ONLINE FIRST

This is a provisional PDF only. Copyedited and fully formatted version will be made available soon.

POLISH GYNECOLOGY
GINEKOLOGIA POLSKA
ORGAN POLSKIEGO TOWARZYSTWA GINEKOLOGICZNEGO
THE OFFICIAL JOURNAL OF THE POLISH GYNECOLOGICAL SOCIETY

ISSN: 0017-0011

e-ISSN: 2543-6767

Why do some patients with stage 1A and 1B endometrial endometrioid carcinoma experience recurrence? A retrospective study in search of prognostic factors

Authors: Birol Ocak, Ahmet Bilgehan Sahin, Fatma Oz Atalay, Mine Ozsen, Bahar Dakiki, Seray Ture, Seda Sali, Ozgur Tanriverdi, Mehmet Bayrak, Hakan Ozan, Candan Demiroz Abakay, Adem Deligonul, Erdem Cubukcu, Turkkan Evrensel

DOI: 10.5603/GP.a2021.0093

Article type: Research paper

Submitted: 2021-01-12

Accepted: 2021-04-01

Published online: 2021-05-14

ORIGINAL PAPER / GYNECOLOGY

Why do some patients with stage 1A and 1B endometrial endometrioid carcinoma experience recurrence? A retrospective study in search of prognostic factors

Short title: Prognostic factors in stage 1 endometrial endometrioid carcinoma

Birol Ocak[1], Ahmet Bilgehan Sahin[1], Fatma Oz Atalay[2], Mine Ozsen[2], Bahar Dakiki[3], Seray Ture[3], Seda Sali[1], Ozgur Tanriverdi[4], Mehmet Bayrak[5], Hakan Ozan[5], Candan Demiroz Abakay[6], Adem Deligonul[1], Erdem Cubukcu[1], Turkkan Evrensel[1]

[1]*Department of Medical Oncology, Faculty of Medicine, Uludag University, Bursa, Turkey*

[2]*Department of Surgical Pathology, Faculty of Medicine, Uludag University, Bursa, Turkey*

[3]*Department of Internal Medicine, Faculty of Medicine, Uludag University, Bursa, Turkey*

[4]*Department of Medical Oncology, Faculty of Medicine, Sitki Kocman University, Mugla, Turkey*

[5]*Department of Gynecologic Oncology, Faculty of Medicine, Uludag University, Bursa, Turkey*

[6]*Department of Radiation Oncology, Faculty of Medicine, Uludag University, Bursa, Turkey*

ABSTRACT

Objectives: Endometrial endometrioid carcinoma (EEC) is the most encountered subtype of endometrial cancer (EC). Our study aimed to investigate the factors affecting recurrence in patients with stage 1A and 1B EEC.

Material and methods: Our study included 284 patients diagnosed with the International Federation of Gynecology and Obstetrics stage 1A/1B EEC in our center from 2010 to 2018.

The clinicopathological characteristics of the patients were obtained retrospectively from their electronic files.

Results: The median age of the patients was 60 years (range 31–89). The median follow-up time of the patients was 63.6 months (range 3.3–185.6). Twenty-two (7.74%) patients relapsed during follow-up. Among the relapsed patients, 59.1% were at stage 1A ECC, and 40.9% were at stage 1B. In our study, the one-, three-, and five-year recurrence-free survival (RFS) rates were 98.9%, 95.4%, and 92.9%, respectively. In the multivariate analysis, grade and tumor size were found to be independent parameters of RFS in all stage 1 EEC patients. Furthermore, the Ki-67 index was found to affect RFS in stage 1A EEC patients, and tumor grade affected RFS in stage 1B EEC patients. In the time-dependent receiver operating characteristic curve analysis, the statistically significant cut-off values were determined for tumor size and Ki-67 index in stage 1 EEC patients.

Conclusions: Stage 1-EEC patients in the higher risk group in terms of tumor size, Ki-67, and grade should be closely monitored for recurrence. Defining the prognostic factors for recurrence in stage 1 EEC patients may lead to changes in follow-up algorithms.

Key words: endometrial endometrioid carcinoma; early stage; recurrence-free survival; ki-67; grade; tumor size

INTRODUCTION

While the most common gynecological malignancy in developed countries is endometrial cancer (EC), it ranks second after cervical cancer in developing countries [1]. Approximately 75–90% of patients with EC present with abnormal uterine bleeding, and the most important risk factors are obesity, type 2 diabetes mellitus (DM), high fatty diet, early menarche, nulliparity, late menopause, Lynch syndrome, age > 55 years and chronic tamoxifen use [2–6].

In the traditional classification, EC is divided into two types: estrogen-driven type 1, which includes grades 1–2 endometrial endometrioid carcinomas (EEC), and non-estrogen-driven type 2, which consists of grade 3 EEC and non-endometrioid carcinomas [7]. EEC is the most common subtype, comprising 75%–80% of EC [8].

The stage of EC can be determined using the International Federation of Gynecology and Obstetrics (FIGO) system. In the FIGO staging system, less than half of myometrial invasion is defined as stage 1A, and invasion equal to or more than half of the myometrium is defined as stage 1B EEC [9]. However, FIGO staging alone is inadequate for treatment planning in patients with stage 1 EEC. In the National Comprehensive Cancer Network (NCCN) guidelines, besides myometrial invasion, risk factors such as pathological grade, ≥ 60 years, and lymphovascular invasion are recommended for making therapy decisions. According to risk factors, observation or brachytherapy is recommended after surgery in stage 1A disease [10]. The NCCN uterine cancer guideline recommends brachytherapy ± external beam radiation therapy or radiation therapy ± chemotherapy after surgery in stage 1B disease [10]. In stage 1A and 1B EEC disease, a few patients relapse despite current treatment options.

