1_{00}$ (Gy; Gy_{ab10})	33 (22-38) 38 (33-47)
D_{90} (Gy; Gy_{ab10})	45 (40-51) 56 (48-67)
Bladder (Gy; Gy_{ab3})	
$D_{0.1cc}$	31 (27-33) 43 (37-e46)
D_{1cc}	26 (24-29) 36 (33-40)
D_{2cc}	24 (22-28) 34 (31-40)
Rectum (Gy; Gy_{ab3})	
$D_{0.1cc}$	33 (19-42) 46 (26-59)
D_{1cc}	25 (12-33) 35 (17-46)
D_{2cc}	21 (9-29) 31 (13-43)
Sigmoid (Gy; Gy_{ab3})	
$D_{0.1cc}$	32 (18-38) 45 (25-53)
D_{1cc}	23 (13-27) 32 (18-38)
D_{2cc}	19 (12-23) 28 (18-34)
Vagina (Gy; Gy_{ab3})	
$D_{0.1cc}$	33 (31-36) 46 (43-50)
D_{1cc}	29 (27-31) 40 (37-43)
D_{2cc}	25 (23-27) 38 (35-41)
Jastaniyah, 2016	
GTV_D (cm^3)	Total, Group 1, Group 2, Group 3, Group 4, Group 5, P value
Mean (SD)	50.4 (40.2), 12.6 (8.0), 47.5 (26.7), 23.9 (9.4), 73.4 (30.9), 79.4 (58.6), <0.001
Median	42.3, 10.9, 39.1, 23.5, 65.5, 65.4
GTV_D width (cm)	
Mean (SD)	4.9 (13.7), 3.2 (1.0), 4.7 (1.0), 4.2 (0.9), 5.8 (0.9), 6.0 (1.2), <0.001
Median	5.0, 3.1, 4.6, 4.1, 5.7, 5.6
Concurrent chemotherapy given	457 (95%), 50 (91%), 75 (96%), 116 (94%), 143 (97%), 70 (93%), 0.37
EBRT dose at 1st BT fraction (Gy)	
Mean (SD)	42.9 (4.8), 42.6 (4.9), 42.9 (4.7), 42.8 (5.5), 42.8 (4.6), 43.4 (3.9), 0.97
CTV_{HR} (cm^3)	
Mean (SD)	4.4 (1.0), 3.6 (0.9), 3.8 (1.0), 4.3 (0.8), 4.5 (0.7), 5.3 (0.8), <0.001
Median	30.9, 23.3, 21.7, 27.6, 35.3, 54.3
CTV_{HR} width (cm)	
Mean (SD)	35.7 (20.8), 23.7 (10.0), 25.3 (13.2), 29.9 (11.8), 38.5 (16.7), 59.5 (29.8), <0.001
Median	4.3, 3.7, 3.9, 4.2, 4.5, 5.3
GTV_{BT} D_{100} (Gy)	
Mean (SD)	91.3 (18.5), 103.1 (24.8), 91.8 (18.7), 93.5 (20.1), 88.3 (16.0), 87.1 (12.1), 0.00
NA	51, 14 (25%), 7 (9%), 14 (11%), 11 (7%), 5 (7%),
CTV_{HR} D_{90} (Gy)	
Mean (SD)	90.1 (11.9), 95.1 (13.8), 92.1 (13.5), 92.6 (14.6), 87.6 (8.1), 88.4 (7.9), <0.001
Brachytherapy technique	
Intracavitary alone	260 (55%), 53 (96%), 71 (91%), 70 (57%), 60 (41%), 8 (11%), <0.001
With interstitial needles	218 (45%), 2 (4%), 7 (9%), 53 (43%), 87 (59%), 67 (89%)
Number of active needles	
1-2	45 (21%), 2 (100%), 4 (57%), 17 (32%), 17 (20%), 5 (7%)

Study	
>2	173 (79%), 0, 3 (43%), 36 (68%), 70 (80%), 62 (93%)
Kamran, 2017	
MRI vs. CT	Treatment characteristics
Med. no. fractions	5 (4–9) vs. 5 (2–9) p=0.92
Med. dose per fraction – GY	5.0 (3.0–6.0) vs. 5.5 (3.0–9.0) p=0.17
Median dose (EQD2) - Gy	
Prescription	35.4 (27.2–43.2) vs. 35.4 (27.2–43.2) p=0.45
D_{90}	33.5 (18.6–55.8) vs. 32.1 (11.7–58.9) p=0.96
