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Original Article

Therapeutic significance of full lymphadenectomy in early-stage ovarian clear cell carcinoma

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ABSTRACT

Objectives: This study evaluated the therapeutic significance of full lymphadenectomy in early-stage ovarian clear cell carcinoma (OCCC).
Methods: We retrospectively reviewed records of 127 consecutive patients with pT1/pT2 and M0 OCCC who were treated between January 1995 and December 2015. We compared survival outcomes between those who did and did not undergo para-aortic lymph node dissection (PAND), and analyzed independent prognostic factors (Cox proportional hazards model with backward stepwise elimination).
Results: Of the 127 patients, 36 (28%) did not undergo lymphadenectomy; 12 (10%) patients underwent pelvic lymph node dissection (PLND) only; and 79 (62%) patients underwent both PLND and PAND. Of the 91 patients with lymphadenectomy, 11 (12%) had lymph node metastasis (LNM). The PAND$^-$ and PAND$^+$ groups did not significantly differ in age, distribution of pT status, radiologically enlarged lymph nodes, positive peritoneal cytology, capsule rupture, peritoneal involvement, and combined chemotherapy. Cox regression multivariate analysis confirmed that older age (hazard ratio [HR]=2.1; 95% confidence interval [CI]=1.0–4.3), LNM (HR=4.4; 95% CI=1.7–11.6), and positive peritoneal cytology (HR=4.2; 95% CI=2.1–8.4) were significantly and independently related to poor disease-specific survival (DSS), but implementation of both PLND and PAND (HR=0.4; 95% CI=0.2–0.8) were significantly and independently related to longer DSS.
Conclusion: Although few in number, there are some patients with early-stage OCCC who can benefit from full lymphadenectomy. Its therapeutic role should be continuously investigated in OCCC patients at potential risk of LNM.

Keywords: Ovarian Neoplasms; Clear Cell Adenocarcinoma; Lymph Node Excision; Lymphatic Metastasis; Prognosis

INTRODUCTION

Ovarian cancer is relatively uncommon, with an estimated number of 22,400 new cases in the United States in 2017 [1]. However, it is the leading cause of cancer death among malignancies of the female genital tract and the fifth leading cause of all cancer-related deaths among women [1]. Primary treatment for ovarian cancer consists of appropriate surgical staging and cytoreduction followed by systemic chemotherapy (CT). Although

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No potential conflict of interest relevant to this article was reported.

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pelvic and para-aortic lymphadenectomy is an essential part of surgical staging procedures, there has been conflicting views on its therapeutic significance in ovarian cancer [2-7]. Among them, some prospective randomized studies failed to show a superiority of systematic lymphadenectomy to lymph node sampling [2,3]. A recent ongoing randomized controlled trial (RCT), German Arbeitsgemeinschaft Gynaekologische Onkologie Society of Gynecological Oncology (AGO)-lymphadenectomy in ovarian neoplasm (LION) study, is also expected to show a negative result. RCTs are suited for confirming a standard treatment in patients with low-risk prognoses, but may not be the best format for evaluating surgical treatment in high-risk subjects [8]. In contrast, a large epidemiologic study based on the Surveillance, Epidemiology, and End Results (SEER) database showed a potential benefit of systematic lymphadenectomy for patients with stage I ovarian cancer [4]. In addition, several exploratory analyses demonstrated a survival benefit of systematic lymphadenectomy for patients with early-stage [5] or less advanced ovarian cancer [6,7] by using surgical data of phase III trials for selecting the best chemotherapeutic regimen.

Ovarian clear cell carcinoma (OCCC) is a morphologically and biologically distinct neoplasm [9-13]. It is likely to be found at an early-stage and its prognosis is relatively good, while advanced-stage disease has notoriously poor prognosis due to its chemo-resistant characteristics. Opinions vary regarding the therapeutic significance of systematic lymphadenectomy in OCCC [14-20]. Despite some negative reports on its therapeutic significance [14,15], recent retrospective studies showed a potential survival benefit of more extensive lymphadenectomy in OCCC [16,17]. In light of its chemo-resistant nature, complete surgical resection might be critical in successful OCCC treatment. In the present study, therapeutic significance of both pelvic and para-aortic lymphadenectomy in OCCC were investigated.

