



Case report

Omission of adjuvant therapy in stage I clear cell ovarian cancer: Review of the BC Cancer experience

Shiru L. Liu, Anna V. Tinker*

Department of Medical Oncology, BC Cancer, Vancouver, BC, Canada

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ABSTRACT

Background: Since 2012, the BC Cancer provincial treatment guideline for surgically staged stage IA/B and IC1 (defined by intraoperative rupture only) clear cell ovarian cancer (CCOC) has been to offer observation only. We reviewed the clinical outcomes of all stage I CCOC patients since policy implementation.

Methods: A retrospective, population-based cohort study of all stage I CCOC patients operated on between April 2012 and December 2017 was conducted. Patient, tumor, surgical and clinical outcome data were collected. Survival analysis was conducted using Kaplan-Meier methods.

Results: 78 patients with stage I disease were identified. 40 patients with stages IA/B and IC1, who underwent post-operative observation, were included in the analysis. Lymph node dissection was omitted in 20 patients (50%). Median duration of follow-up was 36 months. There were 4 recurrences (10%), 3 metastatic. The 5-year disease-free survival is 90%, and the 5-year overall survival is 95% for stage IA/B and 90% for stage IC1 ($p = 0.645$). In comparison, 5-year overall survival for stage IC2 (surface involvement) and IC1 with sharp dissection (all received adjuvant chemotherapy) is 82% ($p < 0.001$) and for stage IC3 (positive washings) was 23% ($p < 0.001$).

Conclusion: Adjuvant therapy can be safely omitted in patients with stage I A/B and IC1 CCOC. Recurrence rates are low and survival is $> 90\%$ at 5 years. Stage IC2 /IC3 had worse outcomes, thus stage I substage is instrumental in predicting clinical outcomes for CCOC. Lymph node metastases are rare in stage IA/B/IC1 CCOC as absence of lymphadenectomy did not increase the risk of disease recurrence.

1. Introduction

Clear cell ovarian carcinoma (CCOC) is an uncommon subtype of ovarian cancer, but in advanced stages it has been associated with a poorer prognosis (Gounaris and Brenton, 2015; Chan et al., 2008), due to inherent resistance to platinum-based chemotherapy, resulting in worse outcomes than patients with other epithelial ovarian cancers (Pathar and Quinn, 2005; Goff et al., 1996; Kolasa et al., 2009; Takano et al., 2006; Takano et al., 2010). However, patients with early stage disease have excellent 5-year disease survival of over 80% (Takano et al., 2006). Standard of care up until 2012 in British Columbia (BC) included debulking surgery with total-abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, washings, and lymphadenectomy, followed by adjuvant chemoradiotherapy with 3 cycles of carboplatin and paclitaxel followed by total abdominal irradiation.

Currently, the National Comprehensive Cancer Network (NCCN) recommends adjuvant platinum-based chemotherapy for stage IA-C CCOC (Morgan et al., 2016). In 2012, a review of BC outcomes data for

stage I and II CCOC, which included 241 cases diagnosed between 1984 and 2008, showed that while stage II and stage IC2/3 (defined by surface or cytologic positivity) patients may benefit from adjuvant treatment with irradiation, patients with stage IA/B and IC1 (defined by rupture only, without surface or cytologic positivity) did not seem to derive any survival benefit in comparison. A review of published series demonstrated a 5-year disease free survivals of 84 to 100% and 86 to 89%, respectively, for stage IA/B and IC1 (Hoskins et al., 2012). The surgical standard in BC during this time included lymphadenectomy only for suspicious nodes. Given the expected excellent survival outcomes for the optimal early stage cohorts and the short- and long-term morbidity associated with chemotherapy and radiation, in BC the guidelines were changed in 2012 to no longer recommend adjuvant treatment for CCOC patients with stage IA/B and IC1 (defined as rupture only) disease.

The objective of the current study is to evaluate the outcomes of stage IA/B and IC1 (defined by rupture only) treated with surgery only, without adjuvant therapy, since policy implementation. We

* Corresponding author at: BC Cancer, 600 West 10th Ave, Vancouver, BC V5Z 4E6, Canada.

