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

**ISSN:** 0017-0011

**e-ISSN:** 2543-6767

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**DOI:** 10.5603/GP.a2021.0258

**Article type:** Research paper

**Submitted:** 2021-02-14

**Accepted:** 2021-06-11

**Published online:** 2022-03-07

[ORIGINAL PAPER / GYNECOLOGY]

# Effect of mucinous differentiation in endometrioid type endometrial cancers on prognosis

## Prognosis of mucinous differentiated endometrioid endometrial cancer

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## ABSTRACT

**Objectives:** To evaluate the influence of mucinous differentiation in endometrioid endometrial cancer regarding spread and prognosis.

**Material and methods:** Endometrioid endometrial cancer cases between 2015 and 2020 were collected retrospectively and divided into two groups according to the cytoplasmic mucin including. Prognostic factors and cancer spread related parameters were evaluated.

**Results:** A total of 219 patients were enrolled in this study. One hundred twenty-two (55.7%) were endometrioid and 97 (44.3%) were in the mucinous differentiated endometrioid catagory. Age was similar between the groups (59.3 vs 58.7, $p = 0.62$), however, grade 3 lesions were more frequent in endometrioid type endometrial cancer (8.7% vs 1.4%, $p < 0.01$). Poor prognostic factors including myometrial invasion, lymphovascular space invasion (LVSI), lymph node metastases, peritoneal cytology, endocervical involvement, and stage were not significantly different between groups ($p = 0.23$, $p = 0.49$, $p = 0.40$, $p = 0.15$, $p = 0.17$, $p = 0.55$). The median overall survival time of endometrioid and mucinous differentiated endometrioid type endometrial cancer patients was determined 88.5 and 96.8 months, respectively ($p = 0.46$).

**Conclusions:** Mucinous differentiation in the endometrioid type of endometrial cancer does not seem to affect the prognosis in endometrioid endometrial cancer patients.

**Key words:** mucinous differantiation; endometrioid endometrial cancer; endometrial cancer prognosis

## INTRODUCTION

Endometrial cancer (EC) is the most frequently seen gynecologic malignancy worldwide [1]. Thirty percent of the newly diagnosed endometrial cancers are grade 1 — endometrioid subtype according to the studies [2]. The disease is mostly limited to the uterus and does not spread extrauterine space except 15% of cases [3]. Risks for extra-uterine metastasis, recurrence, and death were a myometrial invasion, lymphovascular space invasion (LVSI), and lymph node invasion [4, 5]. On the other hand, serous and clear cell types of EC are associated with poor prognostic factors including higher tumor grade, later stage, and decreased overall survival compared with endometrioid and mucinous types [6]. In addition, deep myometrial invasion, LVSI, and lymph node involvement are more frequent in serous papillary type EC than endometrioid type EC [7].

Mucinous EC is a rare histopathologic subtype defined as including intracytoplasmic mucin of more than 50% of the cancer cells [8, 9]. However, sometimes endometrioid EC cells may have mucinous differentiation less than 50% of the cells [10]. This entity may be called endometrioid cancer with mucinous differentiation. Advanced stages and pelvic lymph node metastasis were detected more frequently in pure mucinous EC rather than mucinous, squamous, or tubal differentiation variant of endometrioid EC [10, 11]. This study aims to evaluate the influence of mucinous differentiation of the endometrioid EC on myometrial invasion, LVSI, endocervical involvement, lymph node involvement, peritoneal washing cytology, stage, and overall survival (OS).

## MATERIAL AND METHODS

### Study population

Clinicopathological data of the patients with the diagnosis of endometrial cancer (EC) who applied to the Dokuz Eylul University Hospital from January 2015 to January 2020 were collected from the hospital database retrospectively. Ethical approval from the local ethics committee was obtained for this study. Patients with the diagnosis of primary EC who

were performed hysterectomy with bilateral salpingo-oophorectomy were included in the conducted study. Performing pelvic and/or para-aortic lymphadenectomy decision was made with being grade 3 carcinoma or more than 50% cancer invasion of the myometrium or endocervical involvement in frozen section evaluation. Eligible patients had been undergone detailed physical and gynecological examinations. Patients with insufficient clinicopathological data, or those that were treated with chemotherapy or radiotherapy before the surgery were excluded.

