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Assessing the Significance of Lymphadenectomy in Older Patients with Stage I Endometrial Cancer: A Single-Center, Retrospective Cohort Study

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Advantages of lymphadenectomy for early stage endometrial cancer remain controversial. Lymphadenectomy had been routinely omitted for patients aged ≥ 70 years at our institute if lymph node metastasis was unsuspected due to an increased risk of peri- and postsurgical complications. Since 2013, with the introduction of minimally invasive surgery and considering the heterogeneous medical conditions, we started performing lymphadenectomy in patients who were considered well-tolerated. We retrospectively investigated our clinical database to assess the effect of lymphadenectomy in older patients with early stage endometrial carcinoma. Patients aged ≥ 70 years, preoperatively diagnosed with stage I endometrial carcinoma, and who underwent lymphadenectomy between 2013 and 2021 at Tohoku University Hospital were included in the lymphadenectomy group (n = 33), whereas patients who underwent surgery without lymphadenectomy before the end of 2012 were included in the no-lymphadenectomy group (n = 49). Clinical parameters and patient outcomes, such as disease-free survival (DFS) and disease-specific survival (DSS), were compared. The median age was significantly higher and fewer patients received adjuvant chemotherapy in the no-lymphadenectomy group. Neither DSS nor DFS differed significantly between the two groups. Five-year-DFS rates were 77.2% and 82.5% and 5-year-DSS rates were 89.7% and 97.8% for the lymphadenectomy and no-lymphadenectomy groups, respectively. No significant differences were observed in the subsequent survival analysis by substage, histological subtype, or risk of recurrence. Our results suggest that the indications for lymphadenectomy in older patients should be individually optimized according to the risk of recurrence and postoperative complications.

Keywords: endometrial neoplasm; lymph node excision; older individuals; prognosis; survival
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Introduction

Endometrial cancer is one of the most common malignancies of the female genital tract in Japan and other developed countries (Sung et al. 2021; National Cancer Center Japan 2023). Its incidence rate in Japan is increasing annually, reaching more than 17,000 cases in 2019 (Shigeta et al. 2017; Nagase et al. 2021, 2022; Yoshino et al. 2022; National Cancer Center Japan 2023).

Surgical treatment is the primary therapeutic strategy for patients with stage I to III endometrial cancer, and the need for postoperative adjuvant therapy is determined based on the histopathological examination of surgical specimens. The Japan Society of Gynecologic Oncology (JSGO) 2018 guidelines for the treatment of uterine body neoplasms recommend platinum-based chemotherapy as a postoperative adjuvant therapy for patients with intermediate/high-risk endometrial cancer (Yamagami et al. 2020). In Japan, the

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reported 5-year overall survival rate for stage I patients is more than 90% (Shigeta et al. 2017; Nagase et al. 2021, 2022; Yoshino et al. 2022), indicating that most of the stage I endometrial cancers are curable with current therapeutic strategies.

One of the major concerns in surgery for early stage endometrial cancer is the need for lymphadenectomy, which is associated with several complications, such as increased blood loss, longer surgical duration, postoperative ileus, deep vein thrombosis, lymphedema, and lymphocele (Deura et al. 2015; Frost et al. 2017; Latif et al. 2021). Lymphadenectomy is considered beneficial in determining the cancer stage; however, its benefit on patient survival remains controversial.

In major randomized controlled trials, lymphadenectomy did not improve patient prognosis when tumors were preoperatively thought to be confined to the uterus (Benedetti Panici et al. 2008; ASTEC study group et al. 2009). However, several large-scale retrospective studies have suggested a possible benefit of lymphadenectomy in certain populations, even among patients with stage I endometrial cancer (Trimble et al. 1998; Chan et al. 2006; Todo et al. 2010). The latest Japanese guidelines published in 2018 recommend that clinicians consider lymphadenectomy for accurate staging and subsequent appropriate adjuvant therapy regardless of preoperative stage or histological subtype (Yamagami et al. 2020). In accordance with the guideline recommendations, lymphadenectomy has been included in the principal surgical procedures for endometrial cancer at our institute, except for patients at high risk of perioperative morbidity.

Advanced age is one of the important risk factors for not only major perioperative systemic complications but also other morbidities peculiar to older patients, such as delirium, dementia, and impaired activity of daily living (Hamel et al. 2005; Korc-Grodzicki et al. 2015). Thus, the balance between curability and surgical stress is an important concern in older patients. For decades, we had routinely opted not to perform lymphadenectomy for patients aged ≥ 70 years if their disease was preoperatively presumed to be stage I endometrial cancer without apparent lymph node enlargement on preoperative imaging evaluation. However, older patients have become quite diverse in the era of an aging society that requires physicians to personalize therapeutic strategies in geriatric medicine. Since 2013, with the spread of minimally invasive surgery (MIS), we started performing lymphadenectomy for patients aged ≥ 70 years if they were considered to be well tolerated without major preoperative complications at a physician's discretion.

It should be noted that older patients are less likely to be involved in clinical trials (Pitkala and Strandberg 2022) because conditions that are more common in older individuals are frequently listed as exclusion criteria. Furthermore, it is common to set an upper age limit in clinical trials that excludes older participants. In fact, major ongoing clinical trials investigating the importance of lymphadenectomy in patients with endometrial cancer have set the upper age limit as 75 years (Watari et al. 2017; Emons et al. 2021; Konno et al. 2021). As prospective clinical trials for older patients are still challenging, we retrospectively assessed the significance of lymphadenectomy in the prognosis of older patients with stage I endometrial cancer by reviewing the clinical database at our institute.

Materials and Methods

Study design

Patients aged ≥ 70 years who were preoperatively diagnosed with stage I endometrial cancer and primarily treated by surgery at Tohoku University Hospital from January 2007 to June 2021 were retrospectively reviewed. The study was approved by the hospital's Institutional Review Board (approval number: 2021-1-1179). Due to the retrospective nature of the study, the requirement for informed consent was waived. The International Federation of Gynecology and Obstetrics (FIGO) 2008 criteria were adopted for cancer staging in all cases (Creasman 2009). As the FIGO 2008 endometrial cancer staging criteria were officially adopted by the Japan Society of Obstetrics and Gynecology in 2011, patients diagnosed with endometrial cancer from 2007 to 2010 were restaged based on the FIGO 2008 criteria.

Clinical information, including age, postsurgical cancer stage, body mass index (BMI) at the time of surgery, type of adjuvant therapy, disease-free survival (DFS), disease-specific survival (DSS), histopathological subtype, cancer grade of the endometrioid subtype, and the presence or absence of lymphovascular space invasion (LVSI), was reviewed. Risks of recurrence were defined in accordance with the guidelines by the JSGO for endometrial cancer as follows: myometrial invasion to the outer half, positive LVSI, non-endometrioid grade 1/2 histology, cervical stromal invasion, and extrauterine spread. Patients without these risk factors were considered to be at low risk of recurrence. Patients with any of the risk factors were categorized into the intermediate-to-high-risk of recurrence group. Surgery-related information was also collected, including the type of surgical procedure, operative time, volume of blood loss, length of hospital stay, pre-existing complications, and postoperative complications of any grade according to the Clavien−Dindo classification (Dindo et al. 2004).

