VERSITA

Cent. Eur. J. Med. • 6(3) • 2011 • 294-299
DOI: 10.2478/s11536-011-0007-3

Central European Journal of **Medicine**

Independent prognostic factors in endometrial cancer: a single institution review

Research Article

P. Uharček*, M. Mlynček, J. Ravinger, E. Lajtman, M. Matejka

Department of Obstetrics and Gynecology, Faculty Hospital Nitra, 949 01 Nitra, Slovakia

Received 7 August 2010; Accepted 27 October 2010

Abstract: The purpose of this study was to conduct a clinical and pathologic review of endometrial cancers diagnosed and surgically treated in our institution to evaluate results of treatment in relation to current international recommendations. We retrospectively evaluated the clinical history, treatment and follow-up of patients with histologically confirmed endometrial cancer treated in Faculty Hospital Nitra, Slovakia from 1990 to 2005. Data were abstracted regarding tumor histology, grade, age, parity, stage, diabetes, use of oral contraceptives, BMI, survival and treatment modalities including surgery, radiation therapy, chemotherapy, hormonal therapy, and combinations thereof. One hundred and thirty nine patients received surgical treatment for endometrial cancer: stage I –101 (72,6%), stage II – 9 (6,5%) , stage III – 23 (16,6%) and stage IV – 6 (4,3%). Tumors were well differentiated in 87(62,6%), moderately differentiated in 32 (23%) and poorly differentiated in 20 (14,4%). There were 45 (32,4%) premenopausal patients and 94 (67,6%) postmenopausal. In multivariate statistical analysis we identified FIGO stage, tumor type, tumor grade, nodal status and depth of myometrial invasion as independent prognostic factors for overall survival, and FIGO stage, nodal status, and tumor grade as independent prognostic factors for recurrence-free interval.

Keywords: *Endometrial cancer • Prognostic factors • Survival*

1. Introduction

Endometrial cancer is the most common gynecologic malignancy, with an incidence of 25 cases per 100,000 women in Slovakia in 2000 [1]. In 1988 the International Federation of Gynecology and Obstetrics (FIGO) changed the clinical staging of endometrial carcinoma to the surgically based system [2]. The change was based on the prospective surgical staging studies conducted by the Gynaecologic Oncology Group, which demonstrated that the prognosis is related to the presence or absence of histopathologically determined uterine and extrauterine risk factors [3,4]. The optimal surgical treatment for endometrial cancer includes an adequate abdominal incision, peritoneal washing, total hysterectomy, bilateral salpingo-oophorectomy, and also pelvic and para-aortic lymphadenectomy in some cases. In most patients the disease is confined to the uterine corpus. Lymph node involvement is reportedly one of the most potent prognostic factors [4-6]. The new FIGO classification adopted in 2009 addressed new information about prognostic predictors. However, the extent of surgical staging, the definition of high-risk patients who benefit from complete staging especially lymphadenectomy in paraaortic areas is still widely discussed [7].

A great variety of uterine and extrauterine prognostic factors (including histologic type, stage, grade, depth of myometrial invasion, vascular invasion, hormone receptor status, DNA index, peritoneal cytology, p53, c-erb-B2 (HER2/neu)) have been described and evaluated in literature [8]. The aim of this study was to determine and quantify overall survival and recurrence-free interval of endometrial cancer patients over the 15 years period to evaluate multivariate independent prognostic factors in the prognosis of patients with carcinoma of the endometrium.

* *E-mail: uharcek@gmx.net*

2. Material and Methods

We reviewed medical chart data on patients with primary endometrial cancer who were treated at Faculty Hospital, Nitra, Slovakia. 308 consecutive patients with endometrial carcinoma were treated between January 1990 and December 2005. The diagnosis of endometrial carcinoma was established by dilatation and curretage in all patients. Before surgical treatment in all patients vaginal ultrasound was performed to asses depth of myometrial invasion. FIGO surgical staging system adopted in 2009 involving peritoneal washing cytology, total abdominal hysterectomy, bilateral salpingooophorectomy with pelvic and paraaortic lymph node dissection was used. Only patients with complete surgical staging and complete follow-up were included to study. A total of 139 patients were identified. One hundred and sixty nine patients were not eligible for the study because they were not surgically staged. Most of them (152) did not undergo any surgical procedure because of multimorbidity and poor physical status. All of them were older than 70 years of age and were treated by radiotherapy.