MATERIALS AND METHODS

1. Patients

A total of 760 patients with epithelial ovarian/tubal/peritoneal cancer were treated in the National Hospital Organization, Hokkaido Cancer Center from January 1995 to December 2015. Information concerning age, histological subtype, disease stage, treatment, and follow-up was collected by reviewing their medical records. We then identified 170 with OCCC. Of these patients, 42 patients with pT3 were excluded from the present study. One patient with pT1 and distant metastasis was also excluded from this study. Finally, we carried out this study with data from 127 patients with pT1/pT2 and M0 OCCC.

2. Image analysis

Radiological lymph node size before initial treatment was investigated as a surrogate for bulky nodes. All 127 patients underwent computed tomography scans before their initial treatments, with parameters that included pelvic lymph node size, para-aortic lymph node size, and distant metastasis. Lymph node enlargement was defined as a minimal lymph node diameter >10 mm, determined radiologically.

3. Treatments

All treatments were performed at the discretion of the attending physicians. Surgery is the cornerstone of treatment for OCCC. Basic procedures included total abdominal hysterectomy, bilateral salpingo-oophorectomy, cytologic evaluation of ascites or peritoneal

washing, excision or biopsy of suspicious peritoneal implants, omentectomy, and pelvic lymph node dissection (PLND) and para-aortic lymph node dissection (PAND). However, completion of all these procedures was not mandatory. Lymph node dissection (LND) was performed after confirmation of a histological diagnosis of malignancy. However, some patients refused subsequent lymphadenectomy following their initial surgery, despite our recommendations. Management of ovarian cancer at our institution changed during the study period: before 2004, PAND was not generally performed in patients with ovarian cancer, but after 2004, our group's preference changed to perform both PAND and PLND for patients with ovarian cancer. This study compared full lymphadenectomy (PLND+PAND) with no lymphadenectomy/PLND-only because we regard PLND+PAND as a potentially optimal lymphadenectomy. Adjuvant treatment was CT as our institutional policy. Adjuvant CT was not mandatory, but was recommended for patients with OCCC irrespective of International Federation of Gynecology and Obstetrics (FIGO) staging. Throughout the study period, several CT regimens were used as follow:

1) irinotecan-mitomycin combination CT: irinotecan hydrochloride (100 mg/m^2, day 1) and mitomycin (10 mg/m^2, day 1) every 4 weeks
2) platinum-irinotecan combination CT: cisplatin (60 mg/m^2, day 1) and irinotecan hydrochloride (60 mg/m^2, days 1, 8, and 15) every 4 weeks
3) platinum-taxane combination CT:

   i) TP therapy: paclitaxel (135 mg/m2, day 1) and cisplatin (50 mg/m2, day 1) every 3–4 weeks
   ii) TC therapy: paclitaxel (180 mg/m^2, day 1) and carboplatin (area under the receiver operating characteristic curve [AUC]=5, day 1) every 3–4 weeks
   iii) DC therapy: docetaxel (60 mg/m^2, day 1) and carboplatin (AUC=5, day 1) every 3–4 weeks
   iv) DP therapy: docetaxel (60 mg/m^2, day 1) and cisplatin (50 mg/m^2, day 1) every 3–4 weeks
   v) TN therapy: paclitaxel (175 mg/m^2, day 1) and nedaplatin (80 mg/m^2, day 1) every 3–4 weeks
   vi) DN therapy: docetaxel (70 mg/m^2, day 1) and nedaplatin (80 mg/m^2, day 1) every 3–4 weeks

Patients received 3–6 cycles of primary CT.

4. Statistical analysis

Correlation of variables was evaluated with Fisher's exact test, χ^2 test, and Mann-Whitney U test. Survival rates were estimated by the Kaplan-Meier method. The log-rank test was used to compare survival curves. Outcome measures were disease-free survival (DFS) and disease-specific survival (DSS). We defined DFS as the time from initial treatment to first evidence of recurrent disease or death from any cause. DSS was defined as the time from the start of the initial treatment to death from ovarian carcinoma or death secondary to treatment. Patients known to be still alive or lost to follow-up at the time of analysis were censored at their last follow-up. Cox regression analysis was used to select the risk factors for prognosis. Eleven variables were included, and each was dichotomized as follows: age (less than the median vs. at or higher than the median), study period (1995–2004 vs. 2005–2015), histology (pure type vs. mixed type), pT (pT1 vs. pT2), peritoneal cytology (negative/not available vs. positive), lymph node metastasis (LNM; pN0/pNx vs. pN1), radiologically enlarged lymph nodes (no

vs. yes), capsule rupture (no rupture/intraoperative capsule rupture vs. preoperative capsule rupture/surface involvement), pathological peritoneal involvement (negative/not available vs. positive), combined CT (not done vs. done), and type of lymphadenectomy (none/PLND-only vs. PLND+PAND). The statistical significance level was set at 0.05. Statistical analyses were performed with StatView J-5.0 (SAS Institute, Cary, NC, USA).

