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ARAŞTIRMA / RESEARCH

Evaluation of clinical and pathological features of mixed endometrial carcinoma in a tertiary medical center

Miks endometriyal karsinomun klinik ve patolojik özelliklerinin tersiyer bir merkezde değerlendirilmesi

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Abstract

Purpose: The aim of this study was to evaluate the clinical and pathological characteristics of mixed endometrial carcinoma (MEC).

Materials and Methods: The clinical and pathological records of the 29 MEC patients, who were operated on and regularly followed up in the clinic between January 2000 and December 2019, were reviewed. Clinic-pathologic features and survival in the MEC group (n=29) were compared to pure serous (n=42) and pure clear cell adenocarcinomas (n=13). Clinical features, operation characteristics, pathological findings, myometrial invasion degree (MI), lymph node involvement (LNI), lymphovascular space invasion (LVSI), adjuvant therapies, and follow-up data of the patients and their effects on survival were investigated.

Results: Eighteen of the cases had endometrioid + serous, 7 had endometrioid + clear, 3 had endometrioid + serous, and 1 had clear + serous histopathology. Laparoscopic surgery was performed in 8 of the cases (27.6%) in the mixed group. Stage, the rate of LVSI, LNI, MI ≥50%, and omental metastasis were similar among the groups. There were no significant differences in the rates of receiving adjuvant therapy among the groups. Overall survive (OS) was similar among the groups.

Conclusion: MECs are tumors that can be difficult to diagnose and manage. There was no difference between MEC and pure serous carcinoma (SC) and pure clear cell carcinoma (CC) in terms of clinicopathological features and prognosis. In addition to histopathological features, revealing and evaluating their molecular properties will help us to better understand this group of tumors.

Keywords:. Mixed tumor, carcinoma of endometrium, survival, prognosis

Öz

Amaç: Bu çalışmada miks endometrial karsinomun (MEK) klinik ve patolojik özelliklerini değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Ocak 2000 - Aralık 2019 tarihleri arasında kliniğimizde ameliyat edilen ve düzenli takip edilen 29 MEK hastasının klinik ve patolojik kayıtları gözden geçirildi. MEK grubundaki (n = 29) klinik-patolojik özellikler ve sağkalım, saf seröz (n = 42) ve saf berrak hücreli adenokarsinomlar (n = 13) ile karşılaştırıldı. Hastaların klinik bulguları, operasyon özellikleri, patolojik bulguları, miyometriyal invazyon derecesi (MI), lenf nodu tutulumu (LNI), lenfovasküler alan invazyonu (LVSI), adjuvan tedaviler ve takip verileri ve sağkalıma etkileri araştırıldı.

Bulgular: Olguların 18'inde endometrioid + seröz, 7'sinde endometrioid + berrak hücreli, 3'ünde endometrioid + seröz ve 1'inde berrak hücreli+ seröz histopatoloji vardı. Hastaların ortalama yaşı 63,2 ± 12,1 yıldı. Mikst gruptaki olguların 8'ine (% 27,6) laparoskopik cerrahi uygulandı. Evre, LVSI, LNI, MI ≥% 50 ve omental metastaz oranları gruplar arasında benzerdi. Adjuvan tedavi alma oranları için gruplar arasında önemli bir fark yoktu. Genel olarak hayatta kalma süresi gruplar arasında benzerdi.

Sonuç: MEK'ler, teşhis edilmesi ve yönetilmesi zor olabilen tümörlerdir. Klinikopatolojik özellikler ve prognoz açısından MEK ile saf seröz karsinom ve saf berrak hücreli karsinom arasında fark yoktu. Histopatolojik özelliklerinin yanı sıra moleküler özelliklerinin ortaya çıkarılması ve değerlendirilmesi bu grup tümörleri daha iyi anlamamıza yardımcı olacaktır.

Anahtar kelimeler: Miks tümör, endometriyum karsinomu, yaşam, prognoz

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INTRODUCTION

Endometrial cancer is the most common gynecological cancer in developed countries[1]. The management of patients is decided considering the risk groups evaluated according to their clinical and pathological features[2]. Endometrial cancer is divided into two groups as type 1 and 2 according to their etiopathogenesis, clinical and pathological features by Bockman[3]. While endometrioid tumors constitute the type 1 group, non-endometrioid tumors (serous, clear cell and mixed) are accepted to be in the type 2 group. Although advances in the classification and management of endometrial cancer according to its molecular characteristics are very current[4-6], Bockman's classification is still widely used due to its practical meaning[2,7]. Approximately 15% of all cases[6] are described in the high-risk group and they mainly consist of grade 3 EC and type 2 non-endometrioid tumors[8].

