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A cost-utility analysis comparing magnetic resonance image-guided brachytherapy to two-dimensional brachytherapy for patients with locally advanced cervical cancer in Ontario, Canada

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Abstract

Background: The standard treatment for locally advanced cervical cancer in Ontario is external beam radiotherapy and concurrent cisplatin followed by 2D brachytherapy (2DBT). Magnetic resonance image-guided intracavitary and interstitial brachytherapy (MRgBT) improves cure rates and reduces treatment side effects compared to 2DBT, and is increasingly recognized as the new standard of care. This study was undertaken to evaluate the cost-effectiveness of implementing best-practice MRgBT compared to 2DBT in Ontario.

Methods: A Markov model was used for the cost-utility analysis (CUA) from the perspective of the Ontario Ministry of Health and Long-Term Care (MOHLTC) with a five-year time horizon. The CUA evaluated treatment effectiveness, expressed as quality adjusted life years (QALYs), and costs, expressed in 2016 Canadian dollars, for MRgBT and 2DBT. All parameters were

obtained from published literature and reviewed by a clinical expert panel. Results were reported as incremental cost-effectiveness ratios (ICERs) comparing MRgBT to 2DBT, for all patients combined, and separately for low (FIGO Stages IB-IIA) and high-risk (FIGO Stages IIB-IV) patients. Parameter uncertainty was explored using one-way and probabilistic sensitivity analyses.

Findings: MRgBT was a dominant strategy (more effective and less costly) compared to 2DBT for the full population and for both subgroups. The incremental effectiveness was 0.35, 0.19, and 0.43 QALYs per patient for the full population, low-risk subgroup and high-risk subgroup, respectively. The corresponding per patient incremental cost-savings were $1,892, $134, and $2,643, respectively. From the deterministic sensitivity analysis, varying the model parameter value for the cost of a cancer recurrence influenced the conclusions. However, the ICER remained well below the $20,000/QALY threshold value. The probabilistic sensitivity analysis provided further evidence to support the robustness of the findings.

Interpretations: MRgBT was a more effective and less costly than 2DBT even when uncertainties in the parameters were considered. From the Ontario MOHLTC perspective, implementation of this technology cannot be justifiably withheld on the basis of cost. These finding will assist health care providers and policy-makers in Ontario with future infrastructure and human resource planning to assure optimal care of women with locally advanced cervical cancer.

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List of Acronyms

2D	Two-dimensional
2DBT	Two-dimensional brachytherapy
3D	Three-dimensional
CI	Confidence interval
CT	Computerized tomography
CUA	Cost-utility analysis
DSA	Deterministic sensitivity analysis
FIGO Stages	International Federation of Gynecology and Obstetrics Stages
High-risk	FIGO Stages IB-IIA
ICER	Incremental cost-effectiveness ratio
Low-risk	FIGO Stages IIB-IV
MOHLTC	Ministry of Health and Long-Term Care
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MRgBT	Magnetic resonance image-guided brachytherapy
OAR	Organs at risk
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SD	Standard deviation

Background

Cervical cancer remains a significant health problem in Canada, and globally, despite routine screening and, more recently, human papillomavirus vaccination programs.[1] At time of presentation, a significant proportion of cervical cancer patients are found to have locally advanced disease or nodal involvement. Such cases cannot be cured surgically; however, historical data have shown that 50-60% of patients with advanced cervical cancer can be cured with external beam radiation therapy delivered with weekly concurrent cisplatin and subsequent brachytherapy.[2]

Brachytherapy is a form of radiation therapy whereby the treatment applicator is placed adjacent to or directly into the tumour allowing delivery of high dose rate to the tumour while also ensuring a rapid dose drop off in surrounding tissue. The role of cervical brachytherapy has been questioned in the past, but recently it has been identified to be an essential independent component of the radiation therapy care pathway associated with improved pelvic control and clincial outcomes.[3]

Traditionally, brachytherapy for cervical cancer has been delivered using two-dimensional (2D) orthogonal radiographs and a point-based dose prescription using an intracavitary applicator.[4] Whilst this 2D brachytherapy (2DBT) method of delivering cervical brachytherapy involves little investment in terms of infrastructure, imaging equipment, and personnel (based on existing resources), this method offers little flexibility to tailor the treatment plan to the unique tumor and normal organ characteristics in individual patients.[4,5] Moreover, the standard 2DBT plans with a symmetric pear-shaped isodose distribution are delivered for every patient and do not take into account individual variation in tumour size, extent of local disease, and location of organs at risk

(OAR). Therefore, patients treated with 2DBT are at risk of having incomplete tumour coverage, excess dose delivered to OAR, poor local control, and unacceptable treatment complications.[6]

