

Could the Long-Term Oncological Safety of Laparoscopic Surgery in Low Risk Endometrial Cancer be also valid for the High Intermediate and High-Risk Patients? A Multi-center Turkish Gynecologic Oncology Group Study Conducted with 2745 Endometrial Cancer Cases. (TRSGO-End-001)

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Abstract

Could the Long-Term Oncological Safety of Laparoscopic Surgery in Low Risk Endometrial Cancer be also valid for the High Intermediate and High-Risk Patients? A Multi-center Turkish Gynecologic Oncology Group Study Conducted with 2745 Endometrial Cancer Cases. (TRSGO-End-001)

Aim: to compare the long-term oncological outcomes of laparotomy and laparoscopic surgeries in endometrial cancer under the light of 2016 ESMO-ESGO-ESTRO risk classification system with particular focus on the high intermediate and high-risk categories.

Methods: Using multicentric database between January 2005 and January 2016, disease-free and overall survivals of 2745 endometrial cancer cases were compared according to the surgery route, laparotomy vs laparoscopy. The high intermediate and high-risk patients were defined with respect to the 2016 ESMO-ESGO-ESTRO risk classification system and they were analyzed with respect to difference in survival rates.

Results: Of the 2745 patients 1743 (63.5%) were operated by laparotomy, and the remaining were operated with laparoscopy. The total numbers of high intermediate and high-risk endometrial cancer cases were 734 (45%) patients in the LT group and 307 (30.7%) patients in the LS group. Disease-free and overall survivals were not statistically different when compared between laparoscopy and laparotomy groups in terms of low, intermediate, high intermediate and high-risk endometrial cancer.

Conclusions: Regardless of the endometrial cancer risk category, long-term oncological outcomes of laparoscopic approach were found to be comparable to those treated with laparotomy. Our results are encouraging to consider laparoscopic surgery for high intermediate and high-risk endometrial cancer cases.

Introduction

Endometrial cancer is the most common gynecological cancer among women in the developed world [1]. Surgery, including total hysterectomy (TH), bilateral salpingo-oophorectomy (BSO) with or without lymphadenectomy and omentectomy is the mainstay of endometrial cancer treatment [1-3]. Postoperative adjuvant treatments are decided according to the risk category of the patients. Recently, ESMO-ESGO-ESTRO classified endometrial cancer to low, intermediate, high intermediate and high-risk categories in order to tailor the adjuvant therapy after surgery [4]. Surgery of the endometrial cancer can be performed by either laparotomy (LT) or laparoscopic approach. In 1990s, the laparoscopic surgery of the gynecologic malignancies was pioneered by the studies of Dargent et al. [5] and Querleu et al. [6] from France and Childers et al. [7] and Spirtos et al. [8] from the United States [9]. Nevertheless, since the publication of the LACC study, in which laparoscopic approach was found to be associated with poor oncological outcomes in cervical cancer, concerns regarding laparoscopy in gynecological malignancies have been raised [10]. On the other side, the safety of laparoscopy (LS) in endometrial cancer has been demonstrated previously in the randomized GOG lap2 and LACE studies [11, 12]. Numerous studies including the abovementioned landmark studies have found comparable safety and oncological outcomes between laparotomy and laparoscopic modalities in low-risk endometrial cancer [3, 11-17]. However, such studies in the high-risk patients are scarce [18-22]. Therefore, it is necessary to increase the studies investigating the oncological safety of laparoscopic surgery in endometrial cancer, particularly those encompassing the high-risk category. Hence, as the Turkish Society of Gynecologic Oncology (TRSGO), we designed this multi-centric retrospective study to compare the oncologic outcomes of the laparotomy and laparoscopic surgeries in endometrial cancer focusing on the high intermediate and high-risk categories.

Materials And Methods

Data were collected from 12 TRSGO centers between January 2005 and January 2016, and it was entered by the investigators of each center and controlled by the biostatistician (GS). Approval for this study was obtained from the Research Ethics Committee at Çukurova University Faculty of Medicine. A written informed consent for the use of research and educational purpose was attained from all patients. All participating centers are known for their long-standing experience in laparoscopic surgery for endometrial cancer. Expert gynecologic pathologists in each of these centers evaluated the pathological materials.