RESULTS

Patients' clinical and pathological characteristics are shown in **Table 1**. Their median age was 53 years. Of the 127 patients, 112 (88%) had pT1 disease. Four patients (3%) had bulky (radiologically enlarged) lymph nodes. Thirty-six patients (28%) did not undergo lymphadenectomy; 12 (10%) underwent PLND but did not PAND; and 79 (62%) patients underwent PLND+PAND. All patients with bulky lymph nodes underwent PLND+PAND. Of the 91 patients with lymphadenectomy, eleven (12%) had LNM. The pT1a and pT1c/pT2 groups

Table 1. Clinical characteristics of 127 patients with pT1/pT2 OCCC and without distant metastasis

Characteristics	Value
Age (yr)	Median 53 (range: 34–79)
Histological variant	
Pure type	118 (92.9)
Mixed type	9 (7.1)
pT	
Ia	34 (26.8)
Ic	78 (61.4)
II	15 (11.8)
pN	
pN0	80 (63.0)
pNx	36 (28.3)
pN1	11 (8.7)
Radiologically enlarged lymph nodes	
No	123 (96.9)
Yes	4 (3.1)
Peritoneal cytology	
Negative	92 (72.4)
Not available	2 (1.6)
Positive	33 (26.0)
Capsule rupture	
No rupture	35 (27.5)
Intraoperative capsule rupture	67 (52.8)
Preoperative capsule rupture/surface involvement	24 (18.9)
Not available	1 (0.8)
Pathological peritoneal involvement	
Negative/not available	116 (91.3)
Positive	11 (8.7)
Type of LND	
Not done	36 (28.3)
PLND-only	12 (9.5)
PLND+PAND	79 (62.2)
Combined CT	
Not done	34 (26.8)
Platinum-based CT	61 (48.0)
Nonplatinum-based CT	32 (25.2)

Values are presented as number of patients (%).
CT, chemotherapy; LND, lymph node dissection; OCCC, ovarian clear cell carcinoma; PAND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection.

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did not significantly differ in LNM (9% [2/23] vs. 13% [9/68], p=0.720). Two patients with pT1a and pN1 had bulky lymph nodes. The median number of harvested lymph node was 55 from these 91 patients, and 22 from the 12 patients who underwent PLND-only. The PLND+PAND group (n=79) had a median 41 pelvic lymph nodes and 18 para-aortic lymph nodes removed. Most patients (n=126) had no macroscopically residual disease after surgical treatment. Ninety-three (73%) patients received systemic CT as a primary treatment. Adjuvant CT was administered to 86.0% of patients with pT1c/pT2 disease, but only 38.2% of patients with pT1a disease (p<0.001). All patients with pN1 received adjuvant CT. The most frequent use of systemic CT was platinum-taxane combination CT (n=37), followed by irinotecan-mitomycin combination CT (n=26), and platinum-irinotecan combination CT (n=19).

Comparability of clinicopathological characteristics with or without PAND were shown in **Table 2**. The 2 groups did not significantly differ in age, histological variant, pT status, pN status, radiologically enlarged lymph nodes, capsule rupture, peritoneal involvement, or combined CT. The $PAND^-$ group had nonsignificant 11.8% higher rate of positive peritoneal cytology than did the $PAND^+$ group (p=0.140).

