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When ovarian cancer is not: characterizing non-ovarian cancer pathology in a laparoscopy-based triage system

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Abstract

Objective—Establishing an accurate histological diagnosis is essential for determining the appropriate course of therapy for ovarian cancer. This study sought to investigate and describe non-ovarian cancer pathologies discovered during the systematic laparoscopic workup of presumed advanced ovarian cancer.

Methods—A retrospective cohort of presumed advanced ovarian cancer patients (based on elevated CA125 and/or imaging) presenting to our center without confirmed pathologic diagnosis were identified and characterized. Patients without ovarian cancer on final pathology were described and compared to those with confirmed epithelial ovarian cancer using standard statistical methods.

Results—Non-ovarian cancer was found in 26/365 cases (7.1%) over 3.5 years of study, and included benign ovarian pathology, and metastatic uterine, breast and gastrointestinal cancers. Most non-ovarian cancer cases could not be diagnosed with percutaneous biopsy, and instead used diagnostic laparoscopy or assessment at time of laparotomy for diagnosis (58%). No patient received inappropriate treatment. Non-ovarian cancer cases were more likely to be non-white ($p=0.003$) have a better ECOG performance status ($p<0.001$), a lower CA125 value ($p<0.001$), and were less likely to have pleural effusions ($p=0.04$).

Conclusions—A systematic laparoscopic triage approach to advanced stage ovarian cancer eliminates incorrect neoadjuvant chemotherapy administration and inappropriate laparotomy. This algorithm identified a population of women who are more likely to have non-ovarian cancer pathology. Increasing screening efforts should be focused on conclusive diagnosis with the least invasive testing possible.

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INTRODUCTION

Ovarian cancer remains the eighth leading cause of death among cancers[1]. It lacks a reliable screening test and often eludes detection causing the majority of women with ovarian, fallopian tube, and primary peritoneal cancer (grouped here as ovarian cancer) to present at advanced stages (III-IV), with diffuse peritoneal carcinomatosis and ascites on imaging, and/or an elevated CA125 - prior to a definitive diagnosis[2]. These symptoms of metastatic disease may represent a primary ovarian malignancy, or other metastatic non-ovarian malignancies such as breast, gastrointestinal, or uterine cancers[3]. Therefore, the National Comprehensive Care Network (NCCN) guidelines clearly indicate the importance of referral to a gynecologic oncologist and a requirement to obtain a histopathologic diagnosis prior to the consideration of a definitive treatment plan, such as neo-adjuvant chemotherapy or primary debulking surgery[4]. This is essential, as either of these two treatments for non-ovarian malignancies may lead to inappropriate chemotherapies or non-indicated surgeries that compromise the delivery of quality care for the patient.

In 2013, the University of Texas MD Anderson adopted a triage algorithm to maximize patients who have no gross residual disease after primary debulking surgery, as women with microscopic residual disease have been shown to have superior survival[5]. In this algorithm[6], patients present with presumed advanced stage ovarian malignancy by clinical evaluation and imaging. Biopsy or fine-needle aspiration of extra-ovarian metastases or cytology of peritoneal fluid obtained via paracentesis is performed for histopathologic diagnosis when indicated. Patients who are deemed surgical candidates and do not have obvious signs of extra-peritoneal disease by imaging proceed to laparoscopy where assessment of the predictive index value (PIV) is performed by grading presence of tumor at six key sites, assigning two points for presence of tumor at each site. After full workup including staging laparoscopy and confirmation of ovarian malignancy, the assessed PIV is then used to decide on neo-adjuvant chemotherapy versus up-front debulking surgery, assigning patients to a primary debulking when less than eight, which has been shown to maximize optimal debulking rates[7]. This laparoscopic assessment also provides an additional diagnostic opportunity prior to laparotomy in patients without confirmed histopathologic diagnosis.

The rate of non-ovarian pathology in a clinically-assembled cohort of presumed advanced stage ovarian cancer presenting to a gynecologic oncologist has not been well defined[8–10]. This retrospective cohort study sought to identify women with unconfirmed but presumed advanced stage ovarian malignancy presenting to a tertiary care center implementing a systematic laparoscopy-based assessment, outline their clinical course, and to identify demographic and clinical covariates that may distinguish patients with an ovarian malignancy versus other pathology that may include benign disease or other non-ovarian pathology.

