

Does the Serous Component Rate Affect Survival in Patients with Mixed Type Endometrium Cancer?

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ABSTRACT

Objective: This research aimed to investigate whether the proportion of the serous carcinoma component influences the prognosis of patients diagnosed with mixed-type endometrial carcinoma.

Methods: Based on the relative percentage of the serous component, patients were grouped into two categories: $\leq 50\%$ and $> 50\%$. These groups were analyzed and compared with respect to demographic characteristics (age, body mass index, and parity), and histopathological features (grade, level of myometrial invasion, lymphovascular space invasion, tumor size, and FIGO stage). Cox regression and Kaplan–Meier survival analyses were used for the evaluation of overall survival (OS), disease-free survival (DFS), recurrence, and mortality rates.

Results: Individuals with a serous component exceeding 50% had significantly reduced DFS and OS (DFS: 42.9 ± 25.9 vs. 60.2 ± 25.9 months, $p = 0.04$; OS: 47.9 ± 24.8 vs. 68.7 ± 20.5 months, $p = 0.007$). Multivariate analysis identified age, deep myometrial invasion, and serous predominance ($> 50\%$) as independent predictors of poorer DFS and OS ($p < 0.05$). Tumor size and lymphovascular space invasion (LVSI) did not have statistically significant correlations with survival outcomes.

Conclusion: Although rare, mixed-type endometrial carcinoma with a dominant serous component appears to exhibit more aggressive behavior and poorer survival. The proportion of serous histology should be regarded as a critical prognostic indicator during clinical assessment and treatment planning.

Keywords: endometrial cancer, mixed type, survival

INTRODUCTION

Among gynecologic malignancies, endometrial cancer (EC) is the most frequently diagnosed type in women, and it is also one of the leading overall cancers, surpassed only by colorectal, lung, and breast cancer in incidence [1]. Globally, approximately 420,242 new cases were reported in 2022 [2]. Numerous risk factors contribute to its development, including advanced age, ethnicity, high body mass index (BMI), prolonged estrogen exposure (endogenous or exogenous), tamoxifen usage, early menarche, late menopause, low parity, metabolic syndrome, family history, and genetic predisposition [3].

Histological subtype is a fundamental determinant of prognosis. In 1983, Bokhman introduced a dualistic model classifying EC into two types based on hormonal influences, molecular profiles, and clinical outcomes [4]. Type I endometrial tumors usually exhibit endometrioid histology, are influenced by estrogen, and tend to be low-grade, with relatively favorable clinical outcomes [5]. In contrast, Type II tumors—typically high-grade serous or clear cell carcinomas—develop independently of hormonal influence and are linked to a more severe clinical trajectory and reduced survival rates [4,5].

Mixed-type endometrial carcinoma is characterized by the coexistence of two or more histologically distinct components

within a single tumor, one of which must be a Type II component [6]. Based on WHO guidelines, mixed-type endometrial carcinoma requires a minimum of 10% representation of a Type II histologic component within the tumor [7,8]. The most frequent combination involves serous and endometrioid histologies [9].

Recent evidence indicates that endometrial tumors with a dominant serous component, particularly when it exceeds 50%, may be linked to more unfavorable survival outcomes [10]. Nonetheless, the current body of literature is limited, often relying on small patient cohorts and retrospective data, leading to inconsistent conclusions.

In this investigation, we aimed to analyze how the proportion of serous carcinoma within tumors influences prognosis, with a focus on DFS and OS among individuals diagnosed with mixed-type EC.

MATERIALS AND METHODS

A retrospective analysis was conducted on individuals who had undergone surgery for EC at Izmir Tepecik Training and Research Hospital from January 2015 to January 2022. From this population, cases diagnosed with mixed-type endometrial carcinoma featuring both serous and endometrioid components were identified. Patients with other histologic types, such as mucinous or clear cell carcinoma, or those without a defined percentage of serous component were excluded. Forty individuals met the requirements for inclusion.

