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The Prognosis of Patients with Endometrial Cancer is Affected by Obesity?

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Introduction

Endometrial cancer is the most common gynecologic cancer with an increasing incidence in the developed world. Most endometrial carcinoma occur in postmenopausal women, however they can also affect young women. In most cases it is diagnosed in early disease stages and the 5-year relative survival rate for women diagnosed with endometrial cancer is over 80%.

Despite the fact that most cases are diagnosed in early, more favorable stages, endometrial cancer incidence and mortality rates are on the rise. Endometrial carcinoma are divided, based on their histopathological characteristics, into Type I and Type II carcinoma [1].

Type I tumors are mostly endometrioid carcinomas, represent up to ~80% of endometrial cancers, and are generally associated with endometrial hyperplasia. Type II tumors are more often serous papillary, clear cell, or squamous carcinomas, and generally develop from atrophic endometrial tissue in older women. Type II cancers were associated with a higher risk of relapse compared with type I.

Tumours are graded according to the International Federation of Gynecology and Obstetrics (FIGO) defined criteria.

For surgical planning, endometrial cancers have traditionally been classified on the basis of uterine factors that can be evaluated preoperatively or intraoperatively: (1) low risk group (grade 1–2 endometrioid carcinoma, <50% myometrial invasion); (2) intermediate-risk group (endometrioid carcinomas grade 1–2, >50% myometrial invasion, or grade 3, <50% myometrial invasion); (3) high risk group (endometrioid carcinoma grade 3, >50% myometrial invasion, or all non-endometrioid carcinomas) [1, 2]. After surgery, other factors revealed by final histology, for example, lymph vascular space invasion (LVSI), cervical involvement, and lymph node metastasis, may predict risk of recurrence and death [3, 4]. The ESGO-ESTRO-ESP (European Society of Gynecological Oncology-European Society for Radiotherapy & Oncology-European Society for Pathology) has therefore further refined risk classification, primarily in the 2016 guidelines (ESGO 2016) and in the 2020 guidelines (ESGO 2020) to help clinicians decide on postoperative adjuvant therapy [1, 4].

With these two risk classifications (molecular classification unknown), patients with endometrial cancer are classified into five categories. The main changes are reclassification of cases with (1) non-endometrioid tumors stage IA with no myometrial invasion from the high to the intermediate-risk group; (2) stage II endometrioid cancers from high to high-intermediate risk group; (3) stage IA grade 3 tumors

from the high-intermediate risk to the intermediate-risk group if no substantial LVSI is present; and (4) stage IB grade 3 tumors from the high to the high-intermediate risk group.

Obesity is strongly associated with an increased risk of several types of cancer [5] ; an estimated 55% of all cancers in women and 24% of all cancers in men are associated with overweight (body mass index [BMI] = 25.0–29.9 kg/m2) or obesity (BMI ≥ 30 kg/m2). The International Agency for Research on Cancer (IARC) working group has listed 14 types of cancer as having sufficient evidence for an association with overweight or obesity [6, 7] .

Excess body weight is known to be associated with an increased risk of many malignancies and the risk of endometrial cancer is strongly associated with obesity [8]. Obesity is predominantly associated with type 1 (endometroid) endometrial cancers, rather than type 2 (non-endometroid type such as serous or carcinosarcoma) endometrial cancer; however, both subtypes are increased with obesity. Risk of endometrial cancer is increased in women with a body mass index (BMI) greater than 30 kg/m2 and the risk increases linearly with increasing BMI [9].

Increased endometrial cancer risk has been associated with early menarche and late menopause, suggesting a relationship of risk with greater lifetime exposure to estrogens at premenopausal levels. Other hormone-related factors associated with risk are parity and use of exogenous estrogens for oral contraception or postmenopausal replacement therapy. It is generally thought that excess weight influences endometrial cancer risk through changes in endogenous hormone metabolism.

Standard treatment for endometrial cancer is surgery (historically total abdominal hysterectomy and bilateral salpingo-oophorectomy, removal of uterus, cervix, tubes and ovaries, with or without lymph node dissection) with adjuvant treatment in the form of radiotherapy and/or chemotherapy as indicated. Preoperative assessment of endometrial cancer may be problematic in obese women. A BMI >30 kg/m2 indicates obesity and is associated with an increased risk of perioperative complications, while a BMI >40 kg/m2 is described as morbid obesity and is associated with higher rates of complications [9].

