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Challenges on the morbidly obese endometrial cancer surgery: Laparotomy or laparoscopy, lymphadenectomy or no lymphadenectomy?

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ABSTRACT

Objectives: A considerable proportion of endometrial cancer patients are morbidly obese. Management of these cases is a serious dilemma. The aim of this study was to investigate the relevance of laparoscopic route and omission of lymphadenectomy as morbidity-reducing strategies in this special population.

Material and methods: Endometrial cancer patients' archival records were retrospectively reviewed and cases with body mass index ≥ 40 kg/m^2 were selected. A comparative evaluation of their characteristics and survival rates were performed. Firstly, according to the surgical approach; laparoscopy or laparotomy, and then regarding to performing lymphadenectomy or not.

Results: There were 146 patients enrolled in this study. Whereas, significantly higher postoperative complications and longer hospital stays were determined in the laparotomy compared to laparoscopy groups. Five years disease-free and overall survival were not significantly different (83.6% vs 70.7%, p = 0.184 and 83.9% vs 86.6%, p = 0.571, respectively). On the other hand, operation length, postoperative hospitalization time, both intraoperative and postoperative complications were significantly lower in the non-lymphadenectomy compared to the lymphadenectomy groups. However, five-years disease-free and overall survival were not significantly different (77.3% vs 81.3%, p = 0.586 and 87.5% vs 78%, p = 0.479, respectively).

Conclusions: Laparoscopic approach and omission of lymphadenectomy are worthy policies in the morbidly obese endometrial cancer patients.

Key words: laparoscopic surgery; lymphadenectomy; morbid obesity; endometrial cancer; oncologic outcomes

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INTRODUCTION

Obesity and particularly morbid obesity is a widening issue around the world. The World Health Organization (WHO) had identified morbid obesity as patients with body mass index more than 40 kg/m^2 [1]. The robust association between obesity and endometrial cancer risk has been emphasized in many studies [2–4]. It was reported that morbidly obese patients have nine times increased risk for endometrial cancer comparing to the normal-weight population [3]. Furthermore, 19% to 36% of the endometrial cancer' patients were reported to be morbidly obese [5]. Inadequate activity and obesity-linked medical comorbidities in the morbidly obese endometrial cancer patients were supposed to have contributed in their management complexity [5]. Actually, not just the surgery of the morbidly obese endometrial cancer cases, but dealing with all of their health procedures including examination, evaluation with imaging methods, per-operative and postoperative morbidity and complications, is a serious predicament.

Surgery representing in total hysterectomy and bilateral salpingo-oophorectomy (TH-BSO) with or without lymphadenectomy ± omentectomy is the cornerstone of the endometrial cancer treatment [6]. Surgery can be performed via laparotomy, robotic assisted or conventional laparoscopy. Since minimal invasive surgery has been proven effective in improving the perioperative and postoperative outcomes without compromising survival, it was incorporated in the surgical management of endometrial cancer throughout the last two decades [7]. Besides, laparoscopic surgery had been validated for the long-term outcomes of low risk as

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well as high-risk endometrial cancer cases in many studies [8]. However, morbidly obese patients are a colossal obstacle for all surgical approaches.

While a lymphadenectomy is beneficial for more precise adjuvant treatment triage by obtaining thorough stage designation and prognosis prediction of the EC patients, there is no consensus regarding its therapeutic benefit [9]. In addition, extent (pelvic or pelvic-paraaortic — until the inferior mesenteric artery or up to the left renal vein), manner and technique (full dissection or sampling, based on frozen section or sentinel node) of the lymphadenectomy are controversial, also [9, 10]. Hitherto, therapeutic impact of the lymphadenectomy in the EC was shown only by retrospective studies and was not confirmed by the randomized prospective studies [9–11].

Medically, morbidly obese EC patients are a high risk special population along all their treatment phases. Therefore, morbidity-reducing strategies are essential in these cases. However, such strategies should not harm the long-term oncological outcomes of these patients. In this study we investigated whether choosing the laparoscopic route and omission of the lymphadenectomy are or not appropriate policies in the morbidly obese EC patients.

