Severe Obesity Impacts Recurrence-Free Survival of Women with High-Risk Endometrial Cancer: Results of a French Multicenter Study

Geoffroy Canlorbe, Sofiane Bendifallah, Emilie Raimond, Olivier Graesslin, Delphine Hudry, Charles Coutant, Cyril Touboul, Géraldine Bleu, Pierre Collinet, Emile Darai, et al.

Full names, degrees and affiliations for all authors

Geoffroy Canlorbe, MD[1], Sofiane Bendifallah, MD[1,2], Emilie Raimond, MD[3], Olivier Graesslin, MD, PhD[3], Delphine Hudry, MD[4], Charles Coutant, MD, PhD[4], Cyril Touboul MD, PhD[5], Géraldine Bleu, MD[6], Pierre Collinet, MD, PhD[6], Emile Darai, MD, PhD[1,7], Marcos Ballester, MD, PhD[1,7]

[1] Department of Obstetrics and Gynaecology, Tenon University Hospital, Assistance Publique des Hôpitaux de Paris (AP-HP), University Pierre and Marie Curie, Paris 6, Institut Universitaire de Cancérologie (IUC), Paris, France;

[2] INSERM UMR S 707, Epidemiology, Information Systems, Modeling, University Pierre and Marie Curie, Paris, France;

[3] Department of Obstetrics and Gynaecology, Institute Alix de Champagne University Hospital, Reims, France;

[4] Centre de lutte contre le cancer Georges François Leclerc, Dijon, France;

[5] Department of Obstetrics and Gynecology, Centre Hospitalier Intercommunal, Créteil, France;

[6] Department of Obstetrics and Gynecology, Centre Hospitalier Régional Universitaire, Lille, France;

[7] INSERM UMR S 938, University Pierre et Marie Curie, Paris, France

Full mailing and e-mail address; telephone; and fax number of the author to whom correspondence and proofs should be sent

Doctor Geoffroy CANLORBE, MD

Service de Gynécologie-Obstétrique

Hôpital Tenon, 4 rue de la Chine, 75020 Paris, France

Phone: 33 1 56 01 60 19 ; Fax: 33 1 56 01 73 17 ; e-mail : geoffroy.canlorbe@tnn.aphp.fr

Title and subtitle of the paper

Severe obesity impacts recurrence-free survival of women with high-risk endometrial cancer: results of a French multicentre study

A shortened version of the title for the running head

Severe obesity and survival in endometrial cancer

Disclosure of any commercial interest

None of the authors had any financial and personal relationships with other people or organizations that could inappropriately influence this work.

There was no external funding for this project. Time and effort were volunteered by the authors.

Synopsis

This multicentre study included 729 women with endometrial cancer. Body mass index had no impact on recurrence free survival (RFS) in obese women in low/intermediate-risk groups. A BMI≥35 was correlated to a poorer RFS for women in the high-risk group.

Abstract

Background. Studies focusing on the impact of obesity on survival in endometrial cancer (EC) have reported controversial results and few data exist on the impact of obesity on recurrence rate and Recurrence Free Survival (RFS). The aim of this study was to assess the impact of obesity on surgical staging and RFS in EC according to the European Society of Medical Oncology (ESMO) risk groups.

Methods. Data of 729 EC women who received primary surgical treatment between January 2000 and December 2012 were abstracted from multicentre database (training set). RFS distributions according to body-mass index (BMI) in each ESMO risk group were estimated using the Kaplan-Meier method. Survival was evaluated using the log-rank test. The Cox proportional hazards model was used to determine influence of multiple variables.

Results. Distribution of the 729 women with EC according to BMI was: BMI<30 (n=442; 60.6%), 30≤BMI<35 (n=146; 20%) and BMI≥35 (n=141; 19.4%). Nodal staging was less likely to be performed in women with BMI≥35 (72%) than for those with BMI<30 (90%) (p<0.0001). With a median follow-up of 27 months (IQR: 13–52), the 3-year RFS was 84.5%. BMI had no impact on RFS in obese women in low/intermediate-risk groups but a BMI≥35 was independently correlated to a poorer RFS (HR=12.5 (95% CI, 3.1-51.3)) for women in the high-risk group.

Conclusion. Severe obesity negatively impacts RFS in women with high-risk EC underlining the importance of complete surgical staging and adapted adjuvant therapies in this subgroup of women.

Introduction

Obesity is a well-known risk factor for endometrial cancer (EC) (1, 2): women with a body-mass index (BMI) over 30 have a relative risk of death from EC of 2.53 compared to women of normal weight (3). This increased risk particularly concerns type I ECs, which are associated with long-duration unopposed estrogenic stimulation and arise in a setting of endometrial hyperplasia (4).

In Europe, surgical treatment of presumed early-stage EC is based on the European Society of Medical Oncology (ESMO) guidelines, according to the presumed risk of recurrence. For women with low- or intermediate-risk EC, a total hysterectomy with bilateral salpingo-oophorectomy is recommended. Pelvic and para-aortic lymphadenectomy is recommended for women of high-risk EC (5). Because of associated comorbidities or technical difficulties related to obesity, surgeons are sometimes reluctant to perform complete surgical staging including lymphadenectomy. Moreover, difficulties are also encountered to adapt adjuvant treatment, either for radiotherapy (6) or chemotherapy (7), with a potential impact on survival. However, studies focusing on the impact of obesity on survival in EC have reported controversial results (2, 7-20) and few data exist on the impact of obesity on recurrence rate and Recurrence-Free Survival (RFS) according to the ESMO risk groups.