**Data collection**

The Hospital's electronic medical record database was used to obtain patients' clinicopathological data. (i) Basic information including age, menopause status, years in menopause, reproductive history, history of cancer in the family, comorbidities, and overall survival. (ii) Histopathological data including tumor grade, histopathological subtype, clinical-stage, depth of myometrial invasion, lymphovascular space invasion (LVSI), lymph node invasion, and peritoneal cytology. The International Federation of Gynecology and Obstetrics (FIGO) — 2009 staging and histologic typing system of World Health Organization (WHO) were used to determine tumor grade and clinical stage. Adjuvant therapies (radiation therapy (RT) or chemotherapy (CT)) were decided according to the pathological findings. Adjuvant therapies were given to the patients with extrauterine spread or high-risk early-stage disease.

Patients were divided into two groups as mucinous differentiated endometrioid (cytoplasmic mucin including cells lower than 50% among cancer cells) or pure endometrioid ECs. Endpoints of the present study were clinical-stage, depth of myometrial invasion, LVSI, lymph node invasion, endocervical involvement, and peritoneal cytology.

**Statistical analysis**

Mann-Whitney U and T-test were used to analyze the association between categorical and continuous variables. Associations between continuous variables were evaluated by using Pearson and Spearman correlation test. Kaplan-Meyer and the log-rank test was used to determine the median survival time. The comparison of proportions was calculated by the chi-square test. P-value $< 0.05$ was considered statistically significant. All analyses were performed by using IBM SPSS Statistics Version 25.

**RESULTS**

A total of 219 patients were included in the analysis. One hundred twenty-two were endometrioid and 97 were mucinous differentiated endometrioid subtype of EC. The clinicopathologic data of the patients were shown in Table 1. Mean ages of the enrolled patients were similar in two groups; mean ages in the endometrioid type EC group and mucinous differentiated endometrioid type EC group were 59 ± 9 and 58 ± 9 years, respectively. Age, menopausal status, history of cancer in the family were similar between the groups. Grade 3 tumor was determined more frequent in the endometrioid type EC group (8.7% vs 1.4%, $p < 0.01$)

Association between endometrial cancer spread related parameters and histopathologic subtype was summarized in Table 2. A total of 79 patients were diagnosed with more than 50% myometrial invasion (36.1%), while the remaining 140 patients were determined with less than 50% myometrial invasion (63.9%). Thirty-eight (17.4%) of the patients whose myometrial invasion more than 50% were in mucinous differentiated EC group. However, this difference was not found statistically significant ($p = 0.23$). No significant difference was found between the histopathologic subtype of EC and LVSI, lymph node invasion, peritoneal cytology, endocervical involvement, stage (p values were 0.49, 0.40, 0.15, 0.17, 0.55, respectively).

Median survival times of endometrioid and mucinous differentiated EC groups were determined 88.5 ± 1.6 and 96.8 ± 2.5 months, respectively. On the other hand, the 5-year overall survival rate was 95% in the endometrioid EC group and 93% in the mucinous differentiated EC group (Tab. 3, Fig. 1).

## DISCUSSION

This study represents the effect of mucinous differentiation on endometrioid histologic type of EC. Our hypothesis while performing this study was that mucinous differentiation has a negative effect on the prognosis of endometrioid EC such as deeper myometrial invasion, LVSI, more lymph node metastasis, and advanced stage. These presumes were considered due to the results of certain previous studies [10, 11].

A previous study conducted by Musa et al. [11] represented that, mucinous histology of EC was more likely to invade lymph nodes rather than endometrioid histology subtype of EC (17% vs 3%, $p = 0.01$). However, there was no detected significant difference regarding the myometrial invasion and LVSI. Besides, there was another similar study conducted by

Galic et al. [10] by obtaining data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. Advanced stages (FIGO stage III/IV) were more likely seen in mucinous histology of EC compared to endometrioid histology (12.9% vs 10.7%, p = 0.001). Although lymph node metastasis and advanced stages were determined in mucinous histology according to both studies, survival rates were not affected by the histopathologic subtypes [10, 11]. In another study conducted by Duzguner et al. [8], eleven mucinous type of EC patients were investigated regarding prognostic factors and it was found that mucinous histology is associated with a better prognosis. In their study, only one patient had pelvic lymph node metastasis. Besides, 10 patients were in FIGO stage I, and only one patient was in stage IIIC1 disease. By contrast, another previous study claims that lymph node metastasis was higher in the mucinous type of EC compared with endometrioid type EC. The same study was not found any significant difference between two histopathologic types of EC regarding LVSI, deep myometrial invasion, and cervical involvement [12]**.** In the present study, lymph node metastasis, and the advanced stage had not a statistically significant difference between the two groups (6.8% vs 4.6%, p = 0.4; 5.5% vs 5%, p = 0.55; respectively). These results are similar to the results of a study conducted by Worley et al. [13]. Furthermore, Parameters that have a negative impact on the prognosis of EC including LVSI, endocervical involvement, and peritoneal washing cytology was similar between the mucinous differentiated EC and endometrioid EC similar to the results of the previous study conducted by Worley et al. [12] and Gungorduk et al [13].