Currently, the diagnosis of endometrial carcinoma is based on morphology and sometimes supplemented by immunohistochemistry. Mixed endometrial carcinomas (MECs) are a group of diagnostically challenging endometrial tumors. According to the 2014 WHO classification, mixed endometrial carcinomas are tumors which are composed of two or more different types of endometrial carcinomas and at least one of them is of type II tumor (it is commonly accepted that the serous/clear component should elucidate at least 5% of the tumor volume)[9]. This group constitutes 3% and 10% of all endometrial carcinomas. Of the histologic combinations, the most common one is serous (SC) and endometrioid carcinoma (EC), which is followed by EC and clear cell carcinoma (CC). Because of their relative rarity, knowledge about the clinic-pathologic features of these tumors is limited.

Studies conducted to define the biological and molecular origins of MECs reveal that they mainly show clonal origin and essentially similar molecular properties[10,11]. Recently, Kobel et al. have reported that most of mixed endometrial carcinomas have the same molecular genetic variences in each of their histologic components, which questions whether "true" mixed epithelial carcinomas appear intermittently in the endometrium[10]. To classify endometrial carcinoma histologically poses a challenge, even to subspecialty gynecologic pathologists. The rates of interobserver disagreement that have been reported in high-grade endometrial carcinoma histotype reaches 26% to 37%. Possible explanations for such interobserver variability are as follows: the present diagnostic criteria are insufficiently detailed, diagnostic criteria are not being used, and/or a third of tumors are morphologically ambiguous and inherently difficult to categorize[12].

For MEC, clinical course and prognosis as well as diagnosis and biological characteristics are a matter of concern. In a study evaluating the prognosis of MECs with stage 1A, it was revealed that the prognosis of MECs was poor[13]. This study also revealed that patients having a non-endometrioid proportion of more than 50% and serous subtype also had a significantly more inferior prognosis. A study comparing the prognosis of pure serous with SC + EC showed that the prognosis for pure serous was worse[14].

MEC is a heterogeneous group of cancer not only in histopathological types and diagnosis but also in management. While there are many studies comparing type 1 and 2 endometrial cancer at molecular and histopathological levels, there are few studies comparing MEC in itself considering its clinical features and prognosis. Therefore, we aimed to compare the clinic-pathologic features and survival of patients with pure SC, CC and MEC.

MATERIALS AND METHODS

This is a retrospective study and it was performed by examining the data of 29 patients with MEC, 42 patients with pure SC, and 13 patients with pure CC, who were operated in our clinic and were followed up between January 2000 and December 2019. During the study period, 1110 patients had endometrial cancer. Patients with MEC, pure CC and pure SC were included in the study. Other types of endometrial carcinoma were excluded.

Patients whose pathological examinations were not performed in our faculty and who were not followed up in our clinic were excluded. The patients were evaluated in terms of age, menopausal status, co-morbidity, and surgical history (laparoscopy or laparotomy, and lymph node dissection). Stage, the degree of MI (It was separated as less than 50% and more), LNI, LVSI, omental metastasis, the type of adjuvant treatment (radiotherapy, chemotherapy), and overall- survival (OS) were evaluated and compared among the groups.

Approval of the Çukurova University Faculty of Medicine Ethics Committee was obtained for the study with the date and number of 22.01.2021-44. All patients were informed and informed written notes were taken. The study was carried out in accordance with the ethical standards and principles of the Human Experiments Committee (www.wma.netle / policy / b3.htm) revised in 2000 of the 1975 Helsinki Declaration.

Surgical procedure

MEC pre-diagnosis was made by endometrial biopsy in the preoperative period. The final diagnosis was made with postoperative pathology examination. The staging was performed according to the FIGO 2009. The primary surgical procedures were laparotomic or laparoscopic total hysterectomy and bilateral salpingo-oophorectomy (TH+BSO) and pelvic/para-aortic lymphadenectomy with or without omentectomy.

Chemotherapy and/or radiotherapy were the main adjuvant therapies administered for systemic and locoregional control, respectively. Follow-up was performed at 3-month intervals in the first year, and then at 6-month intervals up to 5 years. The time (months) between the surgery/ diagnosis and death or last follow-up was defined as overall survival (OS).

Statistical analysis

Data were analyzed using the SPSS software version 20.0 (IBM, Armonk, NY, USA). Comparisons of the three groups were performed using the student t-test or one-way ANOVA test. A Chi-Square test was employed for categorical data analysis. Results were demonstrated as mean ± SD and median for OS and n (%). All recorded p-values were two-tailed. With the Kaplan–Meier method, the effects of clinical variables and histopathologic subtypes on survival data were analyzed. The differences of the survival curves were evaluated using the log-rank test.

