

Prognostic factors in endometrial carcinoma – a single-center study

Prognostički čimbenici kod oboljelih od raka endometrija

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Summary

Endometrial cancer (EC) is the fourth most common cancer in women in Croatia and the second most common gynecological malignancy with the trend of increasement in incidence. The aim of this single-centre study was to analyze ECs clinical and pathological characteristics and to assess the correlation between risk factors and the recurrence of the disease. We retrospectively reviewed medical records of 174 women that were diagnosed with endometrial cancer between January 2011 and May 2015. Among the women that were diagnosed ECs in the patohistologic specimen, histologic subtype, grade, cancer stage, depth of myometrial tumor invasion, presence of lymph-vascular space involvement (LVSI), lower uterine segment or surface cervical glandular involvement were documented. In addition, women's age, BMI, number of successful deliveries and comorbidities (diabetes mellitus and hypertension) were obtained and incorporated in the statistical analysis. We demonstrated a strong corellation between higher tumor grade, deeper myometrial invasion, presence of lymphovascular space invasion and disease recurrence in our cohort. Due to rapid increasement in incidence, further education, increasement of public awareness, measures for prevention, diagnostic procedures and advances in therapy are imperative to decrease the overall morbidity and mortality rate.

Key words: endometrial cancer; prognostic factors; recurrence rate

Sažetak

Rak endometrija predstavlja četvrti najčešći uzrok maligne bolesti kod žena u Hrvatskoj i ukupno je na drugom mjestu po učestalosti ginekoloških maligniteta, s jasno naznačenom tendencijom porasta incidencije u budućnosti. Cilj istraživanja bio je analizirati kliničko-patološke čimbenike i njihove uzročno-posljedične veze s nastankom recidiva. Retrospektivno smo obradili 174 žene liječene u Klinici za ženske bolesti i porode kojima je dijagnosticiran karcinom endometrija u razdoblju od siječnja 2011. do svibnja 2015. godine. Analizirali smo histološke nalaze i stadij tumora, stupanj, dubinu invazije miometrija, prisutnost/odsutnost limfokapilarne invazije, te invazije strome i donjeg uterinog segmenta. Analizirani su podaci o dobi, indeksu tjelesne mase, paritetu i prisutnim komorbiditetima (dijabetes melitus i arterijska hipertenzija). Rezultati istraživanja pokazuju da na razvoj recidiva karcinoma endometrija značajno utječu sljedeći prognostički čimbenici: dubina invazije tumora, stupanj tumora, limfokapilarna invazija, metastaze u limfnim čvorovima, invazija istmusa i invazija cerviksa.

Ključne riječi: karcinom endometrija; prognostički čimbenici; stopa recidiva.

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Introduction

Endometrial cancer (EC) is the fourth most common cancer in women in Croatia and the second most common site of gynecologic cancer in women

after breast cancer with 659 new cases in Croatia in 2015 and an overall proportion of 6% among all female malignancies.¹ The incidence of this tumor tends to increase with population aging, obesity and comorbidities (e.g. diabetes mellitus and hypertension).²

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Moreover, the EC incidence is estimated to increase by 1-2% annually with EC accounting annually for about 3% of deaths due to cancer.³

The cornerstone of treatment for most of the newly diagnosed women consists of surgery with total hysterectomy and bilateral salpingo-oophorectomy, complemented with pelvic and paraaortal lymphadenectomy in selected cases. Contemporary management of EC is based on personalized surgical and adjuvant treatment. A proper management strategy and its implementation is still controversial with currently used risk assessment methods. Specifically, the issue of lymphadenectomy remains under debate.⁴ About 75% of women with EC are diagnosed in the early stages and have relatively good survival rates; however, women who are diagnosed in advanced-stage or have recurrent disease have a poor prognosis.³

The aim of the present study was to analyze EC clinical and pathological characteristics and to assess the correlation between these risk factors and recurrence development.

