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Which factors predict parametrial involvement in early stage cervical cancer? A Turkish multicenter study

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ABSTRACT

Objective: To evaluate the clinical and pathological factors for predicting the parametrial involvement (PI) in early stage cervical cancer.
Study design: This study included 406 patients with type III radical hysterectomy + pelvic ± para-aortic lymphadenectomy and FIGO stage I and II cervical adenocarcinoma, squamous type, and adenosquamous type cervical cancer.
Results: The entire cohort of patients had lymphadenectomy performed. Early stage cervical cancer patients were evaluated. FIGO 2014 stage, uterine invasion, LVSI, surgical border involvement, vaginal metastasis, stromal invasion and lymph node metastasis were found to be effective for PI on univariate analyses. However; age, tumor type and tumor size did not determine the parametrial invasion. LVSI (HR: 4.438, 95%CI: 1.771–11.121; $p = 0.001$), lymph node metastases (HR: 2.418, 95%CI: 1.207–4.847; $p = 0.013$) and vaginal involvement (HR: 4.109, 95%CI: 1.674–10.087; $p = 0.02$) are independent prognostic factors on multivariate analysis.
Conclusion: Lymph node metastases, LVSI and surgical border involvement are independent prognostic factors for PI in early stage cervical cancer patients. Therefore, less radical surgical approaches for early stage tumors with no nodal spread, negative LVSI and no surgical border involvement are applicable.

Introduction

Cervical cancer (CC) is a common cause of death in female genital tract malignancies and among all cancer types worldwide. Because CC is a preventable type of cancer; effective screening policies were enhanced during the past years and a decrease in mortality rates were achieved. Surgery consisting of radical hysterectomy with pelvic lymphadenectomy is the standard initial therapy for early-stage cervical cancer (stage IA, IB and IIA, except for stage IA1). This procedure includes removal of the uterus, upper one third of vagina and uterosacral ligaments with ligation of the uterine artery at its origin and resection of the parametrium and pelvic lymphadenectomy [1]. CC has been staged clinically according to the International Federation of Gynecology and Obstetrics (FIGO) since 1988 [2]. FIGO revised the staging system in 2018 to allow the imaging and pathological findings to assess the lymph node status and the tumor size [3].

Radical hysterectomy includes parametrectomy, which damages the autonomic nerves traversing through the paracervical region. These nerves include the sympathetic fibers from the hypogastric nerve and parasympathetic fibers from the pelvic splanchnic and inferior hypogastric plexus [4]. As a result; long term complications occur such as bladder dysfunction, sexual dysfunction and colorectal motility disorders. Although, in the randomized controlled trial about nerve-sparing radical surgery was effective in preserving bladder function without sacrificing oncologic safety; more prospective trials must be done to confirm this conclusion [5]. As more concerns raised, a search for less

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radical surgery and preoperative assessment of appropriate patients for this less radical approach became essential.

Direct extension and lymphatic dissemination are the most common routes of spread in cervical cancer. Therefore, parametrium and lymph nodes are typical metastasis locations and removal of these tissues is vital in cervical cancer treatment [6]. Although parametrial resection is essential for treatment of cervical cancer; concomitant complications of this procedure have led to develop new algorithms for predicting candidates of less radical surgery without compromising oncologic outcome.

This study was designed to evaluate the clinical and pathological factors for predicting the parametrial involvement (PI) in early stage cervical cancer.

Materials and methods

This study included 406 patients whose surgeries (type III radical hysterectomy + pelvic ± para-aortic lymphadenectomy) had been performed in Health Sciences University Ankara Etlik Zubeyde Hanim Women's Training and Research Hospital Gynecologic Oncology Clinic, Antalya Training and Research Hospital and Istanbul Okmeydani Training and Research Hospital between January 1993 and December 2018. The entire cohort of patients underwent pelvic and rectovaginal examination under general anesthesia. Also they all had pelvic magnetic resonance imaging or intravenous pyelography and positron emission tomography and computed tomography (PET-CT) preoperatively. All surgeries were performed by gynecologic oncologists trained at a single institution certification programme so homogenization in surgeries could be obtained. Patients had FIGO stage IB1, IB2, IIA1 and IIA2 disease, with cervical adenocarcinoma, squamous type, and adenosquamous type cervical cancer according to final pathology results. Data of the patients were obtained from electronic database system, patients' files and pathology reports retrospectively. Patients with microinvasive disease, whose tumors had non-epithelial component and with synchronized primer tumor, and the ones having neo-adjuvant treatment were excluded. The ethical board approval exists for this study. Staging were performed clinically according to FIGO 2014 criteria.