MATERIAL AND METHODS

The archival records and pathological reports of the endometrial cancer cases, who were operated and followed up in Çukurova University Gynecologic Oncology Center between January 2008 and December 2018, were reviewed, retrospectively. Patients with body mass index ≥ 40 kg/m^2 were selected for this study. Body mass index [weight (kg)/height (m^2)] was calculated and classified according to the WHO guidelines. Demographic, clinical, surgical, pathological and follow-up data concerning to these patients were obtained. Comparative evaluations of the patients' characteristics and survival rates were performed, firstly according to the surgical approach; laparoscopy or laparotomy, and then whether or not to perform a lymphadenectomy. Compared variables included age, body mass index (BMI), comorbidities, surgical approach, surgical procedure, operation time, perioperative and postoperative complications, hospitalization time, histological type, stage, grade, myometrial invasion (MI), retroperitoneal lymph node involvement, lymphovascular invasion (LVSI), adjuvant treatments and follow-up data. A routinely informed consent was taken from all participants. An approval for this study was obtained from the local committee.

In general, surgery was performed laparoscopically or by laparotomy based on the patient's choice. The main surgical procedures were total hysterectomy-bilateral salpingo-oophorectomy with or without pelvic and para-aortic lymphadenectomy. While, all cases underwent TH-BSO, the decision of performing a lymphadenectomy and its extent (pelvic or pelvic and paraaortic) was taken upon the case's medical performance, the surgical facility and intraoperative frozen section result. The frozen section was performed in all cases and it was the main router for the lymphadenectomy decision. Hence, a lymphadenectomy was not considered for patients with, stage 1a, FIGO grade 1–2, < 2 cm endometrioid tumors (low-risk factors). In the presence of any of the following circumstances: endometrioid adenocarcinoma grade 3, tumor diameter > 2 cm, ≥ 50% myometrial invasion, stage > 1a or non-endometrioid histologies, a lymphadenectomy was performed in medically and surgically eligible cases. In the case of FIGO grade 1–2 endometrioid adenocarcinoma with < 50% MI and > 2 cm tumor, only a pelvic lymphadenectomy was carried out. An omentectomy was administered to patients with non-endometrioid histology and in case of omental involvement. Pelvic lymphadenectomy was defined as removing bilaterally the lymph nodes located from the circumflex iliac vein to the iliac bifurcation along the external iliac vessels, the nodes along the internal iliac vessels, and within the interiliac distance and the obturator fossa. In addition to the lymph nodes described above as pelvic lymphadenectomy, resection of the lymph nodes located from the bifurcations of the common iliac vessels up to the left renal vein including; presacral, caval, aortocaval, periaortic, left paraaortic (below and above the inferior mesenteric artery), and right paracaval fields, was identified as pelvic and paraaortic lymphadenectomy.

All specimens were assessed by expert gynecologic pathologists. Comorbidities were accepted as any concomitant chronic disease. International Federation of Gynecology and Obstetrics FIGO 2009 staging guideline for endometrial cancer was utilized. Stages of cases operated before 2009 were rearranged accordingly. Grade was also identified according to 1988 FIGO grading system. Adjuvant therapies (brachytherapy, external beam radiotherapy and/or chemotherapy) were considered for patients with ≥ intermediate risk factors. The period between date of the histopathologic diagnosis and recurrence was identified as disease-free survival. Overall survival was defined as time between date of histopathologic diagnosis and date of death from any cause.

Data were analyzed using SPSS software version 23.0 (IBM, Armonk, NY, USA). Descriptive analyses were presented as mean ± standard deviation, number and percentage. Normally distributed continuous variables were analyzed using student t-test. Categorical data were analyzed using Chi- square test or Fisher's exact test. Survival analysis were realized with Kaplan–Meier method and the differences in the survival curves were calculated through the log-rank test. P value was considered significant at the level < 0.05.

RESULTS

During the study period, 146 patients were determined to be eligible for recruitment to this study. Two different comparisons were performed to the study population: Firstly, according to the surgical route and then in regard to applying a lymphadenectomy or not. There were 65 cases in the laparotomy (LT) and 81 in the laparoscopy (LS) groups. Comparison between patients concerning their surgical approach is summarized in Table 1. Patients' mean age was 58.94 ± 11.4 and 58.18 ± 8.9 in the LT and LS groups, respectively (p = 0.652). The average BMI of the LT group (44.37 ± 4.8) was significantly lower comparing to the LS group (46.13 ± 5.3) (p = 0.042). Significant proportion of both groups had comorbidities, 60.3% of the LT and 67.9% of the LS group (p = 0.345). While, a lymphadenectomy was performed in 26 (40%) (pelvic and paraaortic: 18, only pelvic: 8) cases of the LT group, it was only carried out in 14 (17.3%) (pelvic and paraaortic: 8, only pelvic: 6) cases of the LS group (p = 0.007). There were no significant differences between groups with respect to the operation time (LT: 96.0 ± 32.6, LS: 89.5 ± 41.1, p = 0.303). Whereas, no significant differences between LT and LS groups were noted regarding to the intraoperative complications (p = 0.915), there were significantly higher postoperative complications in the LT group comparing to the LS group (15.9% vs 1.2%, respectively, p = 0.002). Wound infection was the most encountered postoperative complication among the LT patients. The mean of postoperative hospital stay was significantly longer in the LT group (5.42 ± 3.3) comparing to the LS group (3.07 ± 1.0) (p < 0.001). Most of the patients