D2CC rectum	22.0 (10.4–38.3) vs. 23.5 (5.0–44.5) p=0.33
D2CC bladder	35.6 (15.5–153.1) vs. 31.4 (14.1–89.3) p=0.18
D2CC sigmoid	21.5 (3.1–41.3) vs. 15.3 (0.0–36.4) p=0.33
Cumulative dose (EQD2) - Gy	
EBRT + BT	80.3 (70.7–89.4) vs. 80.1 (77.1–94.7) p=0.79
D_{90}	79.8 (62.8–100.0) vs. 81.2 (57.9–100.2) p=0.51
D2CC rectum	69.3 (57.3–81.5) vs. 70.2 (56.4–92.5) p=0.43
D2CC bladder	82.4 (58.7–196.3) vs. 81.8 (62.1–185.5) p=0.80
D2CC sigmoid	65.6 (48.9–86.2) vs. 66.2 (46.4–87.5) p=0.96
Karlsson, 2017	
All fractions mean (SD)	0.6 (2.4)
Fractions without needles mean (SD)	1.6 (2.6)
Fractions with needles mean (SD)	0.0 (2.2)
Lakosi, 2015	
CTV_{HR} volume, cm^3	38.1 (27.6)
Dose-parameters, Gy	Dose-volume parameters in EQD2 Mean (SD)
CTV_{HR} D_{90}	84.4 (9)
CTV_{IR} D_{90}	69.1 (4.3)
Rectum	
D_{1cm^3}	73.7 (10.9)
D_{2cm^3}	65 (6.8)
ICRU point	68.7 (11.1)
Bladder	
$D_{0.1cm^3}$	95.8 (23.8)
D_{2cm^3}	77.3 (10.5)
ICRU point	80.1 (16.1)
Sigmoid	
$D_{0.1cm^3}$	70 (11.4)
D_{2cm^3}	63 (7.9)
Bowel	
$D_{0.1cm^3}$	72.1 (14.9)
D_{2cm^3}	64 (9.1)
Lindegaard, 2013	**DVH parameters 2005-2008[stand.] vs. 2005-2008[opt.] vs. 2009-2011[opt.], p-value[first vs. last])**
CTV_{HR} D_{90} (Gy)	92 (62 – 132) vs. 91 (72 – 107) vs. 91 (69 – 102),p=0.82
CTV_{IR} D_{100} (Gy)	– vs. 69 (60 – 78) vs. 67 (60 – 73),p= 0.037
Bladder ICRU point (Gy)	– vs. 67 (49 – 91) vs. 65 (48 – 91),p= 0.22
Bladder D2 cm^3 (Gy)	79 (55 – 177) vs. 73 (56 – 89) vs. 69 (52 – 82),p< 0.001
Rectum ICRU point (Gy)	– vs. 67 (55 – 90) vs. 64 (52 – 83),p= 0.011
Rectum D2 cm^3 (Gy)	68 (53 – 109) vs. 66 (53 – 77) vs. 62 (51 – 75),p< 0.001
Sigmoid D2 cm^3 (Gy)	73 (52 – 107) vs. 69 (53 – 78) vs. 62 (49 – 74), p< 0.001
Planning aim obtained (%)	15/70 (21%) vs. 56/70 (80%) vs. 65/70 (93%), p=0.026
Mahantshetty, 2017	
CTV_{HR} Volume, cm3	46.9 ± 24.6
D_{100}	68.5 ± 8.2
D_{90}	88.3 ±4.4
Average point	94.5 ±32.8
Bladder	

Study	
ICRU bladder	76.7±13.9
D0.1 cm^3	110.3±22.8
D2 cm^3	85.7±9.8
Rectum	
ICRU rectum	70.2±8.9
D0.1 cm^3	79 ±12.1
D2 cm^3	65.5±7.2
Sigmoid	
D0.1 cm^3	85 ± 23.7
D2 cm^3	67 ± 8.8
Mazeron, 2014	
ICRU point (Gy±SD)	56±4
D2 cm^3 (Gy±SD)	59±6
ICRU	1.064±0.06
Mohamed, 2015	
	ICBT vs. ICBT+PB vs. IC-IS BT, [diff. (IC BT+PB)-(IC-IS BT)]
GTV D_{90}	109.1 (16.1) vs. 110.5 (15.9) vs. 106.5 (10.5), [4.0(11.2)], p=0.10
