Published in final edited form as:

Gynecol Oncol. 2013 April ; 129(1): 120–123. doi:10.1016/j.ygyno.2012.12.006.

Serial Sectioning of the Fallopian Tube Allows for Improved Identification of Primary Fallopian Tube Carcinoma

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Abstract

Objective—Serial sectioning of the fallopian tube in women undergoing risk reducing surgery has been shown to increase the detection rate of occult malignancy in BRCA mutation carriers. We undertook this study to determine whether this protocol at the time of surgery for ovarian cancer (OV) or primary peritoneal malignancies (PP) changes the detection rate of fallopian tube carcinoma (FT). We secondarily investigated where this difference affects patient outcomes.

Methods—A retrospective review of 130 patients treated at the University of Chicago Medical Center for ovarian, peritoneal or fallopian tube carcinoma was conducted. Sixty five patients diagnosed with OV, PP or FT who had serial sectioning of the fallopian tubes at the time of diagnoses (SS) were compared to 65 patients whose fallopian tubes were sectioned in a standard fashion (PSS).

Results—Serial sectioning of the fallopian tube at the time of pathologic examination in women with presumed OV or PP led to an increase in the number of women diagnosed with FT as the primary site of origin ($p < 0.001$). Clinical or pathologic risk factors leading to an increased risk of FT were not identified. Survival between the two groups was similar.

Conclusion—In women with presumed OV or PP, serial sectioning identifies women with FT. FT may be more common than previously noted, however distinct biologic or clinical behavior to differentiate it from OV or PP could not be identified. Clinical management of FT should continue to be the same as that of OV or PP.

Introduction

Epithelial ovarian cancer has long been thought to arise from the ovarian surface epithelium. The ovarian surface epithelium has a mesothelial origin whereas the uterus, cervix, and fallopian tube develop from the mullerian (paramesonephric) ducts. Early ovarian cancer has been thought to arise directly from the surface epithelium or its inclusions(1;2). The surface epithelial cells were thought to retain a pluripotent status, explaining their ease of transformation to malignancy. The “incessant ovulation” theory postulated that constant damage and repair to the surface epithelium predisposed this tissue to mutations leading to a

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None of the authors have conflicts of interest to report.

neoplastic transformation. Additionally, the ovary tends to contain the bulk of disease at the time of surgery for advanced pelvic high grade carcinoma(3;4). Studies aimed at defining a precursor lesion within the ovary, however, have to date been unsuccessful(5;6).

Until recently, the fallopian tube received little consideration as a significant source of serous carcinomas, given that the estimated incidence is 0.41 per 100,000 compared with an estimated incidence of 12.7 per 100,000 women for ovarian carcinoma (7-9). The identification and an understanding of the *BRCA* gene (1 and 2) changed this paradigm. As prophylactic bilateral salpingo-oophorectomy (BSO) as a risk reducing strategy for patients at high risk for the development of ovarian carcinoma was demonstrated to be effective at decreasing the incidence of high grade serous carcinoma(10-12), hyperplasia and dysplasia were found to be commonly present in the fallopian tubes of women at risk for the development of ovarian cancer(13). A reassessment of the incidence, prognostic and clinicopathological features of this malignancy became possible with the widespread practice of prophylactic BSO for management of patients with familial high risk. Close examination and rigorous pathologic serial sectioning of prophylactically removed fallopian tubes and ovaries in women carrying the *BRCA* 1 and 2 mutations revealed a higher than expected rate of early serous carcinomas of the fallopian tube as well as in-situ lesions, or serous tubal intraepithelial carcinoma (STIC)(3;14-17).

Subsequent studies in patients with high grade peritoneal carcinoma have also shown high rates of STIC, ranging from 36-47%(18-20). The SEE-FIM (sectioning and extensively examining the fimbriated ends) protocol is now widely used: the tube is serially cross-sectioned except the fimbriated end, which is amputated and sectioned longitudinally to maximize exposure of the fimbriae(18).