The medical records were reviewed retrospectively to define the surgical procedure, the extent of disease and lymph nodes, FIGO stage, the grade and the histology cell type. We assesed depth of myometrial invasion (no invasion, invasion of less than one half of the myometrium, or invasion of one half or more of the myometrium), and retroperitoneal lymph node metastasis (present or absent). Tumor differentiation was categorized as well differentiated (grade 1), moderately differentiated (grade 2) or poorly differentiated (grade 3). The histological types of endometrial cancer in the present study included endometrioid, adenosquamous, clear-cell and papillary serous.

Radiotherapy (brachytherapy or brachytherapy and external beam irradiation) was performed also according to the stage and the patient's comorbidities. Usually, low-risk surgically staged patients (G1,2 tumors, myometrial invasion less than ½ of myometrium) received no radiotherapy, others were treated with brachytherapy, and we added external-beam radiotherapy in high-risk patients.

Routine follow-up consisted of a clinical review at 3-month intervals in the first 2 years and 6–12 month visits thereafter. Also, tumor markers [carcinoembryonic antigen (CEA), Ca125, and Ca19.9] and vaginal ultrasound were performed once a year.

Survival analysis was performed using Kaplan–Meier estimates and the log-rank test. Independent prognostic factors were determined by multivariate Cox regression analysis using a forward stepwise selection procedure. The statistical significance level was set at $p<0.05$. Analyses were performed using SPSS 12.0 (Chicago, IL,USA).

Table 1. Age of endometrial cancer patients.

Age	Number n	%
<45	20	14,3
45-60	58	41,7
>60	61	44
Total	139	100

Table 2. Clinical features of patients.

		n	%
Body mass index	Normal (<25 kg/m^2)	27	19
	Overweight (25-30)	55	40
	Obese (>30)	57	41
Parity	Para 0	30	21
	Para 1	23	17
	Para t2	86	62
Menstrual cycle	Regular	14	70
	Anovulation	6	30
Medical history	Diabetes	31	22
	Hypertension	38	27

3. Results

A total of 139 patients with endometrial carcinoma, 101 (72,6%) were diagnosed as FIGO stage I, 9 (6,5%) as FIGO stage II, 23 (16,6%) as FIGO stage III and 6 (4,3%) as FIGO stage IV. The mean age at diagnosis was 58,8 years (range 25—78). There were 87 patients (62,6%) with tumor grade I, 32 (23%) with tumor grade II, and 20 (14,4%) with grade III tumors, included in this study. The mean age at diagnosis was 55.7 years (range, 25-76 years). There were 45 (32,4%) premenopausal patients and 94 (67,6%) postmenopausal. Age distribution is detailed in Table 1. The majority of our patients were obese. Fourty one percent of patients had a body mass index of more than 30, 40% of patients had a BMI between 25 and 30, and 19% of the patients had a BMI less than 25. There were 30 (21%) nuliparous women and 86 (62%) women were para 2 or more among patients. Thirty-one patients (22%) suffered from diabetes mellitus. Patient characteristics are described in Table 2. The median follow-up time was 80 months (range, 18—152 months) and 18 patients died (12,9%). The cause of the 18 deaths were as follows: in four cases progression of disease without disease free interval resulted in intestinal obstruction, eight recurrences

Table 3. Sites of recurrence in endometrial cancer.

Site of recurrence	N
Vaginal-vault	8
Pelvis	2
Paraaortic lymph nodes	2
Liver	2

(four distant metastases and four pelvic recurrences), six postoperative complications (intestinal obstruction and subsequent complications, pulmonary embolisation in three cases, and a postintervention bleeding with developinng Disseminated intravascular coagulation (DIC) and Multi-Organ System Failure (MOSF) in two cases of severely obese women). Patients with recurrences who died were stage II, IIIA, three cases of IB and four cases of IIIB at diagnosis.

Other eight patients died from unrelated diseases (heart attack, hepatic cirrhosis, stroke, complications of diabetes mellitus) and were not included in the Kaplan-Meier procedure. In 14 (10%) of the patients, recurrent disease could be observed and four (2.9%) patients showed progression of disease without a disease-free interval. The detailed sites of recurrence are described in Table 3. Recurrences were treated with surgery ±radiotherapy ± chemotherapy ± hormonal treatment. Surviving patients with recurrence were in stages 3x IB (follow up after primary treatment 25 months, 38 months and 42 months), 2x IIIA (follow up 32 and 48 months) and II (follow up 18 months). The histopathologic tumor type was an endometrioid adenocarcinoma in 111 cases (79,9%), an adenosquamous carcinoma (10%) in 14 cases. Other histologic types were clear cell carcinoma in eight cases (5,8%) and papillary-serous in six cases (4.3%). The estimated overall survival was 80.4% for patients with adenocarcinoma and adenosquamous carcinoma. This was significantly increased as compared to other tumor types (32.3%). The P-value was 0.0001 for overall survival and 0.0023 for recurrence-free interval. All 139 patients underwent lymph node dissection, 55 had paraaortic lymph node dissection. The median number of lymph nodes obtained was 12.

