Acta Medica Nicomedia

Cilt: 3 Sayı: 3 Ekim 2020 / Vol: 3 Issue: 3 October 2020
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

RELATIONSHIPS OF BODY MASS INDEX WITH PROGNOSTIC FACTORS AND SURVIVAL IN ENDOMETRIAL CANCER

ENDOMETRİUM KANSERİNDE VÜCUT KİTLE İNDEKSİNİN PROGNOSTİK FAKTÖRLER VE SAĞKALIM İLE İLİŞKİSİ

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ABSTRACT

Objective: The aim of the study is to investigate the effect of body mass index (BMI) on prognostic factors and survival in patients with endometrial cancer.

Methods: A total of 247 patients with endometrial cancer were evaluated. The BMI, age of diagnosis, menopausal status, tumor size, histopathological type of tumor, tumor grade, myometrial invasion, cervical invasion, lymph node involvement, radiotherapy (RT) status, RT type, chemotherapy (KT) regimens, recurrence and metastasis status, disease-free survival and overall survival of the patients were determined retrospectively. The relationship between BMI and prognostic factors is evaluated with chi-square test and survival analysis is evaluated using Kaplan-meier and Cox analysis.

Results: The BMI of the patients were categorized into 3 groups as ≤29.9 kg/m^2, 30-39.9 kg/m^2, ≥40 kg/m^2. Age, menopausal status, histological subtype, tumor size, grade, stage, cervical invasion, myometrial invasion, lymph node involvement and relationship with BMI were investigated. The relationship between BMI and grade was significant but its relationship with other prognostic factors was not statistically significant. When the factors affecting overall survival and disease-free survival were analyzed by multivariate analysis, the stage and histological subtypes were found statistically significant. The effect of BMI on overall survival and disease-free survival was not significant.

Conclusion: There was no relationship between BMI and overall survival (OS) and disease-free survival (DFS). The stage and histological subtypes affected DFS and OS.

Keywords: Body mass index, endometrial neoplasms, prognosis, survival

ÖZ

Amaç: Çalışmamızda endometriyum kanseri tanısı almış hastalarda vücut kitle indeksi (VKİ)'nin prognostik faktörler ve sağkalıma etkisini araştırmayı amaçladık.

Yöntem: Endometriyum kanseri tanısı almış 247 hasta değerlendirilmiştir. Hastaların VKİ'si, tanı yaşı, menapoz durumları, tümör çapı, tümörün histopatolojik tipi, gradı, evresi, myometriyal invazyon, servikal invazyon, lenf nodu tutulumu, radyoterapi (RT) durumu, RT tipi, aldığı kemoterapi rejimleri, nüks ve metastaz durumları, hastalıksız sağkalım ve genel sağkalımları belirlendi. VKİ'nin prognostik faktörlerle ilişkisi ki-kare testi, sağkalım analizi ise Kaplan-meier ve Cox analizi kullanılarak değerlendirilmiştir.

Bulgular: Hastaların VKİ'si ≤29,9 kg/m^2, 30-39,9 kg/m^2, ≥40 kg/m^2 olmak üzere 3 gruba kategorize edildi. Prognostik faktörlerden yaş, menapoz durumu, histolojik alt tip, tümör çapı, grad, evre, servikal invazyon, myometriyal invazyon, lenf nodu tutulumu ile VKİ ilişkisi incelenmiştir. VKİ ile grad arasında ilişki anlamlı olup diğer prognostik faktörler ile ilişkisi istatistiksel anlamlı değildi. Genel sağkalım ve hastalıksız sağkalıma etki eden faktörler çok değişkenli analiz ile incelendiğinde evre ve histolojik alt tip istatistiksel olarak anlamlı bulunmuştur. VKİ'nin genel sağkalım ve hastalıksız sağkalıma etkisi anlamlı bulunmamıştır.

Sonuç: Vücut kitle indeksi ile hastalıksız sağkalım ve genel sağkalım arasında anlamlı bir ilişki gösterilememiştir. Evre ve histoloji genel ve hastalıksız sağkalımı etkilemektedir.

