Reports of Practical Oncology and Radiotherapy 25 (2020) 1011–1016

Available online at www.sciencedirect.com

Reports of Practical Oncology and Radiotherapy

journal homepage: http://www.elsevier.com/locate/rpor

Original research article

A prospective comparative dosimetric study between diffusion weighted MRI (DWI) & T2-weighted MRI (T2W) for target delineation and planning in cervical cancer brachytherapy

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ARTICLE INFO

Article history:
Received 4 May 2020
Received in revised form 21 July 2020
Accepted 17 August 2020
Available online 28 October 2020

Keywords:
Diffusion weighted imaging
ADC
IGABT
Brachytherapy
Cervical cancer
MRI

ABSTRACT

Aim: To evaluate the difference between GTVBT (Gross Tumor Volume at Brachytherapy) and HR CTV (High Risk Clinical Tumor Volume) delineated with DWI and T2W MRI. To evaluate doses to organs at risk and targets from plans generated using T2W and DWI.
Background: Functional imaging with DWI can improve cervical tumor distinction as it is more sensitive than T2W MRI even in detecting parametrial invasion. This study does a dosimetric comparison between a T2W and DWI based plan.
Methods: Fifty carcinoma cervix patients were subjected to MRI based brachytherapy. T2W and a diffusion weighted sequence were acquired. Target delineation and brachytherapy planning was done on both T2W and DWI. Standard DVH parameters were recorded and the treatment was given using the plan generated from T2W images.
Results: GTVBT and HRCTV contours on DWI were different when compared with T2W. Mean GTVBT volume on T2W and DWI was 5.25 and 5.23, respectively (p value 0.8). Mean HRCTV on T2W and DWI was 28.3 and 27 cc, respectively (p value 0.003). Planning on the above volumes resulted in a superior coverage in terms of HRCTV D90 and D100 for DWI based plan, HRCTV D90 — 735.1 and 741 cGy for T2W and DWI, respectively (p value 0.006), HRCTV D100 — 441.05 and 444.5 for T2W and DWI plans, respectively (p value = 0.006). Doses to the OAR were not significantly increased.
Conclusion: GEC ESTRO based contouring guidelines cover all the functionally abnormal areas on DWI. DWI should only be used as a supplement to T2W for contouring target volumes.

1. Introduction

The standard treatment for cervical cancer from stage IB2 to IVA is concurrent chemoradiation followed by brachytherapy.[1] Image-guided adaptive brachytherapy (IGABT) has recently shown excellent clinical outcome with superior local control and less toxicity.[2,3] For IGABT, T2W (T2 weighted) MRI is the gold standard.[4] However, studies have shown that target delineation with T2W MRI results in uncertainties, poor interobserver variabilities, and low conformity indices for high risk clinical target volume (HRCTV) contours.[5] This variation is most significant for cases with a large parametrial disease at diagnosis which end up having near-complete response before brachytherapy. It is also postulated that the parametrial scar tissue might harbor microscopic disease, and if missed, may be the cause of parametrial recurrence.[6]

Functional imaging with diffusion-weighted imaging (DWI) and derived apparent diffusion coefficient (ADC) maps has shown great promise and can aid in tumor distinction.[7,8] DWI displays information about water mobility in the extracellular space. The greater the mobility of water molecules in the extracellular space the lesser the restriction. This less restricted movement appears as hypointense or dark areas with higher corresponding ADC values.[9,10] This process is completely reversed in tumor tissues. Due to increased

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https://doi.org/10.1016/j.rpor.2020.08.008
1507-1367/

cellularity in tumors, and less extracellular fluid between the cells, there is restricted movement of water molecules. This ultimately gives a hyperintense or bright area on the image with a corresponding lower ADC. Functional imaging in the form of DWI provides a superior edge contrast over T2W images.[11] The ADCs provide objective data for the presence or absence of the tumor ($0.77–1.28 \times 10^{-3}$ mm^2/s for cervical tumor). This has resulted in high sensitivity (87.5–96%) and higher specificity (91–100%) in distinguishing cervical tumor from healthy tissue.[12–14]

