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ORIGINAL ARTICLE

Short- and long-term outcomes of laparoscopic surgery for elderly patients with clinical stage I endometrial cancer

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Summary

Purpose: *The purpose of this study was to compare the short- and long-term out-comes of laparoscopic surgery in elderly and middle-aged patients with clinical stage I endometrial cancer.*

Methods: *The clinical and follow-up data of 173 patients who were admitted to our hospital due to clinical stage I endometrial cancer and underwent laparoscopic surgery between January 2010 and December 2017 were retrospectively analyzed. The short- and long-term outcomes (including tumor recurrence, disease-free survival rate, and overall survival rate) of the elderly group (≥ 70 years, 69 patients) and the middle-aged group (50-69 years, 104 patients) were compared.*

Results: *In terms of preoperative general data comparison, only the Charlson comorbidity index and American Society of Anesthesiologists (ASA) score were higher in the elderly group than in the middle-aged group; differences in the remaining preoperative data were not statistically significant. Differences in general data, such as the operation time, proportion of patients that underwent lymphadenectomy, intraoperative blood loss, incidence and severity of postoperative 30-day complications, and pathological results were not statistically significant between the two groups. Long-term follow-up results showed that the two groups had similar tumor recurrence rates, as well as similar overall and disease-free survival rates. Multivariate analysis indicated that age was not an inde-pendent predictor for either overall or disease-free survival.*

Conclusions: *The use of laparoscopic surgery for elderly patients with clinical stage I endometrial cancer can achieve short- and long-term outcomes similar to those of middle-aged patients. Advanced age is not a contraindication to laparoscopic surgery.*

Key words: *laparoscopic hysterectomy, elderly, endometrial cancer, minimally inva-sive surgery*

Introduction

Endometrial cancer has become the most common gynecological malignancy in Western and developed countries [1], and in China, its in-cidence is second only to cervical cancer among gynecological malignan-cies [2]. Owing to the typical early-stage symptoms in most patients with endometrial cancer, such as abnormal vaginal bleeding, it is often diag-nosed early in the clinic, when the tumor is confined to the uterus (clini-cal stage I) [3-5]. Because of early diagnosis and treatment, the overall prognosis of clinical stage I endometrial cancer is better than that of cer-vical cancer and ovarian cancer; its 5-year overall survival rate can reach 74% to 95% [3]. For clinical stage I endometrial cancer, the diagnosis and treatment guidelines developed by the International Federation of Gyne-cology and Obstetrics (FIGO) [6], National Comprehensive Cancer Net-work (NCCN) [7], and European Society for Medical Oncology (ESMO) [8] all recommend total hysterectomy with bilateral salpingo-oophorectomy. Additionally, lymphadenectomy may be recom-mended, depending on preoperative auxil-

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iary examination and intraop-erative observation, and adjuvant therapy can be performed, depending on the surgical pathological stage and the presence of high risk factors for tumor recurrence [9-11].

In 2006, half of the newly diagnosed endometrial cancer patients in the United States were over 65 years old [12]. For these elderly endo-metrial cancer patients, the risk of surgery is higher than for non-elderly patients. In 1993, Childers et al first reported the use of laparoscopic sur-gery to treat endometrial cancer [13]. In recent years, randomized clinical trials with large sample sizes and multicenter participation have all sug-gested that, compared with laparotomy, laparoscopic surgery has the ad-vantages of little blood loss, rapid post-operative recovery, comparable or reduced compli-cations, and similar long-term outcomes [14-18]. Laparo-scopic surgery has been gradually applied to the treatment of elderly pa-tients with endometrial cancer [19-25]; however, there is no English lit-erature comparing the laparoscopic surgery treatment outcomes of elderly and middle-aged patients with clinical stage I endometrial cancer. This study is designed to compare the short- and long-term outcomes of laparoscopic surgery in elderly and middle-aged patients with clinical stage I endometrial cancer.

Methods

This retrospective study complied with the tenets of the Declaration of Helsinki and was approved by the local ethics committee. The need for informed consent from all patients was waived because the study was retrospective.

