

Clinicopathological characteristic and prognostic factors for FIGO stage 1A2-1B2 of cervical cancer

Kliničkopatološke karakteristike i prognostički čimbenici za rak vrata maternice FIGO stadija 1A2-1B2

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Summary

Introduction: Cervical cancer is one of the most common malignant tumors of the female reproductive system in women between 15-35 years of age. It takes third place in the frequency of all reproductive system cancers in Croatia. The aim of the present study was to analyze prognostic factors influencing on recurrence to improve therapeutic management.

Materials and Methods: We reviewed medical records and pathological materials obtained from 61 patients with stage 1A2-1B2 between 2003 and 2013. The comparison of women with and without recurrence showed statistical significance in certain factors; age when diagnosed, size of tumor, depth of stromal invasion, lymph vascular space invasion, infiltration of the uterine isthmus and lymph node metastases.

Results: Median age at diagnosis was 46 years. Lymph-vascular space invasion (LVSI) was present in 22 (36.1%) with cervical isthmus involvement in 18 (29.5%) patients. Tumor recurrence within observation interval was present in 6 (9.8%) patients. Median time of recurrence was 24 (range 14-48) months. In univariate statistical analysis lymph-vascular space invasion ($P=0.011$), cervical isthmus involvement ($P=0.002$) and positive lymph nodes ($P=0.005$) were significant parameters for occurrence of recidive while in multivariate statistical analysis cervical isthmus involvement ($P=0.036$) remained as only independent risk factor for recidive occurrence.

Conclusion: Cervical isthmus involvement could be of prognostic importance especially in the early stage of cervical cancer when we might decide in adding radiotherapy and concomitant chemotherapy to improve overall survival and lower recurrence rate.

Key words: cervical cancer, prognostic factors, recurrence rate

Sažetak

Uvod: Rak vrata maternice jedan je od najčešćih malignih tumora ženskog reproduktivnog sustava u dobi između 15. i 35. godine života. U Hrvatskoj zauzima treće mjesto po učestalosti svih maligniteta ženskog reproduktivnog sustava. Osnovni cilj retrospektivnog opažajnog istraživanja bio je analizirati prognostičke čimbenike koji utječu na pojavu recidiva raka vrata maternice, kako bi se poboljšalo planiranje liječenja.

Materijali i metode: Između 2003. i 2013. godine analizirali smo 61 bolesnicu s FIGO stadijem raka vrata maternice 1A2-1B2 u Klinici za ženske bolesti i porode KBC-a Zagreb. Statistička analiza podataka pokazala je da su sljedeće varijable značajno povezane s pojavnošću recidiva kod žena oboljelih od raka vrata maternice: dob pri dijagnozi, veličina tumora, dubina invazije tumora u stromu, zahvaćenost istmusa tumorom, limfokapilarna invazija tumora i metastaze tumora u limfne čvorove.

Rezultati: Medijan dobi pri dijagnozi iznosio je 46 godina. Limfokapilarna invazija tumora otkrivena je kod 22 bolesnice (36.1%), uz zahvaćenost istmusa tumorom u 18 (29.5%) bolesnica. Tijekom razdoblja praćenja stopa recidiva bila je 9.8%. Medijan pojavnosti recidiva iznosio je 24 mjeseca. Univarijantna statistička analiza pokazala je limfokapilarnu invaziju tumora ($p = 0.011$), zahvaćenost istmusa tumorom ($p = 0.002$), te metastaze tumora u limfne čvorove ($p = 0.005$) kao značajne parametre prognoze pojavnosti

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recidiva, dok je zahvaćenost istmusa tumorom ($p = 0.036$) u multivarijantnoj analizi jedini neovisni rizični čimbenik za pojavnost recidiva.

Zaključak: Zahvaćenost istmusa jedan je od važnijih prognostičkih čimbenika ranog raka vrata maternice, koji može utjecati na odluku o uvođenju zračenja i kemoterapije s ciljem poboljšanja ukupnog preživljenja i smanjenja stope recidiva.

Ključne riječi: rak vrata maternice, prognostički čimbenici, stopa recidiva

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Introduction

Cervical cancer is one of the most common malignant tumors of the female reproductive system in women between 15-35 years.¹ It is the third most common tumor of all reproductive system cancers in Croatia. There were 280 newly diagnosed patients with invasive cervical cancer and 479 patients with carcinoma in situ in Croatia in 2015. The cancer incidence rate was 12.9/100.000.² The most concerning fact is the increasing number of young women with cervical cancer in recent years. Such patients must survive with treatment-associated sequelae for a long time. Radical hysterectomy and pelvic lymphadenectomy remains the standard treatment option for most patients with clinical early-stage cervical cancer. With similar success with respect to long-term outcome, primary radiotherapy can be performed for patients with stage Ib–IIb cervical carcinoma.³ Since this therapy is associated with side effects such as sexual and bladder dysfunction, a single modality treatment is suggested by some authors to keep morbidity low.⁴ On the other hand, radical treatment is necessary to improve the overall survival.⁵ The aim of the present study was to analyze the prognostic factors influencing on recurrence to improve surgical management.

