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Staging Lymphadenectomy in Patients with Clear Cell Carcinoma of the Ovary

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Abstract

Objective—The purpose of this study was to assess the rate of lymph node (LN) metastasis in comprehensively staged ovarian clear cell carcinoma (OCCC) clinically confined to the ovary and determine factors associated with LN metastasis.

Methods—We identified all cases of OCCC treated at four institutions from January 1994 through December 2011. We included cases with disease grossly confined to the ovary that had surgical staging performed, including at least 10 LNs sampled. Clinical and pathologic data were abstracted from electronic medical records and a de-identified data set was compiled and processed at a single institution. Factors potentially associated with LN metastasis were tested. Appropriate statistical tests were performed.

Results—We identified 145 eligible cases that met the criteria for this analysis. Median age was 52.9 years (range, 30–81), and median total LN count was 19 (range, 10–74). Seven (4.8%) of 145 comprehensively staged cases had LN metastasis; 6 of these cases (4.1%) were isolated metastasis. Cytologic washings, peritoneal, omental and fallopian tube involvement were not associated with nodal metastasis. Cases with ovarian surface involvement and positive cytology had a 37.5%

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incidence of LN positivity, which was statistically meaningful when compared with all other cases (p=0.003).

Conclusion—Women who underwent comprehensive staging for clinical stage I OCCC had a LN metastasis rate of 4.8%. The subgroup of cases with both ovarian surface involvement and positive cytology had the highest incidence of LN metastasis. This may influence clinical decision making on whether to perform lymphadenectomy in patients with incidental OCCC found after salpingo-oophorectomy.

Keywords

ovarian cancer; lymph node; metastasis; staging

Introduction

Ovarian clear cell carcinoma (OCCC) is a rare histologic subtype comprising approximately 5% of all epithelial ovarian cancers [1–4]. This tumor subtype tends to present in early stages of disease, commonly confined to one ovary. Patients frequently present with a symptomatic dominant ovarian mass and a history of endometriosis or pelvic pain. Thromboembolic events are found disproportionately in this epithelial ovarian cancer subtype [1]. This tumor subtype is associated with poor outcomes and is less sensitive to conventional platinum-based chemotherapy regimens compared with serous type epithelial ovarian cancer.

National guidelines support comprehensive staging for high-risk epithelial ovarian malignancies including clear cell histology. Patients who undergo comprehensive staging will have their uterus, adnexa, omentum, and pelvic and paraaortic lymph nodes removed with directed peritoneal biopsies and pelvic washings based on the current National Comprehensive Cancer Network (NCCN) guidelines. The guidelines for surgical staging are primarily based on serous epithelial ovarian cancer pathophysiology, which has a substantial risk of nodal metastasis of approximately 15% in apparent early-stage disease [5].

Surgical staging of ovarian cancer aids in prognostication and adjuvant treatment decision making. Although clear cell tumors are grouped with serous type epithelial ovarian cancer, it is not clear whether lymph node dissection in these cases improves oncologic outcome [2, 6–10]. We sought to determine the rate of lymph node metastasis in comprehensively staged OCCC clinically confined to one ovary and to determine factors associated with lymph node involvement.

Materials and Methods

Four institutions obtained institutional review board (IRB) approval to retrospectively review medical records from January 1994 through December 2011. There were 336 patients with OCCC identified across all institutions. At each institution, clinical and pathologic data, including patient demographics, were abstracted from the medical records.

Patients were included in the study if they were surgically treated at the primary institution and diagnosed with OCCC by internal pathology review and deemed stage I at the time of

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intraoperative assessment. Patients were excluded from analysis if they did not receive upfront surgery or had disease anywhere outside the ovary at time of initial surgery. With the exception of fertility preservation cases, comprehensive surgical staging included hysterectomy, bilateral salpingo-oopherectomy, and lymph node dissection, with at least 10 lymph nodes sampled. Ten lymph nodes was chosen as a minimum cutoff based on the Gynecologic Oncology Group criteria for adequate lymphadenectomy, keeping in line with current guidelines and publications [4, 10, 11]. The incidence of nodal metastasis in OCCC based on anatomic location has not been comprehensively described, and so patients who did not undergo a paraaortic lymph node dissection were still included if the minimum number of lymph nodes sampled was 10. Fertility preservation cases were included if one ovary and the uterus remained in a premenopausal patient in whom no evidence of extra-ovarian spread was seen at the time of surgery. All cases were reviewed by gynecologic pathologists at each respective cancer center.