In early-stage EC, the aim of surgery is to remove macroscopic tumour, examine for microscopic metastases and stage the tumour to assess the need for adjuvant therapy. Laparotomy has been the traditional surgical approach for the treatment of EC. Large, randomised trials and a meta-analysis have demonstrated that minimally invasive techniques have operative outcomes similar to laparotomy with respect to prognosis [10]. Even though the majority of patients included in these trials were low risk (e.g. G1 or G2), with only 17% of patients at higher risk (e.g. defined by G3), the laparoscopic approach can

be extended to G3 tumours, since detrimental effects were not demonstrated. The risk of lymph node metastases ranges between <5% and 40% depending on grade, myometrial invasion and histology. Because the detection of lymph node metastases has an impact on adjuvant therapy, evaluation of lymph node status is recommended in patients with nonendometrioid histology, FIGO IB or G3 disease. Lymph node evaluation could be omitted in endometrioid FIGO IA G1-G2 disease since the risk of nodal metastasis is very low (<5%) [11].

Aim

The aim in our study was to examine the influence of obesity on patient characteristics and clinicopathological characteristics of endometrial cancer and to determine whether obesity in women with endometrial cancer affect the prognosis.

Methods

In this study, we analyzed the impact that obesity has on the outcome of endometrial cancer and whether there is any relationship between obesity and histological subtypes of endometrial cancer.

The data of 62 consecutive women operated for endometrial cancer at FIGO stage III and IV were retrospectively reviewed. Patients were divided into two categories as 18.5 to <25 kg/m2 and ≥25 kg/m2 according to BMI. The body mass index (BMI) is a measure that uses height and weight to work out if your weight is healthy. The BMI calculation divides an adults weight in kilograms by their height in metres squared. For most adults, an ideal BMI is in the 18.5 to 24.9 range. If you below 18.5 – you're in the underweight range; between 18.5 and 24.9 – you're in the healthy weight range; between 25 and 29.9 – you're in the overweight range; 30 or over – you're in the obese range.

All patients underwent primary surgical treatment including total abdominal hysterectomy, bilateral oophorectomy and peritoneal cytology. Pelvic lymphadenectomy was carried out for all patients except for those with no myometrial invasion regardless of the tumor grade or for whom it was technically impossible. Paraaortic lymphadenectomy was performed when pre- and intraoperative assessments suggested non-endometrioid or grade 3 endometrioid cancer, >50 % myometrial invasion and cervical involvement. Most patients received sequential treatment with chemotherapy and radiotherapy.

Statistical Methods

For normal distribution data testing, the Kolmogorov–Smirnov and Shapiro-Wilk tests were used. Descriptive methods of statistical analysis (frequencies, percentages, mean, median, standard deviation [SD], and range) were used to summarize the data. The statistical significance level was set at $p<0.05$, and for multiple testing at the same data set the Bonferroni correction was used ($p<0.05/3=0.0167$). For comparison between different groups, the Kruskal Wallis, Wilcoxon rank sum and Fisher exact test were used. Curves of probabilities for OS and PFS were constructed using the Kaplan-Meier product-limit method. The median of survival analysis with corresponding 95% CI were used for description, and the Log-rank test was used for testing differences between curves for OS and PFS. The statistical analysis was done with the program R (version 3.3.2 (2016-10-31); "Sincere Pumpkin Patch"; Copyright (C) 2016; The R Foundation for Statistical Computing; Platform: x86_64-w64-mingw32/x64 (64-bit); www.r-project.org; downloaded: 21.01.2021.).

Results

Characteristic	Normal BMI 18.5 to <25 kg/m^2	Overweight BMI ≥25 kg/m^2	Total
Total, No.	34	28	62
Age, mean (SD) /year/	41	66	62
Initial FIGO stage of endometrial carcinoma			
III (NED)	5 (14.7%)	10 (35.7%)	15
III with rest or positive lymphnodes	13 (38.2%)	8 (28.6%)	21
IV	16 (47.1%)	10 (35.7%)	26
Histological subtypes			

Endometroid carcinoma	22 (35.5%)	(40) 64.5%	41 (66.1%)
Clear cell or serous papillary	15 (24.2%)	6 (9.8%)	21 (33.9%)
Treatment, No. (%)[c]			
chemotherapy only	10	11	22 (35.48%)
chemotherapy+radiation therapy	18	22	40 (64.5%)

Table 1. Patient characteristics

Baseline characteristics of the study population, overall and stratified by BMI, are shown in Table 1. Median age was 64 years, the youngest patient had 34 and the oldest 77 years. During a mean time of follow-up, 32 months (range 12–42), a comparison of the relationship between BMI and different histological forms of endometrial cancer was carried out.