Table 1. Comparison between patients concerning to their surgical approach

Variables (mean ± SD)		Laparotomy	Laparoscopy	p
Age [years]		58.94 ± 11.4	58.18 ± 8.9	0.652
Body Mass Index [kg/m^2]		44.37 ± 4.8	46.13 ± 5.3	0.042
Operation time [minute]		96.0 ± 32.6	89.5 ± 41.1	0.303
Postoperative hospitalization time [day]		5.42 ± 3.3	3.07 ± 1.0	< 0.001
		N (%)	N (%)	
Comorbidities	No	25 (39.7)	26 (32.1)	0.345
	Yes	38 (60.3)	55 (67.9)	
Intraoperative complications	No	63 (97.0)	78 (96.3)	0.915
	Yes	2 (3.0)	2 (3.7)	
Postoperative complications	No	53 (84,1)	80 (98.8)	0.002
	Yes	10 (15.9)	1 (1.2)	
LND	No	39 (60.0)	67 (82.7)	0.007
	Pelvic	8 (12.3)	6 (7.4)	
	Pelvic + Paraaortic	18 (27.7)	8 (9.9)	
Histopathology	Endometrioid	50 (76.9)	69 (85.2)	0.201
	Non-endometrioid	15 (23.1)	12 (14.8)	
Grade	1	27 (48.2)	52 (65.8)	0.118
	2	25 (44.6)	24 (30.4)	
	3	4 (7.1)	3 (3.8)	
Stage	Uterus confined (stage 1–2)	51 (78.5)	76 (93.8)	0.006
	Extrauterine spread (stage 3–4)	14 (21.5)	5 (6.2)	
MI	< 50	39 (60.9)	52 (70.3)	0.249
	≥ 50	25 (39.1)	22 (29.7)	
LVSI	No	33 (51.6)	61 (76.3)	0.004
	Yes	31 (48.4)	19 (23.8)	
LN involvement	Negative	56 (88.9)	68 (98.6)	0.020
	Positive	7 (11.1)	1 (1.4)	
Adjuvant treatments	No	31 (48.4)	57 (71.3)	0.005
	Yes	33 (51.6)	23 (28.8)	

LT — laparotomy; LS — laparoscopy; SD — Standard deviation; LND — lymph node dissection; MI — myometrial invasion; LVSI — lymphovascular space invasion

in both groups had endometrioid histology (76.9% of the LT and 85.2% of the LS, p = 0.201). Grade distribution was similar between groups (p = 0.118). Rate of advanced stage (3–4) disease was 21.5% and 6.2% in the LT and LS groups, respectively (p = 0.006). MI was ≥ 1/2 in 25 (39.1%) and 22 (29.7%) cases in the LT and LS groups respectively, without significant differences (p = 0.249). LVSI was observed in 48.4% of the LT group and 23.8% of the LS group (p = 0.004). Lymph node (LN) was involved in 7 (11.1%) cases of the LT group and 1 case (1.4%) of the LS group (p = 0.020). Adjuvant treatments were administered to 33 (51.6%) and 23 (28.8%) patients of the LT and LS groups, respectively (p = 0.005).