Anahtar Kelimeler: Vücut kitle indeksi, endometrial kanser prognoz, sağkalım

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Submitted/Başvuru: 05.09.2020 • **Accepted/Kabul:** 05.10.2020 • **Published Online/Online Yayın:** 29.10.2020

Introduction

Endometrium cancer is the most common cancer of the female genital tract in the developed countries and the second most common cancer in the developing countries.[1] A woman's lifetime risk of developing endometrium cancer is 2-3%.[2] Many risk factors including age, early menarche, late menopause, nulliparity, type 2 diabetes mellitus, birth control pills, family history affect the risk of developing endometrial cancer.[3] Also, obesity is a well-known risk factor for the development of endometrium cancer. Obesity is a common health problem in almost all societies and is becoming a global epidemic.[4] Accordingly, an increase in the incidence of endometrium cancer is predicted.[5] This relationship has been shown to be directly proportional to body mass index (BMI) in many studies.[6,7] Therefore, in this study we aimed to investigate the relationship between BMI and endometrium cancer and other prognostic factors.

Methods

This retrospective analysis included 320 female patients with endometrial cancer. Of these, 247 patients were included in the study. All of the patients were treated and followed-up at Kocaeli University School of Medicine, Department of Medical Oncology, between 2007 and 2017. Information regarding patient BMI, age of diagnosis, menopausal status, tumor size, histopathological type of tumor, tumor grade, myometrial invasion, cervical invasion, lymph node involvement, radiotherapy (RT) status, RT type, chemotherapy (KT) regimens, recurrence and metastasis status, disease-free survival and overall survival were obtained from the medical records of the patients. Stage 1 and 2 patients were grouped as early stage and stage 3-4 patients were grouped as advanced tumors based on a previous study.[8] The histopathology of the tumors was grouped as endometrioid and non-endometrioid types. The patients were followed until their death or last follow-up.

Statistical Analysis

SPSS 21 was used for all analyses. A p-value less than 0.05 was considered to be significant. The relationship between BMI and prognostic factors was evaluated with chi-square and Fisher exact tests. Survival analysis was evaluated according to Kaplan-Meier method and potential prognostic factors were compared by log-rank test. The Cox regression model was used for univariate and multivariate analyses. Overall survival (OS) was calculated from the diagnosis of patient to the date of death from any cause or of the last follow-up. Disease-free survival (DFS) was calculated from the diagnosis of patient to the date of disease progression, recurrence or death from any cause.

Results

Patient and tumor characteristics

Medical records of 320 patients were analyzed retrospectively. Seventy-three patients with incomplete medical records, synchronous tumors and unfollowed were excluded from the study and a total of 247 patients were included in the study. The median age of the patients was 61 (range 33-87). When the patients were divided into 2 groups <65 and ≥65, the number of patients under the age of 65 were 155 (62.8%), and the number of the other group was 92 (37.2%). The median age of menopause was 50. The number of premenopausal patients was 36 (14.6%) and the number of postmenopausal patients was 211 (85.4%) (Table 1).

Table 1. Characteristics of the patients

Characteristic	Patient (n=247)
Age	
Median (range)	61 (33-87)
<65 years	155 (62.8%)
≥65 years	92 (37.2%)
Menopausal patients	
Premenopausal	36 (14.6%)
Postmenopausal	211 (85.4%)
Body mass index	
≤29,9 kg/m2	94 (38.1%)
30-39,9 kg/m2	124 (50.2%)
≥40kg/m2	29 (11.7%)
Histology	
Endometrioid carcinoma	206 (83.4%)
Serous	23 (9.3%)
Clear cell type	5 (2.0%)
Other types	13 (5.3%)
Grade	
Grade 1	53 (21.5%)
Grade 2	117 (47.4%)
Grade 3	77 (31.2%)
Tumor size	
<4 cm	87 (40.7%)
≥4 cm	127 (59.3%)
Stage	
Early stage	188 (76.1%)
Advanced stage	59 (23.9%)
Lymph node involvement	
Yes	185 (74.9%)
No	33 (13.4%)
Not determined	29 (11.7%)
Myometrial invasion	
<1/2	127 (51.4%)
≥1/2	120 (48.6%)
Chemotherapy	
Yes	58 (23.5%)
No	189 (76.5%)
Radiotherapy	
Yes	206 (83.4%)
No	41 (16.6%)