In the past 15 years there has been a significant evolution in novel radiotherapy technologies that aim to increase the treatment therapeutic ratio.[7,8] This therapeutic ratio can be improved by achieving dose escalation to the tumour, thereby improving local control; or by achieving excess dose reduction to OAR, thereby decreasing treatment toxicity. In efforts to improve clinical outcomes for patients with cervical cancer, three-dimensional (3D) imaging to facilitate 3D volumetric planning of brachytherapy was investigated. Currently, there are two types of 3D brachytherapy: 1) with computerized tomography (CT); and 2) with magnetic resonance imaging (MRI), with the latter the current gold standard treatment. Compared to CT and 2D-imaging, MRI is known to provide greater pelvic soft tissue resolution facilitating identification of cervical tumour extent as well as delineation of normal organs.[10-14] The MRI guided brachytherapy (MRgBT) enables treatment with both intracavitary applicator as well as interstitial needles, facilitates improvement in dosimetric conformity specific to each patient's anatomy, and compensates for dynamic changes in the disease and OAR over the course of treatment. An increase in therapeutic ratio is noted with MRgBT which facilitates safe dose escalation to the tumour, while limiting normal tissue toxicity.[4,15,16]

The clinical effectiveness of MRgBT has been demonstrated in a number of single- and multi-institutional clinical studies, which showed that patients receiving 2DBT reported worse clinical outcomes and higher risk of treatment complications than those receiving MRgBT.[4,5,17-20] This improvement in local control due to MRgBT was expected to translate into improvements in overall survival and a reduction in treatment-related morbidity.[4,5,13,20] Sturdza et al. (2016) have

recently confirmed this expectation in their report of RetroEMBRACE multicenter cohort study results, where patients with locally advanced cervical cancer treated with MRgBT were found to have improved pelvic and local control rates, improved overall and cause specific survival rates, and a decrease in late toxicities.[17]

Given these large clinical benefits from MRgBT, it is believed that this technique will become standard of care in Canada within 5 years.[21] Nonetheless, the translation of MRgBT to routine clinical practice is lagging in Canada and North America, with the majority of centers continuing to use traditional 2DBT.[22] Implementation of novel radiotherapy technologies using MRI are associated with a number of challenges such as increased costs of implementation, requirement of up-front investment in new equipment, maintenance cost, personnel training, and development of quality assurance processes.[8] The MRgBT treatment is considerably more demanding of resources including personnel and time, and furthermore is highly reliant on practitioner familiarity with the technique, contouring, and treatment planning.[21] Consequently, one of the largest barriers to implementation of MRgBT has been identified to be the financial implications it would impose on the Ontario's publically funded health care system. Overall costs of oncology care in Ontario are expected to rise, and as such, need for evidence of treatment cost-effectiveness is rising in efforts to control health care spending and guide decisions regarding implementation of new technologies.[8] Given the constraints of the current climate in health care, this project aims to examine the cost-effectiveness of the MRgBT compared to the current 2DBT standard of care from the perspective of the Ontario Ministry of Health and Long-Term Care (MOHLTC).

Methods

Target Population

The study population of interest included females (ages 18+) with locally advanced cervical cancer (using the International Federation of Gynecology and Obstetrics (FIGO) Stages from IB to IV) that required concurrent chemoradiation followed by brachytherapy. Given the variability in prognostic clinical outcomes for FIGO Stages in the target population, the CUA was conducted for the entire target population, and also for a low-risk subgroup, defined as FIGO Stages IB-IIA, and a high-risk subgroup, defined as FIGO Stages IIB-IV. Females that required radiation therapy in adjuvant setting were excluded from the study population.

Comparators

The CUA compared the current standard of care of 2DBT to the novel MRgBT approach. The description of comparators were based on published literature and reviewed by a global gynecological radiation oncology clinical expert panel (The MRgBT Cost Utility Analysis Working Group developed from the Gynecological Cancers Community of Practice at Cancer Care Ontario). The cohorts were treated on outpatient basis using four applicator insertions and high dose rate brachytherapy treatment for both 2DBT and MRgBT. The 2DBT procedure was assumed to take 1.5 hours from the induction of anesthesia to completion of treatment and patient recovery, whereas the MRgBT procedure was assumed to last 3 hours. An interdisciplinary team was required to deliver both 2DBT and MRgBT that included an anesthetist (one hour during the 2DBT and MRgBT procedures), a radiation oncologist (full procedure), a medical physicist (half of the procedure), a radiation therapist (full procedure), and a nurse (full procedure). Conscious sedation was assumed for 2DBT and general anesthesia for MRgBT. The 2DBT was delivered using reusable non-magnetic resonance (MR)-compatible

ring/tandem (or equivalent) intracavitary-only applicators. The MRgBT treatment was delivered using reusable MR-compatible ring/tandem (or equivalent) intracavitary applicators +/- interstitial needles and the GEC-ESTRO EMBRACE II planning parameters were followed.[15] As per manufacturer recommendations, each program was assumed to purchase two applicator sets for replacement every three years. Additional intracavitary brachytherapy devices (e.g., transfer tubes) were also assumed to be replaced every three years for both programs.

