Published in final edited form as:

Obstet Gynecol. 2010 August ; 116(2 0 1): 269–273. doi:10.1097/AOG.0b013e3181e7961d.

Prevalence of lymph node metastasis in primary mucinous carcinoma of the ovary

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Abstract

Objective—Growing evidence suggests that primary mucinous ovarian carcinomas have a distinct clinical course when compared to serous ovarian carcinomas. While comprehensive surgical staging is recommended, little is known about the patterns of metastasis of mucinous ovarian carcinomas. The objective of our study was to estimate the prevalence of lymph node involvement in women with primary mucinous ovarian carcinomas.

Methods—A retrospective study of patients with primary mucinous ovarian carcinomas evaluated at a single institution between 1985 and 2007 was performed. A gynecologic oncology pathologist evaluated all cases. Patients with tumors of low malignant potential and mucinous carcinomas metastatic to the ovary from other primary sites were excluded.

Results—107 patients with primary mucinous ovarian carcinomas were identified. All patients underwent primary surgery. At time of surgery, 93 patients (87%) had tumor that grossly appeared to be confined to the ovary, and 14 patients (13%) had evidence of extraovarian disease. Of the 93 patients with tumor that grossly appeared to be confined to the ovary at surgical exploration, 51 (55%) underwent lymphadenectomy (n=27 pelvic and PA, n=19 pelvic only, n=5 PA only). Of these 51 patients, none had metastatic disease to the pelvic or PA lymph nodes. In addition, there were no significant differences in PFS and OS between the patients that underwent lymphadenectomy and those that did not.

Conclusion—There were no cases of isolated lymph node metastases among women with primary mucinous carcinoma grossly confined to the ovary, suggesting that routine lymphadenectomy may be omitted in these patients.

Introduction

Primary mucinous carcinomas of the ovary account for less than 5% of all invasive epithelial ovarian cancers (1, 2). When compared with serous carcinomas of the ovary, mucinous carcinomas have a distinct presentation, clinical course and response to therapy (2-4). The majority of mucinous ovarian carcinomas are well or moderately differentiated and are confined to the ovary at the time of diagnosis. These early stage mucinous ovarian carcinomas have significantly higher survival rates when compared with early stage serous ovarian carcinomas (3). However, patients with advanced stage mucinous ovarian carcinomas have been shown to have a lower response rate to platinum-based chemotherapy and a poorer prognosis when compared with serous tumors (2, 4-6).

While comprehensive surgical staging is recommended for all epithelial ovarian cancers, little is known about the patterns of metastasis of primary mucinous carcinomas of the ovary. In serous carcinomas of the ovary, approximately 10 to 20% of apparent stage I tumors will have occult nodal metastasis (7, 8). However, recent data suggest that in patients with mucinous tumors that appear to be confined to the ovary on surgical exploration, lymph node involvement is exceedingly low (7, 9). It therefore remains unclear if complete staging with systematic lymphadenectomy and its associated morbidity is beneficial in this group of patients. To further explore this issue, we estimated the prevalence of lymph node involvement in patients with primary mucinous carcinoma of the ovary. In addition, we compared recurrence rates and survival between patients undergoing lymphadenectomy and those who did not.

Materials and Methods

Following approval from the University of Texas M.D. Anderson Cancer Center Institutional Review Board, we searched the institutional databases of the departments of Gynecologic Oncology and Pathology at the University of Texas M.D. Anderson Cancer Center to identify patients with primary mucinous carcinoma of the ovary diagnosed between 1985 and 2007. The medical records were reviewed for age at diagnosis, ethnicity, surgical procedure performed, type and number of chemotherapy cycles administered, and vital status information. A gynecologic oncology pathologist evaluated all cases. Patients with tumors of low malignant potential without evidence of carcinoma and patients with mucinous carcinomas metastatic to the ovary from other primary sites were excluded.

Group comparisons of patient characteristics were conducted. Continuous variables were evaluated using Mann-Whitney and independent t-tests. Categorical variables were evaluated using Chi-square tests. Progression-free survival (PFS) and overall survival (OS) times were estimated using the method of Kaplan and Meier (10). PFS was defined as the date of diagnosis to disease progression or recurrence or to the date of death or last known contact, whichever occurred first. OS was defined as the date of diagnosis to the date of the patient's death or last known contact. The log-rank test was used to compare differences between the survival curves. A *P* value of <.05 was considered statistically significant. All *P* values were two-sided. Data were analyzed using SPSS 17.0 software (Chicago, IL).