Hence, the purpose of this multicentre study was to assess the impact of obesity on surgical staging and RFS in EC according to the ESMO risk groups.

Material And Methods

Study population

Data of all women who received primary surgical treatment between January 2000 and December 2012 were abstracted from five institutions with maintained EC databases in France (Tenon University Hospital, Reims University Hospital, Dijon Cancer Center, Lille University Hospital, Creteil University Hospital), and from the Senti-Endo trial (21). All the women had given informed written consent to participate in the study. The research protocol was approved by the institutional review board of the French College of Obstetrics and Gynecology (CEROG 2014-GYN-020).

Clinical and pathologic variables included patient's age, BMI, surgical procedure, 2009 FIGO stage, final pathological analysis (histological type and grade, depth of myometrial invasion, lymphovascular space invasion (LVSI) status) and adjuvant therapies. BMI was defined as weight (kg) divided by squared height (m2), both measured at the time of diagnosis, and expressed in kg/m2. Normal bodyweight was defined as a BMI of <25 kg/m2, obesity a BMI ≥30 kg/m2 and severe obesity a BMI of ≥35 kg/m2) (22).

Histological staging and grading was performed according to the 2009 FIGO classification (23) system on the basis of the final evaluation of the pathological specimen. The risk of recurrence was defined according to the ESMO guidelines. Histological type I corresponds to endometrioid cancer whatever the histological grade. Histological type 2 corresponds to clear cell carcinomas, serous carcinomas and carcinosarcomas. The three risk groups of EC are defined as follows: low-risk (type 1 EC FIGO stage IA grade 1 or 2); intermediate-risk (type 1 EC, FIGO stage IA grade 3, or FIGO stage IB grade 1 or 2); high-risk (type 1 EC, FIGO stage IB grade 3, and type 2 EC) (5).

Treatment and follow-up

All women underwent primary surgical treatment including at least total hysterectomy with bilateral salpingo-oophorectomy. Until 2010, systematic pelvic lymphadenectomy was recommended and para-aortic lymphadenectomy was only performed in case of high-risk EC or metastatic pelvic lymph node. Since the publication of French guidelines in 2010 (24), lymphadenectomy was no longer recommended for women with low/intermediate risk EC. Women with early-stage EC who were enrolled in the Senti-Endo trial (21), from July 2007 to August 2009, underwent a pelvic sentinel lymph node biopsy (SLN) (25) with systematic pelvic lymphadenectomy. When the pelvic SLN was found to be metastatic at intraoperative histology or after final histology, a para-aortic lymphadenectomy was recommended. Adjuvant therapy was administered according to multidisciplinary committees based on French guidelines (24).

According to French guidelines (24), frequency of clinical follow-up was every 3–4 months for the first 2 years, and then with a 6 months interval until 5 years and every year thereafter. Further imaging investigations were carried out if clinically indicated.

Disease recurrence was diagnosed either by biopsy or imaging studies and defined as a relapse without differentiating between their local or distant nature. RFS was calculated in months from the date of surgery to recurrence. Any woman not presenting for scheduled follow-up visits was contacted.

Statistical analysis

Statistical analysis was based on Student's t-test or ANOVA test, as appropriate, for continuous variables, and the Chi-square test or Fisher's exact test, as appropriate, for categorical variables. Values of $p<0.05$ were considered to denote significant differences.

The Kaplan-Meier method was used to estimate the survival distribution and comparisons of survival were made by the use of the log-rank test. The Cox proportional hazards model was used to account for the influence of multiple variables.

Data were managed with an Excel database (Microsoft, Redmond, WA) and analyzed using R 3.0.1 software, available online.

Results

Characteristics of the whole population (Table 1)

A total of 729 women were included in the study. The median BMI was 28 kg/m2 (inter-quartile range, IQR: 24–33) and the distribution as follows: BMI<30 (n=442; 60.6%), 30≤BMI<35 (n=146; 20%) and BMI≥35 (n=141; 19.4%).

Women with severe obesity were more likely to be younger (63 years old for women with BMI≥35 vs. 65.5 years old for those with a BMI<30, p=0.000873). More women with severe obesity had grade 1 and type 1 EC compared to non-obese women (61% vs. 45% and 96% vs. 84%, respectively). A greater proportion of women with severe obesity met the criteria for the low-risk of recurrence group (56% with a BMI≥35 vs. 40% for a BMI<30), while thinner women had high-risk EC (23% for a BMI<30 vs. 12% for a BMI≥35). However, depth of myometrial invasion, LVSI status and nodal involvement did not differ according to BMI. All women underwent at least a hysterectomy with bilateral salpingo-oophorectomy. Women with a higher BMI were less likely to undergo nodal staging: 72% of women with a BMI≥35 compared to 90% in women with a BMI<30 (p<0.0001). Among the 39 women with BMI≥35 who didn't underwent lymphadenectomy, nodal staging was recommended in three cases

(7.7%) and not performed due to severe comorbidity. Among the women who underwent nodal staging, no difference in the number of lymph nodes removed was found according to BMI.

