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Surgical Stage I high-grade ovarian cancer: is adjuvant chemotherapy warranted?

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Summary

Objective: To review the results of patients with high-grade Stage I ovarian cancer managed without adjuvant treatment. *Materials and Methods:* A retrospective chart review identified patients with newly diagnosed Stage I high-grade ovarian cancer, who underwent comprehensive surgical staging. *Results:* Thirty-three patients with FIGO surgical Stage I high-grade ovarian cancer were identified. After a median follow-up of 40 months, nine patients (27%) recurred. The median time to recurrence was 19 months. Of the nine patients with recurrences, four (44%) are alive with disease, three (33%) patients have no evidence of disease, and two have died of disease (22%). The two- and five-year overall survival is 100% and 90%, respectively. *Conclusions:* It would appear the recurrence rates of Stage I high risk epithelial ovarian cancer completely staged, without adjuvant treatment are comparable to those of treatment arms reported in the literature. A proportion of these patients can be salvaged at recurrence, yielding a high overall survival.

Key words: Ovarian cancer; Surgical staging; Adjuvant chemotherapy; High grade; Early stage.

Introduction

Ovarian cancer is a common gynecologic malignancy. Approximately 20% of patients with ovarian cancer are diagnosed with Stage I. For those diagnosed with epithelial ovarian cancer (EOC) confined to the ovary (IA or IB) and well-differentiated (grade 1) tumors, prognosis is excellent with survival of at least 90% following surgery alone [1]. Those with Stage IC, high grade or clear cell histology have a 30% risk of developing recurrent disease after surgery [2, 3].

In 2003, two large randomized clinical trials- The European Organisation for Research and Treatment of Cancer–Adjuvant ChemoTherapy in Ovarian Neoplasm Trial (EORTC-ACTION Trial) [4] and the International Collaborative Ovarian Neoplasm Trial 1 (ICON1) were published [5]. For analysis purposes, the two studies were combined as neither was able to reach the planned accrual. Both studies included Stage I and II patients, and a significant proportion of the patients were either mucinous or grade 1 tumors. No central pathologic review was done, and the extent of surgical staging was variable. While there was an overall survival benefit with the use of adjuvant chemotherapy, it was confined to those patients with incomplete surgical staging. Adjuvant chemotherapy provided no survival benefit in completely surgically staged patients.

Additional randomized studies, predominantly conducted by the Gynecology Oncology Group (GOG) without an observation only arm, have consistently demonstrated a 20-30% relapse rate [6, 7]. Importantly, in patients that have been treated with adjuvant chemotherapy, recurrence is uncommonly translated into long-term survival [6, 7].

This high recurrence rate in Stage I high-grade EOC has led many clinicians to recommend adjuvant treatment, despite the absence of level I evidence in completely surgically staged patients.

Since 2004 in the present center, the authors have not administered adjuvant therapy for completely surgical Stage I high grade ovarian cancer. The purpose of this study was to review the outcomes of these patients.

Materials and Methods

Following approval from the Research Ethics Board, patients with FIGO Stage I high grade (grade 2-3) EOC diagnosed from 2004 to 2012 were identified from the tumor registry databases at the Sunnybrook Health Sciences Center. Inclusion criteria included; newly diagnosed, Stage I, grade 2 or 3, serous, clear cell, and endometroid histologies, and comprehensive surgical staging. Comprehensive surgical staging in this study was defined as total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, ipsilateral (or bilateral) pelvic and para-aortic lymphadenectomy, and biopsy of any suspicious abnormalities. All surgery was performed by a formally trained gynaecologist oncologist. Patients with Stage II or greater, grade 1, mucinous histology, incomplete surgical staging procedure, neoadjuvant chemotherapy, previous radiation therapy, and use of adjuvant treatment were excluded.

Abstracted data included patient demographics, clinico-pathologic features, surgical substage, co-morbidities, date and location of recurrence, subsequent therapy, and survival.

