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ORIGINAL ARTICLE

Prognostic factors and treatment outcomes in patients with operated endometrial cancer: analysis of 674 patients at a single institution

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Summary

Purpose: *Endometrial carcinoma is the most prevalent gynecologic tumor in developed countries. The aim of the present study was to evaluate the clinical characteristics of the patients with endometrial cancer.*

Methods: *Six hundred and seventy-four patients who had received postoperative therapy were retrospectively investigated. Of the cases, 186 were only monitored, whereas 43 received intracavitary radiotherapy (ICRT) and 54 external beam radiotherapy (EBRT). Two hundred and fifty-nine patients received both EBRT plus ICRT. Eight patients received chemotherapy (CT), whereas 24 patients received both CT and EBRT plus ICRT.*

Results: *Statistical analyses revealed that age, menopausal status, tumor histology, stage, grade, tumor diameter, myometrial invasion, lymphovascular space invasion (LVI), positive cytology of abdominal fluid/washings, omental involvement, adnexal involvement and the type of the therapy significantly affected both the overall survival (OS) and disease-free survival (DFS). Survival was poor in patients over 60 years of age, who had advanced stage (higher than FIGO stage 2a), grade III tumor and myometrial invasion >50%.*

Conclusion: *Age was the most important factor associated with local relapse while survival was affected by age, grade, myometrial invasion and stage.*

Key words: endometrial carcinoma, grade, myometrial invasion, postoperative treatment

Introduction

Endometrial carcinoma is the most prevalent gynecologic tumor in developed countries. Most of the patients are postmenopausal and usually apply to hospital because of postmenopausal vaginal bleeding [1]. Adenocarcinomas account for the majority of endometrial malignancies. Endometrioid carcinoma ranks first, followed by clear cell carcinoma, while papillary serous carcinoma accounts for a few. When patients are diagnosed at early stages, the cure rate is high and survival is favorable.

Surgery is essential in the treatment of endometrial carcinoma. Adjuvant RT and CT are used postoperatively in selected cases [2]. Standard surgical therapy consists of total abdominal hysterectomy (TAH) and bilateral salpingo-oophorectomy (BSO) together with pelvic and paraaortic lymph node dissection [3]. Several prognostic factors have been defined in operable endometrial carcinomas for disease recurrence and patient survival [4]. Adjuvant therapy combinations are recommended according to risk factors. Adjuvant therapies include EBRT, ICRT, CT and hormonal therapy (HT).

The local control rates are considerably high with postoperative RT. However, RT does not contribute to the prevention of distant metastases [5-7]. ICRT can be used for local control at early stages with fewer side effects and similar cure rates [8,9]. The therapeutic approach for more advanced stages includes the combination of the two RT methods and concomitant CT for distant control [10,11]. The efficacy of HT is limited [12].

Common problems encountered in daily practice include inadequate surgical staging, correct determination for the optimal use of the current adjuvant treatment modalities and the management of associated toxicity.

In the present study we aimed to determine the

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treatment-related outcome of the patients treated at our center and to define prognostic factors playing significant roles.

Methods

Patients

Six hundred and seventy-four patients with endometrial adenocarcinoma, treated between 1996 and 2007, were retrospectively investigated and evaluated in terms of general characteristics, treatment administered and survival. The patient medical records were thoroughly reviewed and surgical history and pathological reports, clinical examinations, lab tests and imaging results, as well as follow-up were registered. Patient age, menopausal status, parity, type and date of the operation, histopathological diagnosis and FIGO stage, tumor diameter, localization and grade, myometrial and LVI, positive cytology of ascitic fluid/washings, adnexal and serosal involvement types, duration and doses of treatment, site of relapses and metastases and time to recurrence, last follow-up date and the final status of the patients were recorded.

Treatment

Of the cases, 668 had undergone TAH+BSO, 3 had undergone hysterectomy only, and 3 hysterectomy and unilateral salpingo-oophorectomy. Lymph node dissection was performed in 261 (38.7%) patients; the median number of dissected lymph nodes was 8 (range 1-48).

Postoperatively 186 patients did not receive any further treatment, and were followed up regularly; 43 patients received ICRT alone, 154 received EBRT alone, and 259 received both ICRT and ICRT; 8 patients received CT and 24 received both CT and RT.

