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Risk factors for lymph nodes involvement in obese women with endometrial carcinomas

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HIGHLIGHTS

- Morbid obesity is associated with a reduced sentinel lymph node detection rate.
- Obese patients with a BMI ≥40 are at low risk for lymph nodes involvement.
- Elevated CA-125 is a potential predictor for nodal involvement in obese patients.
- A higher BMI did not affect survival of obese patients with endometrial cancer.

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ABSTRACT

Objective. To assess risk factors for lymph node involvement in patients with endometrial cancer and a body-mass index (BMI) ≥30 kg/m^2.

Materials and methods. A retrospective analysis was performed of obese patients diagnosed with endometrial carcinoma between 2007 and 2015, treated in a single center in Montreal. Preoperative variables evaluated were age, BMI, parity, and preoperative ASA score, grade, CA-125 and histology. Odds ratios (OR) and hazard ratios (HR) and their respective 95% confidence intervals (95%CI) were calculated using multivariable logistic regression and Cox proportional hazard models.

Results. The study included 230 women with BMI ≥30, 223 (97.0%) had complete staging. Pelvic lymph node involvement was detected in 26 patients (11.3%). Sentinel node detection and pelvic lymph node dissection decreased with increasing BMI (adjusted OR 0.86, 95%CI 0.76–0.97 and 0.76, 95%CI 0.59–0.96, respectively, per 1 kg/m^2 increment). Pelvic lymph node involvement was inversely correlated with BMI (adjusted OR 0.88, 95% CI 0.79–0.99) and present in 16/85 (18.8%), 6/56 (10.7%), and 4/82 (4.9%) of patients with a BMI of 30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2, respectively. Preoperative CA-125 was associated with lymph node involvement (adjusted OR 2.77, 95%CI 1.62–4.73, per quartile increment).

Conclusion. Pelvic lymph node dissection might be omitted in selected cases of morbidly obese patients with failed sentinel nodes mapping and a low CA-125.

1. Introduction

Endometrial cancer is the most prevalent gynecologic malignancy in North America, and its incidence and mortality rates are increasing [1,2]. Obesity is an established risk factor for endometrial carcinogenesis, related to the excess estrogen produced in adipose tissue [3,4].

The cornerstone of treatment of endometrial cancer patients is surgical staging, consisting of hysterectomy and bilateral salpingo-oophorectomy. The value of lymphadenectomy remains controversial: while the presence of pelvic lymph node metastases is an important prognostic factor, lymphadenectomy did not result in an overall survival advantage in endometrial cancer patients [5–7], and has been associated with increasing risk of lymphedema and vascular injury [8–10].

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Promising results have been published regarding sentinel lymph node dissection [11]. However, sentinel detection rate decreases with increasing body mass index (BMI) [12,13]. In addition, obese patients present specific perioperative challenges, as their comorbidities contribute to adverse outcomes [14]. A higher BMI has been associated with younger age and endometrial cancers of lower grade [15–17].

Considering the operative difficulties and the lower grade cancers in obese patients with endometrial cancer, it is questionable whether a lymphadenectomy should be conducted in morbidly obese patients if sentinel nodes are not detected or negative. The objective of the present study was to identify determinants for lymph node metastases in obese women with endometrial cancer, and to evaluate whether failed (sentinel) node mapping affected clinical outcomes in these patients.

2. Materials and methods

2.1. Patient selection and procedures performed

This study was conducted at the division of Gynecologic Oncology at the Segal Cancer Center of the Jewish General Hospital, a tertiary care hospital in Montreal, Canada. The study is in accordance with the declaration of Helsinki and was approved by the Institutional Review Board (protocol #2019-1547), with annual reviews.

Between December 2007 and 2015, 544 patients with uterine cancer underwent surgical staging in our institution. We excluded patients with sarcomas (n = 32), endometrial intraepithelial neoplasia (n = 34), patients who received neoadjuvant therapy (n = 6), patients who were not followed in our hospital (n = 2), and patients whose body mass index (BMI) was below 30.0 kg/m^2 (n = 237) or whose BMI was unknown (n = 3).