MATERIALS AND METHODS

This study was approved by the University of Texas MD Anderson institutional review board. Between January 2013 and Nov 2016, we identified all adult (>18 years) women who

presented to our center with presumed advanced stage ovarian malignancy based on imaging findings of an ovarian mass or carcinomatosis, and/or an elevated CA-125. Patients were excluded if they had a prior histopathologic diagnosis or surgery, or were censored prior to obtaining a histopathologic diagnosis due to death, transfer of care, or loss to followup. This defined a cohort of women with unconfirmed, presumed advanced stage ovarian malignancy undergoing our laparoscopy-based triage system. Data were entered in a clinical database maintained in RedCap[11] by a clinical data coordinator. Baseline demographic and clinical criteria were recorded and included the Charlson Comorbidity Index[12] and Eastern Cooperative Oncology Group (ECOG) score[13], among others. A gynecologic oncologist seeking to administer neoadjuvant chemotherapy or perform a primary debulking must determine the first binary question – whether the patient has an ovarian malignancy or not. Therefore, women were then separated into those *with* an ovarian malignancy on final debulking surgical specimen and those *without* an ovarian malignancy. When final surgical specimen was not available because surgery was not performed, the latest biopsy was used for final diagnosis. Centralized U.T. MD Anderson gynecologic pathologists read all specimens. Diagnostic methods and final histopathologic diagnosis were reported. If patients underwent multiple or concurrent procedures (i.e. core biopsy and a video-assisted thorascopic surgery (VATS)), both of these procedures were reported if they yielded conclusive results. Biopsies or final specimen at laparotomy, though, were reported separately if this was the only conclusive diagnosis. Ovarian, fallopian tube, primary peritoneal and abdominal Müllerian adenocarcinoma of unclear origin were all classified as an ovarian malignancy, while benign ovarian disease and non-ovarian metastatic malignancies were grouped together in a “non-ovarian cancer” group. Appropriate parametric and non-parametric tests of difference were used to compare demographic and clinical parameters between those who had an ovarian malignancy and those with other pathologies. A multivariable logistic regression was then performed to identify independent covariates that may predict non-ovarian malignancy[14]. All statistical tests were 2-sided tests of difference with $\alpha=0.05$, and performed in Stata version 12.1 (College Station, TX).

Assuming a 70%[8] rate of ovarian malignancy, this study required 303 women to have 80% power to detect a 20% difference of a hypothetical baseline covariate at 50% prevalence.

RESULTS

Data were recorded for 627 women with presumed advanced ovarian malignancy seen at the University of Texas MD Anderson Cancer Center for initial assessment between 1/23/2013 and 11/16/16 (Figure 1). Some women (n=50) did not receive any follow-up care as they were presenting for a second opinion, or were lost to follow up before further workup was performed. Among those women with complete diagnostic data, 212 had a histopathologic diagnosis prior to presentation for their first visit. A total of 365 were without a histopathologic diagnosis prior to their first appointment. As reported in Table 1, these women were mostly elderly with a median age 62, mostly Caucasian (85%), and of moderate health and performance status (Charlson comorbidity index median 3, ECOG median performance status 1). The majority (59%) had ascites on imaging and 29% had pleural effusions (Table 1). 144 women proceeded to laparotomy without diagnostic laparoscopy. Most women underwent a diagnostic laparoscopy to confirm the

histopathologic diagnosis (44%, Figure 1), while laparotomy was the next most common (29%) method of obtaining a final histopathologic diagnosis. These laparotomies were performed after a diagnostic laparoscopy where an incisional biopsy of the ovarian mass was avoided in lieu of resecting the primary ovarian mass intact via laparotomy, and an extra-ovarian mass was not present for biopsy. The majority (12/15) were in cases of benign disease, with the remaining three a biopsy negative metastatic breast cancer, a uterine clear cell carcinoma with concomitant D&C performed, and a uterine carcinosarcoma without uterine abnormality on CT imaging. No women received neo-adjuvant chemotherapy prior to confirmed tissue-based diagnosis.

The majority of women (93%) indeed had advanced stage ovarian cancer, most commonly serous histology (79%) with the remaining reported in Table 2. There were 26 cases (7%) of pathology other than ovarian cancer. Half had benign disease, mostly ovarian and adnexal cysts and one case of endometriosis (Table 2). The remaining half were non-ovarian cancers metastatic to the ovary and peritoneum. Among non-ovarian primary malignancies, most were of a gastrointestinal origin and included appendiceal mucinous subtypes (n=3), pancreatic origin (n=2), and one small intestinal adenocarcinoma primary. Other metastatic malignancies included uterine (one with clear cell and two with carcinosarcoma), and breast cancers (n=2), one peritoneal mesothelioma and one B-cell lymphoma. Non-ovarian cases were less likely to be diagnosed with a core biopsy ($p=0.02$) or fine-needle aspiration (FNA, $p=0.05$) performed by an interventional radiologist, and more likely to be diagnosed at laparotomy ($p=0.001$). Benign cases were the most likely (92%) to be conclusively diagnosed at laparotomy versus ovarian malignancy (27%) and other malignancies (23%). Among the 159 women who underwent laparoscopy, 10 did not have an ovarian malignancy. Among the 107 who underwent laparotomy only, 15 did not have ovarian cancer. This calculates to pathologies other than ovarian cancer detected in 6.3% in the diagnostic laparoscopy algorithm versus 14.0% in those who proceeded directly to laparotomy, suggesting a number needed to treat (NNT) with laparotomy of 13.7 to avoid futile laparotomy.