E-mail address: atinker@bccancer.bc.ca (A.V. Tinker).

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hypothesized that the disease-free survival (DFS) and overall survival (OS) of early stage CCOC would remain excellent, justifying observation as the standard of care at BC Cancer.

2. Methods

Local Research Ethics Board approval for this study was obtained. We performed a retrospective cohort analysis of all patients with stage I CCOC, including stage IA (confined to one ovary), IB (confined to both ovaries only), and IC, which is further stratified by intraoperative rupture only (IC1), surface involvement (IC2), and/or positive cytology (IC3), referred to BC Cancer between April 2012 (following provincial implementation of the new policy to omit adjuvant therapy for stage I CCOC) and December 2017 (to permit least one year of additional follow-up). BC Cancer is the provincial authority overseeing the delivery of cancer care in British Columbia, a province of 4.9 million people in 2017. Treatment policies are reviewed and issued by disease specific tumour groups and are integrated into provincially disseminated treatment protocols. The treatment guidelines and treatment protocols are available on the BC Cancer website (www.bccancer.bc.ca). Policy and protocols are reviewed regularly, as new data become available. The BC Cancer Registry records all new cancers diagnosed in the province, and whether patients were referred to a BC Cancer treatment centre. In 2016, 78.1% of all newly diagnosed ovarian cancers were referred to a BC Cancer treatment centre within one year of diagnosis. We estimate that approximately 80% of all ovarian cancer cases in BC were accessible for this review.

Patients were identified from the BC Cancer Registry and the Cheryl Brown Gynecologic Cancer Database. Baseline patient information including date and age at diagnosis, medical comorbidities measured using standardized Charlson Comorbidity Index, Eastern Cooperation Oncology Group (ECOG) performance status, prior malignancies, known genetic syndromes, and a clinical or pathologic diagnosis of endometriosis, were collected. Tumor and treatment information including type of surgery, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) surgical staging, lymph node dissection if any, use of sharp dissection, size of tumor, margin status, and any relevant molecular aberrations, were extracted directly from surgical and pathologic reports. Finally, clinical outcome information including follow-up length, date and type of recurrence, date and cause of death, were identified from electronic health records. While pathology information was taken directly from the pathology reports, formal pathology review was not conducted. We also assessed uptake of the provincial guideline and recorded reasons for non-adherence when possible. Survival analysis was conducted using Kaplan-Meier methods, with comparisons made using log-rank and Chi-Square tests. Disease-free survival is defined as time from diagnosis to recurrence, based on radiographic findings, or death. As there is no standard follow-up protocol for these patients, with variability in use of tumor marker or imaging modality, most recurrences were diagnosed following investigations of symptoms or clinical findings. Overall survival is defined as time from diagnosis to death from any cause.

Table 1
Use of Systemic Therapy per Disease Stages.

FIGO Stage ¹	No adjuvant therapy			Adjuvant therapy		
	IA	IB	IC1	IC1	IC2	IC3
N (%)	25 (32.1%)	2 (2.6%)	13 (16.7%)	9 (11.5%) ²	9 (11.5%)	20 (25.6%)

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics

¹ IA: confined to one ovary. IB: confined to both ovaries. IC1: intraoperative rupture only. IC2: surface involvement. IC3: positive cytology.

² 6 of 9 (66.7%) received adjuvant therapy due to use of sharp dissection (none of the IC1 patients on observation had sharp dissection).

Table 2
Baseline Characteristics for Stages IA, IB and IC1 Patients Who Did Not Receive Adjuvant Therapy (N = 40).