Data were collected and de-identified at each institution in order to be compiled and evaluated at a single institution. Intraoperative and pathologic variables were assessed for their possible predictive value in association with lymph node metastasis. The following variables were included in the analysis: positive cytology, ovarian surface involvement, peritoneal involvement, omental involvement, and fallopian tube involvement based on final pathology results. We tested the association between presence of lymph node metastasis with ovarian surface involvement and cytology results. Descriptive statistics were reported as a median or percentage frequency with ranges included when appropriate. Associations between categorical covariates were assessed using χ^2 tests. All p values were reported and, when appropriate, were calculated using the Fisher exact test. All p values <0.05 were considered statistically significant. All statistical analyses were performed in SPSS version 21.0.

Results

Cohort with disease apparently confined to the ovary

We identified 336 cases of OCCC across the four institutional databases. Of these cases, 145 met the study inclusion criteria for analysis. The reasons for excluding the remaining 191 cases included the following: fewer than 10 lymph nodes were sampled (106, 55.5%), extra-ovarian disease was evident at primary surgery (81, 42.4%), neoadjuvant chemotherapy was administered (3, 1.6%), and 1 patient (0.5%) did not meet minimum staging criteria. The clinical, surgical, and pathologic characteristics of the 145 included cases are presented in Table 1. Median age was 52.9 years (range, 30–81 years), and median body mass index (BMI) was 25.8 kg/m^2 (range, 18–47.7 kg/m^2). Thirty cases (20.7%) had a first- or second-degree relative with breast cancer, and 6 (4.1%) had a first- or second-degree relative with ovarian cancer. The median preoperative CA-125 level was 44 units/mL (range, 4–39,180 units/mL).

The following surgical staging procedures were performed in the 145 study patients: bilateral salpingo-oopherectomy (134, 92.4%), hysterectomy (137, 94.5%), pelvic washings (137, 94.5%), peritoneal biopsies (136, 93.8%), and omentectomy (143, 98.6%). All 145 cases had at least 10 pelvic and/or paraaortic lymph nodes removed, with a median pelvic

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lymph node count of 13 (range, 2–45), median paraaortic lymph node count of 7 (range, 0–29), and median total lymph node count of 19 (range, 10–74). There were 6 (4.1%) cases that did not undergo paraaortic lymph node dissection. Disease characteristics were as follows: stage I, 113 (77.9%); unilateral tumors, 139 (95.9%); and median tumor size, 105 mm (range, 1–508 mm).

Upstaging in clinically apparent stage I OCCC

Among the 145 staged cases with ovarian-confined disease at the time of surgery and at least 10 lymph nodes removed, 32 (22.1%) were upstaged on final pathology. Seven (4.8%) had lymph node metastasis; 6 (4.1%) had isolated lymph node metastasis. Three (42.9%) of 7 cases had both pelvic and paraaortic nodal metastasis, and 3 (42.9%) cases had isolated paraaortic nodal metastasis. One case (14.2%) had an isolated pelvic nodal metastasis. In cases with isolated pelvic or paraaortic nodal metastasis, the number of positive nodes ranged from 1–2 lymph nodes. Cases with pelvic and paraaortic nodal metastasis had a range of 3–14 positive lymph nodes. Of the remaining upstaged cases, 10 (6.9%) had isolated fallopian tube or uterine disease, 7 (5.2%) of 136 had disease confined to the peritoneum, 1 (0.7%) had isolated omental disease, and 8 (5.5%) had multi-site disease within the abdomen and pelvis (Table 1). For comparison, among the 199 patients with ovarian-confined disease at the time of surgery in whom any number of lymph nodes were removed, 11 (5.5%) had lymph node metastasis.