The mean age of the patients was not significantly different in the current study. The mean age of the endometrioid histology without mucinous differentiation group was slightly older (59.3 vs 58.7 p = 0.62). However, Galic et al. [10] found that women older than 60 years were more likely to have mucinous differentiation compared to those younger than 60 (62.6% vs 56%, p = 0.0001). The myometrial invasion was not detected significantly different between groups (18.7% vs 17.4%, p = 0.23) as same as the study conducted by Musa et al. [11] and Gungorduk et al. [12] (17.1% vs 22%, p = 0.336). Recent studies showed that the survival rates of EC patients with mucinous differentiation were not significantly different from those without mucinous differentiation [10–13]. In the present study, the median survival time of the mucinous differentiated endometrioid EC and pure endometrioid EC were found similar (88.5 months vs 96.8 months, p = 0.46, respectively).

Besides, in a study conducted by Abdulfatah et al. [14], no difference was found between the mucinous differentiated endometrioid ECs and ECs without mucinous

differentiation in terms of tumor stage, tumor grade, myometrial invasion, LVSI, lymph node involvement, cervical involvement, and overall survival. By contrast with, grade 3 tumors were found significantly higher in the endometrioid type EC in the present study (8.7% vs 1.4%, $p < 0.01$). The other results of the present study are similar to the results of the study of Abdulfatah et al. [14].

There are several limitations of this study. First of all, the present study was designed retrospectively. However, in our center clinical and pathological data of almost all patients were recorded to the hospital database at the first evaluation immediately with minimal data loss. Second, re-evaluation of the pathologic specimens for the present study was not performed. All the pathologic results belong to the first evaluation of the specimens by two pathologists who are especially focused on gynecology.

## CONCLUSIONS

Pure mucinous differentiation was found associated with certain poor prognostic factors according to the previous studies [10, 11, 13]. However, poor prognostic factors including myometrial invasion, LVSI, lymph node metastases, endocervical involvement, peritoneal cytology, and the stage was not found associated with mucinous differentiation in the present study that investigates the influence of mucinous differentiation on endometrioid type EC. As a result of these, it can be said that prognosis does not seem to be affected by mucinous differentiation in endometrioid type EC patients.


### *Acknowledgments*

None.

### *Funding*

None.


### *Contributions*

OI: manuscript writing, data management, data analysis. BS: project development and administration. SK: data collection and analysis. SE: data management and collection. MK: supervision, review of the manuscript. CU: data management, review of the manuscript.

### *Ethical approval*

This study was carried out in consensus with our university´s ethics guidelines. The ethics committee approval was obtained for this study.

### *IRB approval*

This study was carried out in consensus with our university´s ethics guidelines.

### *Conflict of interest*

The authors declare that they have no conflict of interest.

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**Table 1.** Clinicopathologic data of the patients

| | | Endometrioid n = 122 | Mucinous differentiated endometrioid n = 97 | p value |
|---|---|---|---|---|
| Age [years] (mean ± SD) | | 59.3 ± 9.9 | 58.7 ± 9.4 | 0.62 |
| Menopause [years] (mean ± SD) | | 11.4 ± 8 | 9.2 ± 8.9 | 0.06 |
| Menopause status [n (%)] | No | 19 (8.6) | 24 (10.9) | 0.08 |
| | Yes | 103 (47) | 73 (33.3) | |
| History of cancer in family [n (%)] | No | 108 (49.3) | 91 (41.5) | 0.13 |
| | Yes | 14 (6.3) | 6 (2.7) | |
| Diabetes status [n (%)] | No | 83 (37.8) | 67 (30.5) | 0.46 |
| | Yes | 39 (17.8) | 30 (13.6) | |
| Tumor grade [n (%)] | 1 | 72 (32.9) | 66 (30.1) | < 0.01* |
| | 2 | 31 (14.2) | 28 (12.8) | |
| | 3 | 19 (8.7) | 3 (1.4) | |