Characteristics of obese women according to ESMO risk of recurrence groups (Table 2)

The number of obese women with low-, intermediate- or high-risk EC was 137/287 (48%), 99/287 (34%) and 51/287 (18%), respectively. In the low- and intermediate-risk groups, a lower proportion of women with a BMI≥35 had nodal staging compared to women with a BMI<35 ($p<0.05$). In the high-risk group, age, comorbidities (diabetes and hypertension), histological and therapeutic characteristics did not differ according to BMI.

Recurrence rate and RFS

With a median follow-up of 27 months (IQR: 13–52), 103 women (13.9%) experienced a recurrence and 72 (9.7%) died. The 3-year RFS was 84.5%. We found no difference in RFS according to BMI subgroups (Figure 1).

BMI had no impact on RFS in obese women in the low- and intermediate-risk groups.

In the high-risk group of obese women, a lower RFS was found for those with a BMI≥35 compared to those with a BMI<35 (Figure 2). Among women in the high-risk group, multivariate analysis including BMI (< or ≥ 35), age (< or ≥ 65), histological type, LVSI status, adjuvant therapies (VBRT, EBRT and chemotherapy) and nodal staging, showed that BMI≥35 was independently correlated to a poorer RFS (HR=12.5 (95% CI, 3.1-51.3)).

Discussion

Our results show that women with severe obesity are more likely to have low/intermediate-risk ECs with similar RFS than non-obese women. In contrast, among obese women with high-risk EC, those with severe obesity had a lower RFS.

When considering the whole population of obese women with EC, regardless the distribution according to the ESMO risk groups, no relation was observed between obesity and decrease in RFS. These data are in agreement with those of a review of 12 studies evaluating the relation between obesity and survival of patients with EC (26) reporting no impact of obesity either on progression-free (7-9, 13, 17) or disease-specific survival (15, 16). Similarly, in a study of 1 070 women with EC treated within the MRC ASTEC randomized trial with a median follow-up of 34.3 months, Crosbie et al. found no influence of obesity on RFS (27). More recently, in a study including 2 596 women with EC, Gunderson et al. found no association between obesity and disease-specific mortality (28). However, no attempt was made to evaluate the impact of obesity on RFS according to ESMO risk groups.

In the current study, when analyzing RFS in obese patients according to ESMO risk groups, we noted that patients with severe obesity were more likely to have low grade tumors (1-2) type 1 EC and limited myometrial infiltration corresponding to low/intermediate ESMO risk groups. Although obese patients had a lower rate of lymphadenectomy, no difference in RFS in patients with ESMO low/intermediate risk groups was observed between severely obese and obese patients. These results are in full agreement with those of the meta-analysis of May et al. underlining the absence of impact of lymphadenectomy on RFS (29). This absence of difference in RFS can be explained by the low incidence of lymph node metastases in this sub-group of patients. Moreover, patients with low/intermediate risk represented about three quarters of the population in our study, as in previous reports, and this explains why no difference in survival according to BMI was found taking into account the whole population.

For patients with severe obesity in the ESMO high-risk group, a decrease in RFS was observed. This is partly in accordance with Arem et al. who found that patients with poorly differentiated tumors had an EC-specific mortality of HR 1.39 (95% CI 1.04–1.85) per 5-unit BMI increase whereas no differences were detected for well differentiated or moderately differentiated tumors (18). Using multivariable analysis, severe obesity emerged as an independent risk factor of decreased RFS. The difference in RFS was not related to epidemiological characteristics as no difference in co-morbidities such as hypertension and diabetes was noted between patients with a BMI<35 and those with a higher BMI. Differences in survival in obese patients can be explained by various histological parameters. There is a trend for a higher incidence of LVSI in severely obese patients. Indeed, a recent study demonstrated that the recurrence rate for the high-risk group was 25.9% in case of negative LVSI and 45.1% for those with positive LVSI (30). In addition, in a study collecting data of 10 cohorts and 14 case-control studies from the Epidemiology of Endometrial Cancer Consortium with a total of 14,069 EC cases and 35,312 controls, Setiawan et al. concluded that risk factors for high-grade endometrioid and type II cancer were similar (31). Considering specifically type II or high grade endometrial cancers groups, Ko et al. (32) found that BMI was not associated with decreased RFS or OS, which is in contradiction with our results. However, in the latter study, little evidence was provided about the surgical management of patients according to BMI.