A full surgical assessment was performed for each case, incorporating bilateral salpingo-oophorectomy, hysterectomy, excision of the para-aortic and pelvic lymph nodes, and omentectomy. After evaluating the final pathology findings, two groups were formed from patients according to the serous carcinoma proportion: 50% or less, and greater than 50%.

Patient data were collected from hospital records, covering demographic and pathological features, including tumor grade, body mass index (BMI), parity, age, lesion dimensions, depth of myometrial invasion, lymphovascular involvement, FIGO classification, and administered adjuvant therapy. Clinical outcomes—specifically DFS, OS, recurrence, and survival status—were evaluated during follow-up.

Postoperative pathological findings and FIGO 2009 staging served as the basis for planning adjuvant treatment protocols.

Main Points

- This retrospective cohort study evaluates the prognostic significance of the proportion of serous carcinoma in mixed-type endometrial cancer. We analyzed 40 surgically staged patients and compared survival outcomes based on whether the serous component was $\leq 50\%$ or $>50\%$. Our findings demonstrate that a higher serous component ratio is significantly associated with shorter disease-free and overall survival. Multivariate analysis confirmed this relationship, independent of LVSI or tumor size.
- To the best of our knowledge, this is one of the few studies focusing on the 50% cutoff, which may serve as a practical stratification marker in clinical decision making. Given the rarity of mixed-type tumors, our study provides clinically valuable data that may assist in tailoring adjuvant treatment strategies.

Patients with Stage IA disease and no lymphovascular space invasion (LVSI) were treated with vaginal brachytherapy alone. Those with Stage IB or more advanced disease received external beam radiotherapy (EBRT) and/or chemotherapy based on risk stratification.

Follow-up visits occurred quarterly in the first two years, semi-annually during the subsequent three years, and then annually. Imaging (magnetic resonance imaging or computed tomography) was performed once per year. DFS was determined using the surgery date to either last follow-up or recurrence, while OS encompassed the time until death or final contact.

This research received ethical approval from the Ethics Committee of the University of Health Sciences, Izmir Tepecik Training and Research Hospital (Approval no.: 2022/02-14; Date: 15/02/2022) and was carried out based on the Declaration of Helsinki and Good Clinical Practice (GCP).

Statistical Analysis

The data collected during the investigation were analyzed using SPSS version 19.0 (IBM Corp). To assess the normality of the data distribution, the Kolmogorov–Smirnov test was applied. Descriptive statistics, including the mean, standard deviation, frequency, and percentage, were used to summarize the data.

For statistical significance, a t-test was employed for dependent groups with normally distributed data, while the Mann–Whitney U-test was utilized for data that did not follow a normal distribution when comparing binary independent variables. The relationship between categorical variables was examined with the Chi-square test. Survival analysis was conducted using the Cox regression test, and the Kaplan–Meier method was applied to analyze the impact of the serous component ratio on DFS and OS. The log-rank test was employed to determine the statistical significance of the survival analysis results. A p-value less than 0.05 was considered statistically significant.

RESULTS

The final analysis comprised 40 people with mixed-type EC. The mean age was 62.6 ± 10.4 years, and the average BMI was 33.2 ± 5.0 kg/m². The median parity was 2.3 ± 0.9, and the mean tumor diameter measured 50.1 ± 16.8 mm. Based on the proportion of the serous carcinoma component, two groups of patients were formed: those with ≤50% (n = 18) and those with >50% (n = 22). No statistically significant differences were detected among the two groups based on age, BMI, parity, tumor size, tumor grade, LVSI, depth of myometrial invasion (DMI), cervical or adnexal involvement, or lymph node metastasis (p > 0.05 for all) (Table 1).

Table 1. Demographic, histopathological, clinical, adjuvant treatment, and survival characteristics.