Race was statistically significant between groups ($p<0.001$), with non-whites more likely to have other pathologies ($p=0.003$). Patients ultimately diagnosed with benign disease or other metastatic cancers had a better ECOG performance status ($p<0.001$), a lower CA125 ($p<0.001$), and were less likely to have pleural effusions ($p=0.04$), though a similar proportion of ascites ($p=0.80$). Median CA125 was lowest in the benign group (75 mg/dl) when compared to ovarian cancer (520.7 mg/dl) and other malignancies (272.5 mg/dl) and were statistically significant in pair-wise comparisons. In a multivariable regression, CA125, race, and ECOG performance status remained as independent, statistically significant predictors of ovarian malignancy versus other pathology. In a second multivariable regression to predict other primary cancers metastatic to the ovary, race and performance status were predictive at a statistically significant level.

DISCUSSION

This study demonstrated that cases of presumed advanced ovarian cancer are successfully diagnosed with a laparoscopic-based algorithm to avoid inappropriate treatment, and also

identified a population of women more likely to have diagnoses other than ovarian malignancy. Core biopsy, cytology, and FNA were successful in a minority of cases, but diagnostic laparoscopy was successful in arriving at a final histopathologic diagnosis in the majority of cases. Laparotomy was more common in the non-ovarian cancer cohort, though most of these patients had benign diseases that were unable to be conclusively diagnosed without full surgical resection due to size of the ovarian mass or lack of other lesions for biopsy targets. The remaining metastatic non-ovarian primaries had a workup that included biopsies of any target lesion and colonoscopies when indicated. These patients with metastatic non-ovarian primary malignancies presented with pelvic masses or peritoneal carcinomatosis on imaging; those with other easily identifiable disease sites were unlikely to first present to a gynecologic oncologist and would not be present in this cohort. This difficult population, though rare, unfortunately required full surgical resection for conclusive diagnosis.

The diagnostic utility of imaging[8] and biopsy by fine-needle aspiration (FNA)[9], image-guided core biopsy [10], and video-assisted thoracoscopic surgery (VATS)[15] have been described elsewhere, but have not been reported together in a full cohort of women with unconfirmed, presumed advanced stage ovarian malignancy managed with a systematic triage system. These prior studies investigating the diagnostic course of women presenting with unconfirmed presumed ovarian malignancy found rates of ovarian malignancy at 64% [8], 41% [9], and 74% [10]. This study's rate of confirmed ovarian malignancy (93%) is much higher than these other assembled cohorts of women with presumed advanced stage ovarian cancer. Our study was performed at a tertiary/quaternary-level cancer center, where patients often have a histopathologic diagnosis prior to their first visit with an oncologist, and thus enrich the population for true ovarian cancer cases. Additionally, imaging has improved since these prior studies (some as early as 1999), and has likely lead to improved diagnosis and triage to the correct oncologic surgeon or general gynecologist. This cancer center population may not be fully generalizable as 50 patients followed up in other centers, but the utility of diagnostic laparoscopy applies to all patients with suspected advanced stage ovarian cancer who are candidates for a surgical procedure, and the risk factors for non-ovarian cancer would likely apply to other gynecologic oncology practices.

This study demonstrates that women with pathologies other than ovarian cancer can be successfully diagnosed with a systematic diagnostic laparoscopy-based system when feasible, in order to follow NCCN guidelines. This is an important benefit in addition to the utility of diagnostic laparoscopy in triaging patients to neoadjuvant chemotherapy versus primary debulking to maximize surgeries without residual disease. This study identifies a population of women who likely *do not* have advanced ovarian cancer – those with a lower CA125 level, of non-white race, and better performance status. This study can thus help guide the workup leading to a diagnostic laparoscopy prior to laparotomy. The benefits of this diagnostic laparoscopy – avoiding a futile laparotomy and preventing inappropriate neoadjuvant chemotherapy administration, vastly outweigh the negatives of a \$350 reimbursement[16], additional minimally invasive procedure, and 1-week delay in laparotomy, if indicated. This study was not powered to develop and test a predictive model, the study findings could help practitioners direct resources to these patients, including aggressively screening for the metastatic primaries identified in this study. These modalities

are mostly minimally invasive procedures (i.e. endometrial biopsy for uterine malignancy, endoscopy for gastrointestinal malignancy, and mammograms for breast cancer) and should therefore be performed when indicated prior to more invasive surgeries.