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Table 1. — *Characteristics of patients with recurrence.*

	Histology	Stage	Sites of recurrence	Time to recurrence	Treatment for recurrence status	Last (months)	Follow up
1	Clear cell	IB	Vaginal vault	19	Carboplatin - Taxol	AWD*	35
2	Serous	IB	Intraperitoneal	13	Carboplatin - Taxol	AWD	20
3	Clear cell	IA	Intraperitoneal	2	Carboplatin - Taxol	NED**	71
4	Serous	IA	Left pelvic side wall - intraperitoneal	41	Surgery + carboplatin and taxol	NED	108
5	Clear cell	IA	Supraclavicular and mediastinal node	5	Carboplatin and taxol + radiation	DOD***	33
6	Clear cell	IC	Aortocaval- above the area of dissection	23	Carboplatin and taxol + radiation	DOD	37
7	Clear cell	IC	Pelvis-intraperitoneal	9	Carboplatin- taxol	NED	32
8	Clear cell	IA	Left para-aortic node above the area of dissection	30	No treatment	AWD	30
9	Serous	IB	Colon mucosa and abdominal wall	69	Surgery + carboplatin and taxol	AWD	90

*AWD: alive with disease; **NED: no evidence of disease; ***DOD: dead of disease.

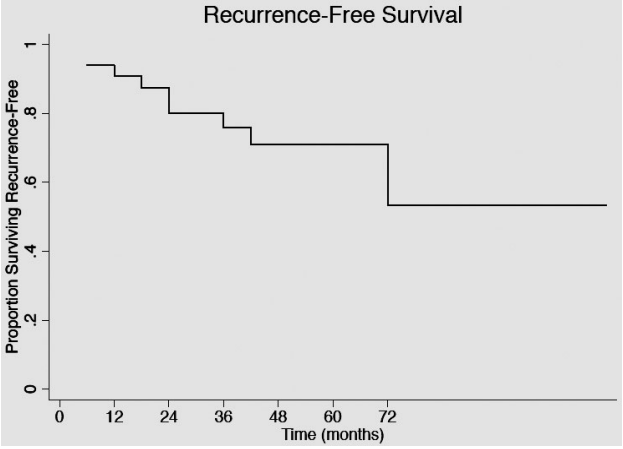

Figure 1. — Recurrence free survival of the cohort.

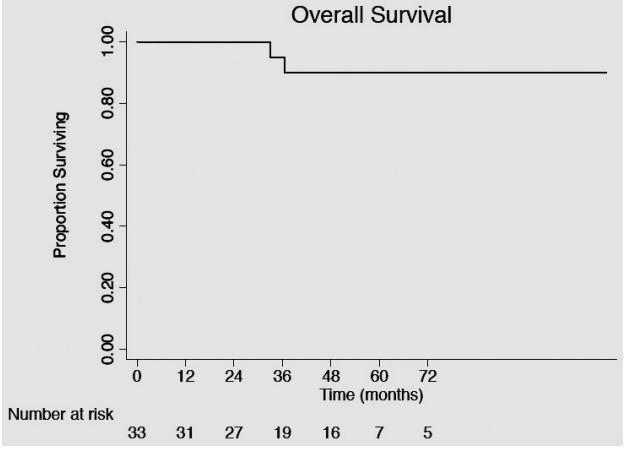

Figure 2. — Overall survival of the cohort.

Results

Of the 550 cases of ovarian cancer treated at the present institution during the above-mentioned period, 33 patients met the above criteria for inclusion in this study. During this time period, while not formally evaluated, approximately twice as many patients were given adjuvant therapy due to incomplete surgical staging or one physician's preference.

The median age of the population was 56 years (range 42-81). Sixteen patients had Stage IA disease, nine Stage IB, and eight Stage IC. Fourteen patients had pure clear cell histology, seven endometroid, five serous, and seven had mixed histology either clear cell/endometroid or serous/endometroid.

The number of lymph nodes evaluated was provided in 100% of the pathology reports. The median number of nodes removed at lymphadenectomy was 18 (range 5–68). Ten patients (30%) had only unilateral lymphadenectomy with a median number of nodes removed among this group of 13.

After a median follow up of 40 months (range 7–116), nine patients (27%) have recurred. The median time to recurrence was 19 months (range 2-69). The details of these patients are listed in Table 1. All of the patients with nodal recurrences were noted superior to the cranial extent of the dissection, none within the dissected nodal bed. Of the three patients that had undergone a unilateral lymphadenectomy only at primary surgery, none recurred in the contralateral non-dissected side.

