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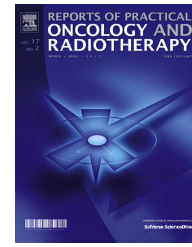

Original research article

Dosimetric comparison of MRI-based HDR brachytherapy and stereotactic radiotherapy in patients with advanced cervical cancer: A virtual brachytherapy study

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ABSTRACT

Aim: To evaluate the treatment plans of 3D image-guided brachytherapy (BT) and stereotactic robotic radiotherapy with online image guidance – CyberKnife (CK) in patients with locally advanced cervix cancer.

Methods and materials: Ten pairs of plans for patients with locally advanced inoperable cervical cancer were created using MR based 3D brachytherapy and stereotaxis CK. The dose that covers 98% of the target volume (HR CTV D98) was taken as a reference and other parameters were compared.

Results: Of the ten studied cases, the dose from D100 GTV was comparable for both devices, on average, the BT GTV D90 was 10–20% higher than for CK. The HR CTV D90 was higher for CK with an average difference of 10–20%, but only fifteen percent of HR CTV (the peripheral part) received a higher dose from CK, while 85% of the target volume received higher doses from BT. We found a significant organ-sparing effect of CK compared to brachytherapy (20–30% lower doses in 0.1 cm^3, 1 cm^3, and 2 cm^3).

Conclusion: BT remains to be the best method for dose escalation. Due to the significant organ-sparing effect of CK, patients that are not candidates for BT could benefit from stereotaxis more than from classical external beam radiotherapy.

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1. Background

Brachytherapy (BT) is an integral component of multimodality treatment for advanced inoperable cervical cancer.[1,2] The ability to deliver a very high target dose with a sharp dose gradient is essential for obtaining excellent treatment results. MRI-navigated BT further increases the therapeutic index due to the precise irradiation of target volume (TV) and better organ sparing.[3–5]

In cervical cancer treatment, external beam radiotherapy (EBRT) is used to irradiate the whole pelvis. Compared to BT, external boost is less effective and more toxic.[6] However, in recent years, advances in EBRT have allowed radiation oncologists to deliver a highly conformal dose to the target, and advances in image guidance enable the reduction of set-up margins.

It is difficult to directly compare BT and EBRT, mainly because of the different dose-volume parameters used for each method. In comparing different radiotherapy plans, it is crucial to establish a reference parameter. The GEC-ESTRO Working Group recommends D90 as the most important parameter for high-risk clinical target volume (HR CTV),[4] but D98 seems to be much better indicator for local tumor control[7]; systematic low-dose regions leading to local recurrence could be detected even when D90 for HR CTV ≥ 87 Gy was applied. Modern EBRT planning systems (mostly for stereotactic RT) are capable of evaluating parameters such as D1 cm^3 or D2 cm^3 that are routinely used in BT. Moreover, stereotactic radiotherapy has proven to be of very good efficacy in treating inoperable relapses of gynecological malignancies,[8] indicating that comparison of stereotaxis and BT would be appropriate.

The present dosimetric study compares the treatment plans of 3D image-guided brachytherapy and stereotactic robotic radiotherapy with online image guidance.

2. Methods and materials

This study included ten patients with locally advanced inoperable cervical cancer, who were treated with 3D MRI-based BT. For each patient, two plans were made—one for BT and one for stereotactic radiotherapy—and their dosimetric characteristics were compared. Median volumes of GTV (gross tumor volume), HR CTV and IR CTV (intermediate-risk clinical tumor volume) were 2.7 cm^3 (range 0.9–16.0 cm^3), 33.1 cm^3 (range 23.1–63.4 cm^3) and 109.4 cm^3 (range 77.0–189.0 cm^3), respectively.

2.1. *BT treatment planning*

Our BT treatment technique using MRI and CT data fusion was described elsewhere.[9] In brief, MRI with brachytherapy applicators in situ (intracavitary with no needle – 7 cases, intracavitary plus one needle – 2 cases, intracavitary plus two needles – 1 case) was performed on a 1.5 T system (Signa Excite HD, GE Healthcare, Milwaukee, WI, USA) using T2-weighted axial, coronal, and sagittal fast spin echo sequences (3 mm slice thickness, no gap). Target volumes and OAR were contoured according to the Gynaecological GEC-ESTRO Working Group recommendations. The treatment planning system BrachyVision 8.6 (Varian, Palo Alto, CA) was used for optimization based on EQD2 values, however physical values were used for comparison with results of stereotactic treatment planning system. The prescribed dose for HR CTV D90 was 6× 5 Gy (six fractions in two weeks after finishing external beam radiotherapy 45 Gy in 25 fractions). Dose volume constraints for the different OAR were 70 Gy EQD2 as a maximum dose for the most exposed tissues of the rectum (rectum D2 cm^3) and sigmoid colon (sigmoid D2 cm^3), and 90 Gy EQD2 in 2 cm^3 of the bladder (Bladder D2 cm^3). No volume constraints were applied for the vagina.

