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The role of adjuvant therapy in stage IA serous and clear cell uterine cancer: A multi-institutional pooled analysis

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HIGHLIGHTS

- Variability in surgical staging and adjuvant practices was seen between centers.
- Adjuvant therapy was associated with better local control compared to observation.
- Observation may be acceptable in patients with adequate surgical staging.

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ABSTRACT

Objective. As the optimal adjuvant management of stage IA serous or clear cell endometrial cancer is controversial, a multi-institutional review was conducted with the objective of evaluating the appropriateness of various strategies including observation.

Methods. Retrospective chart reviews for 414 consecutive patients who underwent hysterectomy for FIGO stage IA endometrial cancer with serous, clear cell or mixed histology between 2004 and 2015 were conducted in 6 North American centers. Time-to-event outcomes were analyzed by Kaplan-Meier estimates, log-rank test, univariable and multivariable cox proportional hazard regression models.

Results. Post-operative management included observation (50%), chemotherapy and radiotherapy (RT) (27%), RT only (16%) and chemotherapy only (7%). The 178 RT patients received external beam (EBRT, 16%), vaginal vault brachytherapy (VVB, 56%) or both (28%). Among patients without any adjuvant treatment, 5-year local control (LC), disease free survival (DFS) and cancer-specific survival (CSS) were 82% (95% confidence interval: 74–88), 70% (62–78) and 90% (82–94), respectively. CSS in patients without adjuvant treatment was improved with adequate surgical staging (100% vs. 87% (77–92), log-rank $p = 0.022$). Adjuvant VVB was associated with improved LC (5-year 96% (91–99) vs. 84% (76–89), log-rank $p = 0.007$) and DFS (5-year 79% (66–88) vs. 71% (63–77), log-rank $p = 0.033$). Adjuvant chemotherapy was associated with better LC (5-year 96% (90–98) vs. 84% (77–89), log-rank $p = 0.014$) and DFS (5-year 84% (74–91) vs. 69% (61–76), log-rank $p = 0.009$). On multivariable analysis, adjuvant chemotherapy and VVB were associated with improved LC while adjuvant chemotherapy and age were significant for DFS.

Conclusions. In stage IA serous or clear cell uterine cancer, adjuvant RT and chemotherapy were associated with better LC and DFS. Observation may be appropriate in patients who have had adequate surgical staging.

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1. Introduction

Uterine cancer is the most common gynecologic malignancy in developed countries and second most common in developing countries [1]. Although uterine serous and clear cell carcinoma only represents 10–15% of endometrial cancer, they are known to have a more aggressive clinical behavior compared to endometrioid carcinoma and accounts for up to 40% of cancer-related death within uterine cancers [2]. Even in stage I disease, patients with non-endometrioid carcinoma are known to have a significantly worse prognosis when compared to the more common uterine endometrioid adenocarcinomas [3].

There is currently a lack of consensus on whether patients with early-stage, Type 2 uterine cancer require any adjuvant treatment [4,5]. In fact, according to the current National Comprehensive Cancer Network (NCCN) guideline, any of observation, chemotherapy with or without vaginal brachytherapy, external beam radiotherapy with or without vaginal brachytherapy are all considered acceptable following hysterectomy in this earliest stage population [6].

Given the uncertainty in the optimum adjuvant management of these patients, the objectives of this study were to conduct a pooled analysis of multi-institutional experience in this relatively rare entity to explore the role of adjuvant therapy in managing serous and clear cell stage IA (FIGO 2009) endometrial cancer and to identify patient characteristics suitable for active surveillance.

2. Methods

2.1. Patient population

After receiving local institutional ethics board review board approval at each contributing center, 6 institutions with experience on the adjuvant management of FIGO 2009 stage IA endometrial cancer with serous or clear cell histology were invited to contribute to this pooled analysis. These included the following six North American centers: British Columbia Cancer Agency (BCCA, British Columbia, Canada; 2004–2012), Cross Cancer Institute (CCI, Alberta, Canada; 2003–2013), Henry Ford Cancer Institute (HFCI, Michigan, United States; 2004–2013), Juravinski Cancer Centre (JCC, Ontario, Canada; 2000–2014), London Regional Cancer Program (LRCP, Ontario, Canada; 2003–2013) and Odette Cancer Centre (OCC, Ontario, Canada; 2010–2015). Following data quality assurance procedures, baseline characteristics, including treatment, pathology and clinical outcome data were assessed using descriptive statistics. Clinical endpoints analyzed included overall survival, disease-free survival, local control, regional control, distant control and cancer-specific survival. Patients who did not meet the definition of stage IA or did not have histologically confirmed serous or clear cell components were excluded from this analysis. Patients with mixed histology with any proportion of serous or clear cell components were included.