In the current study, decreased RFS was not explained by under-treatment of women with severe obesity. According to the current ESMO guidelines, women with high-risk EC should be treated by total hysterectomy with bilateral salpingo-oophorectomy, systematic pelvic and para-aortic lymphadenectomy, pelvic radiotherapy and adjuvant chemotherapy according to nodal status (5). Previous studies documented that increasing obesity significantly impacts the decision to perform lymphadenectomy in patients undergoing laparoscopic surgery,

particularly because of a higher postoperative complication rate (i.e. wound infection and venous thrombophlebitis) (28). However, in the present study, no difference in surgical management was noted especially concerning the rate of pelvic and para-aortic lymphadenectomy. According to the literature, difficulties are also encountered to complete protocols of adjuvant radiotherapy (6) and chemotherapy (7) in obese women. Yet no difference in adjuvant therapies was observed in our population of severely obese women in the high-risk group. Finally, biological changes associated with obesity could be another explanation of a lower RFS. Indeed, obesity is associated with low-grade chronic inflammation (33), chronic hyperinsulinaemia, alterations in the production of peptide and steroid hormones which are postulated mechanisms involved in cancer development (34). Previous studies have shown that the adipose tissue of obese women leads to the synthesis of high levels of estradiol and that frequent anovulation among obese premenopausal women leads to progesterone deficiency and unopposed estrogen exposure (26, 35). Thus, as emphasized by Akhmedkhanov et al., these biological changes are responsible for endometrial cell proliferation, inhibition of apoptosis, and an increased number of DNA replication errors and somatic mutations (36). These biological disturbances and an inflammatory environment promoted by obesity may lead to cancer development or recurrence (37).

Some limitations of the present study deserve to be underlined. First, we cannot exclude bias linked to the retrospective nature of the study. Second, the long period study from 2000 to 2012, meant that the patients included underwent different surgical management (i.e. systematic pelvic lymphadenectomy before 2010 which was only recommended for high risk ECs from 2010 according to the revised French guidelines) (24). Another factor was the introduction of the SLN biopsy in 2004 resulting in the detection of occult lymph node

metastasis. Indeed, Raimond et al. demonstrated the impact of SLN biopsy on indications of adjuvant therapies impacting recurrence rate (38). Third, we did not take into account physical activity and diet although several authors have previously shown that these factors may normalize hormone receptor expression profiles in the endometrium and positively influence survival (39). However, a recent study concerning 983 postmenopausal women with EC, found that physical activity was not associated with survival (18). Finally, we did not include for analysis the type of diabetes treatment. Zhang et al. recently showed that metformin could positively impact progression of EC probably via induction of CGRRF1 (cell growth regulator with ring finger domain) gene expression (40).

Conclusion

Our results support that severe obesity negatively impacts RFS in women with high-risk EC, underlining the importance of complete surgical staging and adapted adjuvant therapies in this subgroup of women. This is of major importance as physicians might be tempted to under-treat severely obese women with EC to avoid complications related to lymphadenectomy and/or adjuvant therapies. Future studies should focus on this subgroup of obese women with high-risk EC and possibly include the evaluation of physical activity, diet and comorbidities.

Acknowledgements: None

References

1. Reeves KW, Carter GC, Rodabough RJ, Lane D, McNeeley SG, Stefanick ML, Paskett ED. Obesity in relation to endometrial cancer risk and disease characteristics in the Women's Health Initiative. Gynecol Oncol. 2011 May 1;121(2):376-82.

2. Jeong NH, Lee JM, Lee JK, Kim JW, Cho CH, Kim SM, Seo SS, et al. Role of body mass index as a risk and prognostic factor of endometrioid uterine cancer in Korean women. Gynecol Oncol. 2010 Jul;118(1):24-8.

3. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003 Apr 24;348(17):1625-38.

4. Nagle CM, Marquart L, Bain CJ, O'Brien S, Lahmann PH, Quinn M, Oehler MK, et al. Impact of weight change and weight cycling on risk of different subtypes of endometrial cancer. Eur J Cancer. 2013 Aug;49(12):2717-26.

5. Colombo N, Preti E, Landoni F, Carinelli S, Colombo A, Marini C, Sessa C. Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2013 Oct;24 Suppl 6:vi33-8.

6. Lin LL, Hertan L, Rengan R, Teo BK. Effect of body mass index on magnitude of setup errors in patients treated with adjuvant radiotherapy for endometrial cancer with daily image guidance. Int J Radiat Oncol Biol Phys. 2012 Jun 1;83(2):670-5.

7. Modesitt SC, Tian C, Kryscio R, Thigpen JT, Randall ME, Gallion HH, Fleming GF. Impact of body mass index on treatment outcomes in endometrial cancer patients receiving doxorubicin and cisplatin: a Gynecologic Oncology Group study. Gynecol Oncol. 2007 Apr;105(1):59-65.

8. Anderson B, Connor JP, Andrews JI, Davis CS, Buller RE, Sorosky JI, Benda JA. Obesity and prognosis in endometrial cancer. Am J Obstet Gynecol. 1996 Apr;174(4):1171-8; discussion 8-9.

9. Everett E, Tamimi H, Greer B, Swisher E, Paley P, Mandel L, Goff B. The effect of body mass index on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer. Gynecol Oncol. 2003 Jul;90(1):150-7.

10. Gates EJ, Hirschfield L, Matthews RP, Yap OW. Body mass index as a prognostic factor in endometrioid adenocarcinoma of the endometrium. J Natl Med Assoc. 2006 Nov;98(11):1814-22.

11. Munstedt K, Wagner M, Kullmer U, Hackethal A, Franke FE. Influence of body mass index on prognosis in gynecological malignancies. Cancer Causes Control. 2008 Nov;19(9):909-16.