Model Structure

The CUA was conducted to compare treatment effectiveness, expressed as quality adjusted life years (QALYs), and costs, expressed in 2016 Canadian dollars, between MRgBT and 2DBT from the perspective of the publically funded health care system in Ontario, the MOHLTC. The CUA was performed using a four-state Markov cohort model; a model where individuals could occupy only one health state at a given time and could remain in the same state or transition to other health states as time progresses.[23] Figure 1 shows the Markov model structure with the four-health states: no disease; metastatic/nodal disease; pelvic/local disease; and death. Patients either completely responded to treatment (no disease state), or did not respond to treatment (disease state). After initial response to treatment, a proportion of patients went on to develop a complication due to treatment in every living health state. A cycle-length of six months and a time-horizon of five years were used in order to capture all relevant differences in future costs and outcomes of the treatments, the natural course of cervical cancer, and the likely impact that treatment would have on the disease. Costs and effectiveness were both discounted at 5% annually, consistent with Canadian practice.[24] Manual model calibration was performed to match real-world data from the 2DBT cohort at Princess Margaret Cancer Centre in Toronto. The

comparison of treatment strategies were reported as the incremental cost-effectiveness ratio (ICER), which represented the incremental per patient costs of MRgBT for one QALY gained.

Parameters

Clinical Data

Table 1 shows the clinical input parameters used in the model. The parameters were obtained from primary data and published literature.[2,17,20,25-34] Estimates from the literature were reviewed by the clinical expert panel who determined the final estimates and their value range for the model. The treatments (2DBT and MRgBT) were assumed to have no impact on the development of para-aortic or distant metastases. Thus, the metastatic/nodal disease recurrence rate was assumed to be the same in patients receiving 2DBT and MRgBT. Grade 3 and 4 toxicity were assumed to be independent of tumor stage and/or primary tumor bulk (rates were the same for both high-risk and low-risk subgroups). Transitions to the death state from disease-free were based on Statistics Canada life table data for Ontario females for all-cause mortality,[35] whereas transitions to the death state from a diseased health state was based on 2DBT relative survival data from a cohort of cervical cancer patients treated with 2DBT at the Princess Margaret Cancer Centre. Relative survival was conservatively assumed to be the same for MRgBT patients. Best-practice MRgBT estimate sources were taken from studies which implemented interstitial needles on >40% of patients and on mono-institutional studies, since these studies represented a benchmark for what is achievable with optimal MRgBT and the appropriate use of interstitial needles.[36]

Effectiveness Data

The effectiveness variable for the CUA were QALYs. Calculation for QALYs involved weighing the duration of health states by a health related quality of life score (or utility), measured on a scale from 0 (death) to 1 (perfect health).[23] Similar to clinical data, utilities were taken from published literature, which were reviewed by the clinical expert panel to determine the mean and their value range for the model. The utilities used for each health state in the Markov model can be found in Table 1. The disease-free state was associated with a higher utility, compared to disease-states with recurrences and complications.[37,38] Patients were assumed to have a lower utility from their first experience of a complication and/or a recurrence for the remainder of the CUA.[37,39]

Cost Data

Data on costs can be found in Table 1. Costs were reported as 2016 Canadian dollars. Per patient costs were divided into two categories: (1) costs that are independent of annual programmatic patient volume (i.e., personnel, anesthesia, MRI time, drugs, and other consumables); and (2) those that vary with annual cervical cancer patient volume (i.e., devices specific to brachytherapy with limited lifespans and manufacturer-specified replacement cycles). Units, quantities, and prices were obtained from standard sources in Ontario, Canada, to estimate total costs of initial treatment and treatment for a disease recurrence. Treatment cost for 2DBT and MRgBT included all costs incurred from the induction of anesthesia to completion of treatment and patient recovery. The additional MRI time costs necessary for the delivery of MRgBT were included in treatment costs and assumed to be purchased from the radiation treatment program (centres with an MR simulator) or diagnostic radiology (centres without an MR simulator); and a half an hour time period was assumed for each patient in order to acquire basic axial, sagittal and coronal T2

imaging without contrast or special MR pulse sequences. Anesthesia and radiation oncology costs were derived from the Ontario Health Insurance Plan Schedule of Benefits.[40] Costs for salaried personnel (medical physicist, radiation therapist and nurse) were derived from hourly pay scales at Princess Margaret Cancer Centre, Toronto, Canada. Fixed and variable (patient dependent) device and consumable costs were based on estimates from a single vendor company. For MRgBT, interstitial one-time-use consumables (needles, guided tubes, and obturator) were included. Initial treatment fixed costs were converted to per-patient costs for modeling purposes in a high volume program, with 50 cervical cancer patients annually.