We performed a univariate analysis to determine the impact of prognostic factors on overall survival. FIGO stage, grade, myometrial invasion >50%, lymph nodes positive for disease (pelvic or para-aortic or both), nonendometrioid histologic subtype, positive peritoneal cytology and distant metastases gave a significant correlation with survival (Table 4). The multivariate analysis revealed that FIGO stage (P<0.001), tumor grade (P<0.009), depth of myometrial invasion (P<0.001), lymph node metastasis (P<0.042), and type of tumor (P<0.001) were associated significantly with the

Table 4. Clinicopathological factors and univariate analysis for overall survival.

Factor		No. of patients (%)	P value
Age	premenopausal	45 (32,4)	NS
	postmenopausal	94 (67,6)	
FIGO stage	I	101 (72,6)	<0,001
	II	9 (6,5)	
	III	23 (16,6)	
	IV	6 (4,3)	
Grade	1	87 (62,6)	0,033
	2	32 (23)	
	3	20 (14,4)	
Myometrial invasion	0	27 (19,4)	<0,001
	≤ ½	72 (51,8)	
	> ½	40 (28,8)	
Lymph node metastasis	negative	121 (87)	<0,001
	positive	18 (13)	
Histologic type	endometrioid	112 (80,6)	<0,001
	adenosquamous	14 (10,1)	
	clear-cell	4 (2,9)	
	papillary serous	9 (6,4)	
Peritoneal cytology	negative	130 (93,5)	0,018
	positive	9 (6,5)	
LVSI	negative	114 (82)	NS
	positive	25 (18)	
Cervical involvement	negative	118 (84,9)	NS
	positive	21 (15,1)	
Adnexal involvement	negative	126 (90,6)	NS
	positive	13 (9,4)	
Distant metastasis	negative	133 (95,7)	0,016
	positive	6 (4,3)	

LVSI – Lymph vascular space invasion
NS – not significant

overall survival (Table 5). FIGO stage (P<0.001), lymph node metastasis (P<0.001), tumor grade (P<0.033), were significantly correlated as independent prognostic factors in multivariate analysis for the disease-free survival (Table 5). We found a strong correlation between FIGO stage and tumor grade (P<0.001) and tumor type (P<0.001). There was no significant correlation between FIGO stage and age, additional diabetes mellitus, or BMI. The tumor grade could be correlated with tumor type (P<0.001). We found a correlation between depth of myometrial invasion and lymph node metastasis (P<0.01). We also observed a strong correlation between depth of myometrial invasion and FIGO stage (P<0.001), and tumor grade (P<0.001). FIGO stage (P<0.001), tumor grade (P<0.033), lymph

Table 5. Multivariate analysis of prognostic factors for overall an recurrence-free survival.

Factor		Overall survival P value	Recurrence free survival P value
Age	premenopausal	NS	NS
	postmenopausal		
FIGO stage	I	<0,001	<0,001
	II		
	III		
	IV		
Grade	1	0,009	0,033
	2		
	3		
Myometrial invasion	0	<0,001	NS
	≤ ½		
	> ½		
Lymph node metastasis	negative	0,042	<0,001
	positive		
Histologic type	endometrioid	<0,001	NS
	adenosquamous		
	clear-cell		
	papillary serous		
Peritoneal cytology	negative	NS	NS
	positive		
LVSI	negative	NS	NS
	positive		
Cervical involvement	negative	NS	NS
	positive		
Adnexal involvement	negative	NS	NS
	positive		
Distant metastasis	negative	NS	NS
	positive		

LVSI – Lymph vascular space invasion
NS – not significant

node metastasis (P<0.001) were significantly correlated as independent prognostic factors in multivariate analysis for recurrence-free survival (Table 5).