Our study aimed to investigate the factors affecting recurrence in patients with stage 1A and 1B EEC and identify the clinicopathological features of patients who should be followed up closely for recurrence.

MATERIAL AND METHODS

Study population and data collection

Our study included 284 patients diagnosed with stage 1A/1B endometrial endometrioid carcinoma according to the FIGO 2009 staging system between 2010 and 2018 in the Departments of Medical and Gynecological Oncology, Bursa Uludag University. The patients who could not be staged, who had a second history of malignancy, and who were under the age of 18 were excluded.

As study variables, the demographic characteristics (age, body mass index, presence of DM and parity), histopathological features (tumor size, lower uterine segment involvement, lymphovascular space invasion, and accompanying non-tumor lesion), total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) and TAH and BSO plus bilateral pelvic paraaortic lymph node dissection (BPPLND) as surgical types, external radiotherapy, brachytherapy and chemoradiotherapy as applied treatments as well as oncological results (follow-up time, any recurrence development and recurrence-free survival) were obtained retrospectively from the patients' electronic files. In addition to all these variables, estrogen receptor (ER), progesterone receptor (PR), Ki-67 level, tumor grade and myometrial invasion were obtained from the histopathological examination.

Treatment features

Surgical treatment of endometrial cancer in our institution is a total hysterectomy and bilateral salpingo-oophorectomy. Intraoperative frozen section analysis was routinely performed in all cases. Pelvic and paraaortic lymphadenectomy is also performed for women whose frozen section analysis reveals a tumour type other than EEC, grade 3 histology, cervical invasion, myometrial invasion greater than 50% depth, and tumour size greater than 2 cm.

Brachytherapy was applied to the patients with stage 1A/grade 1–2 EEC, in the presence of high-risk factors (lymphovascular space invasion and age $\geq$ 60). Brachytherapy was applied to all patients to patients with stage 1A/grade3 and stage 1B. The treatment dose was given to the vaginal 1/3 apex area, 5 mm deep from the vaginal surface with a high dose rate brachytherapy device using the Ir-192 source. The doses applied to the vaginal mucosa,

rectum, and bladder were calculated according to International Commission on Radiation Units and Measurements. A total dose of 18–24 gray (Gy) was planned with a fraction dose of 6–7 Gy. External radiotherapy was applied to stage 1B/grade 3 cases. The total dose of 45 Gy (1.8 Gy per fraction) was delivered to the primary tumor site and pelvic lymph nodes.

Histological examination

Hematoxylin-Eosin and immunohistochemical staining of specimens (Ki-67, ER and PR) were re-evaluated, and histopathological features (grade, myometrial invasion) were recorded. The slides of the cases were evaluated using a light microscope (model BX51TF, Olympus, Tokyo, Japan). Histological grading was performed using the International Federation of Gynecology and Obstetrics (FIGO) grading system. Myometrial invasion depth was evaluated in two categories of being less than half (less than 50%) or more than half (50% or more) in the slide with the deepest tumor penetration. The ER assay clone used was SP1, the PR assay clone used was 1E2, and the Ki-67 assay clone used was 30–9. Only nuclear staining was considered as positive immunostaining for ER, PR, and Ki-67, and staining was scored according to the percentage of nuclear staining. Staining of $> 1\%$ of tumor cell nuclei is considered positive for ER and PR staining. For Ki-67, at least 1000 cells were counted at x400 magnification from the hot-spot areas in each sample.

Outcomes

Recurrence-free survival (RFS) was defined as the time between the date of surgical staging and the date of histologically or radiologically confirmed recurrence. Overall survival (OS) was determined from the time of diagnosis until death from any cause.

Ethics

Our study was conducted in accordance with the 1964 Helsinki declaration. The clinical research ethics committee of the Bursa Uludag University Faculty of Medicine approved the study (Approval number: 2020-6/33). As this study is based on retrospective analysis of encrypted data, informed consent was not needed.

Statistical analysis

The continuous variables were expressed by the mean and median values, and the categorical variables were expressed by frequency and the corresponding percentage values. Survival analysis was calculated using the Kaplan-Meier method. The factors were examined

by Cox Regression Analysis. The enter model was used with the parameters having a p-value below 0.20 to determine the independent factors. The data were statistically processed using IBM SPSS version 22 software. In all statistical analyses, $p < 0.05$ was accepted as statistically significant for the results. A time-dependent receiver operating characteristic (ROC) curve analysis was performed with R software version 3.4.2 and the survival ROC package version 1.0.3. The nearest neighbor estimator with a span of $\lambda = 0.05$ was used. The cut-off point that achieves this maximum Youden-J index was accepted as the optimal cut-off point. The area under the ROC curve (AUC) value was obtained from the ROC curve analysis.

RESULTS

General findings

The clinicopathological features of and treatment options for stage 1 EEC patients are presented in Table 1. The median age of patients was 60 years (range 31–89). The median body mass index (BMI) of the patients was 33.6 (range 20.4–63.7) kg/m^2. Among the patients, 118 (41.6%) had a history of DM, 88.7% were multiparous, 54.6% underwent TAH with BSO and BPPLND, 77.8% were at stage 1A, and 22.2% were at stage 1B. The median tumor size was 3.2 cm (range 0.3–10.0). 42 (14.8%) patients had no myometrial invasion, 179 (63.0%) had less than 50% myometrial invasion, and 63 (22.2%) had 50% or more myometrial invasion.

Most of the patients were in grade 1 (48.9%). The median Ki-67 index was 20 (range 1.0–90.0). Among the patients, 61 (21.5%) had lower uterine segment involvement, 16 (5.6%) had lymphovascular invasion, and 65 (22.9%) had adenomyosis. The number of patients with a positive estrogen receptor (ER) and a positive progesterone receptor (PR) was 243 and 240, respectively. After surgery, 159 (56.0%) patients were treated with radiotherapy, five patients (1.7%) with chemoradiotherapy. Among the patients, 42.3% were followed up without treatment.