We undertook this study to determine whether serial sectioning of the fallopian tube at the time of surgery for ovarian or primary peritoneal malignancies changes the detection rate of fallopian tube carcinoma. We examined the clinical and pathologic risk factors for disease with intraperitoneal serous carcinomas to determine if the site of disease is affected by any of these risk factors. We examined whether site of disease affects or alters survival.

Methods

A review of patients undergoing surgery at the University of Chicago Medical Center for ovarian, primary peritoneal or fallopian tube carcinoma was conducted. Per protocol in the Department of Pathology all patients found to have ovarian or peritoneal carcinomas after April 2006 had their fallopian tubes serially sectioned to look for in situ carcinomas of the FT and to correctly assign a site of primary malignancy to the ovary, FT or peritoneum.

Patients were identified from an established dataset of women treated for ovarian cancer at the University of Chicago from 1992 to 2010. All women with International Federation of Gynecology and Obstetrics stage I–IV epithelial ovarian, fallopian, or peritoneal cancer diagnosed at this single institution are included in the dataset. As previously reported, the ovarian cancer dataset contains information on clinicopathologic parameters, treatment, and outcomes. Follow-up data are obtained from medical records at the University of Chicago, the Illinois Cancer Registry, the United States Social Security Index, and by communicating with physicians involved in the patient's care. This clinical information is stored in a Microsoft Access database (Version 2003-SP2) as previously reported.

Treatment consisted of either primary tumor debulking followed by platinum based chemotherapy or neo-adjuvant chemotherapy followed by surgery for those patients with advanced disease or co-morbidities, or in cases when the attending surgeon thought the cancer was unresectable. All surgical procedures were performed by one of five

Gynecologic Oncologists at the University of Chicago and all pathology was verified by a single gynecologic pathologist at the University of Chicago. All cases examined after April 2006 were examined by a single pathologist using the SEE-FIM (sectioning and extensively examining the fimbriated ends) protocol. The fimbriated end is amputated and sectioned longitudinally to maximize exposure of the fimbriae. The identification of carcinoma in-situ within the fallopian tube resulted in the case being labeled as a fallopian tube primary(20). Optimal debulking was defined by a residual tumor size of less than 1 cm at the completion of surgery.

Chi squared testing was used to compare categorical variables, t-tests and ANOVA testing were used to compare continuous variables and Kaplan-Meier curves were created to examine survival differences. SPSS version 19.0 was used to perform statistical analysis.

Results

130 patients were selected for evaluation. From April of 2006 until June 2009, 65 cases of ovarian, primary peritoneal or fallopian tube carcinoma were identified as cases for the serial sectioning cohort (SS). The 65 consecutive previous cases of ovarian, primary peritoneal or fallopian tube carcinoma were identified as controls. The number of patients diagnosed with ovarian, primary peritoneal or fallopian tube carcinoma in each cohort (prior to serial sectioning (PSS) and serial sectioned (SS)) is described in Table 1. Following the initiation of the serial sectioning protocol, a significant increase in diagnosed cases of fallopian tube carcinoma was seen ($p<0.001$).

Patient characteristics are described in Table 2. Patients were similar in age, racial characterization and family history of breast and ovarian cancer in the PSS and SS groups. Although patients diagnosed with ovarian cancer were statistically younger than those with primary peritoneal or fallopian tube carcinoma, this difference was not clinically meaningful. The patients were primarily diagnosed with serous carcinoma (81%). Although six patients in the PSS group had endometrioid histology, versus no patients in the SS group with endometrioid ovarian cancer, the two groups were similar in terms of the histologic types of cancer diagnosed. The majority of women in both groups had grade 3, stage III ovarian cancer at the time of diagnosis. Rates of optimal cytoreduction were similar in both groups (60% PSS versus 72% SS; $p=0.24$). In the SS group, patients were more likely to have undergone a surgical evaluation of their lymph nodes intraoperatively (70% versus 38%) but rates of positive lymph nodes were similar in both groups.

