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Impact of severe obesity in the management of patients with high-risk endometrial cancer: a FRANCOGYN study.

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Abstract:

Objective: To assess the surgical management and survival of severely obese patients with high-risk endometrial cancer.

Materials and Methods: Data from 269 patients with high-risk endometrial cancer who were treated between 2001 and 2018 were collected from a multicenter database (11 centers). We classified the patients according to their BMI and compared outcomes in two groups: a normal weight group of women with a BMI<25kg/m^2, and a severe obesity group of women with a BMI≥35kg/m^2. The groups were compared for epidemiologic, pathologic, management, relapse-free survival (RFS) and overall survival (OS) elements.

Results: Patients in the severe obesity group were younger (64 years vs. 68 years, $p<0.05$) and had more comorbidities (hypertension, diabetes). They also had more locally advanced tumors and pelvic lymph node involvement (47% vs 24%, $p<0.05$). The severely obese patients were less likely to undergo recommended surgical staging, with fewer lumbar aortic dissections than women of normal weight (23% vs 36%, $p<0.05$) and fewer pelvic sentinel lymph node biopsies (26.5% vs 12.1%, $p<0.05$). No difference in RFS or OS were observed between the two groups.

Conclusion: Patients with severe obesity and high-risk endometrial cancer have more locally advanced tumors, and are less likely to be managed according to surgical recommendations. However, RFS and OS do not seem to be affected.

Key words: endometrial cancer; obesity; surgery; clinical management.

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Introduction

Endometrial cancer is the fourth most common cancer in women in the western world with 120 000 cases in Europe in 2018 (1, 2). Obesity is a well-known risk factor for endometrial cancer, with a relative risk ranging from 2.6 for obese women (with a body mass index (BMI) between 30 and 35 kg/m^2) to 4.7 for women with severe obesity (with a BMI > 35 kg/m^2) (3). Overall, the average BMI at diagnosis is 30 kg/m^2 (4, 5). In obese population, tumors seem to be less aggressive with most patients presenting low-grade endometrioid cancer (4). National and international guidelines (such as ESMO/ESGO/ESTRO) (6), recommend that the surgical treatment of endometrial cancer should include a total hysterectomy and bilateral salpingo-oophorectomy. In addition, patients with high-risk endometrial cancer should also undergo pelvic and para-aortic lymphadenectomy and omentectomy, although the recent ESGO/ESTRO/ESP guidelines mention that sentinel lymph node (SLN) biopsy could be an alternative (7).

The surgical management of endometrial cancer differs between obese and nonobese women as morbidities and surgical difficulties increase with BMI. (8-10). Some studies also suggest that lymphadenectomy is less often performed in the obese population (11, 12). Elsewhere, survival data for obese patients are discordant: while there is a tendency to associate obesity with poor survival (13), in most cases no difference is observed (13-16).

Studies evaluating the specific population of obese patients with high-risk endometrial cancer are scarce. In a previous work of our group, Canlorbe et al (17) showed that severely obese women had a lower recurrence-free survival (RFS), and found no difference in management and treatment when comparing patients with a BMI > 35 kg/m^2 to those with a BMI between

30 and 35 kg/m^2. Similarly, Kawai et al did not show any difference in the robotic surgical management of obese women with high-risk endometrial cancer (11).

In the light of these observations, we thought it interesting to examine this particular population of severely obese women with a larger sample population.

Therefore, this study aimed to evaluate the management of severely obese women (Class II obesity and more: BMI ≥ 35 kg/m^2) with high-risk endometrial cancer and their RFS and overall survival (OS) rates in a large multicenter cohort, and to compare these results with those of women with normal weight.

Material and methods

Patients

Data on women who received surgical treatment for a histologically proven endometrial cancer between 2001 and 2018 were collected in 11 French institutions: Creteil University Hospital, Jean Verdier University Hospital, Lille University Hospital, Poissy University Hospital, Tenon University Hospital, Tours University Hospital, Rennes University Hospital, Reims University Hospital, Clermont-Ferrand University Hospital, Brest University Hospital, and Jean-Francois Leclerc Hospital, and from the SENTI-ENDO trial.