Of the nine patients with recurrence, four (44%) were alive with disease at last contact, and three (33%) have been rendered free of disease at last contact (23, 59, and 70 months post recurrence). Two patients have died of disease (14 and 28 months post recurrence). The five-year progression-free and overall survival is 70% and 90%, respectively (Figures 1, 2). Treatment for recurrence consisted of chemotherapy alone [4], chemotherapy + surgery [2], and chemotherapy + radiation therapy [2], and one patient is under observation only (patient choice).

Discussion

There is no clear consensus, on what, nor if any treatment should be given to surgical Stage I EOC patients with high risk features.

The GOG conducted the first randomized study of adjuvant chemotherapy in early stage moderately or well-differentiated ovarian cancer [8]. Eighty one patients were randomized to oral melphalan or no adjuvant therapy. After a median follow-up of more than six years, there were no significant differences in the five-year disease-free survival and overall survival (94% *vs* 98% for the observed and treated patients, respectively, $p = 0.43$) [8]. In the same study they also assessed 141 patients with poorly differentiated Stage I and II ovarian cancer and compared treatment with either a single intraperitoneal dose of ^{32}P or melphalan. The recurrence rates (19% each group), and five-year overall survival were similar between groups (78% and 81%, respectively, $p = 0.48$) [8].

The GOG conducted several studies comparing various regimens of adjuvant therapy in early stage EOC. While these studies tended to include grade 1 tumours, mucinous histology, and Stage II patients, all were associated with a recurrence rate in the order of 20-35% [6-8].

Bolis *et al.* conducted two randomized studies to evaluate the impact of cisplatin versus no treatment in patients with EOC Stages Ia/Ib, grades 2/3, and cisplatin versus IP chromic phosphate (^{32}P). In both studies cisplatin significantly reduced the recurrence free survival (HR 0.35; $p = 0.028$ and 0.39; $p = 0.007$, respectively). However, while both were statistically significant, no overall survival benefit from adjuvant therapy was observed (the first study: five-year overall survival was 88% and 82% (HR = 1.15; 95% CI = 0.44-2.98; $p = 0.773$) for cisplatin and controls, respectively; for the second study five-year overall survival was 81% and 79% (HR = 0.72; 95% CI = 0.37-1.43; $p = 0.354$) for cisplatin and ^{32}P respectively [9].

Tropé *et al.* randomized patients with Stage I EOC (all grades, including clear cell carcinomas) to either six cycles of carboplatin or no treatment [10]. Surgical staging was not mandatory, and mucinous histology was included. No statistically significant differences in disease free [71% *vs* 70% in the control and treatment groups, respectively (HR = 0.98; 95% CI = 0.52-1.83)] or disease specific survival [85% *vs* 86% in the control and treatment groups respectively (HR = 0.94; 95%CI = 0.37-2.36)] was identified.

The EORTC-ACTION Trial included patients in Stages Ia/b, grades 2/3, Stages Ic and IIa (all grades) [4]. Approximately 18% of the patients had mucinous histology. A multivariate analysis demonstrated that histologic cell type was a statistically significant prognostic factor for overall survival. After ten years of follow-up, the multivariate analysis found no association between cancer-specific survival and histological cell type, however, surgical staging was a significant predictor for survival and recurrence. [10]. The recurrence rate for the entire study was 18% and 27% in the adjuvant chemotherapy and observation groups, respectively. Only 34% were considered to have optimal surgical staging. In the optimally staged patients, there was no difference in recurrence-free (HR = 1.14; 95% CI = 0.54- 2.93, $p = 0.7$) and overall survival (HR = 0.81; 95% CI = 0.32 - 2.05, $p = 0.7$) between the observation and chemotherapy groups [4]. In the optimally staged patients, no difference in cancer specific survival between the observation and treatment groups was observed after ten years of follow-up (HR = 1.58, 95% CI = 0.61 - 4.08, P = 0.34) [11].