Materials and methods

After the approval by the Institutional Ethical Committee of UHC Zagreb, we searched the computerized database of our institution for patients with FIGO (International Federation of Gynecology and Obstetrics 2009.) stage IA2-IB2. We reviewed medical records and pathological materials obtained from 61 patients with stage IA2-IB2 between 2003 and 2013.

The inclusion criteria in this study were as follows: histological type of squamous cell carcinoma, adenocarcinoma and other histological types, FIGO stage IA2-IB2, patients who underwent primary radical hysterectomy and pelvic lymphadenectomy and postoperative follow up for at least four years.

The patients received preoperative chemotherapy or radiotherapy, all patients older than 80 years, who

did not fulfil the staging criteria, and those with loss of follow up were excluded. After meeting the inclusion criteria, two major categories of patients were selected: with and without recidive. Analyzed prognostic factors and patients' characteristics are shown in Table 1.

Statistical analysis

Nominal indicators are shown with incidence, number or percentage. The differences in numeric indicators between two independent samples were tested using the Mann-Whitney test. The differences in the nominal ratios (proportions) between the two samples were tested by χ^2 test and the risk ratio with 95% confidence interval. Predictive variables were tested by multivariate analysis using binary logistic regression – Hosmer-Leveshow goodness-of-fit test. The odds ratio was determined with 95% confidence intervals. $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed with the statistical software package SPSS for Windows (version 15.0; SPSS Inc., Chicago, Illinois, U.S.A.)

Results

In total, 61 patients with FIGO staging IA2 (9.8%), IB1 (82%), IB2 (8.2%) were enrolled in the study. Histological subtypes included squamous cell carcinoma 42 (68.8%), adenocarcinoma 120 (19.7%) and other histological types 7 (11.5%). The median age at diagnosis was 46 (range 24-72). Lymphovascular space invasion (LVSI) was present in 22 (36.1%) with cervical isthmus involvement in 18 (29.5%) patients. Tumor recurrence within the observation interval was present in 6 (9.8%) patients. The median time of recurrence was 24 (range 14-48) months. Four years of disease-free survival was 90.2%. The tumor size on pathohistological finding ranged from 0.45 to 6.50 centimetres (median 1.5) in the group without recurrence and from 2 to 4.1 centimetres (median 3.2 cm) in the group with recidive. In univariate statistical analysis, the age at diagnosis ($P=0.047$), size of tumor ($P=0.004$), lymphovascular space invasion ($P=0.011$), cervical isthmus involvement ($P=0.002$) and positive lymph nodes

Table 1 Patients characteristics and analysed prognostic factors
 Tablica 1. Karakteristike bolesnika i analizirani prognostički čimbenici

Study group N=61 / Studijska grupa	Value (median min.-max.) / Vrijednost (srednje min.-maks.)	
Year of birth / Godina rođenja	1963 (1936-1989)	
Age at time of diagnosis (years) Starost kod dijagnoze (godine)	46 (24-72)	
Menarche (years) / Menarhe (godine)	13 (11-17)	
Number of deliveries / Broj poroda	2 (0-7)	
Size of tumor on pathological specimen (cm) Veličina tumora na patološkom primjerku (cm)	1.5 (0.45-6.50)	
Depth of stromal invasion (mm) Dubina stromalne invazije (mm)	6 (0.6-15)	
Number of removed lymph nodes Broj odstranjenih limfnih čvorova	21 (4-47)	
FIGO stage n (%) / FIGO stadij		
IA2	6 (9.8%)	
1B1	50 (82%)	
1B2	5 (8.2%)	
Hystologic type of tumor* / Histološka vrsta tumora* n (%)		
1	42 (68.8%)	
2	12 (19.7%)	
3	7 (11.5%)	
Lympho-vascular space invasion Invazija limfo-vaskularnog prostora	NO	39 (63.9%)
	YES	22 (36.1%)
Cervical isthmus involvement Uključen cervikalni istmus	NO	43 (70.5%)
	YES	18 (29.5%)
Positive lymph nodes Pozitivni limfni čvorovi	NO	57 (93.4%)
	YES	4 (6.6%)
Adjuvant therapy Adjuvantna terapija	NO	42 (68.9%)
	YES	19 (31.1%)
Recidive Recidiv	NO	55 (90.2%)
	YES	6 (9.8%)
Time to recidive (months) Vrijeme recidiva (mjeseci)	24 (14-48)	

($P=0.005$) were significant parameters for the occurrence of recidive (Table 2). There was a borderline statistical significance ($P=0.05$) found between FIGO stage and recidive. In multivariate statistical analysis, the cervical isthmus involvement ($P=0.036$) remained as the only independent risk factor for recidive occurrence (Table 3). The odds ratio was 15.039 (95% CI 1,193 – 189,576).