The patients received RT in a median of 41 days (range 11-115) after the operation and the therapy was completed in a median of 36 days (range 5-65). Three patients discontinued therapy. Of the cases receiving pelvic RT, 16 were irradiated by means of 4-field box RT technique, and the remaining were irradiated by means of 2 opposed anterior-posterior fields. There were 9 patients who received pelvic and para-aortic field irradiation. The patients were irradiated by means of EBRT at 180-200 cGy daily fractions with a median dose of 50 Gy (range 10-60). Of the cases, 252 were treated with Co60, 159 with 18 mv, 5 with 15 mv, and 4 with 6 mv x-ray energies. ICRT was applied to the vaginal apex via applicators with a median of 3 fractions (range 1-5), to a dose of median 15 Gy (range 10-30), and completed in a median of 14 days (range 7-33). EBRT and ICRT were completed in a median of 69 days (range 50-99).

The median number of the CT courses administered to the patients was 4 (range 2-6). The regimens most frequently used included cisplatin plus cyclophosphamide plus doxorubicin and paclitaxel plus carboplatin. Some of the patients had received medroxyprogesterone as HT. However, we failed to obtain information about the duration of medroxyprogesterone administration. Therapies given according to the disease stage are shown in Table 1.

Statistical analyses

In addition to the descriptive statistical methods (mean, standard deviation, frequency) used in the analyses of the study data, Fisher's exact test, chi-square test were also used for the comparison of qualitative data. Kaplan-Meier's method was used for survival analyses, log-rank test was used for comparisons, and Cox regression method was used for multivariate analysis. Data were evaluated based on 95% confidence interval. Statistical significance level was set at $p < 0.05$. All analyses were performed by using SPSS v. 11.0

Results

Patient and disease characteristics

The median follow-up duration was 67 months (range 7-166). Of the patients, 603 (89%) were still being followed, whereas 71 (11%) were not; despite the postal letters sent to their known addresses, no information could be obtained about their final status. Survival analyses, therefore, were done using the data of 603 patients. The median age of the cases was 56 years (range 29-83). There were 440 (65.3%) patients < 60 years and 234 (34.7%) >60 years (Table 2). Most of the cases (n=498, 73.9%) were postmenopausal. There were 60 (8.9%) nulliparous, 46 (6.8%) primiparous and 508 (75.4%) multiparous patients and the median patient parity was 3 (range 0-13; Table 2).

The histological type of the tumor was endometrioid adenocarcinoma in the majority of the cases (577 patients, 85.6%). The most frequent histological grade was II, seen in 292 (43.3%) patients. The distribution of FIGO stages (1988) among patients was as follows: stage 1A 45 (6.7%) patients, stage 1B 282 (41.8%), stage 1C 167 (24.8%), stage 2A 52 (7.7%), stage 2B 57 (8.5%), stage 3A 34 (5%), stage 3C 29 (4.3%), and stage 4 (0.6%) patients. Most of the patients had stage

Table 1. Treatment according to stage

Stage	*Treatment*						*Total*
	Monitoring n (%)	*EBRT* n (%)	*EBRT + ICRT* n (%)	*ICRT* n (%)	*CT* n (%)	*CT and RT* n (%)	n (%)
1A	41 (6.1)	1 (0.2)	2 (0.3)	1 (0.2)	0 (0)	0 (0)	45 (6.8)
1B	132 (19.8)	55 (8.2)	51 (7.6)	35 (5.2)	3 (0.4)	3 (0.4)	279 (41.6)
1C	6 (0.9)	78 (11.7)	77 (11.6)	5 (0.7)	0 (0)	1 (0)	167 (25.1)
2A	0 (0)	12 (1.8)	39 (5.8)	0 (0)	0 (0)	1 (0)	52 (7.8)
2B	1 (0.2)	4 (0.5)	50 (7.6)	1 (0.2)	0 (0)	3 (0.4)	57 (8.7)
3A	0 (0)	2 (0.3)	23 (3.5)	0 (0)	2 (0.3)	7 (1)	34 (5.1)
3C	0 (0)	2 (0.3)	17 (2.5)	0 (0)	1 (0)	9 (1.3)	29 (4.3)
4	0 (0)	0 (0)	0 (0)	0 (0)	2 (0)	2 (0.3)	4 (0.6)
Total	180 (27)	154 (23)	259 (38.9)	42 (6.3)	83 (12)	24 (3.6)	667 (100)

EBRT: external beam radiotherapy, ICRT: intracavitary radiotherapy, CT: chemotherapy

