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Risk factors for parametrial invasion in early-stage cervical cancer: Toward less radical surgery

Erken evre serviks kanserinde parametrial invazyon risk faktörleri: Daha az radikal cerrahi için ipuçları

Sebile Güler Çekiç[1], Mehmet Bulut[2], Merve Aldıkaçtıoğlu Talmaç[3], Emine Aydın[4], Emine Ufuk Büyükkaya Öcal[4], Aysu Akça[5], Ceyhun Numanoğlu[6], Volkan Ülker[7], Özgür Akbayır[4]

[1]*Koç University Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye*

[2]*Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye*

[3]*Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Obstetrics and Gynecology, Division of Gynecologic Oncology, İstanbul, Türkiye*

[4]*Cemil Taşcıoğlu Training and Research Hospital, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, İstanbul, Türkiye*

[5]*Medipol University Faculty of Medicine, Department of Obstetrics and Gynecology, İstanbul, Türkiye*

[6]*Beykent University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, İstanbul, Türkiye*

[7]*Medipol University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, İstanbul, Türkiye*

Abstract

Objective: Radical hysterectomy with parametrectomy remains the standard treatment for early-stage cervical cancer but is associated with significant morbidity. Identifying patients at low risk for parametrial invasion is critical to support less invasive surgical strategies.

Materials and Methods: This retrospective study evaluated 177 patients with Federation of Gynecology and Obstetrics 2018 stage IA-IIB cervical cancer who underwent type III radical hysterectomy with lymphadenectomy between 2001 and 2020. Clinical and pathological data were analyzed to identify predictors of parametrial invasion.

Results: Parametrial invasion was observed in 40 patients (22.6%). These patients were significantly older (mean age 56.05±11.16 vs. 49.21±10.80 years, p=0.013), and they were more likely to be postmenopausal. Parametrial invasion was associated with larger tumor size (35.10±13.72 mm vs. 24.15±13.50 mm), greater depth of stromal invasion (>10 mm), lymphovascular space invasion (LVSI), and lymph node metastases, (pelvic and paraaortic), all p<0.01. Bivariate logistic regression identified age ≥55 years [odds ratio (OR): 3.302 95% confidence interval (CI): 1.432-7.614, p=0.005], LVSI positivity [OR: 3.952 (95% CI: 1.641-9.518, p=0.002], and stromal invasion depth >10 mm [OR: 5.326 (95% CI: 2.157-13.153, p<0.001] as independent predictors of parametrial invasion.

Conclusion: Age ≥55, LVSI, and deep stromal invasion are significant independent risk factors for parametrial invasion. Careful evaluation of these parameters may guide the selection of patients suitable for less radical surgery, potentially reducing morbidity without compromising oncologic outcomes.

Keywords: Early-stage cervical cancer, parametrial invasion, radical hysterectomy, lymphovascular space invasion

PRECIS: Age over 55, lymphovascular space invasion positivity, and deep stromal invasion are independent risk factors for parametrial invasion in early-stage cervical cancer, supporting careful selection for less radical surgery.

Corresponding Author/Sorumlu Yazar: Sebile Güler Çekiç MD,
Koç University Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Türkiye
E-mail: sebileguler@gmail.com **ORCID ID:** orcid.org/0000-0002-1632-1170

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Öz

Amaç: Erken evre kanserinde parametrektomiyi de içeren radikal histerektomi standart tedavi olmaya devam etmektedir, ancak önemli morbidite ile ilişkilidir. Parametrial invazyon riski düşük hastaların belirlenmesi, daha az invaziv cerrahi stratejilerini desteklemek açısından önemlidir.

Gereç ve Yöntemler: Bu retrospektif çalışmada, Jinekoloji ve Obstetrik Federasyonu 2018'e göre evre IA-IIB serviks kanseri tanısı almış, 2001-2020 yılları arasında tip III radikal histerektomi ve lenfadenektomi uygulanmış 177 hasta değerlendirildi. Klinik ve patolojik veriler analiz edilerek parametrial invazyonu öngören faktörler belirlendi.