Table 1. Clinical and pathological features of the MEC, pure SC and pure CC groups and comparison analysis of the groups

	Pure serous (n=42)	Pure clear cell (n=13)	Mixed carcinoma (n=29)	p
Age	67.5±8.5	64.3±6.7	63.2±12.1	0.168[a]
BMI	34.9±7.1	33.7±4.6	34.0±8.9	0.904[a]
Menopause	40 (95.2%)	13 (100%)	26 (89.6%)	0.213[b]
Co-morbidity	23 (54.7%)	8 (61.5%)	17 (58.6%)	0.792[b]
L/S	7 (16.6%)	2 (15.3%)	8 (27.5%)	0.474[b]
LND	32 (76.1%)	2 (15.3%)	8 (27.5%)	0.953[b]
LVSI +	26 (61.9%)	6 (46.1%)	17 (58.6%)	0.626[b]
Omental metastasis	6 (14.2%)	4 (33.8%)	4 (13.7%)	0.253[b]
MI≥50%	22 (52.3%)	6 (46.1%)	13 (44.8%)	0.424[b]
Stage				0.785[b]
1	18 (42.8%)	5 (38.4%)	16 (55.2%)	
2	9 (21.4%)	2 (15.3%)	4 (13.8%)	
3	14 (33.3%)	5 (38.4%)	9 (31%)	
4	1 (2.3%)	1 (8.4%)	0	
LNI	10 (23.8%)	5 (38.4%)	7 (24.1%)	0.510[b]
Adjuvant therapy	32 (76.1%)	12 (92.3%)	23 (79.3%)	0.763[b]
Radiotherapy	14 (33.3%)	4 (33.8%)	13 (44.8%)	0.186[b]
Chemotherapy	30 (71.4%)	9 (69.2%)	20 (68.9%)	0.328[b]
Status exitus	10 (23.8%)	7 (53.8%)	9 (31%)	0.337[b]
OS mean ±SD Median	22.7±18.3 15.9	21.0±15.9 15.3	25.1±22.2 18.6	0.909[c]

Data are presented as mean ± standard deviation or n (%); P values were obtained by the one-way ANOVA test[a], the Chi-Square test[b] or the Kruskal Wallis test[c]; BMI: Body Mass Index, L/S: Laparascopic Surgery, LND: Lymph Node Dissection, LVSI: Lymphovascular Space Invasion, MI: Myometrial Invasion, LNI: Lymph Node Involvement, OS: Overall Survival, SD: Standard Deviation

RESULTS

During the study period, 29 out of 1110 patients with endometrial cancer had MEC (2.6%). Eighteen of the cases had endometrioid + serous, 7 cases had endometrioid + clear, 3 cases had endometrioid + serous, and 1 case had clear + serous histopathology. Clinic-pathologic features and survival in the MEC group (n=29) were compared to those in pure serous (n=42) and clear cell adenocarcinomas (n=13). There was no significant difference among the groups in terms of age (p=0.168).

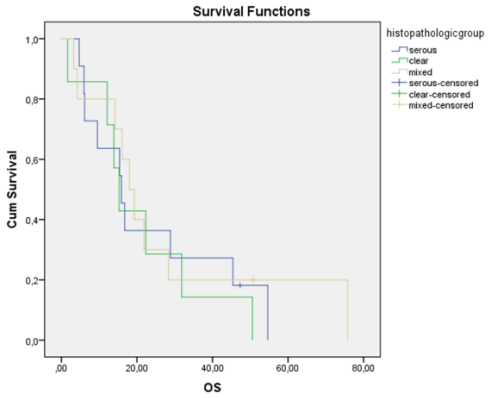

Figure 1. Kaplan-Meier survival curves for the OS among the different histotypes including pure carcinomas (SC, CC) and the MEC

OS: Overall Survival Cum Survival: Cumulative Survival

We did not find statistically significant differences among the groups regarding the BMI (p=0.904), menopausal status (p=0.213), and presence of co-morbidity (p=0.792). Laparoscopic surgery was more frequently performed in the mixed group but did not reach a significant value (p=0.474). Lymph node dissection rates were similar (p=0.953). The groups were similar in terms of stage, LVSI, nodal involvement, MI, and omental metastasis (p=0.785, 0.626, 0.510, 0.424, 0.253, respectively). It was found that the patients mostly received adjuvant therapy and the main adjuvant treatment was chemotherapy.

There was no significant difference in the rates of receiving adjuvant therapy among the groups. Approximately 80 percent of cases received adjuvant therapy, while 69% of the cases received chemotherapy, and this rate was 45% for radiotherapy in the mixed group. The clinical and pathological features of the MEC, pure SC and pure CC groups and comparison analysis of the groups are given in Table 1.