Table 2. Patient characteristics

Characteristics	*n*	*%*	*Characteristics*	*n*	*%*
Age (years)			Stage		
Median	56		IIA	52	7.7
Range	29-83		IIB	57	8.5
< 60	440	65.3	IIIA	34	5
> 60	234	34.7	IIIC	29	4.3
Menopausal status			IV	4	1.2
Premenopausal	168	24.9	Myometrial invasion (%)		
Postmenopausal	498	73.9	No	42	6.2
Unknown	8	1.2	≤ 50	348	51.6
Parity			> 50	274	40.7
Nulliparous	60	8.9	Lymphovascular invasion		
Primiparous	46	6.8	Yes	126	18.7
Multiparous	508	75.4	No	254	37.7
Surgery			Unknown	294	43.6
TAH+ BSO	668	98.8	Tumor diameter (cm)		
Hysterectomy	3	0.6	≤ 2	56	8.3
Hysterectomy+USO	3	0.6	> 2	348	51.6
Lymph node dissection			Unknown	270	40.1
Yes	261	38.7	Abdominal fluid sampling		
No	413	61.3	Positive	28	4.2
Pathologic type			Negative	289	42.9
Endometrioid	577	85.6	Unknown	317	47
Squamous	35	5.2	Omental involvement		
Papillary	22	3.3	Yes	13	1.9
Mixed cell	14	2.1	No	121	18
Papillary serous	8	1.2	Unknown	540	80.1
Clear cell	6	0.9	Adnexal involvement		
Undifferentiated	5	0.7	Yes	19	2.8
Unknown	7	1.0	No	623	92.4
Grade			Treatment		
I	285	42.3	Monitoring	186	27.6
II	292	43.3	Intracavitary radiotherapy	43	6.4
III	67	9.9	External radiotherapy	154	22.8
Stage			External + intracavitary radiotherapy	259	38.4
IA	45	6.7	Chemotherapy	8	1.2
IB	282	41.8	Radiotherapy + chemotherapy	24	3.6
IC	167	24.8			

TAH: total abdominal hysterectomy, BSO: bilateral salpingo-oophorectomy, USO: unilateral salpingo-oophorectomy

1B and 1C. Myometrial invasion was detected in 632 (93.8%) cases. There were 348 (51.6%) patients with myometrial invasion < 50%, and 274 (40.7%) with myometrial invasion > 50%. LVI was present in 126 (18.7%) patients, whereas 254 (37.7%) had no LVI.

Tumor diameter was < 2 cm in 56 (8.3%) patients and > 2 cm in 348 (51.6%). Tumor was localized in the lower segment in 40 (5.9%) patients, in 78 (11.6%) it was localized in the upper segment. No adequate information was present for the rest.

There were 24 (3.6%) patients with lymph node involvement; of them, only pelvic nodes were involved in 16, only paraaortic lymph nodes in 2, and both pelvic and paraaortic lymph nodes in 6 patients.

Information about abdominal fluid/washings and omental involvement could not be found in the pathological reports in the majority of the cases. Abdominal fluid/washings were positive in 28 (4.2%) patients, whereas omental involvement was positive in 13 (1.9%). Adnexal involvement was present in 19 (2.8%) patients.

Local relapse and distant metastasis

Local relapse alone was present in 23 cases and distant metastasis alone in 41 cases, whereas both local relapse and distant metastasis were determined in 5 cases (Table 3). Five- and 10-year local control rates were 97.9% and 94%, respectively. However, distant control rates were 91.2% and 86%, respectively. Recurrences occurred after a median of 26 months. Sixty-five percent (15/23) of the relapses occurred at the vaginal stump. Paraaortic lymph nodes were the second most common site for relapse (8/23). Eleven of the patients with relapse at the vaginal stump received ICRT, whereas the others and those with pelvic and paraaortic lymph node relapse received CT. Seven of the patients with relapse died 30 months later on average and 16 were still alive with disease.

Table 3. Disease relapse and distant metastasis

Relapse site	*n*	*%*
Local-regional	23	3.4
Vaginal stump	15	2.2
Pelvic lymph node	3	0.1
Paraaortic lymph node	8	1.1
Distant metastasis	46	6.8
Lung	17	2.5
Peritoneum	8	1.1
Bone	2	0.3
Liver	3	0.4
Liver+peritoneum	2	0.3
Liver+paraaortic lymph node	2	0.3
Liver+lung	2	0.3
Lung+cervical lymph node	2	0.3
Lung+ peritoneum	3	1.2
Supraclavicular lymph node	1	0.1
Adrenal	1	0.1
Abdominal wall+inguinal lymph node	3	0.4

Regarding the factors that affected relapses, only age showed a statistically significant association with relapse (p=0.001). The local control rates of patients aged >60 years were lower. The 5- and 10-year local control rates of patients aged < 60 years were 98.5% and 97.8%, respectively, and in those aged > 60 years were 96.7% and 85.5%, respectively (p <0.001). Other variables were not found to impact significantly the local relapse rates. Age was the only variable affecting significantly local control/relapse. Even though 5- and 10-year local control rates were substantially high in early stages (98 and 95%, respectively) they began to decline from stage 2B (5- and 10-year 93%) and became lowest (5- and 10-year 66.7%) in stage 3C.