Previously, DWI has been incorporated in the workflow of IGABT. Esthapann et al.[11] found that the volumes contoured with DWI were different from T2W and DWI provided a better edge contrast. Han et al.,[15] in a prospective study, showed that DWI, along with PET and dynamic contrast-enhanced MRI, could be used as a supplement to T2W images to decrease inter-observer variability. Haack et al.[16] found that there is a significant increase in ADC values from GTVBT (Gross Tumor Volume at brachytherapy) to HRCTV to IRCTV (Intermediate Risk Clinical Target Volume). However, even in this study a dosimetric comparison was not done. To the best of our knowledge, no study has compared the dosimetric difference between the brachytherapy plans created on target volumes generated from T2W and DWI. Our prospective study aims to do that.

In this study we aim to investigate whether planning and contouring on DWI is better dosimetrically when compared with T2W MRI.

2. Aims and objectives

To evaluate the difference between GTVBT (Gross Tumor Volume at Brachytherapy) and HR CTV (High Risk Clinical Tumor Volume) & IR CTV (Intermediate Risk Clinical Target Volume) delineated with DWI and T2W MRI.

To evaluate doses to organs at risk by T2W and DWI based planning using dose volume histograms.

3. Materials and methods

3.1. Ethical statement

This prospective study was reviewed by our institutional ethics committee and patients gave their informed consent.

3.2. Source of data

Patients presenting to the Department of Radiation Oncology from May 2015 to December 2016 with biopsy proven carcinoma cervix. FIGO stage IB2, to IVA, in whom definitive chemoradiotherapy or radiotherapy is planned, and who are suitable for ICBT (Intracavitary Brachytherapy) were included in the study. Patients with metastatic disease, previous total or partial hysterectomy, contraindications to anesthesia, previous radiation therapy to the pelvis, and patients with metal implants or any other medical device unsafe for MRI were excluded.

3.3. Sample size calculation

Based on the study done by Jacqueline Esthappan et al., with a power of 80% and alpha-5% for the calculation of ADC and T2W volumes, the sample size based on the difference of means for this study should be 450 but as it was a time bound study a minimum of 50 patients were included.

3.4. EBRT

All patients received EBRT to the whole pelvis. For EBRT, the target delineation was done based on published guidelines by Taylor et al. and Patel et al.[17,18] A four field technique with two opposing antero-posterior and two opposing lateral portals were used for the treatment. The EBRT dose was given in five fractions per week to a total of 50 Gy in 25 fractions, 200 cGy per fraction to the whole pelvis, 5 fractions per week with 15 MV photons. All patients received Injection Cisplatin 40 mg/m^2 intravenously once a week for 5 weeks concurrently with EBRT.

3.5. IGABT

Each patient was informed about the procedure before brachytherapy, consent was obtained. Treatment was performed on an in-patient basis. With the patient under spinal anesthesia, all brachytherapy insertions were performed using CT-compatible metal/MRI-compatible titanium modified Fletcher suit applicators consisting of a uterine tandem with a flange and two ovoids available in 4 different sizes (semismall, small, medium and large). In some patients ring and tandem and ovoid and tandem plastic applicators were also used. Patients undergoing ISBT or combined intracavitary–interstitial implants were not included in this study

All patients were treated using standard 3D planning. T2W MRI was used as imaging of choice for contouring planning and treatment. GEC ESTRO IV guidelines were used for the MRI protocol, details of which are provided in Tables 1 and 2 (Supplementary material). After the application, MRI was done within the maximum of 2 h. Both T2W and DWI were exported to Varian brachy vision software and registered by auto matching. If the clinician was not satisfied with the auto matching of the two sequences, then manual matching with a bony landmark was done.

3.6. Contouring for T2W

Based on GEC ESTRO I guidelines by Haie-Meder et al.[19] the following structures were contoured; GTVBT, HRCTV, rectum, bladder and sigmoid.

GTVBT — included hyperintense and intermediate intensity areas.

HRCTV — included the GTVBT, the entire cervix and any grey areas in the parametria, vagina or uterus. For the rectum, the superior most slice was taken at the point where the rectum starts to become conical and was contoured down to 1–1.5 cm below the coccyx.