Oncological outcomes

The median follow-up time of the patients was 63.6 months (range 3.3–185.6). Twenty-two (7.74%) patients relapsed during follow-up. Among the relapsed patients, 59.1% were at stage 1A ECC, and 40.9% were at stage 1B. The median time between diagnosis and tumor recurrence was 33.4 (range 3.9–100) months. Tumor recurrence occurred in the vagina in nine

patients, in the lung in five patients, in the peritoneum in four patients, in the bladder in one patient, in the colon in one patient, in the intra-abdominal lymph node in one patient, and in the bone in one patient.

In our study, the one-, three-, and five-year RFS rates were 98.9%, 95.4%, and 92.9%, respectively. The OS rates for one, three, and five years were 99.3%, 95.4%, and 93.3%, respectively.

The factors affecting recurrent free survival for all FIGO stage 1 EEC patients in the study

The factors affecting RFS in FIGO stage 1 EEC patients were evaluated after univariate analysis, and grade, myometrial invasion, tumor size, ER, PR, and Ki-67 index were included in the multivariate analysis. In the multivariate analysis, grade and tumor size had a statistically significant effect on disease recurrence ($p = 0.034$, $p = 0.011$, respectively) (Tab. 2).

The time-dependent ROC curve analysis was performed to obtain a cut-off value for tumor size, which had an effect on relapse in stage 1 ECC patients. In the time-dependent ROC curve analysis for tumor size, the AUC was found to be significant for the time intervals of 26.4–32.6 and 74.2–100 (months). The cut-off values corresponding to the maximum Youden-J index were 3 cm and 2.2 cm, respectively. This finding means that a tumor size greater than 3.0 cm predicts recurrence after 26.4 months and that a tumor size greater than 2.2 cm predicts recurrence after 74.2 months significantly. No significant AUC was found for the other time points (Tab. 3). The time-dependent ROC curves of the tumor size for the 26.4–32.6 time interval and for the 74.2–100 time interval are presented in Figure 1.

The factors affecting recurrent free survival for FIGO stage 1A EEC patients

Grade, Ki-67 index, ER, adjuvant therapy and lower uterine segment involvement were included in the multivariate Cox regression analysis in which stage 1A EEC patients were evaluated. The Ki-67 index had a statistically significant effect on RFS ($p = 0.019$) (Table 4). A time-dependent ROC curve analysis was performed to obtain a cut-off value for the Ki-67 index. Stage 1A patients were analyzed for the Ki-67 index, and no significant AUC value was found in the time-dependent ROC curve analysis. Also, time-dependent ROC curve analysis was performed to evaluate the Ki-67 index in all stage 1 EEC patients. For Ki-67, the AUC was found to be significant for the time interval of 64.2–74.1 and 74.1–185.6

(months). The cut-off values were 30% and 20%, respectively. This means that Ki-67 values greater than 30% predicted recurrence after 64.2 months and that Ki-67 values greater than 20% predicted recurrence after 74.1 months significantly. No significant AUC was found for the other time points (Tab. 5).

The factors affecting recurrent free survival for FIGO stage 1B EEC patients

After the univariate analysis, age, BMI, grade, tumor size, and PR status of stage 1B ECC patients were included in the multivariate analysis, and the grade was found to have a statistically significant effect on RFS for stage 1B patients ($p = 0.031$) (Tab. 6). The effect of grade on RFS is presented in Figure 2.

DISCUSSION

In this study, we found tumor size and grade as prognostic factors for recurrence with multivariate analysis in stage 1 EEC patients, while we found that Ki-67 index in stage 1A EEC patients and tumor grade in stage 1B EEC patients were prognostic factors affecting recurrence.

In many studies, EC patients were evaluated according to FIGO staging as stages 1–4 [11–14] or stages 1–2 [15–17]. Although these studies provide general information about relapse-related factors and survival in EC patients, there are a limited number of studies about stage 1 EEC disease. To our knowledge, except for the study of Han et al. [18], there is no large-scale research investigating the recurrence factors in stage 1A and 1B EEC disease.

Many studies have confirmed the prognostic value of grade in EC patients [11, 16, 18]. Han et al. [18] study showed that grade was a statistically significant factor for recurrence in all patients with stage 1 EEC. However, multivariate analysis revealed that tumor grade was an independent factor for recurrence in patients with stage 1B disease, and myometrial invasion was an independent factor in patients with stage 1A disease. Likewise, in our study, we found that tumor grade is an independent prognostic factor on recurrence in stage 1 EEC patients and stage 1B EEC patients, not for stage 1A. Therefore, our study is one of the studies showing that these features are prognostic factors.

Although there are studies in which tumor size is not one of the factors affecting survival in patients with EEC [16, 18, 19], Schink JC. et al. [20] evaluated stage 1 ECC

patients and reported that tumor size was a prognostic factor for survival, as in our study. In this study, the cut-off value was 2 cm. In the time-dependent ROC curve analysis for tumor size, the risk of recurrence increased after 26.4 months in patients with a tumor size greater than 3 cm and after 74.2 months in patients with a tumor size greater than 2.2 cm.

Except for resting cells (G0), Ki-67 protein is expressed at all active cell cycle stages (G1, S, G2, M) [21]. It is used as a marker of cellular proliferation; its prognostic and predictive value was shown in several cancer types, including endometrial cancer [22, 23]. Kitson et al. [24] investigated prognostic factors, including Ki-67 in stages 1–4 EC patients. Ki-67 was associated with worsening of cancer-specific survival in the univariate analysis. However, this significance was not detected in the multivariate analysis. Yu et al. [25], examined stages 1–4 EC patient group and found that Ki-67 was associated with stage, differentiation, depth of myometrial invasion, and lymph node status. The studies investigating the importance of Ki-67 consisted mainly of all EC subtypes and stages 1–4 patient groups. To the best of our knowledge, our research is the first to show the effect of the Ki-67 index on recurrence in stage 1A disease in the multivariate analysis. In the study, no statistically significant cut-off value was determined in the time-dependent ROC analysis for Ki-67 in stage 1A EEC patients. However, in all stage 1 ECC patients, Ki-67 values greater than 30% predicted recurrence after 64.2 months, and Ki-67 values greater than 20% predicted recurrence after 74.1 months significantly.