Materials and methods

We retrospectively reviewed the medical records of 174 women with endometrial cancer at the Department of Obstetrics and Gynecology, University Hospital Centre, Zagreb, Croatia between January 2011 and May 2015 following the Institutional Review Board approval. Statistical analysis was performed by IBM SPSS ver. 20.0 (IBM Corp., Armonk, NY, USA). Among the women that were diagnosed with EC in the pathophysiologic specimen, histologic subtype, grade, cancer stage, depth of myometrial tumor invasion, presence of lymphovascular space invasion (LVSI), lower uterine segment or surface cervical glandular involvement were abstracted. In addition, women's age, BMI, parity and comorbidities (diabetes mellitus and arterial hypertension) were obtained and incorporated in statistical analysis.

The presence of diabetes mellitus proven by laboratory data (fasting plasma glucose of ≥ 7.0 mmol/L or haemoglobin A1C levels $\geq 6.5\%$), obesity (BMI, calculated as $\text{weight (kg)/[height (m)]}^2$ with values $\geq 25 \text{ kg/m}^2$) and arterial hypertension (defined as office systolic blood pressure values ≥ 140 mmHg and/or diastolic blood pressure values ≥ 90 mmHg) was obtained by reviewing the patient files.

Lower uterine segment involvement (LUSI) was defined as the presence of tumor invasion in the uterine isthmus (a specialized portion of uterus lying between the corpus and cervix uteri). The depth of myometrial tumor invasion was measured from the endomyometrial junction to the deepest point of myometrial

invasion. The endomyometrial junction refers to the transition from endometrium to myometrium. LVSI was defined as the presence of viable tumor cells inside the endothelium-lined channels of uterine specimens, outside the bulk of the invasive tumor.

Surgical staging was performed using the International Federation of Gynecology and Obstetrics (FIGO) 2009 classification.

Descriptive analyses including frequencies, ranges, and percentages of variables were conducted for each variable in each group. Continuous variables were examined for normality by the Kolmogorov-Smirnov test expressed with median (range) as appropriate. The characteristics and differences between the groups were compared using chi-square test for categorical variables and using the Mann-Whitney U test for continuous variables. The potentially important risk factors were tested with stepwise multivariate conditional logistic regression analysis to assess its positive or negative relationship with the presence of disease recurrence. Tumor recurrence was confirmed via clinical pelvic exam or imaging study during regular clinical assessment.

The statistical significance was set at P value < 0.05 . For this type of study, a formal consent was not required, and the Ethical Committee gave approval to conduct the study.

Results

Patients characteristics

During the study period, a total of 174 women were diagnosed with endometrial cancer with a median age of 62 (range 33-84) years while 71.84% of them had comorbidities, as in our study were diabetes mellitus, hypertension or/and obesity. FIGO grade distribution was as follows: 53.45% were grade 1A, 31.61% were grade 1B, 5.75% were grade 2, 0.57% were grade 3A, 5.75% were grade 3C1 and 2.87% were grade 4B. The most common subtype was endometrioid adenocarcinoma (95.98%), followed by mucinous adenocarcinoma (2.30%) and mixed serous-endometrioid carcinoma of the uterus (1.72%).

Following surgery, 68 women (39.1%) received different adjuvant therapy modalities selected from brachytherapy, external-beam radiation therapy, chemotherapy, or concurrent chemoradiation based on the known risk factors evaluated by a gynecologic oncologist.

Disease recurrence was confirmed in an overall of 18 (10.34%) women.

Patient characteristics are summarized in Table 1.

