

2019

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Recommended Citation

Mills, Kathryn A.; Lopez, Heather; Sun, Lulu; Cripe, James C.; Litz, Taylor; Thaker, Premal H.; Powell, Matthew A.; Mutch, David G.; and Fuh, Katherine C., "Type II endometrial cancers with minimal, non-invasive residual disease on final pathology: What should we do next?." *Gynecologic Oncology Reports*.29,. 20-24. (2019).
https://digitalcommons.wustl.edu/open_access_pubs/7868

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Case series

Type II endometrial cancers with minimal, non-invasive residual disease on final pathology: What should we do next?



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ARTICLE INFO

Keywords:

Type II endometrial cancer
Early stage endometrial cancer

ABSTRACT

There are minimal data regarding the management of high risk endometrial cancer histologies lacking invasive disease on the final pathology specimen. This study examines a cohort of these patients and assesses outcomes including time to recurrence and risk of death after management with and without adjuvant therapies.

Endometrial cancer patients with minimal or no remaining invasive disease on final pathologic specimen from 1995 to 2010 were included. Surgical procedure was at the discretion of the operating physician. Electronic medical records were used to abstract relevant clinicopathologic data and standard statistical methods were employed.

70 patients met inclusion criteria, of which 26 were high grade histologies. Adjuvant therapies were given in 12 of 26 patients. 6/26 patients recurred, of which 50% were salvaged with therapy at time of recurrence. Overall deaths occurred in 3 of 26 patients in the high risk cohort.

Less than half of the high risk cohort received adjuvant therapies after surgical management. No histologic type was found to increase risk of recurrence, and treatment with initial adjuvant therapy did not significantly reduce recurrence risk. Large scale prospective trials are needed to aid in management of this unique endometrial cancer population.

1. Introduction

Endometrial cancer continues as the most commonly diagnosed gynecologic malignancy with 63,000 new cases in 2018 ([Cancer Facts, and Figures Atlanta, Georgia, 2018](#)). Endometrial cancer is separated into type 1 carcinomas that includes grade 1 and 2 endometrioid histologies that are less aggressive and often associated with excess circulating estrogen, and type 2, high risk carcinomas, which include all other types (serous, clear cell, carcinosarcoma, mixed, undifferentiated and grade 3 endometrioid histology) and portend a poorer prognosis. In addition, type 2 carcinomas tend to present at advanced stages with extrauterine spread at time of diagnosis ([Goff et al., 1994](#)). The NCCN recommendations for stage IA high risk carcinomas include observation or chemotherapy, with or without vaginal brachytherapy (VBT) or external beam radiation, with or without brachytherapy ([National Comprehensive Cancer Network, 2018](#)), demonstrating the wide range

of adjuvant therapies endorsed by experts. A clinical dilemma then arises when an aggressive histology is found on work-up, but on final pathology there is minimal to no residual disease.

The majority of studies do not specifically focus on stage IA patients in this clinical scenario, which would be useful for guiding adjuvant therapies and counseling patients. We therefore aimed to review our institutional experience managing high risk histologies with minimal residual tumor, as well as report the clinical scenarios of patients who recurred. We hypothesized that in those with high risk histologies, treatment with adjuvant therapy after surgery would decrease recurrence risk.

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<https://doi.org/10.1016/j.gore.2019.05.007>

Received 7 March 2019; Received in revised form 13 May 2019; Accepted 16 May 2019

Available online 23 May 2019

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2. Methods

2.1. Patient population

Women age 18–90 undergoing definitive surgical evaluation for suspected early stage uterine cancers at Washington University in St. Louis after endometrial biopsy or dilation and curettage from 1995 to 2010 were eligible for this IRB approved retrospective cohort study. Patients were included if they had no evidence of residual disease, disease confined to a polyp, or non-invasive disease (endometrial involvement only) on final hysterectomy specimen. High risk, high grade histologies were defined as uterine serous (USC), clear cell (CCC), grade 3 endometrioid (HGE), mixed (M), and carcinosarcoma (CS). Surgical approach was performed at the discretion of the surgeon and during this period, full lymph node dissections were performed. Data were abstracted from electronic medical records, and baseline characteristics and demographic data as well as subsequent treatment, pathology, and clinical outcomes were assessed. Patients without adequate staging, had invasive disease, or did not have available follow up data were excluded. Vital status and duration of follow up was recorded for each patient.

