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Erken Evre Serviks Kanserinde (FIGO 2014 Evre IB1–IIA2) Uterin İnvazyonu Öngören Faktörler

Predicting factors of uterine invasion in early-stage (FIGO 2014 Stage IB1–IIA2) cervical cancer

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ÖZ

Amaç: Uterin korpus tutulumu daha önceki çalışmalarda radyolojik olarak gösterilmiş veya endometriyal biyopsi ile teşhis edilmiştir. Bu nedenle, radikal histerektomi örneklerinde uterin korpus tutulumunu saptayan az sayıda çalışma vardır. Bu çalışma, cerrahi olarak tedavi edilen serviks kanseri hastalarında uterin korpus tutulumunu etkileyen faktörleri araştırmak için tasarlanmıştır.

Materyal ve Metot: Ocak 2008-Ağustos 2021 tarihleri arasında Zekai Tahir Burak Kadın Sağlığı Eğitim ve Araştırma Hastanesi ve Ankara Bilkent Şehir Hastanesinde radikal histerektomi ve pelvik-paraaortik lenfadenektomi yapılan klinik erken evre (evreIB1-IIA2) serviks kanserli toplam 269 hasta çalışmaya alındı ve klinikopatolojik verileri hasta dosyalarından veya hastanenin elektronik veri tabanından çıkarıldı.

Bulgular: Uterin invazyon 102 (%37.9) hastada pozitifti. Hastaların tümör boyutu 66 (%24,5) hastada ≤20 mm, 82 (%30,5) hastada >40 mm idi. 44 (%16.4) hastada parametrial invazyon saptandı. Multivariant analizde; tümör tipi (adenokanser ve diğer tümör tipleri) (HR: 8,94; %95 GA: 3,569–22,401; p<0,001), tümör boyutu (>35 mm-≤35 mm) (HR: 2,34; %95 GA: 1,234) –4,440; p=0,009) stromal invazyon derinliği (>1/2 vs. ≤1/2) (HR: 6,63; %95 GA: 2,205–19,952; p<0,001), parametrial metastaz (pozitif vs. negatif) (HR: 2,86; %95 GA: 1,220–6,707; p=0,016) uterin invazyonun bağımsız belirleyicisi olarak bulundu.

Sonuç: Tümör tipi, stromal invazyon derinliği ve parametrial metastaz, uterin korpus invazyonu için bağımsız risk faktörleriydi. Serviks kanseri evrelemesini belirlemede geleneksel olarak cerrahi-patolojik bulgular kullanılmamasına rağmen serviks kanserinin tedavisinde uterin invazyonun varlığının önemli bir rol oynayacağına inanıyoruz.

Anahtar Kelimeler: Serviks kanseri, uterin invazyon, radikal histerektomi

ABSTRACT

Objective: Uterine corpus involvement was demonstrated radiologically or diagnosed by endometrial biopsy in the previous reports. Thus, there are few studies that detect uterine corpus involvement in radical hysterectomy specimens. This study was designed to investigate the factors that influence uterine corpus involvement in surgically treated cervical cancer patients.

Materials and Methods: A total of 269 patients with clinical early-stage (stageIB1-IIA2) cervical cancer who underwent radical hysterectomy and pelvic-paraaortic lymphadenectomy at Zekai Tahir Burak Women's Health Training and Research Hospital and Ankara Bilkent City Hospital between January 2008 and August 2021 were recruited, and their clinicopathologic data were extracted from their patient files or the hospital's electronic database.

Results: Uterine invasion was positive in 102 (37.9%) patients. Tumor size of patients was ≤20 mm in 66 (24.5%) patients and >40 mm in 82 (30.5%). Parametrial invasion was detected in 44 (16.4%) patients. In the multivariate analysis; tumor type (adenocancer vs. other tumor types) (HR: 8.94; 95% CI: 3.569–22.401; p<0.001), tumor size (>35 mm vs. ≤35 mm) (HR: 2.34; 95% CI: 1.234–4.440; p=0.009) depth of stromal invasion (>1/2 vs. ≤1/2) (HR: 6.63; 95% CI: 2.205–19.952; p<0.001), parametrial metastasis (positive vs. negative) (HR: 2.86; 95% CI: 1.220–6.707; p=0.016) were found to be independent predictor of uterine invasion.