4. Discussion

Endometrial carcinoma is the most common malignancy of the female genital tract in industrialized countries, and occurs predominantly after menopause. Although most endometrial carcinomas are detected at low stage, there is still a significant mortality from the disease. In postmenopausal women, prolonged life expectancy, changes in reproductive behavior and prevalence of overweight and obesity, as well as hormone replacement therapy use, may partially account for the observed increases of incidence rates in some countries. In order to improve treatment and follow-up of endometrial carcinoma patients, the importance of large scale prognostic factors has been extensively studied. Various clinical and pathologic variables are reported to be of prognostic significance in univariate or multivariate analysis In present study, different parameters were analyzed to determine which of them were related with recurrence and survival in a set of 139 patients with endometrial cancer.

Our study represents a group of patients with endometrial cancer who were treated under similar comparable conditions. In our multivariate analysis we identified FIGO stage, tumor grade, histologic type, depth of myometrial invasion and lymph node status as independent prognostic factors for overall survival, and FIGO stage, tumor grade, and lymph node status were identified as independent prognostic factors for recurrence-free survival.

The prognostic evidence for FIGO stage, tumor grade, lymph node staus, depth of myometrial invasion, and histologic type were associated with recurrence and survival, in accordance with previously published findings of different groups [4,9,10].

In our study there was no significant correlation between FIGO stage and age, additional diabetes mellitus, or BMI, despite the fact that these factors influence the incidence of endometrial cancer [11,12]. In literature, between 6% [13] and 22% [14] of patients affected with endometrial cancer suffer from diabetes mellitus. In the present study 22 % of patients suffered from diabetes mellitus. It is comparable to the study group published by Tabernero and colleagues in 1995 [15] and also to the study group published by Steiner [14]. In this study, diabetes mellitus was in univariate analysis significant prognostic factor correlated to the depth of myometrial invasion but in multivariate analysis diabetes mellitus was not an independent prognostic marker. An important proportion of patients with clinicaly early disease limited to the uterus has been shown to have extrauterine spread after surgical pathologic staging. In our institution, lymphadenectomy is performed according to preoperative studies (preoperative biopsy, transvaginal ultrasonography, serum CA 125 level) and intraoperative gross examination of myometrial invasion eventually intraoperative biopsy for determining myometrial invasion, so we suppose that this optimal method to identify high-risk patients. The overall incidences of pelvic and para-aortic node metastases are reported to be approximately 9-10% and 6-10% in the literature, respectively [3,4]. The incidence of nodal

metastases in our study was 13%; this is higher than in many recent series, possibly because of the employment of extensive lymphadenectomy in this series instead of a sampling procedure. This was in accordance with the study of Ayhan that had incidences of nodal metastases 15.3% for pelvic and 9.3% for paraaortic [16].

Despite this facts lymphadenectomy in treatment of endometrial cancer patients remains controversial. It appears only to be useful in high-risk patients, with a justified morbidity [17]. The ASTEC study showed a hazard ratio (HR) of 1.16 (95% CI 0.87-1.54; p = 0.31) in favor of hysterectomy and bilateral salpingo-oophorectomy without lymphadenectomy and an absolute difference in 5-year overall survival of 1% (95% CI -4 to 6) [16]. ASTEC trial suggests that unless surgical staging will directly affect adjuvant therapy, routine systematic pelvic lymphadenectomy cannot be recommended in women undergoing primary surgery for stage I endometrial cancer outside of clinical trials [17].

In our series of all the patients with stage I–IV endometrioid uterine cancer, only 14 of 139 patients (10.07%) had recurrence; local recurrence (n=10; 7.19%), distant recurrence (n=4; 2.872%). This recurrent ratio is low compared with other literatures with stage I–III endometrial cancer (recurrence ratio: 20–25%) [18-20], but it is comparable to the study group published by Fujimoto and colleagues in 2009 [21]. Chan et al. [22] reported that there was a relationship between the number of lymph nodes resection and the survival of patients with intermediate/high risk endometrioid uterine cancer. They concluded that the extent of lymph node resection improved the survival of patients with intermediate/high risk endometrioid uterine cancer. The reason by which recurrent ratio became low in our study might be due to complete systematic pelvic and paraaortic lymphadenectomy.

In this study we have described multivariate independent prognostic factors for recurrence-free survival and overall survival of endometrial cancer patients. A drawback of our study is that it is retrospective, and not randomized. The multivariate analysis, the large follow-up, and the consistent results with previous reports give the study some credibility. Although our data of multivariate analysis of prognostic factors probably adds only a small amount to the body of knowledge in endometrial cancer, we think it is important to revaluate these factors.