CTV_{HR} D_{90}	86.8 (5.8) vs. 88.7 (5.3) vs. 89.0 (3.4) , [-0.3(4.8)], p=0.79
CTV_{HR} D_{100}	68.2 (6.4) vs. 71.6 (6.1) vs. 71.7 (4.9) , [-0.2(5.1)], p=0.88
CTV_{HR} D_{50}	122.8 (8.8) vs. 124.4 (8.9) vs. 117.6 (7.4) , [6.8(7.4)], p<0.001
CTV_{IR} D_{90}	67.0 (3.5) vs. 71.8 (3.4) vs. 66.5 (2.5) , [5.3(2.2)], p<0.001
CTV_{IR} D_{100}	57.5 (3.8) vs. 59.8 (4.4) vs. 56.7 (3.3) , [3.1(2.9)], p<0.001
D_{2cm3} Bladder	75.7 (6.9) vs. 77.2 (5.9) vs. 71.8 (5.0) , [5.4(4.0)], p<0.001
D_{2cm3} Rectum	67.4 (6.5) vs. 68.1 (6.3) vs. 64.1 (4.8) , [4.4(2.7)], p<0.001
D_{2cm3} Sigmoid	64.8 (7.0) vs. 67.5 (5.5) vs. 62.6 (5.2) , [5.0(2.9)], p<0.001
D_{2cm3} Bowel	64.8 (8.8) vs. 68.3 (6.9) vs. 62.1 (6.7) , [6.2(3.5)], p<0.001
Mohamed, 2016	Comparison of doses delivered by vaginal dose de-escalation (VDD) and non-VDD
GTV D_{98}	Non-VDD 100 (16); VDD 103 (23); Diff. 4 (13); p=0.08
CTV_{HR} D_{98}	Non-VDD 81 (7); VDD 81 (6); Diff. -0.3 (2) ; p=0.23
CTV_{HR} D_{90}	Non-VDD 90 (7); VDD 90 (7); Diff. 0.2 (2) ; p=0.39
CTV_{HR} D_{50}	Non-VDD 126 (15); VDD 130 (14); Diff. 4 (11) ; p=0.02
CTV_{IR} D_{90}	Non-VDD 69 (5); VDD 68 (4); Diff. -1 (2) ; p<0.01
Bladder D3/2cm	Non-VDD 75 (9); VDD 73 (10); Diff. -2 (2) ; p <0.01
Rectum D3/2cm	Non-VDD 62 (7); VDD 60 (7); Diff. -3 (2) ; p <0.01
Sigmoid D3/2cm	Non-VDD 63 (7); VDD 63 (7); Diff. -0.2 (1) ; p=0.25
Bowel D3/2cm	Non-VDD 64 (10); VDD 64 (11); Diff. 0.07 (2) ; p=0.85
ICRU recto-vaginal point	Non-VDD 69 (11); VDD 64 (11); Diff. -4 (4) ; p <0.01
Vagina 0 mm (mean LT + RT)	Non-VDD 266 (162); VDD 137 (46); Diff. -128 (140); p<0.01
Vagina 5 mm (mean LT + RT)	Non-VDD 111 (57); VDD 80 (18); Diff. -32 (48); p<0.01
Vagina 5 mm ant	Non-VDD 68 (8); VDD 64 (6); Diff. -4 (4);p<0.01
Vagina 5 mm post	Non-VDD 83 (32); VDD 77 (27); Diff. -5 (9);p <0.01
PIBS point	Non-VDD 48 (5); VDD 47 (3); Diff. -1 (2);p <0.01
PIBS + 2 point	Non-VDD 59 (29); VDD 55 (21); Diff. -5 (10);p <0.01
Nomden, 2013 IC vs. ICIS	
Median GTV width at clinical diagnoses	50 cm (20-100)
Median GTV width at diagnoses	51 cm (32-91)
Median GTV width at BT application	40 cm (21-80)
CTV_{HR} (mean)	32 (10) cm^3 (IC) vs. 72 (38) cm^3 (ICIS)
D_{90} CTV_{HR}	91 (38) Gy (IC) vs. 82 (6) Gy (ICIS)
MRI GTV at diagnosis (mm)	IB 45(9), IIA 48(12), IIB 53(10), IIIA 47(0), IIIB 70(13), IVA 56(0), IVB 40(0), TOTAL 53(13), IB-IIA-IIB 51(11) , IIIA-IIIB-IVA- IVB 63(16).