Of the patients who had both relapse and metastasis, 4 died after 15 months on average and one was still alive with disease.

Metastasis occurred after a median 24 months (range 8-55). Lungs were the most common metastatic site (17 of 46 cases). The second most common site was peritoneum with 8 cases. In the patients with metastases, 23 had received only CT, 5 only RT, 4 both CT and RT, 2 had undergone surgical operation, and the remaining had received either HT or had been treated symptomatically. Thirty-five metastatic patients had died after 16 months on average and 11 were still alive with disease.

Prognostic factors such as age (p < 0.01), menopause (p < 0.01), histological type (p=0.027), stage (p< 0.01), grade (p < 0.01), tumor diameter (p=0.028), myometrial invasion (p= 0.005), LVI (p < 0.01), positive cytology of abdominal fluid (p=0.001), omental involvement (p < 0.01), adnexal involvement (p < 0.01) and type of therapy (p <0.01) were significantly associated with distant metastasis.

Distant metastatic rate was higher among postmenopausal patients aged > 60 years (5- and 10-year metastatic rate 6.8 and 11.3%, respectively) as compared to those aged < 60 years and premenopausal (5- and 10-year metastatic rate 24.8 and 50%, respectively). Similarly, high rate (46.7%) of distant metastasis was observed in those with clear cell carcinoma or with mixed type, whereas those who had an adenocarcinoma with squamous differentiation had the lowest (43.8%) rate for 10-year distant control. The distant metastatic rate at 5 and 10 years for stage 3 was 25.7 and 31.4% respectively, which was higher than in earlier stages. Similarly grade III tumors (5- and 10-year distant control rate 79.7 and 65.1%, respectively) had lower rate of distant control as compared to those with grade I (5- and

10-year distant control rate 95.8 and 93.8%, respectively) and grade II (5- and 10-year distant control rate 90.1 and 85%, respectively) tumors. Myometrial invasion > 50% had lower rate of distant control (5- and 10-year distant control rate 85.8 and 80.8%, respectively) as compared to those without myometrial invasion (5- and 10-year distant control rate 94.2%) and with myometrial invasion < 50% (5- and 10-year distant control rate 94.9 and 90%, respectively).

During follow-up 10 patients developed a second primary carcinoma (4 breast, 1 breast and renal cell, 1 lung, 1 rectal, 1 thyroid, 1 gastric stromal tumor, and 1 cervical carcinoma). Four of these patients had died, and the remaining 6 were still alive.

Survival

Five- and 10-year OS rates in 603 patients were 88% ± 1 and 71.9% ± 3, respectively. Five- and 10-year DFS rates were 87.1% ± 1 and 71.1% ± 3 (Figures 1 and 2). Ninety-nine patients (16.4%) died, whereas 508 (83.6%) were still alive. The mean survival rate was 137.1 ± 2 months.

Univariate analysis by using log-rank test revealed that age ($p < 0.001$), menopausal status ($p < 0.001$), histological type ($p=0.001$), stage ($p < 0.001$), grade ($p < 0.001$), tumor size ($p=0.008$), myometrial invasion ($p=0.001$), LVI ($p < 0.001$), positive cytology of abdominal fluid ($p=0.002$), omental involvement ($p < 0.001$), adnexal involvement ($p < 0.001$) and type of therapy ($p < 0.001$) significantly affected OS (Table 4).

Factors significantly affecting DFS at univariate analysis included age ($p < 0.001$), menopause ($p < 0.001$), histological type ($p=0.007$), stage ($p < 0.001$), grade ($p < 0.001$), tumor diameter ($p=0.006$), myometrial invasion ($p < 0.001$), LVI ($p=0.001$), positive cytology of abdominal fluid ($p < 0.001$), omental involvement ($p < 0.001$), adnexal involvement ($p < 0.001$) and the type of the therapy ($p < 0.001$) (Table 4).

Postmenopausal cases aged >60 years had both shorter OS and DFS. There were significant differences between the histological types regarding OS and DFS. OS and DFS were found to be short in patients with clear cell, papillary serous, papillary, and mixed type carcinoma. Similarly, OS and DFS were significantly shorter in patients with stage 2B, 3A, 3C, and 4 as compared to those in lower stages. There were also significant differences between the histological grades regarding OS and DFS. OS and DFS were shorter in patients with grade III tumors as compared to those with grade I and grade II. Likewise, there were significant differences regarding tumor diameters in relation to OS and DFS. OS and DFS were shorter in patients with a tumor ≥ 2 cm.