Features	Total (n = 40 (%))	Serous component ≤50% (n = 18 (%))	Serous component >50% (n = 22 (%))	p
	Mean ± SD	Mean ± SD	Mean ± SD	
Age	62.6 ± 10.4	61.2 ± 10.0	63.7 ± 10.8	0.460
BMI (kg/m ²)	33.2 ± 5.0	32.4 ± 4.5	33.9 ± 5.4	0.400
Parity	2.3 ± 0.9	2.4 ± 1.0	2.2 ± 0.9	0.370
Tumor size (mm)	50.1 ± 16.8	52.2 ± 12.5	48.4 ± 19.7	0.480
DFS (month)	50.7 ± 27.0	60.2 ± 25.9	42.9 ± 25.9	0.040
OS (month)	57.2 ± 25.0	68.7 ± 20.5	47.9 ± 24.8	0.007
Grade				
1	5 (12.5)	2 (11.1)	3 (13.6)	1.000
2	25 (62.5)	11 (61.1)	14 (63.6)	
3	10 (25.0)	5 (27.8)	5 (22.7)	
Abdominal cytology				
Negative	39 (97.5)	18 (100.0)	21 (95.5)	1.000
Positive	1 (2.5)	0 (0.0)	1 (4.5)	

LVSI				0.890
Positive	26 (65.0)	11 (61.1)	15 (68.2)	
Negative	14 (35.0)	7 (38.9)	7 (31.8)	
DMI				0.940
Yes	28 (70.0)	6 (33.3)	6 (27.3)	
None	12 (30.0)	12 (66.7)	16 (72.7)	
Cervical involvement				0.050
Yes	8 (20.0)	1 (5.6)	7 (31.8)	
None	32 (80.0)	17 (94.4)	15 (68.2)	
Uterine involvement				0.240
Yes	3 (7.5)	0 (0.0)	3 (13.6)	
None	37 (92.5)	18 (100.0)	19 (86.4)	
Parametrial involvement				-
Yes	0 (0.0)	0 (0.0)	0 (0.0)	
None	40 (100.0)	18 (100.0)	22 (100.0)	
Adnexial involvement				0.240
Yes	3 (7.5)	0 (0.0)	3 (13.6)	
None	37 (92.5)	18 (100.0)	19 (86.4)	
Omentum involvement				1.000
Yes	2 (5.0)	1 (5.6)	1 (4.5)	
None	38 (95.0)	17 (94.4)	21 (95.5)	
Pelvic LN involvement				0.530
Yes	12 (30.0)	4 (22.2)	8 (36.4)	
None	28 (70.0)	14 (77.8)	14 (63.6)	
Paraaortic LN involvement				1.000
Yes	5 (12.5)	2 (11.1)	3 (13.6)	
None	35 (87.5)	16 (88.9)	19 (86.4)	
Stage				0.590
1 or 2	26 (65.0)	13 (72.2)	13 (59.1)	
3 or 4	14 (35.0)	5 (27.8)	9 (40.9)	
Treatment				0.900
Surgery	1 (2.5)	0 (0.0)	1 (4.5)	
Surgery+RT	5 (12.5)	3 (16.7)	2 (9.1)	
Surgery+CRT	33 (82.5)	15 (83.3)	18 (81.8)	
Surgery+CT	1 (2.5)	0 (0.0)	1 (4.5)	
Recurrence				0.480
None	31 (77.5)	15 (83.3)	16 (72.7)	
Yes	9 (22.5)	3 (16.7)	6 (27.3)	
Follow-up status				0.110
Dead	13 (32.5)	3 (16.7)	10 (45.5)	
Alive	27 (67.5)	15 (83.3)	12 (54.5)	

BMI, body mass index; DFS, disease-free survival; OS, overall survival; LVSI, lymphovascular space invasion; DMI, depth of myometrial invasion; LN, lymph node; RT, radiotherapy; CRT, chemoradiotherapy CT, chemotherapy.