The research protocol was approved by the Institutional Review Board of the College National des Gynécologues et Obstétriciens Français (CEROG 2014-GYN-020)

Data collection

Demographic, clinical, and surgical data were collected: age, BMI (calculated as the weight in kilograms divided by the square of the height in meters), parity, menopausal status, arterial hypertension, diabetes, hormone replacement therapy, history of breast cancer, previous surgical procedures, FIGO stage, final pathologic analysis (histologic type and grade, depth of

myometrial invasion, lymphovascular space invasion), and adjuvant therapy. The date of surgery, and the date of recurrence and death were also reported.

Study design

This was a retrospective cohort study.

Inclusion criteria were patients with a histologically proven high-risk endometrial cancer (according to ESMO/ESGO/ESTRO recommendations (18)) and a BMI < 25 kg/m^2 or ≥ 35 kg/m^2 who received surgical treatment between 2001 and 2018. Exclusion criteria were unknown BMI or a BMI between 25 and 35 kg/m^2. Patients were retrospectively divided into two cohorts for comparison: women with a BMI < 25 and women with a BMI ≥ 35, which were designated as normal weight and severe obesity groups, respectively.

Histology

Tumors were classified according to the FIGO 2009 classification after final pathologic analysis (19). The subgroup of women with high-risk endometrial cancer was defined by the ESMO guidelines (18), and included the following tumors: Type 1, stage IB, grade 3 or stage ≥ II, and all histologic type 2 tumors, any stage. Type 1 histology represents endometrioid adenocarcinomas. This type of tumor is classified into three grades defined by the percentage of the undifferentiated component: grade 1 less than 5% of undifferentiated component, grade 2 from 6% to 50 %, and grade 3 more than 50 %. Type 2 histology represents tumors with a clear cell, serous or carcinosarcoma component.

Treatment and follow-up

The management of patients with high-risk endometrial cancer was based on ESMO/ESGO/ESTRO guidelines (18). The surgical treatment included a total hysterectomy and a bilateral salpingo-oophorectomy, associated with a pelvic and para-aortic lymphadenectomy. When SLN procedure was performed, a double method of detection was

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used: colorimetric using Blue Patent and radioactivity using Technecium. Both (blue patent and Technecium) were injected in uterus cervix at 9 and 3 hours.

Adjuvant therapy consisted of external beam radiotherapy and/or vaginal brachytherapy, and/or chemotherapy. Adjuvant therapies were determined by a multidisciplinary committee and were based on surgical and pathologic findings, according to ESMO/ESGO/ESTRO guidelines.

Follow-up visits were conducted every 3 months for the first 2 years, every 6 months for the following 3 years, and once a year thereafter.

Outcome measures

The primary outcome measures were compliance of surgical staging with national and international guidelines, and the surgical route (minimally invasive surgery, laparotomy, or vaginal surgery). The secondary outcome measures were date of recurrence and date of death.

Statistical analysis

Statistical analysis was based on Chi square and Fisher's exact tests for ordinal variables. For continuous variables, Student's t test or Mann-Whitney test were used (p values < 0.05 were considered significantly different).

RFS was defined as the time between surgery and relapse. OS was calculated from the date of surgery to death. Patients who were still alive or without recurrence were censored at the date of the last follow-up visit. The Kaplan-Meier method was used to estimate the survival distribution and the log-rank test was used to compare survival data (p values < 0.05 were considered significantly different).

Data were managed with an Excel database (Microsoft Corporation, Redmond, WA, USA) and analyzed using SAS v9.4 (SAS Institute, Cary, NC, USA).

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Results

Characteristics of the study population

From 2001 to 2018, 551 patients with high-risk endometrial cancer were identified as having received primary surgical treatment. 184 of these patients had a BMI < 25 kg/m^2 (33%), and 85 had a BMI ≥ 35 kg/m^2 (15%). (Figure 1)

Women with severe obesity were significantly younger (64.6 years of age for women with a BMI ≥ 35 vs 68.1 years for those with a BMI < 25; p = 0.01), and were more likely to have comorbidities as arterial hypertension (65.7% vs 31.4%, p < 0.01) and diabetes (31.6% vs 4.7%, p < 0.01).