12. Temkin SM, Pezzullo JC, Hellmann M, Lee YC, Abulafia O. Is body mass index an independent risk factor of survival among patients with endometrial cancer? Am J Clin Oncol. 2007 Feb;30(1):8-14.

13. Kodama J, Seki N, Ojima Y, Nakamura K, Hongo A, Hiramatsu Y. Risk factors for early and late postoperative complications of patients with endometrial cancer. Eur J Obstet Gynecol Reprod Biol. 2006 Feb 1;124(2):222-6.

14. Studzijnski Z, Zajewski W. Factors affecting the survival of 121 patients treated for endometrial carcinoma at a Polish hospital. Arch Gynecol Obstet. 2003 Jan;267(3):145-7.

15. Chia VM, Newcomb PA, Trentham-Dietz A, Hampton JM. Obesity, diabetes, and other factors in relation to survival after endometrial cancer diagnosis. Int J Gynecol Cancer. 2007 Mar-Apr;17(2):441-6.

16. Mauland KK, Trovik J, Wik E, Raeder MB, Njolstad TS, Stefansson IM, Oyan AM, et al. High BMI is significantly associated with positive progesterone receptor status and

clinico-pathological markers for non-aggressive disease in endometrial cancer. Br J Cancer. 2011 Mar 15;104(6):921-6.

17. von Gruenigen VE, Tian C, Frasure H, Waggoner S, Keys H, Barakat RR. Treatment effects, disease recurrence, and survival in obese women with early endometrial carcinoma : a Gynecologic Oncology Group study. Cancer. 2006 Dec 15;107(12):2786-91.

18. Arem H, Chlebowski R, Stefanick ML, Anderson G, Wactawski-Wende J, Sims S, Gunter MJ, et al. Body mass index, physical activity, and survival after endometrial cancer diagnosis: results from the Women's Health Initiative. Gynecol Oncol. 2013 Feb;128(2):181-6.

19. Flegal KM, Graubard BI, Williamson DF, Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. JAMA. 2007 Nov 7;298(17):2028-37.

20. Zanders MM, Boll D, van Steenbergen LN, van de Poll-Franse LV, Haak HR. Effect of diabetes on endometrial cancer recurrence and survival. Maturitas. 2013 Jan;74(1):37-43.

21. Ballester M, Dubernard G, Lecuru F, Heitz D, Mathevet P, Marret H, Querleu D, et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol. 2011 May;12(5):469-76.

22. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults--The Evidence Report. National Institutes of Health. Obes Res. 1998 Sep;6 Suppl 2:51S-209S.

23. Petru E, Luck HJ, Stuart G, Gaffney D, Millan D, Vergote I. Gynecologic Cancer Intergroup (GCIG) proposals for changes of the current FIGO staging system. Eur J Obstet Gynecol Reprod Biol. 2009 Apr;143(2):69-74.

24. Cancer de l’endomètre, Collection Recommandations & référentiels, INCa, Boulogne-Billancourt, novembre 2010.

25. Delpech Y, Cortez A, Coutant C, Callard P, Uzan S, Darai E, Barranger E. The sentinel node concept in endometrial cancer: histopathologic validation by serial section and immunohistochemistry. Ann Oncol. 2007 Nov;18(11):1799-803.

26. Arem H, Irwin ML. Obesity and endometrial cancer survival: a systematic review. Int J Obes (Lond). 2013 May;37(5):634-9.

27. Crosbie EJ, Roberts C, Qian W, Swart AM, Kitchener HC, Renehan AG. Body mass index does not influence post-treatment survival in early stage endometrial cancer: results from the MRC ASTEC trial. Eur J Cancer. 2012 Apr;48(6):853-64.

28. Gunderson CC, Java J, Moore KN, Walker JL. The impact of obesity on surgical staging, complications, and survival with uterine cancer: A Gynecologic Oncology Group LAP2 ancillary data study. Gynecol Oncol. 2014 Apr;133(1):23-7.

29. May K, Bryant A, Dickinson HO, Kehoe S, Morrison J. Lymphadenectomy for the management of endometrial cancer. Cochrane Database Syst Rev. 2010(1):CD007585.

30. Bendifallah S, Canlorbe G, Raimond E, Hudry D, Coutant C, Graesslin O, Touboul C, et al. A clue towards improving the European Society of Medical Oncology risk group classification in apparent early stage endometrial cancer? Impact of lymphovascular space invasion. Br J Cancer. 2014 May 27;110(11):2640-6.

31. Setiawan VW, Yang HP, Pike MC, McCann SE, Yu H, Xiang YB, Wolk A, et al. Type I and II endometrial cancers: have they different risk factors? J Clin Oncol. 2013 Jul 10;31(20):2607-18.

32. Ko EM, Walter P, Clark L, Jackson A, Franasiak J, Bolac C, Havrilesky L, et al. The complex triad of obesity, diabetes and race in Type I and II endometrial cancers: Prevalence and prognostic significance. Gynecol Oncol. 2014 Apr;133(1):28-32.