Kaplan-Meier curves by LND type are shown in **Fig. 1**. DFS differed significantly between the PLND-only and PLND+PAND groups (log-rank test, p=0.011), but not between the PLND-only and no lymphadenectomy groups (log-rank test, p=0.320). DSS differed significantly between the PLND-only and PLND+PAND groups (log-rank test, p=0.035), but there was

Table 2. Comparability of clinicopathological characteristics with or without PAND

Characteristics	Type of lymphadenectomy		p-value
	None/PLND-only	PLND+PAND	
Age (yr)	53.8 (±9.3)	53.9 (±10.1)	0.910
Study period			
1995–2004	31 (64.6)	16 (20.3)	<0.001
2005–2015	17 (35.4)	63 (79.7)	
Histological variant			0.300
Pure type	43 (90.0)	75 (94.9)	
Mixed type	5 (10.0)	4 (5.1)	
pT			0.850
pT1	42 (87.5)	70 (88.6)	
pT2	6 (12.5)	9 (11.4)	
pN			0.210
pN0/pNx	46 (95.8)	70 (88.6)	
pN1	2 (4.2)	9 (11.4)	
Radiologically enlarged lymph nodes			0.300
No	48 (100.0)	75 (94.9)	
Yes	0 (0)	4 (5.1)	
Peritoneal cytology			0.140
Negative	32 (66.7)	62 (78.5)	
Positive	16 (33.3)	17 (21.5)	
Capsule rupture			0.240
No rupture/intraoperative capsule rupture	36 (75.0)	66 (83.5)	
Preoperative capsule rupture/surface involvement	12 (25.0)	13 (16.5)	
Pathological peritoneal involvement			>0.990
Negative/not available	44 (91.7)	72 (91.1)	
Positive	4 (8.3)	7 (8.9)	
Combined CT			0.730
Not done	12 (25.0)	22 (27.8)	
Done	36 (75.0)	57 (72.2)	

Values are presented as mean (±SD) or number (%).
CT, chemotherapy; PAND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection, SD, standard deviation.

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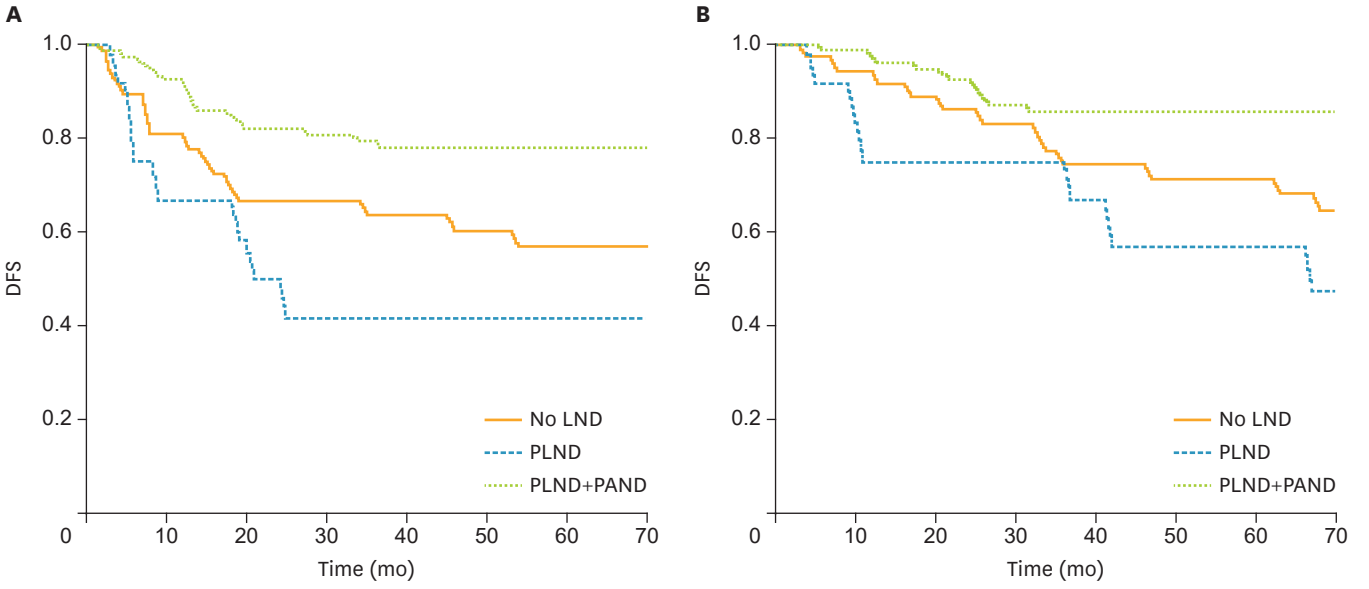

Fig. 1. (A) Univariate Kaplan-Meier survival plot of DFS in 127 patients by type of surgery (log-rank test p=0.011 for PLND+PAND vs. PLND; p=0.320 for PLND vs. No LND). (B) Univariate Kaplan-Meier survival plot of DSS in 127 patients by type of surgery (log-rank test p=0.035 for PLND+PAND vs. PLND; p=0.380 for PLND vs. No LND). DFS, disease-free survival; DSS, disease-specific survival; LND, lymph node dissection; PAND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection.