OS and DFS were shorter in patients with tumor that had invaded >50% of the myometrium as compared to those with smaller or no invasion. There was significant relationship between the presence of LVI and OS and DFS. Patients with LVI had shorter OS and DFS. Similarly, those with positive cytology of abdominal fluid, and with omental or adnexal involvement had shorter OS and DFS. In multivariate analysis (Cox regression method) only age ($p=0.006$), grade ($p=0.016$), myometrial invasion ($p=0.006$) and stage ($p=0.033$) statistically affected OS (Table 5). Multivariate analysis for DFS showed that age ($p=0.004$) and grade ($p=0.016$) statistically affected DFS, while stage ($p=0.061$) and myometrial invasion ($p=0.09$) showed a trend for significance (Table 6).

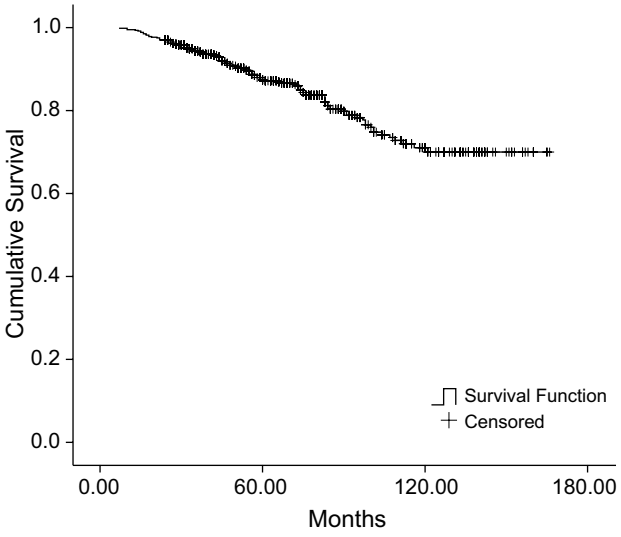

Figure 1. Kaplan-Meier curve for overall survival.

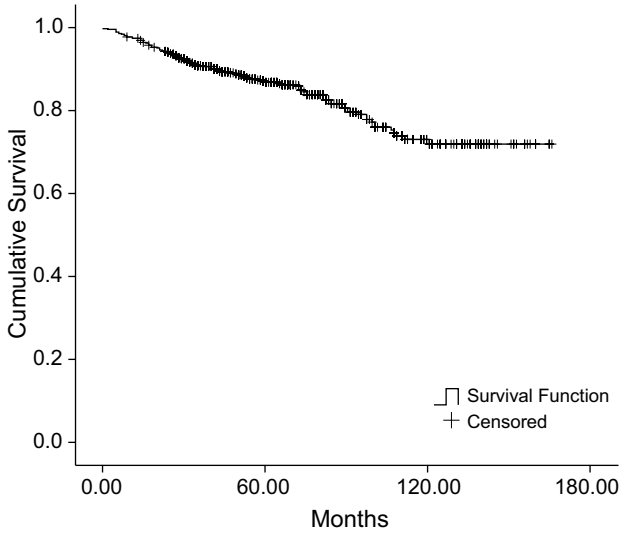

Figure 2. Kaplan-Meier curve for disease-free survival.

Table 4. Survival according to prognostic factors (univariate analysis)

Prognostic factors	*DFS (%)* *5-year*	*10-year*	*p-value*	*OS (%)* *5-year*	*10-year*	*p-value*
Age (years)						
>60	93.2	88.7		93.6	88.9	
<60	75.2	42.5	0.001	84.2	63.3	0.001
Menopausal status						
Premenopausal	95.8	94.1		96.6	93.6	
Postmenopausal	83.2	64	0.001	84.1	63.3	0.001
Histologic types						
Squamous dif. adenoCa	88.1	72.1		92	84.5	
Mixed cell	78.3	78.3		78.9	78.9	
Papillary adenoCa	66.7	66.7		71.4	61.2	
Papillary serous adenoCa	50	0		66.7	66.7	0.001
Clear cell adenoCa	44.4	44.4	0.001	50		
Stage						
IA	89.3	72.2		89.9	74.9	
IB	92.2	76		92.2	77.4	
IC	85.7	72.6		86	74.4	
IIA	86.6	74.2		88.8	74.8	
IIB	79	50.4		79	54.1	
IIIA	66.1	45.8		69.2	59.6	
IIIC	78	44.9		79.2	50.9	
IV	50	35	0.001	75	37.5	0.001
Grade						
I	93.1	77.2		93.7	78.3	
II	85.4	73.6		85.8	73.2	
III	72.8	43	0.001	75.5	44.1	0.001
Tumor diameter (cm)						
≤2	95.8	79.1		96.2	82.8	
>2	85.1	68.4	0.006	86.2	66.4	0.008
Myometrial invasion (%)						
No invasion	88.3	71.5		88.9	74.1	
50	92.2	76.8		92.3	78	
50	80.6	66.3	0.001	81.2	67.7	0.001
Lymphovascular invasion						
Yes	69.2	53.8		70.4	58	
No	90.7	70.5	0.001	91.5	72.2	0.001
Abdominal washing fluid						
Positive	62.3	41.1		71.8	46.6	
Negative	86.5	66.8	0.002	87.4	68.5	0.001
Omental involvement						
Yes	50	25		57.1	28.6	
No	93.1	60	0.001	93.2	60	0.001
Adnexal involvement						
Yes	2.6	38		57.9	43.98	
No	88.2	70.4	0.001	88.5	72.2	0.001