A data sheet of variables related to demographic, clinical, surgical, pathological, follow-up and survival characteristics was recorded from the databases of each center. Only cases with comprehensive data were included, and finally 2745 endometrial cancer patients were selected for analysis. Age, body mass index (BMI), parity, comorbidities, and surgical variables including; type of surgery, conversion rate of laparoscopy to laparotomy, duration of surgery, fall in hemoglobin level, postoperative stay in the hospital (day), intraoperative and postoperative complications, stage, grade, histopathological type, myometrial invasion (MI: as <50% and \geq 50%), lymph node (LN) involvement, lymphovascular space invasion (LVSI), and number of harvested lymph nodes were recorded. Adjuvant therapy modalities, follow-up data and survival outcomes were also gathered.

All patients' diagnoses were made upon a preoperative endometrial biopsy. All patients were preoperatively assessed with transvaginal ultrasonography and chest x-ray. Based on the clinician' decision, further preoperative screenings such as abdomen and thorax computed tomography or magnetic resonance imaging were administered particularly when there was a suspicion of extra-uterine disease or >50% MI, and in case of grade 3 or type 2 carcinomas. As this was a retrospective study, no standard preoperative selection criteria were taken into account for laparoscopic surgery. Unless in case of extrauterine disease existence on the imaging methods, LT was preferred. Similarly, no standardization was set among the institutions in this study regarding patients' discharge decision. Staging was adapted according to the International Federation of Gynecology and Obstetrics 2009 surgical staging classification. Either in LT arm or in LS arm, all cases underwent TH and BSO. Uterine manipulator was used for all laparoscopically- operated cases. Intraoperative frozen section was applied for all included cases, and a decision to pursue or not to pursue on lymphadenectomy was taken based on its result. Lymphadenectomy was not performed in patients with, stage 1a, grade 1-2, <2 cm tumors (low-risk factors). In the presence of any of the following circumstances; endometrioid adenocarcinoma grade 3, tumor diameter >2cm, \geq 50% MI, stage >1a or non-endometrioid histologies, pelvic \pm para-aortic lymphadenectomy (\pm omentectomy) was considered compatible with the Mayo clinic protocol [23]. Adjuvant therapies (brachytherapy, external beam radiotherapy and/or chemotherapy) were kept in view for patients with \geq intermediate risk factors.

A sub-analysis of survival was made between laparoscopy and laparotomy groups according to the pathologic prognostic factors including stage, grade, MI, LVSI, LN status, histopathological type and the recent ESMO- ESGO- ESTRO risk classification system for endometrial cancer [4]. In the ESMO- ESGO- ESTRO classification, patients with Stage I endometrioid, grade 1–2, <50% myometrial invasion, LVSI negative were described as low risk and patients with stage 1 endometrioid, grade 1-2, \geq 50% MI, and LVSI negative were defined as intermediate risk. High intermediate risk category was identified as patients with stage I endometrioid, grade 3, <50% MI, regardless of LVSI status or with stage I endometrioid, grade 1–2, LVSI unequivocally positive, regardless of MI. High-risk category was decided to include patients with; 1- Stage I endometrioid, grade 3, \geq 50% MI, regardless of LVSI status, 2- Stage II endometrioid, 3- Stage III endometrioid, no residual disease, and 4- Non-endometrioid histologies (serous, clear-cell, undifferentiated carcinoma, carcinosarcoma).

Data were analyzed using the SPSS software version 20.0 (IBM, Armonk, NY, USA). The variables were shown as mean \pm standard deviation, median (minimum-maximum) or n (%). The variables were analyzed firstly to detect whether or not they were normally distributed by visual (histograms, probability plots) and analytical methods (Shapiro-Wilk's test). Independent T test and Chi-square test were used for comparisons between the groups. The follow-up period was accepted as the time between patient's primary surgery and the last contact. Disease-free survival was designated as the duration (months) from surgery to recurrence. Overall survival was described as the period in months between the diagnosis and the death or last follow-up. The effect of clinico-pathological variables, ESMO- ESGO- ESTRO risk groups and type of surgery on disease-free and overall survival rates of the patients were analyzed using Kaplan-Meier method. Log-rank test was used to calculate the differences among the survival curves. The significance of multiple variables was assessed using the Cox proportional hazard model without violating the proportional hazards assumption.

