MRI Assessment of Cervical Cancer for Adaptive Radiotherapy

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Purpose: To assess the importance of the information obtained from MRI for adaptive cervix cancer radiotherapy.
Patients and Methods: 49 patients with cervix cancer, treated by external-beam radiotherapy (EBRT) and MRI-assisted high-dose-rate brachytherapy ± concomitant cisplatin, underwent MRI at diagnosis and at the time of brachytherapy fractions. 190 MRI examinations were performed. Pretreatment scans were correlated with clinical examination (CE) findings. Measurements in 3-D of the tumor extension and also of the distance from the tumor to the pelvic side wall were performed using both MRI and CE. The tumor volume regression induced initially by EBRT and the subsequent regression after each brachytherapy fraction were assessed.
Results: MRI and CE showed 92% agreement in overall parametrial staging and 73% agreement in terms of vaginal involvement. There was, however, disagreement in parametrial side (right/left) classification in 25% of the parametria examined. These were patients with unilateral displacement of the cervix and contralateral invasion of the parametrium. The mean tumor volume on the pretreatment MRI scan (GTVD) was 61 cm^3. At the time of the four brachytherapy fractions the mean was 16 cm^3, 10 cm^3, 9 cm^3, and 8 cm^3, defined as the GTVBT plus the gray zones in the parametria.
Conclusion: CE and MRI findings agree well in terms of overall staging. The clinical assessment of side-specific parametrial invasion improved when having access to the additional knowledge obtained from MRI. The greatest decrease in tumor volume occurs during EBRT, whereas tumor regression between the first and subsequent brachytherapy fractions is minor.

Key Words: Cervical cancer · Brachytherapy · MRI · Target definition · Tumor regression

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MR-tomographische Beurteilung des Zervixkarzinoms für die adaptive Radiotherapie

Ziel: Ermittlung der Bedeutung der MRT für die adaptive Radiotherapie des Zervixkarzinoms.
Patienten und Methodik: 49 Patientinnen mit Zervixkarzinom, behandelt mittels Teletherapie und MRT-gestützter High-Dose-Rate-Brachytherapie ± konkomitante Cisplatingabe, erhielten eine MRT zum Zeitpunkt der Diagnose und zum Zeitpunkt der Brachytherapiefraktionen. Insgesamt wurden 190 MRT-Untersuchungen durchgeführt. Der Befund der diagnostischen MRT wurde dem der klinischen Untersuchung gegenübergestellt. Es erfolgten Messungen der Tumorausdehnung in 3-D und der Entfernung zwischen Tumor und Beckenwand. Zusätzlich wurden die primär durch die Teletherapie und anschließend die durch jede Fraktion der Brachytherapie verursachte Regression des Tumorvolumens ermittelt.
Ergebnisse: Die Übereinstimmung zwischen MRT und klinischer Untersuchung für die Ermittlung des parametranen Tumorstadiums betrug 92% (Tabelle 1) und bezüglich der vaginalen Beteiligung 73% (Tabelle 3). Die seitengetrennte Beurteilung der Parametrien (links/rechts) zeigte jedoch inkongruente Ergebnisse in 25% der untersuchten Parametrien (Tabelle 1). Dabei handelte es sich um Patientinnen mit unilateraler Lageveränderung der Zervix und kontralateraler parametraner Infiltration (Abbildung 1). Das mittlere Tumorvolumen bei den diagnostischen MRT-Untersuchungen (GTVD) betrug 61 cm^3 (Abbildung 2). Die Bestimmung der Tumorvolumina der vier einzelnen Fraktionen der Brachytherapie (GTVBT plus graue Zonen in den Parametrien) ergab einen Mittelwert von jeweils 16 cm^3, 10 cm^3, 9 cm^3 und 8 cm^3 (Abbildung 2).
Schlussfolgerung: Die klinische Untersuchung und die MRT zeigen eine gute Übereinstimmung bezüglich der Beurteilung des Gesamttumorstadiums. Die Objektivität der Ergebnisse der seitengetrennten klinischen Untersuchung der Parametrien wird durch die Hinzuziehung der MRT deutlich verbessert. Der Hauptteil der Tumorregression erfolgt während der Teletherapie, wobei die Tumorregression zwischen den einzelnen Fraktionen der Brachytherapie als gering einzuschätzen ist.

