



Case series

Associated characteristics and impact on recurrence and survival of free-floating tumor fragments in the lumen of fallopian tubes in Type I and Type II endometrial cancer

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ABSTRACT

Objective: This study sought to evaluate characteristics of cases of free-floating tumor fragments within the lumen of fallopian tubes ('floaters') on final pathology for Type I and Type II endometrial adenocarcinoma, including relationships with disease recurrence and mortality.

Methods: A single institution experience of 1022 consecutive cases of uterine cancer presenting between 2005 and 2010 was retrospectively reviewed, with data extraction from electronic medical records. Associations of floaters with baseline characteristics were studied with logistic regression, and relationships with disease recurrence and survival were assessed with Cox proportional hazards models.

Results: Among 816 included cases of Type I or Type II endometrial adenocarcinoma, floaters were identified on final pathology for 20 patients (2.5%). Patient characteristics of cases with floaters mirrored the overall sample. With adjustment, presence of floaters trended towards association with laparoscopic/robotic approach (OR = 3.84; 95%CI 0.98-15.1), and was significantly associated with lymphovascular invasion (OR = 9.65; 95%CI 2.35-39.6) and higher stage disease. Although floaters were associated with increased risk of recurrence in unadjusted analysis (HR = 3.22; 95%CI 1.41-7.37), after adjustment for disease type, stage, and patient comorbidities, no evidence for impact on disease recurrence or overall survival was found.

Conclusions: The presence of floaters is rare. Floaters were generally associated with more extensive disease, but no evidence was found to show any independent prognostic impact on risk of recurrence or death. In agreement with prior research, this study found a trend towards association of floaters with laparoscopic/robotic approach, indicating the possibility of floaters sometimes being the result of trauma from uterine manipulator insertion.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy among women in the United States and accounts for 6% of malignancies in women worldwide. In the United States in 2017, 61,380 women will be diagnosed with endometrial cancer and 10,920 women will succumb to the disease (Siegel et al., 2014).

Endometrial cancers exist in two forms, Type I and Type II (Bokhman, 1983). Type I disease (65–70% of all cases) includes International Federation of Gynecology and Obstetrics (FIGO) grade 1 and FIGO grade 2 endometrioid histology, and is often associated with

unopposed estrogen exposure (Lax et al., 1998; Voss et al., 2012; Goff et al., 1994). Type II disease includes FIGO grade 3 endometrioid, serous, or clear cell histology, and has a different genetic profile with development thought to be independent of estrogen exposure. Type II endometrial cancer is typically more aggressive than type I cancer and has a poorer prognosis (Mutch, 2012; Wilson TO et al., 1990; Emons et al., 2000; Hameed and Morgan, 1972; Hamilton et al., 2006).

In 2009, updated staging recommendations were released by FIGO that made a series of small changes to the system, including eliminating a role for positive cytology from peritoneal washings in upstaging disease to stage IIIA (Creasman, 2009; Pecorelli et al., 2009). Another

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pathologic finding that is sometimes noted on pathology reports is the presence of free floating fragments of tumor within the lumen of one or both fallopian tubes (Zaino, 2009). A body of literature has accumulated assessing the role of positive cytology in prognosis, ultimately finding a relatively small impact in otherwise early stage disease, not warranting upstaging. On the other hand, research is lacking into the role of floaters in prognosis, as well as associations with other characteristics of the patient and case.

The true incidence and etiology of floaters is unknown. In the only study of its kind, in 2013, DeLair et al. explored the difference in the incidence of floaters in laparoscopic (LH) versus robotic-assisted (RH) surgery for endometrial cancer (Delair et al., 2013). They found the incidence of floaters in LH to be 2.2% versus 11.7% in RH ($P < 0.001$). The majority of the patients with RH and tumor present in the tubes had Stage I disease (9/16, 56.2%) and Grade 1 tumors (9/16, 56.2%). Patients with floaters had a non-statistically significant higher body mass index. The authors postulated that floaters were a contaminant secondary to the placement of a uterine manipulator and also uterine manipulation, which they postulated was higher in RH (Delair et al., 2013; Sonoda et al., 2001; Lim et al., 2008).

The objective of this study was to examine a series of cases with the finding of floaters on final pathology within a cohort of endometrial cancer patients in order to better understand the role of floaters in disease, including associations with patient, surgical, and pathologic characteristics, and assessment for impact on outcomes of time to progression and overall survival.