MRI GTV at BT1 (mm)	IB 37(8), IIA 39(12), IIB 42(13), IIIA 35(0), IIIB 56(12), IVA 42(0), IVB 37(0), TOTAL 42(12), IB-IIA-IIB 40(12) , IIIA-IIIB-IVA- IVB 50(13).
CTV_{HR} at BT1 (mm)	IB 38(19), IIA 34(19), IIB 52(29), IIIA 48(0), IIIB 111(44), IVA 91(0), IVB 36(0), TOTAL 57(37), IB-IIA-IIB 51(11) , IIIA-IIIB-IVA- IVB 63(16).

Study	
CTV_{HR} D_{90} Gy	IB 92(8), IIA 86(6), IIB 84(10), IIIA 83(0), IIIB 75(6), IVA 79(0), IVB 76(0), TOTAL 84(9), IB-IIA-IIB 86(9), IIIA-IIIB-IVA- IVB 76(6).
Bladder D_{2cc} Gy	IB 81(5), IIA 80(10), IIB 84(6), IIIA 91(0), IIIB 84(8), IVA 88(0), IVB 72(0), TOTAL 83(7), IB-IIA-IIB 83(7) , IIIA-IIIB-IVA- IVB 84(8).
Bladder $D_{0.1cc}$ Gy	IB 100(8), IIA 107(27), IIB 111(16), IIIA 125(0), IIIB 104(13), IVA 101(0), IVB 87(0), TOTAL 107(17), IB-IIA-IIB 108(18), IIIA-IIIB-IVA- IVB 104(14).
Rectum D_{2cc} Gy	IB 67(8), IIA 62(8), IIB 66(6), IIIA 67(0), IIIB 69(5), IVA 67(0), IVB 75(0), TOTAL 66(6), IB-IIA-IIB 65(7) , IIIA-IIIB-IVA- IVB 69(5).
Rectum $D_{0.1cc}$ Gy	IB 83(15), IIA 73(14), IIB 79(10), IIIA 78(0), IIIB 84(11), IVA 80(0), IVB 90(0), TOTAL 80(12), IB-IIA-IIB 79(12) , IIIA-IIIB-IVA- IVB 83(10).
Sigmoid D_{2cc} Gy	IB 61(4), IIA 63(8), IIB 60(5), IIIA 60(0), IIIB 62(7), IVA 60(0), IVB 50(0), TOTAL 61(6), IB-IIA-IIB 61(6) , IIIA-IIIB-IVA- IVB 60(7).
Sigmoid $D_{0.1cc}$ Gy	IB 69(6), IIA 74(11), IIB 71(12), IIIA 69(0), IIIB 70(11), IVA 69(0), IVB 52(0), TOTAL 71(11), IB-IIA-IIB 71(11), IIIA-IIIB-IVA- IVB 68(11).
Bowel D_{2cc} Gy	IB 66(7), IIA 70(8), IIB 63(9), IIIA 52(0), IIIB 60(9), IVA 49(0), IVB 76(0), TOTAL 64(9), IB-IIA-IIB 65(8), IIIA-IIIB-IVA- IVB 60(10).
Bowel $D_{0.1cc}$ Gy	IB 80(10), IIA 96(20), IIB 75(15), IIIA 58(0), IIIB 67(13), IVA 52(0), IVB 96(0), TOTAL 77(17), IB-IIA-IIB 80(17) , IIIA-IIIB-IVA- IVB 68(15).