The depth of myometrial invasion has been used for staging EEC [9]. In Han et al.'s [18] study, myometrial invasion in stage 1A EEC disease was found to be a prognostic factor in recurrence. Our study included similar patient groups, but the depth of myometrial invasion was not detected as a prognostic factor for recurrence in stage 1A EEC patients. Akar et al. [16] found that myometrial invasion was not associated with RFS and disease-specific survival in patients with stages 1–2 EEC. This finding should be compared with those of studies involving larger groups of stage 1A patients. In our study and Han et al.'s [18] study, age, lymphovascular involvement, lower uterine segment involvement, lymph node dissection, and adjuvant therapy were not prognostic factors recurrence in stage 1 EEC patients. In addition to Han et al., we also studied factors such as BMI, DM, parity, ER and PR status, and presence of adenomyosis. These factors were not found to be prognostic factors for recurrence.

Limitations

Our study's main limitations are its retrospective design and the limited number of relapsed patients. Moreover, there were not enough death events to analyze OS or cancer-specific survival.

CONCLUSIONS

Tumor grade and size were found to be the independent parameters for RFS in all stage 1 EEC patients. The Ki-67 index affected RFS in stage 1A EEC patients, and tumor grade affected RFS in stage 1B EEC patients. In the time-dependent ROC curve analysis, statistically significant cut-off values were determined for tumor size and the Ki-67 index in stage 1 EEC patients. Stage 1-EEC patients in a higher risk group for tumor size, Ki-67 index, and grade, should be closely monitored for recurrence. Defining the prognostic factors for recurrence in stage 1 EEC patients may lead to changes in follow-up algorithms.

Conflict of interest

The authors declare no conflict of interest.

Acknowledments

We would like to thank Dr. Deniz Sıgırlı (Department of Biostatistics, Uludag University, Bursa, Turkey) for the time-dependent ROC curve analysis.

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018; 68(6): 394–424, doi: 10.3322/caac.21492, indexed in Pubmed: 30207593.
2. Van den Bosch T, Coosemans An, Morina M, et al. Screening for uterine tumours. Best Pract Res Clin Obstet Gynaecol. 2012; 26(2): 257–266, doi: 10.1016/j.bpobgyn.2011.08.002, indexed in Pubmed: 22078749.
3. Kitchener HC, Trimble EL. Endometrial Cancer Working Group of the Gynecologic Cancer Intergroup. Endometrial cancer state of the science meeting. Int J Gynecol

Cancer. 2009; 19(1): 134–140, doi: 10.1111/IGC.0b013e3181995f90, indexed in Pubmed: 19258955.

4. Dinkelspiel HE, Wright JD, Lewin SN, et al. Contemporary clinical management of endometrial cancer. Obstet Gynecol Int. 2013; 2013: 583891, doi: 10.1155/2013/583891, indexed in Pubmed: 23864861.
5. Obermair A, Youlden DR, Young JP, et al. Risk of endometrial cancer for women diagnosed with HNPCC-related colorectal carcinoma. Int J Cancer. 2010; 127(11): 2678–2684, doi: 10.1002/ijc.25501, indexed in Pubmed: 20533284.
6. Seebacher V, Schmid M, Polterauer S, et al. The presence of postmenopausal bleeding as prognostic parameter in patients with endometrial cancer: a retrospective multi-center study. BMC Cancer. 2009; 9: 460, doi: 10.1186/1471-2407-9-460, indexed in Pubmed: 20028502.
7. Felix AS, Weissfeld JL, Stone RA, et al. Factors associated with Type I and Type II endometrial cancer. Cancer Causes Control. 2010; 21(11): 1851–1856, doi: 10.1007/s10552-010-9612-8, indexed in Pubmed: 20628804.
8. Kurman R, Carcangiu M, Herrington C, et al. WHO classification of tumours of female reproductive organs International Agency for Research on Cancer. World Health Organization Lyon: International Agency for Research on Cancer. 2014: 126–128.
9. Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009; 105(2): 103–104, doi: 10.1016/j.ijgo.2009.02.012, indexed in Pubmed: 19367689.
10. National Comprehensive Cancer Network. Uterine Neoplasms, Version 1.2021. https://www.nccn.org/professionals /physician_gls/pdf/uterine.pdf (2021.01.10).
11. Sorbe B. Predictive and prognostic factors in definition of risk groups in endometrial carcinoma. ISRN Obstet Gynecol. 2012; 2012: 325790, doi: 10.5402/2012/325790, indexed in Pubmed: 23209924.
12. Huijgens ANJ, Mertens HJ. Factors predicting recurrent endometrial cancer. Facts Views Vis Obgyn. 2013; 5(3): 179–186, indexed in Pubmed: 24753943.
13. Kaewpangchan P, Cheewakriangkrai C. Relapse patterns and outcomes following recurrence of endometrial cancer in northern Thai women. Asian Pac J Cancer Prev. 2015; 16(9): 3861–3866, doi: 10.7314/apjcp.2015.16.9.3861, indexed in Pubmed: 25987050.