The demographic characteristics of the population by BMI group are presented in Table 1.

Surgical procedures and adjuvant treatment

Table 2 describes the treatment according to the patients' BMI.

The surgical route did not differ according to the BMI: in the normal weight group, 44.8% of the women underwent laparotomy, 50.6% laparoscopy, and 4.6% a vaginal approach compared with 57.7%, 38.8% and 3.8%, respectively, in the severe obesity group (p = 0.16).

Pelvic lymphadenectomy was equally performed in both groups (82.1% for a BMI < 25 and 74.1% for a BMI ≥ 35, p = 0.13), but fewer para-aortic lymphadenectomies were performed in the severe obesity group (23.5% vs 36.4%, p = 0.03).

In the severe obesity group, SLN biopsy was less frequently performed (26.5 % vs 12.1 %, p = 0.01). Every patient with severe obesity who had an SLN biopsy underwent pelvic lymphadenectomy without para-aortic lymphadenectomy. Among the women who underwent a lymphadenectomy, no difference was found in the number of nodes removed according to the BMI group.

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Adjuvant treatment – chemotherapy, external beam radiotherapy and vaginal brachytherapy – was administered in the same proportion in both groups.

Tumor characteristics

Data about tumor characteristics are reported in Table 3.

More women in the severe obesity group had type I endometrial cancer (52.6 % vs 40.3%, p = 0.04). Tumor size, depth of myometrial invasion, and lymphovascular space involvement status did not differ according to the BMI. However, a greater proportion of positive pelvic nodes was observed in the severe obesity group compared with the normal weight group (47,8% vs 24,2%, $p < 0.01$)

Survival results

The survival curves are shown in Figure 2.

The whole cohort had a mean follow-up period of 28 months. In the whole population, recurrences were observed in 76 of the 269 patients (28 %): 45 in the normal weight group (24.5%) and 31 in the severe obesity group (36.5%), p = 0.06. The median time to recurrence was 64 [36.67 – 85.23] months in the normal weight group and 31 [19.20 - 82.37] months in the severe obesity group (p = 0.62). The details of treatment in patient with recurrence were showed in table 4. This table showed that BMI ≥ 35 patient with recurrence had significantly less combined radiotherapy and chemotherapy (and more radiotherapy alone) than BMI < 35 patient with recurrence.

There was no difference in OS (p (Log Rank) = 0.23) or RFS (p (log-rank) = 0.19) between the two groups.

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Discussion

Present cohort study highlights that woman with severe obesity and high-risk endometrial cancer undergo different surgical management compared with normal weight women, with fewer para-aortic lymphadenectomies and SLN biopsies. Furthermore, severely obese women have significantly higher involvement of pelvic nodes than women of normal weight. Although we found no significative difference in OS or RFS between BMI group, we showed that BMI ≥ 35 patients with recurrence had significantly less combined treatment (radiotherapy plus chemotherapy) and more radiotherapy alone than BMI < 35 patients with recurrence.

In a study comparing patients with a BMI > 40 kg/m^2 with those with normal weight, Pavelka et al found similar results (12). This difference in surgical management could be explained by added surgical complexity and postoperative complications in the obese population (9, 20, 21). The surgeon may well choose to reduce the complexity of the procedure and its potential morbidities by not performing a complete lymphadenectomy thereby avoiding conversion to laparotomy. In contrast, in 2014 Canlorbe et al did not show any difference in surgical staging for women with severe obesity and high-risk endometrial cancer (17), compared with obese women (BMI between 30 and 35 kg/m^2). Similarly, Kawai et al did not find any difference in surgical staging for patients with a BMI > 30 kg/m^2 in the high-risk endometrial cancer subgroup, in a study of patients managed with a robotic approach (11).