Pre-existing comorbidities were quantified using the Charlson comorbidity index (CCI), which is widely used to assess the risk of mortality in clinical trials (Charlson et al. 1987, 2022). In cases where recurrence was observed, the locations of recurrence were also reviewed. DFS was defined as the time from surgery to recurrence. Recurrences were diagnosed using clinical imaging techniques, such as computed tomography, positron emission tomography, or tumor biopsy. DSS was defined as the time from surgery to death owing to endometrial cancer.

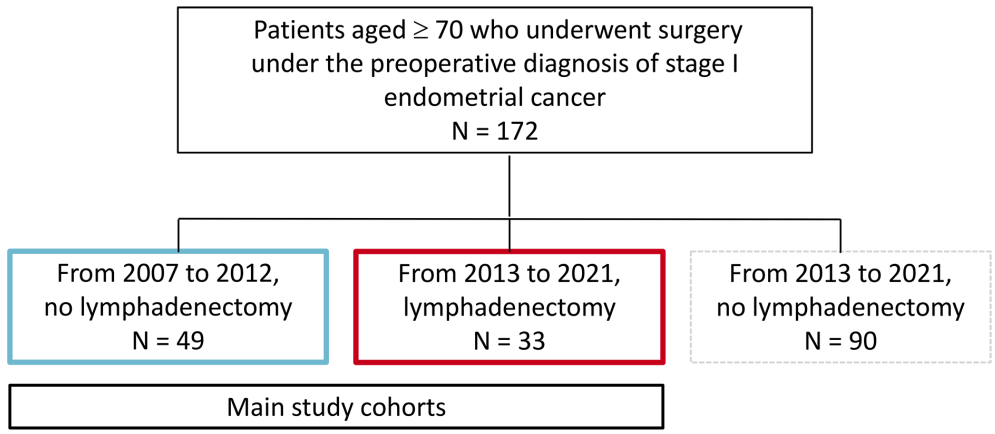

Fig. 1. Patient selection flow diagram.
The groups highlighted in red and blue were the lymphadenectomy and no-lymphadenectomy groups for the main analysis, respectively. Patients highlighted with a gray dotted line were excluded from the main study.

Statistical analysis

The clinicopathological parameters were compared between patients who underwent lymphadenectomy and those who did not. The Mann-Whitney U test, chi-squared test, or Fisher's exact test was performed according to the type of parameter. The Kaplan-Meier method with a log-rank test was used to evaluate and compare patient outcomes. Cox proportional hazards model was utilized for multivariate analysis using JMP® Pro 16.0.0 (SAS Institute Inc., Cary, NC, USA). The other analyses were performed using GraphPad Prism version 6.0.0 for Windows (GraphPad Software, San Diego, CA, USA). Statistical significance was defined as a two-sided P-value < 0.05.

Results

Patient characteristics

One hundred seventy-two patients were eligible for inclusion. All patients in this study underwent total hysterectomy with bilateral salpingo-oophorectomy as the primary surgery. The patients were categorized into two groups. Patients who underwent lymphadenectomy between 2013 and 2021 were included in the lymphadenectomy group. In contrast, we decided to exclude the patients who underwent surgery without lymphadenectomy in or after 2013 from the main study cohort to minimize unfavorable biases, because the patient characteristics were considered significantly different from those of the lymphadenectomy group based on the eligibility criteria for lymphadenectomy described in the introduction. Thus, the no-lymphadenectomy group comprised patients who underwent surgery without lymphadenectomy from 2007 to the end of 2012, the period when lymphadenectomy was routinely opted out. In total, 33 and 49 patients were categorized into the lymphadenectomy and no-lymphadenectomy groups, respectively. Patient selection flow is presented in Fig. 1.

The characteristics of the 82 patients in the study cohort are summarized in Table 1. Three patients whose

Table 1. Patient characteristics.

Parameter	Range	Median
Age	70-95	73
BMI	16-36	24
Parameter	**No. of patients**	**%**
FIGO2008 Stage		
IA	55	67.1
IB	24	29.3
II	1	1.2
IIIC	2	2.4
Histology		
Endometrioid grade 1/2	47	57.3
Endometrioid grade 3/Non-endometrioid	35	42.7
CCI		
0	59	72.0
1-2	22	26.8
> 3	1	1.2
Types of surgery		
Open laparotomy	66	80.5
Minimally invasive surgery	16	19.5
Lymphadenectomy		
Performed	33	40.2
Not performed	49	59.8
LVSI		
Negative	56	68.3
Positive	18	22.0
Unknown	8	9.8
Adjuvant therapy		
Performed	41	50.0
Not performed	41	50.0

BMI, body mass index; CCI, Charlson comorbidity index; LVSI, lymph vascular space invasion; FIGO, International Federation of Gynecology and Obstetrics.

disease was stage II or IIIC but preoperatively estimated to be stage I were included in the lymphadenectomy group to avoid unfavorable bias.

Of the 33 patients in the lymphadenectomy group, 15 underwent para-aortic lymphadenectomy in addition to pelvic lymphadenectomy based on the clinical imaging results, which indicated myometrial invasion in the outer half. Open laparotomy was performed in 66 patients and MIS in 16. MIS was only performed in the lymphadenectomy group. The median numbers of resected pelvic and para-aortic lymph nodes were 28 (range; 9-58) and 17 (4-31), respectively.

Regarding histology, diseases of the 35 patients presented with non-endometrioid grade 1/2 histology including 9, 15, 5, and 6 cases of grade 3 endometrioid carcinoma, serous carcinoma, clear cell carcinoma, and carcinosarcoma, respectively. Approximately half of the patients received up to six cycles of chemotherapy, whereas the

Table 2. Comparison of patient characteristics between the lymphadenectomy and no-lymphadenectomy groups.