Cost of treatment for a recurrence (metastatic, nodal, pelvic, or local) was included. The cost of treatment for a recurrence was taken as the recommended usual care for Ontario cervical cancer patients. Unit costs for a disease recurrence included the cost of scans, personnel, chemotherapy (carboplatin and paclitaxel), and bevacizumab.[40-42] Complications and palliative care costs were taken from a cervical cancer population, estimated from the Canadian Institute for Health Information in a study conducted by Lee et al. (2016).[43] Patients in a diseased state (metastatic or pelvic disease) received a one-time palliative care cost when they transitioned to the death state. Patients who had a complication received a one-time toxicity cost. The cost of a complication was the average cost of all grade 3 and 4 toxicities, which included rectal-vaginal fistula, bladder and vaginal fistula, cystitis, small bowel obstruction, and inflammatory bowel.[43]

Sensitivity Analysis

Uncertainty in cost, effectiveness, and clinical parameters were taken into account by testing range of possible values of each estimate and the model assumptions. We performed deterministic and probabilistic sensitivity analyses to investigate the robustness of the model

results. Table 1 shows the ranges that were used for deterministic sensitivity analysis and distributions that were used for probabilistic sensitivity analysis. For the deterministic sensitivity analysis, we varied each parameter from its potential minimum to its potential maximum, while holding all other parameters at their mean values, in order to determine how influential each individual parameter was on the final results. For the probabilistic sensitivity analysis, we ran the model for 1,000 iterations choosing random combinations of all possible parameter values from their specified distributions.

Findings

Table 2 reports costs and effectiveness between the 2DBT and MRgBT for the full population, low-risk group, and high-risk group, from the perspective of MOHLTC for a 5-year time horizon. Irrespective of population grouping, the base-case analysis results show that MRgBT was less costly and more effective compared to 2DBT (Table 2). The incremental cost savings were $1,892, $134, and $2,643, and incremental QALYs were 0.35, 0.19, and 0.43, for the full population, low-risk group, and high-risk group comparing MRgBT to 2DBT. The MRgBT treatment strategy remained the preferred strategy even when parameters were varied individually, demonstrated by our one-way deterministic sensitivity analysis results (Figure 2). Results were most sensitive when we varied the cost of cancer recurrence parameter from $2,000 to $40,000. The uncertainty in the cost of cancer recurrence was due to the cost of bevacizumab. The drug, bevacizumab, is currently funded publically in Ontario for this type of cancer and included in our base case analysis (average cost of $36,000 for 6 cycles). However, in the instance that the drug is not funded, the lowest possible cost of a cancer recurrence was $2,000, the lower limit of uncertainty in this parameter. When cost of cancer recurrence was varied to its

lowest value, the ICER was $9,000/QALY gained, which remained well below the frequently cited Canadian $20,000-$100,000/QALY cost-effectiveness threshold.[44,45] Other influential parameters included the cost of the treatment for both MRgBT and 2DBT and the pelvic recurrence rates for the high-risk population. However, neither the uncertainty in the cost of the treatment nor the uncertainty in pelvic recurrence rates for the high-risk population changed the sign of the ICER, which remained dominant.

The Monte Carlo probabilistic sensitivity analysis results demonstrated the robustness of the findings when all model parameters were varied simultaneously. Incremental cost-effectiveness scatterplots for the the full population, low-risk group, and high-risk group show the uncertainty of the cost-effectiveness findings (and the joint distribution of costs and effects) comparing MRgBT to 2DBT (Figure 3). For the full population and high-risk group, the majority of estimates suggested that MRgBT was less costly and more effective than 2DBT (located in the southeast quadrant). For the low-risk group, there was uncertainty around the cost estimates as similar amount of estimates located in the northeast and southeast quadrants, suggesting that MRgBT was more effective than 2DBT but could either be less costly or more costly. This demonstrates that MRgBT is more effective and less costly, even under the situation which involves imperfect and unknown information. Overall, results suggested that if MRgBT were to be implemented properly, the MOHLTC could save money overtime and gain health benefits for women with locally advanced cervical cancer that require concurrent chemoradiation followed by brachytherapy.

Discussion

This study is the first Canadian study assessing cost-effectiveness of MRgBT in comparison to conventional 2DBT in treatment of patients with cervical cancer. The CUA provided compelling evidence that MRgBT was an economically attractive option (less costly and more effective) compared to 2DBT over a 5-year time horizon from the perspective of the Ontario MOHLTC. From this perspective, implementation of this technology cannot be justifiably withheld on the basis of cost. This CUA demonstrated that MRgBT would save the health care system money and produce more clinical effectiveness even under conditions of uncertainty.