The 2016 ESMO/ESGO/ESTRO guidelines recommend surgical staging by lymphadenectomy for patients with high-risk endometrial cancer (18). This recommendation was adjusted in the 2021 ESGO/ESTRO/ESP guidelines which introduced SLN and PET scan analysis as an alternative for patients with stage I and II endometrial cancer (7). In our study, the SLN procedure was also less frequently performed in the severe obesity group. However, it should be noted that our population was treated before this recommendation. Pineda et al

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recently studied whether systematic lymphadenectomy could be avoided by performing a single SLN biopsy. They found an overall sensitivity of 85% and a false negative rate of 15% in their population of patients with high-risk endometrial cancer (all stages) (22). On another note, the success of SLN biopsy does not appear to be influenced by BMI (23, 24), and a Canadian study showed that obese women who underwent SLN biopsy without complete lymphadenectomy presented fewer operative adverse events and that their survival was not impacted (25). Therefore, the SLN procedure would appear to be an acceptable alternative for the obese population to avoid complete lymphadenectomy and reduce operative complications and comorbidities.

However, in our population of severely obese women with less surgical staging, we found no significant differences in OS or RFS. The literature is discordant about the influence of obesity on survival in endometrial cancer. While a few studies have demonstrated a significant association between obesity and poorer survival (13), no significant difference was found in most cases (14-16). Canlorbe et al found a better RFS for severely obese women compared to women with a BMI between 30 and 35 kg/m^2, in the specific population of patients with high-risk endometrial cancer (17). Nevertheless, we showed that BMI $\geq$ 35 patients with recurrence had significantly less combined treatment (radiotherapy plus chemotherapy) and more radiotherapy alone than BMI < 35 patients with recurrence. This point could indicate that absence of chemotherapy in obese women lead higher recurrence in a sub-group of obese patients.

Urunsak et al showed that the absence of lymphadenectomy had no influence on survival in their population of severely obese women (BMI >40 kg/m^2), irrespective of the risk of recurrence (21). Nevertheless, a meta-analysis by Kim et al showed that systematic lymphadenectomy did improve OS in women with high-risk endometrial cancer (26). Moreover, several studies, such as the SEPAL study, showed that the combination of para-

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aortic and pelvic lymphadenectomy was more effective in improving OS compared to pelvic lymphadenectomy alone (27, 28). The generalisation of the robotic approach may be a solution for the obese population in this setting by decreasing the rate of intra- and postoperative complications (11, 29-32), and limiting conversion to laparotomy (33). Kawai et al recently showed that with a robotic approach obesity was no longer a limiting factor for practicing a complete lymphadenectomy in women with high-risk endometrial cancer (11).

The strengths of our study lie in its multicenter nature and in the large sample of patients included. However, some limitations should be considered. First, the retrospective nature of the study could result in some analytical bias. However, all patients were managed in tertiary centers using well-documented electronic charts. Secondly, some modifications in the FIGO classification and changes in the indications for surgical staging occurred during the data collection period; particularly for patients with high-risk endometrial cancer for whom para-aortic lymphadenectomy was not systematically recommended before 2010. However, in our population, there was a proportionate distribution of patients managed before and after 2010 in both groups. Similarly, our population was treated before the 2021 recommendation about SLN evaluation, and it could thus be relevant to perform a similar analysis of these patients in the future. Lastly, the use of molecular classification of endometrial cancer (such as POLE or p53 mutation (7)) could lead to a new algorithm of surgical management concerning lymphadenectomy.

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Conclusion

Our large cohort study highlights that woman with severe obesity and high-risk endometrial cancer are less likely to undergo surgical management in line with international guidelines unlike women of normal weight: para-aortic lymphadenectomy and SLN biopsy were less frequent in our severe obesity group. Although we found no significative difference in OS or

RFS between BMI group, we showed that BMI ≥ 35 patients with recurrence had significantly less combined treatment (radiotherapy plus chemotherapy) and more radiotherapy alone than BMI < 35 patients with recurrence. As obese women form the majority of patients with endometrial cancer, and in the absence of clear guidance in the literature and from international recommendations, more research is necessary to adapt surgical and adjuvant management to this specific population, especially in the setting of high-risk endometrial cancer which requires complete surgical management and adjuvant treatment. The generalisation of robotic surgery and SLN biopsy as an alternative to lymphadenectomy could constitute well-adapted options for severely obese patients.