Comparison between patients with respect to adding lymphadenectomy or not to the surgical procedure is summarized in Table 2. The mean age of the non-lymphadenectomy and lymphadenectomy groups were 57.88 ± 10.4 and 60.26 ± 8.8, respectively without significant differences (p = 0.210). Comorbidity rates were also identical between the groups (62.5% vs 70% respectively, p = 0.399). The average BMI was 45.87 ± 5.3 in the non-lymphadenectomy group and 43.96 ± 4.5 in the lymphadenectomy group (p = 0.034). While, laparotomy was the surgical method of 36.8% and 65% of the non-lymphadenectomy and lymphadenectomy groups, respectively, laparoscopy was the surgical route for the rest cases (p = 0.002). The mean operation time was significantly lower in the non-lymphadenectomy group compared to the lymphadenectomy group (79.9 ± 27.3 vs 125.1 ± 41.3, respectively, p < 0.001). Both intraoperative (2.8% vs 5%, p = 0.040) and postoperative (2.8% vs 21%, p = 0.001) complications were significantly lower in the non-lymphadenectomy group compared with the lymphadenectomy group. The average of postoperative hospitalization time was also significantly lower in the non-lymphadenectomy group compared to the lymphadenectomy

Table 2. Comparison between patients according to lymphadenectomy

Variables (mean ± SD)		No lymphadenectomy	Lymphadenectomy	p
Age [years]		57.88 ± 10.4	60.26 ± 8.8	0.210
Body Mass Index [kg/m^2]		45.87 ± 5.3	43.96 ± 4.5	0.034
Operation time [minute]		79.9 ± 27.3	125.1 ± 41.3	< 0.001
Postoperative hospitalization time [day]		3.37 ± 1.1	6.1 ± 4.0	< 0.001
		N (%)	N (%)	
Comorbidities	No	39 (37.5)	12 (30.0)	0.399
	Yes	65 (62.5)	28 (70.0)	
Treatment	Laparotomy	39 (36.8)	26 (65.0)	0.002
	Laparoscopy	67 (63.2)	14 (35.0)	
Intraoperative complications	No	103 (97.2)	38 (95.0)	0.040
	Yes	3 (2.8)	2 (5.0)	
Postoperative complications	No	103 (97.2)	30 (79.0)	0.001
	Yes	3 (2.8)	8 (21.0)	
Histopathology	Endometrioid	88 (83.0)	31 (77.5)	0.444
	Non-endometrioid	18 (17.0)	9 (22.5)	
Grade	1	66 (65.3)	13 (38.2)	0.018
	2	30 (29.7)	19 (55.9)	
	3	5 (5.0)	2 (5.9)	
Stage	Uterus confined (stage 1–2)	97 (91.5)	30 (75.0)	0.008
	Extrauterine spread (stage 3–4)	9 (8.5)	10 (25.0)	
MI	< 50	72 (72.0)	19 (50.0)	0.015
	≥ 50	28 (28.0)	19 (50.0)	
LVSI	No	76 (73.1)	18 (45.0)	0.001
	Yes	28 (26.9)	22 (55.0)	
LN involvement	Negative		32 (82.1)	
	Positive		7 (17.9)	
Adjuvant treatments	No	73 (70.2)	15 (37.5)	< 0.001
	Yes	31 (29.8)	25 (62.5)	

SD — Standard deviation; MI — myometrial invasion; LVSI — lymphovascular space invasion; LN — lymph node