Parameters	Lymphadenectomy (n = 33)	No-Lymphadenectomy (n = 49)	P value*
Median age (range)	72 (70-76)	77 (70-95)	< 0.001
Median BMI (range)	23 (18-31)	24 (16-36)	0.7913
Median follow-up months (range)	37 (12-80)	61.5 (0-104)	0.004
No. of the recorded events			
Disease recurrence	6	7	
Disease-specific death	2	4	
Perioperative mortality	0	1	
Death by other reasons	0	2[#]	
CCI			0.075
0	28	31	
1-2	5	17	
> 3	0	1	
Types of surgery			< 0.001
Open laparotomy	17	49	
Minimally invasive surgery	16	0	
FIGO2008 Stage			0.307**
IA	20	35	
IB	10	14	
II	1	0	
IIIC	2	0	
Histology			0.677
Endometrioid grade 1/2	18	29	
Endometrioid grade 3/Non-endometrioid	15	20	
LVSI			0.916***
Negative	21	35	
Positive	7	11	
Unknown	5	3	
Risk for recurrence			0.878***
Low	10	15	
Intermediate-high	23	32	
Unknown	0	2	
Adjuvant therapy			0.008
Performed	22	18	
Not Performed	11	31	

*Mann-Whitney U test was applied of the comparison of age, BMI, and follow-up months. Fisher's exact test was performed for CCI. Chi-squared test was performed for the other parameters.
**Chi-squared test was performed between IA and the other stages.
***Cases categorized in "Unknown" was excluded for Chi-squared test.
[#]Patients died of the progression of the other cancer or senile decay.
BMI, body mass index; CCI, Charlson comorbidity index; LVSI, lymphovascular space invasion; FIGO, International Federation of Gynecology and Obstetrics.

other half did not receive any adjuvant therapy.

As shown in Table 2, the median age was significantly higher in the no-lymphadenectomy group. Approximately half of the patients in the lymphadenectomy group underwent MIS. All patients in the no-lymphadenectomy group underwent open laparotomy. The distribution of substage, histology, LVSI status, CCI, and presence or absence of risk(s) of recurrence did not statistically differ between the two groups. At our institution, adjuvant chemotherapy is generally considered for a patient categorized into the intermediate/high-risk group according to the JSGO guidelines. Although approximately two-thirds of patients in the lymphadenectomy group received adjuvant therapy, less than 40% received it in the no-lymphadenectomy group (P = 0.015 by chi-square test). One patient in the no-lymphadenectomy group with a CCI score of 3 who had liver cirrhosis died on the seventh postoperative day due to severe liver dysfunction, which is listed as perioperative mortality in Table 2.

Patient outcomes

DFS and DSS were compared between the lymphadenectomy and no-lymphadenectomy groups. To focus on the influence of lymphadenectomy on curability, a patient who experienced perioperative mortality was excluded from the subsequent outcome analyses. As shown in Fig. 2, neither DFS nor DSS differed significantly between the two groups. The 5-year DFS rates were 77.2% and 82.5% in the lymphadenectomy and no-lymphadenectomy groups, respectively, while the 5-year DSS rates were 89.7% and 97.8% in the lymphadenectomy and no-lymphadenectomy groups, respectively. Multivariate analyses with age, histology, adjuvant chemotherapy, and lymphadenectomy as explanatory variables did not identify performing lymphadenectomy as an independent risk reduction factor for disease recurrence (hazard ratio: 4.34, 95% confidence interval: 0.88-21.49) or disease-specific mortality (hazard ratio: 3.02, 95% confidence interval: 0.22-41.79).

Non-endometrioid G1/2 histology or myometrial invasion into the outer half is a well-established risk factor for lymph node metastasis and poor prognosis (Boronow et al. 1984; Kamura et al. 1999; Cohn et al. 2002; Briët et al. 2005; Zhang et al. 2012; Koskas et al. 2013; Pollom et al. 2016). Therefore, we compared DSS and DFS according to substage, histological subtype, and presence or absence of risk(s) of recurrence to evaluate the significance of lymphadenectomy. As shown in Figs. 3, 4 and 5, no significant difference was observed between the lymphadenectomy and no-lymphadenectomy groups in either subgroup comparison. In addition, we compared DSS and DFS after including 90 patients in the no-lymphadenectomy group who did not undergo lymphadenectomy between 2013 to 2021 (Fig. 1). Similar to the main study cohort comparison, neither DSS nor DFS significantly differed between the lymphadenectomy and no-lymphadenectomy groups in the entire analysis or subgroup analysis according to the risk of recurrence (Fig. 6).

Site of recurrence

Six and seven patients experienced disease recurrence in the lymphadenectomy and no-lymphadenectomy groups, respectively, in the main study cohort. As shown in Table 3, most recurrences occurred outside regional lymph nodes. There were two cases of regional lymph node metastasis in both the lymphadenectomy and no-lymphadenectomy groups. Fisher's exact test did not indicate a significant difference between the number of patients and regional lymph node recurrences in each group (P = 1.000).

Complications

The intra- and postoperative complications in the main study cohort are summarized in Table 4. Lymphadenectomy was associated with a longer duration of surgery and intraoperative blood loss. Although the length of hospital stay was significantly shorter in the lymphadenectomy group, it should be noted that the duration of standard hospital stay in the clinical pathway for MIS was shorter than that for open laparotomy. The frequencies of postoperative complications, including ileus, thrombosis, lymphatic cyst infection, and organ injury, were higher in the lymphadenectomy

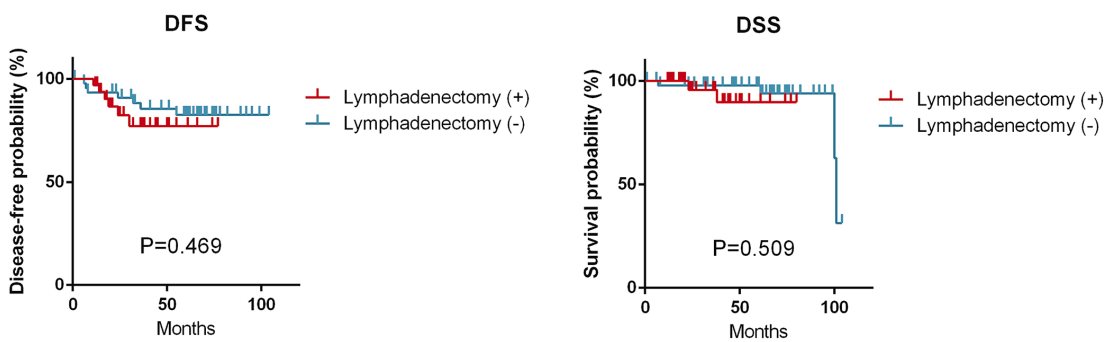

Fig. 2. Survival comparison in all patients.
Disease-free survival (left) and disease-specific survival (right) are compared between the lymphadenectomy and no-lymphadenectomy groups. Log-rank tests were used for statistical comparisons. Red, lymphadenectomy group (n = 48); blue, no-lymphadenectomy group (n = 33). DFS, disease-free survival; DSS, disease-specific survival.