All patients who met the above criteria underwent robotically assisted surgical staging which included total hysterectomy, bilateral salpingoophorectomy and lymphadenectomy. The approach for lymph node dissection at our center changed over the years: patients initially always had a complete pelvic lymph node dissection, but sentinel lymph node dissection was gradually introduced since 2010. During the first year, both sentinel and full lymphadenectomy was performed in all patients. Thereafter, complete lymphadenectomy was performed only if a sentinel node was not identified bilaterally and/or if a patient had high-grade cancer. For the sentinel mapping during the research period, we used a combination of indocyanine green, technetium, and patent blue.

A

	All	BMI 30-35	BMI 35-40	BMI 40+	P-value
Number of patients	230	85	58	87	
Age	62 (55-71)	64 (56-72)	67 (57-76)	60 (54-64)	0.001
BMI	37 (33-42)	32 (31-33)	37 (36-38)	45 (41-47)	<0.001
Gravidity	2 (0-3)	2 (0-3)	2 (1-3)	2 (0-3)	0.70
Parity	2 (0-2)	2 (0-2)	2 (1-2)	1 (0-2)	0.11
Preoperative ASA score					<0.001
- 1	4 (1.7%)	3 (3.5%)	1 (1.7%)	0 (0.0%)	
- 2	117 (50.9%)	57 (67.1%)	30 (51.7%)	30 (34.5%)	
- 3	99 (43.0%)	19 (22.4%)	25 (43.1%)	55 (63.2%)	
- 4	2 (0.9%)	1 (1.2%)	1 (1.7%)	0 (0.0%)	
- Unknown	8 (3.5%)	5 (5.9%)	1 (1.7%)	2 (2.3%)	
Preoperative CA-125 (in kU/L)	13 (7-29)	14 (8-30)	13 (7-23)	11 (6-27)	0.20
Preoperative histology					0.50
- Endometrioid	199 (86.5%)	71 (83.5%)	50 (86.2%)	78 (89.7%)	
- Non-endometrioid	31 (13.5%)	14 (16.5%)	8 (13.8%)	9 (10.3%)	
Preoperative grade					0.12
- Well differentiated	138 (60.0%)	43 (50.6%)	39 (67.2%)	56 (64.4%)	
- Moderately differentiated	43 (18.7%)	20 (23.5%)	6 (10.3%)	17 (19.5%)	
- Poorly differentiated	49 (21.3%)	22 (25.9%)	13 (22.4%)	14 (16.1%)	

B

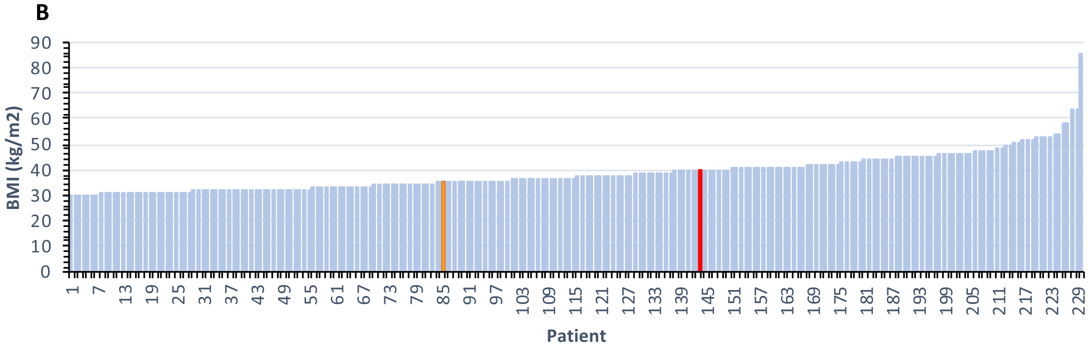

Fig. 1. A. Baseline characteristics of patients by BMI group. Values are median (interquartile range) for continuous variables or number of patients (%) for categorical variables. For statistical analyses, Kruskal-Wallis tests were used for continuous variables, and chi-squared tests for categorical variables. B. Waterfall plot of the BMI of patients with endometrial cancer included in the cohort. The orange bar is the first patient with a BMI of 35.0 or higher, the red line the first patient with a BMI of 40.0 or higher. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2.2. Data collection

Baseline characteristics collected included age, BMI, gravidity, parity, American Society of Anesthesiologists (ASA) score, and preoperative cancer antigen 125 (CA-125) values, histology and grade. Obesity class was defined by the World Health Organization (WHO): (1) BMI 30.0–34.9 kg/m^2, (2) BMI 35.0–39.9 kg/m^2, and (3) BMI ≥40.0 kg/m^2.

