Gynecologic Oncology 139 (2015) 268–274

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

# Canadian high risk endometrial cancer (CHREC) consortium: Analyzing the clinical behavior of high risk endometrial cancers

Alon D. Altman [a], Sarah E. Ferguson [c], Eshetu G. Atenafu [k,l], Martin Köbel [g], Jessica N. McAlpine [i,f], Tony Panzarella [k,l], Susie Lau [d], Lilian T. Gien [c], Blake Gilks [e], Blaise Clarke [b], Anna Cameron [a], Gregg Nelson [h], Guangming Han [b], Vanessa Samouëlian [i], T.C. Ho [c], Kim Louie [j], Marcus Q. Bernardini [c,*]

[a] Division of Gynecologic Oncology, University of Manitoba, Canada
[b] Department of Pathology and Laboratory Medicine, University of Toronto, Canada
[c] Division of Gynecologic Oncology, University of Toronto, Canada
[d] Division of Gynecologic Oncology, McGill University, Canada
[e] Division of Anatomic Pathology, University of British Columbia, Canada
[f] Division of Gynecologic Oncology, University of British Columbia, Canada
[g] Department of Pathology and Laboratory Medicine, University of Calgary, Canada
[h] Division of Gynecologic Oncology, University of Calgary, Canada
[i] Division of Gynecologic Oncology, CHUM-Hôpital Notre-Dame, Canada
[j] Division of Obstetrics and Gynecology, University of British Columbia, Canada
[k] Biostatistics Department, Princess Margaret Cancer Centre, Canada
[l] Division of Biostatistics, Dalla Lana School of Public Health, University of Toronto, Canada

## HIGHLIGHTS

- We outline the rate of recurrence and overall survival in high risk endometrial cancers.
- Lymphovascular invasion and omental involvement varies by histotype.
- Location of recurrence and stage distribution vary by histotype.

## ARTICLE INFO

*Article history:*
Received 31 July 2015
Received in revised form 1 September 2015
Accepted 3 September 2015
Available online 6 September 2015

*Keywords:*
Endometrial carcinoma
Serous carcinoma
Clear cell carcinoma
Carcinosarcoma
High risk histotype

## ABSTRACT

*Objectives.* The objective of this study is to analyze the clinical behavior of endometrial carcinomas by high risk(HR) histotype, including stage, overall survival, recurrence free survival and patterns of failure.

*Methods.* This is a retrospective multi-institutional cohort study performed at 7 tertiary care centers across Canada between 2000 and 2012 and included: grade 3 endometrioid (EC3), endometrial serous cancer (ESC), clear cell carcinomas (CCC) and carcinosarcoma (CS). Clinicopathological and outcome data was collected.

*Results.* 1260 women with endometrial carcinoma with 1013 having staging procedures were identified; 398 EC3, 449 ESC, 236 CS and 91 CCC. 51.8% had lymphovascular space invasion (LVSI) and 18.5% had omental involvement with a statistically significant difference between tumor types ($p = 0.0005$ and 0.0047 respectively); ESC had a significantly greater rate of omental involvement compared to EC3 (22% to 9%, $p = 0.0005$). Within the entire cohort 49.3% were stage 1, 10.6% were stage 2, 27.4% were stage 3 and 12.7% were stage 4. Overall survival and recurrence free survival were significantly different between histotypes ($p < 0.0001$) with CS having the worst outcome. Overall 31.5% of patients recurred. CS and ESC had a higher distant recurrence rate compared to EC3 (29.6%, 31.0% compared to 16.4%, $p = 0.0002$ and $p < 0.001$).

*Conclusion.* This study is one of the largest clinical cohorts of HR endometrial cancers. We have further clarified the impact of histotype and stage on recurrence and survival, and the high likelihood of distant recurrence. However, the differences are modest and risk prediction models will require additional molecular markers.



* Corresponding author at: University of Toronto, Princess Margaret Hospital, M700 610 University Ave, Toronto, Ontario M5G 2M9, Canada.
*E-mail address:* Marcus.Bernardini@uhn.ca (M.Q. Bernardini).

http://dx.doi.org/10.1016/j.ygyno.2015.09.001
0090-8258/

## 1. Introduction

Endometrial cancer is the most common gynecologic malignancy in North America. In 1983, Bokhman first described a two tier classification system into: type 1 endometrioid carcinoma, which was estrogen stimulated, and type 2 non-endometrioid carcinoma, comprised of high risk histologies and associated with worse prognosis [1–5]. Type 2 cancers include: endometrial serous cancer (ESC), clear cell (CCC), grade 3 endometrioid (EC3), carcinosarcoma (CS) and others [2,3,6]. Although traditionally only type 1 cancers have been associated with obesity, there is increased evidence that all endometrial cancers are associated with obesity [3,6,7]; molecular alterations within EC3 adenocarcinomas (e.g. *TP53* mutations) seem to resemble other type 2 tumors [5], creating a less clear division of this dichotomous classification. While this provides a framework of the pathogenesis, the WHO classification by histotype remains the gold standard for subclassification of endometrial carcinomas [8].

High risk endometrial carcinomas behave differently, having a higher likelihood of metastatic disease, poorer prognosis and increased recurrences compared to low risk histologies [6,9]. High risk histotypes may also be associated with an increased age at diagnosis and are more likely to be African-American [2,4,6,9–11]. Several studies have shown that lymphovascular space invasion (LVSI), myometrial invasion, lower uterine segment involvement and tumor size are independent prognostic factors for these cancers [2,9,11–16]. Some studies have shown worse overall survival for ESC compared to EC3 [9,10,12,17,18], while others have not shown any difference in survival between histotypes [5,11,13,19–22], with higher rates of extrauterine spread for EC3 when compared to ESC and CCC [19], completely contradicting each other's findings [4].

