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.

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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

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organizations that could inappropriately influence this work.
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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 $\geq$ 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%), $30 \leq \text{BMI} < 35$ (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 $\geq$ 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 $\geq$ 35 compared to those with a BMI<35 (Figure 2). Among women in the high-risk group, multivariate analysis including BMI ($<$ or $\geq$ 35), age ($<$ or $\geq$ 65), histological type, LVSI status, adjuvant therapies (VBRT, EBRT and chemotherapy) and nodal staging, showed that BMI $\geq$ 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.

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302 **References**

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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.

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

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

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