Growing evidence in support of superiority of clinical outcomes in locally advanced cervical cancer patients treated with MRgBT have been demonstrated by single- and multi-institutional retrospective studies.[4,5,15,17-20] Evidence of improved local control, overall and cause specific survival with MRgBT as well as decrease is late toxicities presents a compelling case for implementation of MRgBT as standard of care for management of locally advanced cervical cancer. Introduction of this technique has been slow in a significant proportion of North American centres, with majority of centres continuing to use 2DBT.[22,46] The introduction of MRgBT treatment is associated with a number of challenges, such as increased upfront costs and scheduling MRI machine time. Given the constraints in the current health care system, this CUA was conducted to assess the cost-effectiveness of MRgBT compared to 2DBT and showed that implementing this new technology could improve clinical outcomes and save costs for this population from the perspective of the Ontario publically funded health care system.

This study has a number of strengths. One of the strengths was that input parameter values were obtained from the literature from a diverse global population and these estimates were validated by an expert panel (The MRgBT Cost Utility Analysis Working Group developed from the

Gynecological Cancers Community of Practice at Cancer Care Ontario). Additionally, given that the effect of MRgBT is different for patients with varying FIGO stages, we were able to stratify patients based on low and high-risk populations. This stratification allowed for more precise clinical effectiveness estimates to be incorporated in our model, and allowed for us to report the cost-effectiveness results for the full population and subgroups. Moreover, identification of utilities for health states were collected from published literature and reviewed by the clinical expert panel. These values were extrapolated from studies assessing patients with early stage cervical cancer as well as on utilities of prostate and anal canal cancer patients. These diseases suffer from similar toxicities and patients would be expected to have a comparable utility score to patients with cervical cancer.

This study also has a number of limitations. A limitation among the recently reported MRgBT studies involved the variability in the use of interstitial needles, an indicator of best-practice MRgBT. Centres utilizing interstitial needles in >40% of cases represent current best practice; however, most MRgBT studies ranged from 12% to 40%. In multi-institutional studies, such as RetroEMBRACE and EMBRACE, brachytherapy technique and dose prescription were based on institutional practice, which varied considerably with regard to total dose, fractionation, dose rate, and brachytherapy applicators.[15,17,34,36] This predisposes for significant variation in dose prescription and as such the results did not necessary represent best practice achievable with a harmonized approach to MRgBT across institutions and patients. Nevertheless, these concerns were taken into account by the expert panel in review of values of clinical outcomes of MRgBT for our model. In addition, the costs included in this CUA did not include capital investment costs (MRI machine purchase) but included: (1) costs that are independent of annual programmatic patient volume; and (2) those that vary with annual cervical cancer patient. Thus,

this CUA included expenses required to make MRgBT available to patients and operational costs which are associated with expenses of maintaining the technology and its use. The MRI use was based on purchasing time from MR unit with the assumption that the MRI is also used for assessment of numerous other disease sites. Furthermore, our study is simulated for a high volume centre, which would treat approximately fifty cervical cancer patients per year, which is appropriate patient volume estimate for cancer centres in Ontario with MRI technology, but may not be generalizable to centres with other levels of demand.

This CUA assessed the cost-effectiveness of MRgBT in comparison to conventional 2DBT in treatment of patients with locally advanced cervical cancer. This analysis showed, from the perspective of the MOHLTC, implementation of best practice MRgBT could be an economically attractive option (saving the health care system resources and producing better clinical outcomes). These finding will assist health care providers and policy-makers in Ontario with future infrastructure and human resource planning to assure optimal care of women with locally advanced cervical cancer.