Conclusion: Tumor type, stromal invasion depth, and parametrial metastasis were independent risk factors for invasion of the uterine corpus. We believe that the presence of uterine invasion will play an important role in the treatment of cervical cancer, despite the fact that surgical-pathologic findings have not traditionally been used to determine cervical cancer staging.

Keywords: Cervical cancer, uterine invasion, radical hysterectomy

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INTRODUCTION

Cervical cancer was the fourth most prevalent cancer in women in 2020 GLOBOCAN, with an estimated 604,000 new cases and 342,000 deaths globally. (1, 2). Traditionally, cervix cancer was staged clinically; however, surgical and radiologic evaluation are now included in the staging criteria. (3-6). Surgical and radiologic staging provides crucial information that can influence treatment. (7). Direct tumor invasion, lateral invasion into the parametria, distant invasion into the upper vagina, and, much less frequently, anterior-posterior invasion into the bladder or rectum are the most common ways that cervical cancer spreads. (8). In the current staging system for cervical cancer, these anatomical sites of direct tumor extension are considered, and the presence of tumor invasion in these anatomical sites is associated with a poorer prognosis. (9). In the 2018 International Federation of Gynecology and Obstetrics (FIGO) cervical cancer staging system, imaging and pathologic findings could be used to determine the stage of the disease. (4). Uterine corpus involvement, on the other hand, has been disregarded in this new model, just as it has been in previous FIGO staging systems. Involvement of adjacent anatomic structures, other than the uterine corpus, is associated with a poor prognosis and changes the FIGO stage, according to the most recent FIGO staging system. (4). Patients with early-stage cervical cancer who underwent radical hysterectomy were found to have uterine corpus invasion at a rate ranging from 4.9% to 26.2%, according to the pathology specimens of several studies. (10-16). Furthermore, previous studies had linked uterine corpus involvement to poorer oncologic outcomes in patients with cervical cancer.(10, 16).

In prior reports, involvement of the uterine corpus was demonstrated radiologically or diagnosed via endometrial biopsy. Thus, studies detecting uterine corpus involvement in radical hysterectomy specimens are limited (12, 17). Therefore, we designed this study to investigate the factors that influence uterine corpus involvement in surgically treated cervical cancer patients.

MATERIALS AND METHODS

A total of 269 patients with clinical early-stage (stageIB1-IIA2) cervical cancer who underwent radical hysterectomy and pelvic-paraaortic lymphadenectomy at Zekai Tahir Burak Women's Health Training and Research Hospital and Ankara Bilkent City Hospital between January 2008 and August 2021 were recruited, and their clinicopathologic data were extracted from their patient files or the hospital's electronic database. Before beginning the study, approval from the institutional review board was obtained. Gynecologic oncologists performed all surgical procedures. A type III radical hysterectomy was carried out, during which the uterus, the cervix, the upper third of the vagina, and the parametrial resection up until the pelvic sidewall were all removed. It was decided to perform a bilateral salpingo-oophorectomy on the patient after evaluating their age and the general appearance of their ovaries. A radical hysterectomy, pelvic lymph node dissection, and paraaortic lymph node dissection consist the standard surgical protocol for cervical cancer. Lymphadenectomy involved dissecting pelvic and paraaortic lymph nodes to the inferior mesenteric artery or left renal vein. All surgical specimens were evaluated by specialized gynecologic pathologists. Before opening the radical hysterectomy specimen to expose the cervix and endometrium for a macroscopic examination of the cervical cancer, the specimen was externally examined. The location, growth pattern, size, and extent of the tumor's spread were all recorded. Deep stromal invasion was defined as tumor invasion of the outer half of the cervical stroma (>1/2 of full thickness). It was determined that lymphovascular space invasion (LVSI) was present when epithelial tumor cells were found in the lumen of vessels, which were lined by endothelial cells. Surgical margin involvement was defined as tumor positivity within a 5-mm margin of the pathology specimen. Vaginal involvement refers to the presence of a tumor elsewhere within the vaginal region. Cervical tumors were categorized into 4 types: squamous cell cancer, adenocancer, adenosquamous and others. Uterine invasion was defined as endometrial and/or myometrial disease that had spread above the internal cervical ostium. For staging, FIGO 2014 criteria are utilized.