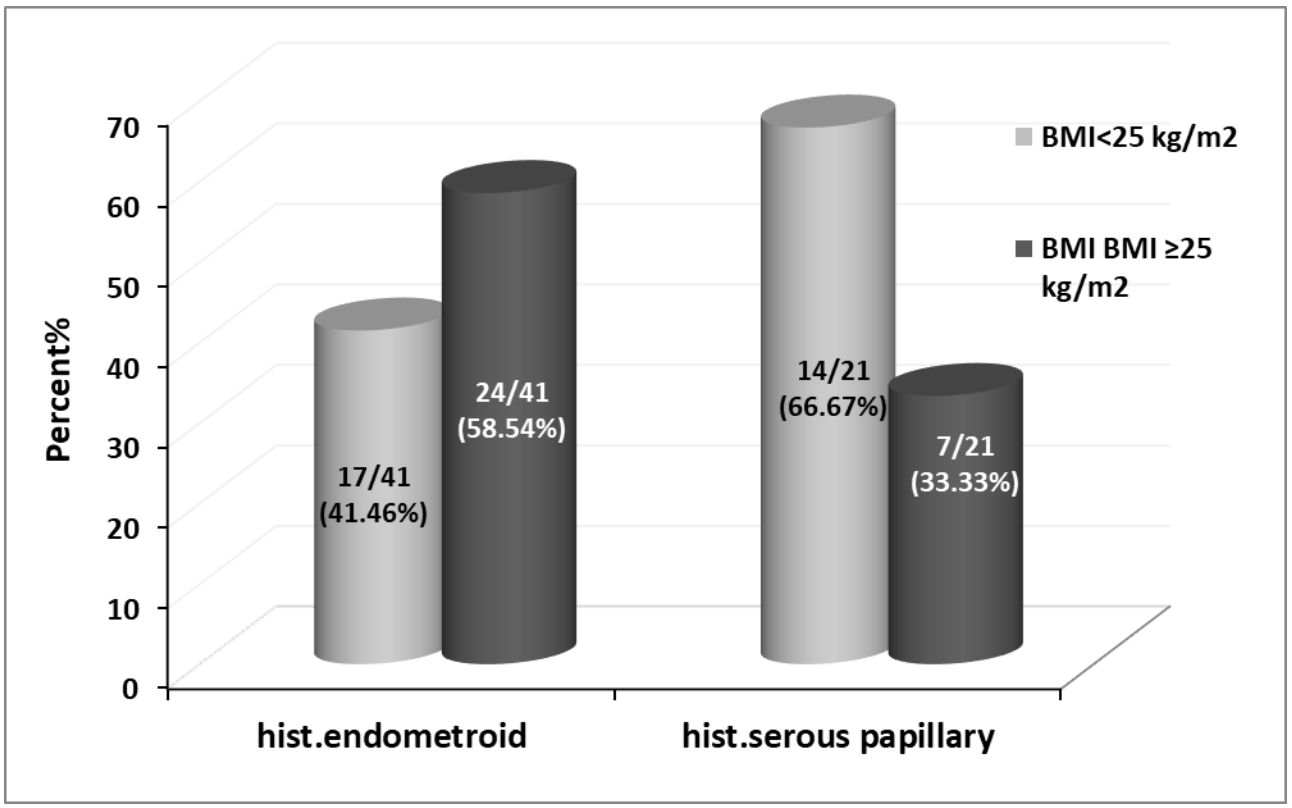
Mean value of BMI was 26.05 kg/m2/ 16.9-39.56/ in the whole group of patients. Approximately half of the patients were overweight and obese (45.1%) at the time of their initial diagnosis. Patients with a BMI (body mass index) of <25 were significantly younger. The mean age at initial endometrial cancer diagnosis was 61.35 (34-77) years, and all patients were Caucasian. Patients with a BMI up to 25kg/m2 were statistically less likely to have >50 % myometrial invasion and more likely to have stage I disease. There were no significant differences in the incidences of positive pelvic and paraaortic lymph nodes and tumor grades according to BMI. Also, there were no differences in surgery type, the mean of removed pelvic and paraaortic lymph node number, hospital stay, blood loss and complications between the groups.