Bladder — the entire bladder was contoured, and for the sigmoid colon, contouring was started from the inferior most slice where the rectum ends, up to 2 slices above the last HRCTV contour

3.7. Contouring for DWI

One of the major drawbacks with DWI is that the normal anatomy is not very well appreciated; hence, DWI cannot be used as a standalone imaging for contouring. Hence, the T2W and DWI were fused with rigid registration and contouring was done after appreciating the normal anatomy from T2W images. While contouring, we ended up having two scenarios:

First when there was a complete or a near complete response where only central disease was seen on T2W with no parametria involvement clinically or radiologically. In these cases, if there were any restricted areas on DWI, they were contoured as GTV BT, contours for HRCTV (volume used for planning) were not changed and the same contours were copied from the T2W to DWI after ensuring that there was no abnormal restriction outside the HRCTV which, in this clinical scenario, would be the entire cervix.

Table 1
MRI protocol.[18]

Protocol	Sequence	Plane orientation	Coverage
Diagnostic MRI	T2 FSE	Para-axial (according to cervix uteri)	Above uterine corpus — inferior border of symphysis pubis/entire vagina if distal vaginal involvement
	T2 FSE	Sagittal	Pelvic side wall (obturator muscle)
	T2 FSE	Para-coronal (according to cervix uteri)	Uterine corpus – cervix – vagina — tumour
	T2 FSE	Axial	Discus L4–L5 — inferior border of symphysis pubis/entire vagina and inguinal regions if distal vaginal involvement
	T1 FSE or 3D GRE without contrast	Axial	Discus L4–L5 — inferior border of symphysis pubis/entire vagina and inguinal regions if distal vaginal involvement
	T1 FSE with contrast	Sagittal	Pelvic side wall (obturator muscle)
	T1 FSE or 3D GRE with contrast	Axial (isotropic 3D GRE)	Uterine corpus – cervix – vagina – tumour
	DWI	Axial	L4–L5 to the introitus
Brachytherapy MRI			
	T2 FSE	Para-axial (according to cervix uteri)	Above uterine corpus — 3 cm below lower surface of vaginal applicator/entire vagina if distal vaginal involvement
	T2 FSE	Para-sagittal (according to cervix uteri)	Pelvic side wall (obturator muscle)
	T2 FSE	Axial	Above uterine corpus — 3 cm below lower surface of vaginal applicator/entire vagina if distal vaginal involvement
	DWI	Axial	L4–L5 to the introitus

Second, presence of parametria, uterine or vaginal involvement on T2W imaging or clinically, or doubtful involvement in the grey zones. In these cases, DWI was used to see the extent of involvement along with the derived ADC maps, if restriction was seen in the parametria, uterus or vagina then the HRCTV contours were extended beyond the cervix to include these abnormal areas.

3.8. Planning for T2W and DWI

For T2W, applicator reconstruction was done with the help of a water dummy in only fifteen cases due to a vendor change. The dummy was inserted into the applicator at the time of CT simulation. After reconstruction and defining the user origin (flange), point A was marked and a dose of 7 Gy was prescribed to point A, initially with standard loading in the tandem and ovoid (2:1)

Now, manual optimization was done at each slice by shortening or increasing the dwell times so that the desired 7 Gy isodose covers the HRCTV contour in a uniform way. After optimization, various DVH parameters were noted, HRCTV D90, HRCTV D100, D2cc to OARs and the structure volumes.

The plan was accepted only when the HRCTV D90 was at least 7 Gy for a 7 Gy prescription, ensuring that the D2cc for the bladder, rectum and sigmoid was not greater than 90%, 70% and 70%, respectively, of the prescribed 7 Gy dose. The patients were treated with the T2W plan.

For the DWI based plan, re-planning was done only for cases in scenario 2, as in scenario 1 the HRCTV was the entire cervix with no disease extending to the parametria, vagina and uterus. Applicator reconstruction for the DWI plan was done on the T2W images due to the distortion associated with titanium based applicators. After contouring on the DWI, the HRCTV and other contours were transferred back to the T2W image and optimization was performed.

3.9. Statistical analysis

The DVH values for HRCTV, GTVBT, HRCTV D90, D100, bladder rectum and sigmoid 2 cc were entered in Microsoft excel 2013. Means along with standard deviations for all mentioned parameters were calculated. The test of significance to compare the means was the paired t-test which was calculated using the SPSS version 23. P value <0.05 was considered statistically significant.