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Table 1 – Patient characteristics

Variable	Global	BMI < 25	BMI ≥ 35	P
Age	267 (2) 67.05 ± 10.85 (35.00 ; 60.00 ; 68.00 ; 75.00 ; 98.00)	183 (1) 68.17 ± 11.25 (35.00 ; 61.00 ; 70.00 ; 77.00 ; 98.00)	84 (1) 64.62 ± 9.56 (39.00 ; 57.90 ; 66.22 ; 71.00 ; 87.00)	**p = 0.0127** (S)
Menopause	252 (17)	172 (12)	80 (5)	p = 0.4248 (K)
No	23 (9.1%)	14 (8.1%)	9 (11.3%)	
Yes	229 (90.9%)	158 (91.9%)	71 (88.8%)	
HRT	201 (68)	141 (43)	60 (25)	**p = 0.0074** (K)
No	161 (80.1%)	106 (75.2%)	55 (91.7%)	
Yes	40 (19.9%)	35 (24.8%)	5 (8.3%)	
Hypertension	226 (43)	156 (28)	70 (15)	**p < 0.0001** (K)
No	131 (58.0%)	107 (68.6%)	24 (34.3%)	
Yes	95 (42.0%)	49 (31.4%)	46 (65.7%)	

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Variable	Global	BMI < 25	BMI ≥ 35	P
Breast cancer	192 (77)	133 (51)	59 (26)	p = 0.0532 (K)
No	165 (85.9%)	110 (82.7%)	55 (93.2%)	
Yes	27 (14.1%)	23 (17.3%)	4 (6.8%)	
Diabetes	251 (18)	172 (12)	79 (6)	**p < 0.0001** (K)
No	218 (86.9%)	164 (95.3%)	54 (68.4%)	
Yes	33 (13.1%)	8 (4.7%)	25 (31.6%)	
Parity	214 (55)	146 (38)	68 (17)	p = 0.1294 (K)
0	36 (16.8%)	27 (18.5%)	9 (13.2%)	
1	48 (22.4%)	37 (25.3%)	11 (16.2%)	
≥ 2	130 (60.7%)	82 (56.2%)	48 (70.6%)	

BMI: Body Mass Index; HRT: Hormonal Replacement Therapy.

Ordinal variables: Total sample size (missing data), sample size (%), Chi square (K)

Continuous variable: Total sample size (missing data), mean +/- SD (min, Q1, median, Q3, max), student's t test (S)

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Table 2 – Treatment according to body mass index

Variable	Global	BMI < 25	BMI ≥ 35	P
Surgical approach	254 (15)	174 (10)	80 (5)	p = 0.1646 (F)
Laparotomy	124 (48.8%)	78 (44.8%)	46 (57.5%)	
Laparoscopy	119 (46.9%)	88 (50.6%)	31 (38.8%)	
Vaginal approach	11 (4.3%)	8 (4.6%)	3 (3.8%)	
Sentinel lymph node biopsy	221 (48)	155 (29)	66 (19)	**p = 0.0189** (K)
No	172 (77.8%)	114 (73.5%)	58 (87.9%)	
Yes	49 (22.2%)	41 (26.5%)	8 (12.1%)	
Pelvic lymphadenectomy	269 (0)	184 (0)	85 (0)	p = 0.1329 (K)
No	55 (20.4%)	33 (17.9%)	22 (25.9%)	
Yes	214 (79.6%)	151 (82.1%)	63 (74.1%)	
Para-aortic lymphadenectomy	269 (0)	184 (0)	85 (0)	**p = 0.0357** (K)
No	182 (67.7%)	117 (63.6%)	65 (76.5%)	
Yes	87 (32.3%)	67 (36.4%)	20 (23.5%)	