Characteristics	N (%)
Median age at diagnosis (range)	55 (38–85)
Charlson Comorbidity Index	
0	26 (65.0%)
1	7 (17.5%)
2	2 (5.0%)
3	3 (7.5%)
4	1 (2.5%)
ECOG performance status	
0	28 (70.0%)
1	8 (20.0%)
2	3 (7.5%)
3	1 (2.5%)
Presence of endometriosis ¹	
Yes	16 (40.0%)
No	24 (60.0%)
Hereditary BRCA	1 (2.5%)
Prior malignancy	5 (12.5%)
Surgical staging	
Complete ²	20 (50.0%)
Lymphadenectomy omitted	20 (50.0%)
Oophorectomy only	4 (10.0%)
FIGO staging	
IA	25 (62.5%)
IB	2 (5.0%)
IC1	13 (32.5%)
Molecular aberrations (N tested ³)	
MMR proficient (16)	16 (100.0%)
AURKA mutation (6)	2 (33.0%)
AKT2 amplification (6)	1 (17.0%)
CDH1 mutation (6)	1 (17.0%)
Recurrence	
Peritoneal/pelvic/omental	1 (2.5%)
Distant metastatic	3 (7.5%)

Abbreviations: ECOG = Eastern cooperative oncology group, FIGO = International Federation of Gynecology and Obstetrics.

¹ Presence of endometriosis defined either through history or on final pathology report.

² TAH/BSO, omentectomy, lymphadenectomy, washing. Including 14 (70%) cases which required repeat surgery to complete staging.

³ Testing based on either immunohistochemical stain or next generation sequencing, when offered.

3. Results

Seventy-eight patients with stage I disease were identified (Table 1). Forty patients with stages IA/B and IC1 (rupture only), who underwent post-operative observation only, were the primary focus of this analysis. The patient baseline characteristics for this population are shown in Table 2. Median duration of follow-up was 36 months. Median age at diagnosis was 55 years and > 50% of patients had a Charlson Comorbidity Index of 0 (N = 26) and an ECOG performance status of 0 (N = 28) at diagnosis. Twenty patients underwent complete surgical staging, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, omentectomy, lymphadenectomy, and peritoneal washings. Lymph node dissection was not performed in 20 patients.

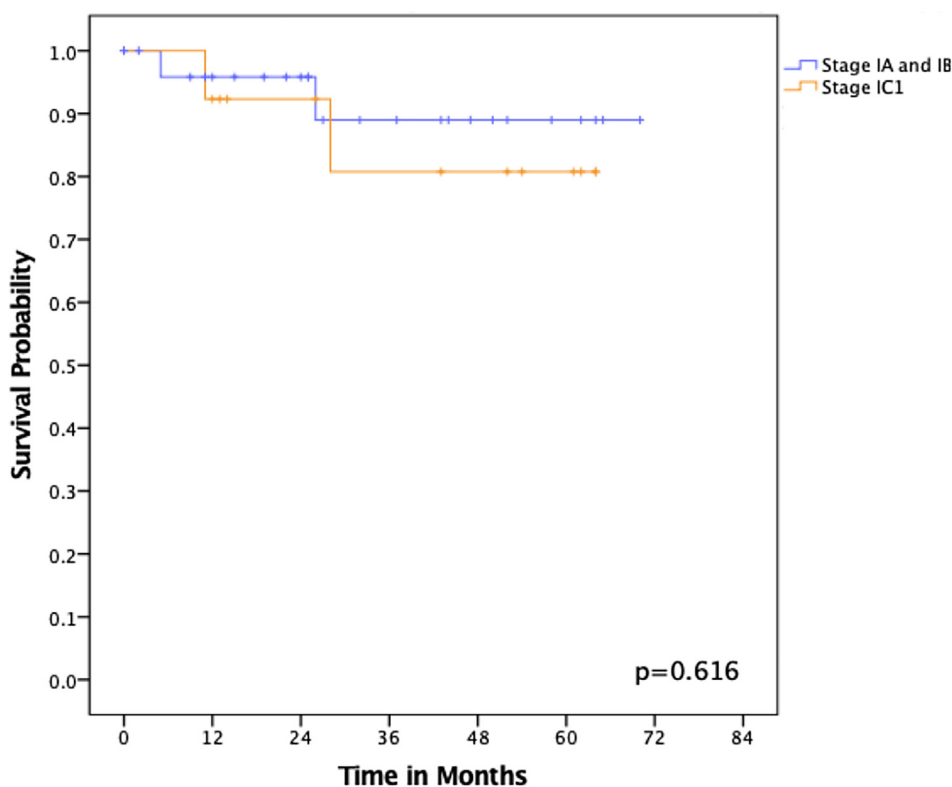


Fig. 1. Kaplan Meier curve for DFS for stage IA + IB and IC1 (rupture only) CCOC, who did not receive adjuvant therapy. Log-rank test shows no significant difference for DFS between these two groups ($p = 0.616$).