Schlüsselwörter: Zervixkarzinom · Brachytherapie · MRT · Zielgebietsdefinition · Tumorrückbildung

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Introduction

The treatment of choice for locally advanced cervix cancer comprises external-beam radiotherapy (EBRT), intracavitary (± interstitial) brachytherapy, and concomitant cisplatin-based chemotherapy [4, 8, 11, 12, 17, 22, 28, 37, 41]. At present, significant improvement in outcome can mostly only be expected from the integration of modern conformal radiotherapy techniques such as intensity-modulated radiation therapy (IMRT) and 3-D image-guided brachytherapy (IGBT) [3, 10, 15, 16, 31, 35, 38, 40, 42].

The value of MRI for the delineation procedure in IGBT has already been validated by us [9]. The gross tumor volume at diagnosis (GTV_D) and at brachytherapy (GTV_{BT}), the high-risk clinical target volume (HR-CTV), the anatomic structures of interest (bladder, rectum, sigmoid, parametria), and the applicator can all be accurately imaged [9]. However, despite this, in the recently published GYN GEC ESTRO recommendations on the clinical implementation of IGBT, it is suggested that the information obtained from both MRI and clinical examination (CE), even if weighted to different degrees, has to be taken into account for the target contouring process [19, 39].

In our study, the pretreatment scans were correlated with CE findings, based on a prospectively planned protocol. MRI and CE were used for overall staging and for describing the topography of disease spread. Measurements in 3-D of the tumor extension and also of the distance from the tumor to the pelvic side wall were performed using both MRI and CE.

In spite of the proven relevance of tumor volume changes on topography during radiotherapy, most of the observations monitoring tumor volume using MRI, are directed toward the prognostic value of tumor regression [1, 2, 13, 29, 30, 32, 42]. The possible effect of the MRI-determined factors on adaptive radiotherapy is, to date, only poorly investigated. However, to the best of our knowledge, there are no reports of volume measurements at the time of all brachytherapy fractions with the applicator in place. These will include parts of the intracervical and extracervical regions (GTV_{BT} and gray zones) of a target which is assumed to have a high probability of carrying tumor load, i.e., the HR-CTV [19]. The knowledge of the volume reduction of these regions is of major importance since their magnitudes and the dose (mainly the D_{90}) they receive during IGBT are predictive for local control [7].

Patients and Methods

Patients

The study population consisted of 49 biopsy-proven cervix cancer patients treated between 1998 and 2003 by definitive radiotherapy in the Department of Radiotherapy of the Medical University of Vienna, Austria. All received 45–50 Gy EBRT delivered by a four-field box technique with CT-based treatment planning, followed by four to six fractions of 7 Gy MRI-based high-dose-rate (HDR) brachytherapy. 84 Gy (EQD2) were prescribed to the HR-CTV [24]. Both types of examination, MRI and CE, were based on a prospective protocol. The FIGO stage distribution was as follows: IB1 n = 5, IIA n = 1, IIB n = 27, IIIA n = 1, IIIB n = 13, IVA n = 1, IVB n = 1. The median age was 59 years (range: 37–79 years). The histological subtype was squamous cell carcinoma in 37/49 cases, adenocarcinoma in 8/49 with rare histological subtypes in 4/49. A total of 42/49 received concurrent chemotherapy with cisplatin (5×40 mg/m^2).