Significant differences in survival outcomes were found between the two groups. Those with a serous component greater than 50% demonstrated significantly shorter durations of both DFS and OS. Patients with more than 50% serous histology had a mean DFS of 42.9 ± 25.9 months, while those with 50% or less exhibited a mean of 60.2 ± 25.9 months ($p = 0.04$). Mean OS reached 47.9 ± 24.8 months in the higher serous component group, versus 68.7 ± 20.5 months in those with a lower proportion ($p = 0.007$). Although recurrence was observed in nine participants (22.5%)—three in the $\leq 50\%$ group and 6 in the $>50\%$ group—this difference was not statistically significant ($p = 0.48$). Similarly, mortality was higher in the $>50\%$ group (45.5%) compared to the $\leq 50\%$ group (16.7%), but the difference was not statistically significant ($p = 0.11$).

According to multivariate Cox regression, advancing age, extensive myometrial infiltration, and serous proportion exceeding 50% emerged as independent negative prognostic indicators for both DFS and OS. For DFS, the hazard ratios (HRs) were 1.1 for age (95% CI: 1.0–1.2; $p = 0.008$), 9.9 for DMI (95% CI: 1.3–78.5; $p = 0.03$), and 5.8 for serous component $>50\%$ (95% CI: 1.2–28.6; $p = 0.03$). For OS, the HRs were 5.2 for age (95% CI: 0.5–55.5; $p = 0.001$), 12.7 for DMI (95% CI:

1.2–133.3; $p = 0.03$), and 12.8 for serous component $>50\%$ (95% CI: 2.3–72.6; $p = 0.004$). Neither LVSI nor tumor size showed a significant association with survival outcomes ($p > 0.05$). Kaplan–Meier survival analyses illustrated notably reduced DFS and OS among patients harboring a predominantly serous tumor pattern (Table 2 and Figures 1 and 2).

DISCUSSION

Our research aimed to evaluate whether the extent of serous histology within mixed-type endometrial carcinoma has an impact on patient prognosis. The analysis demonstrated that individuals with a serous component greater than 50% had notably reduced DFS and OS, underscoring the inherently aggressive behavior of serous histology.

Advanced age at the time of diagnosis is commonly associated with less favorable clinical outcomes, particularly among individuals with Type II endometrial carcinoma—subtypes that are predominantly observed in older populations and typically exhibit a more aggressive disease pattern. [5,11]. In our multivariate evaluation, age emerged as an independent factor significantly associated with both DFS and OS, aligning with findings from earlier studies.

Table 2. Cox regression analysis.

Outcome	DFS		OS	
	HR (95% CI)	p	HR (95% CI)	p
Age	1.1 (1.0-1.2)	0.008	5.2 (0.5-55.5)	0.001
Tumor size	1.0 (0.9-1.1)	0.600	1.0 (0.9-1.1)	0.380
LVSI		0.180		0.180
Negative	Ref		Ref	
Positive	4.1 (0.5-32.4)		5.2 (0.5-55.5)	
DMI		0.030		0.030
Yes	9.9 (1.3-78.5)		12.7 (1.2-133.3)	
None	Ref		Ref	
Serous component		0.030		0.004
$\leq 50\%$	Ref		Ref	
$>50\%$	5.8 (1.2-28.6)		12.8 (2.3-72.6)	

DFS, disease-free survival; OS, overall survival; LVSI, lymphovascular space invasion; DMI, depth of myometrial invasion