Surgical variables collected were operative histology and grade, tumor size, staging including lymph node status, as well as the presence of peritoneal, adnexal, myometrial, lower uterine and cervical involvement, and the presence of distant metastases. Patients were staged following the International Federation of Gynecologic Oncologists (FIGO) 2009 staging for endometrial cancer [18].

Postoperatively, routine follow-up examinations were conducted every four months during the first two years, followed by examinations every six months until five years post-surgery [19], and yearly examinations thereafter. Progression-free survival (PFS) was defined as the time from surgery to date of recurrence. Recurrences were diagnosed clinically, and confirmed by imaging using computed tomography (CT) or positron emission tomography (PET) and biopsy when appropriate. Overall survival (OS) was defined as time from diagnosis to death or the last date they were known to be alive (censored). Patients were assumed to have died from their disease if they had advanced disease at the last follow-up, whereas patients were assumed to have died from other causes if they had their last follow-up less than one year before death and were free of disease at this visit.

2.3. Statistical analyses

For continuous variables in the baseline characteristics, medians with interquartile ranges were calculated for the whole cohort and the three BMI groups; differences in baseline characteristics between the BMI groups were evaluated using the non-parametric Kruskal-Wallis tests due to non-normal distribution of the variables. For categorical variables, chi-squared tests were used to evaluate differences between BMI groups. Uni- and multivariable (ordered) logistic regression models were used to identify determinants for lymph node dissection and surgery outcome. In multivariable analyses, we adjusted for all baseline characteristics except for gravidity (due to its close relation with parity) unless otherwise specified. Recurrence-free, overall, and disease-specific survival were analyzed using the Kaplan-Meier method and log-rank tests; hazard ratios and their 95% confidence interval (95%CI) were calculated using uni- and multivariable Cox proportional hazards models. All statistical analyses were conducted using Stata v15.1.

3. Results

Of the 544 women operated for endometrial cancer in our division between December 2007 and January 2015, 230 patients met the study inclusion criteria (Supplementary Fig. 1). The baseline characteristics of the study population are displayed in Fig. 1A. Median age was 62 years, median BMI was 37 kg/m^2. Eighty-five, 58, and 87 patients had a BMI of 30.0–34.9 kg/m^2, 35.0–39.9 kg/m^2, and ≥40.0 kg/m^2, respectively (Fig. 1B). The vast majority of patients had a preoperative ASA score of 2 or 3. In preoperative biopsies, most patients had endometrioid tumors (86.5%) that were well differentiated (60.0%). Comparing patients in different BMI groups, patients with a BMI ≥40 kg/m^2 were younger and had a higher ASA score ($P < 0.001$ for both variables). Finally, patients with a BMI above 35 kg/m^2 seemed to have more well differentiated tumors (65.5%) as compared to patients with a BMI of 30–35 kg/m^2 (50.6%), but this difference did not reach statistical significance ($P = 0.12$).

Sentinel lymph node dissection was conducted in a majority of patients (61.2%; Table 1). In multivariable analyses, patients with a higher BMI had more frequently a failure in sentinel lymph node detection (18.5% of patients with a BMI ≥40.0 kg/m^2 versus 3.8% of patients with a BMI of 30.0–34.9 kg/m^2; adjusted odds ratio per 1 kg/m^2 increment:

Table 1
Lymph node dissection at surgery, by BMI.