The Statistical Package for the Social Sciences (IBM SPSS Inc., Chicago, IL) version 20.0 was utilized for data recording and statistical analysis. The Kolmogorov–Smirnov test was used to assess the normality of continuous variable distributions. The analysis of categorical variables was conducted using either Pearson's Chi-square ($\chi 2$) test or Fisher's exact test, depending on which method was deemed more appropriate for the circumstances. The difference between samples from non-normal distributions was analyzed using the Mann-Whitney-U test. Multivariate Backward Stepwise Cox Proportional Hazard Regression Analysis was used to determine the effects of variables effective on uterine invasion. Variables that were statistically significant in univariate analysis were incorporated into a model for multivariate analysis.

RESULTS

A total of 269 patients with a mean age of 51.8 years (range, 26–80 years) were analyzed. The mean tumor size of the patients was 35.8 mm (range, 5–130 mm). The mean number of removed lymph nodes was 56.4 (range, 8–140). The mean number of metastatic lymph node was 6.5 (range, 1–73).

Tumor type of patients was squamous cell carcinoma in 190 (70.6%) patients, adenocarcinoma in 48 (17.8%), adenosquamous cell carcinoma in 25 (9.3%) and other in 6 (2.2%). Patients FIGO 2014 stage was IB1 in 148 (55%) patients, IB2 in 57 (21.2%), IIA1 in 38 (14.1%) and IIA2 in 26 (9.7%). Uterine invasion was positive in 102 (37.9%) patients. Tumor size of patients was ≤20 mm in 66 (24.5%) patients and >40 mm in 82 (30.5%). Parametrial invasion was detected in 44 (16.4%) patients. Surgical border involvement was positive in 22 (8.2%) of the patients. Vaginal invasion was positive in 68 (25.3%) of the patients. LVSI was positive in 197 (73.2%) patients. Deep stromal invasion was detected in 209 (77.7%) patients. Bilateral salpingo-oophorectomy was performed in 256 (95.2%) patients. Ovarian metastasis was positive in 15 (5.6%) patients. Lymph node metastasis was positive in 98 (36.4%) patients (Table 1).

Table 1. Clinical Features

Features		**Mean±SD**	**Median (Range)**
Age at initial diagnosis		51.8±11.5	52 (26-80)
Tumor size (mm)		35.8±17.4	35 (5-130)
Number of removed lymph nodes		56.4±23.1	53 (8-140)
Number of metastatic lymph node		6.5±12.2	2 (1-73)
		n	**Percentage**
Tumor type	Squamous cell carcinoma	190	70.6
	Adenocarcinoma	48	17.8
	Adenosquamous cell carcinoma	25	9.3
	Other [1]	6	2.2
FIGO 2014 stage	IB1	148	55
	IB2	57	21.2
	IIA1	38	14.1
	IIA2	26	9.7
Tumor size	≤20 mm	66	24.5
	>20 mm - ≤40 mm	121	45
	>40 mm	82	30.5
Parametrial invasion	Negative	225	83.6
	Positive	44	46.4
Surgical border involvement	Negative	247	91.8
	Positive	22	8.2
Vaginal invasion	Negative	201	74.7
	Positive	68	25.3
Lymphovascular space invasion	Negative	72	26.8
	Positive	197	73.2
Stromal invasion	≤%50	60	22.3
	>%50	209	77.7
Bilateral salpingo-oophorectomy	Not performed	13	4.8
	Performed	256	95.2
Ovarian metastasis	Negative	241	94.1
	Positive	15	5.6
Uterine invasion	Negative	167	62.1
	Positive	102	37.9
Lymph node metastasis	Negative	171	63.6
	Positive	98	36.4
Site of metastatic lymph node	Only pelvic	80	81.6
	Only paraaortic	-	-
	Pelvic and paraaortic	18	18.4

[1]: Neuroendocrine (n:3), lymphoepithelioma (n:2), basoloid (n:1) Clinic, surgical and pathologic factors predicting uterine invasion is shown in table 2. Histopathology, tumor size, FIGO 2014 stage, LVSI, vaginal involvement, deep stromal invasion, parametrial invasion, and ovarian metastasis were statistically significant ($p<0.05$) for uterine invasion in univariate analysis.

Clinic, surgical and pathologic factors predicting uterine invasion is shown in table 2. Histopathology, tumor size, FIGO 2014 stage, LVSI, vaginal involvement, deep stromal invasion, parametrial invasion, and ovarian metastasis were statistically significant (p<0.05) for uterine invasion in univariate analysis.