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Tables

Table 1. Model input parameters

Variables		DSA		PSA		
Costs ($)	**Mean**	**Min**	**Max**	**SD**	**Distribution**	**Source**
2DBT treatment	8,180	6,680	9,680	500	Gamma	[40]
MRgBT treatment	13,120	11,620	14,620	500	Gamma	[40]
Cancer recurrence	38,994	2,994	40,000	1000	Gamma	[40-42]
Toxicity	5,666	3,812	7,065	1000	Gamma	[43]
Palliative care	8,875	0	10,000	1000	Gamma	[43]
Utilities						
No disease	0.85	0.80	0.90	0.03	Beta	[37,39]
Disease and/or toxicity	0.55	0.50	0.60	0.03	Beta	[37,38]
Proportions[a]						
Patients with low risk cervical cancer	0.30	0.25	0.35	0.03	Beta	[47]
2DBT low risk patients with complete response	0.93	0.90	0.95	0.01	Beta	[47]
2DBT high risk patients with complete response	0.80	0.75	0.85	0.03	Beta	[47]
MRgBT patients with complete response	0.95	0.93	0.98	0.01	Beta	[20,25]
Rates[b]						
Low risk metastatic recurrence [b]	0.10	0.08	0.13	0.01	Beta	[17,20,31,34]
High risk metastatic recurrence [b]	0.25	0.20	0.30	0.03	Beta	[17,20,31,33,34]
2DBT low risk pelvic recurrence [b]	0.15	0.10	0.20	0.03	Beta	[20,31,32]
2DBT high risk pelvic recurrence [b]	0.25	0.20	0.30	0.03	Beta	[2,25,31,32]
MRgBT low risk pelvic recurrence [b]	0.05	0.03	0.08	0.01	Beta	[17,20,34]
MRgBT high risk pelvic recurrence [b]	0.15	0.10	0.20	0.03	Beta	[17,20,25,33]
Survival after recurrence [c]	0.20	0.15	0.25	0.03	Beta	[47]
2DBT toxicity [b]	0.15	0.13	0.18	0.01	Beta	[25,27]
MRgBT toxicity [b]	0.08	0.05	0.10	0.01	Beta	[17,20,25-30,34]

Note: 2DBT = two-dimensional image-guided brachytherapy; DSA = deterministic sensitivity analysis; low risk = FIGO Stage IB-IIA; high risk = FIGO Stage IIB-IV; Min = minimum; Max = maximum; MRgBT = magnetic resonance image-guided brachytherapy; PSA = probabilistic sensitivity analysis; SD = standard deviation

[a] Proportions are either prevalence estimates for FIGO Stages or initial response rates to treatment strategy

[b] Rates are based on 3-year follow-up estimates after treatment

[c] Rates are based on 5-year follow-up estimates after treatment

Table 2. Results for cost-utility analysis comparing MRgBT to 2DBT

Full population	**MRgBT**	**2DBT**
QALY, mean	3.27	2.92
QALY, SD	0.09	0.09
QALY, lower 95% CI	3.09	2.77
QALY, upper 95% CI	3.45	3.09
Cost ($), mean	27,595	29,487
Cost ($), SD	1,093	1,129
Cost ($), lower 95% CI	25,485	27,334
Cost ($), upper 95% CI	29,731	31,613
Difference (QALY, mean)	0.35	
Difference (cost ($), mean)	-1,892	
ICER (cost/QALY)	Dominant	
Low-risk group (IB-IIA)	**MRgBT**	**2DBT**
QALY, mean	3.47	3.28
QALY, SD	0.10	0.10
QALY, lower 95% CI	3.25	3.10
QALY, upper 95% CI	3.67	3.48
Cost ($), mean	21,689	21,823
Cost ($), SD	993	1,202
Cost ($), lower 95% CI	19,919	19,701
Cost ($), upper 95% CI	23,773	24,486
Difference (QALY, mean)	0.19	
Difference (cost ($), mean)	-134	
ICER (cost/QALY)	Dominant	
High-risk group (IIB-IV)	**MRgBT**	**2DBT**
QALY, mean	3.20	2.77
QALY, SD	0.09	0.09
QALY, lower 95% CI	3.00	2.60
QALY, upper 95% CI	3.37	2.96
Cost ($), mean	30,122	32,765
Cost ($), SD	1,344	1,358
Cost ($), lower 95% CI	27,521	30,031
Cost ($), upper 95% CI	32,859	35,344
Difference (QALY, mean)	0.43	
Difference (cost ($), mean)	-2,643	
ICER (cost/QALY)	Dominant	

Note: MRgBT = magnetic resonance image-guided brachytherapy; 2DBT = two-dimensional image-guided brachytherapy; low-risk = FIGO Stage IB-IIA; high-risk = FIGO Stage IIB-IV; QALY = quality adjusted life year; SD = standard deviation; CI = confidence interval; ICER = incremental cost-effectiveness ratio. The probabilistic sensitivity analysis was run for 1,000 iterations.