Results

Our database search and pathology review identified 107 eligible patients with primary mucinous carcinoma of the ovary. Patient characteristics are shown in Table 1. Median age at diagnosis was 41 years (mean 43 years, range 16-82 years). Median tumor size was 16 cm (mean 19 cm, range 6-40 cm). Pre-operative CA 125 levels were available for 44 patients (median 35.4 U/ml, mean 75.1 U/ml, range 6.5 to 520.9 U/ml), and pre-operative carcinoembryonic antigen (CEA) levels were available for 18 patients (median 1.0 ng/ml, mean 24.3 ng/ml, range 1.0-178.4 ng/ml).

All 107 patients underwent primary surgery. None of the patients received neoadjuvant chemotherapy. At the time of surgery, 93 patients (87%) had tumor that grossly appeared to be confined to the ovary, and 14 patients (13%) had evidence of extraovarian disease (Figure 1). The sites of macroscopic disease in patients with extraovarian disease included the peritoneum (n=7), omentum and peritoneum (n=3), omentum (n=2), liver (n=1), and supraclavicular lymph node (n=1). Of the 14 patients with evidence of extraovarian disease, 6 (43%) underwent lymphadenectomy (pelvic and PA, n=1; pelvic only, n=4; PA only, n=1). Of these 6 patients with gross extraovarian disease who underwent lymphadenectomy, none had metastatic disease to the pelvic or PA lymph nodes.

Of the 93 patients with tumor that grossly appeared to be confined to the ovary at surgical exploration, 51 (55%) underwent lymphadenectomy (pelvic and PA, n=27; pelvic only, n=19; PA only, n=5) based on surgeon preference. Of these 51 patients, none had metastatic disease to the pelvic or PA lymph nodes. However eight patients (16%; 95%CI [8%, 28%]) had evidence of other microscopic disease (positive washings, n=6; peritoneum, n=1; diaphragm cytology, n=1). Of the 42 patients who did not undergo lymphadenectomy, five (12%; 95%CI [5%, 25%]) had evidence of microscopic disease (positive washings, n=4; omentum, n=1). Of all 93 patients with no gross extraovarian disease, 13 patients (14%; 95%CI [8%, 23%]) were upstaged based on additional biopsies at the time of surgery; however, none of these patients were upstaged based on lymph node involvement. Appendectomy with normal findings was performed at the time of primary surgery in 46 patients (43%), and there was documentation of previous appendectomy for benign reasons in 5 patients (5%).

There were no significant differences in age at diagnosis, tumor size and proportion of patients receiving chemotherapy between the group that underwent lymphadenectomy and the group that did not (Table 2). In addition, there were no significant differences in progression free survival (PFS) (p=.12) or overall survival (OS) (p=.23) between the two groups (Figure 2). The five-year PFS in the lymphadenectomy group was 80% (95% CI: 63-90%), compared with 63% in the group that did not undergo lymphadenectomy (95% CI: 44-76%). Similarly, the five-year OS rate was 83% (95% CI: 67-91%) in the patients who underwent lymphadenectomy compared with 69% (95%CI: 50% - 82%) in the patients who did not, and the ten-year overall survival rate was 75% (95%CI: 52%-88%) in the lymphadenectomy group and 69% (95%CI: 50%-82%) in the non-lymphadenectomy group.

Of the 93 patients with tumor that grossly appeared to be confined to the ovary at surgical exploration, 18 patients (19%) eventually developed recurrent disease, including 7 of the 51 patients (14%) who underwent lymphadenectomy and 11 of the 42 patients (26%) who did not undergo lymphadenectomy ($p=.13$). Recurrent disease included metastasis to lymph nodes in two patients. The first patient initially underwent hysterectomy, bilateral salpingo-oophorectomy, pelvic washings, omentectomy as well as pelvic and para-aortic lymphadenectomy. The final pathology showed positive pelvic washings, but no other evidence of extraovarian disease. She was subsequently treated with six cycles of paclitaxel and carboplatin. Six months following the completion of therapy, the patient was noted to have metastatic disease to the pelvic and para-aortic lymph nodes as well as several peritoneal implants and lung nodules. The second patient initially underwent a hysterectomy, bilateral salpingo-oophorectomy, omental and peritoneal biopsies. No lymphadenectomy was performed. The final pathology showed no evidence of extraovarian disease. The patient was subsequently treated with six cycles of paclitaxel and carboplatin. Five months after completing chemotherapy, she developed recurrent disease consisting of lung nodules, as well as mediastinal and para-aortic lymphadenopathy.

