EJGO European Journal of Gynaecological Oncology

Chemotherapy improves survival rate in Stage 1 ovarian cancers

L. Dewick, J. Raut, V. Asher

[1] *Department of Obstetrics & Gynaecology, Royal Derby Hospital, Derby (United Kingdom)*

Summary

Purpose of Investigation: The role of adjuvant chemotherapy in Stage 1 ovarian cancer is conflicting with no clear evidence to support adjuvant chemotherapy versus observation alone. The authors sought to establish the survival benefit of adjuvant chemotherapy in all Stage 1 ovarian cancers. *Materials and Methods:* Retrospective data including age, stage, grade, histology, RMI, and chemotherapy status on all patients undergoing treatment for Stage 1 ovarian cancer between May 2003 and November 2013 at Royal Derby Hospital was collected. *Results:* Eighty-nine cases of Stage 1 ovarian cancer were included. A total of 73 patients (84.88%) received adjuvant chemotherapy while 13 (15.12%) did not. The patients receiving adjuvant chemotherapy had a median overall survival (OS) of 108 months (CI 99.07−118.33) while the median OS for the patients who did not receive any adjuvant treatment was 63.71 months (CI 43.06−83.35) $p = 0.003$. *Conclusion:* Adjuvant chemotherapy significantly improves OS in Stage 1 ovarian cancer patients.

Key words: Ovarian cancer; Stage 1; Adjuvant; Chemotherapy.

Introduction

Ovarian cancer is the fifth most common cancer in women in the UK and accounts for 4% of new cancer cases in females. In 2012 there were 7,029 new cases of ovarian cancer in the UK [1]. About 30% of patients are Stage 1 at diagnosis and this is associated with a 90% five-year survival; this falls to only 19% in women with Stage 3 disease [1].

The role of adjuvant chemotherapy in Stage 1 cancers is still not clear with the National Institute of Clinical Excellence (NICE) recommending adjuvant chemotherapy in women with 'high risk' disease (Stage 1c or grade 3 disease)[2], while the Cochrane review suggests that adjuvant chemotherapy is beneficial in improving overall survival (OS) in all Stage 1 patients. Furthermore they suggest that chemotherapy can be withheld in well differentiated early stage disease (Stage 1a/ grade 1) or optimally staged 1b and grade 1/2 disease [3].

No randomized control trial has conclusively shown the benefit of either observation with no chemotherapy or adjuvant chemotherapy in this group of patients.[4] The combined analysis of ICON1 and ACTION randomized controlled trials compared adjuvant chemotherapy in Stage 1 ovarian cancer to observation alone, and has shown that in the total of 925 patients from both trials, the group that received chemotherapy had an 82% five-year OS compared to 74% in the observation arm with a hazard ratio (HR) = 0.67 favoring the chemotherapy arm. There was also improved progression-free survival (PFS) with a HR of 0.64 favoring the chemotherapy arm [5]. Furthermore this improvement in OS and PFS is still maintained in the ICON1 trial patients even ten years after treatment. [6]

In this study the authors evaluated the effect of adjuvant chemotherapy in patients with Stage 1 ovarian cancer.

Materials and Methods

Data for all Stage 1 ovarian cancer patients that underwent surgery between May 2003 and November 2013 at the Royal Derby Hospital Cancer Centre was collected retrospectively using a proforma and recorded on an Excel spreadsheet. All patients underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, and infracolic omentectomy with assessment of peritoneal surfaces and palpation of para-aortic lymph nodes.

These women were then reviewed in outpatient clinic every three months for the first two years, followed by six monthly reviews for five years. At each assessment women were examined clinically and underwent repeat ultrasound and Ca125 testing to identify any evidence of recurrence. All patients coded as Stage 1 ovarian cancer were identified and staging reconfirmed before data was entered into a proforma using information obtained from electronic records and medical notes.