MRI Examination

All 49 patients underwent MRI prior to EBRT and at the time of the first brachytherapy fraction after having received a mean dose of 37 Gy EBRT. A total of 190 MRI examinations were performed using a 0.2-Tesla low field system (Siemens Magnetom Open-Viva®). MRI scans with the applicator in place were performed prior to the second fraction in 39/49, prior to the third fraction in 31/49, prior to the fourth fraction in 16/49, and prior to the fifth and sixth fractions in 6/49 patients. In 7/49 was marking gel in the vagina used for the pretreatment scans. Our MRI technique has previously been described by Dimopoulos et al. [9]. MR images were retrospectively and independently interpreted by a radiologist (T.H.H.) and a radiation oncologist (J.C.A.D.) without any knowledge of the CE findings. Anatomic drawings were used for the recording of findings at diagnosis and at the time of each brachytherapy fraction.

Tumor Staging Using MRI

Tumor invasion of the parametria, vagina, bladder and rectum was assumed, as described by Hricak et al. [21] and Boss et al. [2].

Definition of GTV and Gray Zones

The GTV at the time of diagnosis (GTV_D) was defined by the visible tumor mass with a high signal intensity on T2-weighted images. The GTV on images after EBRT and during brachytherapy (GTV_{BT}) included the high signal intensity mass on T2-weighted images. Gray zones of intermediate signal intensity in the parametria at the time of brachytherapy, and at the exact location of tumor tissue prior to EBRT were considered to be residual pathologic tissue [2, 14, 20].

Clinical Examination

Clinical staging was performed according to FIGO criteria by both the referring gynecologist and the radiation oncologist. Clinical findings were recorded in 3-D using anatomic drawings (axial, coronal and sagittal views) in addition to recording the speculum examination results.

Pathologic Features Analyzed

Two features were analyzed from both the MRI and the CE at the time of diagnosis: (1) side-specific invasion of the parametria, and invasion of the vagina, bladder and rectum; (2) tumor dimension and distances to the right and left pelvic wall.

Additionally for MRI, tumor dimensions were measured at the time of each brachytherapy fraction. The tumor volume at the time of diagnosis is the GTV_D and at the time of brachytherapy this tumor volume comprises the GTV_{BT} and the gray zones. To calculate the tumor volume, the ellipsoid formula (height × width × thickness × π/6) was used [29].

Statistical Analysis

SPSS software was used for the statistical analyses (version 11.0.1. for Windows, © SPSS Inc. 1989–2001) of linear regression for an estimation of the Pearson correlation coefficient r.

Results

Results for the MRI and CE assessments of side-specific parametrial involvement are given in Table 1. There was only agreement between CE and MRI in 28/49 patients (57%). Results for the assessments of vaginal involvement are given in Table 2.

CE and MRI findings for tumor width and for tumor distance to the pelvic walls are not well correlated for GTV_D width and distances from the tumor to the pelvic walls. The Pearson correlation coefficient, r, for tumor width gives r = 0.70, and for tumor distance to right and left pelvic walls gives r = 0.64 and r = 0.58. Visually, the lack of correlation is obvious from the scatter diagrams constructed from the data. Table 3 shows the differences in measurement between MRI and CE from which it is seen that for tumor width there is a trend toward CE assessing the width as larger than the MRI assessment. There is also such a trend toward MRI assessing the distance to pelvic walls as larger than the CE assessment.

Results for the average GTV as recorded on MRI scans are given in Figure 1. It is seen that the GTV reduces dramatically from 61 cm^3 (range: 1–381 cm^3) prior to EBRT to 16 cm^3 at the first brachytherapy fraction and then changing very little to 8 cm^3 at the time of the fourth brachytherapy fraction. The volumes measured at the time of a brachytherapy fraction are those defined by GTV_{BT} plus the gray zones.

Patient rates with a volume decrease of ≥ 30 cm^3, ≥ 40 cm^3, and ≥ 50 cm^3 during EBRT were 49% (n = 24), 37% (n = 18), and 31% (n = 15), respectively. Table 4 gives the tumor volume changes between various defined times: before EBRT, and at first, second, and third brachytherapy fractions.