2.2. Surgery and surgical staging

Total hysterectomy and bilateral salpingo-oophorectomy was the standard surgery performed in most patients although there were some variations. Approaches such as abdominal, laparoscopic, vaginal or choice of other surgical technique varied as per the treating surgeon's discretion and center preference.

Surgical staging including sampling of pelvic lymph node (LN), para-aortic LN, omentum and peritoneal washing were performed per institutional practice. Sentinel lymph node biopsy was not performed. We pre-defined adequate staging as patients meeting all three of these criteria: 1) at least 10 pelvic LN removed; 2) any sample of para-aortic LN; 3) omental biopsy or omentectomy [7].

2.3. Adjuvant chemotherapy

Adjuvant chemotherapy was based on the practice at each center. The most commonly used chemotherapy regimen was carboplatin/paclitaxel, which were offered in all six centers. Less commonly employed regimens were carboplatin alone and cisplatin/adriamycin each offered at one center. Treatment sequencing for adjuvant chemotherapy and radiotherapy (RT) varied between centers.

2.4. Adjuvant radiation

Adjuvant radiation was offered based on each center's practice. When utilized, external beam radiation (EBRT) to the whole pelvis with 45 Gy in 1.8 Gy daily fractions (Monday to Friday) was the standard dose offered in all 6 centers. A small proportion of patients (n = 6, 8%) received other dose fractionations (range 43.2–52 Gy). Radiation dose was compared across fractionation schedules by converting to 2 Gy-per-fraction equivalent dose (EQD2) with an alpha beta ratio of 4.5 [8]. When utilized, vaginal vault brachytherapy (VVB) was delivered using high dose rate (HDR) brachytherapy to the upper 3–4 cm of the vagina.

2.5. Statistical analysis

Descriptive statistics were generated for patient and treatment characteristics for all patients from participating centers. Kaplan-Meier estimates were generated for all time-to-event survival and recurrence end points calculated from date of surgery and compared using the log-rank test. Median follow-up time was estimated by the reverse Kaplan-Meier method. Cox proportional hazard regression models were used to identify significant prognostic factors on univariable and multivariable analysis. Interaction testing among disease characteristics and various treatment modalities was performed. Variables with univariable p-values <0.05 were selected for multivariable analysis and sequentially removed using backward elimination retaining only factors with p-values <0.2. All statistical analyses were performed on SAS version 9.4 (SAS Institute, Inc.; Cary, North Carolina), using two-sided statistical testing at the 0.05 significance level.

3. Results

3.1. Patients and disease characteristics

A total of 414 patients met the inclusion criteria and were included in this analysis. The patient and disease characteristics are listed in Table 1. The median age was 67 years (range 41–90) and the most common histologies were pure serous (64%, n = 266) followed by mixed (one or two types of Type 2 histology with or without endometrioid type) (27%, n = 112) and pure clear cell (9%, n = 36). Inner half myometrial invasion was identified in 54% (n = 222).

3.2. Treatment

Treatment specifics of surgery and adjuvant therapy delivered are listed in Table 1. Hysterectomy was most commonly performed via abdominal approach (73%, n = 301) and almost all women (99%, n = 409) had bilateral salpingo-oophorectomy. Most patients underwent a surgical staging procedure including sampling of pelvic lymph nodes (LN) (81%, n = 335), para-aortic LN (35%, n = 146), omentum (58%, n = 239) and peritoneal washing (53%, n = 219). Twenty-three percent (n = 95) had adequate surgical staging per our pre-defined definition.

Thirty-four percent of patients (n = 140) received adjuvant chemotherapy and carboplatin/paclitaxel was most commonly used (77%, n = 108). The median number of chemotherapy cycles received was 6 (range 3–8).

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