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Number of pelvic nodes removed	214 (55)	152 (32)	62 (23)	p = 0.9001 (W)
	12.07 ± 6.98 (0.00 ; 7.00 ; 11.00 ; 16.00 ; 44.00)	12.07 ± 6.82 (0.00 ; 7.00 ; 11.00 ; 16.00 ; 44.00)	12.10 ± 7.40 (0.00 ; 8.00 ; 11.00 ; 16.00 ; 36.00)	
Number of para-aortic nodes removed	87 (182)	67 (117)	20 (65)	p = 0.9597 (W)
	13.53 ± 10.39 (1.00 ; 7.00 ; 10.00 ; 17.00 ; 61.00)	13.30 ± 9.55 (1.00 ; 7.00 ; 11.00 ; 17.00 ; 47.00)	14.30 ± 13.10 (3.00 ; 7.50 ; 9.50 ; 16.50 ; 61.00)	
Radiotherapy	218 (51)	147 (37)	71 (14)	p = 0.2225 (K)
No	64 (29.4%)	47 (32.0%)	17 (23.9%)	
Yes	154 (70.6%)	100 (68.0%)	54 (76.1%)	
Chemotherapy	236 (33)	160 (24)	76 (9)	p = 0.6706 (K)
No	157 (66.5%)	105 (65.6%)	52 (68.4%)	
Yes	79 (33.5%)	55 (34.4%)	24 (31.6%)	
Brachytherapy	214 (55)	144 (40)	70 (15)	p = 0.6027 (K)
No	91 (42.5%)	63 (43.8%)	28 (40.0%)	

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Yes	123 (57.5%)	81 (56.3%)	42 (60.0%)

Ordinal variables: Total sample size (missing data), sample size (%), Chi square's (K), Fisher's exact test (F)

Continuous variable: Total sample size (missing data), mean +/- SD (min, Q1, median, Q3, max), Mann-Whitney test (W)`

BMI: Body Mass Index.

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Table 3 – Pathologic characteristics

Variable	Global	BMI < 25	BMI ≥ 35	P
Tumor size (cm)	169 (100)	120 (64)	49 (36)	p = 0.9007 (K)
< 3,5	54 (32.0%)	38 (31.7%)	16 (32.7%)	
≥ 3,5	115 (68.0%)	82 (68.3%)	33 (67.3%)	
Myometrial invasion	162 (107)	116 (68)	46 (39)	p = 0.1053 (K)
No	42 (25.9%)	26 (22.4%)	16 (34.8%)	
Yes	120 (74.1%)	90 (77.6%)	30 (65.2%)	
Histology	262 (7)	183 (1)	79 (6)	p = 0.2961 (K)
Endometrioid	107 (40.8%)	69 (37.7%)	38 (48.1%)	
Serous	78 (29.8%)	58 (31.7%)	20 (25.3%)	
Clear cell	41 (15.6%)	32 (17.5%)	9 (11.4%)	
Other	36 (13.7%)	24 (13.1%)	12 (15.2%)	
Histologic type	257 (12)	181 (3)	76 (9)	**p = 0.0404** (F)
1	113 (44.0%)	73 (40.3%)	40 (52.6%)	
2	143 (55.6%)	108 (59.7%)	35 (46.1%)	
Other	1 (0.4%)	0 (0.0%)	1 (1.3%)	
Histologic grade	107 (162)	67 (117)	40 (45)	p = 0.7112 (K)
1	16 (15.0%)	10 (14.9%)	6 (15.0%)	
2	30 (28.0%)	17 (25.4%)	13 (32.5%)	

