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Patterns and utility of routine surveillance in high grade endometrial cancer

Jessica Hunn [a], Meaghan E. Tenney [a], Ana I. Tergas [a], Erin A. Bishop [b], Kathleen Moore [b], William Watkin [c], Carolyn Kirschner [d], Jean Hurteau [d], Gustavo C. Rodriguez [d], Ernst Lengyel [a], Nita K. Lee [a], S. Diane Yamada [a,*]

[a] Department of Obstetrics and Gynecology, Section of Gynecologic Oncology, University of Chicago, Chicago, IL, USA
[b] University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA
[c] Department of Pathology, NorthShore University HealthSystem, Evanston, IL, USA
[d] Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, NorthShore University HealthSystem, Evanston, IL, USA

HIGHLIGHTS

- The majority of recurrences, amongst all stages, had a distant component
- CT scan detected 15% of locoregional recurrences in the absence of symptoms or exam findings
- The majority of locoregional and distant recurrences are detected by symptoms and physical exam

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ABSTRACT

Objective. To evaluate surveillance methods and their utility in detecting recurrence of disease in a high grade endometrial cancer population.

Methods. We performed a multi-institutional retrospective chart review of women diagnosed with high grade endometrial cancer between the years 2000 and 2011. Surveillance data was abstracted and analyzed. Surveillance method leading to detection of recurrence was identified and compared by stage of disease and site of recurrence.

Results. Two hundred and fifty-four patients met the criteria for inclusion. Vaginal cytology was performed in the majority of early stage patients, but was utilized less in advanced stage patients. CA-125 and CT imaging were used more frequently in advanced stage patients compared to early stage. Thirty-six percent of patients experienced a recurrence and the majority of initial recurrences (76%) had a distant component. Modalities that detected cancer recurrences were: symptoms (56%), physical exam (18%), surveillance CT (15%), CA-125 (10%), and vaginal cytology (1%). All local recurrences were detected by symptoms or physical exam findings. While the majority of loco-regional and distant recurrences (68%) were detected by symptoms or physical exam, 28% were detected by surveillance CT scan or CA 125. One loco-regional recurrence was identified by vaginal cytology but no recurrences with a distant component detected by this modality.

Conclusions. Symptoms and physical examination identify the majority of high grade endometrial cancer recurrences, while vaginal cytology is the least likely surveillance modality to identify a recurrence. The role of CT and CA-125 surveillance outside of a clinical trial needs to be further reviewed

Introduction

Endometrial cancer is subdivided into two types based on histopathology, molecular profile and clinical prognosis. Type I encompasses the low grade (grades 1 and 2) endometrioid tumors. Type II endometrial cancers include the more aggressive grade 3 endometrioid, clear cell, papillary serous and carcinosarcomas [1]. The recurrence rate of all histologic subtypes of endometrial cancer ranges from 13%–17% in large reported studies [2,3]. While the Type II, or high grade, endometrial cancers represent only a small proportion of all endometrial cancers, they are disproportionately responsible for 75% of deaths [4]. In general, the anatomic location of endometrial cancer recurrences is equally divided between local and distant sites [5–9]. While low grade and early stage endometrial cancers generally have a low recurrence rate and often present with a local recurrence, high grade endometrial cancers will more frequently recur with a distant component. There have been several studies that have focused on the best practices for followup

* Corresponding author at: Section of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Chicago Medicine, 5841 S. Maryland Avenue, MC 2050, Chicago, IL 60637, USA. Tel.: +1 773 702 6118; fax: +1 773 702 5411.
E-mail address: sdyamada@uchicago.edu (S.D. Yamada).

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and surveillance but most have focused on Type I and early stage cancers [10–13]. In this subgroup, vaginal cytology and imaging studies have not been shown to be cost effective. Additionally, these modalities have not identified recurrences earlier or improved survival compared with a thorough clinical evaluation [14]. The smaller number of high grade endometrial cancers has made it more difficult to define an optimal surveillance strategy that balances the detection of salvageable or treatable recurrences, psychosocial reassurance for the patient and cost effectiveness. The National Comprehensive Cancer Network (NCCN) guidelines, updated in 2015 (version 2.2015), recommend that a physical exam be performed every 3 to 6 months for 2–3 years then every 6 months or annually. In addition, providing patient education regarding symptoms of recurrence is encouraged while vaginal cytology has been designated category 3, inappropriate for incorporation into surveillance. Imaging studies are recommended as clinically indicated and CA-125 is optional [15]. Despite general awareness of these recommendations, practitioners continue to practice a variety of surveillance methods. The objective of this retrospective multi-institutional study was to evaluate contemporary surveillance methods and the utility of vaginal cytology, imaging studies, and tumor markers in detecting sites of recurrent disease that are unique to high grade endometrial cancer.