* — **???**

**Table 2.** Association between endometrial cancer spread and histopathologic subtype

| | | Endometrioid n (%) | Mucinous differentiated endometrioid n (%) | p value |
|---|---|---|---|---|
| Myometrial invasion | < 50% | 81 (37.0) | 59 (26.9) | 0.23 |
| | > 50% | 41 (18.7) | 38 (17.4) | |
| Lymphovascular space invasion | Negative | 78 (35.6) | 61 (27.9) | 0.49 |
| | Positive | 44 (20.1) | 36 (16.4) | |
| Lymph node invasion | Negative | 107 (48.9) | 87 (39.7) | 0.40 |
| | Positive | 15 (6.8) | 10 (4.6) | |
| Peritoneal cytology | Negative | 110 (50.2) | 92 (42.0) | 0.15 |
| | Positive | 12 (5.5) | 5 (2.3) | |
| Endocervical involvement | Negative | 84 (38.4) | 60 (27.4) | 0.17 |
| | Positive | 38 (17.4) | 37 (16.9) | |
| Stage | IA | 63 (28.8) | 41 (18.7) | 0.55 |
| | IB | 17 (7.8) | 18 (8.2) | |
| | II | 30 (13.7) | 27 (12.3) | |
| | III | 11 (5.0) | 11 (5.0) | |
| | IV | 1 (0.5) | 1 (0) | |

**Table 3.** Survival outcomes between histopathologic subtypes

| | Endometrioid n = 122 | Mucinous differentiated endometrioid n = 97 | p value |
|---|---|---|---|
| Survival time [months] (mean ± SD) | 88.5 ± 1.6 | 96.8 ± 2.5 | 0.46 |
| Five year overall survival rate [%] | 95 | 93 | |

SD — standard deviation

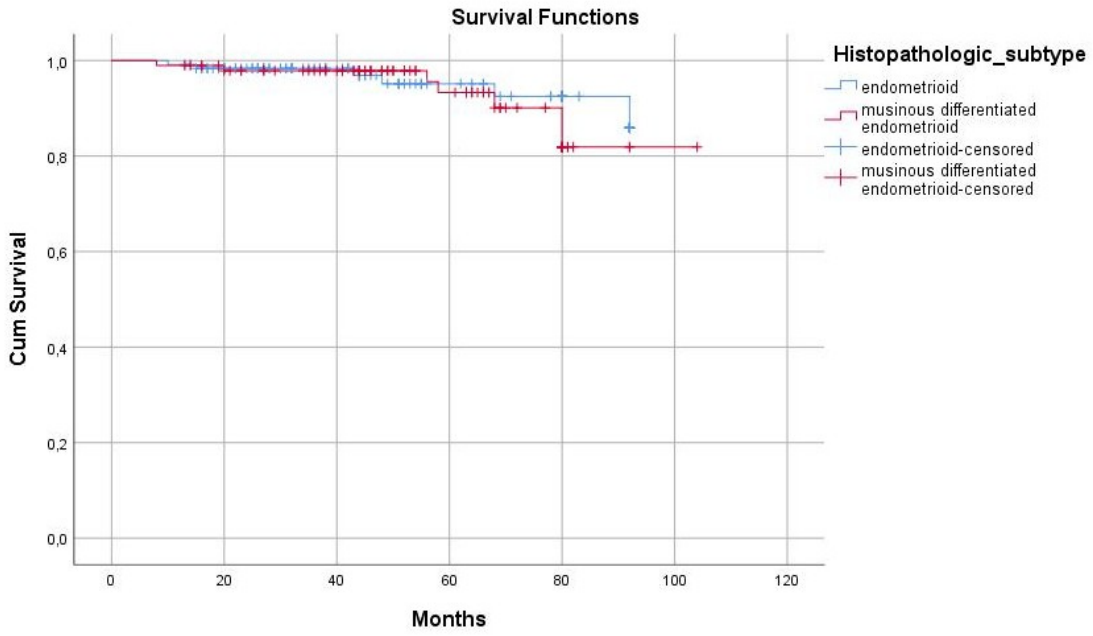


**Figure 1.** Survival curve of histopathologic subtypes