Table 3
Patient characteristics.

Characteristic	Result
Age, median	49 (40–65)
Stage, n, (%)	
IB2	2 (4)
IIA	6 (12)
IIB	17 (34)
IIIA	9 (18)
IIIB	10 (20)
IVA	6 (12)
Tumor volume, median, cc, (range)	95.6 (21–234)
Tumor size MRI, median, (range)	5.2 (3–7.5)
Squamous cell carcinoma, n, (%)	45 (90)
Adenocarcinoma, n, (%)	5 (10)
Nodal mets, n, (%)	
None, n, (%)	24 (48)
Pelvic or paraaortic, n, (%)	26 (52)
HPV, n, (%)	
16	42 (84)
18	8 (16)

4. Results

Details of patient characteristics are provided in Table 3. The GTV volumes contoured on T2W and DWI were 5.25 cc (S.D-2.23) and 5.23 (S.D-2.4), respectively, with volume contoured on T2W being marginally larger but this change was not statistically significant. In the case of HRCTV, the volume contoured on T2W was 28.4 cc (S.D-5.3) which was significantly higher than the volume contoured on DWI 27.1 cc with a p value of 0.003. The complete details of the DVH for various targets and OARs can be seen in Table 4. Out of the fifty patients, eleven had a complete response at brachytherapy and the remaining ones had a partial response. Out of the partial responders, eighteen had parametria involvement at brachytherapy. It was for these eighteen cases that DWI was useful in changing the contours, but in none of these cases an abnormal ADC or an abnormal DWI finding was seen outside the HRCTV. HRCTV D90 and D100 were used to evaluate the plan. The minimum of 7 Gy to

Table 4
DVH parameters for coverage (single fraction).

Parameters	Coverage (cGy), dose to 2 cc OAR (cGy) and volume (cc)		p Value
Imaging	T2W	DWI	
GTV vol	5.25 (SD 2.2)	5.23 (SD 2.4)	0.8
HRCTV vol	28.4 (SD 5.3)	27.1 (3.5)	0.003
HRCTV D90	735 (SD 37.5)	741 (SD 34.9)	0.006
HRCTV D100	441 (SD 22.5)	444.5 (SD20.9)	0.006
Bladder D2cc	551.3 (SD 28.1)	551 (SD 27.7)	0.9
Rectum D2cc	404.3 (SD 20.6)	404.1 SD (20.6)	0.8
Sigmoid D2cc	330.8 (SD 16.9)	330.5 (SD 16.5)	0.85
Point A dose mean	695 (SD 35)	701 (SD 32.4)	0.006

the HRCTV D90 was required to accept the plan. The mean HRCTV D90 dose for T2W was 735 cGy (S.D-37.55), this was lower when compared to 740.9 cGy (S.D-34.9) achieved on DWI and this change was statistically significant (p value = 0.006). HRCTV D100 was also higher for the DWI based plan when compared with the T2W plan: 444.5 vs. 441 cGy (p value 0.006).

For OARs, the mean D2cc for the bladder in the DWI based plan was 551 cGy, which was comparable with the T2W plan (551.32) and was not found to be significantly different. The mean D2cc for the rectum in the DWI based plan was 404.1 cGy, which was also comparable with the T2W plan (404.3) and the same was found to be true for sigmoid, with a D2cc of 330.8 (T2W) and 330.5 (DWI). Fig 5 (Supplementary material) depicts a graphical representation of the above findings. The clinical results in terms of response, survival and toxicity of this study can be found elsewhere.[20]

5. Discussion

MRI is the gold standard to delineate target volumes in IGABT for cervical cancer.[4,21] T2W imaging is a form of anatomical imaging and gives no information on the functional aspect of the disease. We tried to investigate the role of functional imaging in brachytherapy treatment planning for cervical cancer, as post EBRT it is sometimes difficult to differentiate between a normal and a tumor tissue. By using DWI we wanted to see whether uncertainties in the contouring of the grey zones can be reduced, and whether any tumor tissue exists outside the HRCTV volume that cannot be picked up on T2W imaging.