Between January 2009 and December 2017, a total of 173 patients who underwent laparoscopic surgery to treat clinical stage I endometrial cancer and met the following inclusion criteria were included in this study. The inclusion criteria were: (1) primary surgical operation; (2) age ≥ 50 years; and (3) complete clinical and follow-

Table 1. Baseline characteristics in the elderly and middle-aged patients un-dergoing laparoscopic surgery for endometrial cancer

Characteristics	*Elderly group (n=69)*	*Middle-aged group (n=104)*	*p value*
Age (years)	72 (70-76)	51 (50-69)	0.000
BMI (kg/m^2)	24 (22-28)	25 (23-28)	0.128
ASA score			0.019
I	50	90	
II	16	13	
III	3	1	
Charlson Comorbidity Index			0.029
<3	57	97	
≥3	12	7	

BMI: body mass index, ASA: American Society of Anesthesiologists

Table 2. Surgical outcomes in the elderly and middle-aged patients undergoing laparoscopic surgery for endometrial cancer

Outcomes	*Elderly group (n=69)*	*Middle-aged group (n=104)*	*p value*
Lymph node dissection			
Pelvic	34	58	0.402
Para-aortic	11	16	0.921
Surgical time (min)	180 (110-290)	170 (100-270)	0.098
Blood loss (ml)	110 (70-450)	100 (80-390)	0.091
Blood transfusion	1	1	1.000
Conversion to open surgery	4	7	1.000
Patients with intraoperative complication	4	9	0.485
Patients with postoperative 30-day complication	12	14	0.479
Patients with minor complication	11	13	0.521
Patients with major complication	1	1	1.000
Postoperative 30-day death	0	0	-

up data. Patients were ex-cluded if they had: (1) recurrent endometrial cancer; (2) other sites of ma-lignancy; or (3) incomplete clinical and follow-up data. The enrolled patients were then divided into two groups according to the age when laparoscopic surgery was performed: the elderly group (≥ 70 years, 69 patients) and the middle-aged group (50-69 years, 104 patients). All pa-tients underwent preoperative diagnostic dilatation and curettage of the uterus or hysteroscopy, as well as other examinations, such as tumor marker examination, chest and abdominal computed tomography (CT), gynecological ultrasound, and pelvic magnetic resonance imaging (MRI), so as to identify the clinical stage and exclude distant metastases [26-30]. Staging was performed according to the 2009 FIGO staging system for endometrial cancer. Baseline medical comorbidities were compared by calculating the Charlson Comorbidity Index (CCI) for each patient. The CCI is a validated instrument used to estimate the risk of death. This weighted index assigns a score to each patient based on the presence of various diseases, such as coronary artery disease, diabetes, kidney or liver disease, metastatic solid tumors, and acquired immunodeficiency syn-drome (AIDS) [31]. All patients underwent total hysterectomy and bilat-eral salpingo-oophorectomy. Patients were risk-stratified by the Mayo Criteria [32]. Those considered at low risk did not undergo lym-phadenectomy. Low risk was defined as the tumor having grade 1 or 2 endometrioid histology with an invasion depth of 50% or less, and a tu-mor size of 2 cm or less. The remainder of the patients received pelvic and/or paraaortic lymphadenectomy. Laparoscopic surgery was per-formed as previously published [14]. Perioperative management was performed according to the concept of fast-track surgery (FTS) [33].

Postoperative 30-day complications were graded according to the Clavien-Dindo classification system. Major complications were defined as those of grades 3, 4, and 5, while minor complications were defined as those of grades 1 and 2 [34-38]. Operative death was defined as mortality occurring intraoperatively or within postoperative 30-days.

After the patients were discharged from the hospital, follow-ups were conducted in the form of outpatient visits, home visits, and contact with community health

Table 3. The pathological outcomes in the elderly and middle-aged patients un-dergoing laparoscopic surgery for endometrial cancer

Pathological outcomes	*Elderly group (n=69)*	*Middle-aged group (n=104)*	*p value*
FIGO surgical stage			0.837
I	61	93	
II	3	4	
III	5	7	
FIGO differentiation grade determined by surgery			0.945
G1 (Well differentiated)	27	41	0.945
G2 (Moderately differentiated)	23	35	
G3 (Poorly or undifferentiated)	19	28	
Cell type			
Endometrioid	62	94	0.909
Clear cell	2	3	1.000
Sarcoma	2	2	1.000
Serous	3	5	1.000
Myometrial deep invasion (%)			0.701
<50	52	81	
≥50	17	23	
Lymphovascular space invasion			0.873
No	51	78	
Yes	18	26	
No. of lymph nodes harvested	20 (13-28)	22 (14-35)	0.178
Lymph node metastasis			1.000
No	64	97	
Yes	5	7	
Resection margin			1.000
Negative	69	104	
Positive	0	0	

FIGO: International Federation of Gynecology and Obstetrics

service centers. In the first 2 years after surgery, patients were followed up once every 3 months, and then once every 6 months for the subsequent 3 years, followed by once every year for the next 5 years [8]. Clinical assessments, including gynecological examina-tions, were performed at each visit [8]. Routine medical imaging of as-ymptomatic patients was not performed [8]. However, medical imaging was performed to evaluate patients with symptoms that were consistent with cancer recurrence. The last follow-up date was June 30, 2018.