	BMI 30–35[a]	BMI 35–40[a]	BMI 40+[a]	Odds ratio[b]	
				Univariable	Multivariable[c]
Sentinel lymph node					
- performed	61.2% (52/85)	60.3% (35/58)	62.1% (54/87)	0.98 (0.95–1.02)	**0.95 (0.91–1.00)**
- detection rate	96.2% (50/52)	85.7% (30/35)	81.5% (44/54)	**0.89 (0.82–0.96)**	**0.86 (0.76–0.97)**
- Bilateral detection rate	74.0% (37/50)	73.3% (22/30)	79.5% (35/44)	1.03 (0.96–1.11)	1.03 (0.94–1.13)
- Number of pelvic lymph nodes removed (excl. 0)	2 (2–3)	2 (2–3)	2 (2–3)	1.01 (0.95–1.07)	1.03 (0.96–1.10)
- Number of paraaortic lymph nodes removed (excl. 0)	1 (1–2)	2 (1–2)	2 (1–4)	1.07 (0.86–1.33)	1.04 (0.74–1.46)
- Positive lymph nodes[d]	20.0% (10/50)	6.7% (2/30)	6.8% (3/44)	0.93 (0.83–1.03)	0.93 (0.80–1.07)
PLN dissection or SLN					
- Performed (sentinel and/or full)	100.0% (85/85)	96.6% (56/58)	94.3% (82/87)	**0.81 (0.73–0.91)**	**0.76 (0.59–0.96)**
- Number removed	10 (7–15)	7 (4–11)	9 (5–13)	0.98 (0.95–1.02)	0.98 (0.94–1.03)
- Invasion	18.8% (16/85)	10.7% (6/56)	4.9% (4/82)	**0.91 (0.83–0.99)**	**0.88 (0.79–0.99)**
Paraaortic lymph node dissection					
- Performed (sentinel and/or full)	44.7% (38/85)	20.7% (12/58)	16.1% (14/87)	**0.87 (0.82–0.93)**	**0.90 (0.83–0.96)**
- Number removed	4 (2–8)	2 (1–6)	3 (2–6)	**0.90 (0.82–0.99)**	**0.93 (0.83–1.05)**
- Invasion	13.2% (5/38)	8.3% (1/12)	0.0% (0/14)	0.82 (0.61–1.11)	0.69 (0.41–1.18)

[a] Values are median (interquartile range) for continuous variables or number of percentages (patient numbers) for categorical variables.
[b] BMI is used in the model as a continuous independent variable. Odds ratios were calculated using binomial/ordered logistic regression models when appropriate.
[c] Adjusted for age, parity, and preoperative ASA score, grade, CA-125 and histology.
[d] The denominator includes all individuals in which sentinel lymph nodes were removed.

0.86, 95%CI 0.76–0.97). Similarly, pelvic and para-aortic lymph node dissections (whether sentinel or complete) were less frequently done with increasing BMI (adjusted odds ratios of 0.76 (95%CI 0.59–0.96) and 0.90 (95%CI 0.83–0.96) per 1 kg/m^2 increment, respectively). Seven patients did not have any pelvic lymph node removed, of whom five with a BMI ≥40.0 kg/m^2. Obesity-related technical difficulties impeded lymph node dissection in five patients, such as difficult ventilation in the Trendelenburg position; for one patient it had already been determined

Table 2
Surgery outcome, by BMI.