Table 2. Clinic, surgical and pathologic factors predicting uterine invasion

Factors		**Uterine Invasion**				***P* Value**
	Negative		**Positive**			
	n	**%**	**n**	**%**		
Age at initial diagnosis [1]	≤52 years	96	65.3	51	34.7	*0.254*
	>52 years	69	58.5	49	41.5	
Histopathology	Squamous cell carcinoma	133	70	57	30	***<0.001***
	Adenocancer	17	35.4	31	64.6	
	Adenosquamous	14	56	11	44	
	Other type	3	50	3	50	
Tumor size	≤20 mm	57	86.4	9	13.6	***<0.001***
	>20 mm - ≤40 mm	71	58.7	50	41.3	
	>40 mm	39	47.6	43	52.4	
Tumor size [1]	≤35 mm	107	74.8	36	25.2	***<0.001***
	>35 mm	60	47.6	66	52.4	
FIGO 2014 stage	IB1	109	73.6	39	26.4	***<0.001***
	IB2	28	49.1	29	50.9	
	IIA1	19	50	19	50	
	IIA2	11	42.3	15	57.7	
FIGO 2014 stage	I	137	66.8	68	33.2	***0.004***
	II	30	46.9	34	53.1	
Lymphovascular space invasion	Negative	53	73.6	19	26.4	***0.018***
	Positive	114	57.9	83	42.1	
Surgical border involvement	Negative	157	63.6	90	36.4	*0.093*
	Positive	10	45.5	12	54.5	
Vaginal involvement	Negative	136	67.7	65	32.3	***0.001***
	Positive	31	45.6	37	54.4	
Stromal invasion	≤%50	57	91.9	5	8.1	***<0.001***
	>%50	110	53.1	97	46.9	
Parametrial invasion	Negative	153	68	72	32	***<0.001***
	Positive	14	31.8	30	68.2	
Lymph node metastasis [2]	Negative	116	67.8	55	32.2	***0.010***
	Positive	51	52	47	48	
Ovarian metastasis	Negative	153	63.5	88	36.5	***<0.001***
	Positive	2	13.3	13	86.7	

[1] **Other tumor types:** Squamous cell cancer + Adenosquamous cell carcinoma + Neuroendocrine + Lymphoepithelioma + Basoloid

In the multivariate analysis; tumor type (adenocancer vs. other tumor types) (HR: 8.94; 95% CI: 3.569–22.401; p<0.001), tumor size (>35 mm vs. ≤35 mm) (HR: 2.34; 95% CI: 1.234–4.440; p=0.009) depth of stromal invasion (>1/2 vs. ≤1/2) (HR: 6.63; 95% CI: 2.205–19.952; p<0.001), parametrial metastasis (positive vs. negative) (HR: 2.86; 95% CI: 1.220–6.707; p=0.016) were found to be independent predictor of uterine invasion (Table 3).

Table 3. Multivariate Analysis

Factors	Hazard Ratio	95% Confidence Interval
Tumor type (a*denocancer vs. other tumor types* [1])	8.941	3.569-22.401
Tumor size (*>35 mm vs. ≤35 mm*)	2.340	1.234-4.440
FIGO stage (*II vs. I*)	2.698	0.227-32.032
Lymphovascular invasion (*positive vs. negative*)	1.247	0.591-2.633
Vaginal spread (*positive vs. negative*)	3.766	0.329-43.054
Depth of stromal invasion (*>1/2 vs. ≤1/2*)	6.633	2.205-19.952
Lymph node metastasis (*positive vs. negative*)	1.093	0.564-2.118
Ovarian metastasis (*positive vs. negative*)	3.679	0.698-19.396
Parametrial metastasis (*positive vs. negative*)	2.861	1.220-6.707

DISCUSSION

Cervical cancer spreads primarily through direct extension and lymphatic dissemination. In our study of early-stage cervical cancer patients treated with radical hysterectomy, uterine invasion was detected in 37.9% of patients. The remarkable findings of the present study were that tumor type (HR: 8.94; 95% CI: 3.569–22.401; p<0.001), tumor size >35 mm (HR: 2.34; 95% CI: 1.234–4.440; p=0.009), depth of stromal invasion (HR: 6.63; 95% CI: 2.205–19.952; p<0.001), and parametrial metastasis (HR: 2.86; 95% CI: 1.220–6.707; p=0.016) were independent predictors of uterine invasion.