Statistics

Variables were presented as mean and standard deviations for vari-ables following normal distribution and were analyzed by *t*-test. For variables following non-normal distribution, data were expressed as me-dian and range and were compared by Wilcoxon test. Differences of semiquantitative results were analyzed by Mann-Whitney *U* test. Differ-ences of qualitative results were analyzed by chi-square test or Fisher ex-act test. Survival rates were analyzed using the Kaplan-Meier method and differences between two groups were analyzed with the log-rank test. Univariate analyses were performed to identify prognostic variables re-lated to overall and disease-free survival. Univariate variables with prob-ability values less than 0.10 were selected for inclusion in the multivariate Cox proportional hazard regression model. Adjusted hazard ratios (HR) along with the corresponding 95% confidence intervals (CI) were calcu-lated. All statistical tests were two-sided, with the threshold of signifi-cance set at $p<0.05$ level. SPSS 13.0 for Microsoft ® Windows® version (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

The baseline characteristics of the two groups of patients are shown in Table 1. Age, CCI, and American Society of Anesthesiologists (ASA) score of the elderly group were higher than those of the middle-aged group; differences in the remaining general data were not statistically significant.

Details of the short-term outcomes of the two groups of patients are listed in Table 2. The proportion of patients who underwent lym-phadenectomy, operation time, intraoperative blood loss, intraoperative and postoperative transfusion rate, number

Table 4. The follow-up data of the elderly and middle-aged patients undergoing laparoscopic surgery for endometrial cancer

Follow-up data	*Elderly group (n=69)*	*Middle-aged group (n=104)*	*p value*
Tumor recurrence, n	9	13	0.916
Locoregional	2	3	
Distant	5	6	
Mixed	2	4	
Time to first recurrence (median, months)	22 (10-54)	25 (10-50)	0.288
Mortality	9	12	0.767
Died of cancer recurrence	7	10	
Died of non-oncological causes	2	2	

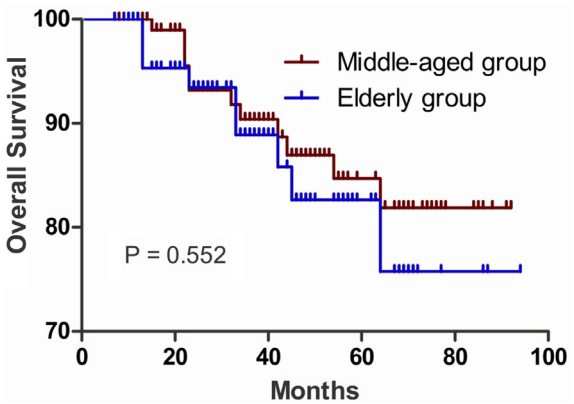

Figure 1. Comparison of overall survival rate between elderly group (age ≥ 70 years old, 69 cases) and the middle-aged group (50 years old ≤ age ≤ 69 years old, 104 cases). There was no significant difference between the two groups (p=0.552).

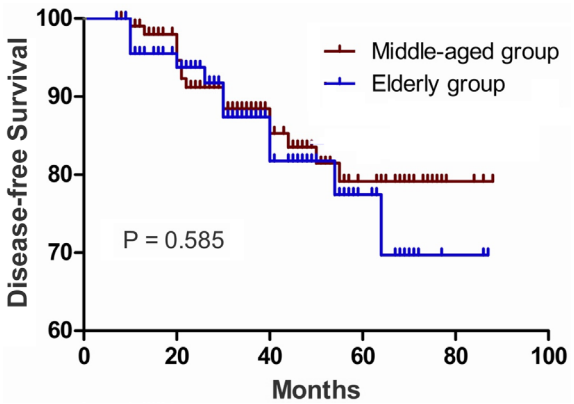

Figure 2. Comparison of disease-free survival rate between elderly group (age ≥ 70 years old, 69 cases) and the middle-aged group (50 years old ≤ age ≤ 69 years old, 104 cases). There was no significant difference between the two groups (p=0.585).

of days for hospital admission, and incidence and severity of complications at 30 days after surgery were not significantly different between the two groups (Table 2). No patient died during surgery in either group. There were no statistically significant differences in the pathological results between the two groups (Table 3).