no difference between the PLND-only and no-lymphadenectomy groups (log-rank test, p=0.39). **Table 3** shows the results of Cox regression analysis of prognostic factors for DFS. Multivariate analysis confirmed that older age (hazard ratio [HR]=1.9; 95% confidence interval [CI]=1.0–3.6), LNM (HR=4.3; 95% CI=1.9–9.9), and positive peritoneal cytology (HR=4.8; 95% CI=2.5–9.0) were significantly and independently related to poor outcomes, but implementation of full lymphadenectomy (HR=0.4; 95% CI=0.2–0.8) were significantly and independently related to improved outcomes. **Table 4** shows the results of Cox regression analysis of prognostic factors for DSS. Multivariate analysis confirmed that older age (HR=2.1; 95% CI=1.0–4.3), LNM (HR=4.4; 95% CI=1.7–11.6), and positive peritoneal cytology (HR=4.2; 95% CI=2.1–8.4) were significantly and independently related to poor outcomes, but implementation of PLND+PAND (HR=0.4; 95% CI=0.2–0.8) were significantly and independently related to improved outcomes.

Initial failure according to the type of surgery is shown in **Table 5**. Lymphatic failure was significantly higher in the PLND-only/no lymphadenectomy group compared with the PLND+PAND group (25% [12/48] vs. 6% [5/79], p=0.003). There was no significant difference in hematologic failure (4% [2/48] vs. 6% [5/79], p=0.600) or peritoneal failure between the 2 groups (25% [12/48] vs. 15% [12/79], p=0.170).

DISCUSSION

The therapeutic significance of systematic lymphadenectomy in OCCC has been the subject of conflicting views. Although some studies have shown negative results [14,15], their limitations imply that their findings are inconclusive. First, these studies lacked information on postoperative resection status. As previously described, OCCC tends to respond poorly to conventional platinum-based CT. Therefore, macroscopic residual disease must be a critical predictor of poor survival, and this factor might have greatly influenced their results.

Table 3. Prognostic factors for DFS rates selected by Cox proportional hazard model analysis

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (yr)						
≤53	1.00	-	-	1.00	-	-
≥54	1.26	0.69–2.30	0.460	1.90	1.01–3.56	0.046
Study period						
1995–2004	1.00	-	-			
2005–2015	0.69	0.38–1.27	0.240			
Histology						
Pure type	1.00	-	-			
Mixed type	1.06	0.33–3.44	0.920			
pT						
pT1	1.00	-	-			
pT2	4.10	1.98–8.47	<0.001			
pN						
pN0/pNx	1.00	-	-	1.00	-	-
pN1	3.98	1.82–8.70	<0.001	4.27	1.85–9.90	<0.001
Radiologically enlarged lymph nodes						
No	1.00	-	-			
Yes	3.51	1.08–11.40	0.040			
Peritoneal cytology						
Negative/not available	1.00	-	-	1.00	-	-
Positive	5.21	2.82–9.62	<0.001	4.78	2.54–9.01	<0.001
Capsule rupture						
No rupture/intraoperative capsule rupture	1.00	-	-			
Preoperative capsule rupture/surface involvement	3.00	1.57–5.72	<0.001			
Pathological peritoneal involvement						
Negative/not available	1.00	-	-			
Positive	3.36	1.47–7.63	0.004			
Combined CT						
Not done	1.00	-	-			
Done	2.31	0.97–5.49	0.058			
Type of lymphadenectomy						
None/PLND-only	1.00	-	-	1.00	-	-
PLND+PAND	0.48	0.26–0.88	0.018	0.41	0.21–0.79	0.007

CI, confidence interval; CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; PAND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection.