Clinico-pathological variables recorded included age, co-morbidities, stage, histology, grade, Risk of Malignancy Index (RMI), months of survival (OS and PFS), and chemotherapy received. Survival time was calculated from operation date to December 31st, 2013 when remaining survivors were censored. All borderline and germ cell tumours were excluded from the study.

SPSS (Version 22) was used to analyse all data sets, with continuous data analysed using median and 95% confidence intervals (CI). Fisher exact test and Chi-squared were used to compare cat-

Revised manuscript accepted for publication May 17, 2016

Eur. J. Gynaecol. Oncol. - ISSN: 0392-2936
XXXVIX, n. 1, 2018
doi: 10.12892/ejgo3715.2018

7847050 Canada Inc.
www.irog.net

Table 1. — *Patient characteristics.*

		n (%)
Number of patients		89
Median age		62.5 years
Median survival		65 months
Stage	1a	27 (30.7)
	1b	6 (6.8)
	1c	55 (62.5)
Grade	1	21 (25.6)
	2	22 (26.8)
	3	39 (47.6)
Chemotherapy	Yes	73 (84)
	No	14 (16)
Histological type	Serous	11 (12.6)
	Mucinous	16 (18.4)
	Endometrioid	30 (34.5)
	Clear cell	17 (19.5)
	Adenosquamous	10 (11.5)
	Undifferentiated	3 (3.4)
RMI	< 250	32 (38.1)
	> 250	52 (61.9)

Table 2. — *Overall survival by covariates (Interquartile range: IQR).*

Covariates		Median survival in months (IQR)	*p* value
Stage	1a	119.8 (109.7−129.9)	0.068
	1b	84.33 (40.2−128.4)	
	1c	93.2 (79.1−107.3)	
Grade	1	104.5 (88.4−120.5)	0.183
	2	115.8 (101.0−130.5)	
	3	94.2 (79.7−108.7)	
Chemotherapy	No	68.3 (50.76−85.9)	0.003*
	Yes	108.9 (99.3−118.5)	

**Statistically significant.*

egorical data. A p value of ≤ 0.05 was deemed to be of statistical significance. Estimates of survival differences between variables were obtained using Kaplan-Meier curves using the log rank test. Cox's proportional hazards model was used to perform multivariate analysis to establish independent significance of single variables.

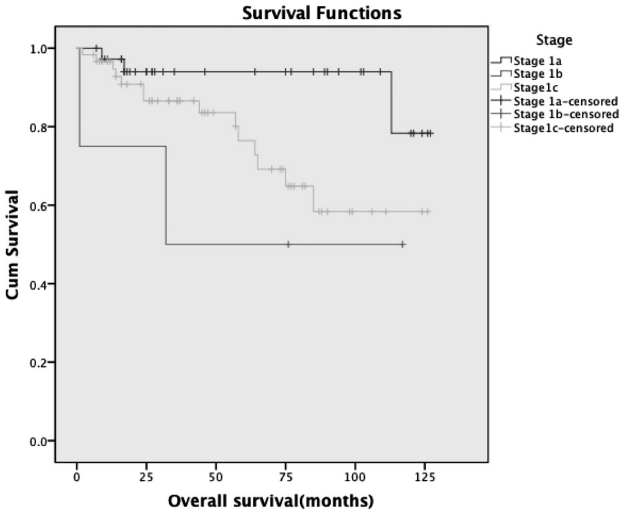

Figure 1. — Overall survival by stage.