In histopathological examination, 206 (83.4%) of tumor were detected as endometrioid carcinoma and 41(16.6%) were non-endometrioid type carcinoma. The median tumor diameter was 4 cm (range 1-11). The number of patients with grade 1 tumor was 53 (21.5%), while it was 117 (47.4%) and 77 (31.2%), in grade 2 and grade 3, respectively. The number of patients with <½ myometrial

invasion was 127 (51.4%) and ≥½ was 120 (48.6%), respectively. Seventy percent of the patients had cervical invasion. When the pathology reports were examined, the number of patients without lymph node involvement was 185 (74.9%), the number of patients with LN involvement was 33 (13.4%) and 29 patients (11.7%) did not undergo lymph node sampling.

At the time of diagnosis, 188 (76.1%) patients had early stage (stage 1-2) and 59 (23.9%) patients had advanced stage (stage 3-4) disease. The number of patients that received adjuvant chemotherapy was 58 (23.5%) and 83.4% of the patients received radiotherapy (Table 1).

Body mass index and prognostic factors

The patients were divided into 3 groups as ≤29,9 kg/m^2, 30-39.9 kg/m^2, ≥40 kg/m^2 according to the body mass index (BMI). The number of patients with BMI ≤ 29.9 kg/m^2 was 94 (38.1%), the number of patients between 30 and 39.9 kg/m^2 was 124 (50.2%) and ≥40 kg/m^2 was 29 (11.7%). When BMI and prognostic factors were analyzed, there was no statistically significant relationship between age, tumor size and histology, menopausal status, stage, lymph node involvement and myometrial invasion. The relationship between BMI and grade was significant (p=0.025). Grade 1 and 2 tumors were higher and grade 3 tumors were less in patients with BMI ≥40 kg/m^2 (Table 2).

Table 2. Relationship between body mass index and prognostic factors

	17.3-29.9 kg/m^2 n=94	**30-39.9 kg/m^2** n=124	**≥40 kg/m^2** n=29	**p value**
Age <65	61 (64.9%)	71 (57.3%)	23 (%79.3)	p=0.075
Age ≥65	33 (35.1%)	53 (42.7%)	6 (%20.7)	
Lymph node involvement				
Yes	12 (12.8%)	20 (16.1%)	1 (3.4%)	p=0.415
No	72 (76.6%)	90 (72.6%)	23 (79.3%)	
Not determined	10 (10.6%)	14 (11.3%)	5 (17.2%)	
Histopathology				
Endometrioid type	81 (86.2%)	98 (79%)	27 (93.1%)	p=0.122
Non-endometrioid type	13 (13.8%)	26 (21%)	2 (6.9%)	
Tumor size				
<4 cm	24 (30.8%)	51 (46.4%)	12 (46.2%)	p=0.83
≥4 cm	54 (69.2%)	59 (53.6%)	14 (53.8%)	
Stage				
Early stage	72 (76.6%)	90 (72.6%)	26 (89.7%)	p=0.150
Advanced stage	22 (23.4%)	34 (27.4%)	3 (10.3%)	
Grade				
Grade1	14 (14.9%)	30 (24.2%)	9 (31%)	
Grade2	50 (53.2%)	50 (40.3%)	17 (58.6%)	**p=0.025**
Grade3	30 (31.9%)	44 (35.5%)	3 (10.3%)	
Myometrial invasion				
<1/2	49 (52.1%)	58 (46.8%)	12 (42.9%)	p=0.607
≥1/2	45 (47.9%)	66 (53.2%)	16 (57.1%)	
Menopausal status				
Premenopausal	14 (14.9%)	19 (15.3%)	3 (10.3%)	p=0.787
Postmenopausal	80 (85.1%)	105(84.7%)	26 (89.7%)	

Body mass index and survival

The median DFS for the entire group has not been reached with 1- and 2-year survival rates of 95.0% and 90.0%, respectively. In univariate analysis, stage, grade, histology, tumor size, chemotherapy and radiotherapy affected DFS (p>0.05). There was no relationship between age, lymph node involvement, myometrial invasion, menopausal status and DFS. In multivariate analysis, tumor stage and histology affected DFS (Table 3).