Tumor size was measured as the longest tumor diameter in uterine cervix after fixation in paraffin block. Lymphovascular space invasion (LVSI) was defined as the tumoral cells or cell clusters holding on vessels' walls that were stained with hematoxylin and eosin (H&E) in the pathologic sections containing both tumor and the surrounding healthy tissue. Uterine invasion was described as tumor spread to endometrial and/or myometrial regions above the level of internal cervical ostium. Surgical border involvement was admitted as tumor positivity within $\leq$0.5 cm of pathology material obtained from surgical procedure. Vaginal involvement was described as detecting tumor elsewhere in vaginal region. Stromal invasion more than $\geq$1/2 of cervical wall was defined as deep stromal invasion. Pathologic examination of the hysterectomy material and parametrium was performed with cutout sections containing at least 5 mm width and a total number of 2 and 6 pieces. Lymph nodes less than 1 cm were taken into paraffin block directly and nodes which have a size more than 1 cm with cutting horizontally at least two pieces. In the presence of the macroscopic tumor, only that part was directly taken into paraffin block. The sections has been evaluated through hematoxylin and eosin stain.

The standard surgery included type III radical hysterectomy ± bilateral salphingo-oophorectomy + systematic pelvic ± para-aortic lymphadenectomy. Lymphadenectomy was performed in most of the patients by skeletonizing pelvic with/without para-aortic regions. Bilateral pelvic lymphadenectomy was performed to complete skeletonization, with all lymphatic tissue of the common, external and internal iliac vessels and the obturator fossa that was removed after visualization of the obturator nerve. The superior surgical dissection margin for the pelvic nodes was the aortic bifurcation, and the anterior distal surgical dissection margin was the circumflex iliac vein. The upper limit of para-aortic lymphadenectomy was inferior mesenteric artery or left renal vein. The standard surgery including type III radical hysterectomy was performed without preservation of autonomic nerves which corresponds Type C2 radical hysterectomy for Kyoto Classification. The necessity of adjuvant therapy was decided by the senior surgeon or gynecologic oncology council regarding the major and minor risk factors obtained from patients' pathology results.

Categorical variables were analyzed with Kaplan-Meier Survival Analysis using Log-Rank Test to determine whether they had statistically significant effects on parametrial involvement. Whether the continuous and discrete numeric variables had statistically significant effects were calculated using univariate Cox Proportional Hazard Regression Analysis. Multivariate Backward Stepwise Cox Proportional Hazard Regression Analysis was used to determine the effects of variables effective on parametrial involvement after univariate statistical analysis. p value <0.05 was considered statistically significant for the results. Data analyses were performed by using SPSS for Windows 20 package programme.

Results

The mean age of patients was 52 years and ranged between 26 and 80. The tumor type was squamous cell carcinoma in 322 (79.3 %) patients, adenocarcinoma in 62 (15.3 %), adenosquamous cell carcinoma in 16 (3.9 %) and mixed (adenocarcinoma and squamous cell carcinoma) type in four (1 %). Three hundred and three (74.6 %) patients were stage IB1, 60 (14.8 %) were stage IB2, 37 were stage IIA1 (9.1 %) and six (1.5%) were stage IIA2 according to FIGO 2014 criteria. Median tumor size was 30 mm (range; 6–80 mm). The tumor size was <20 mm in 53 (13.1 %) patients, $\geq$20 mm- <40 mm in 226 (55.7 %) and $\geq$40 mm in 127 (31.3 %). Median number of removed lymph nodes was 47 and ranged between 10 and 128. A hundred (24.6 %) patients have lymph node metastasis. Patients with metastatic lymph nodes in only pelvic region was 86 (21.2 %), in only para-aortic region was two (0.5%) and in both pelvic and para-aortic regions was 12 (3 %). PI was positive in 70 (17.2 %) patients. LVSI was positive in 223 (54.9 %) patients, vaginal involvement was positive in 74 (18.2 %) and 29 (7.1 %) patients had positive surgical border. Uterine invasion was detected in 61 (15 %) patients and deep stromal invasion was detected in 262 (64.5%). Data related to clinical and surgico-pathologic factors were detailed in Table 1.