14. Ayık Aydın H, Erdoğan G, Pestereli HE, et al. Role of less commonly agreed risk factors on disease recurrence in endometrial cancer: a propensity scorematched comparison. Turk J Obstet Gynecol. 2019; 16(1): 55–62, doi: 10.4274/tjod.galenos.2019.24571, indexed in Pubmed: 31019841.
15. Ayhan A, Tuncer Z, Tuncer R, et al. Risk factors for recurrence in clinically early endometrial carcinoma: an analysis of 183 consecutive cases. European Journal of Obstetrics & Gynecology and Reproductive Biology. 1994; 57(3): 167–170, doi: 10.1016/0028-2243(94)90294-1.
16. Akar S, Harmankaya I, Celik C. Prognostic significance of tumor grade in early-stage endometrioid endometrial cancer. Annals of Medical Research. 2019; 26(9): 1777, doi: 10.5455/annalsmedres.2019.07.442.
17. Jeppesen MM, Jensen PT, Gilså Hansen D, et al. The nature of early-stage endometrial cancer recurrence-A national cohort study. Eur J Cancer. 2016; 69: 51–60, doi: 10.1016/j.ejca.2016.09.033, indexed in Pubmed: 27816832.
18. Han KH, Kim HS, Lee M, et al. Prognostic factors for tumor recurrence in endometrioid endometrial cancer stages IA and IB. Medicine (Baltimore). 2017; 96(21): e6976, doi: 10.1097/MD.0000000000006976, indexed in Pubmed: 28538399.
19. Çakır C, Kılıç İÇ, Yüksel D, et al. Does tumor size have prognostic value in patients undergoing lymphadenectomy in endometrioid-type endometrial cancer confined to the uterine corpus? Turk J Med Sci. 2019; 49(5): 1403–1410, doi: 10.3906/sag-1902-224, indexed in Pubmed: 31650820.
20. Schink J, Miller D, Lurain J, et al. Tumor size in endometrial cancer. Cancer. 1991; 67(11): 2791–2794, doi: 10.1002/1097-0142(19910601)67:11<2791::aid-cncr2820671113>3.0.co;2-s.
21. Scholzen T, Gerdes J. The Ki-67 protein: From the known and the unknown. Journal of Cellular Physiology. 2000; 182(3): 311–322, doi: 10.1002/(sici)1097-4652(200003)182:3<311::aid-jcp1>3.0.co;2-9.
22. National Comprehensive Cancer Network. Breast Cancer, Version 6.2020. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf (2020.10.15).
23. National Comprehensive Cancer Network. Neuroendocrine and Adrenal Tumors, Version 2.2020. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine. pdf (2020.10.15).

24. Kitson S, Sivalingam VN, Bolton J, et al. Ki-67 in endometrial cancer: scoring optimization and prognostic relevance for window studies. Mod Pathol. 2017; 30(3): 459–468, doi: 10.1038/modpathol.2016.203, indexed in Pubmed: 27910946.
25. Yu CG, Jiang XY, Li B, et al. Expression of ER, PR, C-erbB-2 and Ki-67 in Endometrial Carcinoma and their Relationships with the Clinicopathological Features. Asian Pac J Cancer Prev. 2015; 16(15): 6789–6794, doi: 10.7314/apjcp.2015.16.15.6789, indexed in Pubmed: 26434913.

Table 1. Clinicopathological features and treatment options of stage 1 EEC patients

Characteristic		N	(%)
Age (Median) (Range, years)		60.0 (31.0–89.0)	
BMI (Median) (Range, kg/m^2)		33.6 (20.4–63.7)	
Diabetes mellitus	Present	118	41.6
	Absent	166	58.4
Parity	≥ 1	252	88.7
	0	32	11.3
Surgery	TAH with BSO	129	45.4
	TAH with BSO and BPPLND	155	54.6
Stage	1A	221	77.8
	1B	63	22.2
Tumor size (Median) (Range, cm)		3.2 (0.3–10.0)	
Myometrial invasion	Absent	42	14.8
	< 1/2	179	63.0
	> 1/2	63	22.2
Grade	1	139	48.9
	2	124	43.7
	3	21	7.4
Ki-67 (median) (range, %)		20 (1.0–90.0)	
Lower uterine segment involvement	Absent	223	78.5
	Present	61	21.5
Lymphovascular space invasion	Absent	268	94.4
	Present	16	5.6
Adenomyosis	Absent	219	77.1
	Present	65	22.9
Estrogen receptor status	Positive	240	84.5
	Negative	11	3.9
	Missed Data	33	11.6
Progesterone receptor status	Positive	243	85.6
	Negative	8	2.8
	Missed Data	33	11.6
Postoperative treatment	Observation	120	42.3
	Radiotherapy	159	56.0
	Chemoradiotherapy	5	1.7

EEC — endometrial endometrioid carcinomas; ECOG — Eastern Cooperative Oncology Group; BMI — body mass index; TAH — total abdominal hysterectomy; BSO — bilateral salpingo-oophorectomy; BPPLND — bilateral pelvic paraaortic lymph node dissection

Table 2. Univariate and multivariate cox regression analysis of the predictors for all patients recurrence

Factor		**Univariate Analysis**			**Multivariate Analysis**		
		HR	**% 95 CI**	**p**	**HR**	**% 95 CI**	**p**
Age	Years	1.001	0.959–1.044	0.962			
BMI	kg/m^2	0.997	0.943–1.054	0.918			
Diabetes mellitus	Absent (RC) vs Present	1.037	0.455–2.363	0.931			
Parity	Nullipar (RC) vs Multipar	1.017	0.300–3.446	0.978			
Grade		**3.914**	**2.068–7.408**	**< 0.001**	**2.5**	**1.066–5.901**	**0.035**
Myometrial invasion	< 50% (RC) vs ≥ 50%	**1.899**	**0.796–4.534**	**0.148**	0.9	0.311–3.116	0.980
Tumor size	cm	**1.303**	**1.035–1.642**	**0.025**	**1.3**	**1.058–1.818**	**0.018**
Lymphovascular space invasion	Absent (RC) vs Present	1.732	0.639–4.698	0.281			
Lymph node dissection	Absent (RC) vs Present	1.153	0.497–2.675	0.741			
Adenomyosis	Absent (RC) vs Present	1.294	0.497–2.675	0.741			
Ki-67	%	**1.027**	**1.007–1.048**	**0.009**	1.0	0.992–1.044	0.171
Estrogen receptor status	Negative (RC) vs Positive	**3.395**	**0.974–11.834**	**0.055**	6.8	0.774–60.077	0.084
Progesterone receptor status	Negative (RC) vs Positive	**3.360**	**0.776–14.558**	**0.105**	0.2	0.015–5.303	0.398
Lower uterine segment involvement	Absent (RC) vs Present	1.392	0.565–3.428	0.472			
Adjuvant therapy	Absent (RC) vs Present	3.585	0.478–26.876	0.214			