Results

Overall, 2745 patients with endometrial cancer were enrolled in this study. Of them, 1743 (63.5%) cases were operated by LT, and 1002 (36.5%) were operated with conventional LS. Demographic and surgical characteristics of the groups are summarized in Table 1. Mean age of the laparotomy and laparoscopy groups was 59.3 ± 10.7 and 57.5 ± 10.1 , respectively. Patients < 50 years were 16.5% and 18.8% in the LT and LS groups, respectively. Mean of BMI was significantly higher in the LS arm (38.8 ± 4.79)

than the LT (32.1 ± 5.9). Only TH + BSO was performed for 510 (29%) patients in the LT and for 329 (32.9%) patients in the LS groups. Staging procedures (retroperitoneal lymphadenectomy \pm omentectomy) were added to TH-BSO in the remaining cases of both groups. Mean resected LN number in patients who underwent pelvic lymphadenectomy was 16.3 in the LT vs 20.9 in the LS groups ($p < 0.001$); and 35.5 in the LT vs 40.9 in the LS groups for patients who underwent pelvic plus para-aortic lymphadenectomy ($p < 0.001$). Perioperative and postoperative complications were significantly lower in the LS group compared to the LT group (3% vs 4.8%; $p < 0.001$ and 4.3% vs 7.6%; $p < 0.001$, respectively). However, peri- and postoperative complications related to the urinary and intestinal injuries were noticed more frequently in the LS group. Operation time was significantly lower in the LT group, while estimated blood loss, drop in hemoglobin and postoperative hospital stay were significantly lower in the LS group. Conversion from LS to LT was required in 27 (3%) cases.

Table 1
Demographic and surgical characteristics of the patients.

Variables	LT		LS		P	
	(Mean)/N	SD/(%)	(Mean)/N	SD/(%)		
Age (years)	(59,3)	10,7	(57,5)	10,1	< 0.05	
Parity	(3,1)	2,3	(2,7)	1,9	< 0.05	
BMI (kg/m ²)	(32,1)	5,9	(38,8)	4,7	< 0.05	
BMI group	< 30	449	(33,2)	331	(36,8)	< 0.001
	30–35	560	(41,5)	258	(28,7)	
	35–40	184	(13,6)	171	(19,0)	
	> 40	158	(11,7)	139	(15,5)	
Comorbidities	No	565	(34,5)	480	(48,0)	< 0.001
	Yes	1072	(65,5)	521	(52,0)	
Menopausal status	Premenopausal	307	(35,2)	248	(32,8)	< 0.001
	Postmenopausal	566	(64,8)	507	(67,2)	
Operation type	TH + BSO	510	(29)	329	(32,9)	< 0.001
	TH + BSO + BPLND ± OMENTECTOMY	386	(21,3)	440	(44,0)	
	TH + BSO + BPPALND ± OMENTECTOMY	847	(49,7)	233	(14,2)	
Perioperative complications	No	1255	(95,2)	736	(97,0)	< 0.001
	Bleeding	54	(4,1)	9	(1,2)	
	Urinary system injury	4	(,3)	8	(1,1)	
	Intestinal injury	2	(,2)	4	(,5)	
	Others	3	(,2)	2	(,3)	
Postoperative complications	No	1221	(92,4)	727	(95,7)	< 0.001
	Infection	88	(6,7)	15	(2,0)	
	Urinary system injury	0	(,0)	1	(,1)	
	Intestinal injury	1	(,1)	2	(,3)	
	Others	12	(,9)	15	(2,0)	
Operation time (minute)	(119,3)	42,8	(142,2)	66,4	< 0.05	
Estimated blood loss (ml)	(243,3)	167,2	(114,6)	81,7	< 0.05	

LT: laparotomy, LS: laparoscopy, N: count, SD: Standard deviation, BMI: body mass index, TH + BSO: total hysterectomy bilateral salpingo-oophorectomy, BPLND: bilateral pelvic lymph node dissection, BPPALND: bilateral pelvic para-aortic lymph node dissection.

