Intermediate-risk factors affecting oncological outcome in patients with FIGO 2018 stage IB2 cervical cancer who do not receive adjuvant therapy

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Abstract. The objective of the present study was to examine how intermediate-risk factors affect the oncological outcomes of patients diagnosed with International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IB2 cervical cancer who do not undergo any adjuvant treatment. A multicentric retrospective study that involved 612 patients who were diagnosed with stage IA-IB2 cervical cancer at seven tertiary gynaecological oncology centres between 1993 and 2023 was conducted. A total of 232 patients were classified as FIGO 2018 stage IB2. Patients who had received neoadjuvant chemotherapy, parametrial or surgical border involvement, received adjuvant therapy and synchronous tumours were excluded from the present cohort. Therefore, the present study cohort consisted of 120 patients who had undergone radical hysterectomy and lymphadenectomy. Among the 120 patients, 89 (74.2%) had squamous cell cancer, 18 (15%) had adenocarcinoma, 2 (1.7%) had a mixed type tumour consisting of squamous cell cancer and adenocarcinoma and 11 (9.1%) had other types of tumours (adenosquamous cancer and glassy cell cancer). Deep cervical stromal invasion was found in 68 (56.7%) patients. The duration of patient follow-up varied from 1 to 246 months, with a median of 36 months. Overall, 6 patients (5%) experienced recurrence and 1 patient (0.8%) succumbed to the disease. The 3-year disease-free survival (DFS) rate was 94%, whereas the 3-year overall survival rate was 99%. The presence of deep cervical stromal invasion had a statistically significant impact on DFS (P=0.038). Deep cervical stromal invasion was found to be associated with recurrence in patients with stage IB2 cervical cancer. Hence, the present study demonstrated that the presence of deep cervical stromal invasion may be considered a key parameter in determining whether adjuvant treatment should be applied in patients with stage IB2 cervical cancer.

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Introduction

According to recent Global Cancer Observatory data, cervical cancer ranked third in terms of prevalence among women, with an estimated 661,021 newly diagnosed cases

and 348,189 deaths globally in 2022 (1). Cervical cancer rates remain significantly high in nations lacking population-based cervical cancer screening initiatives and contribute substantially to cancer-related deaths and morbidity (2).

The staging of cervical cancer has traditionally been performed at the clinical level. However, since the introduction of the 2018 International Federation of Gynecology and Obstetrics (FIGO) staging criteria, surgical and radiological evaluations have been incorporated into the process (3-5). Surgical and radiological data provide key information that can influence treatment (5). According to the FIGO criteria, stage IB1 disease involves an invasive carcinoma that invades the stroma to a depth of >5 mm and is ≤2 cm in its greatest dimension, stage IB2 disease involves an invasive carcinoma that is >2 cm but ≤4 cm in its greatest dimension and stage IB3 disease involves an invasive carcinoma that is >4 cm in its greatest dimension (5). Patients diagnosed with stage IB2 cervical cancer typically undergo radical hysterectomy and pelvic with or without paraaortic lymphadenectomy as standard treatment. This surgical procedure involves the excision of a substantial quantity of vaginal tissue, extending up to the upper half, along with parametrial tissue (6).

Adjuvant therapy is administered in accordance with the presence of histopathological risk factors (7). Lymph node involvement, positive surgical margins and parametrial invasion are considered to be significant risk factors for tumour recurrence (8). It is generally accepted that adjuvant therapy should be part of the standard care provided to patients who have these risk factors (8-10). Nevertheless, there is ongoing debate regarding the 'intermediate-risk' factors. Intermediate-risk factors were established as tumour dimensions of 2-3.99 cm associated with lymphovascular space invasion (LVSI), deep stromal invasion or tumour dimensions of ≥4 cm (11). It is currently unknown whether radical surgery alone or combined with adjuvant (chemo)radiation is a more effective treatment for FIGO 2018 stage IB2 cervical cancer (7,9,11,12). In a previous study, patients with FIGO 2018 stage IB2 who underwent radical hysterectomy and lymphadenectomy had an 83.3% 5-year overall survival (OS) rate (13). In addition, in patients with FIGO 2018 stage IB2-IIA2 cervical cancer with intermediate-risk factors, radical surgery alone achieved similar disease-free survival (DFS) and OS rates as combining radical surgery with adjuvant (chemo)radiotherapy (14).