	BMI 30–35[a]	BMI 35–40[a]	BMI 40+[a]	Odds ratio[b]	
				Univariable	Multivariable[c]
Operative histology, endometrioid	81.2% (69/85)	84.5% (49/58)	87.4% (76/87)	0.96 (0.90–1.02)	1.01 (0.92–1.12)
Operative grade				**0.96**	1.01
- Well differentiated	42.4% (36/85)	44.8% (26/58)	49.4% (43/87)	**(0.93–0.99)**	(0.96–1.06)
- Moderately differentiated	21.2% (18/85)	34.5% (20/58)	32.2% (28/87)		
- Poorly differentiated	35.3% (30/85)	19.0% (11/58)	14.9% (13/87)		
- None (EIN)	1.2% (1/85)	1.7% (1/58)	3.4% (3/87)		
Difference operative and preoperative grade					
- Downgrading after surgery	11.8% (10/85)	6.9% (4/58)	12.6% (11/87)	0.97 (0.91–1.04)	0.96 (0.88–1.05)
- Upgrading after surgery	28.2% (24/86)	27.6% (16/58)	19.5% (17/87)	0.98 (0.94–1.03)	0.98 (0.93–1.04)
Stage				**0.96**	0.98
- EIN	1.2% (1/85)	1.7% (1/58)	3.4% (3/87)	**(0.92–1.00)**	(0.93–1.02)
- 1a	55.3% (47/85)	62.1% (36/58)	70.1% (61/87)		
- 1b	16.5% (14/85)	15.5% (9/58)	8.0% (7/87)		
- 2	5.9% (5/85)	6.9% (4/58)	6.9% (6/87)		
- 3a	1.2% (1/85)	0.0% (0/58)	4.6% (4/87)		
- 3b	1.2% (1/85)	0.0% (0/58)	0.0% (0/87)		
- 3c	18.8% (16/85)	12.1% (7/58)	4.6% (4/87)		
- 4	0.0% (0/85)	1.7% (1/58)	2.3% (2/87)		
Maximum tumor size				1.02	1.03
- 0.0–1.7 cm	23.5% (20/85)	17.2% (10/58)	19.5% (17/87)	(0.99–1.05)	(0.99–1.07)
- 1.7–3.0 cm	17.6% (15/85)	20.7% (12/58)	19.5% (17/87)		
- 3.0–4.0 cm	22.4% (19/85)	25.9% (15/58)	20.7% (18/87)		
- ≥4.0 cm	36.5% (31/85)	36.2% (21/58)	40.2% (35/87)		
Extrauterine disease	21.2% (18/85)	13.8% (8/58)	11.6% (10/86)	0.96 (0.90–1.01)	0.97 (0.90–1.04)
Myometrial invasion	91.8% (78/85)	87.9% (51/58)	85.1% (74/87)	0.98 (0.94–1.04)	0.99 (0.93–1.06)
Adnexal invasion	4.7% (4/85)	0.0% (0/58)	6.9% (6/87)	1.03 (0.96–1.11)	1.07 (0.97–1.17)
Lower uterine segment involvement	18.8% (16/85)	8.6% (5/58)	12.6% (11/87)	0.98 (0.93–1.04)	1.00 (0.94–1.07)
Cervical involvement	15.3% (13/85)	6.9% (4/58)	16.1% (14/87)	1.01 (0.96–1.06)	1.04 (0.98–1.11)
LVSI	31.8% (27/85)	29.3% (17/58)	19.5% (17/87)	0.96 (0.92–1.01)	0.99 (0.93–1.05)
Distant metastases	0.0% (0/85)	1.7% (1/58)	1.1% (1/87)	1.05 (0.93–1.19)	N/A
Positive peritoneal wash	1.2% (1/85)	0.0% (0/57)	3.4% (3/87)	1.05 (0.96–1.15)	1.07 (0.88–1.31)
Adjuvant therapy	55.3% (47/85)	37.9% (22/58)	33.3% (29/87)	**0.94 (0.90–0.98)**	0.97 (0.92–1.03)
- Adjuvant chemotherapy	37.6% (32/85)	21.4% (12/56)	18.6% (16/86)	**0.93 (0.88–0.98)**	0.94 (0.87–1.02)
- Adjuvant radiotherapy	51.8% (44/85)	36.2% (21/58)	33.3% (29/87)	**0.95 (0.91–0.99)**	0.99 (0.93–1.04)

[a] Values are median (interquartile range) for continuous variables or number of percentages (patient numbers) for categorical variables.
[b] BMI is used in the model as a continuous independent variable. Odds ratios were calculated using binomial/ordered logistic regression models when appropriate.
[c] Adjusted for age, parity, and preoperative ASA score, grade, CA-125 and histology.

she would receive adjuvant therapy due to a deeply invasive high-grade serous tumor; one operative report did not mention the reason for no lymphadenectomy. 18.8% of patients with a BMI of 30.0–34.9 kg/m^2 had pelvic lymph node involvement, compared to 4.9% with a BMI ≥40.0 kg/m^2 who had pelvic lymph nodes removed (adjusted odds ratio 0.88 per 1 kg/m^2 increment, 95%CI 0.79–0.99). Although not statistically significant, similar findings were observed for paraaortic lymph node invasion (adjusted odds ratio 0.69 per 1 kg/m^2 increment, 95%CI 0.41–1.18).

We evaluated whether other surgical outcomes differed based on their BMI (Table 2). In univariable analyses, an increasing BMI was inversely associated with worse operative grade (odds ratio 0.96, 95%CI 0.93–0.99, per 1 kg/m^2 increment) and stage (odds ratio 0.96, 95%CI 0.92–1.00). Patients with a higher BMI were less frequently selected for adjuvant therapy (odds ratio 0.94, 95%CI 0.90–0.98). However, once adjusting for other discrepancies at baseline, such as differences in preoperative grading at biopsy, BMI did not predict any surgical outcomes other than pelvic lymph node invasion.

In view of the inverse association between BMI and pelvic lymph node invasion in obese endometrial patients, we evaluated preoperative determinants for positive pelvic/para-aortic lymph nodes at surgery (Table 3). In a univariable analysis, BMI (odds ratio 0.91, 95%CI 0.83–0.99, per 1 kg/m^2 increment), preoperative CA-125 (odds ratio 2.76, 95%CI 1.69–4.50, per quartile increment), and preoperative grade (poorly differentiated cancer: odds ratio 2.68, 95% confidence interval 1.07–6.68) predicted positive lymph nodes. In the multivariable model, only BMI (adjusted odds ratio 0.87, 95%CI 0.78–0.98) and preoperative CA-125 (adjusted odds ratio 2.77, 95%CI 1.62–4.73) independently predicted positive lymph nodes.