Variables	LT		LS		P
	(Mean)/N	SD/(%)	(Mean)/N	SD/(%)	
Drop in hemoglobin (gr/dl)	(1,6)	1,1	(1,4)	1,1	< 0.05
Conversion of laparoscopy to laparotomy			27	(3,0)	
Postoperative hospitalization (day)	(5.4)	3.3	(3.3)	1.7	< 0.05

LT: laparotomy, LS: laparoscopy, N: count, SD: Standard deviation, BMI: body mass index, TH+ BSO: total hysterectomy bilateral salpingo-oophorectomy, BPLND: bilateral pelvic lymph node dissection, BPPALND: bilateral pelvic para-aortic lymph node dissection.

Histopathological results of the LT and LS groups are documented in Table 2. Stage 3–4 cases were noted in 23.9% of the LT arm vs 11.3% of the LS arm. The grade 3 cases were determined as 12.7% of the LT group and 7.8% of the LS group. Ratios of grade 3 and advanced stage were significantly higher in the LT group than the LS group. Type 2 (non-endometrioid) histologies were reported in 20.9% and 12.1% of the LT and LS groups, respectively ($p < 0.001$). More than 50% MI was observed in 38.2% and 25.3% of LT and LS groups, respectively ($p < 0.001$). Cervix was invaded in 16.5% and 4.6% of the LT and LS arms, respectively ($p < 0.001$). LVSI was found in 36% of the LT and 22.7% of the LS arm ($p < 0.001$). Removed lymph nodes' count was 1–20, 21–40, >40 in 26.3%, 26.1%, 18.3% and 26.7%, 25.9%, 14.6% of the LT and LS groups, respectively. Metastatic LN ratio was 13.2% in the LT group vs 7.1% in the LS group ($p < 0.001$). Isolated para-aortic LN metastases were recorded in 2.3% and 0.7% of LT and LS cases, respectively.

Table 2
Histopathological features of the groups.

Variables		LT		LS		P
		(Mean)/N	SD/(%)	(Mean)/N	SD/(%)	
Stage	1a	825	(47,3)	664	(66,2)	< 0.001
	1b	372	(21,4)	195	(19,4)	
	2	130	(7,4)	31	(3,1)	
	3a + 3b + 3c + 4	414	(23,9)	114	(11,3)	
Histopathology	Endometrioid	1280	(79,1)	875	(87,9)	< 0.001
	Serous	113	(7,0)	38	(3,8)	
	Clear	33	(2,0)	2	(,2)	
	Mixed	128	(7,9)	67	(6,7)	
	Carcinosarcoma	65	(4,0)	14	(1,4)	
Histologic type	Type1	1280	(79,1)	875	(87,9)	< 0.001
	Type2	339	(20,9)	121	(12,1)	
Grade	1	715	(43,9)	537	(54,7)	< 0.001
	2	524	(32,2)	342	(34,9)	
	3	389	(23,9)	102	(10,4)	
Myometrial invasion	No	324	(20,1)	239	(24,0)	< 0.001
	<%50	670	(41,6)	506	(50,8)	
	≥%50	615	(38,2)	252	(25,3)	
Cervical invasion	No	1065	(83,5)	711	(95,4)	< 0.001
	Yes	211	(16,5)	34	(4,6)	
LVSI	No	988	(64,0)	749	(77,3)	< 0.001
	Yes	555	(36,0)	220	(22,7)	
LN count	No lymphadenectomy	510	(29,3)	329	(32,7)	0.037
	1–20	460	(26,3)	267	(26,7)	
	21–40	453	(26,1)	259	(25,9)	
	> 40	320	(18,3)	147	(14,6)	
Metastatic LN	No	1512	(86,8)	931	(93,0)	< 0.001
	Pelvic	103	(5,9)	46	(4,6)	
	Paraortic	41	(2,3)	8	(0,7)	
	Pelvic + paraortic	87	(5,0)	17	(1,7)	

LT: laparotomy, LS: laparoscopy, N: count, SD: Standard deviation, LVSI: lymphovascular space invasion; LN: lymph node.

The patients were categorized according to the 2016 ESMO-ESGO-ESTRO risk classification system. There was 1226 (46.6%), 363 (13.8%), 389 (14.8%), and 652 (24.8%) patients in the low, intermediate, high intermediate and high-risk categories,

respectively. There was no statistically significant difference between LS and LT groups according to the subcategories of 2016 ESMO-ESGO-ESTRO risk classification system, in terms of disease-free survival and overall survival (Table 3, Fig. 1).

