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THE ROLE OF MAGNETIC RESONANCE IMAGING IN THE PREOPERATIVE STAGING OF INVASIVE CERVICAL CANCER

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Abstract

Aim: To evaluate the diagnostic performance of magnetic resonance imaging (MRI) in the preoperative evaluation of patients with invasive cervical cancer, in terms of parametrial involvement, lymph node metastases and tumor size.

Methods: The retrospective study included 48 patients with histologicaly verified invasive cervical cancer, treated surgically with radical hysterectomy and pelvic lymphadenectomy in the period January 2012 - December 2013. All patients had preoperative MRIs. The reference standard for comparison was the histopathologic findings from the operative specimens.

Results: Six patients in our study (12.5%) had parametrial involvement verified on hystopathologic analysis. MRI identified probable parametrial involvement in 8 (16.7%) patients. The sensitivity, specificity, positive predictive value and negative predictive value (PPV and NPV) of MRI in detecting parametrial involvement were 83.3%, 92.7%, 62.5% and 97.5%, respectively. Histopathologic analysis of the operative specimens identified 11 (22.9%) patients with lymph node metastases. The MRI scans detected probable lymph node metastases in 15 (31.3%). The sensitivity, specificity, PPV and NPV of MRI in detecting lymph node metastases were 63.6%, 78.4%, 46.7% and 87.9%, respectively. MRI was better at estimating the tumor size (r_s=0.67, p<0.001) when compared to clinical examination (r_s=0.34, p<0.001).

Conclusion: Preoperative MRI showed low PPV in detecting lymph node metastases and parametrial involvement. MRI was superior, compared to the clinical examination, in the estimation of tumor size. Further research is required to determine the cost-effectiveness of using MRI instead of conventional clinical staging tests.

Keyword: cervical cancer, MRI, evaluation, lymph nodes, parametria

УЛОГАТА НА МАГНЕТНАТА РЕЗОНАНЦА ВО ПРЕДОПЕРАТИВНОТО ОДРЕДУВАЊЕ НА СТАДИУМОТ НА БОЛЕСТА КАЈ ПАЦИЕНТКИ СО ИНВАЗИВЕН ЦЕРВИКАЛЕН КАРЦИНОМ

АПСТРАКТ

Цел: Да се евалуираат дијагностичките перформанси на магнетната резонанца (MRI) во предтретманската евалуација на пациентки со инвазивен цервикален карцином, особено во поглед на инволвираност на параметриумите, метастази во лимфните јазли и туморскиот дијаметар.

Методи: Во оваа ретроспективна студија беа вклучени вкупно 48 пациентки со хистолошки верифициран инвазивен цервикален карцином, кои беа оперативно третирани со радикална хистеректомија и пелвична лимфаденектомија во периодот

од јануари 2012 до декември 2013 и кај кои предоперативно беше направена магнетната резонанца (MRI). Како референтен стандард за споредба беа користени хистопатолошките наоди од оперативниот материјал.

Резултати: Шест од пациентките во нашата студија (12.5%) имаа продор на туморот во параметријалното ткиво верифициран при хистопатолошка анализа. MRI идентификуваше веројатен продор на туморот во параметријалното ткиво кај 8 (16.7%). Сензитивноста, специфичноста, позитивната и негативната предиктивна вредност (PPV и NPV) на MRI во детекцијата на продор на туморот во параметриумите беа 83.3%, 92.7%, 62.5% и 97.5%, соодветно. Хистопатолошката анализа на оперативниот материјал идентификуваше 11 (22.9%) пациентки со метастази во пелвичните лимфни јазли. MRI скеновите детектираа веројатно позитивни лимфни јазли кај 15 (31.3%) од пациентките. Сензитивноста, специфичноста, PPV и NPV на MRI во детекцијата на "позитивни" лимфни јазли беа 63.6%, 78.4%, 46.7% и 87.9%, соодветно. MRI беше подобра во проценка на дијаметарот на туморот (r_s=0.67, p<0.001) во споредба со клиничкиот преглед (r_s=0.34, p<0.001).

Заклучок: Предоперативната MRI покажа ниска PPV за детекција на метастази во лимфните јазли и пробој на туморот во параметриумите. MRI беше супериорна во однос на клиничкиот преглед за проценка на големината на туморот. Потребни се натамошни студии за да се одреди кост-ефективноста од користењето на MRI наместо конвенционалните клинички стејџинг тестови.

