# Survival in Women with Ovarian Cancer Before and After the Introduction of Adjuvant Paclitaxel; A 25-Year, Single Institution Review

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***Abstract***
Adjuvant chemotherapy regime for ovarian cancer patients remains to be a contentious issue. The aim of this study was to compare the overall and progression-free survival of women with ovarian cancer before and after introduction of paclitaxel in our unit in 1992. A sample of 112 women who received adjuvant therapy following surgery for ovarian cancer was collected, 68 (61%) received platinum+alkylating agent before 1992 and later 44 (39%) received platinum+paclitaxel. Five-year survival was same in both treatment groups when there was no macroscopic disease after surgery (78% versus 70%) and when residual disease was <2cm (50% versus 40%). Survival was greater in women with residual disease >2cm in the platinum+paclitaxel group (50% versus 24%), (p = 0.04). However, progression-free survival was similar in both groups irrespective of stage or residual volume of disease. Therefore consideration to selective use of paclitaxel could reduce patient morbidity and costs significantly.

***Introduction***
Platinum was introduced as chemotherapeutic agent for ovarian cancer in 1979 and since then has had a significant impact on the survival of patients with epithelial ovarian cancer. Chemotherapy has evolved over the last three decades, and although the role of platinum-based compounds is well established, a degree of uncertainty exists regarding optimum adjuvant chemotherapy regimens for EOC. The U.S. Drug and Food Authority approved paclitaxel in 1992 as the first line chemotherapeutic agent in the management of patients with ovarian cancer. Four randomized controlled trials - GOG111, OV10, GOG132 and ICON3 have compared the progression-free and overall survival of patients with ovarian cancer receiving paclitaxel versus platinum alone, and have reported conflicting results regarding the role of paclitaxel. The GOG111 and OV10 trials [2] favoured paclitaxel in combination with platinum however results from GOG132 [3] and ICON3 [4] trials failed to show statistically significant difference in survival between combination of paclitaxel/platinum and platinum alone. It should be noted both of the positive trials were conducted in patients with advanced disease. GOG 111 was conducted in patients with stage III and IV disease and the majority of patients in OV10 had sub-optimally debulked advanced stage disease. In contrast ICON3, which did not favour paclitaxel contained more patients with early stage disease and fewer patients with serous carcinoma.

In January 2003, the National Institute for Clinical Excellence published a review on the use of paclitaxel in treatment of patients with ovarian cancer and suggested the choice of treatment for first-line chemotherapy should be made after careful discussion between the physician and the patient regarding the side effect of different treatment regimes, the stage of the womanâ s disease and the extent of the surgical treatment of the disease [8]. Despite inconclusive evidence, paclitaxel in combination with platinum remains the first-line adjuvant treatment for epithelial ovarian cancer and has been endorsed by the US National Comprehensive Cancer Network and the 2010 GCIG Ovarian Cancer Consensus Conference which confirmed paclitaxel and carboplatin as the standard 1st-line adjuvant ovarian cancer treatment against which trial treatments should be judged. The aim of our study over a 25 year period was to compare the outcome or survival of women with primary epithelial ovarian cancer, before and after the introduction of paclitaxel in a unit. In addition we sought to compare overall survival in our unit to international series. All of the cases were managed by the same four gynaecologists (three of whom were on site from the start of the study) with a surgical objective of achieving maximum debulking with minimum impact on the patient.

***Methods***
The study population consisted of women diagnosed with primary invasive epithelial ovarian cancer treated at a University Teaching Hospital between the years 1982 to 2008. Each case was presented and discussed at a monthly oncology conference. Data were collated prospectively and reported in an Annual Hospital Report. Low grade, early stage and benign or borderline tumours, non-epithelial tumours and cases with histological features typical of metastatic ovarian cancer were excluded from the study The standard surgical approach was to perform a total abdominal hysterectomy, bilateral oophorectomy and omentectomy with cytological evaluation of free fluid or washings. Residual disease was resected where possible but this did not include for example bowel resection although on occasion this was necessary to relieve obstruction or where perforation following surgery seemed likely. The stage and volume of residual disease (no residual disease, residual disease greater or less than 2 cm) was recorded in all cases and a detailed pathology report was provided.

Chemotherapy consisted of cisplatin or carboplatin prior to 1992 and combined with paclitaxel after that and commenced within four to six weeks of surgery. Prior to 1992 patients received a variety of platinum regimens including single agent platinum, platinum and an alkylating agent, or cycophosphamide, adriamycin and cisplatin (CAP). After 1992 patients received either cisplatin or carboplatinum and paclitaxel, which was administered at a dose of 175mgs per square metre of patientâ s body surface area as a 3-hourly intravenous infusion at three-weekly intervals for six courses as tolerated. Patients were followed up three monthly for one year, 6 monthly for the following year and then annually up to five years. Assessment was by pelvic examination and Ca-125.