Table 3
Comparison of DFS and OS rates between groups with respect to the ESMO-ESGO-ESTRO risk classification system.

Risk group	DFS					OS				
	LT		LS		P	LT		LS		P
	Total n /censored%	Mean	Total n /censored%	Mean		Total n/ censored%	Mean	Total n/ censored%	Mean	
Low	668/96,4	121,6	564/98,2	120,7	0,274	668/96,9	122,8	564/98,4	121,2	0,320
Intermediate	234/84,2	89,6	130/91,5	105,3	0,180	234/90,6	109,7	130/96,2	110,8	0,129
High-intermediate	271/75,6	80,0	121/75,2	77,7	0,366	271/87,8	101,9	121/94,2	98,2	0,153
High	464/53,2	32,4	186/54,3	23,9	0,106	464/72,8	60,5	186/78,0	58,8	0,231
P		< 0.001		< 0.001			< 0.001		< 0.001	
DFS: Disease-free survival; OS: Overall survival; LT: laparotomy, LS: laparoscopy, n: count.										

Univariate and multivariate analyses are shown in Table 4 and Table 5, respectively. Only age, BMI, LN status, stage, histopathological type and risk group for disease-free survival and age, BMI, cervical invasion, LN status, and risk group for overall survival, were determined as independent prognostic factors on the multivariate analysis. No superiority between surgical groups were found in the multivariate analysis regarding both disease-free survival and overall survival.

Table 4
Univariate analysis of DFS and OS.

Variables			
	Total / Dead n	DFS Mean	OS Mean
Metastatic lymph node			
No	2317/132	98.5	115.9
Yes	283/109	19.5	44.9
P		< 0.001	< 0.001
Stage			
1a	1502/47	120.0	121.3
1b	567/40	74.0	112.5
2	162/31	52.8	82.5
3a + 3b + 3c + 4	394/130	23.4	54.9
p		< 0.001	< 0.001
Grade			
1	1208/49	122.1	129.3
2	798/63	92.3	114.1
3	231/51	24.0	74.6
p		< 0.001	< 0.001
Myometrial invasion			
None	867/153	119.3	121.3
<%50	1176/64	110.4	115.2
≥%50	271/80	51.5	93.3
p		< 0.001	< 0.001
Lymphovascular space invasion			
No	1737/77	110.9	118.4
Yes	775/154	51.8	85.3
p		< 0.001	< 0.001
Histopathological type			
Type1	2155/141	103.9	114.7
Type2	460/103	30.9	62.2
p		< 0.001	< 0.001
DFS: Disease-free survival, OS: Overall survival, n: count.			

Table 5
Multivariate analysis of DFS and OS.

Variables	HR (95,0% CI)			
	DFS	P	OS	P
Age	1,025 (1,012 – 1,038)	< 0.001	1,038 (1,020 – 1,055)	< 0.001
Surgery type	1,055 (0,869-1,282)	0.587	1,338 (0,895-1,999)	0.156
Comorbidities	0,980 (0,762-1,262)	0.877	0,959 (0,669-1,374)	0.820
BMI <30	ref	0.109	1,831 (1,150-2,914)	0.011
30–40	1,281 (0,946-1,735)	0.003	2,133 (1,353-3,361)	0.001
>40	1,386 (1,032 – 1,863)	0.115	0,640 (0,381-1,076)	0.092
MI None	ref	0.975	0,770 (0,427-1,387)	0.383
<%50	0,689 (0,434-1,095)	0.517	0,713 (0,398-1,275)	0.253
>%50	1,008 (0,599-1,698)	0.060	1,982 (1,288-3,050)	0.002
LVSI	0,887 (0,618-1,274)	0.011	3,139 (1,662-5,926)	< 0.001
Cervical invasion	1,374 (0,987-1,912)	0.828	0,576 (0,268-1,241)	0.159
Metastatic LN	1,713 (1,131-2,595)	0.024	1,379 (0,623-3,052)	0.427
Stage 1a	ref	0.006	1,519 (0,685-3,368)	0.304
1b	1,051 (0,669-1,652)	0.146	0,643 (0,392-1,054)	0.280
2	1,847 (1,083 – 3,150)	0.761	0,791 (0,518-1,210)	0.458
3a + 3b + 3c + 4	2,012 (1,226-3,303)	< 0.001	1,462 (0,974-2,196)	0.067
Grade 1	ref	0.082	2,411 (1,076 – 5,405)	0.036
2	0,428 (0,313-0,585)	0.002	2,406 (1,084 – 5,337)	0.019
3	0,827 (0,641-1,067)	< 0.001	3,216 (1,482-6,978)	< 0.001
Histopathological type	1,973 (1,495-2,605)			
Risk group Low	ref			
Intermediate	1,204 (0,935-1,549)			
High-intermediate	2,833 (1,452-5,529)			
High	6,349 (3,569 – 11,294)			