2.2. *Treatment planning of stereotactic radiotherapy*

We used the CyberKnife (CK) system with a 6 MeV linear accelerator. The treatment plans were non-isocentric (sequential optimization) and non-coplanar with approximately 200 pencil beams. Plans were designed to cover 100% of HR CTV with the prescribed dose, the constraint for the homogeneity index was higher than 2.0 and constraints for OAR were the same as for BT optimization. For each patient, the CT images with structures contoured for BT were transferred to the CK treatment planning system (MultiPlan 3.5.2, Accuray, Sunnyvale, CA). Because of the proven sub-millimeter precision of the CK system,[10,11] we omitted the set-up margin, such that planning target volume (PTV) was equal to HR CTV. Since systematic low-dose regions leading to local recurrence can be detected even when HR CTV D90 is optimal,[7] we used the dose that covers 98% of the target volume (D98 HR CTV) as reference and compared other parameters, including HR CTV D90, GTV D100, D90, and intermediate risk (IR) CTV D100, D90, according to the recommendation of GEC ESTRO.[4] For different OARs, we compared the typically recommended parameters: D0.1 cm^3, 1 cm^3, and 2 cm^3. In addition, the HR CTV D60 and 30 were compared, and an averaged DVH curve for both methods was constructed. We also compared the Dmean values obtained for the scanned part of the body in order to evaluate differences in the integral dose of radiation between plans.

2.3. *Statistics*

For statistical analyses, GraphPad Prism 4 for Windows was used (GraphPad Software Inc., San Diego, CA). All dosimetric data were compared with a paired two-tailed Student's *t*-test, and statistical significance was assumed at $p < 0.05$.

3. Results

Of the ten studied cases, the dose from D100 GTV was comparable for both devices, on average, the BT GTV D90 was 10–20% higher than for CK, due to the dose inhomogeneity of BT around the applicator (Table 1). On the other hand, the HR CTV D90 was higher for CK in eight of ten cases, with an average difference of 10–20% (Table 2). In low-dose parameters, such as D60 or D30, the BT plans reached higher doses by 25% and 45%, respectively (Table 2). Based on these findings, we developed typical DVH plans (the DVH curves were created from average values of 10 patients.) for BT and

Table 1 – Comparison of D100 and D90 GTV and IR CTV values for CyberKnife (CK) and brachytherapy (BT). Comparison between IR CTV D90 and D100 values clearly shows steeper gradient outside the HR CTV for CK.

	GTV				IR CTV			
D (Gy)	D100 CK	D100 BT	D90 CK	D90 BT	D100 CK	D100 BT	D90 CK	D90 BT
Average	7.8	7.7	8.9	9.8	0.6	1.7	2.8	2.7
Median	7.2	7.9	8.0	11.2	0.6	1.7	2.8	2.6
Min	5.5	4.3	7.1	5.4	0.4	0.9	2.1	2.3
Max	11.3	10.4	12.5	14.1	1.1	2.9	3.8	4.1

Table 2 – Comparison of D100, D90, D60 and D30 HR CTV values for CyberKnife (CK) and brachytherapy (BT). The values in the second column are the same for CK and BT.

D (Gy)	D98 CK + BT	D100CK	D100 BT	D90 CK	D90 BT	D60 CK	D60 BT	D30 CK	D30 BT
Average	5.1	4.4	4.6	7.3	6.1	8.5	11.5	9.4	17.9
Median	5.0	4.3	4.5	6.8	6.1	8.0	10.6	8.7	16.1
Min	4.4	3.7	3.9	6.1	5.1	6.8	7.8	7.6	11.8
Max	6.5	5.6	5.8	10.3	7.2	11.8	15.8	13.2	27.0

stereotaxis, and a parameter D85 where the two curves crossed and the doses were equal for both techniques was found (Fig. 1). Fifteen percent of HR CTV (the peripheral part) received a higher dose from CK, while 85% of the target volume received higher doses from BT, including 60% of the volume with a dose higher than 200% the prescribed dose (Fig. 2). IR CTV D90 was similar for both methods, while the D100 was lower for CK (Table 1).