Discussion

It has been shown that the favorable characteristics of MRI enable a systematic 3-D image-based treatment-planning process with accurate 3-D delineation of relevant structures for IGBT [5, 9, 27, 33]. Nevertheless, there is some limitation in the accuracy of detecting residual disease after EBRT and also during brachytherapy. Therefore, during the brachytherapy target delineation procedure the findings obtained from both the MRI and the CE, even if weighted in importance to different degrees, must be taken into account to provide an accurate as possible assessment of the GTV and HR-CTV [19, 36, 39].

Table 1. Parametrial disease assessment comparison: MRI versus clinical examination (CE). FREE: free of parametrial invasion; LT: invasion of left side only; RT: invasion of right side only; RT + LT: invasion of both sides. The numbers in the body of the table show the correlations between MRI and CE.

Tabelle 1. Vergleich für die Bestimmung der parametranen Infiltration: MRT versus klinische Untersuchung (CE). FREE: keine parametrane Infiltration; LT: Infiltration der linken Seite; RT: Infiltration der rechten Seite; RT + LT: Infiltration beider Seiten. Die Zahlen im Tabellenkörper beziehen sich auf die Korrelation zwischen MRT und klinischer Untersuchung.

	FREE (MRI)	RT (MRI)	LT (MRI)	RT + LT (MRI)	Totals (MRI)
FREE (CE)	**5**	0	0	3	8
RT (CE)	1	**0**	0	9	10
LT (CE)	0	0	**3**	6	9
RT + LT (CE)	0	2	0	**20**	22
Totals (CE)	6	2	3	38	**49**

Table 2. Vaginal disease assessment comparison: MRI versus clinical examination (CE). FREE: free of vaginal invasion; INV: vaginal invasion present; UNC: uncertain about vaginal invasion. The numbers in the body of the table show the correlations between MRI and CE.

Tabelle 2. Vergleich für die Bestimmung der vaginalen Infiltration: MRT versus klinische Untersuchung (CE). FREE: keine vaginale Infiltration; INV: vaginale Infiltration vorhanden; UNC: Unklarheit bezüglich vaginaler Infiltration. Die Zahlen im Tabellenkörper beziehen sich auf die Korrelation zwischen MRT und klinischer Untersuchung.

	FREE (MRI)	INV (MRI)	UNC (MRI)	Totals (MRI)
FREE (CE)	**23**	1	1	25
INV (CE)	8	**13**	3	24
UNC (CE)	0	0	**0**	0
Totals (CE)	31	14	4	**49**

Table 3. Comparison at time of diagnosis of three different tumor parameters measured using MRI and clinical examination (CE) for the study population of 49 patients.

Tabelle 3. Vergleich für die Messung von drei Tumorparametern zum Zeitpunkt der Diagnose an 49 Patientinnen: MRT versus klinische Untersuchung (CE).

Measurement difference CE–MRI (cm)	Patients (n) Tumor width	Tumor to right pelvic wall	Tumor to left pelvic wall
4	1	0	0
3	4	0	0
2	6	2	1
1	15	4	4
0	7	14	11
–1	12	7	14
–2	1	11	11
–3	2	8	7
–4	1	3	1

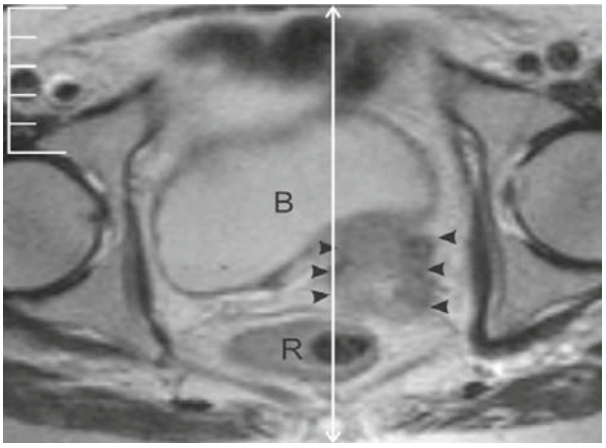

Figure 1. Diagnostic axial T2-weighted MRI image of a 67-year-old patient with FIGO IIB cervical cancer. MRI findings are indicating bilateral parametrial invasion (arrowheads), complete replacement of the cervical rim by the tumor and dislocation of the cervix from the midline to the left side. The vertical white line is drawn through the midline. In contrast to the MRI findings, CE suggested only unilateral invasion of the parametrium on the left side. B: urinary bladder; R: rectum.