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References

- [1]. Howlander N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJCK (eds). Cancer Statistics Review, 1975–2014 - SEER Statistics [Internet]. SEER Cancer Statistics Review, 1975–2014. 2016 [cited 2017 May 16]. Available from: https://seer.cancer.gov/csr/1975_2014/
- [2]. Matz M, Coleman MP, Carreira H, Salmerón D, Dolores Chirlaque M, Allemani C, et al. Worldwide comparison of ovarian cancer survival: Histological group and stage at diagnosis (CONCORD-2). *Gynecol Oncol* [Internet]. 2016 [cited 2017 Oct 9];144:396–404. Available from: 10.1016/j.ygyno.2016.11.019 [PubMed: 27919574]
- [3]. Keeble S, Abel GA, Saunders CL, McPhail S, Walter FM, Neal RD, et al. Variation in promptness of presentation among 10,297 patients subsequently diagnosed with one of 18 cancers: Evidence from a National Audit of Cancer Diagnosis in Primary Care. *Int J Cancer*. 2014;135(5):1220–8. [PubMed: 24515930]
- [4]. Alvarez RD, Bakkum-Gamez JN, Barroilhet L, Behbakht K, Chen L, Ann Crispens M, et al. NCCN Guidelines Index Ovarian Cancer TOC Discussion Continue. 2017 [cited 2017 Apr 28]; Available from: https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
- [5]. Bristow RE, Tomacruz RS, Armstrong DK, Trimble EL, Montz FJ. Survival Effect of Maximal Cytoreductive Surgery for Advanced Ovarian Carcinoma During the Platinum Era: A Meta-Analysis. *J Clin Oncol* [Internet]. 2002 3 1 [cited 2017 May 1];20(5):1248–59. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/11870167> [PubMed: 11870167]
- [6]. Gómez-Hidalgo NR, Martinez-Cannon BA, Nick AM, Lu KH, Sood AK, Coleman RL, et al. Predictors of optimal cytoreduction in patients with newly diagnosed advanced-stage epithelial ovarian cancer: Time to incorporate laparoscopic assessment into the standard of care. *Gynecol Oncol* [Internet]. 2015 [cited 2017 Apr 28];137(3):553–8. Available from: <http://www.sciencedirect.com/science/article/pii/S0090825815007775> [PubMed: 25827290]
- [7]. Fagotti A, Ferrandina G, Fanfani F, Garganese G, Vizzielli G, Carone V, et al. Prospective validation of a laparoscopic predictive model for optimal cytoreduction in advanced ovarian carcinoma. *Am J Obstet Gynecol* [Internet]. 2008 12 [cited 2017 May 1];199(6):642.e1–642.e6. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/18801470> [PubMed: 18801470]
- [8]. Castellucci P, Perrone AM, Picchio M, Ghi T, Farsad M, Nanni C, et al. Diagnostic accuracy of 18F-FDG PET/CT in characterizing ovarian lesions and staging ovarian cancer: Correlation with transvaginal ultrasonography, computed tomography, and histology. *Nucl Med Commun* [Internet]. 2007 8 [cited 2017 May 10];28(8):589–95. Available from: <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00006231-200708000-00002> [PubMed: 17625380]
- [9]. Ansari H, Ansari M, Mehdi G, Maheshwari V, Afzal S. Image-guided fine-needle aspiration cytology of ovarian tumors: An assessment of diagnostic efficacy. *J Cytol* [Internet]. 2010 [cited 2017 Apr 28];27(3):91 Available from: <http://www.jcytol.org/text.asp?2010/27/3/91/71872> [PubMed: 21187883]
- [10]. Hewitt M, Anderson K, Hall G, Weston M, Hutson R, Wilkinson N, et al. Women with peritoneal carcinomatosis of unknown origin: efficacy of image-guided biopsy to determine site-specific diagnosis. *BJOG An Int J Obstet Gynaecol* [Internet]. 2006 12 6 [cited 2017 Apr 28];114(1):46–50. Available from: <http://doi.wiley.com/10.1111/j.1471-0528.2006.01176.x>