Figures

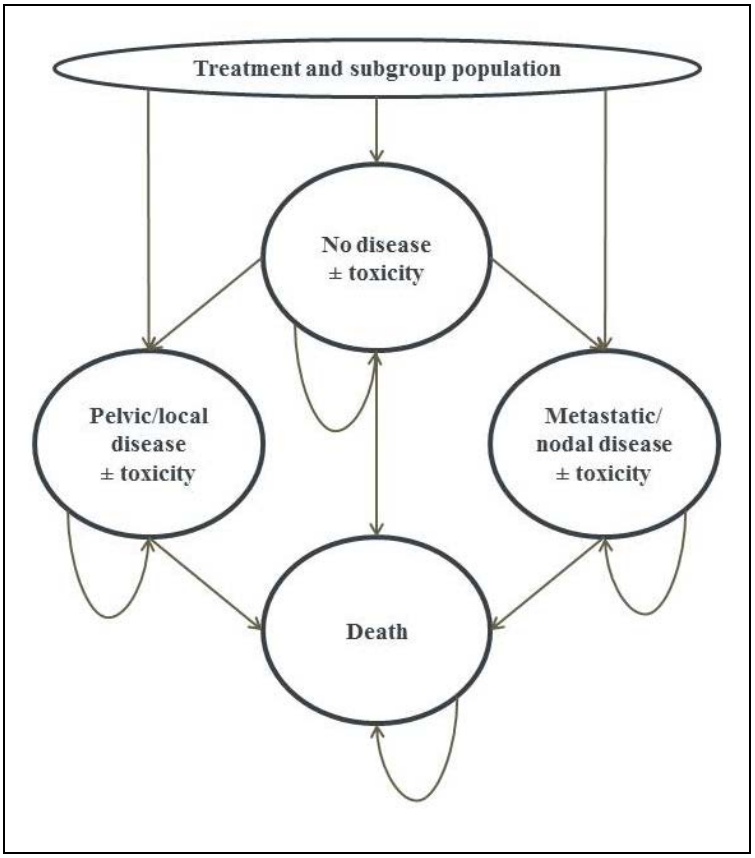

Figure 1. The structure of the Markov model for cervical cancer health states. The treatment comparison was between 2DBT and MRgBT. The subgroups were high-risk and low-risk populations. The Markov structure has four-health states, disease-free, metastatic/nodal disease, pelvic/local disease, and death. Patients either completely responded to treatment (no disease state), or did not respond to treatment (disease state). All live health states contain a proportion of patients with complications.

Note: MRgBT = magnetic resonance image-guided brachytherapy; 2DBT = two dimensional image-guided brachytherapy; low-risk = FIGO Stage IB-IIA; high-risk = FIGO Stage IIB-IV.