Bulgular: Parametrial invazyon 40 hastada (%22,6) saptandı. Bu hastalar anlamlı olarak daha yaşlı (ortalama yaş 56,05±11,16'ya karşı 49,21±10,80 yıl, p=0,013) ve çoğunlukla menopozdaki hastalardı. Parametrial invazyon; tümör boyutunun büyüklüğü (35,10±13,72 mm'ye karşı 24,15±13,50 mm), derin stromal invazyon (>10 mm), lenfovasküler alan invazyonu (LVSI) ve lenf nodu metastazı (pelvik ve paraaortik) (p<0,01) ile ilişkili olarak değerlendirildi. Lojistik regresyon analizinde 55 yaş ve üzeri olmak [risk oranı (RO): 3,302 %95 güven aralığı (GA): 1,432-7,614), p=0,005], LVSI pozitifliği [RO: 3,52 (%95 GA: 1,641-9,518), p=0,002] ve stromal invazyon derinliği >10 mm [RO: 5,326 (%95 GA: 2,157-13,153), p<0,001] parametrial invazyonun bağımsız risk faktörleri olarak saptandı.

Sonuç: Elli beş yaş ve üzeri olmak, LVSI pozitifliği ve derin stromal invazyon, parametrial invazyon için anlamlı bağımsız risk faktörleridir. Bu parametrelerin dikkatli değerlendirilmesi, daha az radikal cerrahiye uygun hastaların seçimini yönlendirebilir ve onkolojik sonuçlardan ödün vermeden morbiditeyi azaltabilir.

Anahtar Kelimeler: Erken evre serviks kanseri, parametrial invazyon, radikal histerektomi, lenfovasküler alan invazyonu

Introduction

Cervical cancer has one of the highest mortality rates among gynecologic cancers. The Global Cancer Observatory 2020 study[1] estimated 604,127 cases and 341,831 deaths from the disease in 2020 based on the World Health Organization data[2]. The approved treatment for early-stage cervical cancer is radical type 3 hysterectomy, and removal of the parametrium, and lymph node dissection. These treatments, in particular, removal of the parametrium, causes several morbidities like bladder, bowel, and sexual dysfunction due to the extensive dissection of autonomic nerve fibers controlling these organs[3,4].

The shift toward less radical surgery in early-stage cervical cancer began with Dargent's pioneering retrospective analysis in 2000, which demonstrated that patients with tumor size >2 cm and invasion depth >10 mm had higher recurrence after fertility-preserving surgery[5]. Subsequent studies reinforced the idea that a subset of patients had minimal risk of parametrial invasion, particularly those with tumors <2 cm and invasion depth <10 mm. Reported parametrial invasion rates in this group were 1.94%[6], 0.4%[7], and 0.6%[8]. Frumovitz et al.[9] found a 7.7% parametrial invasion rate among 350 patients with stage IA1-IB1 tumors [Federation of Gynecology and Obstetrics (FIGO) 2009 classification] and identified risk factors for parametrial invasion: tumor size >2 cm, high grade, lymphovascular space invasion (LVSI), and pelvic lymph node involvement.

Based on these studies, the European Society of Gynecological Oncology (ESGO) recommended minimally invasive treatment options for stage 1A-1B1 cervical cancer patients in 2018[10]. Later on, a systematic review of 21 studies, reported that stage IA and a small portion of Stage IB1 patients were suitable for minimal invasive surgery and they emphasized potential increased risk of mortality among IB1 patients[11].

Recently, Plante et al.[12] reported their non-inferiority trial -the simple hysterectomy and pelvic node assessment trial- in patients with a tumor size less than 2 cm and cervical invasion depth less than 10 mm that simple hysterectomy did not worsen the 3-year outcomes of early-stage cervical cancer. However, extra-pelvic recurrence and death from cervical cancer were higher in the simple hysterectomy group, although statistically insignificant.

It is well known that parametrial invasion is an important risk factor for the prognosis of cervical cancer[9,13-17]. In this study, we aimed to identify the risk factors affecting parametrial invasion in our prospectively collected data.