Progression free (PFS) and overall survival (OS) were similar when patients were compared by primary site of disease (Figure 1). Patients with the ovary as their primary site of disease had a median PFS of 16.1 months (95% CI = 11.1-21.1) versus 11.3 months (95% CI = 6.8–15.8) for primary peritoneal and 21.8 months (95% CI = 10.9–32.6) for women with primary fallopian tube carcinoma ($p=0.09$). Overall survival was 41.5 months (95% CI = 29.8-53.1) among women with ovarian cancer, 28.7 months (95% CI = 23.5-33.2) in women with primary peritoneal and 56.7 months (95% CI = 15.3-98.0) in women with fallopian tube primaries ($p=0.23$).

Overall survival was similar among the two study groups (PSS and SS) as shown in Figure 2 ($p=0.48$ and 0.12). PFS was 14.6 months (95% CI = 11.1-18.0) in the PSS group versus 16.1 months in the SS group (95% CI = 11.8-20.4). OS was 34.6 months (95% CI = 27.5-41.6) in the PSS group versus 41.5 months (95% CI = 21.7-61.2) in the SS group.

Survival was compared by disease site combined with group. There were no differences in median PFS or OS between patients with ovary PSS, peritoneum PSS, fallopian tube PSS, ovary SS, peritoneum SS or fallopian tube SS ($p=0.16$ and 0.08).

Patients with advanced (Stage III and IV) cancers had similar overall survival regardless of site of their primary disease ($p=0.16$). Patients with advanced ovarian cancer survived a median of 38.5 months (95% CI = 31.3-45.7) versus 28.4 months among women with primary peritoneal carcinoma (95% CI = 23.5-33.2) and 56.7 months (95% CI = 15.3-98.0) among women with fallopian tube carcinoma. When patients with clear cell, endometrioid and mucinous carcinomas were excluded from analysis, patients with serous carcinoma only had similar PFS and OS whether they were classified as FT, OV or PP ($p=0.22$ and 0.14 respectively). The median OS in women with serous ovarian cancer was 41.3 months (95% CI = 26.3-56.2), primary peritoneal was 28.4 months (95% CI = 23.5-33.2) and fallopian tube was 56.7 months (95% CI = 19.2-94.1).

Discussion

Extrauterine serous carcinoma has been presumed to arise in three different locations in the female pelvis: the ovary, the fallopian tube, and on the peritoneal surface. As the assignment of tumor origin by pathologists has been based upon pathologic criteria that focus on the location of the bulk of the disease, the diagnosis of fallopian tube carcinoma as the primary site of disease has been rare. Recently, it has been suggested that a subset of carcinomas that appear to be primary ovarian or peritoneal high-grade serous carcinoma may be of fallopian tube origin. This is based upon the identification of high-grade intraepithelial serous carcinomas in the fallopian tube of women at high risk of developing ovarian cancer, as well as in women with sporadic (non-hereditary) ovarian carcinoma (15-21).

In this study, we show that a substantial number of primary fallopian tube carcinomas can be identified by routine serial sectioning of the fallopian tube in patients with presumed ovarian carcinomas. Of 124 cases of metastatic pelvic malignancy (serous and endometrioid), Roh, et al. found a rate of in-situ carcinoma in the fallopian tube of 25%, which is very similar to our finding of 26.1%. The presence of a dominant ovarian mass in patients with metastatic pelvic carcinoma was infrequently associated with the finding of in-situ tubal carcinoma (11%) as compared to those women without a dominant ovarian mass (78%)(21).

Our study furthermore evaluated survival in women with fallopian tube, peritoneal and ovarian primary carcinomas. We found progression free and overall survival to be similar among these three groups. Previously, survival in patients with primary fallopian tube carcinoma had been largely determined by retrospective case series. In the single previous study to address the issue of survival in women with fallopian tube carcinoma, Moore et al. matched women with fallopian tube and ovarian carcinomas in a case-controlled study. Survival was similar between the 46 advanced staged tubal carcinomas and the 92 ovarian cancer controls(22).