33. Catalan V, Gomez-Ambrosi J, Rodriguez A, Fruhbeck G. Adipose tissue immunity and cancer. Front Physiol. 2013;4:275.

34. Calle EE, Thun MJ. Obesity and cancer. Oncogene. 2004 Aug 23;23(38):6365-78.

35. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer. 2004 Aug;4(8):579-91.

36. Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P. Role of exogenous and endogenous hormones in endometrial cancer: review of the evidence and research perspectives. Ann N Y Acad Sci. 2001 Sep;943:296-315.

37. Dossus L, Rinaldi S, Becker S, Lukanova A, Tjonneland A, Olsen A, et al. Obesity, inflammatory markers, and endometrial cancer risk: a prospective case-control study. Endocr Relat Cancer. 2010 Dec;17(4):1007-19.

38. Raimond E, Ballester M, Hudry D, Bendifallah S, Darai E, Graesslin O, Stegger J, et al. Impact of sentinel lymph node biopsy on the therapeutic management of early-stage endometrial cancer: Results of a retrospective multicenter study. Gynecol Oncol. 2014 Mar 15.

39. Pekmezi DW, Demark-Wahnefried W. Updated evidence in support of diet and exercise interventions in cancer survivors. Acta Oncol. 2011 Feb;50(2):167-78.

40. Zhang Q, Schmandt R, Celestino J, McCampbell A, Yates MS, Urbauer DL, Broaddus RR, et al. CGRRF1 as a novel biomarker of tissue response to metformin in the context of obesity. Gynecol Oncol. 2014 Apr;133(1):83-9.

Table and figure legends

Table 1. Epidemiological, histological and therapeutic characteristics by BMI in the whole population. IQR: interquartile range.

Table 2. Characteristics of obese women according to ESMO risk groups of recurrence. IQR: interquartile range.

Figure 1. Recurrence-Free Survival according to BMI subgroup in the whole population.

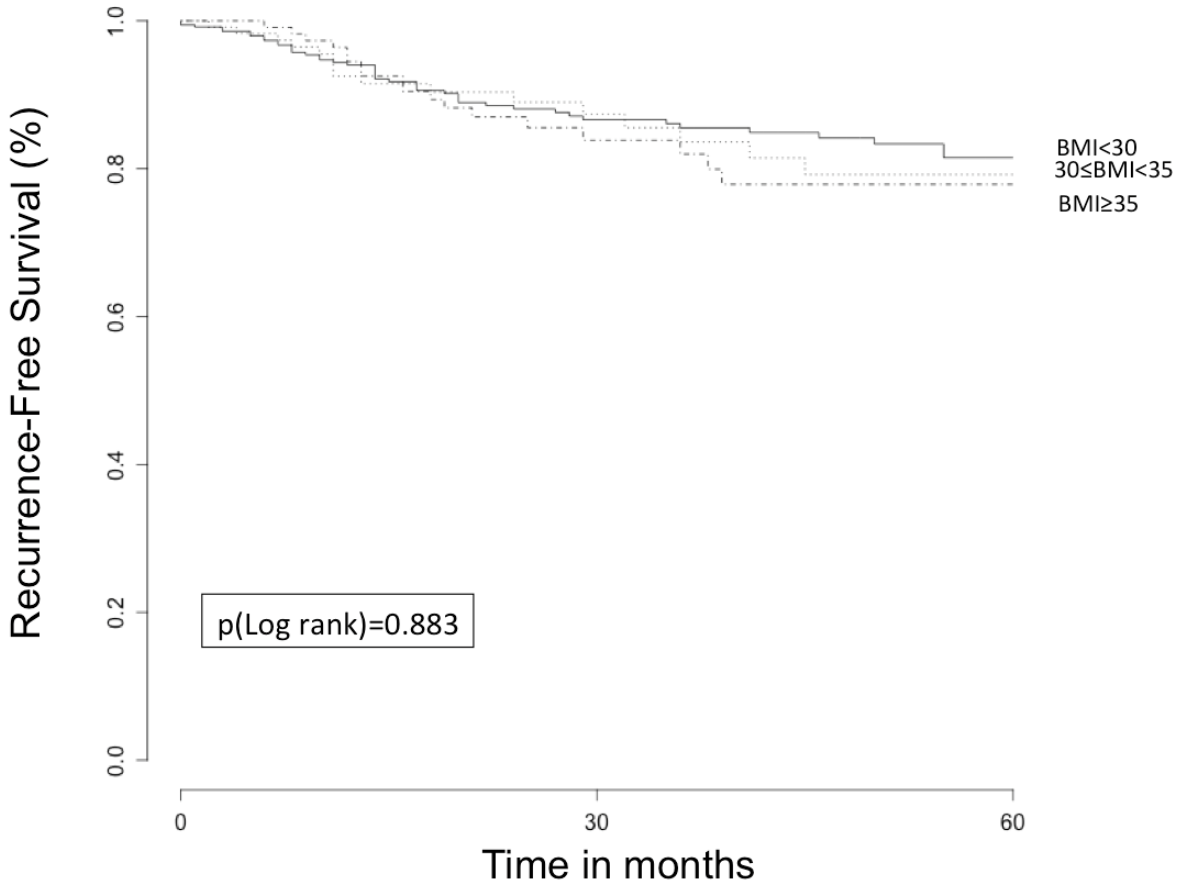
Figure 2. Recurrence-Free Survival in obese women in high-risk group.