2. Methods

2.1. Study design

This study represents the experience of a single health system (Yale New Haven Health including Yale New Haven Hospital and the affiliated Bridgeport Hospital) with a new diagnosis of uterine cancer over a six year period. A retrospective cohort was formed from consecutive patients presenting to the health system's Division of Gynecologic Oncology with uterine cancer between January 1, 2005 and December 31, 2010. Diagnosis of pathologic subtype of uterine cancer was performed by trained gynecologic pathologists and all cases were reviewed at a multidisciplinary tumor board. This sample included both patients with preoperative biopsy showing uterine cancer followed by benign final pathology at the time of surgery, as well as patients with no sampling or benign preoperative pathology, and invasive cancer on final pathology of the surgical specimen. Study follow up was completed at the start of data extraction, defined as June 1st, 2016.

2.2. Data extraction

Institutional Review Board (IRB) approval was obtained before starting the study. Data was manually extracted from electronic health records. Extracted data included baseline patient characteristics, treatment, and outcomes (age, gravidity, parity, menopausal status, BMI, OCP use, HRT use, smoking status, medical and surgical history, adjuvant treatment, recurrence, death) from provider clinic and hospital notes, surgical characteristics (surgeon, approach, additional procedures) from operative notes, and pathological characteristics from preoperative, frozen, and final pathology notes. It should be noted that the presence of "floaters" on final pathology had no impact on the stage assigned to a patient as the International Federation of Gynecology and Obstetrics (FIGO) does not consider it in their staging system. The FIGO 2009 staging system was used for all patients (Creasman, 2009). Dates of death were confirmed with publically available obituary data. For patients lost to follow up, the date of last contact was used for the date of censure. For patients known to have died, but with no identifiable date of death, the date of last contact was approximated as the date of

Table 1
Demographic characteristics of single institution cohort of patients with type I and type II endometrial adenocarcinoma, by presence or absence of floaters.^a

	Floaters (n = 20)	No floaters (n = 796)	P value
Age at diagnosis (years)	65.6 (12.9)	63.3 (11.5)	0.38
Race (%)			0.32
White	85.0%	84.0%	
Black	5.0%	8.7%	
Hispanic	10.0%	2.8%	
Asian	0%	1.4%	
Other	0%	3.2%	
Gravidity	1.85 (1.63)	2.29 (1.88)	0.30
Parity	1.70 (1.53)	1.89 (1.78)	0.60
Body mass index (kg/m ²)	34.2 (8.6)	33.6 (12.2)	0.85
Menopausal (%)	90.0%	85.5%	0.57
Smoker (≥ 5 pack-years, %)	35.0%	24.1%	0.26
HRT use (> 3 months, %)	18.8%	21.6%	0.79
OCP use (> 3 months, %)	26.7%	31.4%	0.70
Medical history (%)			
Hypertension	65.0%	58.8%	0.58
Diabetes	45.0%	23.8%	0.03
Major CV disease ^b	10.5%	5.2%	0.30
Psychiatric disease ^c	10.5%	8.7%	0.77
Other cancer	15.8%	10.1%	0.42
Prior abdominal surgery	35.0%	38.4%	0.76

HRT = hormone replacement therapy; OCP = oral contraceptive pills.

^a For continuous variables, mean (standard deviation) shown, Student's *t*-test for significance; for dichotomous and categorical variables, percent with characteristic shown, Pearson's χ^2 test for significance. Floaters were defined as evidence of free-floating tumor fragments within the fallopian tubes on final pathologic specimen analysis.

^b Includes history of congestive heart failure, myocardial infarction, and stroke.

^c Includes diagnoses of depression, anxiety, bipolar, and schizophrenia.

death. Data extraction was performed in parallel by four researchers (BA, JB, SG, MW, RP) in a standardized fashion using a single data entry form.

2.3. Study sample

The analysis in this study was performed on a subset of the above described cohort of patients with endometrial cancer, limited to patients with Type I (FIGO Grade 1 and 2 endometrioid adenocarcinoma) or Type II (FIGO Grade 3 endometrioid adenocarcinoma, clear cell carcinoma of the endometrium, uterine papillary serous carcinoma, and mixed endometrial carcinomas) disease. Patients with uterine sarcomas, carcinosarcomas, and squamous cell carcinomas were excluded. The study sample was further limited by excluding patients with missing data for variables critical for defining the type of disease (cellular histology on the final pathologic specimen), and for determining the outcome in time-to-event analysis (date of diagnosis and current disease status).

2.4. Analyses

The primary characteristics of interest in this study was the presence or absence of 'floaters.' For the purposes of this study, 'floaters' was defined as the presence of free floating tumor fragments identified within the fallopian tubes on sectioning and final pathological analysis of the specimen. Baseline characteristics of patients having pathology with and without the presence of floaters were compared using Student's *t*-test for continuous variables, and Pearson's χ^2 test for dichotomous and categorical variables. Descriptive statistics were used to describe the prevalence of floaters by cancer stage and nuclear grade at the time of surgery, as well as the relationship to positive peritoneal cytology. Of note, peritoneal cytology status was not originally included in the extracted data and was only assessed and available for cases with the presence of floaters. Associations of the presence of floaters with

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