DFS: disease free survival, OS: overall survival

Discussion

In the majority of the cases endometrial adenocarcinoma is limited to the uterus at the time of diagnosis. Abnormal vaginal bleeding is the principle symptom. Because it is seen mainly in the postmenopausal period, vaginal bleeding attracts attention. It can be diagnosed at early stages because of its relatively slow progress and early signs. Therefore, survival in this disease is high. However, approximately 25% of the cases are premenopausal and 3% are under the age of 40 years [13]. In the present study, the median patient age at diagnosis was 56 years; 73.9% of the patients were postmenopausal, 24.9% were premenopausal and 3.26% were under the age of 40 years. In many previous studies, age was found as an independent predictor of survival, and disease progression was unfavorable in patients > 60 years [5,6]. In our study, patients were dichotomized between > 60 and

Table 5. Multivariate analysis for overall survival

Parameters	*B*	*SE*	*Wald*	*df*	*Sig.*	*Exp(B)*	*95% CI for Exp(B)*	
							Lower	*Upper*
Age	2.116	0.773	7.489	1	0.006	8.300	1.823	37.786
Histology	-0.085	0.197	0.188	1	0.665	0.918	0.625	1.350
Grade	1.201	0.498	5.819	1	0.016	3.322	1.252	8.810
MI	-1.389	0.504	7.590	1	0.006	0.249	0.093	0.670
LVI	0.234	0.525	0.199	1	0.655	1.264	0.452	3.538
Diameter	-0.225	0.650	0.120	1	0.729	0.799	0.223	2.855
Stage	0.411	0.193	4.562	1	0.033	1.509	1.034	2.200
MS	0.041	1.069	0.002	1	0.969	1.042	0.128	8.465
Fluid	-0.762	0.941	0.656	1	0.418	0.467	0.074	2.951

MI: myometrial invasion, LVI: lymphovascular space invasion, Diameter: tumor diameter, MS: Menopausal status, Fluid: positive cytology of ascitic fluid/washings

Table 6. Multivariate analysis for disease-free survival

Parameters	*B*	*SE*	*Wald*	*df*	*Sig.*	*Exp(B)*	*95% CI for Exp(B)*	
							Lower	*Upper*
Age	2.207	0.774	8.135	1	0.004	9.087	1.994	41.399
Histology	-0.129	0.186	0.479	1	0.489	0.879	0.611	1.266
Grade	1.164	0.482	5.831	1	0.016	3.202	1.245	8.233
MI	-1.290	0.492	6.881	1	0.009	0.275	0.105	0.722
LVI	0.211	0.508	0.172	1	0.678	1.235	0.457	3.339
Diameter	0.035	0.640	0.003	1	0.956	1.036	0.295	3.630
Stage	0.352	0.188	3.509	1	0.061	1.421	0.984	2.053
MS	-0.137	1.067	0.017	1	0.898	0.872	0.108	7.049
Fluid	-0.570	0.926	0.380	1	0.538	0.565	0.092	3.471

For abbreviations see footnote of Table 5

< 60 years and it was observed that 92.9% of the patients in the group < 60 years and 66.2% of the patients in the group >60 years were alive ($p < 0.001$). The finding that the survival of the patients >60 years was shorter seems to be consistent with the literature.

Although nulliparity has been considered as a risk factor in the development of endometrial carcinoma, its effect on survival could not be demonstrated. Despite the data of previous studies reporting that nulliparous patients have shorter survival, we failed to determine a difference between nulliparous and multiparous patients in terms of survival [14].

Epithelial tumors account for 97% of uterine malignancies and sarcomas account for the remaining 3%. The majority of epithelial tumors are adenocarcinomas [15]. In the present study, we observed that the histological type of the tumor in approximately 85% of the patients was adenocarcinoma. This rate reaches up to 94% by including papillary adenocarcinomas combined with squamous differentiation carcinomas, indicating a higher rate than that reported in the relevant literature.