		BMI<30 n=442	30≤BMI<35 n= 146	BMI≥35 n= 141	p
Median age, years (IQR)		65.5 (59 – 74.5)	66 (60 – 71)	63 (56 – 70)	0.000873
Histological type (%)					
	Type I	371 (84)	126 (86)	135 (96)	<0.005
	Type II	71(16)	20 (14)	6 (4)	
Histological grade (%)					
	Grade 1	201 (45)	66 (45)	86 (61)	0.009
	Grade 2	122 (28)	38 (26)	34 (24)	
	Grade 3	119 (27)	42 (29)	21 (15)	
Depth of myometrial invasion (%)					
	<50%	239 (54)	74 (51)	86 (61)	0.2628
	>50%	195 (44)	68 (47)	54 (38)	
ESMO risk group(%)					
	Low risk	198 (45)	58 (40)	79 (56)	0.01595
	Intermediate risk	141 (32)	54 (37)	45 (32)	
	High risk	103 (23)	34 (23)	17 (12)	
Lymphovascular space invasion (%)					
	Present	119 (27)	40 (27)	32 (23)	0.442
	Not present	284 (64)	91 (62)	100 (71)	
FIGO stage (%)					
	IA	209 (47)	61 (42)	72 (51)	0.8437
	IB	112 (25)	46 (32)	38 (27)	
	II	32 (7)	9 (6)	9 (6)	
	IIIA	16 (4)	6 (4)	7 (5)	
	IIIB	4 (1)	3 (2)	2 (1)	
	IIIC	58 (13)	16 (11)	12 (9)	
	IVA	3 (<1)	1 (1)	0	
	IVB	6 (1)	3 (2)	1 (1)	
Lymphadenectomy (%)					
	Yes	399 (90)	133 (91)	102 (72)	<0.0001
	No	43 (10)	13 (9)	39 (28)	
Nodal involvement (%)					
	Yes	63 (14)	21 (14)	13 (9)	0.7363
	No	336(76)	112 (77)	89 (63)	
External beam radiotherapy (%)					
	Yes	163 (37)	64 (44)	51 (36)	0.2245
	No	259 (59)	73 (50)	81 (57)	
Brachytherapy (%)					
	Yes	222 (50)	76 (52)	76 (54)	0.5451
	No	187(42)	56 (38)	52 (37)	
Chemotherapy (%)					
	Yes	73 (17)	16 (11)	15 (11)	0.1197
	No	350 (79)	120 (82)	118 (84)	
Recurrence					
	Yes	62 (14)	20 (14)	21 (15)	0.9541
	No	380 (86)	126 (86)	120 (85)	

Table 1. Epidemiological, histological and therapeutic characteristics by BMI in the whole population. IQR: interquartile range.

		Low-risk group, n=137			Intermediate-risk group, n=99			High-risk group, n=51		
		30≤BMI<35 n=58	BMI≥35 n=79	p	30≤BMI<35 n=54	BMI≥35 n=45	p	30≤BMI<35 n=34	BMI≥35 n=17	p
Median age, years (IQR)		64.5 (60-71)	60 (56-68)	0.1305	66 (62-71)	64 (54-70.2)	0.1285	66 (60-73)	69 (64-71)	0.4074
Histological type, n(%)										
	Type I	58 (100)	79 (100)	-	54 (100)	45 (100)	-	14 (41)	11 (65)	0.1441
	Type II	0	0		0	0		20 (59)	6 (35)	
Lymphovascular space invasion, n(%)										
	Present	6 (10)	2 (3)	0.062	15 (28)	19 (42)	0.3192	19 (56)	11 (65)	0.5382
	Not Present	45 (78)	72 (91)		31 (57)	23 (51)		15 (44)	5 (29)	
FIGO stage, n (%)										
	IA	49 (84)	68 (86)	0.9849	4 (7)	2 (4)	0.2032	8 (24)	2 (12)	0.3215
	IB	3 (5)	5 (6)		37 (69)	25 (56)		6 (18)	8 (47)	
	II	2 (3)	2 (3)		5 (9)	6 (13)		2 (6)	1 (6)	
	IIIA	1 (2)	1 (1)		1 (2)	6 (13)		4 (12)	0	
	IIIB	0	0		1 (2)	0		2 (6)	2 (12)	
	IIIC	3 (5)	3 (4)		5 (9)	6 (13)		8 (24)	3 (18)	
	IVA	0	0		1 (2)	0		0	0	
	IVB	0	0		0	0		3 (9)	1 (6)	
Lymphadenectomy, n(%)										
	Yes	54 (93)	56 (71)	0.00107	48 (89)	32 (71)	0.030	31 (91)	14 (82)	0.3871
	No	4 (7)	23 (29)		6 (11)	13 (29)		3 (9)	3 (18)	
Number of nodes removed, median (IQR)		11 (10-17)	11.5 (8-12)	0.3504	13 (9-15.7)	13(10.5-17.5)	0.7474	17 (11.5-23)	12 (7.5-19.2)	0.1151
Nodal involvement, n(%)										
	Yes	4 (7)	3 (4)	0.7137	6 (11)	7 (16)	0.3558	11 (32)	3 (18)	0.4921
	No	50 (86)	53 (67)		42 (78)	25 (56)		20 (59)	11 (65)	
External Beam Radiotherapy, n(%)										
	Yes	12 (21)	11 (14)	0.4308	29 (54)	27 (60)	0.6885	23 (68)	13 (76)	0.7252
	No	43 (74)	63 (80)		21 (39)	15 (33)		9 (26)	3 (18)	
Brachytherapy, n(%)										
	Yes	25 (43)	36 (46)	0.8557	37 (69)	33 (73)	0.8956	14 (41)	7 (41)	1
	No	27 (47)	35 (44)		11 (20)	8 (18)		18 (53)	9 (53)	
Chemotherapy, n(%)										
	Yes	3 (5)	1 (1)	0.3096	3 (6)	7 (16)	0.1785	10 (29)	7 (41)	0.5242
	No	51 (88)	73 (92)		47 (87)	36 (80)		22 (65)	9 (53)	
Recurrence, n(%)										
	Yes	2 (3)	3 (4)	1	5 (9)	9 (20)	0.1542	13 (38)	9 (53)	0.4841
	No	56 (97)	76 (96)		49 (91)	36 (80)		21 (62)	8 (47)	