Materials and Methods

This study was approved by the Kanuni Sultan Süleyman Training and Research Hospital Local Ethics Committee (approval number: KAEK/2014/3/10, date: 31.12.20214). Our clinic has a prospectively collected database of all the oncologic patients starting from 1998, in which demographic information, type of surgery, postoperative complications, and postoperative follow-ups are documented. In this study, patients in this database who had cervical cancer stages IA-IIB according to the FIGO 2009 classification were analyzed retrospectively from 2001 to 2020. Only patients operated by Özgür Akbayır, Volkan Ülker, Ceyhun Numanoğlu and Merve Aldıkaçtıoğlu Talmaç were included. Clinical staging was performed by pelvic examination under general anesthesia and magnetic resonance imaging, following the diagnosis from cervical biopsies, endocervical curettage, and cold conization. They all had type III radical hysterectomy, including resection of pelvic and paraaortic lymph nodes and parametria, and most had bilateral salpingo-oophorectomy according to their menopausal status. The patients were analyzed for their age, menopausal status, parity, body mass index (BMI),

pathological type of the tumor, diameter of the tumor, clinical stage of the tumor, grade of the tumor, LVSI, pelvic lymph node metastasis, parametrial invasion, paraaortic lymph node metastasis, and depth of the invasion. The stages were then converted to FIGO 2018 classification when preparing the data.

Patients with concomitant cancer, those who received neo-adjuvant therapy, those without pelvic lymph node dissection, or those with missing data were excluded.

After informed consent was obtained, the standard surgery applied to all patients was type III radical hysterectomy (type C2 according to Querleu-Morrow classification) with pelvic and paraaortic lymph node dissection. Paraaortic lymph node dissection was applied to patients with indications such as palpable lymph nodes or patients with occult disease. In those without indications, inspection of paraaortic lymph nodes was still performed. The largest diameter of the tumor was regarded as the tumor size on the pathologic specimen. The presence of tumoral cells within lymphatic vessels outside the main tumor was defined as LVSI. Lymph node positivity was determined by the pathologist.

Statistical Analysis

The data were presented as mean ± standard error for normally distributed variables, where normality was checked using the Kolmogorov-Smirnov test. Variables with non-normal distributions were expressed as medians (ranges). All statistical analyses were performed using the IBM SPSS Statistics 22 software (New York, USA). ANOVA was applied for the differences in age and BMI in different stages of the patients and Kruskal-Wallis test was applied for gravida, parity and menopause state. Pearson's chi-square test was applied to evaluate the patient surgical characteristics. For the evaluation of the factors related to parametrial invasion, independent samples t-test or chi-square tests were performed. Receiver operating characteristic (ROC) analysis was performed to define a cut-off for the effect of age on parametrial invasion. Bivariate logistic regression was applied to evaluate the factors associated with parametrial invasion. A *p*-value less than 0.05 was considered statistically significant.

Results

There were 177 patients included in the study. The mean age of the patients was 50.76±11.22; of these, 57.60% were premenopausal and 42.40% were postmenopausal. Only 3 (1.69%) patients did not have any pregnancies, and the median parity was 3 (0-13). Mean BMI was 27.20±4.98 kg/m^2. Details of demographic variables by groups are presented in Table 1a.

The majority of the patients were stage IB2 (39.0%) according to FIGO 2018 classification, followed by stage IB1 (24.3%) and IIB (15.8%) as presented in Table 1b. Squamous cell carcinoma (88.07%) was the most prominent pathology. Among the pathology specimens, 55 were grade I (29.9%), 100 were grade II (56.5%), and 24 (13.6%) were grade III. The average diameter of the tumor was 26.62±13.72 mm, and cervical invasion size was 11.23±7.83 mm. LVSI was positive in 80 (45.2%) patients, pelvic lymph nodes were positive in 49 (27.6%) patients, and paraaortic lymph nodes were positive in 10 (5.6%) patients. All patients had pelvic and paraaortic lymph node dissection, and the median number of pelvic and paraaortic lymph nodes dissected was 20 (7-66) and 3 (0-60), respectively. The number of patients without paraaortic lymph node dissections was 12 (Stage IA1 and IA2).