Regarding OAR, median D1 cm^3, D2 cm^3 values for BT plans were 4.9 Gy (range 4.0–5.3), 4.6 Gy (range 3.8–4.8), 3.3 Gy (range 3.1–3.6), 3.0 Gy (range 2.8–3.3) and 3.5 Gy (range 2.6–4.0), 3.2 Gy (range 2.4–3.6) for the bladder, rectum and sigmoid, respectively. Fig. 3 and Table 3 demonstrate a significant organ-sparing effect of CK compared to brachytherapy (20–30% lower doses in 0.1 cm^3, 1 cm^3, and 2 cm^3).

To estimate the probability of radiation-induced second cancers, we calculated the Dmean of the contoured body. The integral dose was higher for BT than for CK (0.2 Gy and 0.1 Gy, respectively), but CK create larger areas with lower doses (Fig. 2).

4. Discussion

The combination of brachytherapy and external beam radiotherapy is considered to be the gold standard treatment for advanced cervical cancer.[1] Historically, the dosing parameters for brachytherapy have used a system that specified the dose to standardized points A and B as well as to rectal and bladder points. This system, based on 2D images, is still used in the majority of current clinical practice.[3] In recent years, more sophisticated recommendations have been published that put emphasis on using 3D image-guided brachytherapy to optimize the dose coverage to the tumor while reducing the dose to adjacent critical structures.[4] Direct comparison of 2D and 3D brachytherapy appears to favor the 3D approach.[5] In 3D brachytherapy, precise definition of target volume is of utmost importance. Our previously published data demonstrate the feasibility and precision of MRI-based pre-planning,[12] so this approach was used as a reference for the comparison with CK plans.

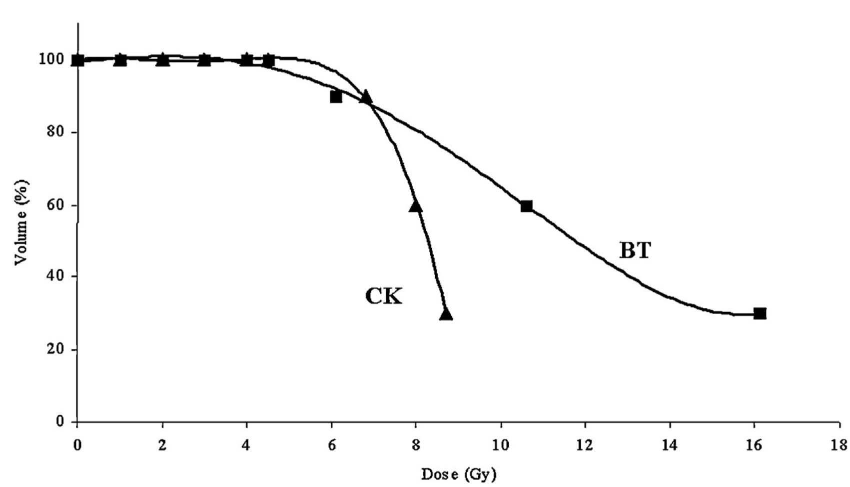

Fig. 1 – Derived dose volume histogram (DVH) of HR CTV for CyberKnife (CK) and brachytherapy (BT). The DVH curves for HR CTV D100, D98, D90, D60 and D30 were created from average values of 10 patients. D30 values comparison clearly shows much higher dose for BT.

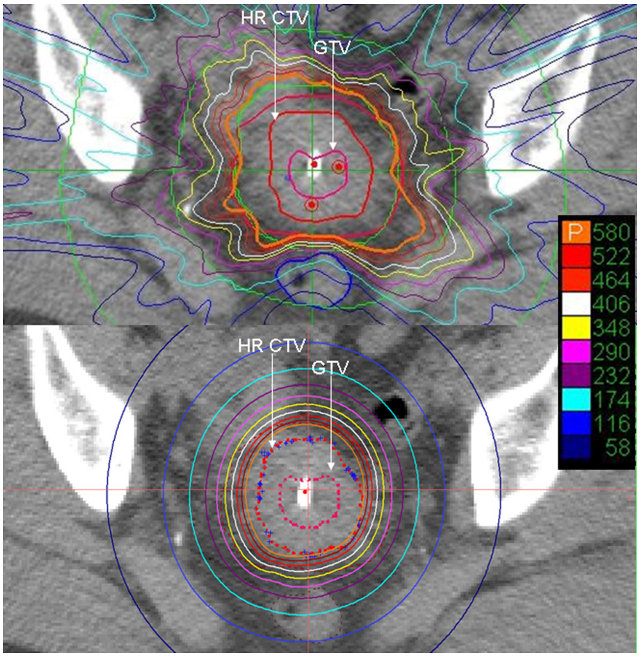

Fig. 2 – Example of dose distributions (cGy) on axial views for one fraction; CyberKnife-CK (top) and brachytherapy-BT (bottom). Almost the same coverage of HR CTV (high risk clinical target volume) by prescribed isodose line for both methods. Irregular isodose lines, larger region of low dose and rectum sparing dose distribution for CK compared to BT.