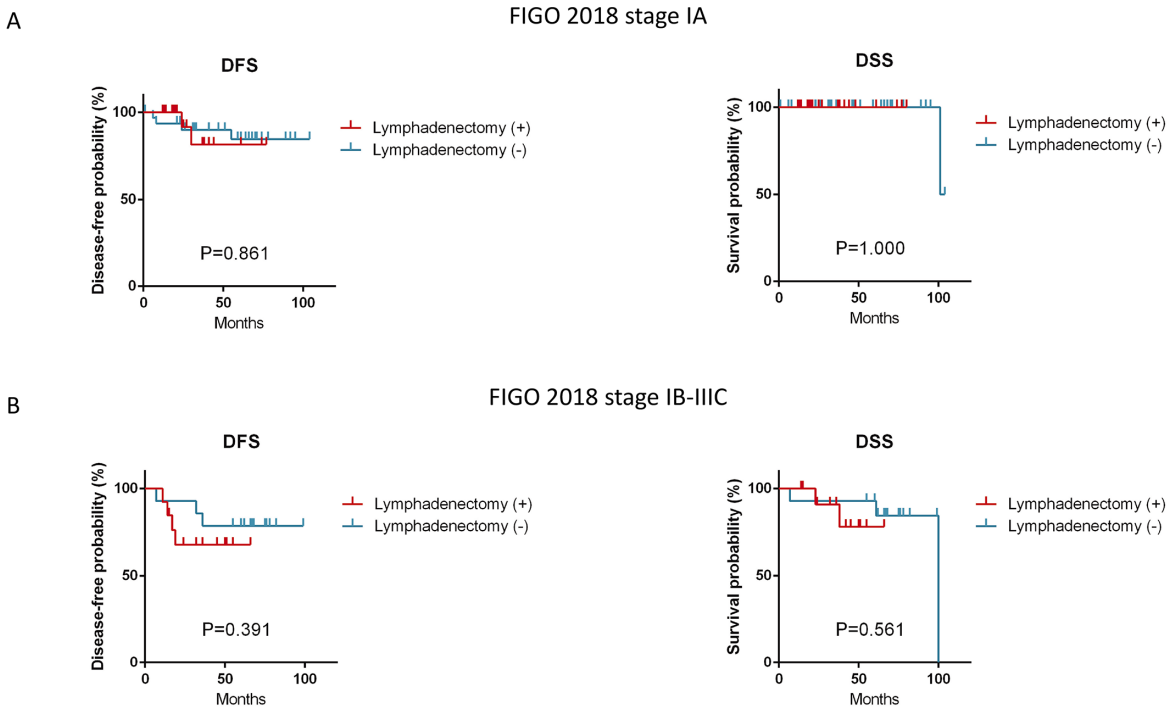

Fig. 3. Survival comparison by substage.
Disease-free and disease-specific survival rates were compared according to the substage. Log-rank tests were used for statistical comparisons. A. FIGO 2018 stage IA (n = 54). Red, lymphadenectomy group (n = 20); blue, no-lymphadenectomy group (n = 24). B. FIGO 2018 stage IB-IIIC (n = 27). Red, lymphadenectomy group (n = 13); blue, no-lymphadenectomy group (n = 14). FIGO, International Federation of Gynecology and Obstetrics; DFS, disease-free survival; DSS, disease-specific survival.

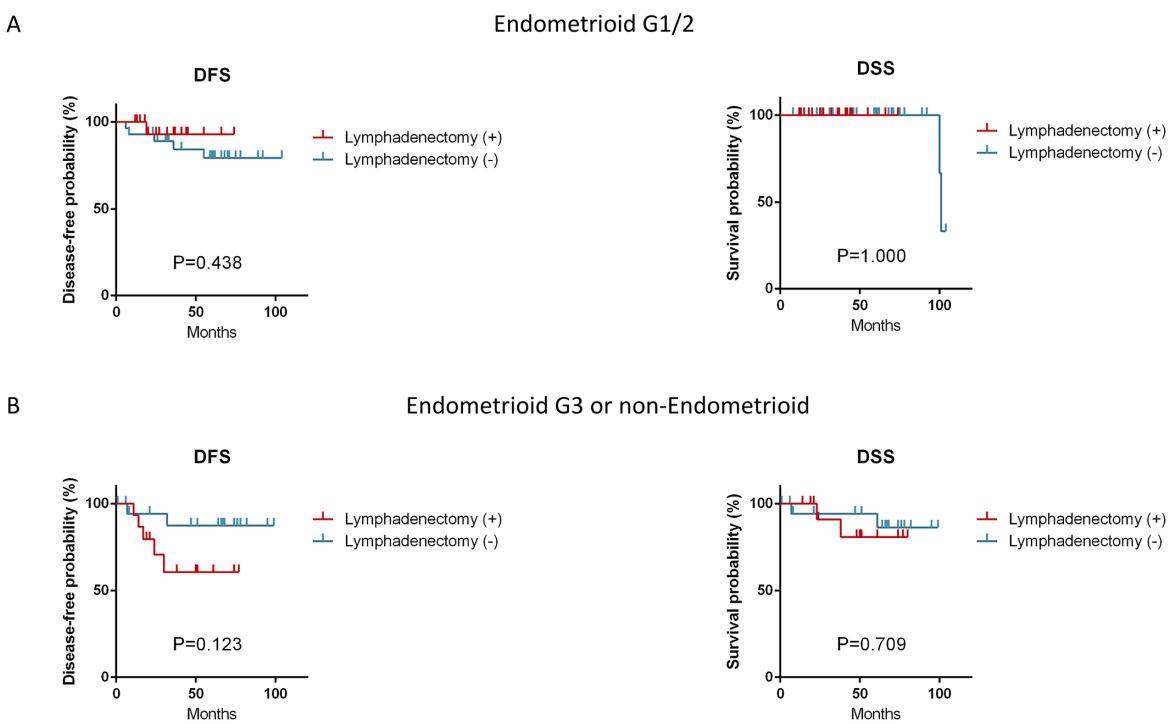

Fig. 4. Survival comparison by histological subtype.
Disease-free survival and disease-specific survival were compared according to the histological subtype. Log-rank tests were used for statistical comparisons. A. Endometrioid G1/G2 (n = 46). Red, lymphadenectomy group (n = 18); blue, no-lymphadenectomy group (n = 28). B. Endometrioid G3/non-endometrioid (n = 35). Red, lymphadenectomy group (n = 15); blue, no-lymphadenectomy group (n = 20). G, grade; DFS, disease-free survival; DSS, disease-specific survival.

group. However, perioperative death due to severe liver function was recorded in the no-lymphadenectomy group.

Discussion

We conducted a retrospective study to assess the significance of lymphadenectomy in older patients who were clinically diagnosed with stage I endometrial cancer. Although lymphadenectomy was associated with prolonged surgical duration and increased blood loss, no benefit of lymphadenectomy on patient outcomes was observed.