Potter, 2011	**Dose volume adaptation and dose escalation**
Mean D_{90}±1SD	93±13Gy, tumours 2-5cm 96±15Gy, tumours >5cm 91±11Gy
Mean D_{90}±1SD (2001-2003)	90±15Gy, tumours 2-5cm 94±16Gy, tumours >5cm 87±14Gy
Mean D_{90}±1SD (2004-2008)	94±10Gy, tumours 2-5cm 100±10Gy, tumours >5cm 93±9G
Mean D2cc(bladder)	86±17Gy
Mean D2cc(rectum)	65±9Gy
Mean D2cc(sigmoid)	64±9Gy
Rijkmans, 2014	**EDQ2 dose (image-guided BT) Gy (Range)**
CTV_{HR} D_{90}	80.8 (55.4–98.6)
CTV_{IR} D_{90}	63.4 (37.9–80.2)
EQD2 D2cc bladder	76.1 (59.3–91.0)
EQD2 D2cc rectum	66.0 (51.7–77.0)
EQD2 D2cc sigmoid	62.6 (48.5–78.0)
EQD2 D2cc bowel	59.8 (47.0–77.3)
Ribeiro, 2016	
CTV_{HR} Volume (cc)	*all* 35.7±21.0, *lim. Opt*. 48.1±19.1, *Opt*. 34.4±20.9
D_{90} (Gy)	*all* 84.8±8.4, *lim. Opt*. 75.8±9.0, *Opt*. 85.8±7.7
$D1_{00}$ (Gy)	*all* 67.5±6.3, *lim. Opt*. 61.5±5.7, *Opt*. 68.1±6.0
CTV_{IR} D_{90} (Gy)	*all* 68.7±5.5, *lim. Opt*. 65.3±4.7, *Opt*. 69.0±5.5
D_{100} (Gy)	*all* 56.5±6.2, *lim. Opt*. 55.4±3.0, *Opt*. 56.6±6.5
OAR Rectum D2 cm^3 (Gy)	*all* 61.7±7.8, *lim. Opt*. 59.3±2.8, *Opt*. 62.0±8.2
OAR Bladder D2 cm^3 (Gy)	*all* 83.0±8.6, *lim. Opt*. 86.1±8.5, *Opt*. 82.7±8.5
OAR Sigmoid D2 cm^3 (Gy)	*all* 62.5±9.2, *lim. Opt*. 70.1±12.4, *Opt*. 61.7±8.4
Schmid, 2011 (matched-pair)	
Mean GTV at diag. cm^3	LR 75±43, CCLR 71±79; p=0.841
Mean **CTV_{HR}** cm^3	LR 50±22, CCLR 47±33; p=0.78
Tanderup, 2010	**Mean and standard deviation for volumes and dose parameters in optimised dose plans.**
Volume (CTV, CTV_{HR}, CTV_{IR})	-, 38±20 cc; 111±43 cc.
D_{100} (CTV, CTV_{HR}, CTV_{IR})	89±19 Gy; 74±6 Gy; 61±3 Gy.
D_{90} (CTV, CTV_{HR}, CTV_{IR})	112±26 Gy; 91±7 Gy; 68±3 Gy.
D_{50} (CTV, CTV_{HR}, CTV_{IR})	-; 124±17 Gy; -.
Bladder (D_{2cc}, $D_{0.1cc}$, D_{1CRU})	73±6Gy; 85±10Gy; 67±8Gy.
Rectum (D_{2cc}, $D_{0.1cc}$, D_{1CRU})	66±5Gy; 74±8Gy; 67±7Gy; 78±9Gy.
Sigmoid (D_{2cc}, $D_{0.1cc}$, D_{1CRU})	69±5Gy; 78±9Gy; -.
Tinkle, 2015	**Median cumulative EQD_2 (range)**
D_{90} CTV_{HR} (Gy)	85.1 (76.4-94.3)
D1cc bladder (Gy)	75.2 (56.9-97.9)
D1cc rectum (Gy)	72.0 (49.7-92.2)
Tharavichitkul, 2013	**Dose distributions to CTV_{HR} and OAR – Mean doses (Gy) in EQD2**

Study	
D_{90} CTV_{HR} (α/β = 10)	93.1±7.7
D2cc bladder (α/β = 3)	88.2±7.2
D2cc rectum (α/β = 3)	69.6±6.6
D2cc sigmoid (α/β = 3)	72.0±6.9
Yoshida, 2015	
GTVD (cm^3)	51.7 (40.2); 50.9 (40.9); 52.2 (39.8) p=.24
GTVD width (cm)	5.0 (1.3) 4.9 (1.4) 5.1 (1.3) p=0.16
CTV_{HR} (cm^3)	36.0 (20.4) 33.3 (18.8) 37.9 (21.2) p=.004
CTV_{HR} width (cm)	4.4 (1.0) 4.1 (1.0) 4.6 (1.0) p<.001