The FIGO 2018 staging system currently lacks sufficient data to accurately predict the overall oncological outcomes for patients with stage IB2 cancer, particularly those who have undergone radical surgery. The aim of the present study was to examine the effect of intermediate-risk factors on the oncological prognosis of patients with stage FIGO 2018 IB2 cervical cancer who did not receive adjuvant therapy.

Materials and methods

Patient cohort. The present multicentric retrospective study enrolled 612 patients diagnosed with early-stage cervical cancer at seven tertiary gynaecological oncology centres between 1993 and 2023. The seven gynaecological oncology centres were Ankara Bilkent City Hospital (Ankara, Turkiye), Ankara Etlik City Hospital (Ankara, Turkiye), Antalya Training and Research Hospital (Antalya, Turkiye), Etlik Zubeyde Hanim Women's Health Training and Research Hospital (Ankara, Turkiye), Hacettepe University (Ankara, Turkiye), Istinye University (Istanbul, Turkiye) and Bahcesehir University (Istanbul, Turkiye). A total of 232 patients were classified with FIGO 2018 stage IB2 disease. Patients other than those with FIGO 2018 stage IB2 disease, received neoadjuvant chemotherapy, surgical margin positive, who had parametrial invasion, received adjuvant external beam radiotherapy and brachytherapy, received adjuvant chemoradiotherapy, received adjuvant chemotherapy and had synchronous tumours were excluded from the present study. The present study cohort consisted of 120 patients who had undergone radical hysterectomy and lymphadenectomy (Fig. 1). The clinicopathological data of the patients were acquired from their patient files or the hospital's electronic database. Ethical approval in accordance with the Declaration of Helsinki was obtained from the Institutional Review Board of Ankara Bilkent City Hospital (approval no. E2-23-4600; Ankara, Turkiye). Approval was obtained from all institutions participating in the study. All patients provided informed consent for the institution to utilise their clinical data. Gynaecological oncologists were the main professionals responsible for conducting the surgical procedures.

Tumour specimen analysis. The specimens obtained during the surgical procedures were examined by gynaecological pathologists. The tumour size was taken as the maximum diameter of the tumour listed in the final pathology report. The depth of cervical stromal invasion was not determined. Tumours that infiltrated >50% of the full thickness of the cervical stroma are referred to here as showing 'deep cervical stromal invasion'. LVSI was defined by the presence of tumour cells or clusters attached to the walls of blood or lymphatic vessels, as observed using haematoxylin and eosin staining of pathological sections that included both the tumour and surrounding healthy tissue. The presence of surgical border involvement as an indicator of tumour positivity was deemed acceptable when the tumour was detected within a 5 mm margin of the pathological specimen. The detection of tumours in other areas of the vaginal region was referred to as microscopic vaginal involvement. Uterine invasion was characterised by the extension of the disease into the endometrium and/or myometrium, beyond the internal cervical ostium. The histopathological evaluations were performed following the criteria set by the World Health Organization in 2014 (15).