Also, the median overall survival for the entire group has not been reached with a 5 years survival rate of 88.0% (Figure 1). In univariate analysis, age, stage, grade, histology, lymph node involvement, myometrial invasion, tumor size and chemotherapy and radiotherapy affected OS. There was no relationship between menopausal status and OS. In multivariate analysis, only tumor stage and histology affected OS (Table 3).

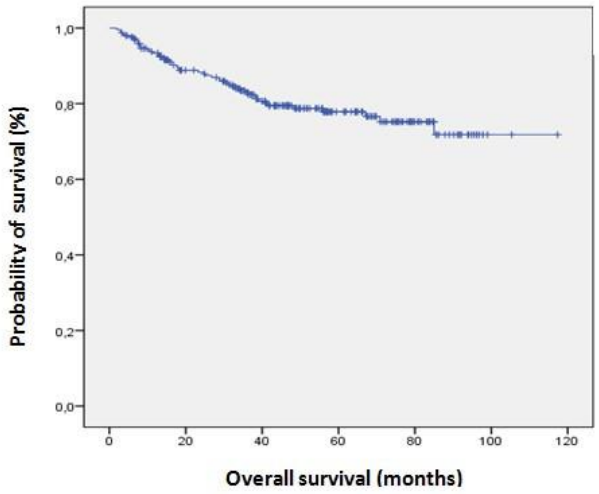

Figure 1. Overall survival of the patients with endometrial cancer

There was no statistically significant relationship of BMI with DFS and OS (Figures 2 and 3).

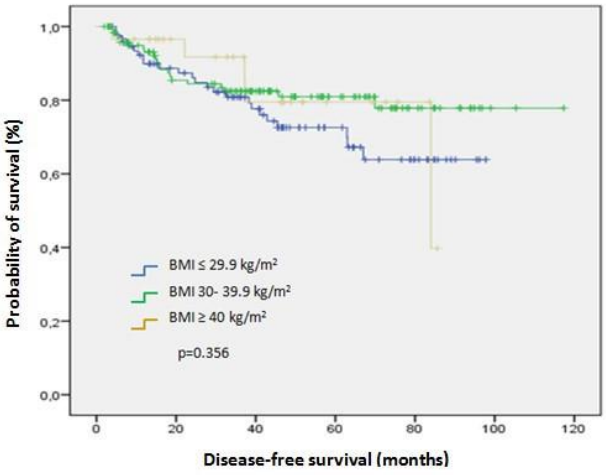

Figure 2. Relationship between disease-free survival and body mass index

Table 3: Relationship between patient characteristics and disease-free survival and overall survival