None of the 16 cases tested for mismatch repair protein expression by immunohistochemistry demonstrated deficiencies.

Four patients on post-operative observation experienced disease recurrence (10%), 3 with distant metastases and one with pelvic peritoneal recurrence (stage IA $N = 1$, IB $N = 1$, and IC1 $N = 2$). Two of the patients with recurrence did not have lymphadenectomy. The median time to first recurrence was 18 months (range 5–28 months). Treatment at the time of recurrence was with systemic therapy in all cases. One patient had genomic tumour profiling and based on the results was started on everolimus. There were two cancer-related deaths at the time of this review. The overall 5-year DFS was 90%. Kaplan Meier analysis (Fig. 1) demonstrated a 5-year DFS of 93% for stage IA and IB and of 85% for stage IC1 ($p = 0.616$). The 5-year OS were 95% for stage IA/B and 90% for stage IC1 ($p = 0.645$). The 5-year OS for stage IC2 (surface involvement, $N = 9$) and IC1 with sharp dissection (intraoperative rupture, $N = 9$) combined was 82% ($p < 0.001$), and 23% ($p < 0.001$) for stage IC3 (positive washings, $N = 20$), all of whom received adjuvant chemotherapy and radiation (Fig. 2).

Nine patients with stage IC1 disease received adjuvant therapy; 6 due to the use of sharp dissection at the time of surgical resection and staging, and 3 were for unspecified reasons. Sharp dissection was not used in the IC1 patients who underwent postoperative observation only. Neither the recurrences nor the use of sharp dissection occurred in patients with clinical or pathologic findings of endometriosis.

4. Discussion

Our results demonstrate that following the implementation of a provincial policy to omit adjuvant therapy in stage IA/B and IC1 (rupture only, without sharp dissection) CCOC, recurrence rates remained low and DFS is high at 90% at 5 years (93% stage IA/B and 85% stage IC1). These results confirm our past data (Hoskins et al., 2012) and are comparable with most of the published series that report on untreated early stage/stage I CCOC (Table 3). Our proposed approach

to the management of stage I CCOC is depicted in Fig. 3.

A recent large ($N = 2325$) cohort analysis of stage I CCOC from the National Cancer Database revealed improved overall survival associated with the use of adjuvant chemotherapy after controlling for baseline variables including disease sub-stage, for the entire population, all of whom underwent lymphadenectomy (Nasioudis et al., 2018). This study included cases diagnosed between 2004 and 2015 and data were collected from hospital-based databases. The median 5-year OS for stage IA/B clear cell cancers who did not receive adjuvant therapy was 84%, versus 92% in those who did ($p < 0.001$). Limitations of the study include the possibility of histotype mis-classification given the older case series and the inclusion of non-academic centres where clinical experience and expertise may be lower. In addition, the study included a large number of institutions of varied types (e.g. community, academic, etc.) thus variability in practice was likely quite large. Finally, it is not clear what treatment policies were used to guide treatment decisions. While our review is small, it is contemporary, and assesses the impact of a single, prospectively applied provincial management guideline that was made known at all the provincial treating centres in BC through the Provincial Gynecologic Oncology Tumour Group (e.g. annual tumour group meeting) and its availability on the institutional website (www.bccancer.bc.ca). Thus, a more consistent approach to patient care is expected, although not enforced.

Although not our primary objective, we note in our review that patients with stage IC2 (ovarian capsule surface involvement) and IC3 (positive peritoneal cytology) and those who required sharp dissection had higher risk for recurrence, consistent with our previous data (Hoskins et al., 2012) and the data of others (Takano et al., 2010; Takano et al., 2009). While surface involvement and peritoneal cytology are reported as part of standard pathologic staging, sharp dissection may not always be accurately documented, and thus its prognostic value is less certain, and is not consistently reported by others.