2.2. Adjuvant therapies

Initial therapies included observation, chemotherapy or radiation. Patients who went on to recur were identified and location of recurrence and type of treatment offered was abstracted.

2.3. Statistical analysis

All analyses were performed using SAS Software (v.9.4.; SAS Institute, Cary, NC) and statistical significance was defined as $p < .05$. Demographic and clinical data were compared among groups using Fisher's exact tests for categorical data and Wilcoxon rank sum tests for non-normal data distribution. Median disease recurrence durations were compared using Wilcoxon rank sum and Kruskal-Wallis tests. Kaplan-Meier curves were produced to visually demonstrate duration to disease recurrence by histology type and treatment type.

3. Results

3.1. Demographics

A total of 26 patients with high grade, high risk histology were identified out of 70 patients without residual disease, disease confined to a polyp, or endometrium confined disease within the study period (Table 1). Overall the high risk cohort was comprised of grade 3 endometrioid (23.1%, $n = 6$), clear cell (19.2%, $n = 5$), serous (34.6%, $n = 9$), mixed (19.2%, $n = 5$), and carcinosarcoma (3.8%, $n = 1$), respectively. Compared to low grade patients, high risk patients were significantly older (64.3 vs 59.9 years, $p = .04$), had been followed longer (5.5 vs 2.2 years, $p < .01$), and had a higher risk of recurrence (6 vs 0, $p \leq .01$), but otherwise had similar ASA scores, race distribution, and co-morbidities including hypertension, diabetes, and BMI. All patients within the high risk cohort had residual disease on final specimen, versus 33 (75%) of the low grade IA patients. No low grade patients received adjuvant therapies.

3.2. Initial treatment

14 of the high risk cohort received no further therapy, while 12 total patients received adjuvant therapies. 9 patients received adjuvant chemotherapy in addition to surgery (34.6%) and 3 received chemotherapy along with radiation (11.5%). No patients were treated with radiation alone. There was no significant difference in the average age of those observed versus those receiving adjuvant therapy (68.8 vs.

Table 1
Demographics.

	Grade 1 & 2 (n = 44)	Grade 3 (n = 26)	P
Age at diagnosis	59.5 (54.4–68.3)	64.3 (58.5–72.9)	0.04
Race			0.41
Black	6 (13.6)	2 (7.7)	
Caucasian	38 (86.4)	23 (88.5)	
Other	0 (0.0)	1 (3.9)	
Ethnicity			0.37
Hispanic	0 (0.0)	1 (3.9)	
Comorbidities			
Hypertension	17 (38.6)	12 (46.2)	0.54
Diabetes	7 (15.9)	9 (34.6)	0.07
BMI at Time of Surgery	34.0 (30.0–42.5)	31.0 (28.0–38.0)	0.26
Histology			
Endometrioid	44 (100.0)	6 (23.1)	< 0.01
Clear cell	0 (0.0)	5 (19.2)	< 0.01
Papillary serous	0 (0.0)	9 (34.6)	< 0.01
Carcinosarcoma	0 (0.0)	1 (3.8)	0.37
Mixed	0 (0.0)	5 (19.2)	< 0.01
Surgical Pathology			< 0.01
No residual malignancy	11 (25.0)	0 (0.0)	
Malignancy limited to polyp	2 (4.6)	8 (30.8)	
Malignancy limited to endometrium	31 (70.5)	18 (69.2)	
Initial treatment			< 0.01
Surgery only	44 (100.0)	14 (53.8)	
Surgery and chemotherapy	0 (0.0)	9 (34.6)	
Surgery, chemotherapy, and radiation	0 (0.0)	3 (11.5)	
ASA Score			0.73
2	9 (20.5)	7 (26.9)	
3	34 (77.3)	19 (73.1)	
4	1 (2.3)	0 (0.0)	
Vital status ^a			0.14
NED	36 (81.8)	16 (61.5)	
DOD	0 (0.0)	3 (11.5)	
LTFU	8 (18.2)	7 (26.9)	
Recurrence	0 (0.0)	6 (23.1)	< 0.01
Years from diagnosis to last contact	2.2 (0.1–5.9)	5.5 (3.7–7.6)	< 0.01

^a NED = No evidence of disease, DOD = dead of disease, LTFU = Lost to follow up.