Клучни зборови: цервикален карцином, MRI, евалуација, лимфни јазли, параметриуми

Introduction

Invasive cervical cancer is the second most common malignant neoplasm in the female population in the world[1]. The incidence is estimated at around 529000 new cases annually, which corresponds with an age standardized incidence rate (ASR) of 15.2 per 100000[2]. In 2008, there were 274 883 lethal outcomes associated with this disease, which means that invasive cervical cancer accounts for 8% of the total mortality associated with malignant neoplasms in the female population[2]. Still, the developed countries mark a continued decline of the incidence and mortality rates, starting from the 1950s until today. This decline is attributed to the wide implementation of the cytological screening programs which facilitate the early detection of the disease in a precancerous state[3]. Additionally, the improvement of surgical and radiological treatment techniques further improved the survival rates in patients with invasive cervical cancer.

Macedonia is a country with a high incidence rate of cervical cancer. There are approximately 200 new cases registered each year, making cervical cancer the second most common neoplasm in the female population of the country. According to the GLOBOCAN data for 2008, Macedonia had an ASR 22.0 per 100000 women annually, which is more than double the ASR of the developed European region (10 per 100000 women).

The prognosis and survival rates in patients with invasive cervical cancer depend greatly on disease stage. The treatment modality is determined by the stage[4-6]. Patients with stage IB-IIA cervical cancer can be treated surgically with radical hysterectomy. In patients with locally advanced cervical cancer (stage IIB-IVA), radical surgical treatment is not a recommended therapeutic option. Instead, these patients are treated by a combination of radiation and cisplatin based chemotherapy[7-9]. Patient that had radical hysterectomy due to early stage cervical cancer, and that have a high risk of disease recurrence, require

additional adjuvant radiation and/or chemotherapy in order to reduce the incidence of local recurrences and improve survival[10-16].

The errors in the staging before the beginning of the treatment are associated with worse prognosis[17]. The International federation of gynecology and obstetrics (FIGO) staging system is based primarily on clinical exam. When compared to surgical staging, the clinical staging by the FIGO criteria underestimates 20-30% of the stage IB patients, 23% of the stage IIB patients and almost 40% of the stage IIIB patients, and overstages approximately 64% of the patients stage IIIB[18-21], which corresponds to an accuracy of 60%. The biggest problem in these patients is the inability to diagnose lymph node metastases[22-24].

According to the previous revision of the FIGO criteria in 2003, the pre-treatment evaluation of patients with invasive cervical cancer comprises of mandatory clinical exam under anesthesia, chest x-ray, intravenous pyelogram, and optional invasive procedures such as cystoscopy and sygmoidoscopy to evaluate the local invasion of close visceral organs[25]. Still, these tests were less than adequate in providing additional information about the loco-regional spread of the disease, especially in terms of nodal status and distant metastases. The discrepancy between different physicians in the determination of clinical stage, according to the study of Bipat et al.[26] ranged between 65-90%. The consequences of the discrepancy were over- and understaging of a significant portion of patients which lead to inadequate treatment and inability to compare outcomes.

The improvement of the imaging modalities, especially computerized tomography (CT) and MRI in the 1980s led to the decrease in use of additional invasive tests listed in the 2003 FIGO recommendations. Most authors consider MRI the most reliable imaging modality for patients with cervical cancer. Although a few multicenter studies showed that spiral CT had similar accuracy to MRI, it had greater inter-observer variability in the same population[27, 28]. As a result of the better soft tissue resolution, and the multiplanar imaging capability, MRI provides better results in the evaluation of the local spread of the disease[29, 30]. Still, these imaging methods are not widely used in countries with a high incidence of cervical cancer. In addition, there is no scientific consensus in terms of the most appropriate imaging modality[26, 27]. Because of that, the revised FIGO recommendations from 2009[31] encourage but do not require the use of imaging modalities. The new recommendations render the formerly required tests such as cistoscopy, sygmoidoscopy and intravenous pyelography as optional.

Aim

The aim of the study was to evaluate the diagnostic performance of MRI in pre-treatment evaluation of patients with invasive cervical cancer, in terms of parametrial involvement, lymph node metastases and tumor size, using histopathology as a reference standard.