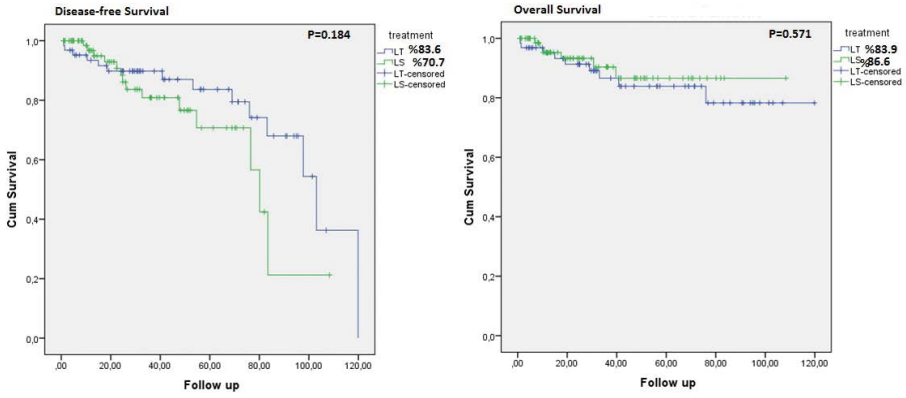

Figure 1. DFS and OS of the LS and LT groups

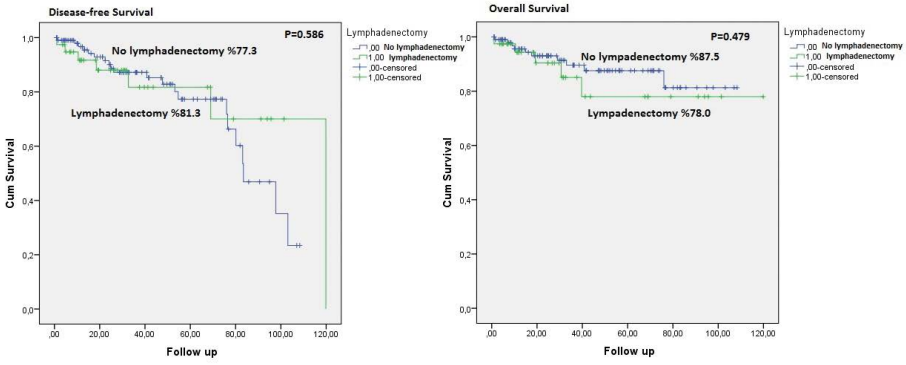

Figure 2. DFS and OS of the lymphadenectomy and non-lymphadenectomy groups

group (3.37 ± 1.1 vs 6.1 ± 4.0, respectively, p < 0.001). Endometrioid type endometrial cancer consisted 83% of the non-lymphadenectomy patients and 77.5% of the lymphadenectomy group. With respect to the histopathological type, no significant differences were determined between groups (p = 0.444). Whereas, the majority of cases in the non-lymphadenectomy group was grade 1 (65.3%) and significant proportion of the lymphadenectomy group was grade 2 (55.9%), both groups had similar rates of grade 3 cases (5% and 5.9%, respectively). Most of the cases in both groups were confined to the uterus, only 8.5% and 25% of the non-lymphadenectomy and lymphadenectomy groups, respectively, were determined to have extrauterine disease (p = 0.008). Myometrium was invaded ≥ 1/2 in 28% and 50% of the non-lymphadenectomy and lymphadenectomy groups, respectively (p = 0.015). The ratio of lymphovascular invasion was 26.9% in the patients who did not undergo a lymphadenectomy and 55% in patients who underwent lymphadenectomy (p = 0.001). Among patients who underwent a lymphadenectomy, seven (17.9%) cases harbored positive LNs. Adjuvant treatments were applied in 31 (29.8%) and 25 (62.5%) patients of the non-lymphadenectomy and lymphadenectomy group, respectively (p < 0.001).

The mean of the follow-up period was 51 months. Five-years disease-free survival (DFS) and overall survival (OS) rates of the LT and LS groups were 83.6% vs 70.7% (p = 0.184), and 83.9% vs 86.6% (p = 0.571), respectively (Fig. 1). Five-year DFS and OS rates of the non-lymphadenectomy and lymphadenectomy groups were 77.3% vs 81.3% (p = 0.586), and 87.5% vs 78% (p = 0.479), respectively (Fig. 2). A multivariate analysis was performed, and only age (HR: 1.105, 1.034–1.182) with histology (HR: 3.262, 1.017–10.463) for DFS and stage (HR: 7.182, 1.310–39.393) for OS were determined as independent prognostic factors (Tab. 3).

DISCUSSION

The morbidly obese patients are known for their high risk for endometrial cancer. However, endometrial cancer tends to have low grade, early stage, endometrioid type and good prognosis, in this special population [2, 3, 12]. Nevertheless, treatment of these patients encompasses high risk of many morbidities such as; hemodynamic instability, tension pneumothorax, wound infection, healing, and thrombosis [13]. Hence, operating, postoperative management and dealing with possible complications of these cases are serious dilemmas. Furthermore, the increased healthcare

Table 3. Multivariate analysis of the patients' DFS and OS

Covariates	HR (95.0% CI)	
	DFS	OS
Age	1.105 (1.034–1.182)	1.045 (0.966–1.131)
Comorbidities	0.832 (0.306–2.258)	3.585 (0.524–24.513)
Surgical route	1.686 (0.692–4.111)	1.289 (0.326–5.102)
Stage	0.631 (0.070–5.726)	7.182 (1.310–39.393)
Grade	1.616 (0.681–3.837)	1.534 (0.497–4.735)
Histology	3.262 (1.017–10.463)	1.843 (0.416–8.156)
MI	1.889 (0.296–12.079)	1.607 (0.195–13.256)
LVSI	0.298 (0.080–1.103)	0.191 (0.030–1.202)
LN involvement	8.285 (0.704–97.467)	1.143 (0.400–3.262)
Adjuvant treatments	1.115 (0.175–7.097)	2.655 (0.309–22.792)

DFS — disease-free survival; OS — overall survival; HR — hazard ratio; CI — confidence interval; MI — myometrial invasion; LVS — lymphovascular space invasion; LN — lymph node dissection

utilization in these cases leads to high costs. Therefore, optimal treatment to minimize the morbidity of these patients is essential. Herein, two morbidity-reducing strategies for this population (laparoscopic surgery and omitting lymphadenectomy) were suggested and tested in this study. No significant difference was observed in term of both DFS and OS between LT and LS groups, in the current study. Similarly, both of DFS and OS did not significantly differ whether lymphadenectomy was performed or not.