The median follow-up times for the elderly and the middle-aged groups were 57 and 59 months, respectively, which were not significantly different. During follow-up, 9 patients in the elderly group died, 7 of tu-mor recurrence and 2 of non-neoplastic factors (1 of ischemic stroke and 1 of hemorrhagic stroke). Pairwise comparisons of the tumor recurrence location showed no statistically significant differences between the groups (Table 4).

The 5-year overall survival rates for the elderly and the middle-aged groups were 82% and 85%, respectively, which were not significantly different (Figure 1, p=0.552). Multivariate analysis indicated that stage and pathological grade were independent predictors of overall survival (Table 5). The 5-year disease-free survival rates for the elderly and the middle-aged groups were 76% and 78%, respectively, which were not significantly different (Figure 2, p=0.585). Multivariate analysis indicated that stage and pathological grade were independent predictors of dis-ease-free survival. Age was not an independent predictor for either over-all or disease-free survival (Table 6).

Discussion

Endometrial cancer is highly prevalent in the elderly population, and is mainly treated with surgery [8]. However, the proportion of elderly patients who undergo surgery is lower than that of non-elderly patients, be-cause the risk of surgery in elderly endometrial cancer patients is higher than that in younger patients, and the wounds of laparotomy are relatively large [12]. The use of laparoscopic surgery to treat clinical stage I endo-metrial cancer has the advantages of small wounds and a similar on-cologic outcome to that of laparotomy [14-18]. In recent years, owing to the accumulation of surgical experience, continuous improvement of equipment, and device manufacturers' promotion of laparoscopic surgery, the use of laparoscopic surgery to treat clinical stage I endometrial cancer has been gradually initiated in multiple medical centers [39-41] . Since laparo-

Table 5. Multivariate analysis of overall survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
FIGO stage			0.016
I	1.00		
II-III	2.29	1.45-4.08	
Histological type			0.016
Endometroid histology	1.00		
Non-endometroid histology	2.11	1.77-2.99	
Lymph node metastasis			0.0.33
No	1.00		
Yes	1.79	1.34-3.01	

Table 6. Multivariate analysis of disease-free survival

Regression variables	*Adjusted hazard ratio*	*95%CI*	*p value*
FIGO stage			0.024
I	1.00		
II-III	1.74	1.34-2.74	
Histological grade			0.030
G1-G2	1.00		
G3	1.75	1.44-2.58	
Histological type			0.031
Endometroid histology	1.00		
Non-endometroid histology	2.05	1.58-2.58	

FIGO: International Federation of Gynecology and Obstetrics

scopic surgery has the advantage of being minimally invasive, some researchers have recently successively studied laparoscopic surgery in the treatment of elderly patients with clinical stage I endometrial can-cer [19-25]. However, most of these studies have only focused on the short-term outcomes, and few studies examined long-term outcomes. We examined searchable literature databases, such as MEDLINE, Embase, and Chemical Abstracts, and found no English literature reporting the short- and long-term outcomes of laparoscopic surgery in elderly patients (≥ 70 years) and middle-aged patients (between 50 and 69 years) with clinical stage I endometrial cancer. Therefore, this study is the first to compare the short- and long-term outcomes of laparoscopic surgery in elderly and middle-aged patients with clinical stage I endometrial cancer. The results of the study suggest that, although the risk of surgery is higher in elderly patients than in middle-aged patients (specifically embodied in that elderly patients have a higher CCI and ASA score than middle-aged patients), using laparoscopic surgery to treat elderly patients with clinical stage I endometrial cancer can achieve short- and long-term outcomes similar to those of middle-aged patients. Multivariate analysis showed that age was not an independent predictor of either overall or disease-free survival.