Patient characteristics	Mean DFS (months)	p value		Mean OS (months)	p value	
		Univariate analysis	Multivariate analysis		Univariate analysis	Multivariate analysis
Age						
<65	86.52 (80.31-92.72)	p=0.111		91.98 (86.72-97.24)	**p=0.001**	p=0.130
≥65	88.05 (77.64-98.45)			81.61 (70.61-92.60)		
Lymph node involvement						
Yes	72.24 (58.20-86.28)			65.11 (51.13-79.08)		
No	93.55 (86.77-100.34)	p=0.562		96.20 (89.30-103.09)	**p=0.028**	p=0.561
Not determined	81.89 (70.39-93.39)			82.32 (70.83-93.81)		
Histopathology						
Endometrioid type	97.76 (91.63-103.89)	**p<0.001**	**p=0.049**	103.12 (98.04-108.20)	**p<0.001**	**p=0.005**
Non-endometrioid type	47.06 (33.86-60.26)			44.01 (32.46-55.56)		
Tumor size						
<4 cm	103.20 (95.44-110.96)	**p=0.007**	p=0.074	106.86 (99.99-113.74)	**p=0.001**	p=0.061
≥4 cm	72.87(65.65-80.09)			73.93 (67.05-80.81)		
Stage						
Early stage	103.84 (98.58-109.10)	**p<0.001**	**p=0.021**	103.84 (98.58-109.10)	**p<0.001**	**p=0.049**
Advanced stage	58.03 (47.51-68.55)			58.03 (47.51-68.55)		
Grade						
Grade1	101.14 (90.23-112.04)			108.47 (100.2-116.75)		
Grade2	85.79 (79.96-91.62)	**p<0.001**	p=0.084	88.01 (82.69-93.33)	**p<0.001**	p=0.490
Grade3	60.02 (50.82-69.22)			60.52 (51.98-69.05)		
Myometrial invasion						
<1/2	81.23 (73.47-88.99)	p=0.365		79.51 (71.81-87.20)	**p=0.024**	p=0.561
≥1/2	95.76 (87.89-103.63)			100.97 (94.03-107.92)		
BMI						
≤ 29,9 kg/m²	74.59 (66.83-82.35)			79.28 (72.21-86.35)		
30-39,9 kg/m²	96.81 (88.85-104.77)	p=0.356		91.84 (83.18-100.49)	p=0.303	
≥ 40 kg/m²	73.15 (62.82-83.47)			79.52 (71.63-87.42)		
Radiotherapy						
No	68.50 (53.40-83.61)	**p=0.006**	p=0.123	77.05 (47.86-76.29)	**p<0.001**	p=0.792
Yes	80.33 (74.63-86.02)			83.56 (46.70-94.83)		
Chemotherapy						
No	76.14 (67.67-84.62)	**p=0.042**	p=0.094	87.14 (52.27-89.62)	**p=0.001**	p=0.089
Yes	94.51 (87.40-101.62)			94.51 (58.40-104.68)		
Menopausal status						
Premenopausal	72.14 (65.65-83.60)	p=0.334		79.54 (57.65-88.62)	p=0.232	
Postmenopausal	93.42 (83.40-100.32)			99.32 (53.40-103.36)		

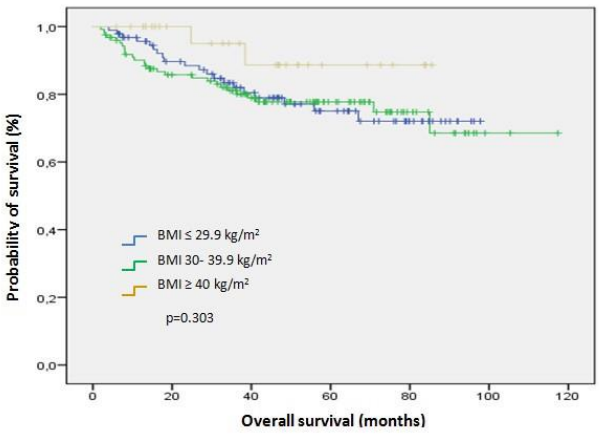

Figure 3. Relationship between overall survival and body mass index

Discussion

Endometrial cancer is the most common female genital cancer in the developed world, with several histologic types; of these, endometrioid adenocarcinoma histology is the most common type.[9] Based on the 2014-2016 data, an estimated 3.1% of women will be diagnosed with endometrial cancer in their lifetime.[10] There are multiple prognostic factors for endometrial cancer which are generally related to surgical pathologic findings and affect overall survival.[3] In our study, we aimed to investigate the effect of body mass index on prognostic factors and survival.

Age, which is one of the exceptions, is an independent risk factor for survival. In one study, women who were diagnosed under the age of 40 were found more likely to have early stage endometrioid type and well differentiated endometrial carcinoma.[11] Lurain et al. found increased age as an independent risk factor for recurrence.[12] In our study, we determined the cut-off level of 65 years for age as in a previous study.[13] As in other studies, we found age as an independent prognostic factor for survival.[12,14] Nevadunsky et al. stated that there was an inverse relationship between BMI and age of diagnosis in endometrioid type endometrial carcinoma.[15] This was explained by the fact that the patients with increased BMI had endometrioid type and low grade endometrial carcinoma. We found no relationship between BMI and age in our study. This may be related to the cut-off level of 65 years of age and to the short median time of follow-up in our study.

Five-year DFS-OS rates were found 61.2% and 60.6%, respectively, for endometrioid adenocarcinoma and these rates were significantly higher than non-endometrioid histologies.[16] Also, in our study, endometrioid type endometrial carcinoma had increased DFS and OS. Painter et al. showed that there was a significant relationship between the increase in BMI and the development of endometrial carcinoma and this relationship was more pronounced in the endometrioid type.[17] However, we couldn't find any relationship between BMI and histological subtypes in our study. This may be explained by the low number of patients with non-endometrioid type endometrial carcinoma.