Most cases were diagnosed at stage IV (41.9%), but it was noticed that obese women were slightly more likely to be diagnosed at stage III with no evidence of disease (NED) 35.7% than in stage III with pelvic tumor (28.6%) or stage IV (35.7%) compared with women with normal BMI.

The treatment was consistent according to the stage of the disease, where 64.5% of patients with endometrial cancer received chemotherapy sequentially with radiation therapy, and 35.48% only chemotherapy treatment.

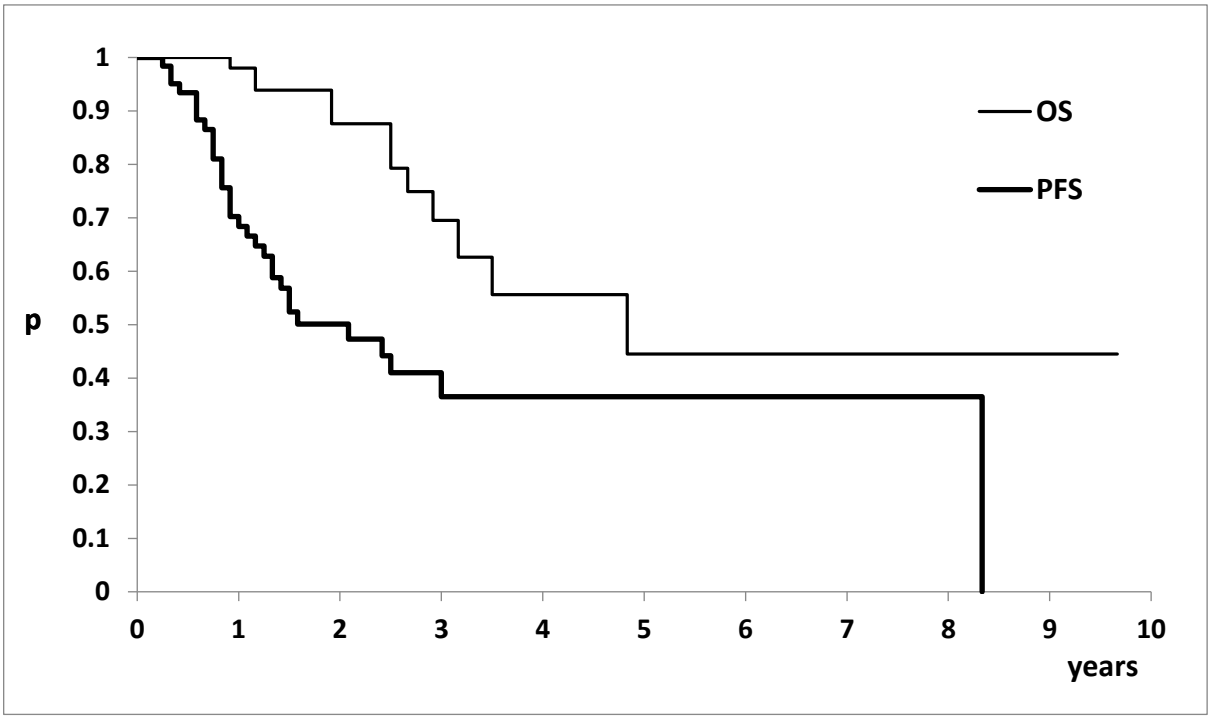
The majority of the patients in this study were found to have endometrioid histology subtype (41/62, 66.1%). However, the non-endometrioid histologic subtypes were well presented in our population (serous papillar 12/62, and clear cell 9/62).

The most overweight patient was in endometroid histology group, with median BMI of 27.16 kg/m2. The median BMI in non-endometroid histologic subtypes was around 22 kg/m2. In the endometroid histology group most of the patient were obese, 64.5%, and 35.5% had normal BMI. In serous papillar and clear cell subgroup 9.8% were obese.