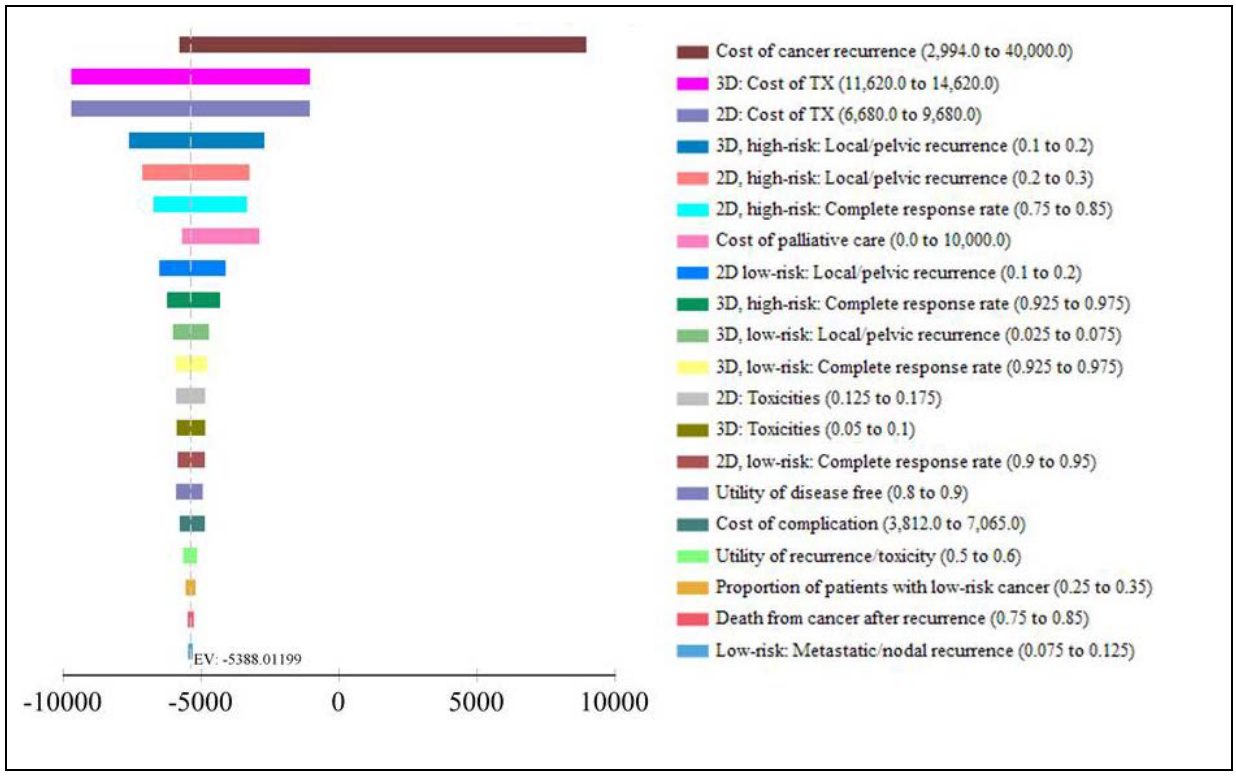

Figure 2. Deterministic one-way sensitivity analysis presented at an Incremental Cost-Effectiveness Ratio (ICER), comparing MRgBT to 2DBT for the full population. The x-axis displays the expected value (EV) of the ICER when the single parameter is varied from maximum to minimum. The tornado diagram ranks the most influential parameters on the ICER results from top to bottom.

Note: TX = treatment; 2D = two-dimensional image-guided brachytherapy; 3D = magnetic resonance image-guided brachytherapy; low-risk = FIGO Stage IB-IIA; high-risk = FIGO Stage IIB-IV.

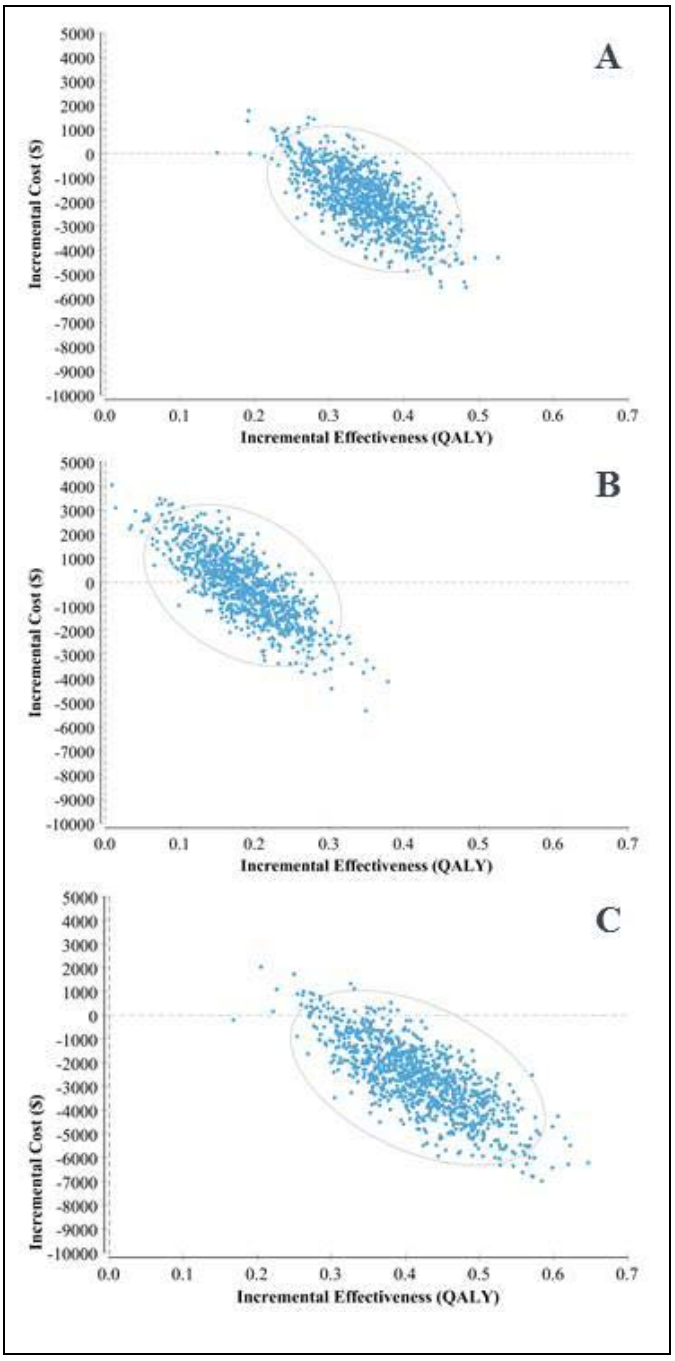

Figure 3. Incremental cost-effectiveness scatterplots of MRgBT vs. 2DBT for the full population (A), the low risk subgroup (B), and the high risk subgroup (C) from probabilistic sensitivity analyses. The x-axis displays the incremental effectiveness in QALYs, whereas the y-axis displays the incremental costs in 2016 Canadian dollars.

Note: QALY = quality adjusted life year; MRgBT = magnetic resonance image-guided brachytherapy; 2DBT = two dimensional image-guided brachytherapy; low-risk = FIGO Stage IB-IIA; high-risk = FIGO Stage IIB-IV.