Fifty percent of our patients did not undergo lymphadenectomy. Of the four cases with recurrence during our follow-up period, two did not

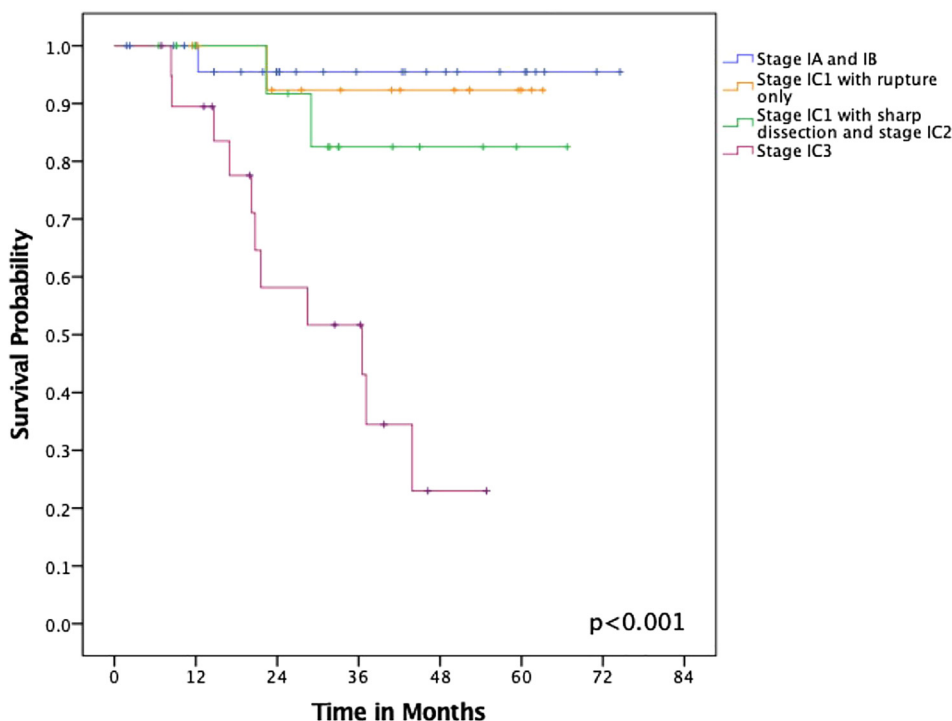


Fig. 2. Kaplan Meier curve for OS for all stage I CCOC, stratified by disease substage. Log-rank test shows significant difference between stages IA, IB and IC1 (rupture only) when compared to stages IC1 (sharp dissection), IC2, and IC3 ($p < 0.001$), regardless of chemotherapy receipt.

have lymphadenectomy. Despite this, the prognosis remains excellent for stage IA/B and IC1 without lymphadenectomy, likely because the risk of lymph nodal metastases in apparent early stage CCOC is generally low ($< 5\%$) (Mueller et al., 2016 Jan; Mahdi et al., 2013 Sep) Given that patients with lymph node metastases have a worse prognosis (Takano et al., 2009) and should be offered adjuvant therapy, surgical pelvic and para-aortic nodal assessments are part of the management recommendations for apparent stage I ovarian cancers (www.bccancer.bc.ca). Unfortunately, it was not always possible to determine why some cases did not have a lymphadenectomy.

Inherent deficiencies of this retrospective review include the small

sample size that is associated with unrecognized and immeasurable biases that may influence the patient outcomes, and incomplete or missing data (e.g. use of sharp dissection). Given the small number of events observed, a multivariate analysis to adjust for possible confounding variables was not performed. Finally, a pathology review was not conducted; however, in British Columbia, most suspected cases of gynecologic cancer are operated on at one of two centres majors centres by Gynecologic Oncologists and the samples are reported by pathologists specializing in gynecologic malignancies. The inter-observer variability in diagnosing ovarian cancer cell types is relatively low, and only slightly improved by the additions of immunostaining (Köbel

Table 3

Summary of retrospective studies reporting outcomes in stage I CCOC treated with and without adjuvant chemotherapy.