The potential benefit of full lymphadenectomy should be discussed on the premise that all macroscopic local disease can be removed. Second, major problem of a negative study was distribution imbalance of peritoneal cytology [14]. Earlier studies have reported that peritoneal cytology [15], pT status [21-23], and LNM [15,16] to be potential prognostic factors for patients with OCCC. Survival impact and clinical relevance of lymphadenectomy should be assessed by adjusting these potential prognostic factors. Third, eligible subjects were OCCC grossly confined to the ovary in another negative study [15]; a major problem of this study might have been its low rate of LNM (7.1% [10/134]). LNM rate in stage I OCCC is 4%–10% [16,18,19], which is lower than that in ovarian serous adenocarcinoma [20], and might be too low to detect a survival benefit for lymphadenectomy statistically. We do not intend to raise an objection to results of previous negative study for therapeutic efficacy of lymphadenectomy. Their results may be correct, as the probability of LNM in early-stage OCCC may be considered low enough to forego lymphadenectomy. However, this could be considered to be a utilitarian approach with an emphasis on economic efficiency, at the potential expense of a minority of patients with poor prognoses, who would thus be deprived of the opportunity to undergo optimal surgeries. Regarding the treatment strategy for OCCC patients at risk LNM, we wish to question the emphasis placed on the low prevalence of LNM in OCCC and ask if its prognostic risk has been fairly assessed.

Table 4. Prognostic factors for DSS rates selected by Cox proportional hazard model analysis

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (yr)						
≤53	1.00	-	-	1.00	-	-
≥54	1.46	0.73–2.92	0.280	2.09	1.01–4.31	0.046
Study period						
1995–2004	1.00	-	-			
2005–2015	0.91	0.45–1.84	0.790			
Histology						
Pure type	1.00	-	-			
Mixed type	1.37	0.42–4.49	0.600			
pT						
pT1	1.00	-	-			
pT2	3.33	1.43–7.75	0.005			
pN						
pN0/pNx	1.00	-	-	1.00	-	-
pN1	3.76	1.54–9.17	0.004	4.42	1.68–11.60	0.003
Radiologically enlarged lymph nodes						
No	1.00	-	-			
Yes	2.51	0.60–10.50	0.210			
Peritoneal cytology						
Negative/not available	1.00	-	-	1.00	-	-
Positive	4.59	2.30–9.17	<0.001	4.18	2.07–8.40	<0.001
Capsule rupture						
No rupture/intraoperative capsule rupture	1.00	-	-			
Preoperative capsule rupture/surface involvement	2.22	1.05–4.67	0.036			
Pathological peritoneal involvement						
Negative/not available	1.00	-	-			
Positive	2.07	0.72–5.92	0.170			
Combined CT						
Not done	1.00	-	-			
Done	2.53	0.89–7.22	0.083			
Type of lymphadenectomy						
None/PLND-only	1.00	-	-	1.00	-	-
PLND+PAND	0.45	0.23–0.90	0.025	0.36	0.17–0.77	0.008

CI, confidence interval; CT, chemotherapy; DSS, disease-specific survival; HR, hazard ratio; PAND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection.

Table 5. Initial failure pattern according to type of surgery

Failure patterns	No LND(n=36)	PLND-only(n=12)	PLND+PAND(n=79)	p-value
Lymphatic spread	9 (25.0)	3 (25.0)	5 (6.3)	0.012
Lymphatic spread only	8 (22.2)	2 (16.7)	4 (5.1)	0.020
Regional node* only	5 (13.9)	1 (8.3)	1 (1.3)	0.021
Hematologic spread	1 (2.8)	1 (8.3)	5 (6.3)	0.670
Peritoneal spread	6 (16.7)	6 (50.0)	12 (15.2)	0.015

Values are presented as number (%).
LND, lymph node dissection; PAND, para-aortic lymph node dissection; PLND, pelvic lymph node dissection.
*Pelvic and para-aortic lymph nodes.

The present results suggest that some patients with selected early-stage OCCC benefit from full lymphadenectomy. Other studies also supported survival benefit of more extensive lymphadenectomy in OCCC. A large population-based study based on the SEER database [16] indicated a nonsignificant trend toward longer survival in patients without LNM who undergo more extensive lymphadenectomies (HR=0.71; 95% CI=0.49–1.02; p=0.064), which implies an importance of complete resection, including microscopic nodal metastasis, in the treatment of OCCC. In 2011, a multicenter cooperated study based on data from 240 patients with OCCC [17] found DFS was longer in patients who underwent lymphadenectomy

(p<0.001), both in early-stage (p=0.026) and advanced-stage disease (p=0.004); and independently associated lymphadenectomy (done vs. not done) and stage (I and II vs. III and IV) with longer DFS and overall survival in multivariate analysis. These positive results regarding the clinical relevance of lymphadenectomy in OCCC should not be disregarded by totally opposite conclusions in some previous RCTs [2,3]. These RCTs were targeted at ovarian cancers that are not otherwise specified. In such a population, therapeutic significance of lymphadenectomy must be reduced by conventional platinum-based CT because many subjects should have shown its chemo-sensitive nature. In light of its chemo-resistant nature, OCCC should not be discussed in the same category as other types of ovarian histology.