HR: Hazard Ratio; CI: Confidence Interval; DFS: Disease-free survival; OS: Overall survival; BMI: Body mass index; MI: Myometrial invasion; LVSI: Lymphovascular space invasion; LN: Lymph node.

Discussion

This retrospective multicentric study was conducted to evaluate the oncologic safety and efficacy of the conventional laparoscopy in endometrial cancer by stratifying patients with respect to 2016 ESMO- ESGO- ESTRO risk classification system. Lower pain, lower postoperative complications, shorter hospital stay and recovery, and less cost were the well-known advantages of LS compared to LT in numerous studies [2, 19]. These short-term advantages are valid for all patients regardless of their risk category. The similar long-term oncological outcomes of LS in low risk endometrial cancer patients have been demonstrated in

the literature to be comparable to the open surgery [3, 11, 13–15]. The literature is scarce on the issue of high intermediate and high-risk endometrial cancer [18–20]. As a reflection of this reality, the European guidelines' recommendation for the management of low and intermediate risk endometrial cancer with minimally invasive surgery (MIS) was -level of evidence: I, strength of recommendation: A-, whereas it was considered as -level of evidence: IV, strength of recommendation: C- for the management of high-risk endometrial cancer [4]. Consequently, this gap in the literature has inspired us to compare the long-term oncologic outcomes of LS and LT in different risk categories of endometrial cancer. Herein, 2745 endometrial cancer cases were investigated. Of them, 389 (269 LT vs 120 LS) cases were in the high intermediate and 652 (465 LT vs 187 LS) in the high-risk categories. To the best of our knowledge, with the exclusion of the National Cancer Database study on the non-endometrioid uterine cancers including sarcomas by Nieto and colleagues, [24] none of the previous papers had compared such a high number of cases.

Compatible with the literature, short-term advantages of LS such as less blood loss, less perioperative and postoperative complications and shorter hospitalization were observed even with the addition of high intermediate and high-risk patients in our study. Moreover, BMI of the LS cohort was significantly higher from the LT group. Mean BMI (38.8 ± 4.7) of our LS group was higher than many published studies including the landmark study LAP2, which was 28.4 [13, 14, 18]. In addition, more than half of the LS group had at least one comorbidity.

The participating centers in this study are well-known tertiary gynecologic oncology centers in Turkey, which are highly experienced in treating such obese and comorbid patients laparoscopically.

Therefore, even with these patients' characteristics, sufficient number of LNs were harvested and low conversion rates were obtained. In LS arm, the resected LN number in patients who underwent pelvic lymphadenectomy was 20.91 and it was 40.93 in pelvic plus para-aortic lymphadenectomy; which is in accordance with the literature [2, 14, 18, 25–29].

Conversion from laparoscopy to laparotomy was required only in 3% of our series, despite the high volume of high-risk patients. Even though it is clearly less than those in the landmark LAP2 study (25.8%), and comparable to the following literature, which is mainly below 20% and varies between 0% and 25.8% [2, 13, 18, 19]. The conversion rate in our study was in accordance with the Italian type 2 endometrial cancer series (2.1%) [21]. The low rate of conversion in our series can be attributed to the high expertise of the participating centers in gyne-oncological laparoscopy. According to a multi-centric study in high-volume experienced centers, even when high-risk cases were included, a proposed MIS rate of 80% was found to be an achievable benchmark for the management of women with newly diagnosed endometrial cancer [30]. Hence, patients with endometrial cancer including high-risk cases should be referred to centers where this benchmark can be achieved [30].