When patients were grouped according to their stages, there were no differences in age, BMI, gravida, parity, menopausal status, and tumor histology between the groups (Tables 1a and 1b). Histological grades, LVSI, parametrial invasion, pelvic lymph node positivity, and paraaortic lymph node positivity were higher in more advanced stages, as reported in Table 1b. The average age of the patients with parametrial invasion was 56.05±11.16; higher than the average age of patients without parametrial invasion (p=0.013, Table 2). BMI, gravida, and parity of the patients with parametrial invasion were similar to those of patients without invasion (Table 2). Parametrial invasion was more common among menopausal patients (p=0.01, Table 2). To determine a cut-off value for the impact of age on parametrial invasion, we performed a ROC analysis. The area under the curve (AUC) was found to be 68% [AUC: 0.679 (95% confidence interval (CI): 0.579-0.778), p <0.001]. Age was set at 55 with 60.0% sensitivity and 73.7% specificity. For patients with parametrial invasion, mean tumor size was 35.10±13.72 mm, larger than those without invasion whose was 24.15±13.50 mm (p<0.01, Table 3). Moreover, for those whose tumor size was greater than 2 cm, parametrial invasion was prevalent, occurring in 90.00% of cases (n=36) (p<0.001, Table 2). Among those with parametrial invasion, 22.50% of patients were in stage IB, 7.50% were in stage IIA, and 70.00% were in stage IIB (p=0.009, Table 3). Grade I tumor was detected in 12.50%, whereas grades II and III were detected in 87.50% (p=0.006, Table 3). LVSI was positive in 75.00% of the patients with parametrial invasion (p<0.001, Table 3). Pelvic lymph node metastasis was present in 45.00% of the cases (p=0.005, Table 3), and paraaortic lymph node metastasis was present in 15.00% (p=0.004, Table 3) among patients with parametrial invasion. Lastly, average invasion depth was 17.10±7.37 mm (p<0.001, Table 3) for those with parametrial invasion, and for 80.00% of this group, the ratio of cervical invasion was greater than 10 mm (p<0.001, Table 2).

Table 1a. Demographic data of the study population

		Age	BMI	Gravida	Parity	Menopause
Clinical Stage	n (%) Total: 177	Mean ± SD	Mean ± SD	Median (range)	Median (range)	n (%)
Stage IA1	8 (4.2)	49.63±8.60	26.38±2.72	3 (2-12)	2 (1-4)	4 (50.0)
Stage IA2	4 (2.3)	54.75±16.70	26.25±1.50	4 (2-5)	2 (2-3)	2 (50.0)
Stage IB1	43 (24.3)	49.84±11.43	27.30±5.07	4 (0-11)	3 (0-10)	16 (37.2)
Stage IB2	69 (39.0)	49.46±10.54	27.00±5.00	4 (2-13)	3 (1-13)	25 (36.2)
Stage IB3	17 (9.6)	50.11±11.93	26.18±4.33	3 (2-12)	2 (1-10)	5 (29.4)
Stage IIA1	4 (2.3)	54.25±7.04	27.25±6.65	4 (2-6)	4 (2-6)	1 (25.0)
Stage IIA2	4 (2.3)	47.25±13.4	23.75±2.06	2 (1-5)	2 (1-5)	2 (50.0)
Stage IIB	28 (15.8)	55.50±11.92	29.00±5.80	4 (0-10)	3 (0-9)	19 (67.8)
p		0.369[a]	0.456[a]	0.869[b]	0.665[b]	0.161[b]

BMI: Body mass index, SD: Standard deviation, [a]: ANOVA test, [b]: Kruskal-Wallis test

Table 1b. Surgical properties of the study group

	Pathology			Grade			LSVI	Parametrial invasion	Pelvic lymph node positivity	Paraaortic lymph node positivity
Clinical Stage	SCC	AdCa	Others	I	II	III	n (%)	n (%)	n (%)	n (%)
Stage IA1	7	1	0	7	1	0	0	0	0	0
Stage IA2	3	0	1	3	1	0	0	0	0	0
Stage IB1	39	3	1	18	23	2	14 (32.6)	0	6 (14.0)	1 (2.3)
Stage IB2	60	9	0	17	45	7	28 (41.1)	7 (10.1)	19 (27.5)	0
Stage IB3	14	1	2	2	9	6	12 (70.5)	2 (11.8)	7 (41.2)	4 (23.5)
Stage IIA1	3	0	1	0	3	1	3 (75.0)	3 (75.0)	1 (25.0)	0
Stage IIA2	4	0	0	2	1	1	3 (75.0)	0	3 (75.0)	0
Stage IIB	25	2	1	4	17	7	20 (71.4)	28 (100)	13 (46.4)	5 (17.9)
p	0.861			**<0.001**[a*]			**<0.001**[a*]	**<0.001**[a*]	**0.007**[a*]	**0.001**[a*]