Methods

Study population

The cancer registries, pathology database and multidisciplinary tumor board notes at the University of Chicago and NorthShore University HealthSystem were searched for the high grade endometrial cancer subtypes (grade 3 endometrioid, papillary serous, carcinosarcoma and clear cell) between the years 2000–2011. The endometrial cancer registry at the University of Oklahoma was similarly searched for these high grade endometrial cancer histologies. Institutional Review Board approval was obtained at each of these institutions. All the patients included in this retrospective study underwent comprehensive surgical staging, which included hysterectomy, bilateral salpingo-oophorectomy, lymph node dissection and omentectomy, when appropriate, to determine stage. Pathology was reviewed at each institution's multidisciplinary tumor board conference. The patients were excluded if they did not undergo comprehensive surgical staging or if no followup data was available. The medical record and pathology reports were abstracted for age, histology, stage, adjuvant therapy, months of followup, number of appointments, symptoms reported, physical exam, Pap tests and results, type and results of imaging studies, CA-125, sites of recurrence and modality that detected a recurrence.

Recurrence of disease

Information regarding a subject's first recurrence was abstracted from the medical record. If multiple sites of recurrence were identified, the most distant site was used to define the type of recurrence. A local recurrence was defined as a vaginal recurrence. Regional recurrences (regional and local/regional) were defined as pelvic or nodal recurrences. Distant recurrences (distant, regional/distant, local/regional/distant and local/distant) were defined as recurrences outside of the pelvis. If a patient developed a recurrence, the surveillance method used to detect the recurrence was identified and categorized. If more than one surveillance technique identified a recurrence, the method that first detected the recurrence and initiated a workup was defined as the method of detection for the recurrence.

Statistical analysis and data review

Clinicopathologic, followup data, and surveillance techniques were examined and compared utilizing SAS version 9.2. Fisher's exact test was used for categorical variables and Student's t-test for continuous variables. We analyzed the surveillance tests utilized and compared them by stage of disease. The patients with a recurrence of disease were separately identified and the site of recurrence was stratified by stage. The overall utilization of each surveillance technique that detected a recurrence was noted and then categorized by stage and site. Progression free survival (PFS) was calculated from the date of surgery until first recurrence. Overall survival (OS) was calculated from date of surgery until last known followup or death. Survival was analyzed using the Kaplan–Meier method and log-rank analysis. The chi-square test or Fisher exact test was used to evaluate categorical variables. Statistical significance was set at a P value < 0.05. All statistical analyses were performed using SAS version 9.1 software (SAS Institute Inc., Cary, NC, USA, 2003).

Results

Study population

We identified a total of 324 patients with grade 3 endometrioid, papillary serous, carcinosarcoma and clear cell carcinoma of the uterus who underwent primary surgical staging at the 3 designated institutions between 2000 and 2011. Of these, 254 patients had adequate followup data available for analysis and are the subject of this study. The patient demographics and clinicopathologic characteristics are summarized in Table 1 and are consistent with other high grade endometrial cancer patient populations [16–18]. The median followup time was 25 months (range 1–178). The patient population was evenly divided between early Stage (I and II) and advanced Stage (III and IV) patients. The most common histologic types were grade 3 endometrioid (34%), papillary serous (34%) and carcinosarcoma (22%). The majority of patients (80%) received adjuvant treatment post-operatively: 22% received chemotherapy alone, 31% radiation alone, and 27% had a combination of chemotherapy and radiation. The median number of followup appointments was 7 (1–43). The median number of Pap tests, imaging studies and CA-125 performed was 2 (range 0–24), 2 (range 0–20) and 2 (range 0–37) respectively.

Surveillance methods

Table 2 identifies the surveillance techniques used for the patients stratified by stage of disease. All the patients, regardless of stage,

Table 1
Demographics and clinicopathologic characteristics.

Demographics		
Number of patients		254
Age at diagnosis (median)		67 (36–107)
Stage N (%)		
	I	103 (41)
	II	33 (13)
	III	83 (33)
	IV	35 (14)
Histology N (%)		
	Grade 3 Endometrioid	86 (34)
	Papillary Serous	87 (34)
	Carcinosarcoma	57 (22)
	Clear Cell	14 (6)
	Mixed	10 (4)
Post-operative therapy N (%)		
	Chemotherapy	57 (22)
	Radiation	79 (31)
	Chemo/radiation	68 (27)
	None	38 (15)
	Unknown	12 (5)
Months follow-up (median)		25 (1–178)
Number of follow-up appointments		7 (1–43)
Number of Pap smears per patient		2 (0–24)
Number of imaging studies per patient		2 (0–20)
Number of CA-125 tests		2 (0–37)