Low grade tumors were much more and high grade tumors were less in patients with BMI≥40 kg/m^2, in our study. In the study performed by Temkin et al., it was shown that the decrease in the tumor grade was inversely proportional to the increase in BMI.[18] This relationship can be explained by the increase of estrogen in peripheral fat tissue aromatization in obese patients. Also, the frequency of endometrioid type endometrial carcinoma which is estrogen-dependent increases with increased BMI. As a result, this situation increases the likelihood of low grade tumors in obese patients.[9,19,20]

The stage of the disease is the most important prognostic factor in endometrial cancer. As the stage increases, the survival rates decrease. Lewin et al. reported a 5 years survival rate of 83% in stage 1, 73% in stage 2 and 52% in stage 3 patients.[20] In our study, the 5-year overall survival rate in our study was 88.8%. We found a statistically significant relationship between stage and DFS and OS. There are conflicting results between BMI and stage. There was an inverse relationship between BMI and stage in two studies. It was stated that the BMI was higher in patients who had early stage disease.[8,18] In contrast, there was no relationship between BMI and stage in the other two studies.[15,21] We also couldn't find a relationship between BMI and stage in our study. These different results may be explained by the differences in the designs and the number of patients in these studies.

Ko et al. reported that patients with low BMI had more recurrences and lower survival rates than patients with higher BMI.[22] In similar, patients with BMI≥40 kg/m^2 had decreased survival in stage 2 endometrial cancer in another study.[23] In other two studies, no relationship was shown between BMI and survival.[24,25] Everett et al. evaluated survival by dividing BMI into three groups similar to our study and found that obese patients had low grade, early stage and endometrioid type which is the less aggressive form. However, there were no significant survival differences between 3 groups.[26] In our study, we could not find a relationship between BMI and DFS and OS. These differences can be explained firstly by the differences in the characterization of BMI groups in these studies. Moreover, in our study, histologic types can affect the survival rates due to the low number of non-endometrioid type endometrial carcinoma patients which has poorer prognosis.

Potential limitations exist to the interpretation of the data in this study. First of all, these data were collected from a single institution and retrospectively designed. Therefore, we could not directly complete information regarding other risk factors and co-morbidities. Also, this resulted in the absence of socio-demographic information of the patients. Moreover, during the characterization of groups (eg. histopathology, stage), some of the groups had low number of patients. Thus, this may affect the results by preventing the adjustment for analysis.

We observed that there was no relationship between BMI and survival. Survival was mainly affected by tumor stage and tumor histology. BMI had no effect on prognostic factors except the grade of the tumors. High grade tumors were less in patients with higher BMIs. These findings show that a risk factor for a cancer type does not necessarily worsen the outcomes. Stage and histological subtypes had inferior outcomes and should be taken in consideration when deciding to a treatment strategy.

Acknowledgments

This article is produced from a thesis planned and completed at Kocaeli University Faculty of Medicine. The authors thank Canan Baydemir (Kocaeli University School of Medicine, Department of Biostatistics and Medical Informatics) for statistical analysis.

Compliance with Ethical Standards

The study was approved by the Non-invasive Clinical Research Ethics Committee of the Kocaeli University (Date: 07.02.2018, Project no: KU GOKAEK 2018/59) and was conducted according to the principles of the Declaration of Helsinki. Due to the retrospective nature of the study, informed consent was not obtained from patients or their families that was planned prior to study.

Conflict of Interest

The authors have no conflicts of interest relevant to this article.

Author Contribution

UK, EMY: Concept; UK, DÇ, KU: Design; UK, DÇ, KU: Supervision; EMY, YÇ, UI, EO: Resources; EMY, YÇ, UI, EO: Materials; EMY, UI, YÇ, EO: Data collection and/or processing; CB, UK: Analysis and/or interpretation; UI, YÇ, EO, EMY: Literature search; UK, EMY, DÇ, KU: Writing manuscript; UK, DÇ, KU: Critical review.

Financial Disclosure

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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