As mentioned in the Introduction, older patients tend to have multiple comorbidities, require multiple medications, and exhibit a lower functional status than younger patients, resulting in an increased risk of postsurgical complications (Hamel et al. 2005). At the same time, the rapidly aging society in our nation has brought about heterogeneity in physical and cognitive conditions among older populations of similar ages. In our study, the indication for lymphadenectomy was determined subjectively at a physician's discretion according to the clinical status of each patient. Comprehensive geriatric assessment (CGA) has been globally used to objectively evaluate the physical and mental function of older patients (Eamer et al. 2018). CGA was also reported to accurately predict the risk of postoperative morbidity in older patients undergoing oncosurgery, including those with gynecologic malignancy (Anic et al. 2023; Cioli Puviani et al. 2023). In addition to CGA, CCI is a widely accepted index in clinical trials which is associated with short-term risk of mortality (Charlson et al. 1987, 2022). Although time efficiency remains a concern in CGA, the indication for lymphadenectomy can be more objectively personalized among older patients by utilizing these quantitative evaluation strategies.

We experienced a case of postsurgical acute mortality in the patients with a CCI score of 3 who presented with moderate liver cirrhosis and portal hypertension in the no-lymphadenectomy group. This indicates that surgery is unignorable stress regardless of lymphadenectomy. Thus, an objective evaluation of preoperative comorbidities with CGA and/or CCI should be further discussed, particularly in older patients.

Lymphadenectomy is associated with acute and chronic complications, some of which were observed in the current study. However, the therapeutic benefits of lymphadenectomy in stage I endometrial cancer remain controversial. The European Society for Medical Oncology 2013 guidelines do not recommend lymphadenectomy for stage IA endometrial cancer with endometrioid grade 1 or 2 histology based on the results of major randomized controlled trials (Colombo et al. 2013). Although lymphadenectomy is proposed for precise cancer staging, according to the latest 2018 JSGO guidelines, it is mentioned that lymphadenectomy may be omitted in patients with a low risk of recurrence (Yamagami et al. 2020). Considering the risk of lymphadenectomy for older patients and global consensus, we consider it fair not to recommend lymphadenectomy for

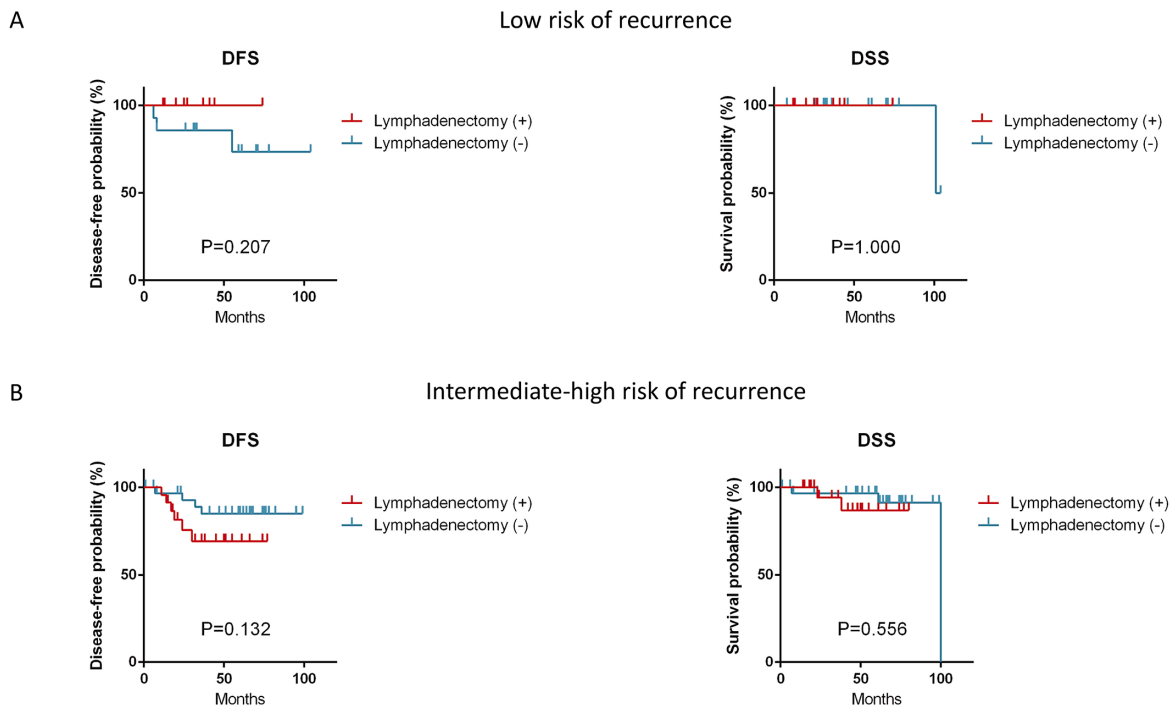

Fig. 5. Survival comparison by risk of recurrence.
Disease-free and disease-specific survival rates were compared based on the risk of recurrence. Log-rank tests were used for statistical comparisons. A. Low risk of recurrence (n = 24). Red, lymphadenectomy group (n = 10); blue, no-lymphadenectomy group (n = 14). B. Intermediate-to-high risk of recurrence (n = 55). Red, lymphadenectomy group (n = 23); blue, no-lymphadenectomy group (n = 32). DFS, disease-free survival; DSS, disease-specific survival.