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Variable	Global	BMI < 25	BMI ≥ 35	P
3	61 (57.0%)	40 (59.7%)	21 (52.5%)	
Lymphovascular space involvement	234 (35)	159 (25)	75 (10)	p = 0.9971 (K)
No	103 (44.0%)	70 (44.0%)	33 (44.0%)	
Yes	131 (56.0%)	89 (56.0%)	42 (56.0%)	
Pelvic lymph node metastasis	166 (103)	120 (64)	46 (39)	**p = 0.0031** (K)
No	115 (69.3%)	91 (75.8%)	24 (52.2%)	
Yes	51 (30.7%)	29 (24.2%)	22 (47.8%)	
Para-aortic lymph node metastasis	83 (186)	63 (121)	20 (65)	p = 0.9716 (K)
No	62 (74.7%)	47 (74.6%)	15 (75.0%)	
Yes	21 (25.3%)	16 (25.4%)	5 (25.0%)	
FIGO Stage	268 (1)	183 (1)	85 (0)	p = 0.4658 (F)
I	101 (37.7%)	71 (38.8%)	30 (35.3%)	
II	42 (15.7%)	32 (17.5%)	10 (11.8%)	
III	112 (41.8%)	72 (39.3%)	40 (47.1%)	
IV	13 (4.9%)	8 (4.4%)	5 (5.9%)	

Total sample size (missing data), sample size (%), Chi square (K), Fisher's exact test (F); BMI: Body Mass Index

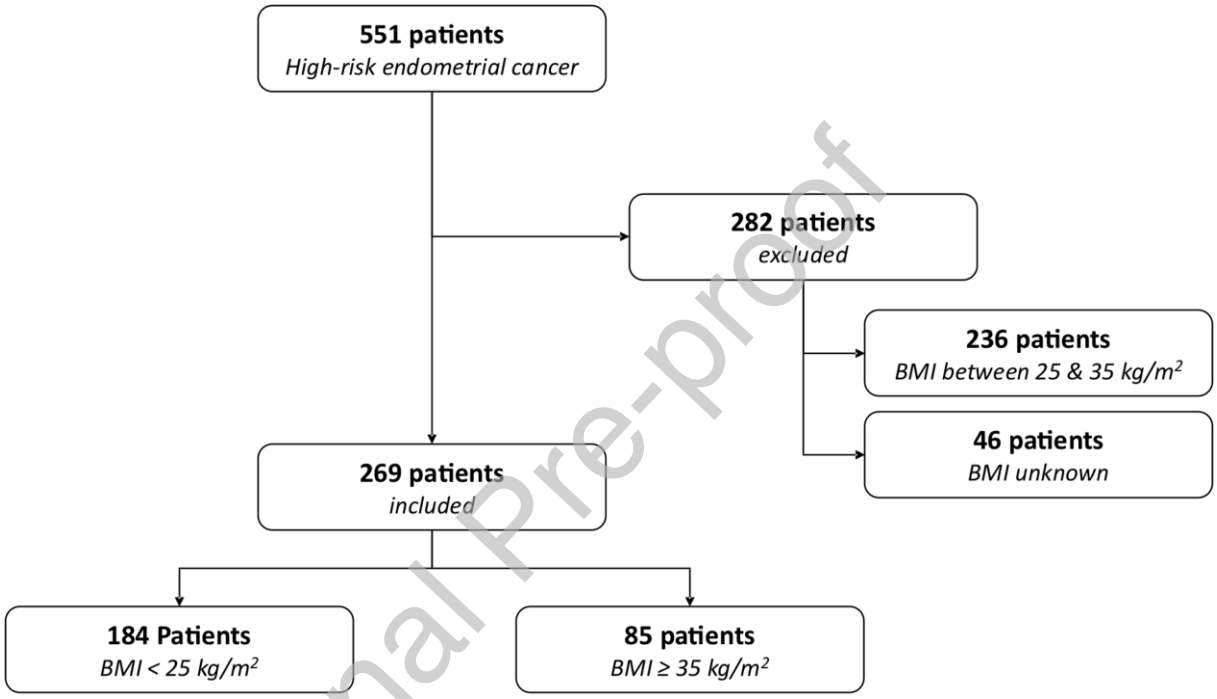
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Table 4: treatment characteristics of patient with recurrence according BMI group