- [11]. Harris Paul A., Taylor Robert, Thielke Robert, Payne Jonathon, Nathaniel Gonzalez JGC. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support [Internet]. J Biomed Inform. 2009 [cited 2017 May 22]. p. 4;42(2):377–81. Available from: <https://redcapinfo.ucdenver.edu/citing-redcap.html> [PubMed: 18929686]
- [12]. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis [Internet]. 1987 [cited 2017 Oct 20];40(5):373–83. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/3558716> [PubMed: 3558716]
- [13]. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol [Internet]. 1982 12 [cited 2017 Oct 20];5(6):649–55. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/7165009> [PubMed: 7165009]
- [14]. Hosmer DW, Lemeshow S. Applied Logistic Regression. Second Edition. 2nd ed. Vol. 2nd 2000.
- [15]. Chi DS, Abu-Rustum NR, Sonoda Y, Chen SW-W, Flores RM, Downey R, et al. The benefit of video-assisted thoracoscopic surgery before planned abdominal exploration in patients with suspected advanced ovarian cancer and moderate to large pleural effusions. Gynecol Oncol [Internet]. 2004 [cited 2017 Apr 28];94(2):307–11. Available from: <http://www.sciencedirect.com/science/article/pii/S0090825804002665> [PubMed: 15297166]
- [16]. Overview of the Medicare Physician Fee Schedule Search [Internet]. [cited 2018 Apr 24]. Available from: <https://www.cms.gov/apps/physician-fee-schedule/overview.aspx>

Figure 1: Cohort generation

The above diagram demonstrates the application of exclusion criteria to arrive at the final cohort of women with unconfirmed advanced ovarian cancer. When reporting the diagnostic details, note that some patients underwent multiple procedures, so totals reported here add to greater than the group sum. FNA = fine needle aspiration

Table 1:

Baseline Covariates

Covariate	All women n=365	Ovarian Cancer n=339	Non-Ovarian Cancer n=26	p-value
Age, mean (range)	61 (18–89)	62 (18–89)	56 (36–76)	0.98 [†]
Race, n (%)				<0.001 [‡]
American Indian/Alaskan Native	3 (0.8)	1 (0.3)	2 (7.4)	
Asian	16 (4.4)	13 (3.9)	3 (11.1)	
African American	28 (7.7)	26 (7.7)	2 (7.4)	
Caucasian	311 (85)	294 (86.7)	17 (65.4)	
Unknown	7 (1.9)	5 (1.5)	2 (7.4)	
Ethnicity, n=Hispanic (%)	35 (9.6)	32 (9.4)	3 (11.5)	0.81 [‡]
Obesity, n=yes (%)	132 (36.3)	120 (35.5)	12 (46.2)	0.28 [‡]
Prior malignancy, n=yes (%)	64 (17.5)	58 (17.1)	6 (23.1)	0.44 [‡]
Charlson Comorbidity Index, median (range)	3 (0–14)	3 (0–14)	2 (0–9)	0.32 [§]
ECOG [*] performance status, median (range)	1 (0–4)	1 (0–4)	1 (0–1)	<0.001 [§]
CA125, median (range)	486.5 (7.2–12472)	520.7 (9.4–12472)	165.4 (7.2–1067)	<0.001 [§]
Ascites on imaging, n=yes (%)	215 (75.7)	199 (75.7)	16 (76.2)	0.80 [‡]
Pleural effusion on imaging, n=yes (%)	106 (29.0)	103 (30.4)	3 (11.5)	0.04 [‡]

^{*} **Legend:** Eastern Cooperative Oncology Group (ECOG).

[†] Student's t-test.

[‡] χ^2 test.

[§] Wilcoxon rank-sum test.

Table 2:

Histopathologic Diagnosis

Ovarian malignancy	n=339	Benign Disease	n=13	Metastatic disease to ovary	n=13
Serous	269	Ovarian fibroma	4	Uterus	3
Endometrioid	11	Ovarian mucinous cystadenoma	3	Breast	2
Mucinous	4	Ovarian fibrothecoma	1	Gastro-intestinal	6
Clear cell	11	Ovarian serous adenofibroma	1	Lymphoma	1
Müllerian adenocarcinoma	5	Endometriosis	1	Peritoneal mesothelioma	1
Squamous	1	Adnexal inclusion cyst	3		
Carcinosarcoma	11				
Germ cell	1				
Sex cord stromal	2				
Ependymoma	1				
Neuroendocrine	2				
Mixed	15				

Legend: "Mixed" represents ovarian tumors containing >1 histologic sub-type