Analysis of variables that may be associated with lymph node metastasis

Lymph node metastasis was noted in 3 (10.3%) of 29 cases with positive cytology compared to 3 (2.8%) of 108 cases with negative cytology (p=0.11). Lymph node metastasis was noted in 4 (11.8%) of 34 cases with tumor extension onto ovarian surface compared to 3 (2.8%) of 107 cases without ovarian surface involvement (p=0.06). Fallopian tube, omental, and peritoneal involvement were also assessed, but there were no statistically significant differences between lymph node positive and lymph node negative cases.

Of 133 cases with cytology and ovarian surface data, 8 (6.0%) had positive cytology and ovarian surface involvement. Lymph node metastasis was found in 3 (37.5%) of these 8 cases. There were only 3 (2.4%) cases with lymph node metastasis among the remaining 125 cases (p=0.003) (Table 2).

Discussion

In our multi-center retrospective study, 4.8% of all cases with disease grossly confined to the ovary had metastasis to lymph nodes. This rate is similar to those of prior published reports on the incidence of lymph node metastasis in apparent early-stage OCCC (Table 3) [4, 6, 10, 12]. The largest published series that examined lymph node metastasis in OCCC grossly confined to the ovary utilized population-based data. In 2013, Mahdi *et al.* published on nearly 1900 patients with OCCC confined to the ovary identified from the Surveillance, Epidemiology, and End Results (SEER) program. Of the 1359 (72%) cases undergoing surgery that included lymph node dissection, 61 (4.5%) were found to have positive lymph nodes and were subsequently upstaged to stage IIIC [4].

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Cases with clinically apparent stage I OCCC with positive cytology and ovarian surface involvement had a 37.5% incidence of lymph node metastasis, representing a relevant subgroup in our cohort. Our findings suggest it is plausible to limit the extent of lymph node dissection in select cases. This is also worthwhile when considering the potential morbidity associated with pelvic lymph node dissection, both intraoperatively (vascular and neurologic injury) and postoperatively (lymphedema and lymphocyst formation) with the aim of detecting a positive lymph node in only a minority of cases.

These findings may enrich clinical discussion with patients with an incidentally discovered OCCC who then present for oncologic consultation to consider completion staging.

Our data suggest staging lymphadenectomy is low yield in detecting nodal metastasis in OCCC cases lacking surface involvement or positive cytology. It is important to note, however, that due to small numbers, these data can be incorporated into a risks and benefits discussion but do not replace standard staging guidelines. Takada *et al.* published survival and recurrence data on 73 patients with stage I OCCC who were comprehensively staged over a 9-year study period [13]. On multivariate analysis, positive washings and/or ovarian surface involvement were independently related to both overall survival and progression-free survival regardless of adjuvant treatment. Findings from Takada *et al.* suggest patients with ovarian surface involvement and positive washings have the worst clinical outcomes regardless of nodal involvement. Takada's study lacks lymph node counts and combines two distinct groups—those with either positive cytology or surface involvement and those with both positive cytology and surface involvement, which limits interpretation. The median follow-up between the adjuvant treatment and no adjuvant treatment group was 30 versus 56 months, respectively. These follow-up times were significantly different and may have influenced patient outcomes.

The current management strategy for stage I OCCC is to administer 3–6 cycles of a platinum-containing chemotherapy regimen [13–17]. The results of a phase III randomized clinical trial presented at the 2014 American Society of Clinical Oncology (ASCO) Annual Meeting [18] showed that a standard regimen of paclitaxel and carboplatin provides similar benefit to an alternative regimen of cisplatin with irinotecan. Both regimens were generally well tolerated, with more hematologic toxicity seen in the standard arm and more frequent gastrointestinal toxicity seen in the alternative regimen. The question remains as to whether a nodal metastasis rate of 4–5% is clinically relevant if adjuvant treatment is recommended even in stage IA cases. Based on current standard treatment guidelines for epithelial ovarian cancer, detecting nodal disease would not necessarily further tailor adjuvant treatment. Despite this, discussions about prognosis, fertility preservation, time to recurrence, and survival are impacted by stage and are relevant in the counseling and preparation for women facing this disease. Our study has several strengths when compared with the available literature. All of our cases were surgically managed by gynecologic oncologists at major cancer centers and underwent review by a gynecologic pathologist. In addition, we were able to collect data on the anatomic locations of lymphadenectomy. Future research for this and all other rare ovarian tumor types will benefit from multi-institutional, prospective databases and tumor registries in order to gain a more comprehensive understanding of patterns of disease, recurrence, and response to treatment.