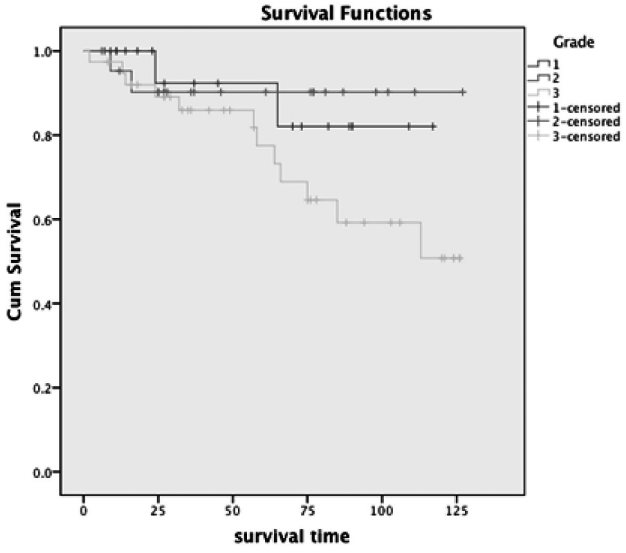

Figure 2. — Overall survival by grade.

Results

A total of 89 patients were identified during the study period, with a median age of 62.5 years and a median survival of 65 months (Table 1). 30.7% of the patients had Stage 1a disease while 62.5% of patients presented with Stage 1c disease, and almost half of the patients (47.6%) had a grade 3 cancer. Majority of the patients (61.9%) had a RMI > 250. The most common histological subtype was endometrioid (34.5%) and the majority (84%) of patients received adjuvant chemotherapy (Table 1).

On univariate analysis, patients receiving chemotherapy had significantly improved OS while the sub-stage and different grades showed no significant effect on OS in these groups of patients. (Table 2) There was a trend of improved survival in Stage 1a (119.8 months) and grade 1 (104.5 months) compared to patients with Stage 1b and 1c and grade 2 and 3 disease, respectively (corresponding Kaplan Meier survival curves are shown in Figures 1-3).

On further analysis, stage, grade, and histology of the tumour was not significantly different between patients that received chemotherapy and those that did not receive any adjuvant treatment (Table 3).

Multivariate analysis using stage, grade, and chemotherapy status showed that chemotherapy did not retain its statistical significance, but has a trend towards improved

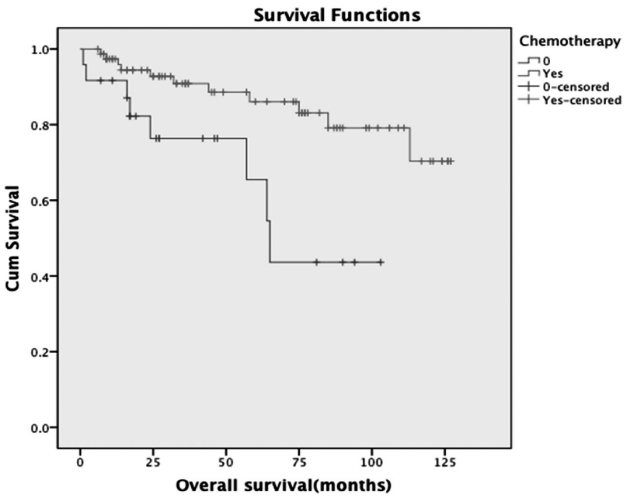

Figure 3. — Overall survival by chemotherapy.

survival in Stage 1 ovarian cancer patients with a hazard ratio of 1.689 (95% CI 0.598–4.769) (Table 4).

Discussion

The median age of the present cohort was 62.5 years, and this is representative of this group of these patients [7]. There was no survival difference in the group of patients, with Stage 1b showing the worst survival, which could be due to small numbers. Patients with Stage 1a disease had the best survival. Grade of cancer had no effect on survival which is in contrast to a study by Vergote *et al.* [8] who showed that grade is an independent prognostic indicator in patients with Stage 1 ovarian cancer. In the present study the authors have shown that patients receiving chemotherapy have significantly improved survival and this is consistent with long term data from ACTION/ICON1 studies [4] and the Cochrane review [9].

In order to evaluate the impact of other prognostic factors like stage, grade, and histology on chemotherapy status, the present authors compared these factors with patients who received chemotherapy and those who did not. There was no overall difference in the above groups indicating that this study cohort was equally distributed and was not affected by stage, grade, and histology of the cancer.