Minimally invasive surgery is the developmental direction of mod-ern surgery. Single-port laparoscopic surgery, as a more minimally invasive surgical technique, has been gradually applied to operations for ma-lignant tumors (for example, use of single-port laparoscopic gastrectomy to treat gastric cancer [42] and use of single-port laparoscopic colectomy to treat colon cancer [43]). Since Fanfani et al first reported the use of gynecological single-port laparoscopic surgery to treat endometrial cancer in 2012 [44], single-port laparoscopic surgery has been gradually applied to the treatment of endometrial cancer. In 2014, a study by Cai et al com-pared single-port and multi-port laparoscopic surgery in early stage en-dometrial cancer, and found that, compared with multi-port laparoscopic surgery, single-port laparoscopic surgery had the advantages of rapid re-covery and good cosmetic effect [45]. Our hospital plans to start gyneco-logical single-port laparoscopic surgery in the near future, and the results will be summarized once relevant experience is accumulated.

The FTS concept is a novel surgical treatment mode that was re-cently proposed. Evidence-based medical studies have shown that it op-timizes and integrates a series of perioperative interventions, so as to minimize surgical stress response, as well as accelerate postoperative re-habilitation and reduce surgical complications. The application of the FTS concept in endometrial cancer surgery can accelerate the patient's postoperative rehabilitation and ensure maximum medical safety [46]. We believe that the application of the FTS concept explains why the rate of postoperative complications and recovery were similar between the eld-erly and the middle-aged groups. With the use of FTS, patients in the eld-erly group could recover faster after surgery and postoperative adjuvant therapy could be performed earlier, which contributed to the long-term outcomes of the two groups being similar.

Conversion to laparotomy is common in laparoscopic surgery. Stud-ies have reported that, when using laparoscopic surgery to treat clinical stage I endometrial cancer, the conversion rate ranges from 0% to 25.8%, which is correlated with the specific cases and the surgeon's surgical ex-perience [47]. In this study, the conversion rates of the elderly group and the non-elderly group were 5.8% and 6.7%, respectively, which were consistent with previous studies [14-18]. This study is the first to demon-strate that, when using laparoscopic surgery to treat clinical stage I en-dometrial cancer patients, the conversion rate of elderly patients was similar to that of non-elderly patients.

In the gynecological oncology community, whether all endometrial cancer patients need to undergo lymphadenectomy or whether pelvic lymphadenectomy or combined pelvic and para-aortic lymphadenectomy should be performed has always been controversial [47]. This study adopted the NCCN guidelines, that is, for low-risk patients, lym-phadenectomy was not performed; for patients with G3 endometroid his-tology, tumor size more than 2 cm, or myometrial invasion greater than 1/2, pelvic lymphadenectomy was performed. For patients with non-endometroid histology, or positive pelvic lymph node, combined pelvic and para-aortic lymphadenectomy was performed. In this study, the proportions of patients who underwent lymphadenectomy were simi-lar in the elderly group and in the middle-aged group. In addition, the postoperative complications were similar in the two groups. These results suggest that laparoscopic lymphadenectomy can be safely performed for elderly endometrial cancer patients.

Previous studies have reported that for elderly patients with clinical stage I endometrial cancer who underwent laparoscopic surgery, the 5-year overall survival rate and disease-free survival rate were 80% to 95% and 70% to 80%, respectively [14-25]. The 5-year overall survival rate and disease-free survival rate of elderly patients reported by

this study were similar to those previously reported, as well as to those of the middle-aged group. In this study, most elderly patients died of tumor re-currence; only a small percentage died of non-neoplastic diseases. These results indicate that, for elderly patients with clinical stage I endometrial cancer, as long as the laparoscopic surgery indications are present, laparoscopic surgery should be actively applied, so as to achieve a similar long-term outcome to that of middle-aged patients. Currently, in China, the expected life span of the elderly population is increasing. Therefore, advanced age is no longer a bottleneck for the radical treatment of pa-tients with endometrial cancer.

The present study has two important limitations. First, the retrospec-tive design is associated with known risks of bias, and a prospective, randomized, controlled trial is needed to confirm that laparoscopic sur-gery is safe and effective in elderly patients with endometrial cancer. Second, we only examined data from a single center with a small sample size, and it is possible that our findings may not be generalizable to other centers and/or patient groups.

Conclusion

In conclusion, the results of this study suggest that the use of laparoscopic surgery in elderly patients with clinical stage I endometrial cancer does not increase postoperative complication incidence and mor-tality and can achieve a long-term outcome similar to that of middle-aged patients.

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Conflict of interests

The authors declare no conflict of interests.

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