Abbildung 2. Transversales T2-gewichtetes MRT-Bild einer 67-jährigen Patientin mit Zervixkarzinom FIGO IIB zum Zeitpunkt der Diagnose. In der MRT zeigt sich eine beidseitige parametrane Infiltration (Pfeilspitzen) mit kompletter Ersetzung des Zervixstromas durch den Tumor. Die Zervix ist von der Mittellinie auf die linke Seite verlagert. Die weiße vertikale Linie entspricht der Mittellinie. Im Unterschied zu den MRT-Befunden zeigte sich in der klinischen Untersuchung lediglich eine einseitige parametrane Infiltration links. B: Harnblase; R: Rektum.

In this and other series, agreement regarding parametrial staging was excellent (92%) [2]. However, in terms of side-specific parametrial invasion the level of agreement decreased (75% [74/98 parametria]).

An interesting observation for the 15 patients with unilateral invasion assessed by CE was that on MRI the cervix was dislocated to one side and that both parametria were invaded (Table 1). An example of this situation is shown in Figure 1.

In a meta-analysis, Boss et al. [2] have shown the limited ability of MRI to define the extent of vaginal invasion. Our findings showed that the extent of agreement between MRI and CE for vaginal invasion was 36/49 when the upper third was examined (Table 2), and 41/49 when the middle third of the vagina was examined. The use of marking gel in the vagina on the pretreatment MRI scan enables better imaging of the vaginal fornices, thus being able to reveal any signs of invasion and of exophytic tumor growth [43]. However, this was applied only in seven patients. In this small group, the agreement for vaginal invasion between MRI and CE was 6/7 compared to 28/42 for patients without gel.

Adaptive radiotherapy with repetitive imaging and treatment planning is obviously a more precise strategy than using only techniques with a single imaging and planning process [1, 18, 25, 26, 34, 42]. IGBT represents an adaptive boost modality which is applied at the end of EBRT. Treatment planning is repeated for every brachytherapy fraction and the dose is prescribed to a shrinking target (HR-CTV). The time-related topography of the tumor/target, as well as of the organs at risk are taken into consideration [24]. Studies have demonstrated that the magnitude of tumor volume regression influences organ topography and, consequently, the dosimetric results of IMRT [1, 25, 26, 42].

In a treatment-planning study, Van de Bunt et al. [42] investigated whether the addition of a single IMRT replan after delivering 30 Gy EBRT resulted in significant reduction in dose to the bowel. In a dose-volume histogram analysis they found that the volume of the bowel receiving > 95% of the prescribed dose decreased significantly in those cervix cancer patients who had substantial tumor regression on MRI (> 30 cm^3, average 45% or 32 cm^3). In our study, we found for EBRT, 49% (24/49) of patients with a volume reduction of > 30 cm^3, 37% (18/49) with a reduction of > 40 cm^3 and 31% (15/49) with a reduction of > 50 cm^3.

If more frequent imaging is performed during the course of IMRT we can assume this must have an impact on organ sparing in a selected group of patients with rapidly involving tumors and a significant proportion of volume reduction during the last third of EBRT. However, this must be validated by future studies including those concerning image-guided radiotherapy.

It is emphasized that the volume measurements at the time of brachytherapy comprised the intracervical and extracervical areas which are assumed to have a high probability of carrying tumor load (GTV_{BT} and gray zones) and hence represent the core parts of the HR-CTV [19]. A knowledge of the volume reduction of these regions between subsequent brachytherapy fractions is also of major importance, since it has been shown that their magnitudes and the dose (D_{90}) they receive during IGBT are predictive for local control [7]. However, future investigations on the prognostic value of volume reduction, as well as of other factors, like the expression of endogenous tumor markers, e.g., HIF-1α (hypoxia-inducible factor-1α) are necessary [6].