The mean follow-up time was 40.2 months. The mean OS was 22.7 months for the pure SC group, 21.0 months for the CC group, and 25.1 months for the mixed group. The difference among the groups in terms of OS did not reach a significant level (p=0.909). Figure 1 shows the prognosis of the groups in terms of OS.

DISCUSSION

In our study, we aimed to compare the clinical-pathological features and prognosis of the MECs with pure serous and clear cell carcinoma of the endometrium. The MEC rate was found to be 2.7% at the time of the study and it is compatible with the literature. The fact that the most common MECs are endometrioid and serous is consistent with the literature[9-11]. We demonstrated that there was no difference among the groups in terms of clinical-pathological features and prognosis. There are problems both in definition and in clinical management of MECs. In clinical management, which component accompanies and its percentage are important for avoiding the undertreatment surgery and adjuvant therapy. Although there are some studies on this subject, our knowledge on the biology of MECs is limited[10,11,15,16].

This study showed that all three groups were similar in terms of OS. The MEC group had the highest OS, while the pure CC group had the lowest OS. The number of studies comparing these groups is also limited since the frequency of this group of tumors is low and the results of the current studies are restricted and contradictory because of low number of cases, difficulties in pathological evaluation and identification, inclusion criteria, and variety of adjuvant treatments. It has been demonstrated that the prognosis gets worse even in the existence of very small amounts of type 2 components in stage 1 endometrial cancer and should be considered as high grade[17]. In addition to studies showing that the prognosis for the presence of a serous component is similar to pure serous carcinomas[8,18], there are studies showing that prognosis of the MECs are better than that of pure serous carcinomas[14-16,19,20]. Rossi et al.[20] drew attention to the high grade of endometrioid component for MEC in their study and suggested that they were likely to be considered more as pure type II carcinomas than MEC. Coenegrachts et al.[21]

compared clinical results of 23 patients having MEC (serous and endometrioid) with pure SC and EC and they reported that MECs were molecularly ambiguous and outcome of the MECs intermediate between that of patients with pure endometrioid and pure SC. Roelofsen et al.[14] showed that the prognosis for pure serous carcinomas was worse than for MECs. Matrai et al.[22] immumohistochemically investigated 18 cases with MEC and they concluded that these tumors might not display the immunohistochemical prototype of their components and support for the complex evolution of mixed carcinomas. As a result of our study, we can say that, in the presence of more than 5% type 2 components, the prognosis is not different from those with pure type 2 endometrial carcinoma. It is certain that these cases must be managed correctly to avoid incomplete surgery and adjuvant therapy. Currently, this group of patients has been managed as the other type 2 EC such as pure serous or clear cell carcinomas. In our study, the rate of receiving adjuvant therapy in the MEC group was 79.3%, which was not different from the other groups. Understanding the molecular changes of MEC will also allow for better management and personalized treatment of these patients. Köbel et al.[23] evaluated 41 endometrioid and clear cell MEC cases in terms of mismatch repair (MMR) protein deficiency and reported that endometrial carcinomas with mixed endometrioid and clear cell histology were frequently MMR protein deficient. Köbel et al.[10] studied to reveal the molecular properties of 18 MEC. They showed that different components had similar molecular features and they concluded that molecular analysis of mixed endometrial carcinomas revealed clonality in most cases. In another molecular study of 8 MEC cases demonstrated that targetable mutations might be existent in only one component of mixed tumors[11].

Similar to other studies, our study revealed similar clinical and pathological features among the groups[14,20]. The correct diagnosis of the second component is essential to determine treatment options and outcome for these patients, since it has been suggested that the presence of type II component might negatively affect the outcome of patient regardless of the amount.

Although we have a relatively good number of cases (for only one center), more cases are needed to reveal differences in prognosis. This is one of the limitation of our study. It would not be appropriate to discuss the results of adjuvant therapy with these patient numbers. It is not easy to reach a conclusion for the studies on relatively rare group tumors. Actually, even in a single group, heterogeneity is high at the molecular level. This is the second limitation of our study. The study findings cannot be generalized due to these limitations. Molecular investigation was not done in our study.

As a conclusion, our study suggests that the presence of type 2 component worsens the prognosis similar to pure type 2 carcinomas. A better understanding of these tumors at the molecular level will allow them to be better managed. It is certain that both the identification and management of these patients should be more precise and individualized.

Yazar Katkıları: Çalışma konsepti/Tasarımı: ABG; Veri toplama: ÖFG; Veri analizi ve yorumlama: MS; Yazı taslağı: MS; İçeriğin eleştirel incelenmesi: ÜKG; Son onay ve sorumluluk: MS, ÖFG, ÇA, GK, ÜKG, ABG, MAV; Teknik ve malzeme desteği: ÇA,; Süpervizyon: MAV; Fon sağlama (mevcut ise): yok.
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