Statistical analysis. SPSS statistical software (version 22.0; SPSS Inc.) was used for the statistical analyses. DFS was calculated as the time between the surgical procedure and the identification of disease recurrence or the date of the most recent follow-up. OS was defined as the time between the initial surgical procedure and subsequent follow-up visits or death due to the disease. The Kaplan-Meier method was utilised to determine the survival curves, and the curves were compared utilising the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

The present study involved 120 patients with a median age of 50 years (range, 26-76 years). The median tumour size

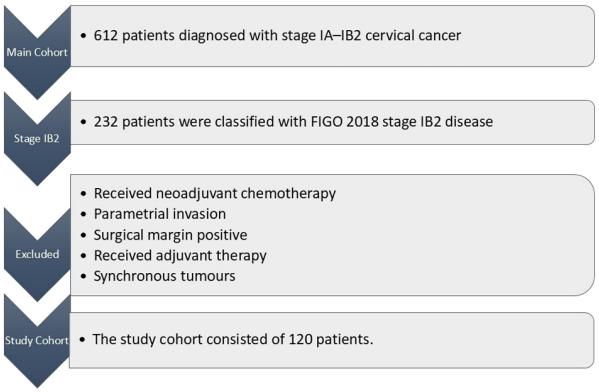

Figure 1. Study cohort selection process. FIGO, International Federation of Gynecology and Obstetrics.

was 30 mm (range, 21-40 mm) and the median lymph node removal count was 45 (range, 14-113). In terms of the tumour types found, 89 (74.2%) patients had squamous cell cancer, 18 (15.0%) had adenocarcinoma, 2 (1.7%) had a mixed type tumour consisting of squamous cell cancer and adenocarcinoma and 11 (9.1%) had other types of tumours (adenosquamous cancer and glassy cell cancer). All patients presented with negative surgical border involvement. LVSI was found in 43 (35.8%) patients, while microscopic vaginal involvement was present in 5 (4.2%) patients. Deep cervical stromal invasion was found in 68 (56.7%) patients. Uterine invasion was present in 7 (5.8%) patients. The present study cohort characteristics are shown in Table I.

The duration of patient follow-up varied from 1 to 246 months and the median was 36 months. Recurrence was observed between 9-42 months in 6 patients (5%; Table II). In 3 (50%) of the patients with recurrence, the disease was located at pelvic sites and in the other 3 (50%) patients, the disease was located at extra-pelvic with or without pelvic sites. Of the 6 patients with recurrence, 1 patient (0.8%) succumbed to the disease. The 3-year OS rate was 99% and the 3-year DFS rate was 94%. Overall, 1 patient had microscopic vaginal involvement. LVSI was observed in 4 patients. All patients with recurrence had deep cervical stromal invasion.

The patient and clinicopathological factors analysed in relation to 3-year DFS are shown in Table III. Patient age, histopathology, tumour size, vaginal metastasis, uterine invasion, LVSI, number of total lymph nodes removed and bilateral salpingo-oophorectomy were not statistically significantly associated with 3-year DFS. In the present study, deep cervical stromal invasion was determined as >50% of stromal invasion. Deep cervical stromal invasion was significantly associated with 3-year DFS (P=0.038; Fig. 2).

Table I. Characteristics of present study group (n=120).

Characteristics	Values
Age at initial diagnosis, years	
Mean ± SD	50.9±10.6
Median, (range)	50 (26-76)
Tumor size, mm	
Mean ± SD	31.3±5.5
Median, (range)	30 (21-40)
No. of removed lymph nodes	
Mean ± SD	47±18.6
Median, (range)	45 (14-113)
Tumor type[a], n (%)	
Squamous cell cancer	89 (74.2)
Adenocarcinoma	18 (15.0)
Mixed type[b]	2 (1.7)
Others[c]	11 (9.1)
Microscopic vaginal involvement, n (%)	
Negative	115 (95.8)
Positive	5 (4.2)
Lymphovascular space invasion, n (%)	
Negative	69 (57.5)
Positive	43 (35.8)
Not reported	8 (6.7)
Depth of cervical stromal invasion, n (%)	
≤50%	48 (40.0)
>50%	68 (56.7)
Not reported	4 (3.3)
Uterine invasion, n (%)	
Negative	112 (93.3)
Positive	7 (5.8)
Not reported	1 (0.8)
Ovarian transposition, n (%)	
Not performed	88 (73.3)
Performed[d]	32 (26.7)
Ovarian metastasis, n (%)	
Negative[e]	91 (75.8)
Positive	0 (0.0)