Laparoscopic surgery is recommended as –level of evidence: I, strength of recommendation: A- for the management of low and intermediate risk endometrial cancer according to the European guidelines [14]. In addition, several studies have demonstrated the efficacy and oncological safety of laparoscopy in the high-risk endometrial cancer [8, 15]. Nevertheless, there are no randomized prospective trials nor sufficient researches on the oncological safety of the surgical approach for endometrial cancer that exclusively concentrates on the morbidly obese patients [16, 17]. Lower blood loss, less pain, lower postoperative complications, shorter hospital stay and recovery, and less cost are well-known advantages of laparoscopic surgery comparing to the laparotomy [6]. Cheng et al. [16] postoperative complications, length of hospital stay, blood loss and need of transfusion were significantly lower in the morbidly obese endometrial cancer patients who were treated with LS comparing to those with open surgery. Mendivil and colleagues, [13] also reported a shorter postoperative hospitalization period and less blood loss with minimally invasive surgery (MIS) relative to the open surgery in the morbidly obese endometrial cancer cases. Similarly, comparing to laparotomy MIS was linked to less intraoperative and postoperative complications including: blood transfusions, mechanical ventilation, urinary and gastrointestinal injuries, wound infection, thromboembolism, and lymphedema for the morbidly obese endometrial cancer population in a comparative analysis by Chan et al. [18] Compatible with these results, LS was associated with significantly lower postoperative complications and shorter postoperative hospitalization time in the current study. Beside the advantages of the short-term surgical results, long-term oncologic outcomes were shown to be comparable between the LS and LT arms, in the present study.

The lymphadenectomy in endometrial cancer is beneficial for accurate staging, prognosis prediction and more precise adjuvant treatments selection [10]. However, its therapeutic utility remains controversial since it has never been proven by the prospective studies [9, 10]. Furthermore, a benefit of the lymphadenectomy in term of disease-free survival (HR: 1.23, 95% GA: 0.96–1.58) or overall survival (HR: 1.07, 95% GA: 0.81–1.43) was not reported in the last 2017 updated Cochrane review on the role of lymphadenectomy in endometrial cancer [9]. On the other hand, surgery related systemic morbidity (RR: 3.72, 95% GA: 1.04–13.27) and formation of lymphocyst/lymphedema (RR: 8.39, 95% GA: 4.06–17.33) were clearly increased in the lymphadenectomy patients comparing to the non-lymphadenectomy [9]. Even a lymphadenectomy in the morbidly obese endometrial cancer is an applicable procedure in high-volume qualified centers; it still harbors (particularly para-aortic part) serious surgical difficulties and morbidities [3, 17]. Therefore, simply we argued that if there is no survival benefit of lymphadenectomy procedures in this risky population, it is reasonable to neglect lymphadenectomies in these patients. In our study, patients who underwent a lymphadenectomy were compared with those who did not, and no significant difference was obtained between groups in terms of both DFS and OS. However, it should be noted that the insufficient number of intermediate/high risk or type two cases in our study had restricted us to perform a sub-analysis concerning these patients.

Through this investigation, laparoscopic surgery and omitting lymphadenectomy in the morbidly obese endometrial cancer were found effective as morbidity-reducing strategies without harming the survival outcome. In addition, remarkable reduction in the total cost could be achieved with these strategies, due to the decreased procedures and morbidities. However, this argument needs to be supported by a cost-effectiveness analysis, which was not performed in the current study. Withal, the retrospective nature and its potential biases were the main weaknesses of our study. On the contrary, restricting the study population to morbidly obese women (BMI of 40 kg/m^2 or more), operating and evaluation of all cases by the same team of gynecological oncologists and gynecological pathologists from single

academic center, and the long follow-up period were the main strengths.

In conclusion, parallel to our study results, laparoscopy should be preferred, and lymphadenectomy could be omitted in the morbidly obese endometrial cancer patients.

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