On multivariate analysis, chemotherapy lost its prognostic significance although there was a trend in improved survival with a HR of 1.6. This could be due to the present small sample size and the worse prognosis of patients with Stage 1b disease.

The present study is limited due to its small sample size, its retrospective design, and small proportion of patients in the subgroups to derive meaningful subgroup analysis data.

Table 3. — *Effect of various covariates on status of chemotherapy.*

Variable		Chemotherapy		*p* value
		Yes	No	
Stage	1a	22	5	0.994
	1b	5	1	
	1c	45	10	
Grade	1	17	4	0.175
	2	21	1	
	3	30	9	
Histology	Serous	11	0	0.128
	Mucinous	12	4	
	Endometrioid	26	4	
	Clear cell	15	2	
	Adenosquamous	2	1	
	Undifferentiated	6	4	

Table 4. — *Cox regression analysis.*

Covariates		Hazard ratio HR (1QR)	*p* value
Stage	1a	1	
	1b	0.622 (0.173−2.132)	0.466
	1c	0.812 (0.101−6.530)	0.845
Grade	1	1	
	2	0.613 (0.169−2.225)	0.457
	3	0.645 (0.074−1.608)	0.175
Chemotherapy	No	1	
	Yes	1.689 (0.598−4.769)	0.322

Conclusion

In conclusion, the present data has shown a survival benefit of chemotherapy in women with Stage 1 ovarian cancer, although this data needs further validation in a well-designed randomised control trial.

Acknowledgments

Many thanks to Jeanette Steward and Jane Trower in retrieving patient case notes for review.

References

[1] UK Cancer Research, 2015. Available at: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/ovarian-cancer/incidence - heading-Zero.

[2] NICE Clinical Guideline 122: The recognition and initial management of ovarian cancer. *2011*: Cardiff (UK). Available at: https://www.nice.org.uk/Guidance/CG122

[3] Winter-Roach B.A., Kitchener H.C., Lawrie T.A.: Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer. *Cochrane Database Syst. Rev.*, 2012, *3*, CD004706.

[4] Colombo N., Pecorelli S.: "What have we learned from ICON1 and ACTION?" *Int. J. Gynecol. Cancer*, 2003, *13*, 140.

[5] Trimbos J.B., Parmar M., Vergote I., Guthrie D., Bolis G., Colombo N., *et al.*: "International Collaborative Ovarian Neoplasm trial 1 and Adjuvant ChemoTherapy In Ovarian Neoplasm trial: two parallel randomized phase III trials of adjuvant chemotherapy in patients with early-stage ovarian carcinoma". *J. Natl. Cancer. Inst.*,

2003, *95*, 105.
[6] Collinson F., Qian W., Fossati R., Lissoni A., Williams C., Parmar M., *et al.*: "Optimal treatment of early-stage ovarian cancer". *Ann. Oncol.*, 2014, *25*, 1165.
[7] Ovarian Cancer National Alliance: "Risk factors". 2015. Available at: http://www.ovariancancer.org/about/risk-factors/
[8] Vergote, I., De Brabanter J., Fyles A., Bertelsen K., Einhorn N., Sevelda P. "Prognostic importance of degree of differentiation and cyst rupture in stage I invasive epithelial ovarian carcinoma". *Lancet*, 2001, *357*, 176.
[9] Winter-Roach B.A., Kitchener H. C., Lawrie T.A.: "Adjuvant (post-surgery) chemotherapy for early stage epithelial ovarian cancer". *Cochrane Database Syst. Rev.*, 2015, *12*, CD004706.

Corresponding Author:
L.E. DEWICK, M.D.
Department of Obstetrics & Gynecology
Royal Derby Hospital
Uttoxeter Road
Derby DE22 3NE (United Kingdom)
e-mail: louisedewick@nhs.net