64.0 years, $p = .16$). 10 out of the 12 (83.3%) of the adjuvantly-treated patients had either mixed serous or pure serous histologies. The patient with carcinosarcoma was recommended to receive adjuvant therapy but did not receive it. The mean number of chemotherapy cycles given was 4 ± 1.8 , and in all cases a platinum and taxane regimen was given. All patients who received radiation underwent high dose rate VBT to the upper 3–4 cm of the vagina to a total of 21–36 Gy.

3.3. Outcomes

Of the high risk cohort, 6 patients recurred (23.1%) with a median follow up time of 5.5 years, and 50% of those recurrences were distant recurrences that were not salvageable (Table 2). 3 out of 6 recurrences were CCC and all 3 were treated with radiation with or without surgery and all were alive without evidence of disease at recent follow up. The other 3 were either pure serous or mixed serous, all of whom are now dead from disease.

There was no increased risk of recurrence based on malignancy limited to a polyp versus limited to the endometrium, histology, or treatment with initial adjuvant therapy (Table 3). BMI was significantly higher in those who recurred (43.0 vs 30.5, $p = .01$), and hypertension (100% vs 30%, $p < .01$) and diabetes (83% vs 20%, $p < .01$) were more frequent, as well. 7 of the 26 patients (23.1%) were lost to follow

Table 2
Details of Recurrences.

Histology	Initial Therapy	Recurrence Location	Treatment for Recurrence	Outcome at last follow up ^a
Clear Cell	None	Vaginal cuff	Surgical resection plus radiation	NED
Clear Cell	None	Vaginal cuff	Radiation	NED
Clear Cell	None	Vaginal cuff	Surgical resection plus radiation	NED
Serous	6 cycles of platinum and taxane	Distant	Surgery plus chemotherapy	DOD
Serous	3 cycles of platinum and taxane	Distant	Chemotherapy	DOD
Mixed endometrioid and serous	1 cycle of platinum and taxane, refused additional cycles	Distant and vaginal cuff	Declined offered chemotherapy	DOD

^a NED = No evidence of disease, DOD = Dead of disease.

Table 3
Characteristics of Grade 3 patients by recurrence status.

	Recurred (n = 6)	No recurrence (n = 20)	P
Age at diagnosis	69.5 (63.3–72.0)	64.0 (57.9–73.3)	0.62
Race			> 0.99
Black	0 (0.0)	2 (10.0)	
Caucasian	6 (100.0)	17 (85.0)	
Other	0 (0.0)	1 (5.0)	
Ethnicity			> 0.99
Hispanic	0 (0.0)	1 (5.0)	
Comorbidities			
Hypertension	6 (100.0)	6 (30.0)	< 0.01
Diabetes	5 (83.3)	4 (20.0)	< 0.01
Histology			
Endometrioid	0 (0.0)	6 (30.0)	0.28
Clear cell	3 (50.0)	2 (10.0)	0.06
Serous	2 (33.3)	7 (35.0)	> 0.99
Carcinosarcoma	0 (0.0)	1 (5.0)	> 0.99
Mixed	1 (16.7)	4 (20.0)	< 0.99
Surgical Pathology			0.33
No residual malignancy	0 (0.0)	0 (0.0)	
Malignancy limited to polyp	3 (50.0)	5 (25.0)	
Malignancy limited to endometrium	3 (50.0)	15 (75.0)	
Initial treatment			> 0.99
Surgery only	3 (50.0)	11 (55.0)	
Surgery and chemotherapy	2 (33.3)	7 (35.0)	
Surgery, chemotherapy, and radiation	1 (16.7)	2 (10.0)	
BMI at time of surgery, Median (32.0–47.0)	43.0	30.5 (27.5–35.5)	0.01
ASA Score			> 0.99
2	1 (16.7)	6 (30.0)	
3	5 (83.3)	14 (70.0)	
4	0 (0.0)	0 (0.0)	
Vital status ^a			< 0.01
NED	3 (50.0)	13 (65.0)	
DOD	3 (50.0)	0 (0.0)	
LTFU	0 (0.0)	7 (35.0)	
Years from diagnosis to last contact, Median (IQR)	7.0 (3.7–9.0)	5.0 (2.0–7.6)	0.47

^a NED = No evidence of disease, DOD = dead of disease, LTFU = Lost to follow up.

up, defined as no follow up within the prior three years until study end, and were all within the no recurrence group. Overall, 3 of the 26 total patients (11.5%) were dead of disease at study end.