Endometrial serous carcinoma (ESC) is an uncommon malignancy, making up only 5–10% of endometrial cancers, but accounts for approximately 40% of endometrial cancer deaths [2,3,10]. This entity was first described by Hendrickson in 1982, who noted a histology similarity to tubo-ovarian high-grade serous carcinoma, with a higher propensity for peritoneal spread and recurrent disease [6,23,24]. These tumors are also found to have high prevalence of *TP53* mutations and *Her2/neu* amplification [2,6,25]. CCC was first described by de Bonneville in 1911 and only accounts for 2–4% of uterine malignancies [2,9], but also has a high rate of recurrence and poor overall outcome accounting for 8% of uterine cancer deaths [9,25,26].

Although initially believed to be sarcomas, uterine CSs are now thought to be metaplastic carcinomas. Historically, they were often excluded from endometrial carcinoma studies [10,20,27,28], but rather included in sarcoma studies and incompletely staged [20]. Recurrence rates and overall survival range from 0 to 66% and 33–100% respectively, with some studies showing no difference between CS compared to other histologies [20] and others showing worse outcomes for CS [27,28].

Although high risk endometrial histotypes clearly behave worse than low risk endometrial carcinomas, the overall survival and recurrence rates differ widely between studies with 5 year survival rates varying between 33 and 79% [9,10,12,13,17–19,21,22,29], and the role of chemotherapy and radiation remains questionable [2,6,9,11,14,16,19,24,25,30]. Since high risk endometrial cancers comprise a relatively smaller proportion of patients in prospective randomized studies, it is difficult to compare outcomes and come to conclusions because of small numbers. In this collaboration, we have the opportunity to analyze a large cohort of patients with high risk histology.

The purpose of this study is to analyze the clinical behavior of high risk endometrial cancers in a large nationwide cohort of patients including stage distribution, overall survival, recurrence free survival and patterns of failure. We believe that this study will be critical for providing clinicians with a central reference for discussions with their patients about prognosis and disease course.

## 2. Materials and methods

This retrospective multi-institutional cohort study was performed at 7 centers (Princess Margaret Cancer Centre/University Health Network, Vancouver General Hospital, Tom Baker Cancer Center, Jewish General Hospital, CancerCare Manitoba, Centre Hospitalier de l'Université de Montréal, and Odette Cancer Centre), in 5 cities (Vancouver BC, Calgary AB, Winnipeg MB, Toronto ON, Montreal QC) across Canada between 2000 and 2012. Charts were reviewed from each cancer center's electronic medical records. Inclusion criteria included any women with high risk endometrial cancer, including EC3, ESC, CCC and CS of any stage. Charts were excluded if they had a diagnosis of grade 1 or 2 endometrioid adenocarcinoma, or if the primary site of disease was unknown. Data on mixed tumor histotypes were collected but were excluded from the analysis.

All data were collected and reviewed by two individuals from every center, and all pathology was reviewed by a subspecialty gynecologic pathologist prior to inclusion in the study. A standardized data collection sheet was created and tested on an initial subset of cancer patients. The database was then formatted to ensure standardized information from all participating centers.

The primary objective was to determine the clinical behavior of high risk endometrial cancers, including: stage distribution, overall survival (rates and durations), recurrence free survival (rates and durations), and patterns of failure/locations of recurrence. The secondary objective of this study was to establish a pan-Canadian, multi-centered, repository of "high risk" endometrial cancers, and create one of the largest collections of high risk endometrial cancers to date.

Overall survival was defined as the interval from the date of initial diagnosis to the date of death or, if alive, censored at the date of last known contact. Recurrence free survival was defined as the interval from the date of initial diagnosis to the date of first recurrence or date of death, whichever occurs first. Patients who were alive and recurrence free were censored on the date of last known contact. No distinction was made between cancer-related and non-cancer related deaths. Data was also collected on patient characteristics, clinical presentation and primary treatment, including surgery, chemotherapy and radiation. Complete staging was defined as surgery with pelvic lymphadenectomy +/− paraaortic lymphadenectomy +/− omentectomy.

Each site attained individual Research Ethics Board approval according to local protocol. This study is a retrospective review based on acquired data. The study did not interfere with the care that the women received during the course of their cancer care, and subjects were not contacted directly.

### 2.1. Statistical analysis

Summary statistics were used to describe patient and treatment-related characteristics and outcomes. Categorical variables such as stage, histology, extent of surgical staging, LVSI, omental involvement, and recurrence was expressed as count and proportions, whereas continuous variables such as age and follow-up were expressed as mean and standard deviation and/or median and range as appropriate. Chi-square/Fisher's exact test, as appropriate, was used to assess any association of the categorical variables of interest with histotypes or among histotypes. Analysis of variance (ANOVA) was also used to compare mean age of patients among histotypes and further pair-wise analysis, when there was significant association, was done using Tukey–Kramer adjustment for multiple comparison. Overall survival (OS) rates were calculated using the Kaplan–Meier product-limit method. The log-rank test was used to assess any difference among histology to the outcome OS. Gray's test for competing risk was used to assess any difference among histology to the outcome of cumulative incidence of relapse considering death as competing risk. All p-values were 2-sided and for the statistical analyses, $p < 0.05$ was considered to indicate a statistically significant result. Statistical analysis was performed using