Whereas tumors with endometrioid histology are estrogen-dependent and have good prognosis in general, those with non-endometrioid histology have poorer prognosis [16]. Consistent with the literature, in the present study survival was shorter in patients with papillary serous, clear cell and mixed cell carcinoma. However, we observed that the number of patients with papillary adenocarcinoma was higher than that in the literature and survival was shorter as is in the other histological types with poor prognosis. There are studies showing that the potential for malignancy increases as the histological papillary character increases from endometrioid adenocarcinoma, to papillary endometrioid, to papillary serous [17,18]. At this point, the importance of histological differentiation between papillary adenocarcinoma and other non-endometrioid types, particularly those with papillary character, comes to mind.

In previous studies, a number of factors influencing prognosis have been defined in patients with endometrial carcinoma. These factors include age, stage, grade, histological type, myometrial invasion, lymph node involvement, tumor size, cervical invasion, adnexal involvement, and intraperitoneal spread [19,20]. In our study, multivariate analysis revealed that age, myometrial invasion, grade and stage were in the forefront as the factors that affect prognosis.

The primary treatment modality of endometrial carcinoma is TAH plus BSO. Routine lymph node dissection remains as one of the controversial issues. Many studies have been conducted seeking for an answer on this issue. One opinion defends that lymphadenectomy

would likely lay bare the extension of disease and may have therapeutic effect due to the resection of occult nodal metastases. Although it prolongs operation duration, increases blood loss during operation, and prolongs hospitalization time, it has acceptable morbidity, mortality and postoperative complication rates, and would likely decrease the need for adjuvant radiotherapy and reduce therapy costs [21]. But nonetheless, some authors think that complications such as deep vein thrombosis, pulmonary embolism, lymphedema and vascular damaging are increased in patients in which extensive staging has been done, that these complications are prominent in old and obese patients, particularly in patients with co-morbid diseases such as diabetes, hypertension, chronic obstructive pulmonary disease and coronary disease, and that such factors mentioned above lead to more severe enteric discomfort along with postoperative RT application [22].

The number of the lymph nodes that would be resected is another issue of discussion. In their study, Chan et al. [23] reported that the probability of detecting at least one positive lymph node is highest when 21-25 lymph nodes are resected and stated that the resection of > 25 lymph nodes does not increase this probability. In another study, it was reported that at least 10 lymph nodes should be resected to call it "adequate nodal dissection" [24]. Furthermore, it has also been shown that dissecting ≥ 12 lymph nodes improves both OS and DFS in high risk patients [25]. It is difficult to define "adequate lymph node dissection" according to the number of resected lymph nodes using currently available data. The ASTEC study, published in 2009, is the most comprehensive one, designed in recent years to answer these issues. In this prospective study that included 1408 patients, with a median follow-up of 37 months, it was reported that lymph node dissection made no contribution to survival [26]. In the present study, 38.7% of the patients had undergone lymph node dissection and the median number of the resected lymph nodes was 8; no difference was found between patients with or without lymph node dissection in terms of either OS or DFS.

The question "When and how should the adjuvant therapy be performed in endometrial carcinoma?" remained unanswered. Until 1990, the adjuvant therapy applied to stage I patients was as follows: ICRT for those with myometrial invasion < 50% or with grade I-II, and EBRT±ICRT for those with myometrial invasion > 50% or with grade III. With advances after 1990, the place of pelvic RT in pN0 after nodal dissection and surgical staging has been questioned. The randomized GOG-99 and PORTEC 1 trials showed no benefit in survival after adjuvant EBRT, but longer survival was observed with rescue therapy in pelvic (vaginal) relapses [5,7]. Nevertheless, CT has become a therapy option in early and advanced stages. Because of the fact that vaginal relapses occur in low risk groups (<50% invasion, grade I-II), only ICRT is used in this group, whereas EBRT is used in the groups with intermediate risk (>50% invasion, grade I-III), since relapses occur in the lymph nodes, and CT is used in high risk groups (serosal invasion, nodal involvement) due to the high probability of distant metastases. In the studies conducted after 2006, the fact that adding ICRT to TAH+BSO, with sampling and cytology in low risk patients (IA-IB, grade I-II), showed no benefit on survival but it only reduced the risk for vaginal relapse from 3.1% to 1.2%, decreased the prevalence of RT in this group [27]. The comparison between monitoring and EBRT in patients with intermediate risk (IB, grade II-III, and IC, grade I-II) revealed that survival in the RT arm remained the same, whereas vaginal relapse and RT-related complications were increased [28]. In this group, a 50-60% control rate was achieved with rescue therapies after local relapses [5,29]. Factors that increased the risk in this group included grade III, myometrial invasion >50%, presence of LVI, and age >60 years. In the present study, it was observed that different therapeutic approaches had been applied in time, and the above mentioned factors were statistically significant in multivariate analyses concerning both relapses and survival. In the PORTEC 2 trial, which only sought for an answer to the question "Is ICRT equal to EBRT for intermediate risk group?", no significant difference was observed regarding survival. However, vaginal relapse was 1.9% with EBRT and 0.9% with ICRT. Pelvic recurrence was 2.5% with EBRT and 4% with ICRT [30]. In the SEER retrospective analysis it was established that adjuvant EBRT significantly prolonged survival in stage IC [31].