Discussion

The key finding from our study is that isolated lymph node metastasis in mucinous carcinoma of the ovary is exceedingly rare. In our cohort, 51 patients with mucinous carcinoma that grossly appeared to be confined to the ovary at surgical exploration underwent lymphadenectomy. None of these patients were found to have lymph node metastases. In addition, there were no significant differences in recurrence rates, PFS or OS between the women who underwent lymphadenectomy and those who did not.

Our findings are similar to previous studies. Morice and colleagues (7) evaluated lymphatic spread in 276 women with epithelial ovarian carcinoma who underwent systematic pelvic and para-aortic lymphadenectomy. Of the 30 patients with mucinous carcinomas, 4 (11%) had positive lymph nodes. However, of the 20 patients with mucinous tumors apparently confined to the ovary at surgical exploration, none were found to have nodal involvement (7).

A recent study by Cho *et al.* (9) reviewed the records of 264 patients with apparent early stage ovarian mucinous tumors. Of these, 85 patients had invasive ovarian cancer with 26 (31%) undergoing complete surgical staging and 59 (69%) incomplete surgical staging. Histopathologic results of extraovarian disease led to upstaging in 5 patients (6%) due to positive peritoneal cytology. However, there were no patients upstaged due to occult lymph node or omental metastasis. Similar to our findings, the authors noted no significant differences in recurrence rates, tumor-related death, PFS or OS relative to the completeness of staging. They concluded that complete surgical staging in patients with apparent stage I mucinous epithelial ovarian tumors would identify few patients requiring adjuvant therapy and could probably be omitted (9).

In summary, we found that none of the patients in our study with apparent early stage mucinous ovarian cancer had lymph node metastasis. This is consistent with previous

reports that also found no cases of isolated lymph node metastasis in primary mucinous ovarian cancer. Our study is limited by retrospective data collection, a long study period, small sample size and possible referral bias. In addition, there were varying surgical and chemotherapy treatment types used based on clinician preference. It also remains unclear if the lack of significant differences in recurrence rates and survival between patients undergoing lymphadenectomy compared with those that did not are due to our small sample size. Despite these limitations, our results suggest that routine lymphadenectomy may be omitted in women with clinically apparent early stage primary mucinous carcinoma of the ovary. In addition, our findings provide hypothesis-generating information to help in the design of future studies for this group of patients. Given the distinct clinical and pathologic characteristics of mucinous carcinomas, these tumors should be considered separately from other epithelial ovarian cancers. Prospective, multi-institutional clinical trials, focused specifically on mucinous ovarian carcinoma are needed to make meaningful advances in the treatment of this disease.

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Fig. 1.
Surgical and pathological findings.

a. Progression-free survival

b. Overall survival

Figure 2.

Progression-free (a) and overall survival (b) of patients with mucinous ovarian carcinomas.

Table 1

Demographic and Clinical Characteristics

Characteristic	Total (N = 107)	Disease confined to the ovary (N=93)	Extraovarian disease (N=14)
Age at diagnosis (years):			
Mean	43	42	49
Median	41	40	46
Range	16 - 82	16 - 82	32 - 77
Ethnicity:			
Caucasian	82 (77%)	70 (75%)	12 (86%)
African American	3 (3%)	2 (2%)	1 (7%)
Hispanic	10 (9%)	9 (10%)	1 (7%)
Asian	8 (7%)	8 (9%)	0 (0%)
Unknown	4 (4%)	4 (4%)	0 (0%)
Tumor size (cm):			
Mean	19	19	15
Median	16	16	16
Range	6 - 40	7 - 40	6 - 20

Table 2

Characteristics of patients undergoing lymphadenectomy compared with patients not undergoing lymphadenectomy

Characteristic	Lymphadenectomy (N = 51)	No Lymphadenectomy (N = 42)	P value
Age at diagnosis (years):			
Mean	40.5	43.1	.40
Median	41.0	39.5	
Range	16.5 – 69.7	22.4 – 81.9	
Tumor size (cm) ¹ :			
Mean	17.7	21.4	.12
Median	15.0	19.0	
Range	7.0 – 33.0	8.0 – 40.0	
Adjuvant chemotherapy (N (%)) ² :			
Yes	13 (25%)	10 (24%)	.47
No	37 (73%)	29 (69%)	
Unknown	1 (2%)	3 (7%)	
Recurrence (N (%)):			
Yes	7 (14%)	11 (26%)	.13
No	44 (86%)	31 (64%)	
Follow-up (months):			
Mean	63	67	
Median	34	46	
Range	1 - 254	2 - 220	

¹ Tumor size not available for 33 patients (lymphadenectomy, n=15; no lymphadenectomy, n=18)

² Unknown for 4 patients (lymphadenectomy, n=1; no lymphadenectomy, n=3)