Materials and methods

This retrospective study included all patients with verified invasive cervical cancer, treated surgically, based on a previous clinical evaluation at the University clinic of gynecology and obstetrics (UCGO), Medical faculty, University "Ss. Cyril and Methodius" in Skopje, Macedonia, in the time period from January 2012 until December 2013. The study included patients with invasive cervical cancer treated with type II and type III radical hysterectomy and pelvic lymphadenectomy as a primary treatment options that met the following inclusion criteria: (1) histologicaly verified squamous, adeno- or adeno-squamous cancer of the uterine cervix; (2) clinical stage IA-IIA1, verified by the Tumor board of UCGO; (3) no

medical or surgical contraindications to pelvic lymphadenectomy; (4) no contraindicatior for MRI and (5) no clinical finding suggesting distant metastases. The mean interval from MRI to operative treatment was 12 days (range 8-34 days). Exclusion criteria were: (1 histology suggesting a type of malignant neoplasm of the uterine cervix, other than the previously suggested; (2) previous radiation/chemotherapy for cervical cancer; (3 contraindications for MRI and (4) previous diagnosis of another malignant neoplasm Before the surgical treatment, informed consent was obtained for all patients for the treatment and the participation in the study.

After histopathological verification of the existence of invasive cervical cancer, the Tumc board of UCGO determined the FIGO stage of the disease based on the following clinica parameters: bimanual exam, radiological tests (chest x-ray, intravenous pyelography) and the Board deemed necessary, endoscopic exams such as cystoscopy and sygmoidoscopy.

All MRI scans were performed either at the University Clinic of Radiology or The Cit General Hospital "8th September" in Skopje, Macedonia on 1.5T systems (General Electr Medical Systems, Milwaukee, WI) with a pelvic array coil for pelvic scans and a torso phas array coil for para-aortic scans. Scans were obtained by using the following fixed protocc for the pelvic region, an axial T1-weighted, fast spin-echo sequence (TR/TE, 600/10 m slice thickness, 5 mm; interslice gap, 2 mm; field of view, 24 cm x 24 cm; matrix, 256 x 19 echo train length, 4; three signals acquired; no fat saturation; bandwidth, 31.25 kHz); a axial T2-weighted, fast spin-echo sequence (TR/TE, 5000/68 ms; slice thickness, 3 mı interslice gap, 1 mm; field of view, 24 cm x 24 cm, matrix, 256 x 192; echo train length, 2 four signals acquired; no fat saturation; bandwidth, 31.25 kHz); and a sagittal T2-weighte fast spin-echo sequence (TR/TE, 5000/68 ms; slice thickness, 3 mm; interslice gap, 3 m field of view, 24 cm x 24 cm; matrix, 256 x 192; echo train length, 26; four signals acquire no fat saturation; bandwidth, 31.25 kHz); and, for the para-aortic region, an axial T weighted, fast spin-echo sequence with 16 s of breath holding (TR/TE, 2000/68 ms; sl thickness, 8 mm; interslice gap 2 mm; field of view, 32 cm x 24 cm; matrix, 256 x 160; ec train length, 20; one signal acquired; no fat saturation; bandwidth, 31 kHz).

The image analysis was done by radiology specialists that were blinded to the clinical sta Interpretation was always performed at the institution where the imaging took pla Individual imaging findings relevant for staging of cervical cancer were recorded standardized data forms; they included tumor presence, tumor location (endocervix ver external os), tumor size, stromal invasion, primary tumor extension to the vagi parametrium or adjacent tissues, and presence of lymph node metastases. A posi lymph node on MRI was defined as any node with a shortest diameter of 1cm or grea Parametrial involvement on MRI was defined as a complete disruption of the stromal with a nodular or irregular intensity of the tumor signal extending into the parametrium the T2 images. The tumor diameter was determined as the largest detected diamete any plane.

All patients underwent identical preoperative procedures including bowel preparation prophylactic antibiotics 2 days before surgery. All surgeries were performed by th gynecologic-oncologists that were aware of the preoperative results from the clir examinations and MRI. Systematic pelvic lymphadenectomy from the common iliac ar external iliac artery, internal iliac artery and obturator fossa regions was performed i patients.

The histopathologic analysis of the surgical specimens was performed at the Institut pathology, Medical faculty, University "Ss. Cyril and Methodius" in Skopje, Macedonia

standardized fashion and in accordance to the institutional protocols. The surgical staging was performed according to the seventh revision of the American Joint Committee on Cancer (AJCC) staging manual from 2010[32].

The statistical analysis of the data was done using the IBM SPSS Statistics software package, version 20.0. The correlation of the tumor diameter measured with MRI, clinical examination and histologic analysis of the surgical specimens was calculated using Spearman's rank of correlation test. The study analyzed the diagnostic performance of MRI in terms of detection of parametrial involvement and lymph node metastasis, compared to the histopathologic analysis of the surgical specimens, calculating the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV).