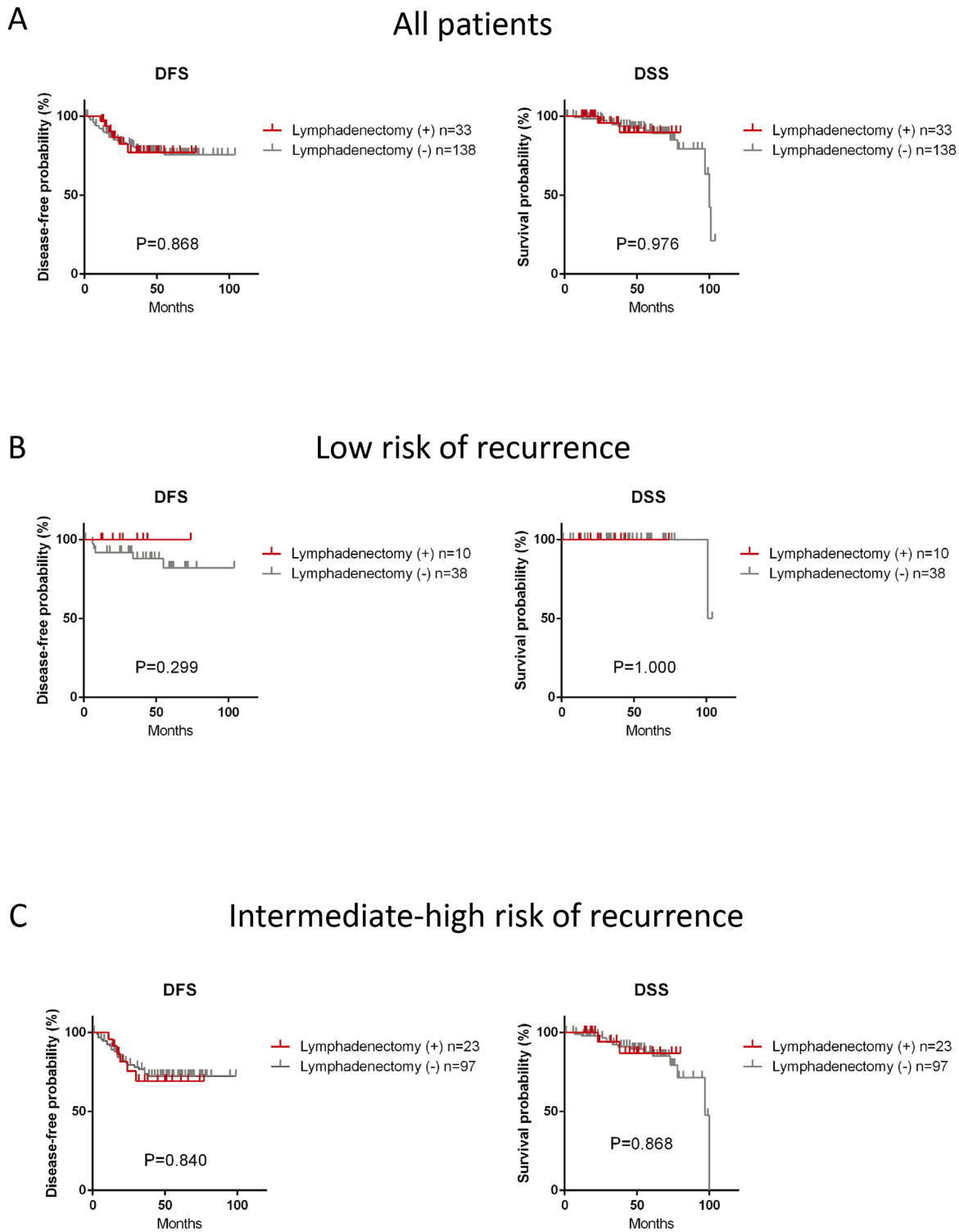

Fig. 6. Complementary survival comparison with 171 patients.
Ninety patients who did not undergo lymphadenectomy between 2013 to 2021 were included in the no-lymphadenectomy group, and patient prognoses were compared. A. Disease-free survival and disease-specific survival for all patients (n = 171). B. DFS and DSS for low risk of recurrence (n = 48). C. DFS and DSS for intermediate-to-high risk of recurrence (n = 120). Red, lymphadenectomy group; gray, no-lymphadenectomy group. DFS, disease-free survival; DSS, disease-specific survival.

older patients with stage I endometrial cancer who are estimated to be at low risk of recurrence by strict preoperative evaluation.

In contrast, lymphadenectomy for older patients with an intermediate-to-high risk of recurrence should be discussed separately. Although no conclusion has yet been reached, several retrospective studies have reported the survival advantage of lymphadenectomy in patients at risk of recurrence (Trimble et al. 1998; Chan et al. 2006; Todo et al. 2010). Focusing on older patients, Racin et al. (2019) reported that the omission of lymphadenectomy was a poor prognostic factor in patients aged ≥ 70 years with high-risk or advanced endometrial cancer. Importantly, non-endometrioid grade 1/2 histological subtype, a risk factor for recurrence, is more frequently observed in older patients (Bokhman 1983; Hecht and Mutter 2006; Shigeta et al. 2017). Although we did not observe the statistically supported survival benefit of lymphadenectomy among the older patients at intermediate-to-high-risk of recurrence, the indication of lymphadenectomy should be carefully determined.

Our study reported that 2 out of 33 patients (6%) in the lymphadenectomy group were positive for lymph node metastasis, which is similar to the findings of Cragun et al. (2005) who reported the frequencies of occult pelvic and para-aortic lymph node metastasis as 5% and 3%, respectively, among patients clinically diagnosed with early stage endometrial cancer. The absence of a statistically significant influence of lymphadenectomy in the current study cohort could be attributed to the low frequency of occult lymph node metastasis. In other words, these small subsets of patients constitute the population who truly benefit from systemic lymphadenectomy. This raises a great concern on the stratification of systemic lymphadenectomy by intraoperative sentinel node biopsy, particularly for older patients with endometrial carcinoma. Although sentinel lymph node biopsy is still considered an experimental strategy in Japan, extensive research has been conducted on the feasibility of excluding systemic lymphadenectomy based on the results of intraoperative sentinel lymph node evaluation (Niikura et al. 2019, 2021). The results of this study warrant further investigation on sentinel lymph node biopsy in older patients with endometrial carcinoma.

As this was a relatively small-sized, single-institution retrospective investigation with a significant difference in patient background and treatment era between the two groups, there is no doubt that less-biased studies are needed to reach the appropriate conclusion.

In conclusion, the indications for lymphadenectomy in older patients with clinical stage I endometrial cancer

Table 3. Site of recurrence in the lymphadenectomy and no-lymphadenectomy groups.

	Lymphadenectomy (n = 33)	No-Lymphadenectomy (n = 49)
No. of recurrence (%)	6 (18.2)	7 (14.3)
Site of recurrence		
Vagina	1	4
Regional lymph node	2	2
Peritonum	2	0
Distal site	3	4

Table 4. Comparison of intra- and post-operative complications between the lymphadenectomy and no-lymphadenectomy groups.

	Lymphadenectomy group (n = 33)	No-lymphadenectomy group (n = 49)	P value
Duration of operation* (min)	298.4 ± 147.4	105.5 ± 33.4	< 0.001
Blood loss** (mL)	388.5 (7-3,125)	175.3 (5-785)***	0.026
Length of hospital stay* (days)	11.5 ± 2.1	13.0 ± 4.0	0.003
Complication (%)			
Any of the below	9 (27.3)	3 (6.1)	0.031****
Ileus	2 (6.0)	1 (2.0)	
Lymphatic cyst infection	3 (9.1)	0	
Organ injury	1 (3.0)	0	
Thrombosis	3 (9.1)	0	
Heart failure	0	1 (2.0)	
Liver disfunction	0	1 (2.0)	

*Data are represented as the mean ± standard deviation. P values were determined using the Mann-Whitney U test.
**Data are represented as the mean (range). P values were determined using the Mann-Whitney U test.
***The blood loss was recorded as "small" in one case, which was replaced with the least blood loss among the other 48 patients in the no-lymphadenectomy group as 5 mL.
****Fisher's exact test was applied.

should be optimized by considering both curability and the risk of preoperative complications. Preoperative objective evaluation using quantitative scoring methods is considered helpful to understand the heterogeneity of comorbidities in the older population. Although further investigation is required, intraoperative sentinel lymph node biopsy might be beneficial for older patients with risks of disease recurrence and perioperative morbidity.