Since patients with worse obesity were at lower risk for lymph node involvement, we evaluated whether their clinical outcome was better. Median follow-up time was 72 months (95%CI 51--93 months). Recurrence-free survival was similar between patients of different BMI groups (log-rank test: P = 0.57; Fig. 2), with a 5-year recurrence-free survival rate of 87.1% (95%CI 81.7–91.1%). However, overall survival rates significantly improved with increasing BMI (log-rank test, P = 0.02; Fig. 3). Five-year survival rates were 87.3% (95%CI 77.6–92.9%), 86.0% (95%CI 72.9–93.1%), and 91.0% (95%CI 82.0–95.6%) for patients with a BMI of 30–35, 35–40 and 40 or higher, respectively. When limiting to disease-specific deaths, a similar trend was observed, but few patients had died from the cancer and the difference between groups did not reach statistical significance (P = 0.29, Supplementary Fig. 2).

Considering that lymph node removal was less frequently successful in patients with a higher BMI, we were concerned that invasive lymph nodes may have remained in situ in such patients. However, when comparing patients who did and did not have pelvic lymph nodes removed, we did not see any difference in recurrence-free or overall survival (log-rank tests: P = 0.80 and P = 0.31, respectively; Supplementary Fig. 3), and all patients without pelvic lymph node removal were alive at the end of follow-up.

Table 3
Determinants for positive pelvic/para-aortic lymph nodes at surgery.

	Negative lymph nodes	Positive lymph nodes	Odds ratio	
			Univariable	Multivariable[1]
BMI, median (IQR)	37.5	33.9	**0.91**	**0.87**
(per 1 kg/m^2 increment)	(33.0–42.1)	(31.8–37.1)	**(0.83–0.99)**	**(0.78–0.98)**
Age, median (IQR)	62y	66y	1.02	0.99
(per 1 year increment)	(55-71y)	(52-74y)	(0.98–1.06)	(0.94–1.03)
Parity			1.13	1.04
- 0	31.3%	30.8%	(0.78–1.62)	(0.68–1.58)
	(62/198)	(8/26)		
- 1	17.2%	15.4%		
	(34/198)	(4/26)		
- 2	32.8%	23.1%		
	(65/198)	(6/26)		
- ≥3	18.7%	30.8%		
	(37/198)	(8/26)		
ASA			0.70	1.09
- 1	1.0%	8.3%	(0.31–1.57)	(0.40–2.95)
	(2/192)	(2/24)		
- 2	54.7%	50.0%		
	(105/192)	(12/24)		
- 3–4	44.3%	41.7%		
	(85/192)	(10/24)		
Preoperative non-endometrioid histology	12.1%	23.1%	2.18	0.74
	(24/198)	(6/26)	(0.79–5.95)	(0.15–3.66)
Preoperative grade				
- Well differentiated	61.6%	46.2%	1.0 (ref)	1.0 (ref)
	(122/198)	(12/26)		
- Moderately differentiated	19.2%	15.4%	1.07	0.42
	(38/198)	(4/26)	(0.33–3.51)	(0.10–1.73)
- Poorly differentiated	19.2%	38.5%	**2.68**	1.15
	(38/198)	(10/26)	**(1.07–6.68)**	(0.28–4.72)
Preoperative CA-125 (per quartile increment)			**2.76**	**2.77**
- 0–7 kU/L	29.6%	3.8%	**(1.69–4.50)**	**(1.62–4.73)**
	(56/189)	(1/26)		
- 8–13 kU/L	27.5%	7.7%		
	(52/189)	(2/26)		
- 14–28 kU/L	21.7%	30.8%		
	(41/189)	(8/26)		
- ≥29 kU/L	21.2%	57.7%		
	(40/189)	(15/26)		

Odds ratios are displayed with their respective 95% confidence intervals. Patients without removal of pelvic lymph nodes were excluded from the analyses. In the multivariable analysis, we mutually adjusted for all baseline preoperative characteristics measured.

[1] Adjusted for age, parity, and preoperative ASA score, grade, CA-125 and histology.