We did see a trend towards improved overall survival in women diagnosed with ovarian or fallopian tube carcinoma as compared to those with primary peritoneal cancer ($p=0.09$). There are several possible explanations for this finding. All patients with primary peritoneal carcinoma are diagnosed with Stage III/IV disease as opposed to ovarian or tubal carcinomas, which can present as Stage I/II. When overall survival was compared only amongst advanced staged patients this difference became less pronounced. Although lymph nodes sampling was more common in the SS group, the rates of positive lymph nodes were similar. This difference in sampling is unlikely to have altered survival. The majority (74%) of women with primary peritoneal carcinoma were diagnosed in the PSS group. Although not statistically significant ($p=0.08$), overall survival was improved in the more recent group of patients presumably as a result of advances in care such as intraperitoneal chemotherapy and availability of anti-angiogenic and targeted therapies.

In conclusion, we have demonstrated an improved ability to differentiate ovarian from fallopian tube from primary peritoneal carcinomas in women with pelvic carcinomas when serial sectioning of the fallopian tube is performed. We have additionally demonstrated that survival for these three malignancies is similar when similar treatment is administered. In the setting of metastatic Mullerian carcinoma serial sectioning of the tube, despite allowing improved detection of fallopian tube carcinomas, does not alter treatment or improve prognosis.

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Figure 1. Progression free and overall survival in patients with ovarian, peritoneum and fallopian tube carcinoma during the study time period. $P = 0.23$ and 0.09 respectively.

Figure 2. Progression free and overall survival in patients prior to and following serial sectioning of the fallopian tube. $P = 0.48$ and 0.12 respectively.

Table 1

Number of patients diagnosed with ovarian, primary peritoneal or fallopian tube carcinoma in each cohort (prior to serial sectioning and serial sectioned).

		Prior to serial sectioning n (%)	Serial sectioned n (%)
Primary Site	Ovary	50 (76.9)	43 (66.2)
	Peritoneum	14 (21.5)	5 (7.7)
	Fallopian Tube	1 (1.6)	17 (26.1)
	Total	65	65

Table 2

Characteristics of patients.

Characteristic	Ovary (mean or N)	Peritoneum (mean or N)	Fallopian Tube (mean or N)	P Value
Age at diagnosis (yr)	58.13	66.11	68.56	<0.001
Ca-125 Pre-op	1544.15	1584.84	1082.22	0.932
Histology	93	19	18	0.266
Clear Cell	12	0	2	
Endometrioid	6	0	0	
Mucinous	4	0	0	
Serous-Papillary	71	19	16	
Ethnicity	93	19	18	0.701
African-American	21	3	2	
Asian	6	0	0	
Caucasian	64	16	16	
Hispanic	1	0	0	
Unknown	1	0	0	
Platinum Sensitivity	93	19	17	0.167
Sensitive	60	8	12	
Resistant	33	11	6	
Family History (Breast or Ovarian cancer)	93	19	18	0.676
No	72	12	12	
Yes	17	6	5	
Missing	4	1	1	
Stage	93	19	18	0.260
1	7	0	0	
2	2	0	0	
3	64	11	15	
4	20	8	3	
Tumor Grade	93	19	18	0.797
Well Differentiated	6	1	0	
Moderately Differentiated	15	3	2	
Poorly Differentiated	72	15	16	
Lymph Nodes	93	19	18	0.047
Negative	38	1	6	
Positive	17	4	4	
Missing	38	14	8	
Debulking	93	19	18	0.295
Optimal	66	9	11	

Characteristic	Ovary (mean or N)	Peritoneum (mean or N)	Fallopian Tube (mean or N)	P Value
Suboptimal	26	10	7	
Unknown	1	0	0	