Results

Patient characteristics

The study included a total of 48 patients. The average patient age was 49.9 ranging from 27 to 63 years. Table 1 sums up the clinical and histopathological characteristics of the patients included in the study. A large part of the patient (36 patients, 75%) had squamous cell carcinoma, 8 (16.7%) patients had adenocarcinoma and 4 patients (8.3%) had adenosqamous cancer. According to the clinical FIGO criteria, the patients were staged as follows: Stage IB1 - 28 (58.3%) patients; Stage IB2 – 7 (14.6%) patients and Stage IIA1 - 13 (27.1%) patients. The MRI scans revealed probable parametrial involvement in 8 (16.7$) of patients and probable lymph node metastases in 15 (31.3%) of patients. Subsequent histopathologic analysis verified parametrial involvement in 6 (12.5%) patients and positive pelvic lymph nodes in 11 (22.9%) of patients.

Table 1. Patient characteristics

	Број	%
Histologic type		
Squamous cell carcinoma	36	75
Adenocarcinoma	8	16.7
Adenosquamous carcinoma	4	8.3
Clinical FIGO stage		
IB1	28	58.3
IB2	7	14.6
IIA1	13	27.1
MRI nodal status		
Positive pelvic lymph nodes	15	31.3
Negative pelvic lymph nodes	33	68.7
Surgical specimen nodal status (pN)		
Positive pelvic lymph nodes	11	22.9
Negative pelvic lymph nodes	37	77.1
MRI parametrial involvement		
Yes	8	16.7
No	40	83.3
Surgical specimen parametrial involvement		
Yes	6	12.5

No	42	87.5
Дијаметар на туморот		
Mean	2.44cm ± 1.12cm	
Range	0.9cm - 4.4cm	

Staging accuracy

Table 2 shows the comparison between the postoperative tumor size (pT) identified by histopathologic analysis of the surgical specimens, the clinical stage and the MRI stage. Seven (14.6%) patients were clinically overstaged, and 6 (12.5%) were understaged, yielding an error rate for the clinical FIGO staging, compared to the surgical staging, of 27.1%. The MRI staging was slightly more precise with an error rate of 16.7%. However, the use of this staging method understaged 7 (14.6%) of the patients.

Table 2. Comparison of postoperative tumor status (pT) and clinical and MRI staging

	Postoperative tumor status (pT) (according to AJCC[32])		
	pT1b	pT2a	pT2b
FIGO clinical stage			
IB	34	0	1
IIA	7	1	5
MRI stage			
IB	40	1	5
IIA	0	0	1
IIB	1	0	0

Tumor size evaluation

The estimation of the tumor diameter using clinical exam, MRI and histopathologic analysis is shown in Table 3. The mean tumor diameter, determined by histopathologic analysis of the surgical specimens was 2.44cm ± 1.12cm (range: 0.9cm-4.4cm). The estimated tumor diameter by MRI and clinical exam was calculated from the mean value of the estimation of at leas 2 gynecologic-oncologists, for clinical exams, and at least 2 radiologists, for MRI. MRI was better at estimating the tumor diameter (r_s=0.67, p<0.001) compared to clinical examination (r_s=0.34, p<0.001).

Table 3. Correlation of tumor diameters measured by clinical examination, MRI and histopathologic analysis.

Tumor size	**Clinical examination**		**MRI**		**Histopatologic analysis**	
	n	%	n	%	n	%
< 1cm	2	4.17	8	16.67	7	14.58
1 – 2cm	9	18.75	22	45.83	16	33.33
3 – 4cm	27	56.25	17	35.42	19	39.58
> 4cm	10	20.83	1	2.08	6	12.51

Parametrial involvement detection

Six patients in our study (12.5%) had parametrial involvement verified by histopatholog analysis (pT2b). MRI identified probable parametrial involvement in 8 (16.7%) patients. Tl sensitivity, specificity, PPV and NPV of MRI in the detection of parametrial involveme

were 83.3%, 92.7%, 62.5% and 97.5%, respectively. According to the results, the MRI scans significantly overestimated parametrial involvement in our population (PPV=62.5%).

Lymph node metastases detection

The histopathologic analysis of the surgical specimens revealed positive lymph nodes in 11 (22.9%) of the patients. MRI showed probable positive lymph nodes in 15 (31.3%) of the patients. The sensitivity, specificity, PPV and NPV of MRI in the detection of lymph node metastases were 63.6%, 78.4%, 46.7% and 87.9%, respectively. The histopathologic analysis of lymph nodes that had no metastatic deposits and that were deemed as metastatic on MRI revealed reactive hyperplasia and/or inflammation, and the false negative lymph nodes were interpreted as negative preoperatively due to the fact that their diameter was less than 1cm on MRI. The accuracy of MRI in the preoperative evaluation of patients with invasive cervical cancer is shown on Table 4.