Study and Period	Stage	Treatment	Results	Comments
Nasioudis(Nasioudis et al., 2018) 2004–2015	IA/B = 1298 IC = 1007	No Chemo = 486 Chemo = 1839	<u>5-yr OS</u> 82.6% 89.2% ($p < 0.001$) <u>5-yr OS</u>	Use of adjuvant chemotherapy was a prognostic factor on multivariate analysis.
Oseledchyk (Oseledchyk et al., 2017 Dec 1) 2000–2013	IA/B = 1214	No Chemo = 455 Chemo = 759	84% 87% ($p = 0.308$) <u>5-yr DSS</u>	Patients with stage I and known negative cytology had no recurrences.
Hogen(Hogen et al., 2016 Nov) 1995–2014	IA/B = 25 IC = 35	No Chemo – 31 Chemo – 29	73.6% 92.8% ($p = 0.13$) <u>5-yr PFS/OS</u>	No recurrences observed among 20 patients with stage 1A disease.
Takada(Takada et al., 2012 May)	IA = 20 IC = 53	No Chemo = 43 Chemo = 30	87.4% 80.1% ($p = 0.610, p = 0.557$, respectively)	Multivariate analysis indicated that the use of chemotherapy was not a prognostic indicator.
Takano(Takano et al., 2010) 1992–2005		No Chemo = 24 Chemo = 195	<u>PFS/OS</u> No difference	Multivariate analysis revealed that positive peritoneal cytology was the only independent prognostic risk factor for PFS.

OS – overall survival, DSS – disease specific survival, PFS – progression free survival.

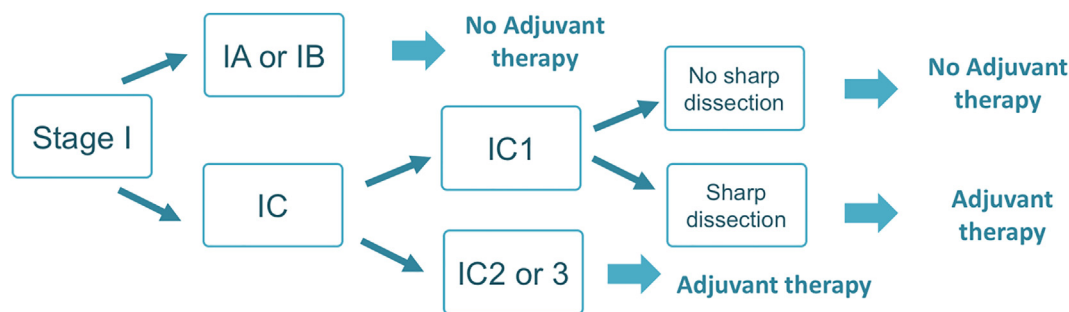


Fig. 3. BC Cancer Treatment Algorithm for stage I clear cell ovarian cancer.

et al., 2010; Kurman et al., 2014). Therefore, the diagnostic accuracy of this contemporary patient series is expected to be quite high. This study did not include in its objectives a comparison of adjuvant chemotherapy to adjuvant chemotherapy and radiotherapy.

5. Conclusion

In British Columbia, the provincially applied policy to omit adjuvant chemoradiotherapy for stage IA/B and IC1 (intraoperative rupture only) CCOC has so far yielded excellent survival outcomes. We report low recurrence rates and disease-free survival of over 90% since implementation of the provincial policy. We offer adjuvant therapy to stage IC1 that is associated with sharp dissection, which we identify to be a high-risk feature. Based on our results, stage I substage is valuable in predicting clinical outcomes and can be used to identify those who may omit adjuvant therapy.

CRedit authorship contribution statement

Shiru L. Liu: Data curation, Formal analysis, Methodology, Project administration, Writing - original draft. **Anna V. Tinker:** Conceptualization, Methodology, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors acknowledge the Cheryl Brown Gynecologic Cancer Registry for the database provided. The authors have no conflicts of interest to disclose and the study was unfunded.

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