It was recently reported that the CK plan is comparable to the 2D BT plan.[13] The comparison of 3D BT and IMRT/IMPT has also been previously published, showing clear superiority of BT.[14] To the best of our knowledge, this is the first study to compare CK stereotactic RT with 3D MRI-based brachytherapy. Our results demonstrate that the conformality, homogeneity and target coverage of CK plans are higher to those of 3D brachytherapy, which is in agreement with the published article.[13] CK plans showed a very strong dose gradient with lower values on D100 IR CTV, while CK was equal to BT at D90. Moreover, stereotactic radiotherapy is noninvasive and can easily be delivered, even to patients that cannot tolerate anesthesia and to tumors for which brachytherapy cannot be feasible.

Before we declare CK's superiority to brachytherapy, several very important questions must be answered. The first of them is the question of sufficient image guidance. The uterus is a mobile structure that can move beyond 1 cm between fractions[15] depending on the filling status of the bladder and rectum,[16] so intrafraction movement can be expected as well. Candidates for CK virtual brachytherapy would certainly need urethral catheter and an empty rectum in order to minimize uterine moving. To ensure precise image guidance, fiducials must be placed in the cervix and vaginal vault or parametria.[17] When target motion is tracked in real time using fiducial marker, the same submillimeter dose delivery precision can be achieved as in other localities [18] and no CTV-PTV is needed for cervix carcinoma as reported previously.[13] Moreover, overview of some uncertainties related to 3D volumetric image guided BT has been published recently.[19]

There are also some dosimetric concerns. As mentioned above, brachytherapy dose distribution is more inhomogeneous to that of CK, with hot areas inside and around the catheters. In principle, it is difficult to compare two