HR — hazard ratio; CI — confidential interval; BMI — body mass index; RC — reference category

*Cox regression model is statistically significant (p = 0.001)

Table 3. Time-dependent ROC curve analysis results and accuracy summaries for tumor size

Time Interval	AUC	p-value	cut-off	Youden J	Sensitivity	Specificity	LR+	LR–
[3.3–4.3)	0.005	1.000	–	–	–	–	–	–
[4.3–6.5)	0.214	0.999	–	–	–	–	–	–
[6.5–9.2)	0.245	0.893	–	–	–	–	–	–
[9.2–13.4	0.559	0.401	–	–	–	–	–	–
[13.4–20)	0.539	1.000	–	–	–	–	–	–
[20–21.3)	0.512	0.464	–	–	–	–	–	–
[21.3–22.1)	0.558	0.322	–	–	–	–	–	–
[22.1–25.8)	0.578	0.220	–	–	–	–	–	–
[25.8–26)	0.592	0.137	–	–	–	–	–	–
[26–26.4)	0.629	0.061	–	–	–	–	–	–
[26.4–32.6)	**0.635**	**0.039**	**3**	**0.250**	**0.745**	**0.505**	**1.505**	**0.505**
[32.6–34.2)	0.562	0.226	–	–	–	–	–	–
[34.2–36.3)	0.531	0.350	–	–	–	–	–	–
[36.3–38)	0.519	0.399	–	–	–	–	–	–
[38–40)	0.543	0.271	–	–	–	–	–	–
[40–46.7)	0.539	0.272	–	–	–	–	–	–
[46.7–51)	0.565	0.272	–	–	–	–	–	–
[51–60.1)	0.544	0.245	–	–	–	–	–	–
[60.1–64.2)	0.583	0.245	–	–	–	–	–	–
[64.2–74.1)	0.593	0.068	–	–	–	–	–	–
[74.1–74.2)	0.620	0.068	–	–	–	–	–	–
[74.2–100)	**0.611**	**0.034**	**2.2**	**0.159**	**0.872**	**0.286**	**1.222**	**0.446**
[100–185.6]	0.582	0.096	–	–	–	–	–	–

AUC — area under the ROC curve; LR+ — positive likelihood ratio; LR — negative likelihood ratio

Table 4. Univariate and multivariate cox regression analysis of the predictors for stage 1A patients recurrence

Factor		**Univariate Analysis**			**Multivariate Analysis**		
		HR	**%95 CI**	**p**	**HR**	**%95 CI**	**p**
Age	Years	1.039	0.974–1.109	0.247			
BMI	kg/m^2	0.976	0.905–1.052	0.519			
Diabetes mellitus	Absent (RC) vs Present	0.734	0.244–2.206	0.581			
Parity	Nullipar (RC) vs Multipar	2.030	0.263–15.676	0.497			
Grade		**2.723**	**1.127–6.580**	**0.026**	1.096	0.345–3.481	0.87
Myometrial invasion	Absent (RC) vs Present	0.185	0.008–4.085	0.286			
Tumor size	cm	1.121	0.793–1.584	0.519			
Lymphovascular space invasion	Absent (RC) vs Present	1.706	0.377–7.729	0.488			
Lymph node dissection	Absent (RC) vs Present	1.741	0.567–5.340	0.332			
Adenomiyozis	Absent (RC) vs Present	1.959	0.640–5.994	0.239			
Ki-67	%	**1.030**	**1.001–1.060**	**0.045**	**1.036**	**1.006–1.067**	**0.01**
Estrogen receptor status	Negative (RC) vs Positive	**4.451**	**0.937–21.137**	**0.060**	5.65	0.651–49.137	0.11
Progesterone receptor status	Negative (RC) vs Positive	2.508	0.322–19.530	0.380			
Lower uterine segment involvement	Absent (RC) vs Present	**2.192**	**0.712–6.744**	**0.171**	0.683	0.134–3.474	0.64
Adjuvant therapy	Absent (RC) vs Present	**3.584**	**0.986–13.031**	**0.053**	3.255	0.651–16.262	0.15

HR — hazard ratio; CI — confidential interval; BMI — cody mass index; RC — reference category

*Cox regression model is statistically significant (p = 0.001)

Table 5. Time-dependent ROC curve analysis results and accuracy summaries for Ki-67