Every possibly relevant prognostic factor was investigated and compared between the 2 groups in our study, including data on bulky lymph nodes and postoperative resection status, which have not been widely addressed in previous studies. Nevertheless, this study was inevitably subject to selection bias because of its retrospective nature, and because it was a single-institution study. In addition, the number of patients was too small to produce conclusive results. Therefore, our findings should be verified in a larger study. In particular, full lymphadenectomy should be assessed because OCCC has a poor response to conventional platinum-based CT, making complete resection more critical. As the para-aortic lymph nodes are inarguably regional lymph nodes in ovarian cancer, PLND+PAND is the only procedure that covers all regional lymph nodes and is therefore a potentially optimal lymphadenectomy. In terms of study eligibility, low-risk patients with early-stage OCCC—namely, those who have pT1a disease without bulky lymph nodes—might not be investigated because they are much less likely to benefit from systematic lymphadenectomy. In addition, the premise that every macroscopic disease is removed may affect eligibility. Subjects who might benefit from full lymphadenectomy include those with pT1a disease with bulky lymph nodes, pT1c disease, or macroscopically resected pT2 disease. Speculatively, a prospective RCT that compares full lymphadenectomy vs. no lymphadenectomy in such selected patients with early-stage OCCC is ideal. We suggest that gynecologic oncologists should consider establishing treatment strategies aimed at the specific care of high-risk minorities, such as OCCC patients at risk for LNM.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7-30.
PUBMED | CROSSREF
2. Panici PB, Maggioni A, Hacker N, Landoni F, Ackermann S, Campagnutta E, et al. Systematic aortic and pelvic lymphadenectomy versus resection of bulky nodes only in optimally debulked advanced ovarian cancer: a randomized clinical trial. J Natl Cancer Inst 2005;97:560-6.
PUBMED | CROSSREF
3. Maggioni A, Benedetti Panici P, Dell'Anna T, Landoni F, Lissoni A, Pellegrino A, et al. Randomised study of systematic lymphadenectomy in patients with epithelial ovarian cancer macroscopically confined to the pelvis. Br J Cancer 2006;95:699-704.
PUBMED | CROSSREF
4. Chan JK, Munro EG, Cheung MK, Husain A, Teng NN, Berek JS, et al. Association of lymphadenectomy and survival in stage I ovarian cancer patients. Obstet Gynecol 2007;109:12-9.
PUBMED | CROSSREF
5. Trimbos JB, Vergote I, Bolis G, Vermorken JB, Mangioni C, Madronal C, et al. Impact of adjuvant chemotherapy and surgical staging in early-stage ovarian carcinoma: European Organisation for Research and Treatment of Cancer-Adjuvant ChemoTherapy in Ovarian Neoplasm trial. J Natl Cancer Inst 2003;95:113-25.
PUBMED | CROSSREF