SCC: Squamous cell carcinoma, AdCa: Adenocarcinoma, [a]: Pearson chi-square test, *: p<0.05

The factors significantly associated with parametrial invasion (age, menopausal status, tumors larger than 2 cm, grade, LVSI positivity, pelvic lymph node positivity, paraaortic lymph node positivity, cervical invasion depth greater than 10 mm) were then analyzed again using the backward regression method. Only age ≥55, LVSI positivity and cervical invasion depth >10 mm were significantly associated with parametrial invasion p=0.007, p=0.011 and p=0.011, respectively; Table 3). Bivariate logistic regression analysis was performed with these three independent factors, and all three were found to be statistically significant (Table 4). Age ≥55 increased the odds of parametrial invasion 3.3-fold [odds ratio (OR): 3.302 (95% CI: 1.432-7.614, p=0.005], LVSI positivity 4 fold [OR: 3.952 (95% CI: 1.641-9.518, p=0.002], and cervical invasion more than 10 mm by 5.3 fold [OR: 5.326 (95% CI: 2.157-13.153, p<0.001] (Table 4).

A subgroup analysis of our cohort (tumor size <2 cm and cervical invasion <10 mm) identified 4 patients with parametrial invasion among 62 patients (6.45%). Within these patients, three were older than 55; one had LVSI; and one had both LVSI and pelvic lymph node positivity. Among patients younger than 55 years who had no LVSI, tumor size <2 cm, and stromal invasion <10 mm, only 1 of 49 (2.0%) had parametrial involvement.

Table 5 summarizes the distribution of key pathological variables according to age groups. Parametrial invasion was observed in 25 of 65 patients (38.46%) aged 55 years or older, compared to 15 of 112 patients (13.39%) under the age of 55.

Table 2. Factors related with parametrial invasion (n=177)

	Parametrial invasion		
	Absent (n=137)	Presence (n=40)	
Parameters	n (%)	n (%)	p
Age (mean ± SD)	49.21±10.80	56.05±1 1.16	**0.013**[a*]
<55	97 (70.8)	15 (37.5)	**<0.001**[b*]
≥55	40 (29.2)	25 (62.5)	
Menopausal state			**0.010**[b*]
Premenopausal	86 (62.8)	16 (40.0)	
Postmenopausal	51 (37.2)	24 (60.0)	
Gravida (median, range)	4 (0-13)	4 (0-12)	0.943[b]
Parity (median, range)	3 (0-13)	3 (0-10)	0.923[b]
BMI (mean ± SD)	26.85±4.78	28.36±5.50	0.089[a]
<30	100 (73.0)	26 (65.0)	0.326[b]
≥30	37 (27.0)	14 (35.9)	
Pathology			0.269[b]
SCC	122 (89.0)	33 (82.5)	
Others	15 (11.0)	7 (17.5)	
Tumor maximum dimension (mm) (mean ± SD)	24.15±13.50	35.10±13.72	**<0.001**[a*]
≤20 mm	61 (44.5)	4 (10.0)	**<0.001**[b*]
>20 mm	76 (55.5)	36 (90.0)	
Clinical stage			**<0.001**[b*]
Stage IA1-2	12 (8.8)	0 (0.0)	
Stage IB1-3	120 (87.5)	9 (22.5)	
Stage IIA1-2	5 (3.7)	3 (7.5)	
Stage IIB	0 (0.0)	28 (70.0)	
Grade			**0.006**[b*]
I	48 (35.0)	5 (12.5)	
II-III	89 (65.0)	35 (87.5)	
LVSI			**<0.001**[b*]
None	87 (63.5)	10 (25.0)	
Present	50 (36.5)	30 (75.0)	
Pelvic lymph node positivity			**0.005**[b*]
None	106 (77.3)	22 (55.0)	
Present	31 (22.7)	18 (45.0)	
Paraortic lymph node positivity			**0.004**[b*]
None	133 (97.1)	34 (85.0)	
Present	4 (2.9)	6 (15.0)	
Invasion deepness (mm) (mean ± SD)	9.52±7.12	17.10±7.37	**<0.001**[a*]
≤10 mm	92 (67.2)	8 (20.0)	**<0.001**[b*]
>10 mm	45 (32.8)	32 (80.0)	