An important question which still remains unanswered is whether tumor regression between subsequent HDR fractions is influencing the IGBT application technique. If we assume that there is only a minor decrease in the absolute tumor volume during HDR brachytherapy, as revealed by the results of our study (mean reduction of 8 cm^3), then it can be expected that only minor modifications of the application technique are required. Now in the 21st century, unlike in previous years when MRI guidance was not available, we can draw conclusions about the interapplication variation of the target [23].

According to our findings, tumor regression during HDR brachytherapy certainly appears to have some impact on tumor topography, since the mean volume (see Figure 2) was re-

Table 4. Tumor volume changes between defined event times measured using MRI. BT: brachytherapy; EBRT: external-beam radiotherapy.

Tabelle 4. Veränderungen des mittels MRT bestimmten Tumorvolumens zwischen definierten Zeitpunkten. BT: Brachytherapie; EBRT: Teletherapie.

Event difference	Patients (n)	Number of patients (percentage) for a tumor volume regression defined as a percentage of the volume "before EBRT"		
		Regression > 50%	Regression 50–75%	Regression > 75%
Before EBRT and 1st BT	49	36 (74)	21 (43)	15 (31)
Before EBRT and 2nd BT	39	35 (90)	10 (26)	25 (64)
Before EBRT and 3rd BT	31	28 (90)	7 (22)	21 (68)
1st BT and 2nd BT	39	10 (26)	0	0
2nd BT and 3rd BT	31	3 (11)	0	0

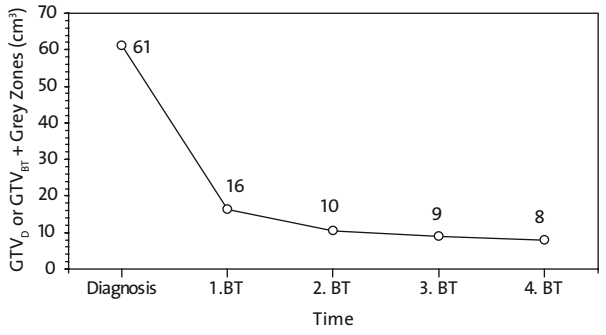

Figure 2. Average GTV_D or GTV_{BT} + gray zones volume variation measured on MRI scans. At time of diagnosis the volume is only the GTVD, whereas for all BT fractions the volume is GTV_{BT} + gray zones.

Abbildung 2. Mittlere Variation der Volumina von GTV_D oder GTV_{BT} + graue Zonen, mittels MRT bestimmt. Zum Zeitpunkt der Diagnose ist das gemessene Volumen durch das GTV_D und zum Zeitpunkt der Fraktionen der Brachytherapie durch GTV_{BT} + graue Zonen definiert.

duced from 16 cm^3 at the first fraction to 10 cm^3 at the second fraction, and then to 9 cm^3 and 8 cm^3 at the third and fourth fractions.

Finally, we suggest that in the future, it would be interesting to study the degree of correlation of the increase of the D90HR-CTV with the systematic shrinkage of the HR-CTV and to specify patient subgroups with features (e.g., limited or slow-responding disease) which would make a single plan technique an optimal strategy.

Conclusion

Although CE and MRI assessments agree well in terms of overall staging, clinical assessment of side-specific parametrial invasion is improved by the additional knowledge obtained from MRI.

The greatest decrease in tumor volume occurs during EBRT, of the order of 75% reduction, whereas regression throughout the time period of the brachytherapy fractions is minor, only some 10%. Based on these findings, it appears reasonable to apply repetitive imaging and treatment planning during the course of modern EBRT techniques. For the first fraction of the adaptive IGBT boost it is imperative to define the target by taking the major amount of tumor shrinkage during EBRT into account. For the subsequent fractions only minor modifications can be expected.

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