[a]Tumor type defined according to 2014 WHO cervical cancer categorization criteria. [b]Mixed type included squamous cell cancer and adenocarcinoma. [c]Others included adenosquamous cancer and glassy cell cancer. [d]n=32; 29 patients had bilateral ovary transposed to pelvic side wall and 3 patients had unilateral salpingo-oophorectomy and the other ovary transposed to pelvic side wall. [e]n=91; 88 patients underwent bilateral salpingo-oophorectomy and 3 patients underwent unilateral salpingo-oophorectomy. SD, standard deviation.

Discussion

The survival of patients with cervical carcinoma is influenced by several prognostic factors: Stage, tumour volume, depth of cervical stromal invasion, LVSI, lymph node involvement, parametrium involvement and surgical margin involvement (11,16). The present study involved 120 patients with FIGO 2018 stage IB2 cervical cancer who did not have any high-risk prognostic factors and did not receive any adjuvant treatment. For the present patient group, the mean duration of follow-up was 36 months, the 3-year DFS rate was 94% and the recurrence rate was 5%. Deep cervical stromal invasion was present in 56.7% of the patients and was found to be statistically significantly related to DFS in this group.

Table II. Features of 6 patients with recurrence.

Patient no.	Age, years	Tumor type	Tumor size, mm	Microscopic vaginal involvement	Cervical stromal invasion, %	Spread of endometrium	Over transposition	Lymphovascular space invasion	Recurrence time, months	Recurrence site	Succumbed to disease
1	76	SCC	22	+	>50	-	-	-	42	Pelvic	No
2	42	SCC	30	-	>50	-	+	+	14	Extra-pelvic[a]	Yes
3	70	SCC	35	-	>50	-	-	+	9	Extra-pelvic[b]	No
4	41	SCC	40	-	>50	-	+	+	12	Pelvic	No
5	41	SCC	40	-	>50	-	+	-	28	Extra-pelvic[c]	No
6	58	AC	40	-	>50	+	-	+	15	Pelvic	No

Recurrence sites as follows: [a]Liver, upper abdomen and pelvic; [b]lymphatic, bone and pelvic; [c]lymphatic, liver and pelvic. -, negative; +, positive; SCC, squamous cell cancer; AC, adenocarcinoma.

Table III. Factors related to 3-year DFS in the study cohort (n=120).

Factors	3-year DFS, %	P-value
Median age, years		0.967
≤50	93	
>50	95	
Histopathology[a]		0.825
Squamous cell	94	
Non-squamous cell cancer	94	
Median tumor size, mm		0.169
≤30	98	
>30	88	
Vaginal metastasis		0.122
Negative	94	
Positive	67	
Uterine invasion		0.096
Negative	95	
Positive	67	
Lymphovascular space invasion		0.141
Negative	98	
Positive	88	
Depth of cervical stromal invasion, %		0.038
≤50	100	
>50	90	
Median no. of total lymph nodes removed		0.200
≤45	91	
>45	96	
Bilateral salpingo-oophorectomy		0.132
Not performed	85	
Performed	97	

[a]n=118, 2 patients with mixed type cancer were excluded and were not included in the analysis. DFS, disease-free survival.

It is recommended that patients with early-stage cervical cancer who have had primary surgery and whose risk of disease recurrence is established by the final pathology report receive adjuvant treatment (17). Patients are considered to be at high-risk of recurrence when the pathological findings show that the parametrium is microscopically involved, there is involvement of the pelvic lymph nodes and the surgical margins are positive (17). For patients at intermediate-risk, the Sedlis criteria are employed to classify the disease (11). A comprehensive retrospective analysis of 861 patients with intermediate-risk stage IB1-IIA2 disease reported that there were no substantial disparities in DFS and disease-specific survival between groups that received adjuvant therapy and a group that did not receive adjuvant therapy (18). In a previous study with 765 patients with intermediate-risk FIGO 2018 stage IB disease, adjuvant radiotherapy with or