Time interval	AUC	p-value	cut-off	Youden J	Sensitivity	Specificity	LR+	LR–
[3.3–3.9)	0.012	1.000	–	–	–	–	–	–
[3.9–6.5)	0.495	0.511	–	–	–	–	–	–
[6.5–9.2)	0.480	0.555	–	–	–	–	–	–
[9.2–13.4)	0.592	0.341	–	–	–	–	–	–
[13.4–20)	0.480	0.541	–	–	–	–	–	–
[20–21.3)	0.469	0.582	–	–	–	–	–	–
[21.3–22.1)	0.523	0.435	–	–	–	–	–	–
[22.1–25.8)	0.465	0.601	–	–	–	–	–	–
[25.8–26)	0.452	0.668	–	–	–	–	–	–
[26–26.4)	0.507	0.474	–	–	–	–	–	–
[26.4–32.6)	0.553	0.323	–	–	–	–	–	–
[32.6–34.1)	0.520	0.425	–	–	–	–	–	–
[34.1–36.2)	0.554	0.309	–	–	–	–	–	–
[36.2–38)	0.575	0.225	–	–	–	–	–	–
[38–46.7)	0.581	0.185	–	–	–	–	–	–
[46.7–51)	0.615	0.101	–	–	–	–	–	–
[51–60.1)	0.649	0.052	–	–	–	–	–	–
[60.1–64.2)	0.641	0.057	–	–	–	–	–	–
[64.2–74.1)	**0.658**	**0.030**	**30**	**0.276**	**0.534**	**0.742**	**2.072**	**0.628**
[74.1–185.6]	**0.659**	**0.016**	**20**	**0.268**	**0.686**	**0.583**	**1.643**	**0.539**

AUC — area under the ROC curve; LR+ — positive likelihood ratio; LR– — negative likelihood ratio

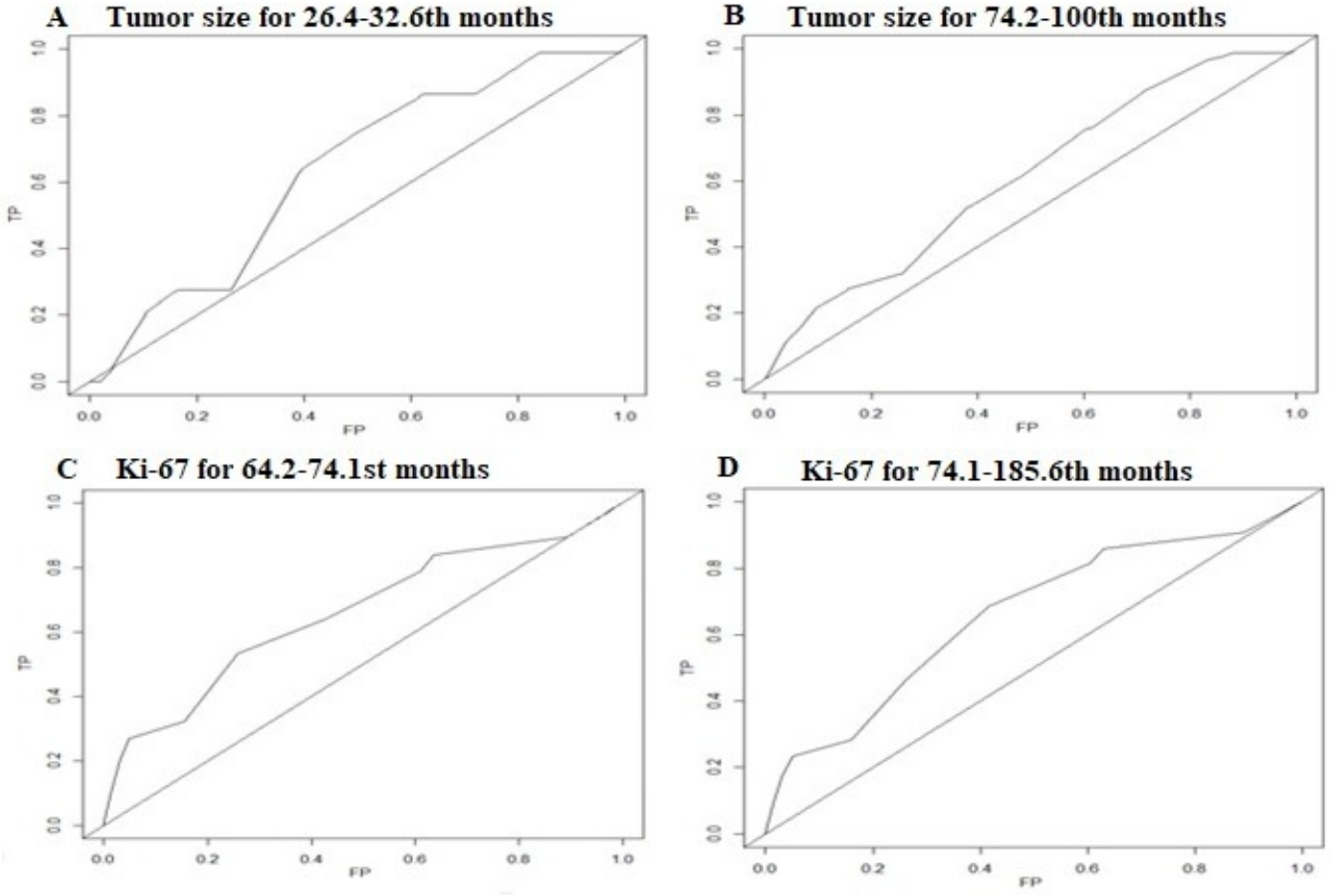
Table 6. Univariate and multivariate cox regression analysis of the predictors for stage 1B patients recurrence