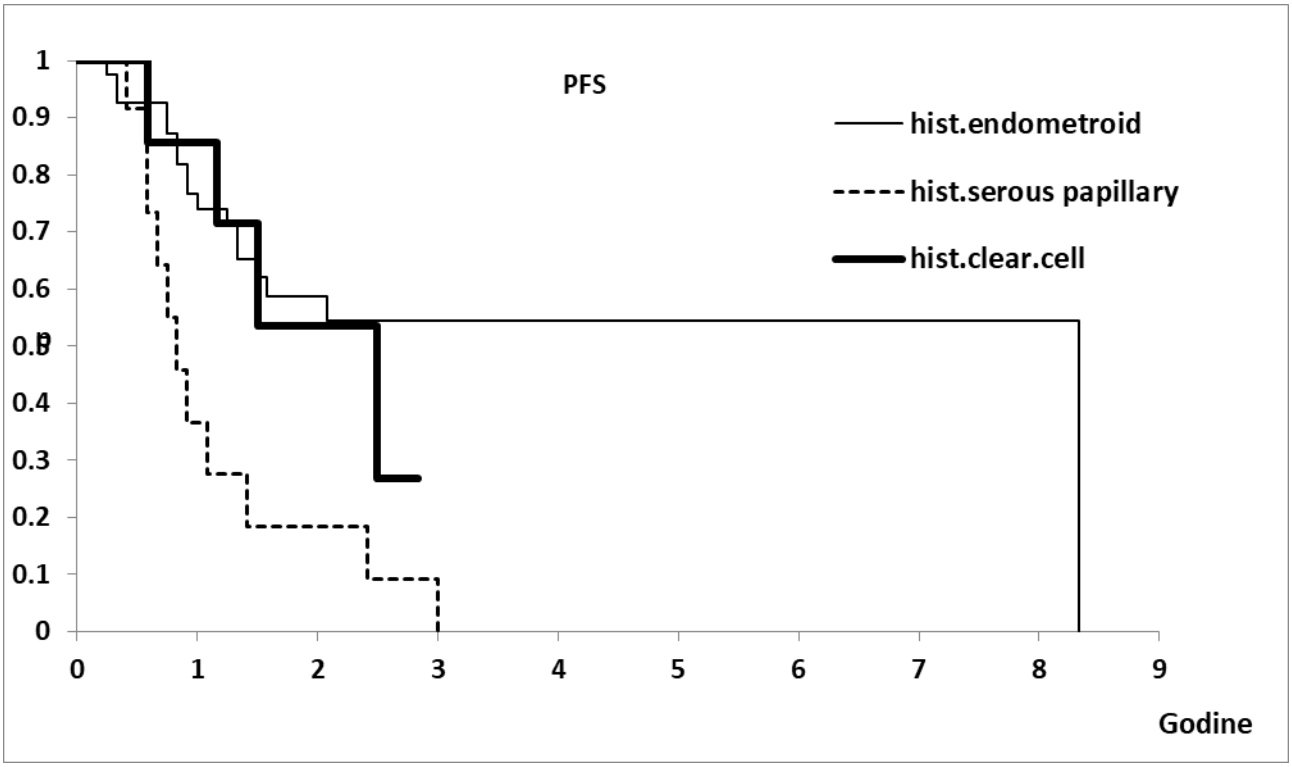


Statistical analysis showed that there was a clear statistically significant difference between BMI and different histological subtypes, predominantly between endometroid and serous papillary histological forms in terms that there is more obese patients within endometroid histology; 58.54 % Pearson Chi-squared Test: X-squared= 3.52845528455285 ; df= 1 ; p= 0.0603239649270856