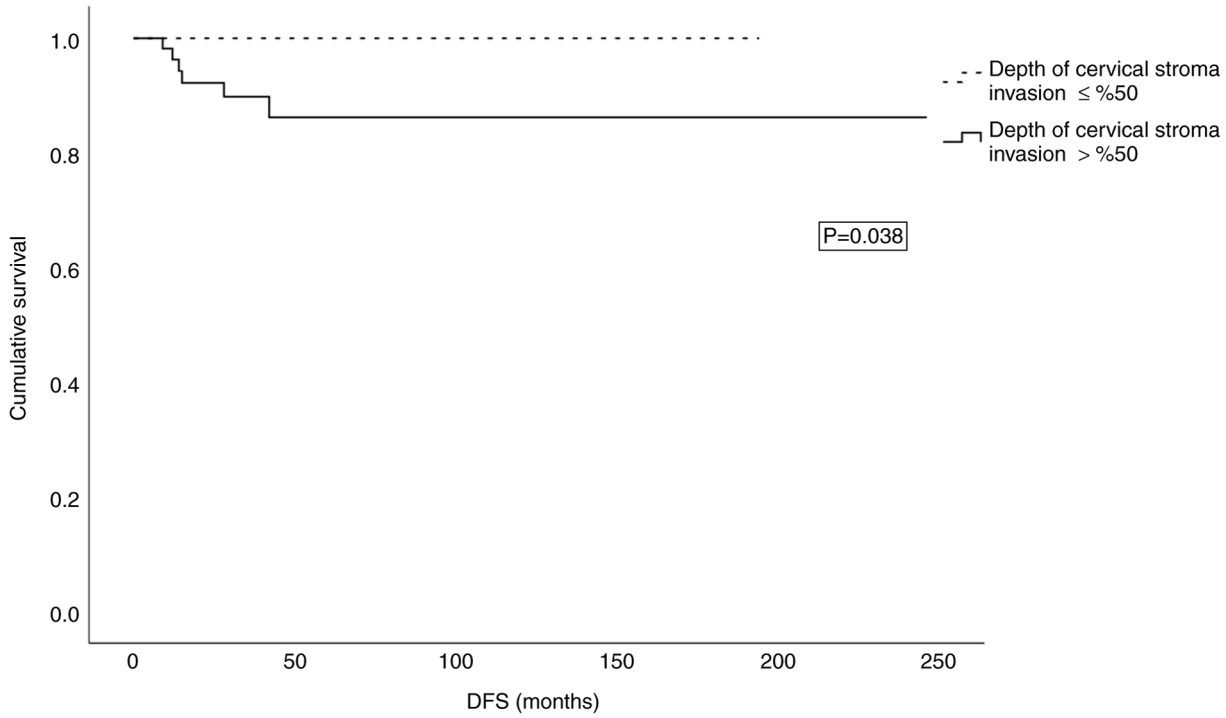

Figure 2. Cumulative survival. Kaplan-Meier curve illustrating 3-year DFS in patients stratified by presence of deep cervical stromal invasion. Deep cervical stromal invasion was significantly associated with 3-year DFS. DFS, disease-free survival.

without ± chemotherapy administered after radical hysterectomy and pelvic lymphadenectomy did not provide a survival advantage (19).