[a]: Independent Samples t-test, [b]: Chi-square tests (pearson chi-square, continuity correction, Fisher's exact test), [*]: p<0.05, SD: Standard deviation

Table 3. The factors related with parametrial invasion

Factors	Unstandardized coefficients		Standardized coefficients			95% CI	
	B	S.E.	Beta	t	p	Lower	Upper
Constant	-0.192	0.128		-1.499	0.136	-0.445	0.061
Menopausal status	-0.145	0.106	-0.171	-1.364	0.174	-0.354	0.065
LVSI positivity	0.176	0.068	0.209	2.577	0.011	0.041	0.310
Pelvic lymph node positivity	-0.011	0.080	-0.012	-0.139	0.890	-0.168	0.146
Paraaortic lymph node positivity	0.204	0.134	0.113	1.525	0.129	-0.060	0.469
Age ≥55	0.298	0.109	0.343	2.738	0.007	0.083	0.513
Tumor size >2 cm	0.040	0.076	0.046	0.526	0.599	-0.110	0.190
Cervical invasion >10 mm	0.196	0.076	0.231	2.579	0.011	0.046	0.345
BMI	0.064	0.064	0.069	1.003	0.317	-0.062	0.190
Grade	0.053	0.065	0.058	0.819	0.414	-0.075	0.181

LVSI: Lymphovascular space invasion, BMI: Body mass index, S.E.: Standard error, Method: Backward regression, Model1: R^2 = 0.279; p<0.001, CI: Confidence interval

Table 4. Independent parameters associated with parametrial invasion (Logistic regression analysis results)

Factors	Reference group	B	S.E.	Wald	df	p	OR	95% CI
LVSI	No	1.374	0.448	9.389	1	0.002	3.952	1.641-9.518
Depth of invasion	≤10 mm	1.673	0.461	13.152	1	<0.001	5.326	2.157-13.153
Age	<55	1.194	0.426	7.849	1	0.005	3.302	1.432-7.614
Constant	-	-3.508	0.514	46.545	1	<0.001	0.030	-

LVSI: Lymphovascular space invasion, S.E.: Standard error, Method: Forward stepwise, Model2: X^2 = 47.143; p<0.001, CI: Confidence interval

Table 5. Stratified analysis of patients according to age

	Parametrial invasion in those <55 years (n=112)			Parametrial invasion in those ≥55 years (n=65)		
	Absent (n=97)	Present (n=15)		Absent (n=40)	Present (n=25)	
Parameters	n (%)	n (%)	p	n (%)	n (%)	p
Age (mean ± SD)	43.67±6.51	43.73±6.44	0.972[a]	62.65±6.37	63.44±5.15	0.604[a]
Menopausal state			0.801[b]			0.281[b]
Premenopausal	86 (88.7)	14 (93.3)		0 (0.0)	2 (8.0)	
Postmenopausal	11 (11.3)	1 (6.7)		40 (100.0)	23 (92.0)	
Gravida (median, range)	3 (0-13)	3 (0-8)	0.479[c]	5 (2-13)	5 (0-12)	0.531[c]
Parity (median, range)	2 (0-13)	2 (0-6)	0.343[c]	4 (1-13)	3 (0-10)	0.465[c]
BMI (mean ± SD)	26.48±4.77	25.40±4.13	0.407[a]	27.75±4.74	30.16±5.52	0.066[a]
<30	73 (75.3)	12 (80.0)	0.940[b]	23 (63.9)	13 (54.2)	0.451[b]
≥30	24 (24.7)	3 (20.0)		13 (36.1)	11 (45.8)	
Pathology			0.600[b]			0.743[b]
SCC	86 (88.7)	12 (80.0)		36 (90.0)	21 (84.0)	
Others	11 (11.3)	3 (20.0)		4 (10.0)	4 (16.0)	