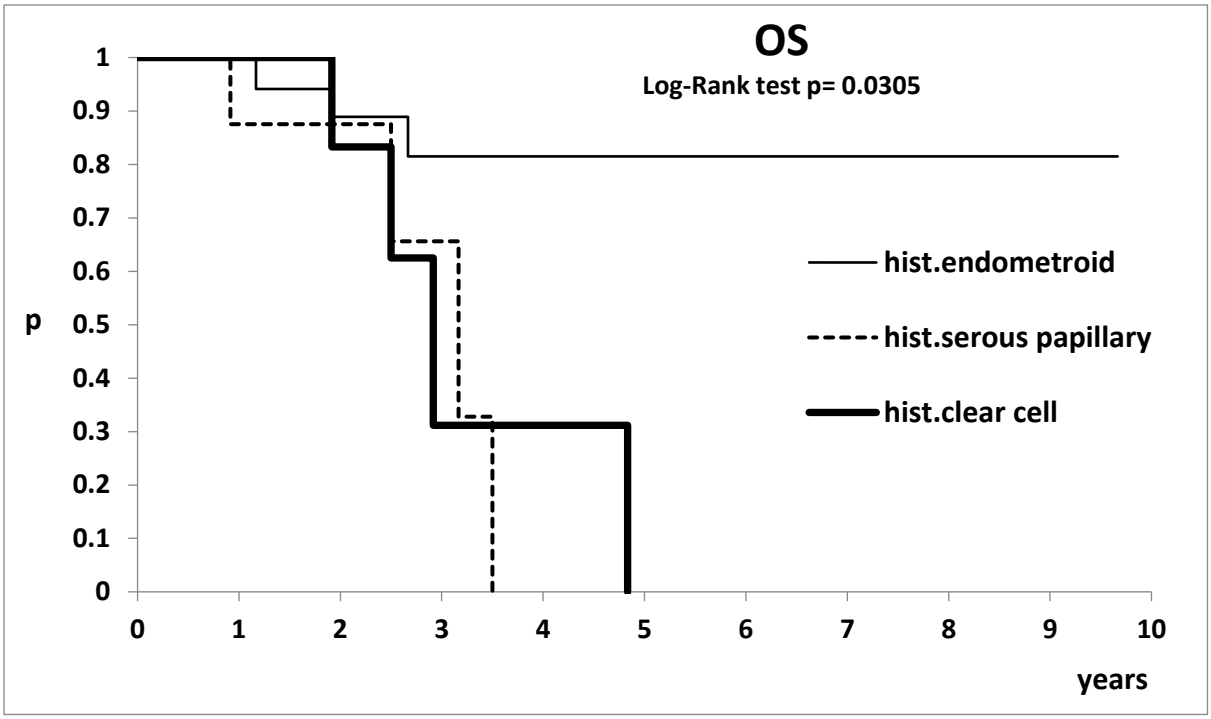
During the follow-up period of 32 months, it was shown that the median PFS in the entire study group was 16 months and median OS was 21months.



There is a statistically significant difference in terms of the median number of months at recurrence and PFS according to different histological subtypes, where it has been shown that patient with endometrioid histology have a longer PFS (Log-Rank test; x2= 14,416 degrees of freedom – 2, p= 0.00074632551914366) than patients with clear cell and serous papillary histological form.



There is a statistically significant difference in terms of OS according to different histological subtypes, where it has been clear that patient with endometrioid histology have a longer OS (Log-Rank test; p= p= 0.0305899951215101) than patients with clear cell and serous papillary histological form.



There were no statistically significant differences in the type of the site of recurrence between the two groups related to BMI, but it has been verified that more aggressive histological forms are more frequently associated with predominant metastases in the liver (Fisher Exact Test: p= 0.0795879834374964; Bonferroni korekcija: 0.05/3=0.0167- p= 0.0702122358377295).

In our study, it was shown that patients with serous papillary endometrial carcinoma often had elevated CA 125 compared to patients with the endometrioid subtype. Multivariate proportional hazard models identified stage III with residual disease and stage IV disease as significant covariates for mortality rates and it can also affect more aggressive EC behavior and a worse prognosis.

Discussion

In this cohort of women diagnosed with an invasive endometrial cancer in the Institute of Oncology and Radiology of Serbia, we found a small but statistically significant correlation between age of our patients and obesity, where patients with a BMI (body mass index) of more than 25 were significantly older. The

association was more pronounced when the analysis was related to different histological forms, where the most overweight patient was in endometroid histology group, with median BMI of 27.16 kg/m2.

Multiple mechanisms have been proposed to explain the association between obesity and cancer. In postmenopausal women, circulating estrogens are derived largely from extraglandular aromatization of androstenedione to estrone in the adipose tissue. Thus, circulating estrogen in postmenopausal women is directly correlated with body weight [2,12]. During the follow-up period of 32 months, it was shown that the median PFS in the entire study group was 16 months and mediana OS was 21months.

There is a statistically significant correlation of endometroid histological forms with better outcome, which is related to improved PFS and OS in patients with endometroid histological sybtypes, which correlates with literature data.

Conclusion

Patients with endometroid histology had a better prognosis, and were more likely to be overweight.

The present results suggested that the endometroid histology was independently associated with a better prognosis of endometrial cancer. Additional research will elucidate the main molecular mechanism by which the obesity of women affects the prognosis of patients with endometrial cancer.

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