Table 4. Accuracy of MRI in the preoperative evaluation of patients with invasive cervical cancer with regard to parametrial involvement and nodal status.

Variables (%)	Nodal status	Parametrial involvement
Sensitivity	83.3	63.6
Specificity	92.7	78.4
PPV	62.5	46.7
NPV	97.5	87.9

Discussion

The aim of our study was to evaluate the diagnostic performance of MRI in the pre-treatment evaluation of patients with invasive cancer of the uterine cervix, in terms of nodal status, parametrial involvement and tumor diameter, using histopathologic analysis of surgical specimens as a reference. In our study, the preoperative MRI showed low PPV in the detection of metastatic lymph nodes and parametrial involvement. The presence of metastatic lymph nodes radically changes the treatment plan and the prognosis in patients with cervical cancer[20, 21, 33, 34]. In patients with locally advanced disease staged surgically, the 5 year survival rates with positive lymph nodes were markedly lower than in patients with negative lymph nodes[35].

The diagnostic efficiency of MRI in the evaluation of pelvic and para-aortic lymph nodes is controversial. The clinical merit of the preoperative detection of lymph node metastases depends on the rate of detection and NPV for negative nodes. Reinhardt et al.[36] published a surgical pathological prospective study in patients with cervical cancer treated with radical hysterectomy and pelvic lymphadenectomy that had a preoperative MRI. The sensitivity of the imaging method on patient basis was 73%, and the PPV was 64%, when the analysis was conducted for specific lymph node regions. Even though the sensitivity is similar, our study showed a worse PPV, when compared to results from other studies.

The imaging studies that detected probable parametrial involvement did not influence the choice of treatment modality in our study. Contrary to that, all patients with probable parametrial involvement detected by MRI underwent a radical hysterectomy with pelvic lymphadenectomy. Although the sensitivity and NPV were excellent, the PPV for the detection of parametrial involvement was 62.5%, yielding an overestimation of 37.5%.

Most of the patients included in the study underwent conventional diagnostic tests, as recommended by FIGO. In fact, MRI was performed as an addition to all other clinical

examinations necessary for clinical FIGO staging. The high rate of use of these tests is not consistent with data presented by other authors[27, 37], who published that the use of conventional test for cervical cancer staging is declining and that their use is slowly replaced by comprehensive imaging modalities such as MRI and CT. Furthermore, there are controversies regarding the value of positron emission tomography (PET) scanning in the pre-treatment staging of cervical cancer[38, 39]. Considering the current FIGO staging system for cervical cancer, it is clear that the anatomical data is much more valuable than the metabolic data. In our study, the physician uses MRI as an additional tool to determine the surgical spread of the disease. If we were to look at the cost-effectiveness of the procedure, it might not be the most optimal tool for this purpose, which implies the need of further evaluation of this problem.

MRI is relatively successful at predicting the probability of lymph node metastases in the logo-regional nodes, based on their size. The most commonly used cut-off value for the node size is 1cm in the shotest axis[36, 40, 41]. Still, even nodes smaller than 1cm can carry metastatic deposits, while lymph nodes with larger diameters might just have reactive changes. In a recent study that used MRI coupled with iron oxide nanoparticles prior to performing a lymphadenectomy, the analysis of lymph nodes from specific locations had far better sensitivity in the detection of metastatic deposits, compared to conventional size-based criteria. In spite of that, due to the resolution of MRI, it is likely that the micro metastases in the lymph nodes will continue to present a significant challenge.

Our study showed that MRI was a better at determining the tumor diameter, compared to clinical examination, which is in compliance with the published data so far. According to Sahdev et al[42], the average error in the estimation of the tumor diameter was 9mm; the error was reduced to 3mm for tumors larger than 10mm. For that type fo tumors, Sehu et al.[43] concluded that there was an overestimation of the diameter due to the inability to differentiate tumor tissue from the surrounding edema of the healthy tissue that appeared as a result of previous forceps or cone biopsy and that there was an underestimation due to the inability to see a clear tumor border.

Conclusion

Although preoperative MRI is widely used as a substitute for the conventional staging test in patients with cervical cancer, it's accuracy, especially in regard to the PPV for the detection of lymph node metastases and parametrial involvement, is limited. The superiority of MRI, compared to clinical examination in the determination of tumor size and the delineation of tumor margins, besides the obvious benefits for the surgical treatment, can be useful in the planning of brachitherapy and other forms of radiation. Further investigation is necessary to determine the cost-effectiveness of the use of MRI instead of the conventional clinical staging tests.

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