Table 5. Continued

	Parametrial invasion in those <55 years (n=112)			Parametrial invasion in those ≥55 years (n=65)		
	Absent (n=97)	Present (n=15)		Absent (n=40)	Present (n=25)	
Parameters	n (%)	n (%)	p	n (%)	n (%)	p
Tumor max dimension (mm) (mean ± SD)	23.65±12.39	37.60±11.30	**<0.001**[a*]	25.38±15.97	33.60±10.65	**0.026**[a*]
≤20 mm	43 (44.3)	1 (6.7)	**0.005**[b*]	18 (45.0)	3 (12.0)	**0.012**[b*]
>20 mm	54 (55.7)	14 (93.3)		22 (55.0)	22 (88.0)	
Clinical stage			**<0.001**[b*]			**<0.001**[b*]
Stage IA1-2	8 (8.2)	0 (0.0)		4 (10.0)	0 (0.0)	
Stage IB1-3	86 (88.7)	4 (26.7)		34 (85.0)	5 (20.0)	
Stage IIA1-2	3 (3.1)	1 (6.7)		2 (5.0)	2 (8.0)	
Stage IIB	0 (0.0)	10 (66.6)		0 (0.0)	18 (72.0)	
Grade			0.070[b]			0.159[b]
I	36 (37.1)	2 (13.3)		12 (30.0)	3 (12.0)	
II-III	61 (62.9)	13 (86.7)		28 (70.0)	22 (88.0)	
LVSI			**<0.001**[b*]			**0.017**[b*]
None	61 (63.5)	2 (13.3)		25 (62.5)	8 (32.0)	
Present	35 (36.5)	13 (86.7)		15 (37.5)	17 (68.0)	
Pelvic lymph node positivity			**0.010**[b*]			0.153[b]
None	74 (76.3)	6 (40.0)		32 (80.0)	16 (64.0)	
Present	23 (23.7)	9 (60.0)		8 (20.0)	9 (36.0)	
Paraortic lymph node positivity			**0.037**[b*]			0.308[b]
None	94 (97.0)	12 (80.0)		39 (97.5)	22 (88.0)	
Present	3 (3.0)	3 (20.0)		1 (2.5)	3 (12.0)	
Invasion deepness (mm) (mean ± SD)	8.95±6.70	16.47±7.58	**<0.001**[a*]	10.90±7.98	17.48±7.38	**0.001**[a*]
≤10 mm	70 (72.2)	3 (20.0)	**<0.001**[b*]	22 (55.0)	5 (20.0)	**0.005**[b*]
>10 mm	27 (27.8)	12 (80.0)		18 (45.0)	20 (80.0)	

[a]: Independent Samples t-test, [b]: Chi-square tests (pearson chi-square, continuity correction, Fisher's exact test), [c]: Mann-Whitney U test, [*]: p<0.05
SD: Standard deviation

Discussion

In this study, we aimed to identify the risk factors associated with parametrial invasion in early-stage cervical cancer patients who underwent radical hysterectomy. Our findings indicate that age ≥55 years, LVSI positivity, and cervical invasion depth >10 mm are significant independent risk factors for parametrial invasion.

Our results suggested that the incidence of parametrial involvement in early-stage cervical cancer is relatively low, at 6%, particularly in tumors <2 cm with a cervical invasion depth <10 mm. This finding is in line with the literature[6,7,9,18,19]. The ESGO guidelines have already proposed less radical surgical options for carefully selected cases with early-stage disease[10]. Recently, a systematic review found that while less radical surgery is feasible for stage 1A and some stage 1B1 patients, it may be associated with an increased risk of recurrence in patients with larger tumors[11]. We aimed to examine the risk factors that would aid in better patient selection for future studies, especially in this IB1 group.

Our study revealed that patients with parametrial invasion

were significantly older than those without invasion, and menopausal status was significantly associated with higher parametrial involvement. After the logistic regression analysis, determined with ROC analysis, we showed that age ≥55 years increases the odds of parametrial invasion by 3.3-fold. Most studies on risk factors affecting parametrial invasion did not show age differences in parametrial invasion[20-22]. A study of a Taiwanese cohort demonstrated that the average age of patients with parametrial invasion was around 56 years, which supported our findings[16]. A French cohort suggested that age over 65 is an independent risk factor for parametrial invasion[13]. Taskum et al.[23] found that older age was associated with LVSI positivity, however, was not an independent risk factor.