FIGO 2014 stage, uterine invasion, LVSI, surgical border involvement, vaginal metastasis, stromal invasion and lymph node metastasis were found to be effective for PI on univariate analyses (Table 2). However; age, tumor type and tumor size did not determine the parametrial invasion. An analysis adjusted to stage, uterine invasion, stromal invasion revealed that LVSI (HR: 4.438, 95%CI: 1.771–11.121; $p = 0.001$), lymph node metastases (HR: 2.418, 95%CI: 1.207–4.847; $p = 0.013$) and vaginal involvement (HR: 4.109, 95%CI: 1.674–10.087; $p = 0.02$) are independent prognostic factors on multivariate analysis (Table 2).

Comment

The presented study was conducted to evaluate the clinical and surgico-pathological factors which has considerable value to predict the PI in early stage cervical cancer. There are two approaches for cervical cancer treatment consisting of surgery and radiotherapy (with or without concurrent chemotherapy). The initial decision of therapy modality depends on stage; surgery for early stage (stage I-IIA) and radiotherapy for locally advanced disease (stage IIB-IV). Adjuvant radiotherapy decision after surgery

Table 1
Clinical Features of 406 Patients.

Features	Mean	Median (range)
Age at initial diagnosis	52.5	52 (26-80)
Tumor size (mm)	30.3	30 (6-80)
Number of removed lymph nodes	50.5	47 (10-128)
Number of metastatic lymph node	3.1	2 (1-19)

		Number of patient	Percentage
Tumor type	Squamous cell carcinoma	322	79.3
	Adenocarcinoma	62	15.3
	Adenosquamous cell carcinoma	16	3.9
	Other	2	0.5
	Mixed type[a]	4	1
FIGO 2014 stage	IB1	303	74.6
	IB2	60	14.8
	IIA1	37	9.1
	IIA2	6	1.5
Tumor size	<20 mm	53	13.1
	≥20 mm - <40 mm	226	55.7
	≥40 mm	127	31.3
Parametrial invasion	Negative	336	82.8
	Positive	70	17.2
Surgical border involvement	Negative	377	92.9
	Positive	29	7.1
Vaginal invasion	Negative	332	81.8
	Positive	74	18.2
Lymphovascular space invasion	Negative	165	40.6
	Positive	223	54.9
	Not reported	18	4.4
Stromal invasion	≤ %50	129	31.8
	> %50	262	64.5
	Not reported	15	3.7
Bilateral salpingo-oophorectomy	Not performed[b]	72	17.7
	Performed	334	82.3
Adnexal metastasis	Negative	338	83.3
	Positive	4	1
	Not reported[c]	64	15.8
Uterine invasion	Negative	317	78.1
	Positive	61	15
	Not reported	28	6.9
Lymph node metastasis	Negative	306	75.4
	Positive	100	24.6
Site of metastatic lymph node	Only pelvic	86	21.2
	Only paraaortic	2	0.5
	Pelvic and paraaortic	12	3

[a] Adenocancer and squamous cell cancer.
[b] Sixty-four patients received bilateral ovarian transposition and 8 patients had unilateral salpingo-oophorectomy and unilateral ovarian transposition before radical hysterectomy.
[c] Patient underwent bilateral ovarian transposition before radical hysterectomy.

is made due to surgico-pathologic factors. PI, lymph node metastases and surgical border positivity are three major factors for determining adjuvant radiotherapy.

Our study suggested that clinical, surgical and pathological factors except for LVSI, vaginal involvement and lymph node metastases had no predictive value for parametrial involvement in early stage cervical cancer. Identification of a low-risk population for PI in patients with early stage cervical cancer is essential because of a subset of long term complications such as urinary, anorectal and sexual dysfunction related to surgical radicality.

In our study, PI was reported as 17.2 % (15.4 % for FIGO stage I and 32.6 % for FIGO stage II). In a recent study; Baiocchi et al. found that PI for early stage disease was 4.6 % [7]. Chang et al. reported a similar rate in early stage cervical cancer; 5.4 % for PI [8]. In different studies, parametrial invasion rate was 10 % and 32 % [9,11]. Our PI rate was compatible with the reported literature.

This current study suggested that LVSI was one of the independent predictors for PI (positive 26.5% *vs.* negative 4.8 % with hazard ratio: 4.438; 95% CI: 1.771–11.121, $p = 0.001$). Frumovitz et al. achieved similar results in their study by evaluating a cohort of 350 patients [10]. In addition, different studies reported similar findings [9,11,13]. The LVSI status of the tumor can be assessed preoperatively by performing a conization procedure and this information can be useful in deciding the radicality of the operation. In a meta-analysis, it was reported that LVSI can be detected on conization specimens (CS) and show high sensitivity in early stage cervical cancer [14]. Also it was found that LVSI in CS might be a promising predictor for PI in tumor size less than 2 cm [15].