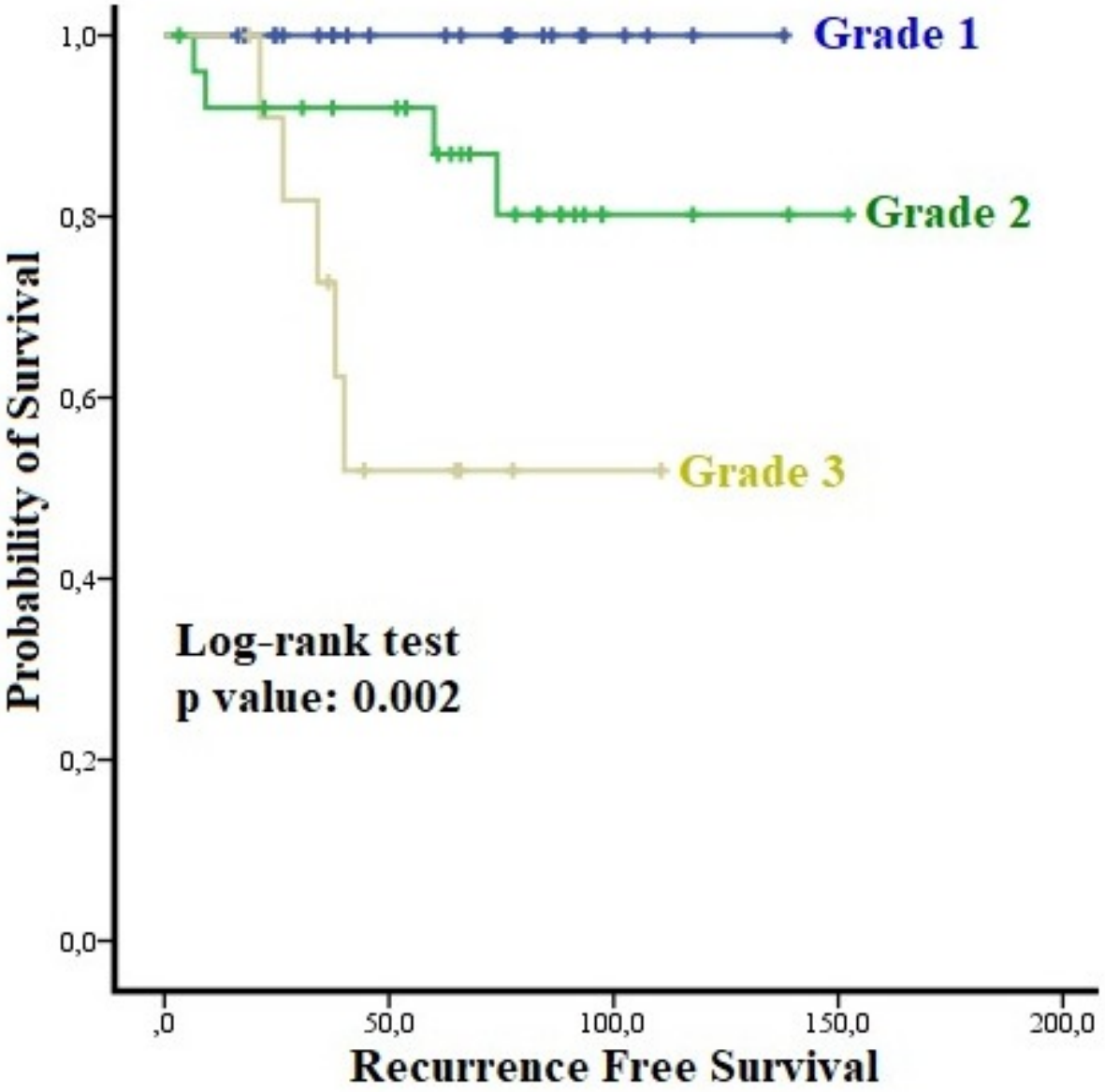
Factor		**Univariate Analysis**			**Multivariate Analysis**		
		HR	**% 95 CI**	**p**	**HR**	**% 95 CI**	**p**
Age	Years	**0.955**	**0.907–1.006**	**0.08**	0.959	0.850–1.082	*0.492*
BMI	kg/m^2	**1.090**	**0.983–1.208**	**0.10**	1.084	0.871–1.350	*0.469*
DM	Absent (RC) vs Present	1.993	0.533–7.448	0.30			
Parity	Nullipar (RC) vs Multipar	0.429	0.089–2.072	0.29			
Grade		**5.371**	**1.783–16.185**		**5.508**	**1.169–25.960**	***0.0310***
Tumor size	cm	**1.344**	**0.999–1.808**	**0.05**	1.013	0.434–2.366	*0.977*
Lymphovascular space invasion	Absent (RC) vs Present	0.981	0.139–1.930	0.32			
Lymph node dissection	Absent (RC) vs Present	0.518	0.497–2.675	0.74			
Adenomiyozis	Absent (RC) vs Present	0.842	0.174–4.072	0.83			
Ki-67	%	1.012	0.918–1.045	0.44			
Estrogen receptor status	Negative (RC) vs Positive	1.598	0.191–13.341	0.66			
Progesterone receptor status	Negative (RC) vs Positive	**5.261**	**0.611–45.289**	**0.13**	4.099	0.357–47.125	*0.258*
Lower uterine segment involvement	Absent (RC) vs Present	0.498	0.103–2.416	0.38			
Adjuvant therapy	Absent (RC) vs Present	1.899	0.233–15.469	0.54			

HR — hazard ratio; CI — confidential interval; BMI — body mass index; RC — reference category; *Cox regression model is statistically significant (p = 0.001)

Figure 1: Time-dependent ROC curves of A) tumor size for 26.4-32.6 time interval, B) tumor size for 74.2-100 time interval, C) Ki-67 for 64.2-74.1 time interval, D) Ki-67 for 74.1-185.6 time interval

Figure 2: Kaplan-Meier curves of recurrence-free survival according to histologic grade in FIGO stage 1B endometrioid endometrial cancer. FIGO: International Federation of Gynecology and Obstetrics


A Tumor size for 26.4-32.6th months
B Tumor size for 74.2-100th months
C Ki-67 for 64.2-74.1st months
D Ki-67 for 74.1-185.6th months
TP
FP
0.0
0.2
0.4
0.6
0.8
1.0


Grade 1
Grade 2
Grade 3
Log-rank test
p value: 0.002
Probability of Survival
1,0
0,8
0,6
0,4
0,2
0,0
,0
50,0
100,0
150,0
200,0
Recurrence Free Survival