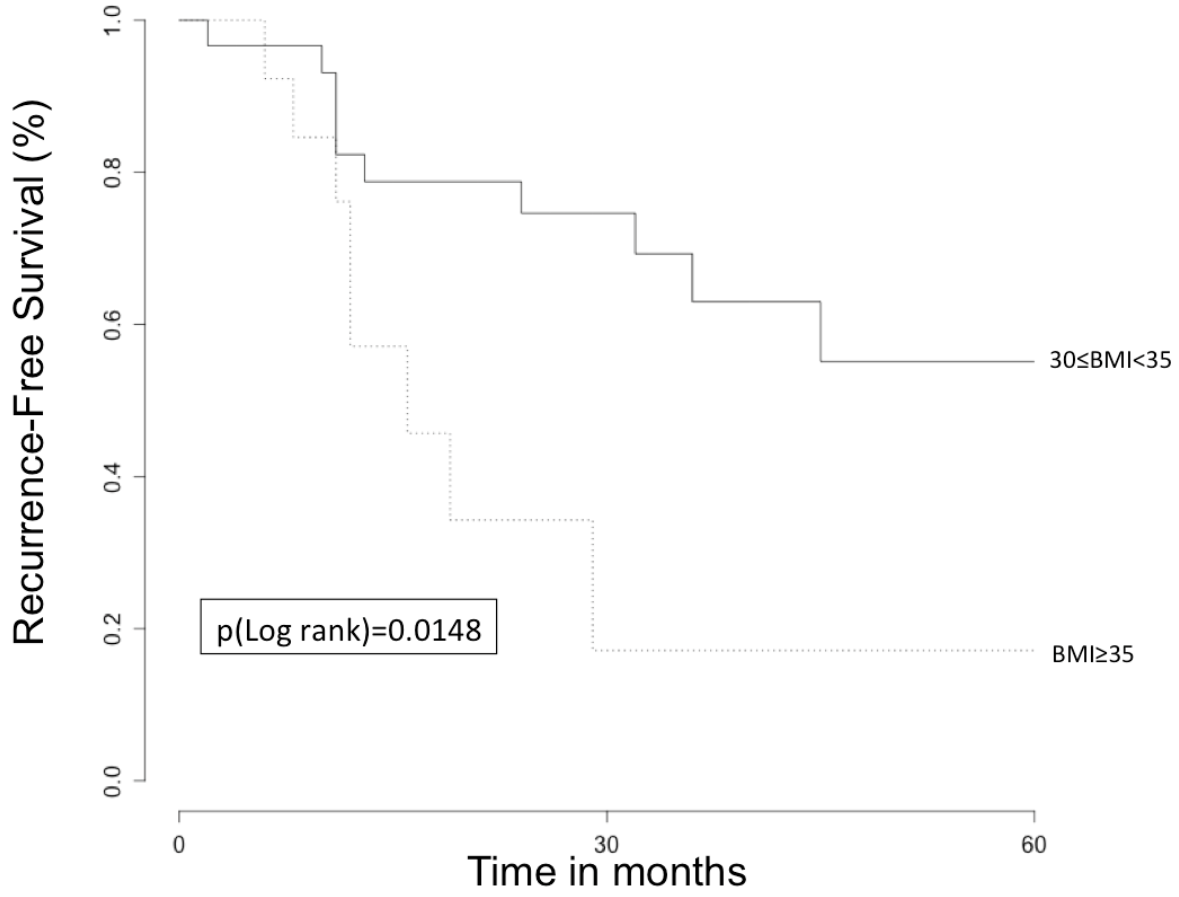
Table 2. Characteristics of obese women according to ESMO risk groups of recurrence. IQR: interquartile range.



440

441 Figure 1. Recurrence-Free Survival according to BMI subgroup in the whole population.

442



443

444 Figure 2. Recurrence-Free Survival in obese women in high-risk group.

445