It is estimated that lymph node metastases was an independent prognostic factor for PI (positive 32 % *vs.* negative 12.4 % with hazard ratio: 2.418, 95% CI: 1.2017–4.847, p = 0.013) in our study. Gemer et al. reached out similar results in their study by evaluating 530 patients [12]. They concluded that lymph node metastases as well as tumor size, deeper invasion, surgical margin positivity and LVSI were prognostic factors for predicting parametrial involvement. In addition; they suggested an algorithm for less radical surgical procedures (simple hysterectomy/simple trachelectomy) for patients with tumors less than 2 cm in size, no nodal spread and LVSI. However, the estimated impact of tumor size on parametrial involvement was not obvious in our study.

Similarly; vaginal involvement was one of the independent predictors for PI in our cohort (positive 55.2 % *vs.* negative 14.3 %

Table 2
Factors predicting the parametrial invasion.

Factors		Univariate Analysis		Multivariate Analysis		
		Positive Parametrial Invasion		Risk of Parametrial Invasion		
		Percentage	*P* value	Hazard Ratio	95% Confidence Interval	***P* value**
Age	≤ 52 years	14.8	*0.160*	1 (Reference)	0.701-2.674	*0.358*
	≥ 52 years	20.1		1.369		
Histopathology	Squamous cell carcinoma	16.8	*0.804*			
	Others	17.9				
Tumor size	< 20 mm	9.4	*0.070*			
	≥ 20 mm - < 40 mm	15.9				
	≥ 40 mm	22.8				
Tumor size [1]	≤ 30 mm	14.7	*0.079*	1 (Reference)	0.704-2.774	*0.339*
	> 30 mm	21.6		1.397		
FIGO 2014 stage	IB1	13.5	***0.006***			
	IB2	25				
	IIA1	32.4				
	IIA2	33.3				
FIGO 2014 stage	Stage I	15.4	***0.005***	1 (Reference)	0.374-3.446	*0.824*
	Stage II	32.6		1.135		
Uterine invasion	Negative	12.9	<***0.001***	1 (Reference)	0.722-3.377	*0.257*
	Positive	31.1		1.562		
Lymphovascular space invasion	Negative	4.8	<***0.001***	1 (Reference)	1.771-11.121	***0.001***
	Positive	26.5		4.438		
Surgical border involvement	Negative	14.3	<***0.001***			
	Positive	55.2				
Vaginal involvement	Negative	13	<***0.001***	1 (Reference)	1.674-10.087	***0.002***
	Positive	36		4.109		
Stromal invasion	≤ %50	10.9	***0.031***	1 (Reference)	0.622-3.018	*0.434*
	> %50	19.5		1.370		
Lymph node metastasis	Negative	12.4	<***0.001***	1 (Reference)	1.207-4.847	***0.013***
	Positive	32		2.418		

Others: Adenocancer and adenosquamous cell carcinoma (4 patients with mixed type tumor [adenocancer + squamous cell carcinoma] and 2 patients with other type were excluded).
Bold and italics signifies p values with statistical significance.

with hazard ratio: 4.109, 95%CI: 1.674–10.087, p = 0.002). In their study, Canaz et al. reported that pathological vaginal invasion was significantly different in PI group with LVSI, tumor size, endophytic clinical presentation and uterine body involvement on univariate analysis [16]. However, on multivariate analysis, the same significance level could not be obtained.

The most important limitation of this study is its retrospective design. On the other hand high number of patients is an advantage. In addition; entire cohort consists of lymphadenectomy performed patients. This allowed us to create a homogenized study group. This is the most remarkable advantage of this study. Besides, the other inclusion and exclusion criteria strengthen study homogenization.

In conclusion; lymph node metastases, LVSI and vaginal involvement are independent prognostic factors for PI in early stage cervical cancer patients. Therefore, less radical surgical approaches for early stage tumors with no nodal spread and negative LVSI are applicable. For more accurate results, more randomized controlled trails should be done in early stage cervical cancer patients.

Declaration of Competing Interest

The authors have no conflict of interest to declare.

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Glossary

CC: Cervical cancer
PI: Parametrial involvement
LVSI: Lymphovascular space invasion