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The effect of adjuvant radiation on survival in early stage clear cell ovarian carcinoma

Liat Hogen [a], Gillian Thomas [b], Marcus Bernardini [a,c], Dina Bassiouny [d], Harinder Brar [a], Lilian T. Gien [a,e], Barry Rosen [a,c], Lisa Le [f], Danielle Vicus [a,e,*]

[a] Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University of Toronto, Toronto, Ontario, Canada
[b] Department of Radiation Oncology, Odette Cancer Centre, Toronto, Ontario, Canada
[c] Division of Gynecologic Oncology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, Ontario, Canada
[d] Department of Anatomic Pathology, Sunnybrook Health Sciences Center, Toronto, Ontario, Canada
[e] Division of Gynecologic Oncology, Odette Cancer Centre, Toronto, Ontario, Canada
[f] Department of Biostatistics, Princess Margaret Cancer Center, Toronto, Ontario, Canada

HIGHLIGHTS

- Clear cell carcinoma of the ovary is a rare subtype which is relatively resistant to platinum based chemotherapy.
- Ovarian clear cell carcinoma is frequently diagnosed at early stage, the role of adjuvant treatment is disputable.
- Our study did not demonstrate a survival benefit for adjuvant radiation in patients with ovarian clear cell carcinoma.

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ABSTRACT

Objective. To assess the impact of adjuvant radiotherapy (RT) on survival in patients with stage I and II ovarian clear cell carcinoma (OCCC).

Methods. Data collection and analysis of stage I and II OCCC patients treated at two tertiary centers in Toronto, between 1995 and 2014, was performed. Descriptive statistics and Kaplan-Meier survival probability estimates were completed. The log-rank test was used to compare survival curves.

Results. 163 patients were eligible. 44 (27%) patients were treated with adjuvant RT: 37 of them received adjuvant chemotherapy (CT), and 7 had RT only. In the no-RT group, there were 119 patients: 83 patients received adjuvant CT and 36 had no adjuvant treatment. The 10 year progression free survival (PFS) was 65% for patients treated with RT, and 59% no-RT patients. There were a total of 41 (25%) recurrences in the cohort: 12 (27.2%) patients in RT group and 29 (24.3%) in the no-RT group. On multivariable analysis, adjuvant RT was not significantly associated with an increased PFS (0.85 (0.44–1.63) $p = 0.63$) or overall survival (OS) (0.84 (0.39–1.82) $p = 0.66$). In the subset of 59 patients defined as high-risk: stage IC with positive cytology and/or surface involvement and stage II: RT was not found to be associated with a better PFS (HR 1.18 (95% CI: 0.55–2.54) or O S(HR 1.04 (95% CI: 0.40–2.69)).

Conclusion. Adjuvant RT was not found to be associated with a survival benefit in patients with stage I and II ovarian clear cell carcinoma or in a high risk subset of patients including stage IC cytology positive/surface involvement and stage II patients.

1. Introduction

Ovarian clear cell carcinoma (OCCC) is a subtype of epithelial ovarian cancer with distinctive histologic, molecular and clinical features. Its incidence varies in different populations representing 3–12% of all ovarian cancers in North America but is far more common in Japan, representing 20–25% of all ovarian cancers [1–6]. When compared to the more common serous counterpart, it is frequently diagnosed at an earlier stage; retrospective studies have shown between 47 and 81% of OCCC are diagnosed at stage I or II [2,4,7–10].

Stage I OCCC has a relatively good prognosis with a 5-year overall survival (OS) of 85%, and for stage IA the reported 5-year OS is

* Corresponding author at: Odette Cancer Centre, 2075 Bayview Ave., T2-018, Toronto, Ontario, M4N 3M5, Canada.
E-mail address: danielle.vicus@sunnybrook.ca (D. Vicus).

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approximately 90% [2,4,11]. The reported survival of stage IC is variable. While patients with stage IC due to capsule rupture alone showed poorer survival than stage IA, their survival was better than patients with stage IC due to positive cytology or surface involvement. A 9-year progression free survival (PFS) of 70.7% and OS of 78.9% were reported in a subgroup of patients with stage IC capsule rupture; a better prognosis than that shown in stage IC positive cytology and/or ovarian surface involvement with a reported 9-year PFS and OS of 56.6% and 61.3%, respectively [12]. A more recent study from Memorial Sloan Kettering further demonstrates the more favorable prognosis of stage IC rupture only when compared to IC positive cytology, with a 3-year OS of 96.2% for the former and 71.9% for the latter ($p = 0.001$) [13]. Several other studies have also demonstrated positive cytology as an adverse prognostic factor [4,9,11,14,15].

There is a paucity of data on the effectiveness of adjuvant treatment in OCCC and hence a lack of consensus regarding the optimal management strategy in early stage disease. This has led to variations in the use of adjuvant treatment including observation, chemotherapy (CT) alone or multimodality treatment with chemotherapy and radiotherapy (RT). [11,16–21] Traditionally, CT has been recommended for all patients with OCCC, despite the relatively favorable outcome and the relative chemoresistance to standard carboplatin based regimens. Reported response rates to chemotherapy for women with OCCC range between 11% and 56%, compared to response rates of over 70% for patients with serous ovarian cancer. [4,11,22–24] Combining the relative good prognosis of stage I OCCC with its relative lack of sensitivity to platinum-based CT, Takano et al. suggested that there is only a "mild beneficial effect" of adjuvant CT for stage I patients, with similar PFS and OS rates in the CT versus no-adjuvant CT groups [11].