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Conflict of Interest

The authors declare no conflict of interest.

References

Anic, K., Flohr, F., Schmidt, M.W., Krajnak, S., Schwab, R., Schmidt, M., Westphalen, C., Eichelsbacher, C., Ruckes, C., Brenner, W., Hasenburg, A. & Battista, M.J. (2023) Frailty assessment tools predict perioperative outcome in elderly patients with endometrial cancer better than age or BMI alone: a retrospective observational cohort study. *J. Cancer Res. Clin. Oncol.*, **149**, 1551-1560.

ASTEC study group, Kitchener, H., Swart, A.M., Qian, Q., Amos, C. & Parmar, M.K. (2009) Efficacy of systematic pelvic lymphadenectomy in endometrial cancer (MRC ASTEC trial): a randomised study. *Lancet*, **373**, 125-136.

Benedetti Panici, P., Basile, S., Maneschi, F., Alberto Lissoni, A., Signorelli, M., Scambia, G., Angioli, R., Tateo, S., Mangili, G., Katsaros, D., Garozzo, G., Campagnutta, E., Donadello, N., Greggi, S., Melpignano, M., et al. (2008) Systematic pelvic lymphadenectomy vs. no lymphadenectomy in early-stage endometrial carcinoma: randomized clinical trial. *J. Natl. Cancer Inst.*, **100**, 1707-1716.

Bokhman, J.V. (1983) Two pathogenetic types of endometrial carcinoma. *Gynecol. Oncol.*, **15**, 10-17.

Boronow, R.C., Morrow, C.P., Creasman, W.T., Disaia, P.J., Silverberg, S.G., Miller, A. & Blessing, J.A. (1984) Surgical staging in endometrial cancer: clinical-pathologic findings of a prospective study. *Obstet. Gynecol.*, **63**, 825-832.

Briët, J.M., Hollema, H., Reesink, N., Aalders, J.G., Mourits, M.J., ten Hoor, K.A., Pras, E., Boezen, H.M., van der Zee, A.G. & Nijman, H.W. (2005) Lymphvascular space involvement: an independent prognostic factor in endometrial cancer. *Gynecol. Oncol.*, **96**, 799-804.

Chan, J.K., Cheung, M.K., Huh, W.K., Osann, K., Husain, A., Teng, N.N. & Kapp, D.S. (2006) Therapeutic role of lymph node resection in endometrioid corpus cancer: a study of 12,333 patients. *Cancer*, **107**, 1823-1830.

Charlson, M.E., Carrozzino, D., Guidi, J. & Patierno, C. (2022) Charlson comorbidity index: a critical review of clinimetric properties. *Psychother. Psychosom.*, **91**, 8-35.

Charlson, M.E., Pompei, P., Ales, K.L. & MacKenzie, C.R. (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J. Chronic Dis.*, **40**, 373-383.

Cioli Puviani, F., Calogero, P., Bianchi, G., De Benedetti, P., Boussedra, S., Dondi, G., Perrone, A.M., De Iaco, P. & Galetti, C. (2023) Pre-operative geriatric screening and assessment as predictors of postoperative complications in older adults with gynecologic cancer: a pilot cohort study on a neglected issue. *J. Geriatr. Oncol.*, **14**, 101419.

Cohn, D.E., Horowitz, N.S., Mutch, D.G., Kim, S.M., Manolitsas, T. & Fowler, J.M. (2002) Should the presence of lymphvascular space involvement be used to assign patients to adjuvant therapy following hysterectomy for unstaged endometrial cancer? *Gynecol. Oncol.*, **87**, 243-246.

Colombo, N., Preti, E., Landoni, F., Carinelli, S., Colombo, A., Marini, C. & Sessa, C.; ESMO Guildlines Working Group (2013) Endometrial cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.*, **24** Suppl 6, vi33-38.

Cragun, J.M., Havrilesky, L.J., Calingaert, B., Synan, I., Secord, A.A., Soper, J.T., Clarke-Pearson, D.L. & Berchuck, A. (2005) Retrospective analysis of selective lymphadenectomy in apparent early-stage endometrial cancer. *J. Clin. Oncol.*, **23**, 3668-3675.

Creasman, W. (2009) Revised FIGO staging for carcinoma of the endometrium. *Int. J. Gynaecol. Obstet.*, **105**, 109.

Deura, I., Shimada, M., Hirashita, K., Sugimura, M., Sato, S., Sato, S., Oishi, T., Itamochi, H., Harada, T. & Kigawa, J. (2015) Incidence and risk factors for lower limb lymphedema after gynecologic cancer surgery with initiation of periodic complex decongestive physiotherapy. *Int. J. Clin. Oncol.*, **20**, 556-560.

Dindo, D., Demartines, N. & Clavien, P.A. (2004) Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann. Surg.*, **240**, 205-213.

Eamer, G., Taheri, A., Chen, S.S., Daviduck, Q., Chambers, T., Shi, X. & Khadaroo, R.G. (2018) Comprehensive geriatric assessment for older people admitted to a surgical service. *Cochrane Database Syst. Rev.*, **1**, CD012485.

Emons, G., Kim, J.W., Weide, K., de Gregorio, N., Wimberger, P., Trillsch, F., Gabriel, B., Denschlag, D., Kommoss, S., Aydogdu, M., Papathemelis, T., Gropp-Meier, M., Muallem, M.Z., Kuhn, C., Muller, A., et al. (2021) Endometrial Cancer Lymphadenectomy Trial (ECLAT) (pelvic and para-aortic lymphadenectomy in patients with stage I or II endometrial cancer with high risk of recurrence; AGO-OP.6). *Int. J. Gynecol. Cancer*, **31**, 1075-1079.

Frost, J.A., Webster, K.E., Bryant, A. & Morrison, J. (2017) Lymphadenectomy for the management of endometrial cancer. *Cochrane Database Syst. Rev.*, **10**, CD007585.

Hamel, M.B., Henderson, W.G., Khuri, S.F. & Daley, J. (2005) Surgical outcomes for patients aged 80 and older: morbidity and mortality from major noncardiac surgery. *J. Am. Geriatr. Soc.*, **53**, 424-429.

Hecht, J.L. & Mutter, G.L. (2006) Molecular and pathologic aspects of endometrial carcinogenesis. *J. Clin. Oncol.*, **24**, 4783-4791.

Kamura, T., Yahata, H., Shigematsu, T., Ogawa, S., Amada, S., Kaku, T. & Nakano, H. (1999) Predicting pelvic lymph node metastasis in endometrial carcinoma. *Gynecol. Oncol.*, **72**, 387-391.