In our recently published single institution study, there was no difference in disease-free survival and overall survival between LS and LT groups according to the risk categories [31]. This result is coherent with the previous publications on the comparison of LS and LT in high-risk endometrial cancer [18–20, 32]. In their multi-centric retrospective study, Fader et al. [18] compared MIS (n = 191) and LT (n = 192) in type 2 and high grade endometrial cancer, and they stated that high-risk histopathologic types were not a contraindication for MIS when managed by expert laparoscopists. Fader et al. [32] addressed again in their 2016 publication that patients with grade 3 endometrioid and type 2 endometrial cancer had similar survival outcomes regardless of the surgical approach, MIS or LT. Koskas et al. [19] conducted a comparative study between MIS (n = 114) and LT (n = 114) in the high risk endometrial cancer. Authors reported identical oncologic outcomes between groups and concluded that their study provides evidence supporting the use of MIS for high-risk endometrial cancer. Therefore, fear for a poor long-term outcome should not be the reason to refrain from laparoscopic procedure in these patients. [19] Nieto et al. [24] evaluated the impact of MIS in 13392 patients with stage I-III non-endometrioid uterine cancer (including sarcomas) who underwent hysterectomy between 2010 and 2014 using the National Cancer Database. Authors reported that the route of surgery does not appear to impact survival adversely in these patients [24]. In a multicentric retrospective study by Monterossi et al. [21] 283 patients with type 2 endometrial cancer were evaluated among 2 groups (LS; 141, LT; 142) and comparable survival outcomes were reported for both of them in stage I-II cases. Favero et al. [20] assessed the oncologic safety of laparoscopic surgery in type 2 endometrial cancer, and found that both 5-year disease-free and overall survival were better among laparoscopically treated patients. However, this superiority was not statistically significant [20]. Consistent with these studies, both disease-free and overall survival of the high intermediate and high-risk patients were not statistically different between groups in the current study. Comparison between groups according

to the 2016 ESMO-ESGO-ESTRO risk classification system was a distinguishable characteristic of our study from the former studies. A recently published review on the comparison between MIS and open surgery in the high-risk endometrial cancer addressed that MIS showed better perioperative and postoperative outcomes and comparable oncological outcomes than open surgery [22]. However, authors pointed out to the need of prospective randomized studies to approve these results.

Because of the numerous advantages of LS, its importance in the endometrial cancer surgery is raising day by day and its increased frequent use more than LT has been shown in some studies [25, 33]. According to the data from National Cancer Database provided in the study of Nieto and colleagues [24], on the non-endometrioid uterine cancers, > 50% of the hysterectomies were performed with MIS for all of the histologic subtypes (except leiomyosarcoma), by 2014. Authors stated that their findings suggest that MIS has already been widely accepted among clinicians for non-endometrioid uterine cancers, despite the lack of data supporting the procedure's efficacy and safety. They attributed this condition to the widespread acceptance of MIS for endometrioid endometrial cancers, which likely boosted the acceleration of MIS for other histologic subtypes [24]. However limited the studies are, availability of comparable oncologic outcomes with MIS versus to LT in high-risk endometrial cancer are promising and encouraging. The present study has strived to strengthen the assertion that laparoscopy was equal to laparotomy in the high intermediate and high-risk endometrial cancer patients, in terms of long-term oncologic outcomes. Nevertheless, this result should cautiously be interpreted considering the retrospective nature and possible selection biases, which is the main weakness of our study. Heterogeneous histologic subtypes, stages and adjuvant treatments were the other limitations. On the other hand, however, pioneering the concept of ESMO-ESGO-ESTRO risk-based comparative survival analysis and including the large number of patients from academic comprehensive cancer centers with expert gynecologic pathologists and gynecologic oncologists who are familiar with LS in gynecologic oncology are the main strengths of our study.