Epithelial ovarian cancer is known to be a radiosensitive tumor. The benefit of adjuvant RT in patients with early-stage epithelial ovarian cancer has been evaluated in a series of studies [25–27]. It has been suggested that the addition of RT to CT for subsets of patients may have a broader indication [20,28,29]. In the majority of studies looking at the effectiveness of RT, all epithelial malignancies were included. However, for clear cell carcinomas particularly, the beneficial effect of adjuvant RT might be more pronounced due to its unique pattern of spread with the majority of cases being confined to the pelvis and its relative resistance to standard CT. Nagai and associates compared adjuvant platinum-based CT to adjuvant whole abdominal radiation (WAR) alone in 28 women with stage I to III OCCC. [28] They found a significantly higher five-year OS and PFS; with considerably improved local regional control in the adjuvant RT arm. Dinniwell and associates performed a prospective study of 29 patients with stage I to III epithelial ovarian cancer combining surgery, CT and WAR. The subset of 11 patients with clear cell and 5 with endometrioid histologies showed the greatest gains from this multimodality approach [29]. Finally, a retrospective study by Swenerton et al. reported an improved survival in patients with stage I and II clear cell, endometrioid, and mucinous histotypes with the addition of adjuvant WAR to CT [20]. This group further published in 2012 a study on 241 stage I-II clear cell ovarian cancer patients comparing two groups; those treated with adjuvant CT and RT and those treated with CT only. They demonstrated a potential beneficial effect of WAR with a 20% increase in PFS in a subset of early stage high-risk patients defined as: stage IC positive cytology/surface involvement and stage II [21].

The primary objective of our study was to assess the impact of adjuvant radiotherapy in stage I and II OCCC, and in a subset of early stage high-risk patients, in a large, North American cohort; and to determine whether our experience was in conjunction with the aforementioned studies.

2. Methods:

209 patients with ovarian clear cell carcinoma (OCCC) were treated or seen in consultation at one of two tertiary cancer centers in Toronto, Canada. Of those, 71 patients with no macroscopic extra-ovarian spread underwent full surgical staging including; hysterectomy, bilateral salpingo-oophorectomy, pelvic and para-aortic lymph node dissection and omental biopsy. 11 patients were found to have positive lymph nodes, however, in 4 out of the 11 there was also microscopic involvement of the omentum. A total of 163 patients were found to have stage I or II ovarian clear cell carcinoma (OCCC) and they are the subject of this manuscript: 101 patients seen at Princess Margaret Cancer Center treated between 1995 and 2014 and 62 patients at Sunnybrook Health Sciences Center between 2000 and 2014. At Princess Margaret Cancer Center, the institutional tumor registry was used to identify the patients, and at Sunnybrook Health Sciences Center the patients were identified using the pathology registry. For each patient, a comprehensive review of the electronic medical record was performed including operative, pathology and radiology reports and outpatient clinic notes. Only patients with pure ovarian clear cell carcinomas FIGO stage I (confined to the ovary) or FIGO stage II (extra ovarian spread confined to the pelvis) were included. A gynecologic pathologist reviewed all slides. Patients with adhesions that were biopsied and were negative for malignancy or if a biopsy was not taken from the adhesions were considered as stage I rather than stage II.

The high-risk population was defined as patients with stage IC positive cytology, surface involvement or stage II. Patients identified as stage IC based on rupture only in which cytology was unknown were included in the low risk group; as were patients with stage IA/IB and unknown cytology.

All patients underwent surgery: laparotomy, laparoscopy or robotic assisted. Most surgeries included a hysterectomy, bilateral salpingo-oophorectomy and omentectomy. Cytology, as well as lymph node dissection, was optional, and performed at the surgeon's discretion. When performed, pelvic lymph node dissection included all lymph tissue surrounding the external iliac, internal iliac and obturator vessels, from the common iliac bifurcation to the circumflex iliac vein. The para-aortic lymph node dissection included removal off all lymph barring tissue surrounding the inferior vena cava and aorta, from the common iliac bifurcation to the origin of the renal vessels.

Adjuvant treatment differed according to the institutional guidelines and physician preference. Chemotherapy was predominantly a platinum based doublet, with carboplatin (AUC = 5–6) and paclitaxel (175 mg/m^2) every 3 weeks, for 3–6 cycles. Radiation included pelvic and/or WAR. The RT dosage and number of fractions were in keeping with the standard protocols: abdominopelvic RT usually began 4–6 weeks after chemotherapy, the parallel opposed pair technique was used to deliver 2300 cGy in 100 cGy 23 daily fractions. Posterior kidney shields were introduced at 1500 cGy to maintain the total kidney dose at <2000 cGy. No hepatic shielding was used. The pelvis received a concurrent boost of 1150 cGy in 23 fractions and a further 1050 cGy in 7 fractions after completion of the abdominal treatment. The total pelvic dose was 4500 cGy in 150 cGy daily fractions. In cases of pelvic radiation only, the four-field-box technique was used to deliver a total pelvic dose of 4500 cGy, in 25 daily fractions of 180 cGy.

Not all patients with a pelvic mass that do not present with additional symptoms undergo imaging for staging purposes prior to surgery at our institutions. Post-operative imaging is left to the discretion of the treating physician, however, the majority of patients either receive adjuvant treatment or have assessment of their nodal status surgically. At time of recurrence all patients are assessed with the most appropriate imaging.

Variables included in the univariate analysis were: age, stage, Asian race, endometriosis, cytology, surgical staging, adjuvant chemotherapy and adjuvant RT. In addition to adjuvant radiation, three pre-selected variables: age, stage, and adjuvant CT were included in the multivariable analysis.

3. Statistics

Patient demographics and baseline characteristics were summarized using descriptive statistics. OS was calculated from the date of surgery

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