Konno, Y., Asano, H., Shikama, A., Aoki, D., Tanikawa, M., Oki, A., Horie, K., Mitsuhashi, A., Kikuchi, A., Tokunaga, H., Terao, Y., Satoh, T., Ushijima, K., Ishikawa, M., Yaegashi, N., et al. (2021) Lymphadenectomy issues in endometrial cancer. *J. Gynecol. Oncol.*, **32**, e25.

Korc-Grodzicki, B., Sun, S.W., Zhou, Q., Iasonos, A., Lu, B., Root, J.C., Downey, R.J. & Tew, W.P. (2015) Geriatric assessment as a predictor of delirium and other outcomes in elderly patients with cancer. *Ann. Surg.*, **261**, 1085-1090.

Koskas, M., Bassot, K., Graesslin, O., Aristizabal, P., Barranger, E., Clavel-Chapelon, F., Haddad, B., Luton, D., Darai, E. & Rouzier, R. (2013) Impact of lymphovascular space invasion on a nomogram for predicting lymph node metastasis in endometrial cancer. *Gynecol. Oncol.*, **129**, 292-297.

Latif, N., Oh, J., Brensinger, C., Morgan, M., Lin, L.L., Cory, L. & Ko, E.M. (2021) Lymphadenectomy is associated with an increased risk of postoperative venous thromboembolism in

early stage endometrial cancer. *Gynecol. Oncol.*, **161**, 130-134.

Nagase, S., Ohta, T., Takahashi, F. & Yaegashi, N.; Board members of the 2020 Committee on Gynecologic Oncology of the Japan Society of Obstetrics and Gynecology (2021) Annual report of the Committee on Gynecologic Oncology, the Japan Society of Obstetrics and Gynecology: annual patient report for 2017 and annual treatment report for 2012. *J. Obstet. Gynaecol. Res.*, **47**, 1631-1642.

Nagase, S., Ohta, T., Takahashi, F., Yamagami, W. & Yaegashi, N.; Board members of the 2020 Committee on Gynecologic Oncology of the Japan Society of Obstetrics and Gynecology (2022) Annual report of the Committee on Gynecologic Oncology, the Japan Society of Obstetrics and Gynecology: Annual Patient Report for 2018 and Annual Treatment Report for 2013. *J. Obstet. Gynaecol. Res.*, **48**, 541-552.

National Cancer Center Japan (2023) Cancer Statistics in Japan. https://ganjoho.jp/reg_stat/statistics/data/dl/index.html [*Accessed*: March 1, 2023].

Niikura, H., Toki, A., Nagai, T., Okamoto, S., Shigeta, S., Tokunaga, H., Shimada, M., Watanabe, M. & Yaegashi, N. (2021) Prospective evaluation of sentinel node navigation surgery in Japanese patients with low-risk endometrial cancer-safety and occurrence of lymphedema. *Jpn. J. Clin. Oncol.*, **51**, 584-589.

Niikura, H., Tsuji, K., Tokunaga, H., Shimada, M., Ishikawa, M. & Yaegashi, N. (2019) Sentinel node navigation surgery in cervical and endometrial cancer: a review. *Jpn. J. Clin. Oncol.*, **49**, 495-500.

Pitkala, K.H. & Strandberg, T.E. (2022) Clinical trials in older people. *Age Ageing*, **51,** afab282.

Pollom, E.L., Conklin, C.M., von Eyben, R., Folkins, A.K. & Kidd, E.A. (2016) Nomogram to predict risk of lymph node metastases in patients with endometrioid endometrial cancer. *Int. J. Gynecol. Pathol.*, **35**, 395-401.

Racin, A., Raimond, E., Bendifallah, S., Nyangoh Timoh, K., Ouldamer, L., Canlorbe, G., Hudry, N., Coutant, C., Graesslin, O., Touboul, C., Collinet, P., Bricou, A., Huchon, C., Koskas, M., Ballester, M., et al. (2019) Lymphadenectomy in elderly patients with high-intermediate-risk, high-risk or advanced endometrial cancer: time to move from personalized cancer medicine to personalized patient medicine! *Eur. J. Surg. Oncol.*, **45**, 1388-1395.

Shigeta, S., Nagase, S., Mikami, M., Ikeda, M., Shida, M., Sakaguchi, I., Ushioda, N., Takahashi, F., Yamagami, W., Yaegashi, N., Udagawa, Y. & Katabuchi, H. (2017) Assessing the effect of guideline introduction on clinical practice and outcome in patients with endometrial cancer in Japan: a project of the Japan Society of Gynecologic Oncology (JSGO) guideline evaluation committee. *J. Gynecol. Oncol.*, **28**, e76.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A. & Bray, F. (2021) Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J. Clin.*, **71**, 209-249.

Todo, Y., Kato, H., Kaneuchi, M., Watari, H., Takeda, M. & Sakuragi, N. (2010) Survival effect of para-aortic lymphadenectomy in endometrial cancer (SEPAL study): a retrospective cohort analysis. *Lancet*, **375**, 1165-1172.

Trimble, E.L., Kosary, C. & Park, R.C. (1998) Lymph node sampling and survival in endometrial cancer. *Gynecol. Oncol.*, **71**, 340-343.

Watari, H., Katayama, H., Shibata, T., Ushijima, K., Satoh, T., Onda, T., Aoki, D., Fukuda, H., Yaegashi, N. & Sakuragi, N.; Gynecologic Cancer Study Group of the Japan Clinical Oncology Group (2017) Phase III trial to confirm the superiority of pelvic and para-aortic lymphadenectomy to pelvic lymphadenectomy alone for endometrial cancer: Japan Clinical Oncology Group Study 1412 (SEPAL-P3). *Jpn. J. Clin. Oncol.*, **47**, 986-990.

Yamagami, W., Mikami, M., Nagase, S., Tabata, T., Kobayashi, Y., Kaneuchi, M., Kobayashi, H., Yamada, H., Hasegawa, K., Fujiwara, H., Katabuchi, H. & Aoki, D. (2020) Japan Society of Gynecologic Oncology 2018 guidelines for treatment of uterine body neoplasms. *J. Gynecol. Oncol.*, **31**, e18.

Yoshino, K., Kurita, T., Takahashi, F. & Nagase, S.; Board members of the 2021 Committee on Gynecologic Oncology of the Japan Society of Obsetrics and Gynecology (2022) Annual report of the committee on gynecologic oncology, the Japan Society of Obstetrics and Gynecology: annual patient report for 2019 and annual treatment report for 2014. *J. Obstet. Gynaecol. Res.*, **48**, 1570-1579.

Zhang, C., Wang, C. & Feng, W. (2012) Clinicopathological risk factors for pelvic lymph node metastasis in clinical early-stage endometrioid endometrial adenocarcinoma. *Int. J. Gynecol. Cancer*, **22**, 1373-1377.