Table 1 Patients' characteristics
Tablica 1 Karakteristike pacijenata

Study group (N = 174) <i>Studijska grupa</i>		Value / Vrijednost (median, min.-max.)
Age at time of diagnosis <i>Starost kod dijagnoze</i>		62 (33-84)
Age distribution <i>Raspodjela godina</i>	> 42 < 42	168 (96.55%) 6 (3.45%)
Parity / <i>Broj poroda</i>		2 (0-6)
Depth of myometrial invasion (mm) <i>Dubina miometrijalne invazije</i>		7 (0-21)
Comorbidities <i>Komorbideti</i>	YES / DA NO / NE	125 (71.84%) 49 (28.16%)
Histologic subtype* <i>Histološki podtip</i>	1 2 3	167 (95.98%) 3 (1.72%) 4 (2.30%)
Grade <i>Stupanj prošivenosti</i>	GI GII GIII	139 (79.89%) 24 (13.79%) 11 (6.32%)
Lymphovascular space invasion (LVSI) <i>Invazija limfovaskularnog prostora</i>	YES / DA NO / NE	36 (20.69%) 138 (79.31%)
Lymph node involvement <i>Zahvaćanje limfnih čvorova</i>	Without dissection / <i>Bez disekcije</i> Negative / <i>Negativno</i> Positive / <i>Pozitivno</i>	49 (28.16%) 114 (65.52%) 11 (6.32%)
Lower uterine segment involvement <i>Zahvaćanje donjeg segmenta maternice</i>	Without involvement / <i>Bez uključivanja</i> Mucosa / <i>Sluznica</i> Stroma Mucosa and stroma combined/ <i>Kombinirano sluznica i stroma</i>	126 (72.41%) 16 (9.20%) 29 (16.67%) 3 (1.72%)
Cervical involvement <i>Zahvaćanje vrata maternice</i>	Without involvement / <i>Bez uključivanja</i> Mucosa / <i>Sluznica</i> Stroma Mucosa and stroma combined/ <i>Kombinirano sluznica i stroma</i>	142 (81.61%) 17 (9.77%) 14 (8.05%) 1 (0.57%)
FIGO 2009.	IA IB II IIIA IIIB IIIC1 IIIC2 IVA IVB	93 (53.45%) 54 (31.61%) 10 (5.75%) 1(0.57%) 1(0.57%) 10 (5.75%) 0 0 5 (2.87%)
Adjuvant therapy <i>Adjuvantna terapija</i>	YES / DA NO / NE	68 (39.1%) 106 (60.9%)
Disease recurrence <i>Recidiv bolesti</i>	YES / DA NO / NE	18 (10.34%) 156 (89.66%)

* 1 = endometrioid adenocarcinoma, 2 = mixed serous-endometrioid carcinoma of the uterus, 3 = mucinous adenocarcinoma
1 = endometrioidni adenokarcinom, 2 = mješoviti serozno-endometrioidni karcinom maternice, 3 = mucinozni adenokarcinom

Univariate and multivariate analysis

Univariate analysis (using disease recurrence as main outcome) showed that tumor grade ($P = 0,004$), lymph node involvement ($P = 0,023$), presence of lymph vascular space invasion ($P = 0,009$), depth of

stromal tumor invasion ($P = 0,001$), lower uterine segment and cervical involvement ($P = 0,024$ and $P = 0,030$, respectively) had influence (Table 2).

On multivariate analysis, there was no statistical significance due to a relatively small number of disease recurrence in cohort ($N = 18$).

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

		Disease recurrence <i>Recidiv bolesti</i>		Total <i>Sveukupno</i>
		YES/DA	NO/NE	
Lymph node involvement <i>Zahvaćanje limfnih čvorova</i>	YES/DA	3 (27.27%)	8 (7.02%)	11
	NO/NE	8 (72.73%)	106 (92.98%)	114
Total / <i>Sveukupno</i>		11	114	125

		Disease recurrence <i>Recidiv bolesti</i>		Total <i>Sveukupno</i>
		YES/DA	NO/NE	
Lymphovascular space invasion (lvs) <i>Invazija imfovaskularnog prostora</i>	YES/DA	8 (44.44%)	28 (17.95%)	36
	NO/NE	10 (55.56%)	128 (82.05%)	138
Total / <i>Sveukupno</i>		18	156	174

		Disease recurrence <i>Recidiv bolesti</i>		Total <i>Sveukupno</i>
		YES/DA	NO/NE	
Lower uterine segment involvement <i>Zahvaćanje donjeg segmenta maternice</i>	YES/DA	9 (50%)	39 (25%)	48
	NO/NE	9 (50%)	117 (75%)	126
Total / <i>Sveukupno</i>		18	156	174