The ICON 1 randomized 477 patients with early-stage EOC to receive either adjuvant chemotherapy immediately following surgery or no adjuvant chemotherapy. However, it is unclear how many of the patients were completely surgically staged, likely a minority. Moreover, 23% of the cohort had mucinous tumour histology, and 32% of the tumours were grade 1. This study showed improved overall survival (HR = 0.66, 95% CI = 0.45 -0.97; $p = 0.03$) and recurrence free survival (HR = 0.65; 95% CI = 0.46 to 0.91; $p = 0.01$) for patients receiving platinum-based chemotherapy [5].

The benefit of adjuvant chemotherapy in patients with early-stage EOC has been further evaluated in two meta-analyses [11, 12]. Elit *et al.* examined 13 trials conducted between 1965 and 2004 [12]. Only eight of these studies were performed exclusively in stage I EOC. Women with stage I EOC showed a benefit for adjuvant treatment in terms of recurrence-free survival (RR = 0.70, 95% CI = 0.58-0.86) and overall survival (RR = 0.74, 95% CI 0.58-0.94). Five-year overall survival was improved with the use of adjuvant platinum-based therapy (HR = 0.67, 95% CI = 0.50-0.90). No subset analysis for completely staged patients was performed, although the authors mentioned the lack of surgical staging for many of the women as a limitation [12].

Winter –Roach *et al.* looked at five randomized trials conducted between 1990 and 2003 involving 1,277 women [13]. Adjuvant chemotherapy was associated with benefit in terms of both progression-free survival (HR = 0.67, 95% CI = 0.52-0.84) and overall survival (HR = 0.71, 95% CI = 0.53-0.93). In this meta-analysis, women who had optimal staging, did not have an improved overall survival with chemotherapy compared to those observed (HR = 1.22, 95% CI = 0.63-2.37). By comparison, for women who had suboptimal staging, chemotherapy resulted in superior survival when compared with observation (HR= 0.63, 95% CI = 0.46-0.85). Women with high-risk tumours (both optimally and non-optimally staged) had a survival advantage with the use of adjuvant chemotherapy compared to observation (HR = 0.48, 95% CI = 0.32-0.72) Patients with low-risk tumours, (both optimally and non-optimally staged), did not benefit from chemotherapy (HR = 0.95, 95% CI = 0.54-1.66) [12].

Two studies looked at recurrence of early-stage ovarian cancer. The first one by the GOG included patients with Stage IA-IB grade 3, Stage IC and II [14]. All patients underwent complete surgical staging. In this study all patients received adjuvant chemotherapy. The five-year recurrence-free and overall survivals were 75.5% and 81.7%, respectively [14]. For patients that recurred, the median time from completion of primary chemotherapy to recurrence was 21 months, and the median survival after recurrence was 24

months [15]. Kolomainen *et al.* evaluated recurrence among 194 patients with Stage I ovarian cancer [15]. The cohort included mucinous histology and a significant proportion of grade 1 tumors. Complete surgical staging did not include complete pelvic and para-aortic lymphadenectomy, but only nodal examination and biopsy of macroscopically abnormal nodes. The recurrence rate was 31%. All were treated with platinum – based chemotherapy. The overall survival for all 194 patients was 72% at ten years [16].

The present study is unique in that all the patients had high-grade histology (confirmed by a gynaecologic pathologist), mucinous tumors were excluded, and all patients were surgically staged. This is the first study evaluating recurrence and survival among high-grade, Stage I epithelial ovarian cancer after complete surgical staging without adjuvant therapy. As a significant proportion (33%) of patients with recurrence can be rendered disease-free with chemotherapy (+/- surgery and radiation), the differences in recurrence-free survival may be minimized if prolonged follow-up confirms these responses to be durable (in the present study, two of the recurrences rendered NED, have been so for over 60 months, and are likely cured). It is interesting to note that all of the recurrences were either clear cell or serous cancers. None of the endometrioid or mixed tumours recurred.

The limitations of this study are self-evident. It is a small single institution study, retrospective, and non-randomized with no control group. However, the authors believe that this data is provocative, and will further the debate regarding adjuvant therapy in Stage I high-grade EOC. A randomized study of high-grade fully-staged EOC patients managed with and without adjuvant therapy is warranted.

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