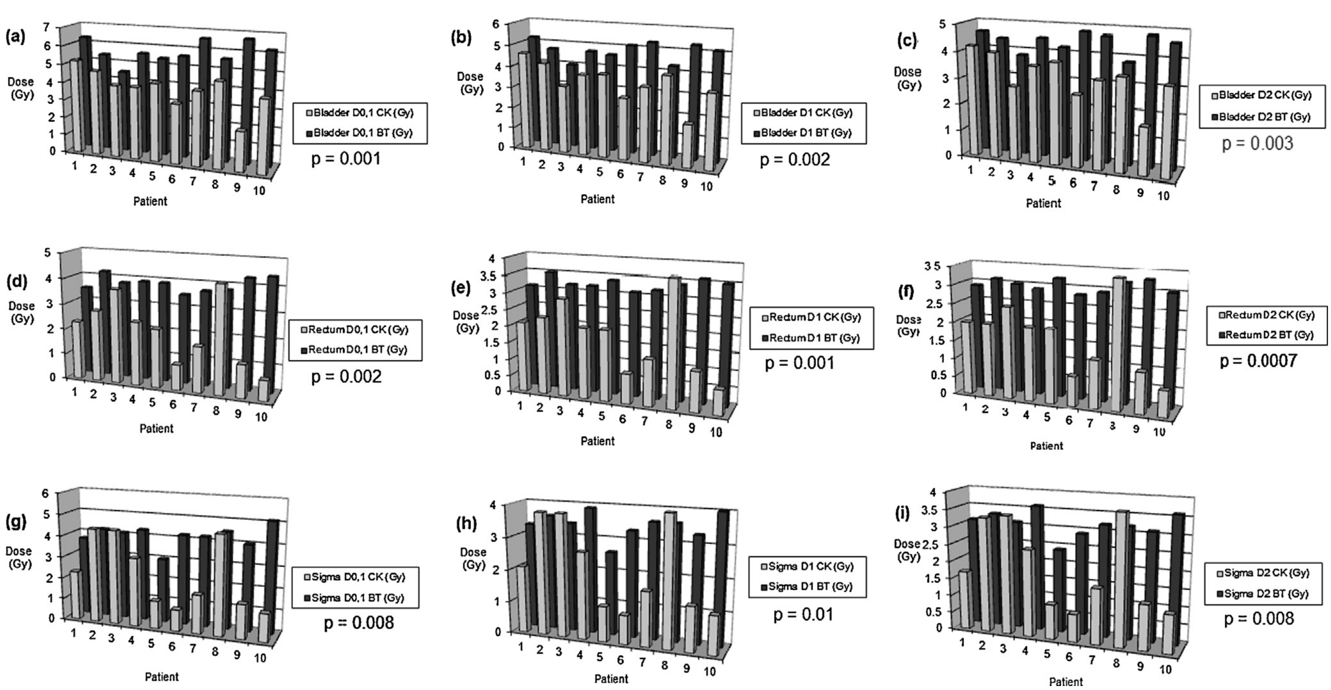

Fig. 3 – (a–i) Comparison between CyberKnife (CK) and brachytherapy (BT) for (a, b, c) bladder, (d, e, f) rectum, and (g, h, i) sigmoid, each with (a, d, g) D0.1, (b, e, h) D1, and (c, f, i) D2.

Table 3 – Organ at risk (OAR) – comparison of D0.1 cm^3, D1 cm^3 and D2 cm^3 values for CyberKnife (CK) and brachytherapy (BT).

OAR	Bladder CK			Bladder BT			Rectum CK			Rectum BT			Sigmoid CK			Sigmoid BT		
D (Gy)	D0.1	D1	D2	D0.1	D1	D2	D0.1	D1	D2	D0.1	D1	D2	D0.1	D1	D2	D0.1	D1	D2
Average	4.1	3.6	3.3	5.8	4.8	4.4	2.3	1.9	1.8	3.9	3.3	3.0	2.6	2.3	2.0	4.1	3.5	3.2
Median	4.1	3.7	3.4	5.6	4.9	4.6	2.3	2.1	2.0	3.9	3.3	3.0	2.1	1.9	1.7	4.2	3.5	3.2
Min	2.2	2.0	1.8	4.5	4.0	3.8	0.8	0.8	0.7	3.5	3.1	2.8	1.0	0.9	0.8	3.0	2.6	2.4
Max	5.2	4.6	4.2	6.7	5.3	4.8	4.2	3.7	3.4	4.4	3.6	3.3	4.6	4.0	3.7	5.1	4.0	3.6

approaches that differ completely in the most important dosimetric parameters. Because low-dose regions leading to local recurrence could be detected even when D90 is optimal,[7] we decided to make HR CTV D98 a benchmark and compare other standard dosimetric parameters. We consider the present study as a starting point for an important discussion about the potential advantages and limitations of stereotactic radiotherapy as a "virtual brachytherapy" method.

Even more important are radiobiological considerations. With identical fractionation regimens, virtual brachytherapy covered the HR CTV more homogenously and with a higher dose to peripheral parts, and had better organ-sparing effects. However, with BT the part of tumor around the catheter is irradiated with a very high dose, much higher than with CK. It could be possible to increase the prescribed dose in virtual brachytherapy, because the dose to critical organs was low. However, the brachytherapy dose distribution cannot be entirely the same as in CK. Therefore, the most important question is whether the overdosage of some parts of the tumor is a factor that contributes to the excellent effectiveness of brachytherapy. However, if there is some benefit of partial overdosage, then we must acknowledge the effectiveness of an ablative dose of radiation to a small part of the target volume; in this case, we need to ask whether it is even necessary to irradiate homogeneously. Until now, this has been one of the paradigms in radiation oncology according to ICRU recommendations; a properly designed set of clinical studies should be performed to test whether it is correct. Significant disadvantage of CK session is the duration of each fraction being longer than that of high dose rate, which can cause a loss in cytotoxicity.

Some patients with advanced cervical cancers are not candidates for brachytherapy due to the problem of successful target coverage.[20] Based on our findings, we are confident that virtual brachytherapy based on stereotactic radiotherapy is a good option for these patients, as it is certainly less toxic and potentially more efficient than classical external beam radiotherapy.

5. Conclusions

Stereotactic radiotherapy with CK produces treatment plans with higher conformality and homogeneity to those produced by 3D MRI-navigated brachytherapy in patients with advanced cervical cancer. However, the higher homogeneity of CK allows the irradiation of only 15% of the target volume (peripheral parts) at a higher dose than BT, while the remaining 85% of the TV (central parts) receive a much higher dose from BT than from CK. While BT remains to be the best method for dose escalation due to the significant organ-sparing effect of CK, patients that are not candidates for BT could benefit from stereotactic robotic radiotherapy more than from classical external beam radiotherapy.

Conflict of interest

None declared.

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