References

[1] Uharcek P, Mlyncek M, Ravinger J. Surgical management of endometrial cancer in Slovak Republic. Eur J Surg Oncol 2006;32(1):94-7

[2] Shepherd JH. Revised FIGO staging for gynaecological cancer. Brit J Obstet Gynaec 1989;96:889-92

[3] Boronow RC, Morrow CP, Creasman WT. Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. Obstet Gynecol 1984;63:825–32

[4] Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical pathologic spread patterns of endometrial cancer (a GOG study). Cancer 1987;60:2035–41

[5] Barakat RR, Park RC, Grigsby PW, Muss HD, Norris HJ. Corpus: epithelial tumors. In: Hoskins WJ, Perez CA, Young RC, (eds). Principles and practice of gynecologic oncology. ed 2. Philadelphia: Lippincott-Raven Publishers, 1997: 859-896

[6] Morrow CP, Bundy BN, Kurman, RJ, et al.: Relationship between surgical-pathologic risk factors and outcome in clinical stage I and II carcinoma of the endometrium: A Gynecologic Oncology Group study. Gynecol. Oncol. 1991; 40: 55–65

[7] Pecorelli S. Revised FIGO staging for carcinoma of the vulva, cervix, and endometrium. Int J Gynaecol Obstet. 2009;105(2):103-104

[8] Prat J. Prognostic parameters of endometrial carcinoma. Hum Pathol. 2004;35:649–662

[9] Mammoliti S, Bruzzone M, Chiara S. Clinical stage I and II endometrial carcinoma: multivariate analysis of prognostic factors. Anticancer Res 1992;12:1415—1418

[10] Ju W, Myung SK, Kim Y, Choi HJ, Kim SC.: Comparison of laparoscopy and laparotomy for management of endometrial carcinoma: a meta-analysis. Int J Gynecol Cancer 2009;19(3):400-406

[11] Gambrell RD, Bagnell CA, Greenblatt RB. Role of estrogens and progesterone in etiology and prevention of endometrial cancer: review. Am J Obstet Gynecol 1983; 15:696—707

[12] Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–1638

[13] Eifel PJ, Ross J, Hendrickson M, Cox RS, Kempson R, Martinez A. Adenocarcinoma of the endometrium. Cancer 1983;52:1026—1031

[14] Steiner E, Eicher O, Sagemüller J, Schmidt M, Pilch H, Tanner B, Hengstler JG, Hofmann M, Knapstein

PG. Multivariate independent prognostic factors in endometrial carcinoma: a clinicopathologic study in 181 patients: 10 years experience at the Department of Obstetrics and Gynecology of the Mainz University. Int J Gynecol Cancer. 2003;13(2):197-203

[15] Tabernero LM, Alonso MC, Ojeda B et al. Endometrial cancer stages I and II. Eur J Gynecol Oncol 1995;16:18—25

[16] Ayhan A, Tuncer R, Tuncer Z, Yuce K, Kucukali T. Correlation between clinical and histopathologic risk factors and lymph node metastases in early endometrial cancer (a multivariate analysis of 183 cases) International Journal of Gynecologic Cancer 1994;4: 306-309

[17] ASTEC study group, Kitchener H, Swart AM, Qian Q, Amos C, Parmar MK. Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. Lancet. 2009;373(9658):125-136

[18] Corn BW, Lanciano RM, D'agostino R, Kiggundu E, Dunton CJ, Purser P, et al. The relationship of local and distant failure from endometrial cancer: defining a clinical paradigm. Gynecol Oncol 1997;66:411–416

[19] Mariani A, Webb MJ, Keeney GL, Aletti G, Podratz KC. Endometrial cancer: predictors of peritoneal failure. Gynecol Oncol 2003;89:236–242

[20] Kuoppala T, Mäenpää J, Tomas E, Puistola U, Salmi T, Grenman S, et al. Surgically staged high-risk endometrial cancer: randomized study of adjuvant radiotherapy alone vs. sequential chemo-radiotherapy. Gynecol Oncol 2008;110:190–195

[21] Fujimoto T, Nanjyo H, Fukuda J, Nakamura A, Mizunuma H, Yaegashi N, Sugiyama T, Kurachi H, Sato A, Tanaka T. Endometrioid uterine cancer: histopathological risk factors of local and distant recurrence. Gynecol Oncol. 2009;112(2):342-347

[22] Chan JK, Cheung MK, Huh WK, Osann K, Husain A, Teng NN, et al. Therapeutic role of lymph node resection in endometrial corpus cancer. Cancer 2006;107:1823–1830