Kaplan Meier curves were used to compare time to recurrence among the different histological subtypes. Interestingly, while the CCC patients recurred quickly (n = 3, average 14.9 months versus 80.1 months in the serous cohort, p = .08), as mentioned, 100% salvage rate was achieved (Fig. 1); no grade 3 endometrioid histology patients recurred during the study period. Given the small sample size, no multivariable analysis could be performed.

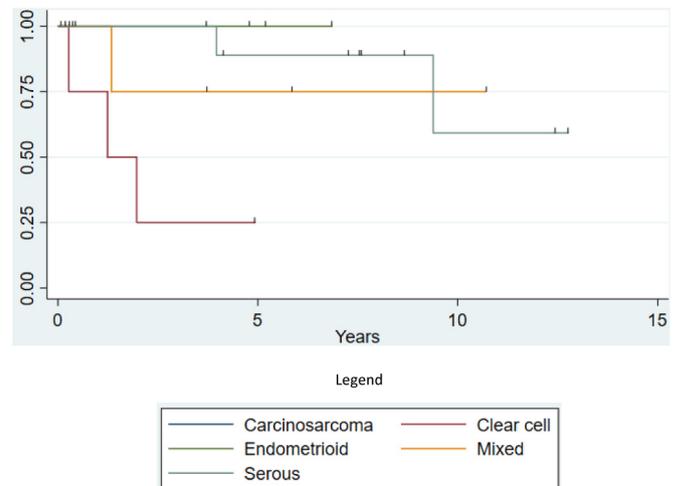


Fig. 1. Time to Recurrence Based on Histology.

4. Discussion

Prior studies have examined the outcomes of early stage patients with various high risk histologies both with and without adjuvant therapies. Huh et al. retrospectively evaluated a series of 60 patients at four academic institutions with surgically staged IA-IC uterine serous cancer treated with observation or combinations of chemotherapy and radiation; there was no demonstrated improvement in overall survival in those treated with adjuvant radiation compared to observation, with no recurrences or disease related deaths in the small number of patients treated with at least chemotherapy (n = 8) (Huh et al., 2003). Further studies attempted to clarify outcomes in USC with minimal invasion. Hui et al. evaluated USC patients, surgically staged, with invasion limited to the endometrium or limited to a polyp, and in 22 patients with disease limited to uterus no recurrence was noted during follow up, although the use of adjuvant therapies is not reported (Hui et al., 2004). Kelly et al. evaluated 74 USC patients stage IA-IC, of which 12 had no residual uterine disease on final specimen; Platinum based therapy was associated with a significant improvement in both disease free and overall survival (Kelly et al., 2005). Specifically, those with no residual disease had no recurrences irrespective of adjuvant therapy given. Our own experience found that the patients who recurred with USC after no residual disease, even in the setting of adjuvant therapy, did poorly and succumbed to disease; however out of the included 9 USC patients, only 3 recurred total. Interestingly, all mixed tumors identified in our study included some component of serous tumor in the prior to surgery specimen. It has been suggested that tumor behavior is often driven by serous histology even in a mixed setting, and in our results 80% of mixed tumors received adjuvant therapy up front, with only 1 recurrence.

Clear cell carcinoma is even rarer with large scale prospective trials evaluating early stage management lacking. The Society of Gynecologic Oncology clinical practice committee recommends consideration for

adjuvant therapies in early stage disease (Olawaiye and Boruta, 2009). A Taiwanese Gynecologic Oncology Group study sought to retrospectively investigate surgically staged CCC and included 80 stage I patients, of which 37 were observed when tumors were < 2 cm and/or stage IA and found an overall survival of 93% (Hsu et al., 2014). Another retrospective investigation of 99 CCC patients, including 16 stage IA patients, found that in the 22 stage I and II patients with thoroughly sampled lymph nodes (> 20 pelvic and paraaortic nodes) and varying therapies including observation pursued, only 1 patient recurred (Thomas et al., 2008). CCC is often studied concurrently with USC or in a mixed setting, making conclusions difficult to apply more broadly. Velker et al. reported a single institution experience of CCC and USC with < 50% myometrial invasion undergoing adjuvant therapy versus observation, of which only 83% of the cohort had lymph node sampling. Of the 77 patients included, 12 total recurrences were documented and were not significantly different between groups. In a subgroup analysis of the observed patients, patients with myometrial invasion had a non-significant trend towards decreased recurrence free survival (75% versus 93%) (Velker et al., 2016). In our cohort, patients with pure clear cell histologies did well even with recurrence, and were alive and without evidence of disease after appropriate therapies.