In this study, when comparing the volumes contoured on T2W and DWI, it was found that two cases who had persistent parametrial disease at the time of brachytherapy, their GTVBT was larger on DWI when compared to T2W imaging (Fig. 3). In other 2 cases, where clinically and radiologically complete response was documented, DWI showed mild restriction in a small area in the cervix (Figs. 1 and 2). The mean GTV contoured in these cases was around 1.3 cc. When compared with T2W which had 0 cc of GTV. In the remaining 46 cases GTVBT was found to be either smaller or similar on DWI when compared with T2W, which resulted in a mean GTVBT volume being lower, but this change in volume was not found to be statistically significant. HRCTV, the volume that is taken for planning, was not changed in DWI for cases that had complete or near complete response. This was done as the GEC ESTRO recommends including the entire cervix in the HRCTV, even if no disease is seen during brachytherapy. Only 18 cases had disease outside the cervix on T2W imaging. DWI was used to change the contours of HRCTV when an abnormality was detected. HRCTV contoured on DWI extended beyond the cervix but was still found to be smaller than the corresponding HRCTV on T2W imaging; hence, HRCTV DWI was significantly smaller than T2W contours with the mean HRCTV volume being 28.4 cc for T2W and 27.1 cc for DWI. Though this result was statistically significant, we feel such a small decrease in volume will have little clinical significance. We also found that no abnormal restriction was present outside the HRCTV volume, which only shows that the volumes hypothesized by GEC ESTRO cover almost all the diseased area on functional imaging. However, this finding does not correlate with the study done by Haack et al.,[16] where it was found that 1/3rd of the abnormal ADC (1.2×10^{-3} mm/s$^{2)}$ was present outside the HRCTV. Nevertheless, clinically, IGABT has shown to have superior local control (90–97% L.C 3 years),[3,20] and the absence of abnormal ADC outside the HRCTV contours according to this study might be the reason.

While delineating the HRCTV, DWI cannot be used independently for contouring, as normal pelvic anatomy is poorly visualized. Hence, in our study contouring was done only on fused images in the presence of a radiologist. It was also seen that the GTVBT contoured on DWI had a better edge contrast when compared with T2W which correlates with the finding reported by Esthapann et al.[11]

HRCTV D90 and D100 was better in the DWI plan when compared with the T2W plan. This is probably so because the volumes, especially HRCTV, were significantly smaller on DWI, which resulted in the 7 Gy isodose line almost completely covering the target. This increase in coverage could be achieved without significantly increasing the dose to the OAR, which, theoretically, could increase local control. The D2cc for OARs did not change significantly and we found little utility in incorporating DWI into the IGABT workflow. DWI does not serve any purpose in cases with complete or near complete response at the time of brachytherapy as the entire cervix is included in the HRCTV. In the case of patients with persistent parametrial disease, again, the abnormal ADC was inside the HRCTV contours. DWI might only be of use in IGABT if optimization is also done for GTVBT and a higher dose is delivered, similar to a few prostate trials.[22]

There are certain limitations of this study and DWI imaging. 1.5T was used for imaging which results in distortion, and high signal to noise ratio for DWI imaging.[23] A 3T MRI would create less noise and a better image but it also results in distortions when the brachytherapy applicator is in situ.[24] Susceptibility artefacts are also quite common with DWI and can result from either the applicator or when the rectum or intestines are close to the cervix.,[16,25] In our study we used B0 maps, hence the susceptibility artefacts were reduced to some extent. It is also important to note that DWI should not be used for applicator reconstruction due to applicator distortion, which can be seen in Fig. 2. Because of geometric uncertainties in applicator reconstruction, we recommend that DWI should not be used as a standalone imaging for brachytherapy. The only purpose of DWI is to ensure that no functionally abnormal areas are missed by the anatomical T2W imaging. Going by the results of our study the chances of having an abnormal ADC outside the HRCTV contours are less.