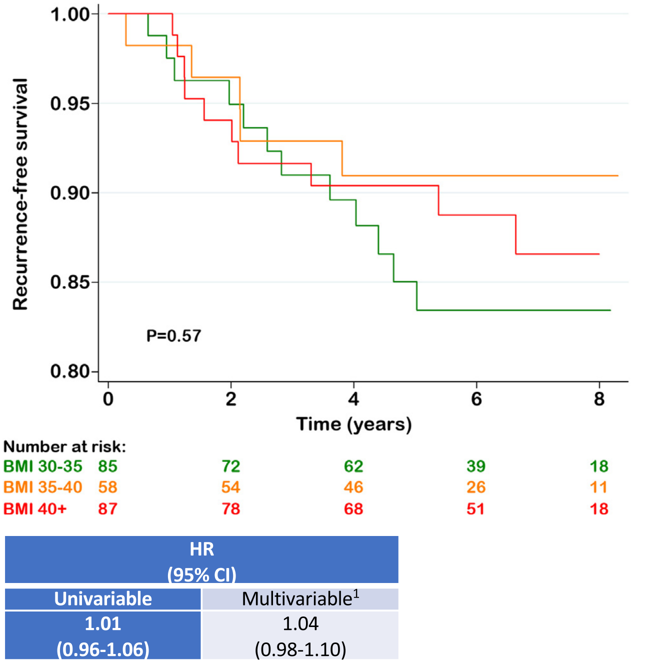

Fig. 2. Recurrence after surgery. Hazard ratios are per 1 kg/m^2 increase. [1]Adjusted for age, parity, and preoperative ASA score, grade, CA-125 and histology.

4. Discussion

In the current study, we evaluated surgical and clinical outcomes in obese patients undergoing surgical staging for endometrial cancer in a single center in Canada.

In our study, pelvic lymph node dissection was completed in 97.0% of patients, as two patients with class II obesity and five patients with class III obesity had no sentinel node identified and no dissection performed, primarily due to perioperative challenges associated with obesity. This is in line with other studies that demonstrated decreased sentinel mapping with increasing BMI in patients with endometrial or breast cancers [12,13,20].

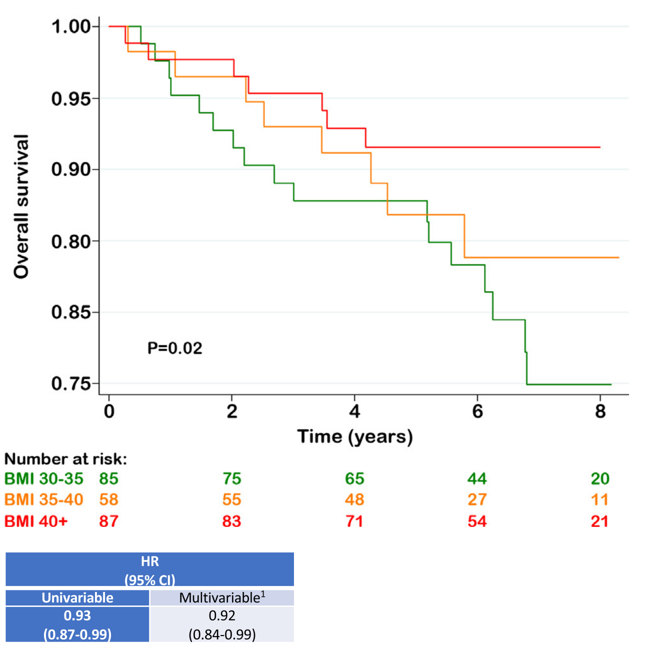

Fig. 3. Overall survival after surgery. Hazard ratios are per 1 kg/m^2 increase. [1]Adjusted for age, parity, and preoperative ASA score, grade, CA-125 and histology.

The overall rate of pelvic lymph node invasion in the obese population was 11.6%; incidence was 18.8%, 10.7%, and 4.9% in patients with a BMI of 30.0–34.9, 35.0–39.9, and ≥40.0 kg/m^2, respectively. These incidences are similar to those reported by a previous study which performed complete surgical staging [21], and those reported in GOG LAP 2 ancillary data [14]. In our study, a higher BMI was associated with a lower age, and lower postoperative grade and stage, which is in concordance with existing data in the literature [14–17,22,23].