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Much of the standard practice surrounding management and treatment of OCCC is extrapolated from larger prospective studies in epithelial ovarian cancer that include clear cell histologic subtypes, but represent only a small subset of all subjects enrolled. Despite this, much of the standard practice surrounding management and treatment of OCCC is extrapolated from these larger trials. Further work is needed to determine the most appropriate management of this rare disease. All women diagnosed with apparent early-stage OCCC need to be thoroughly counseled regarding the risks and benefits of staging including lymphadenectomy.

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Table 1

Cohort characteristics (N=145)

Variable	N (%)
Institution	
MSKCC	92 (63.4)
OU	24 (16.6)
CSMC	23 (15.9)
UA	6 (4.1)
Age, years	
Median (range)	52.9 (30–81)
BMI, kg/m^2	
Median (range)	25.8 (18–47.7)
Race	
Caucasian	121 (83.4)
Asian/Pacific Islander	16 (11.0)
African American/Black	2 (1.4)
American Indian/Native American	2 (1.4)
Other	3 (2.1)
Latino	1 (0.7)
Preoperative CA-125, units/mL	
Median (range)	44 (4–39,180)
Family history	
FDR/SDR with breast cancer	30 (20.7)
FDR/SDR with ovarian cancer	6 (4.1)
Stage *	
IA	43 (29.7)
IB	1 (0.7)
IC	69 (47.6)
IIA	2 (1.4)
IIB	5 (3.4)
IIC	12 (8.3)
IIIA	5 (3.4)
IIIB	1 (0.7)
IIIC	7 (4.8)
Staging procedures	
Hysterectomy	137 (94.5)
Bilateral salpingo-oophorectomy	134 (92.4)
Cytology	137 (94.5)

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Variable	N (%)
Peritoneal biopsy	136 (93.8)
Omentectomy	143 (98.6)
Lymph node dissection	145 (100)
Lymph node count	
Median pelvic (range)	13 (2–45)
Median paraaortic (range)	7 (0–29)
Median total (range)	19 (10–74)
Tumor size, mm	
Median (range)	105 (1–508)
Isolated metastasis on pathology	
Fallopian tube or uterus	10 (6.9)
Peritoneum	7 (5.2)
Omentum	1 (0.7)
Pelvic and/or paraaortic lymph node	6 (4.1)
Multisite disease on pathology	8 (5.5)

MSKCC = Memorial Sloan Kettering Cancer Center
CSMC = Cedars Sinai Medical Center
UA = University of Alabama
OU = Oklahoma University
BMI = body mass index
FDR/SDR = first-degree relative/second-degree relative

* 1998 FIGO staging

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Table 2

Association between pathologic features and nodal metastases

	n	Nodal metastases (%)	p value
Total Cohort	145	7 (4.8%)	
Cytology			
Positive	29	3 (10.3%)	
Negative	108	3 (2.8%)	.109
Total *	137	6 (4.4%)	
Peritoneum			
Positive	15	0	
Negative	121	5 (4.1%)	.552
Total *	136	5 (3.7%)	
Omentum			
Positive	5	0	
Negative	138	7 (5.1%)	.775
Total *	143	7 (4.9%)	
Fallopian Tube or Uterus			
Positive	13	1 (7.7%)	
Negative	132	6 (4.5%)	.489
Total	145	7 (4.8%)	
Ovarian Surface			
Positive	34	4 (11.8%)	
Negative	107	3 (2.8%)	.058
Total *	141	7 (5.0%)	
Ovarian surface/Cytology			
Both positive	8	3 (37.5%)	
All others	125	3 (2.4%)	.003
Total *	133	6 (4.5%)	

* Some totals will not equal 145 as data are missing or not reported in these cases.

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Table 3

Incidence of lymph node metastases in ovarian clear cell carcinoma grossly confined to the ovary

Series	N	No. positive (%)
Mahdi et al [4]	1238	54 (4.4)
Takano et al [6]	135	10 (7.4)
Nomura et al [10]	36	2 (5.6)
Ulker et al [12]	5	1 (20)
Mueller et al. (current study)	145	7 (4.8)
Total	1559	74 (4.7)