6. Crawford SC, Vasey PA, Paul J, Hay A, Davis JA, Kaye SB. Does aggressive surgery only benefit patients with less advanced ovarian cancer? Results from an international comparison within the SCOTROC-1 Trial. J Clin Oncol 2005;23:8802-11.
PUBMED | CROSSREF
7. du Bois A, Reuss A, Harter P, Pujade-Lauraine E, Ray-Coquard I, Pfisterer J, et al. Potential role of lymphadenectomy in advanced ovarian cancer: a combined exploratory analysis of three prospectively randomized phase III multicenter trials. J Clin Oncol 2010;28:1733-9.
PUBMED | CROSSREF
8. Todo Y, Sakuragi N. Randomized controlled trial versus comparative cohort study in verifying the therapeutic role of lymphadenectomy in endometrial cancer. Int J Clin Oncol 2013;18:200-6.
PUBMED | CROSSREF
9. Anglesio MS, Carey MS, Köbel M, Mackay H, Huntsman DGVancouver Ovarian Clear Cell Symposium Speakers. Clear cell carcinoma of the ovary: a report from the first Ovarian Clear Cell Symposium, June 24th, 2010. Gynecol Oncol 2011;121:407-15.
PUBMED | CROSSREF
10. Okamoto A, Glasspool RM, Mabuchi S, Matsumura N, Nomura H, Itamochi H, et al. Gynecologic Cancer InterGroup (GCIG) consensus review for clear cell carcinoma of the ovary. Int J Gynecol Cancer 2014;24:S20-5.
PUBMED | CROSSREF
11. Sugiyama T, Kamura T, Kigawa J, Terakawa N, Kikuchi Y, Kita T, et al. Clinical characteristics of clear cell carcinoma of the ovary: a distinct histologic type with poor prognosis and resistance to platinum-based chemotherapy. Cancer 2000;88:2584-9.
PUBMED | CROSSREF
12. Köbel M, Kalloger SE, Santos JL, Huntsman DG, Gilks CB, Swenerton KD. Tumor type and substage predict survival in stage I and II ovarian carcinoma: insights and implications. Gynecol Oncol 2010;116:50-6.
PUBMED | CROSSREF
13. Chan JK, Teoh D, Hu JM, Shin JY, Osann K, Kapp DS. Do clear cell ovarian carcinomas have poorer prognosis compared to other epithelial cell types? A study of 1411 clear cell ovarian cancers. Gynecol Oncol 2008;109:370-6.
PUBMED | CROSSREF
14. Suzuki S, Kajiyama H, Shibata K, Ino K, Nawa A, Sakakibara K, et al. Is there any association between retroperitoneal lymphadenectomy and survival benefit in ovarian clear cell carcinoma patients? Ann Oncol 2008;19:1284-7.
PUBMED | CROSSREF
15. Takano M, Sugiyama T, Yaegashi N, Suzuki M, Tsuda H, Sagae S, et al. The impact of complete surgical staging upon survival in early-stage ovarian clear cell carcinoma: a multi-institutional retrospective study. Int J Gynecol Cancer 2009;19:1353-7.
PUBMED | CROSSREF
16. Mahdi H, Moslemi-Kebria M, Levinson KL, Gojayev A, Lockhart D, Ali-Fehmi R, et al. Prevalence and prognostic impact of lymphadenectomy and lymph node metastasis in clinically early-stage ovarian clear cell carcinoma. Int J Gynecol Cancer 2013;23:1226-30.
PUBMED | CROSSREF
17. Magazzino F, Katsaros D, Ottaiano A, Gadducci A, Pisano C, Sorio R, et al. Surgical and medical treatment of clear cell ovarian cancer: results from the multicenter Italian Trials in Ovarian Cancer (MITO) 9 retrospective study. Int J Gynecol Cancer 2011;21:1063-70.
PUBMED | CROSSREF
18. Mueller JJ, Holzapfel M, Han CH, Santos K, Gunderson C, Moore K, et al. Staging lymphadenectomy in patients with clear cell carcinoma of the ovary. Int J Gynecol Cancer 2016;26:120-4.
PUBMED | CROSSREF
19. Takano M, Kikuchi Y, Yaegashi N, Kuzuya K, Ueki M, Tsuda H, et al. Clear cell carcinoma of the ovary: a retrospective multicentre experience of 254 patients with complete surgical staging. Br J Cancer 2006;94:1369-74.
PUBMED | CROSSREF
20. Takano M, Tsuda H, Sugiyama T. Clear cell carcinoma of the ovary: is there a role of histology-specific treatment? J Exp Clin Cancer Res 2012;31:53.
PUBMED | CROSSREF
21. Suh DH, Park JY, Lee JY, Kim BG, Lim MC, Kim JW, et al. The clinical value of surgeons' efforts of preventing intraoperative tumor rupture in stage I clear cell carcinoma of the ovary: a Korean multicenter study. Gynecol Oncol 2015;137:412-7.
PUBMED | CROSSREF

22. Higashi M, Kajiyama H, Shibata K, Mizuno M, Mizuno K, Hosono S, et al. Survival impact of capsule rupture in stage I clear cell carcinoma of the ovary in comparison with other histological types. Gynecol Oncol 2011;123:474-8.
PUBMED | CROSSREF
23. Kajiyama H, Mizuno M, Shibata K, Umezu T, Suzuki S, Yamamoto E, et al. A recurrence-predicting prognostic factor for patients with ovarian clear-cell adenocarcinoma at reproductive age. Int J Clin Oncol 2014;19:921-7.
PUBMED | CROSSREF