The inverse association between lymph node involvement and BMI could potentially be explained by differences in gene expression levels in the tumors. Recently, Roque et al. reported that the BMI of patients differed significantly when patients were clustered by gene expression patterns of their endometrioid endometrial cancer as identified in The Cancer Genome Atlas (TCGA) [24]. With increasing BMI, obesity-related genes were upregulated in endometrioid endometrial cancers [24].

Another potential explanation for the inverse association between lymph node involvement and BMI is that obese patients have high levels of endogenous estrogen due to the conversion of androstenedione to estrone and the aromatization of androgens to estradiol in peripheral adipose tissue [25]. Hence, severely obese women may develop estrogen-responsive endometrial cancer, which generally has a less aggressive histologic subtype.

Third, the decreasing rate of lymph node invasion with increasing BMI could have been caused by a diminished lymphatic flow drainage amongst (morbidly) obese women. In vivo studies have reported that obese mice have lymph nodes of a smaller size and with diminished lymphatic flow compared to lean mice [26,27].

While tumor marking testing is not routinely performed prior to surgery for endometrial cancer, retrospective reviews found it to be an independent risk factor for extrauterine disease and lymph node involvement [28–30], and led our group to evaluate pre-operative CA-125 levels. Since the optimal threshold for CA-125 has not been determined yet in endometrial cancer patients and CA-125 is not-normally distributed, we used the 25th, 50th, and 75th percentile to create equally sized quartiles [29]. In doing so, BMI and preoperative CA-125 independently predicted positive lymph nodes in obese patients. While only 3.3% (2/60) of patients with a BMI above 40.0 kg/m^2 and a CA-125 below 28 kU/L had positive pelvic lymph nodes, 10.2% (6/59) of patients with a BMI of 30.0–34.9 kg/m^2 and a similar CA-125 has positive nodes, and 27.6% (16/58) of patients with a CA-125 above 28 kU/L (irrespective of BMI). When conducting a subgroup analysis only including the patients with endometrioid histology at biopsy, this association between BMI, CA-125 and LN involvement remained significant (Supplementary Table 1).

Limitations of the study include its retrospective nature with potential for inherent bias (including selection bias and lead-time bias) and missing data, although it included every consecutive patient treated at our center, and the information is stored in prospectively gathered electronic medical records. In addition, due to the low number of events, our statistical power may have been limited for statistical significance, particularly when comparing cancer-specific survival between groups. This study could not answer whether failed sentinel lymph node mapping affected survival due the low number of patients in this group. Moreover, interpretation of overall survival data, particularly for predominantly early stage endometrial cancers, would require larger numbers of patients than in our cohort. Finally, lower detection and dissection rates in patients with higher BMIs should be taken into account when interpreting data on nodal involvement, as survival data may be an imperfect proxy for information on nodal status.

The main strength of this study was that data were collected in a single tertiary center with 96.9% of the patients undergoing complete staging with pelvic lymph node dissection. In addition, group categorization was performed using the standardized WHO criteria, the participants had relatively evenly distributed body mass indices, and follow-up data was collected prospectively.

In conclusion, in this single-center study evaluating obese women with endometrial cancer, we observed that a lower BMI and increasing preoperative CA-125 were associated with lymph node involvement. While pelvic lymph node dissection was increasingly omitted when patients had a higher BMI, this did not negatively affect their clinical outcomes. The data does not support omitting lymphadenectomy for high-risk patients with morbid obesity, including those with grade 3 tumors, in case of failed mapping. Future studies need to validate whether lymph nodes dissection can be omitted safely in selected low risk patients with a high BMI. Maybe CA-125, could be helpful as suggested by our findings, but ultimately molecular markers probably represent the best approach, specifically in patients with a high operative risk.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.07.016.

Declaration of Competing Interest

The authors report no conflict of interest.

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Authors' contributions

With regards to the authors' contribution, here are the specific inputs:

- Michel Wissing: statistical analysis, results, tables, figures, introduction, discussion, manuscript editing
- Cristina Mitric: abstract, introduction, methods, discussion, data collection, manuscript editing
- Zeinab Amajour, Jeremie Abitbol, Vanessa Lopez-Ozuna, Jeffrey How, Roy Kessous: data collection, discussion
- Walter Gotlieb, Shannon Salvador, Susie Lau, Amber Yasmeen, Neta Eisenberg: discussion, manuscript editing
- Liron Kogan: introduction, results interpretation, methods, discussion, manuscript editing

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