In the meta-analyses over this subject it has been shown that RT reduced the local relapse in early-stage endometrial carcinoma, but made no contribution to survival. RT reduces relapses by 6%, and a trend for survival prolongation in the group with stage IC and grade III has been reported, but without reaching statistical significance [1]. In the ASTEC/EN.5 trial and meta-analysis, no change was observed in OS and DFS with the inclusion of EBRT, while the recurrence rate fell from 6% to 3%. Adjuvant EBRT is not recommended in such intermediate risk group [32].

The JACOG study conducted on intermediate and high risk group patients (stage IC in patients aged >70 years or with grade III endometrioid adenocarcinoma; or stage II-IIIA with positive cytology), compared RT and CT [33]. No difference between these two groups regarding survival, local relapse and site of relapses was identified. The benefit of CT is being investigated in the PROTEC 3 study which has not been yet completed [34].

In one of the studies, in which CT has been included in the treatment, Maggi et al. [35] randomized the high risk patients (stage IC, grade III; stage II, grade III with deep myometrial invasion; and stage III) into the CT and RT arms; 5-year OS was 69% in the RT arm and 66% in the CT arm, whereas DFS was 63% in both groups. The authors concluded that both regimens were well tolerated and with identical efficacy. In another study, Mundt et al. [36] administered postoperatively 4-6 courses of CT consisting primarily of cisplatin and doxorubicin without EBRT and/or ICRT to high-risk patients with stages I-IV. The prevalence of pelvic and extra-pelvic relapses was 39.5 and 55.5%, respectively, and the authors concluded that the combination of CT and RT was favorable in high risk patients. In another study, RT and concomitant administration of paclitaxel was well tolerated by the patients [37].

Whole abdominal irradiation or CT, or the combination of both has also been tried to prevent intra-abdominal or extra-abdominal relapses. In various studies, it has been reported that whole abdominal irradiation can be safely and effectively used [38,39]. In the GOG-122 study, whole abdominal irradiation was compared with cisplatin plus doxorubicin combination, and a survival benefit was observed favoring the CT arm (50 vs. 38%). Pelvic relapses were higher in the CT group, whereas extra-pelvic relapses were higher in RT group [40]. In another study, it was found that patients who had received combination of adjuvant CT and RT had longer survival as compared to those who had received RT alone or CT alone [11]. Simultaneous application of whole abdominal irradiation and weekly cisplatin/paclitaxel combination was found to be convenient despite its acute and chronic gastrointestinal side effects [41]. In their study conducted in patients with stages I and II and serous carcinoma, Alektiar et al. [42] administered a combination of carboplatin and paclitaxel concurrently with ICRT, and found a 5-year OS of 88%. In the RTOG 9708 study, RT was concurrently applied with cisplatin-paclitaxel combination to high risk patients; 5-year OS was 85% and DFS 81%. Local-regional relapse was 2%, whereas distant metastasis was 19% [43].

All these studies indicate that local relapses can be diminished with current RT methods, which - on the other hand - can not prevent distant metastasis. In the present study, 5- and 10-year local control rates in all groups were 97.9% and 94%, respectively. However, distant control was 91.2% and 86%, respectively. Forty-six (6.8%) metastases and 23 (3.4%) local relapses were found in our patients. These data make the need for investigating new therapeutic modalities a current challenge, particularly for high risk patients.

Conclusions

Whereas age is the most important factor that impacts local relapses in endometrial carcinoma, distant metastasis is affected by age, menopausal status, histological type, stage, grade, tumor diameter, myometrial invasion, LVI, positive cytology of abdominal fluid, omental involvement, and adnexal involvement. Survival is influenced by age, grade, myometrial invasion and stage. Patients > 60 years, with myometrial invasion >50%, with stage >IIC and histological grade III had poorer prognosis.

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