Carcinoma (CS), remains an especially difficult disease to manage even at early stages, as greater than half of these patients will have occult metastases (Yamada et al., 2000) and suffer high recurrence rates with a propensity to recur outside the pelvis (Silverberg et al., 1990). A multiinstitutional review of 303 stage I-III patients identified 70 observed stage I patients compared to 29 treated with chemotherapy, 26 radiation therapies, and 30 with combination chemotherapy and radiation. Compared to those stage I and II patients who were treated with chemotherapy, those who were observed had an increased risk of death by greater than four times (Dickson et al., 2015), though authors did not report separate data on stage I patients with minimal or no invasive disease. In our cohort, only one carcinoma without residual disease was evaluable and has unfortunately been lost to follow up for > 3 years. More evaluations of patients in this clinical scenario should be considered critical areas of investigation.

High grade endometrioid histology has historically been included within high intermediate risk studies GOG 99 and 249. GOG 99 aimed to outline high intermediate patient subgroups and determine if the addition of adjuvant external beam irradiation lowered the risk of recurrence (Keys et al., 2004), and GOG 249, of which final publication is pending, showed no improvement in outcomes of high risk patients defined by GOG 99 parameters who were then treated with VBT and chemotherapy as compared to standard whole pelvic radiation (Pelvic Radiation Therapy or Vaginal Implant Radiation Therapy, Paclitaxel, and Carboplatin in Treating Patients With High-Risk Stage I or Stage II Endometrial Cancer, 2018). Neither of these trials delineate if pre-operative findings of a grade 3 tumor without evidence of residual disease warrants postoperative radiation therapy. In addition, the recently published PORTEC 3 trial did not demonstrate an improvement in survival with the addition of chemotherapy to pelvic radiation even those with invasive stage IA, grade 3 disease (de Boer et al., 2018). In our cohort, no pure grade 3, endometrioid histology tumors recurred.

There are a number of limitations to our study. Given its retrospective nature, it is subject to biases including confounders, chart review errors, and in this case, a > 20% loss to follow up rate. In addition, the overall sample size was small and we were unable to create a multivariable model for risk of recurrence or overall survival.

In our study, less than half of the high risk histology patients received adjuvant therapies and treatment with therapy was not conclusively linked to recurrence risk. Concordant with published data (Calle et al., 2003), obesity and metabolic dysfunction were also more common in the recurrence group. Our experience suggests that in patients with high risk histologies, clear cell carcinomas, while recurring quickly after observation in three patients, were 100% curable with salvage therapy, which suggests upfront observation is reasonable. In

addition, while no definitive conclusions can be drawn about the patients who succumbed to recurrence, in all settings pure USC or mixed USC was present on initial biopsy. Additionally, all of these patients received initial adjuvant therapy (ranging from 1 to 6 cycles of carboplatin and taxane). Further studies, including meta-analyses and prospective data if possible, are essential to drawing firm conclusions about management of these patients with high risk but minimal to no residual disease on final pathology.

Author contributions

1. Kathryn A. Mills, M.D.: First author who performed the majority of data collection and quality control, data analysis, and wrote majority of manuscript.
2. Heather Lopez, M.D.: Performed data collection and entry, as well as assisted in manuscript writing and revisions.
3. Lulu Sun, M.D., Ph.D.: Performed data collection and entry, as well as manuscript revision and approval of final submitted version.
4. James C. Cripe, M.D.: Assisted with data analysis and manuscript revisions and approval of final submitted version
5. Taylor Litz MPH: Assisted with statistical analysis and manuscript approval of final submitted version.
6. Premal H. Thaker, M.D., M.S.: Assisted with manuscript revisions and approval of final submitted version.
7. Matthew A. Powell, M.D.: Assisted with manuscript revisions and approval of final submitted version.
8. David G. Mutch, M.D.: Assisted with manuscript revisions and approval of final submitted version.
9. Katherine C. Fuh, M.D., Ph.D. Senior author who helped with initial design, IRB submission, data entry, and manuscript writing and approval of final submitted version.

Conflict of interest statement

The authors declare no competing or conflicts of interest regarding this work.

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