Kissel *et al* (20) conducted a study with 145 patients with FIGO 2018 IB2 cervical cancer who had undergone radical hysterectomy with lymph node staging and found that the 5-year DFS rate for these patients was 74.4%. It was also found that the risk of recurrence increased when the depth of stromal invasion was >10 mm. In the present study, the 3-year DFS rate was 94% and the presence of deep cervical stromal invasion was significantly associated with DFS. Deep cervical stromal invasion was present in all cases of recurrence. The present study group did not include high-risk patients; thus, the present study differs from Kissel *et al* (20) study in terms of DFS. Chen *et al* (21) included 4,065 patients with 2018 FIGO stages IB1, IB2 and IIA1 cervical cancer in their study. The authors found deep cervical stromal invasion was an independent prognostic factor for DFS. This study included patients with stage IB1, IB2 and IIA1 cervical cancer, but the present study included only patients with stage IB2. By contrast, DFS was determined by deep cervical stromal invasion, which was similar to the present research. Zhu *et al* (22) included 3,298 patients with cervical cancer undergoing radical hysterectomy. It found, similar to the present study, that DFS was independently associated with the deep cervical stromal invasion; the authors also demonstrated that postoperative radiotherapy is an independent prognostic factor for DFS (22). Their findings indicated that extra-pelvic recurrence occurred in the majority of patients exhibiting full-thickness cervical stromal invasion following radical surgery. Postoperative radiotherapy in patients with full-thickness cervical stromal invasion may reduce recurrence and enhance survival, which suggests that this population may be suitable for adjuvant radiation therapy (22). The depth of cervical stromal invasion correlated with survival and was proportional to postoperative adjuvant therapy (23-25). Li *et al* (26) conducted a study comparing the DFS of postoperative adjuvant chemotherapy and adjuvant radiation in patients with deep cervical stromal invasion. Their findings indicated that patients demonstrated worse responses to chemotherapy compared with that radiotherapy, and those with full-thickness invasion had an increased risk of recurrence. Moon *et al* (27) found that postoperative radiotherapy may improve DFS in patients with FIGO IB-IIA cervical carcinoma with cervical stromal invasion compared with no adjuvant treatment.

In terms of the location at which cervix cancer recurs, significant variation has been observed. In a previous study that only included patients with FIGO 2018 stage IB2 cervical cancer, recurrence occurred in 14.4% of the patients; 33% of the recurrences were in the central pelvic area, 33% were nodal and 33% were distant metastases (20). In another study conducted with 274 patients with FIGO 2018 stage IB2-IIA2 cervical cancer, 67.4% of the patients had recurrences in the pelvic region and 14% of the patients had a recurrence in another location (14). In the present study, 5% of the patients experienced recurrence, and half of those had recurrence at extra-pelvic with or without pelvic sites.

The main limitation of the present study was its retrospective design. Cervical cancer has been classified as a human papillomavirus-based disease since 2020 (28). Since the present study was retrospective, this new classification was not used and a central pathological review was not conducted. The factors that determined the DFS could not be evaluated in a multivariate analysis, as there were only 6 patients with recurrence. The present study's advantages are its multicentre design and the sample size of participants. Gynaecological

oncologists performed all the surgical procedures and specialised gynaecological pathologists evaluated all the surgical specimens.

In conclusion, patients with FIGO 2018 stage IB2 disease who did not receive adjuvant therapy were found to have a 3-year DFS rate of 94%. Deep cervical stromal invasion was found to be associated with recurrence. Therefore, the presence of deep cervical stromal invasion may be a significant indicator of the need for adjuvant therapy in these patients.

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Availability of data and materials

The data generated in the present study are not publicly available due to privacy or ethical restrictions but may be requested from the corresponding author.

Authors' contributions

AAT designed the study, drafted the manuscript and interpreted the data. OO, OA, AA, AK and VE acquired the data. FK, BE, FC and HEKY performed formal data analysis. OA and OO confirm the authenticity of all the raw data. CC, DY, CK and IS interpreted the data. GKC, NB, DB and IU were responsible for the design of the study. TTo, VK, AK, TTa, OMT, YU, and NO interpreted the data and reviewed the study critically for important intellectual content. TTu analyzed and interpreted the data, critically reviewing it for important intellectual content. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study approved from Ankara Bilkent City Hospital institutional review board (approval no. E2-23-4600; Ankara, Turkiye). Approval was obtained from all institutions participating in the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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