Variable	**Global**	**BMI < 25**	**BMI ≥ 35**	**P**
n	76	45	31	
No adjuvant treatment	7	4 (9%)	3 (10%)	1.0000
Brachytherapy alone	2	1 (2%)	1 (3%)	1.0000
Radiotherapy ((+/-) brachytherapy) alone	30	13 (29%)	17 (55%)	**0,0229**
Chemotherapy alone	9	6 (13%)	3 (10%)	0,6278
Radiotherapy + chemotherapy	28	21 (47%)	7 (23%)	**0,0131**

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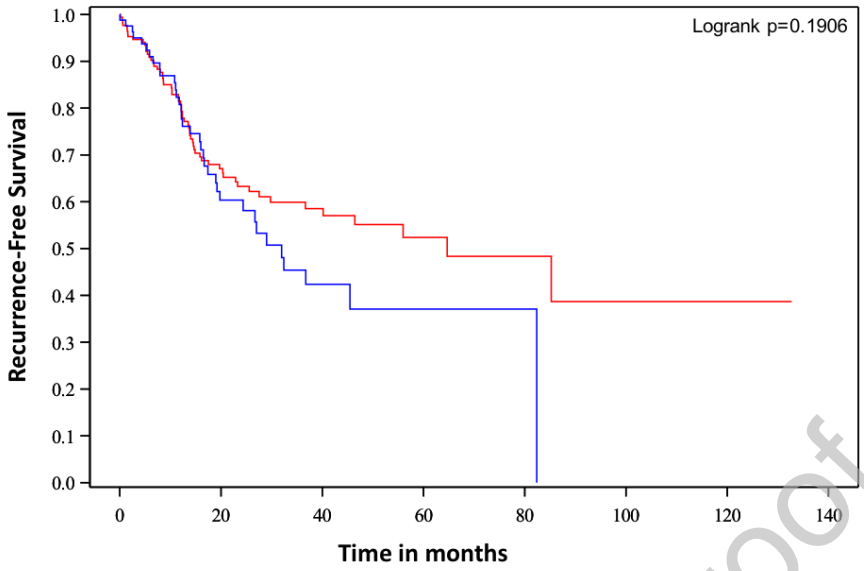
Figure 1 - Flow chart



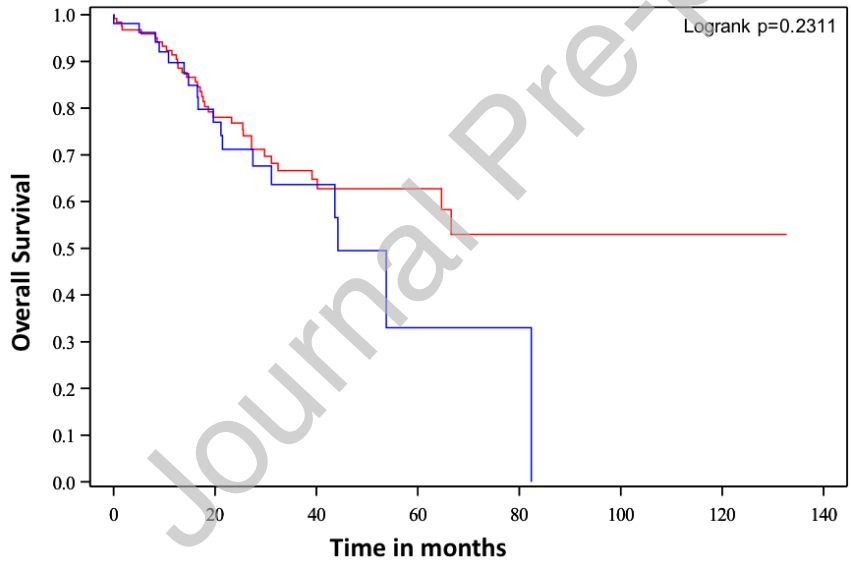
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Figure 2 – Disease-Free Survival and Overall Survival Curve

a-Disease-free survival



b-Overall survival



Red line: Body Mass Index < 25 group

Blue line: Body Mass Index ≥ 35 group

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