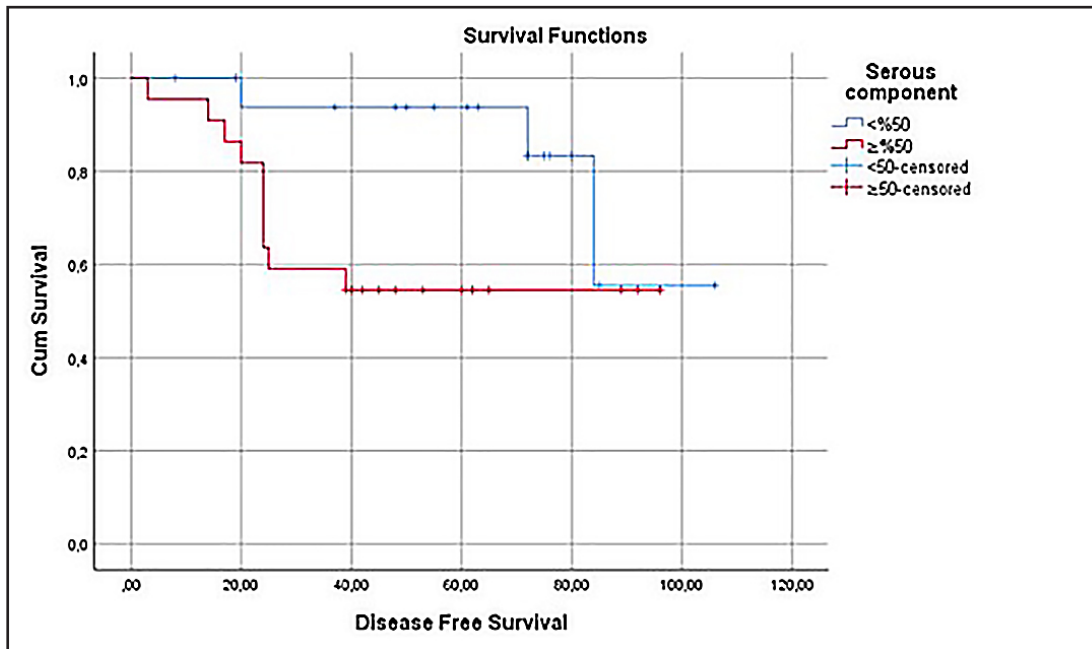


Figure 1. DFS graph based on the serous component ratio.

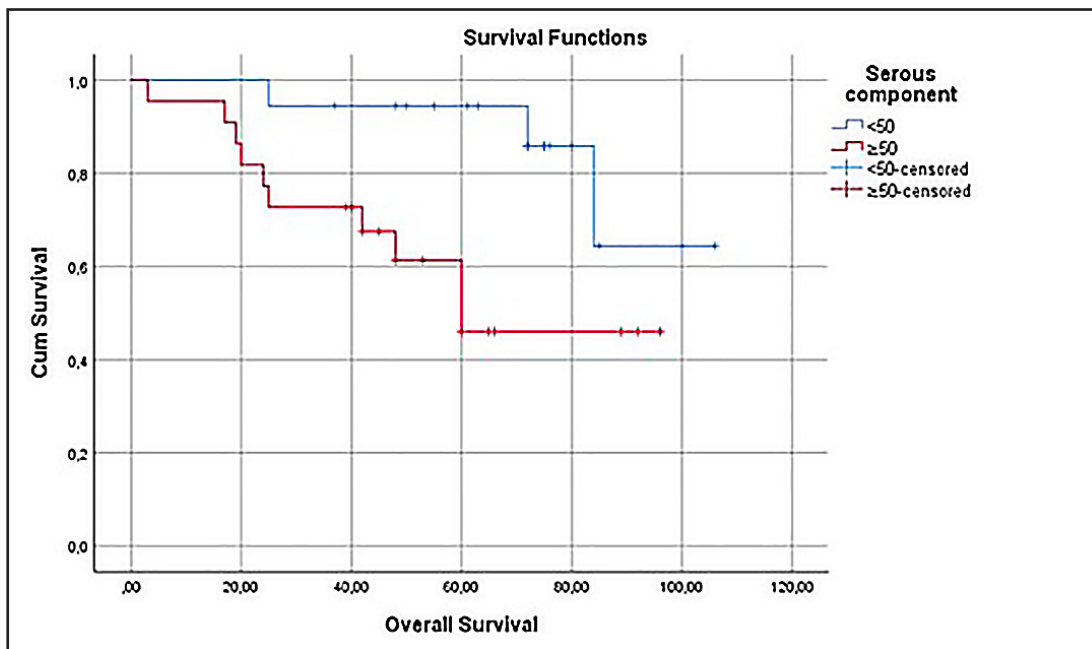


Figure 2. OS graph based on the serous component ratio.