Conclusion

Regardless of the endometrial cancer risk category, long-term oncologic outcomes of LS is comparable to those treated with LT. Since short-term advantages (less complications, short hospitalization, and rapid recovery) of LS are also valid for the high intermediate and high-risk endometrial cancer, it is reasonable to assume that LS has the ability to accelerate treatment with adjuvant therapies in these patients. Therefore, considering the laparoscopic approach as the preferable choice for high intermediate and high-risk endometrial cancer as well as for the low and intermediate risk categories, will probably be the issue of debate for the foreseeable future. Hence, the need for prospective randomized studies on this subject is indisputable.

Declarations

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Ethical Standards:

Approval for this study was obtained from the Research Ethics Committee at Çukurova University Faculty of Medicine.

Conflicts of interest

The authors declared that they have no conflicts of interest.

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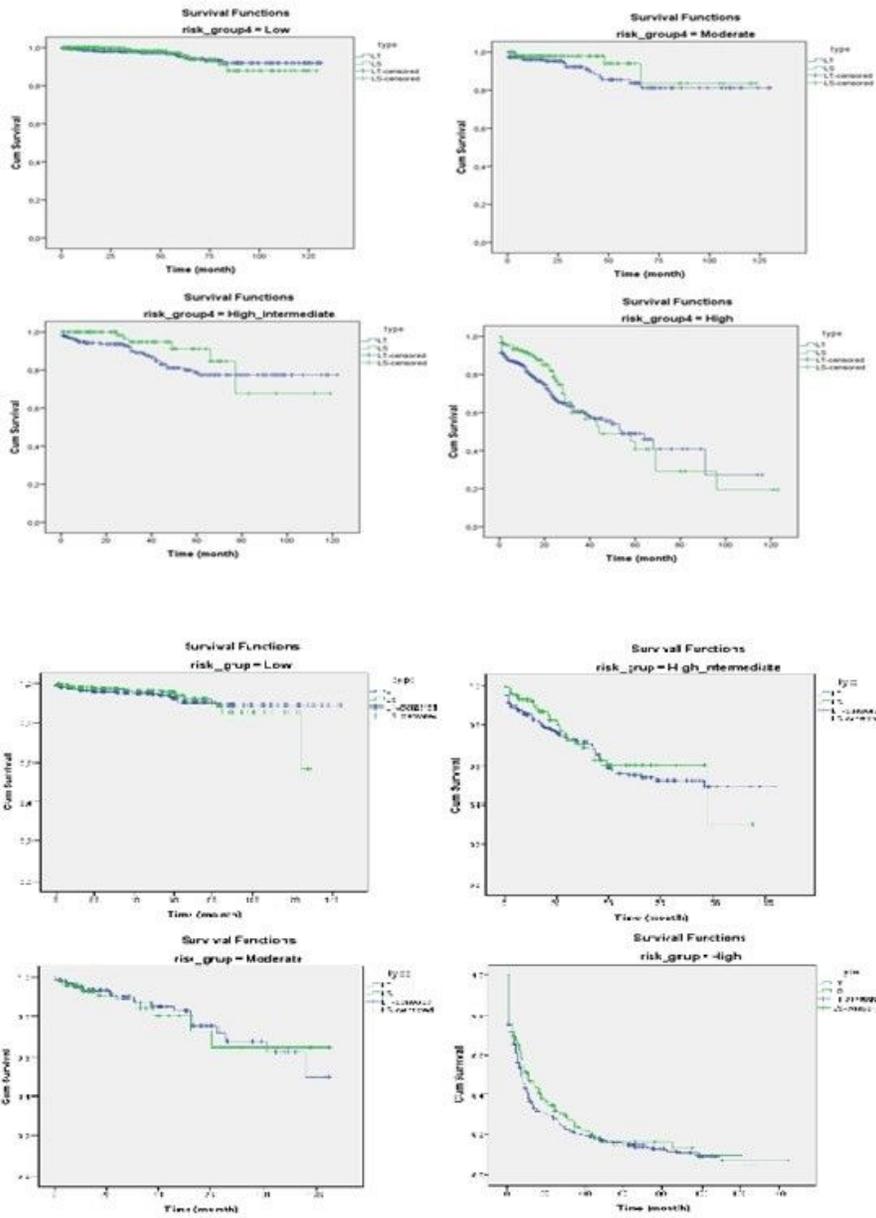
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Figures



OS

DFS

Figure 1

OS and DFS of the groups according to the risk categories.