6. Conclusion

To summarise, volumes contoured using DWI were found to be smaller when compared with T2W imaging, this resulted in a

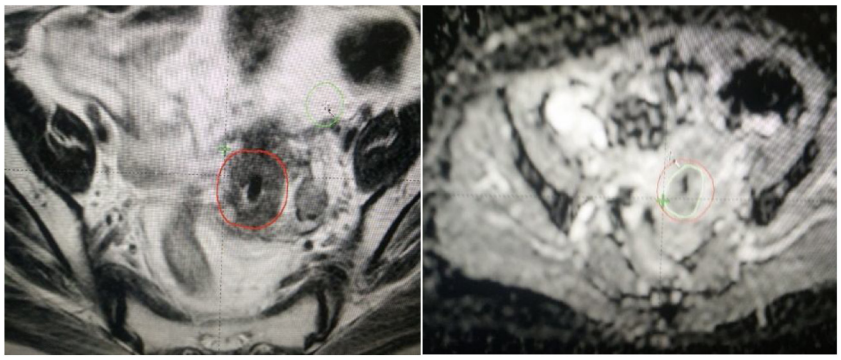

Fig. 1. Image A is a T2W axial MRI section showing a very small central disease component. Image B is the axial section of the ADC map in the same patient. A central restriction is noted around the tandem. The distorted tandem can also been seen, which creates a geometrical uncertainty during applicator reconstruction.

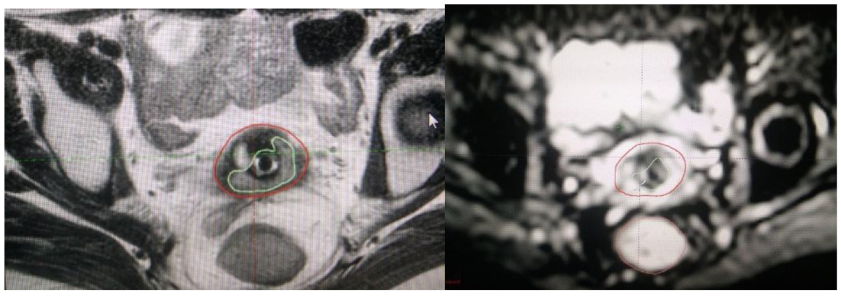

Fig. 2. Image C of a patient with significant central disease on T2W MRI, but a smaller central disease on ADC maps. The functionally abnormal zone is inside the HRCTV.

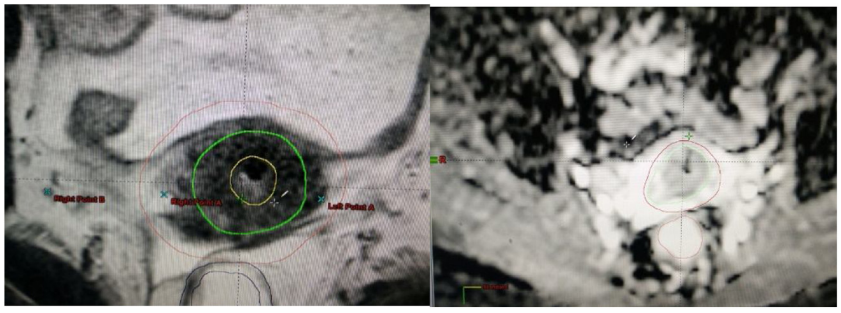

Fig. 3. Image E of a patient with persistent parametrial disease at the time of brachytherapy clinically, T2W imaging shows a grey zone in the right parametria, the ADC map of the same patient in image F shows restriction in the right parametria with a sharper edge contrast when compared to the T2W image. Contours were extended on the ADC but it was still within the HRCTV.

better coverage to the target without increasing dose to the OAR. HRCTV contoured using DWI was within the HRCTV recommended by GEC ESTRO, suggesting that the HRCTV contoured using these guidelines covers all functionally abnormal areas found on DWI. Further prospective clinical studies that allow dose escalation in the functionally abnormal zones found on DWI would be interesting.

DWI as a form of functional imaging should only be used as a supplement to T2W imaging, its addition might provide extra information regarding the extent of the residual disease, especially in cases that have persistent parametrial disease at the time of brachytherapy

DWI should not be used as a standalone imaging due to geometric and applicator reconstruction uncertainties.

Disclosure

The authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

Conflict of interest

None declared.

Funding

Nil.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.rpor.2020.08.008.

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