		Disease recurrence <i>Recidiv bolesti</i>		Total <i>Sveukupno</i>
		YES/DA	NO/NE	
	GI	9 (50%)	130 (83.33%)	139
Grade / <i>Razina</i>	GII	6 (33.33%)	18 (11.54%)	24
	GIII	3 (16.67%)	8 (5.13%)	11
Total / <i>Sveukupno</i>		18	156	174

		Disease recurrence <i>Recidiv bolesti</i>		Total <i>Sveukupno</i>
		YES/DA	NO/NE	
	Without involvement <i>Bez zahvaćanja</i>	11 (61.11%)	131 (84.52%)	142
Cervical involvement <i>Zahvaćanje vrata maternice</i>	Mucosa involvement <i>Zahvaćanje mukoze</i>	3 (16.67%)	14 (9.03%)	17
	Stroma involvement <i>Zahvaćanje strome</i>	4 (22.22%)	10 (6.45%)	14
Total / <i>Sveukupno</i>		18	155	173

Discussion and conclusions

The risk factors for endometrial cancer have been already described and include obesity, long-term estrogen replacement therapy, diabetes mellitus, hypertension, nulliparity, infertility or failure to ovulate, polycystic ovary syndrome, early age at menarche, late age at menopause, and selective-estrogen receptor modulator (SERM, such as tamoxifen, raloxifene) use.⁵ Comorbidities, especially obesity, must be considered in the overall treatment strategy because it negatively affects anesthesiologic parameters and surgical performance, delivery of radiation and chemotherapy, with elevated peri-operative morbidity.^{6,7} Approximately 70% of women with early stage of endometrial cancer are obese.⁸ The management of risk factors such as obesity, diabetes, glucose intolerance, and hypertension is demanding in order to minimize the overall risk for EC occurrence. Almost three out of four women from our cohort had at least one comorbidity, which indicates the importance of increasing public awareness and adequate prevention. According to one multivariate linear regression model, which accounts for the expected changes in obesity, hysterectomy rates, and cessation, the prediction is that by the year 2030, the incidence of endometrial cancer will reach approximately 42 cases per 100,000 women, which represents a 55% increase in incidence compared to the one from 2010.⁹ Exploring other risk factors, such as infertility, metabolic syndrome and usage of intrauterine devices, further advancement is necessary in the understanding of disease pathogenesis.

According to clinicopathological studies, several prognostic factors have been developed for ECs which include: age at diagnosis of EC, size of tumor, depth of myometrial invasion, presence or absence of lymph vascular space invasion, tumor grade and stage, involvement of the lower uterine segment, lymph node metastases and others, not analyzed in our study, such as the presence of hormone receptors.¹⁰

The median age in our group at the time of diagnosis was 62 suggesting that low overall survival could be expected since younger women have a better prognosis and lower recurrence rate compared to women older than 65 years.¹¹ Furthermore, the median age of the participants in the present study was equal to that found by Chen LM et al.¹²

There was a strong correlation between higher tumor grade, deeper myometrial invasion, presence of lymph vascular space invasion and disease recurrence in the present cohort. The median value of myometrial invasion in women with disease recurrence was 9 millimeters, while the median in the group with no

recurrence detected was 5 millimeters. These findings can determine the overall treatment strategy in a great part.

The recurrence rate in our study group was 7.5% at early stage EC, which was like recent literature findings.¹³ Most of the women with recurrence of early stage EC were symptomatic at diagnosis, with vaginal bleeding or abdominal discomfort as a main symptom. The overall recurrence rate in our study group was in range or even slightly lower compared to available literature,¹⁴ although an evaluation is necessary in the years to come.

Despite different study designs, the present study confirms recent literature findings,^{10,15,16} extrapolated on Croatian population.

The limitation of our study is in a low number of non-endometrioid tumors. In addition, there were not enough data concerning death events to analyze the overall survival. Prospective evaluation with long-term follow-up is needed to draw an accurate conclusion.

With rapidly increased incidence, further education, increase of public awareness, prevention, diagnostic and therapeutic advance is imperative to decrease the overall morbidity and mortality rate.

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