Kim et al. investigated the relationships between FIGO stage, tumor volume, and uterine body invasion in a study of 106 patients with IB-IIIB cervical carcinoma. (18). Patients with FIGO stage I had a uterine invasion rate of 33.3%, patients with FIGO stage II had a 63.3% rate, and patients with FIGO stage III had an 83.3% rate. There was a significant correlation between FIGO stage and uterine invasion rate (p = 0.007). Uterine invasion was observed in 44.3% of patients with a small tumor volume (30 ml; n=27) and in 86.7% of patients with a large tumor volume (30 ml; n=39); and was strongly correlated with tumor volume as measured by magnetic resonance imaging. (18).

Weili et al. included 2212 patients in their study; 515 patients with cervical cancer had uterine corpus invasion and 1.697 patients with cervical cancer had no uterine corpus invasion (19). In this study, patients with uterine corpus invasion were significantly older, had significantly larger tumors, and were significantly more likely to have advanced stage disease, adenocarcinoma, grade 1 or 2 disease, stromal invasion depth >1/2, parametrial involvement, resection margin involvement, and lymph node metastasis than those without uterine corpus invasion. (19). Similar to Weili et al., tumor size, histopathology, FIGO 2014 stage, stromal invasion, parametrial invasion, and LVSI were statistically significant in predicting uterine invasion in our study in univariate analysis.

Turan et al. included 354 patients in their study; uterine invasion was detected in 60 (16.9%) patients (20). They found that the presence of uterine invasion was significantly associated with the histologic subtype of the tumor (adenocarcinoma, adenosquamous), the size of the primary tumor (≥20 mm), the presence of LVSI, surgical margin involvement, vaginal involvement, deep stromal invasion, parametrial invasion, and the presence of lymph node metastasis. (20).

Matsuo et al. found that non-squamous histology, which includes adenocarcinoma, is an independent risk factor for uterine corpus tumor invasion in comparison to squamous type. (16). While this finding may partially support the hypothesis that squamous type and adenocarcinoma type have different patterns of tumor spread, with lymphatic spread being more prevalent in squamous histology and hematogenous spread being more common in adenocarcinoma histology, the most likely cause of this association is the anatomical proximity to the uterine corpus. Because the endocervix is anatomically closer to the uterine corpus than the extocervix, there is a greater likelihood of direct extension of adenocarcinoma to the uterine corpus. (16). Similar to Matsuo et al. in our study, adenocarcinoma was the most common (%64.6) histopathology in cervical cancer patients with uterine invasion. Moreover, in this study, Matsuo et al. emphasized that, on multivariate analysis, uterine corpus tumor invasion was independently associated with older age, non-squamous histology, high-grade tumors, and large tumor size (16).

He et al. retrospectively reviewed 1414 patients with stage IA2–IIB cervical cancer from 11 medical institutions in China who underwent radical hysterectomy between 2004 and 2016.They indicated that a myometrial invasion ≥50% within the uterine corpus was an independent factor associated with a poorer prognosis in patients who had cervical cancer. On the other hand, endometrial invasion and myometrial invasion <50% had no effect on the patients' outcomes. Furthermore Turan et al. found that in their study cohort, the 5-year cancer-specific survival rate was 94%. Uterine invasion and lymph node metastasis were identified as independent risk factors for cancer-specific survival (20).

The most important limitation of this study is its retrospective design. Furthermore, there is a lack of preoperative evaluation data for uterine invasion. The inclusion of a moderately large number of patients who underwent radical hysterectomy performed by gynecologic oncologists and the identification of uterine

invasion in pathology specimens by gynecologic pathologists were the study's major strengths.

In conclusion, tumor type, depth of stromal invasion and parametrial metastasis were independent risk factors for uterine corpus invasion. Even though cervical cancer staging has not traditionally been based on surgical-pathologic findings, we believe that the presence of uterine invasion will be important in the treatment. More large-scale prospective studies are needed to determine the significance of uterine invasion in cervical cancer.

Conflict of Interest

None. The manuscript has been read and approved for submission by all the named authors.

Author Contribution

Abdurrahman Alp Tokalioglu conceived and designed the study and wrote the manuscript. Fatih Celik, Okan Aytekin and Burak Ersak collected clinical data. Ilker Selcuk and Izzet Ozgurluk analyzed the histological data. Abdurrahman Alp Tokalioglu wrote, and edited the manuscript. Ozlem Moraloglu Tekin and Bulent Ozdal reviewed the manuscript. All authors participated in interpretation of the results and writing of the report and approved the final version submitted.

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