Some prior studies, such as that by Kaban et al. [12], evaluated lower cutoffs (e.g., 25%) for the serous component and found no significant difference in survival between groups. In contrast, the current study supports the notion that a 50% cutoff point for the serous component may more effectively stratify patients based on survival expectations, with higher proportions of serous histology associated with significantly poorer DFS and OS. Such variation might stem from inconsistencies in sample

size, methodological approaches, or therapeutic strategies employed across studies.

In support of our results, previous studies have also demonstrated that a greater proportion of serous carcinoma—especially beyond the 50% threshold—correlates with worse clinical outcomes [10]. Our analysis confirmed the prognostic impact of serous predominance in both univariate and multivariate

models. Interestingly, traditional pathologic factors such as LVSI and tumor size did not independently influence survival, emphasizing the dominant prognostic role of tumor histology in this subgroup.

The incorporation of molecular classification into the FIGO 2023 staging system for endometrial cancer has highlighted its critical role in guiding treatment planning [13]. Nevertheless, the retrospective design of the present study precluded the inclusion of molecular data. Future investigations integrating molecular classification are warranted to elucidate the biological mechanisms underlying tumor heterogeneity and to clarify the prognostic significance of the variable tumor component ratios observed in mixed-type endometrial carcinomas.

A notable strength of this study is the inclusion of a well-defined patient cohort treated at a single tertiary institution, ensuring consistent surgical management and pathological evaluation. Although mixed-type endometrial carcinomas are relatively rare, our sample size is among the more robust compared to similar studies.

Limitations

Despite this study's contributions, certain limitations should be recognized. Primarily, the retrospective nature of the analysis may have resulted in selection bias. Second, molecular classification—which has recently gained prominence as a key tool for risk stratification in EC—was not available in our cohort. Despite the absence of molecular profiling in our cohort, a dominant serous histological pattern could reflect an inherently more aggressive tumor behavior. Third, while a 50% cutoff was biologically plausible, it warrants further validation in prospective, multi-center studies.

CONCLUSION

Mixed-type endometrial carcinoma, though relatively uncommon, presents a unique clinical challenge due to its dual histologic nature. Our findings indicate that the proportion of the serous carcinoma component plays a critical role in determining patient outcomes. Specifically, patients with serous components exceeding 50% demonstrated significantly shorter DFS and OS durations, underscoring the aggressive biological behavior associated with serous histology.

These results suggest that quantifying the serous component may offer additional prognostic value beyond standard

clinicopathological parameters. Recognizing serous predominance as an adverse prognostic indicator could support more individualized treatment planning and closer postoperative surveillance. In future studies, researchers should aim to validate these findings through prospective studies involving larger cohorts and incorporate molecular classification to enhance prognostic accuracy and therapeutic guidance.

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Conflict of Interest: The authors have no relevant financial or non-financial interests to disclose.

Informed Consent: This study was conducted retrospectively, and all patient data were expressed in numerical form. As there was no identifiable information included, there was no risk to patient confidentiality, and the requirement for informed consent was waived.

Data Availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval: This research received ethical approval from the Ethics Committee of the University of Health Sciences, Izmir Tepecik Training and Research Hospital (Approval no.: 2022/02-14; Date: 15/02/2022) and was carried out based on the Declaration of Helsinki and Good Clinical Practice (GCP).

Author Contributions: G.G.: writing; T.K., E.K., and M.K.: work design and organization; E.D.Ö. and E.Ö.: data collection; A.T.: statistical analysis.

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