Postmenopausal women have been shown to be more susceptible to HPV positivity[24]. This is often attributed to viral reactivation during menopause and changes in sexual behavior, such as, new partner acquisition[25]. This susceptibility is compounded by age-related immunologic changes, including impaired immune surveillance and hormonal alterations, which may contribute to a more aggressive course of cervical cancer in older women compared to their younger counterparts[26]. Supporting this, studies have demonstrated more severe cytological abnormalities in postmenopausal women, along with a reduced number of transformation zone cells in cervical cytology samples - potentially limiting early detection[27].

The average age of menopause in Türkiye is around 45-49[28,29], and in France it is 52[30]. Additionally, several studies have reported that women are less likely to continue routine gynecologic screenings after menopause[31]. This decline in participation can lead to delayed diagnosis, allowing for disease progression before clinical detection. As a result, age over 55 may emerge as an independent risk factor for parametrial invasion— not solely due to chronological age, but as a surrogate marker for physiological changes and decreased screening participation. These combined factors likely increase the probability of detecting cervical cancer at a more advanced pathological stage, contributing to the higher rates of parametrial involvement observed in older women.

The most critical factors associated with parametrial invasion were LVSI and depth of cervical invasion. In our cohort, tumor size was significantly larger in patients with parametrial invasion, and among those with tumors >2 cm, there was a 90% prevalence of parametrial involvement. However, this was not a significant factor for determining parametrial invasion in the bivariate logistic regression model. Previous studies have consistently demonstrated that larger tumors pose a higher risk for parametrial invasion, supporting the need for careful patient selection when considering fertility-sparing or less radical surgeries[6,19].

LVSI positivity was observed in 75% of the patients with parametrial invasion, and increased the odds of parametrial invasion fourfold in bivariate logistic analysis. LVSI has been recognized as a key predictor of lymphatic spread and worse prognosis in cervical cancer, often guiding decisions regarding adjuvant treatment[12]. Similarly, a cervical invasion depth >10 mm was observed in 80% of cases with parametrial invasion, which increased the odds by 5.3-fold, emphasizing its importance in surgical planning. This finding aligns with prior reports indicating that deep stromal invasion is associated with an increased risk of parametrial invasion[14,16,21,22,32].

Additionally, we found a significant association between parametrial invasion and pelvic lymph node metastasis, as well as paraaortic lymph node metastasis. Lymph node metastasis is a well-established factor influencing the prognosis and treatment strategy for cervical cancer, often necessitating adjuvant chemoradiotherapy to reduce recurrence risk[21].

Study Limitations

Our study has some limitations, including its retrospective nature and single-center design, which may limit generalizability. Additionally, although we performed bivariate analysis to control for confounders, the possibility of selection bias remains. Future prospective studies and clinical trials are needed to validate our findings and refine patient selection criteria for less radical surgeries.

Conclusion

In conclusion, our study highlights that age ≥55 years, LVSI positivity, and cervical invasion depth >10 mm are the most significant predictors of parametrial invasion in early-stage cervical cancer. These factors should be carefully considered when selecting candidates for less radical surgical approaches to optimize oncologic outcomes while minimizing morbidity.

Ethics

Ethics Committee Approval: This study was approved by the Kanuni Sultan Süleyman Training and Research Hospital Local Ethics Committee (approval number: KAEK/2014/3/10, date: 31.12.20214).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: S.G.Ç., M.A.T., C.N., V.Ü., Ö.A., Concept: S.G.Ç., A.A., C.N., V.Ü., Ö.A., Design: S.G.Ç., M.A.T., A.A., C.N., V.Ü., Ö.A., Data Collection or Processing: M.B., M.A.T., A.A., Analysis or Interpretation: S.G.Ç., E.A., E.U.B.Ö., Literature Search: S.G.Ç., M.B., E.A., E.U.B.Ö., Writing: S.G.Ç., C.N., V.Ü., Ö.A.

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