Discussion

In this retrospective analysis, we demonstrated that cervical isthmus involvement, LVSI and positive lymph nodes were independent risk factors for the recidive of cervical cancer. Several studies analyzed prognostic factors of stage IB-II cervical cancer treated

with radical hysterectomy using multivariate analysis.^{6,7} In these series, vaginal invasion, number of positive nodes, LVSI, parametria involvement and non-squamous cell carcinoma were identified as independent prognostic factors. In these studies, stage IIB of the disease was analyzed together with the early stage of cervical cancer. Stage IIB was described separately by Kamura et al., and the only positive lymph node was the only independent prognostic factor.⁶ In our study, 7% of patients had positive lymph nodes, 50% of patients with lymph node metastasis had recurrent disease, whereas recurrence was present only in 7% of patients who did not have metastases in the lymph node. As it has been shown in other studies, tumor size is an important prognostic factor for stage IB cervical carcinomas.^{8,9}

Table 2 Univariate analysis of the association between continuous variables and disease recurrence
 Tablica 2. Univarijantna analiza povezanosti između kontinuiranih varijabli i recidiva bolesti

Variables <i>Varijable</i>	With recidive (n=6) <i>S recidivom</i>	Without recidive (n=55) <i>Bez recidiva</i>	Z	P
Number of deliveries <i>Broj poroda</i>	1.5 (1-3)	2 (0-7)	-0.317	0.752
Menarche (years) <i>Menarhe (godine)</i>	13 (13-14)	13 (11-17)	-0.621	0.534
Age at diagnosis <i>Dob kod dijagnoze</i>	55 (40-71)	46 (24-72)	-1.987	0.047
Size of tumor (cm) <i>Veličina tumora (cm)</i>	3.2 (2-4.10)	1.5 (0.45-6.50)	-2.914	0.004
Depth of stromal invasion (mm) <i>Dubina stromalne invazije (mm)</i>	8.5 (6-15)	5 (0.6-14)	-2.368	0.018
Removed lymph nodes (n) <i>Uklonjeni limfni čvorovi (n)</i>	21 (4-27)	19 (5-47)	-0.449	0.654

Table 3 Binar logistic regression of the independent variable "cervical isthmus involvement" with respect to the development of recurrence in women suffering from cervical cancer after adaptation to LVSI, positive lymph nodes and tumor size

Tablica 3. Binarna logistička regresija neovisne varijable "zahvaćenost cervikalnog istmusa" s obzirom na razvoj rekurencije kod žena koje pate od raka grlića maternice nakon prilagodbe na LVSI, pozitivnih limfnih čvorova i veličine tumora

Independent variable / <i>Nezavisna varijabla</i>	OR (95% CI)	P
Isthmus involvement / <i>Zahvaćenost istmusa</i>	15.039 (1.193-189.576)	0.036
LVSI	5.379 (0.441-65.584)	0.187
Positive lymph nodes / <i>Pozitivni limfni čvorovi</i>	5.472 (0.314-95.216)	0.244
Size of tumor on pathological specimen <i>Veličina tumora na patološkom primjerku</i>	1.318 (0.659-2.637)	0.435

Univariate statistical analysis in the present study showed that the tumor size was an independent prognostic factor. Therefore, it might be speculated whether the measurement of a single tumor diameter is enough to determine the size of a single tumor or whether a procedure is required that considers all three dimensions of a tumor and its volume. There are no widely used standardized procedures of assessing the size or volume of cervical carcinomas. In almost 28% of patients with cervical isthmus involvement we found recidive, and only 2% patients without isthmus involvement had recidive. Multivariate statistical analysis showed significant statistical independence of isthmus involvement for the development of cervical cancer recurrence even after modification to LVSI, positive lymph nodes and tumor size. These patients had 15-time greater risk of recurrence.

According to literature, 10-15% patients after radical surgery develop recidive of cervical cancer. The recurrence rate in our study was 10%, which is comparable with similar studies. Vale et al. analyzed

individual patient data from randomized trials of radiotherapy alone (\pm surgery) versus the same radiotherapy (\pm surgery) with additional chemotherapy. Adding concomitant chemotherapy had the greatest effects on both overall and disease-specific survival in stages IA–IIA.¹⁰ Our analysis suggests that except for age, LVSI, lymph node metastasis, size of tumor, cervical isthmus involvement could be of prognostic importance especially in the early stage of cervical cancer when we might decide on adding radiotherapy and concomitant chemotherapy considering age, comorbid condition, potential complications, lifestyle and the desire of the patient to improve the overall survival and lower recurrence rate.

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