The primary endpoint of the study was overall survival (OS). Progression-free survival (PFS) was considered a secondary outcome, however PFS is difficult to calculate in a historic cohort study whereby definitions of disease progression have changed over the study period. Survival was calculated in months from date of commencement of chemotherapy up to the date of last review or died. Disease progression was defined using either clinical examination, a rising CA-125 and/or imaging. Kaplan-Meier survival curves were used to analyse the survival in different groups, and the difference in survival was assessed using the log-rank test. All calculations were performed using SPSS version 18.0 (SPSS Inc, Chicago, IL). P values < 0.05 were considered statistically significant.

***Results***
Our cancer databases from the year 1980 contain 178 cases of epithelial ovarian cancer, of which 32 women were lost to follow-up. Six women had inoperable disease, 20 received no chemotherapy for various reasons, and eight received chlorambucil in the early 1980s, and therefore were excluded. Of the 112 women included in the study, 68 received platinum based chemotherapy and 44 received paclitaxel and platinum as the first-line treatment following debulking surgery. The clinicopathological characteristics of the cohort stratified according to chemotherapy regimen are presented in table 1, which demonstrates that the only difference in the two groups

was a higher proportion of poorly differentiated tumours in the platinum group.

Values in parenthesis are percentages, N/S â  non-significant

*Overall and Progression Free Survival of Entire cohort*
Patients who received adjuvant platinum and paclitaxel had a longer OS than those who received platinum (p = 0.024) (Figure 1). Median OS for the entire cohort was 48 months (95% CI 35.9-60.1). The median OS in the platinum group was 30 months (95% CI 19.2-40.8) and the platinum/paclitaxel group did not reach median survival. There was no difference in PFS in both groups (p = 0.208).  The median PFS in the entire cohort was 18 months (95% CI 9.6-26.2). The median PFS in the platinum group was 12 months (95% CI 4.8-19.2) and the median PFS platinum/paclitaxel group was 36 months (95% CI 14.7-57.3) We therefore proceeded to perform a subset analysis based on stratification according to residual disease after primary surgery, which remains the most important prognostic variable in ovarian cancer. Given the aforementioned issues with the reliability of PFS in a historical cohort study this analysis was restricted to OS.

Figure 1

*Overall Survival Stratified According to Residual Disease*
Subset analysis based on residual disease demonstrated no difference in OS of both treatment groups following debulking to less than 2cm (n = 49). This included 19 patients who were optimally debulked to  no macroscopic disease and 30 patients who were debulked to macroscopic disease less than 2cm, The median survival in the platinum group was 60 months (95% CI 36.3-83.4), while the platinum and paclitxel group did not reach median survival. In women with bulky residual disease greater than 2cm (n = 63), OS was prolonged in the platinum plus paclitaxel group compared to platinum group (p = 0.04) (Figure 2). The median survival in the platinum plus paclitaxel group was 18 months (95% CI 3.0 â  42.8) versus 10 months (95% CI 3.7 â 16.3) in the platinum group.

***Discussion***

The overall survival for all cases of ovarian cancer (including those who did not receive chemotherapy) in the study period was above 50% and was the same before and after the introduction of paclitaxel (56% versus 52%). The median survival for the entire cohort was 48 months. In patients with no macroscopic residual disease after surgery, survival was in the range of 70 to 90%, which is similar to other series [5-8] and the addition of paclitaxel conferred no additional advantage in patients with residual disease less than 2cm. In patients with bulky residual disease (> 2cm), platinum and paclitaxel combined seemed to confer some advantage in OS but not in PFS. The fact that we identified no difference in PFS is not surprising in the context of a historical cohort study as the definition of disease progression would have changed during the study period as would the application of more advanced radiological investigation. It is also likely that some early asymptomatic recurrences were identified based on rising CA-125 levels, which although relatively easy to treat, have recently been shown in the OV05 trial to have no effect on overall survival [9]. Therefore as the clinical follow-up and definition of disease recurrence or progression in ovarian cancer remains a controversial issue, a historic cohort study is not an ideal platform to measure PFS.

Although the numbers in this study are small, our finding that the combination of platinum and paclitaxel only conferred a survival benefit in patients who were sub-optimally debulked raises a number of interesting questions. As discussed above, the two trials that initially favoured the addition of paclitaxel, GOG111 [1] and OV10 [2], were performed in patients who had been sub-optimally debulked, while the negative ICON3[4] trial had a different population. Likewise recent data from the ICON7 trial, which examined the addition of the anti-VEGF monoclonal antibody bevacizumab to combination platinum and paclitaxel, suggests an OS advantage in suboptimally debulked patients [10]. These data point to the fact that a â one size fits allâ approach to the treatment of ovarian cancer is not effective. It is also likely that the resectability of disease is a reflection of the underlying biology and patients who were optimally debulked in a conservative unit are likely to have less aggressive disease. Therefore future trials should consider examining optimally debulked patients separately.

Despite a lack of conclusive evidence, current practice is to advocate adjuvant platinum and paclitaxel for all advanced stage ovarian cancer patients. Paclitaxel, a mitotic spindle inhibitor, is expensive and associated with side effects like alopecia, neutropenia, hypersensitivity, anaphylactic reactions, cardiovascular and neuromotor disorders. The use of paclitaxel as a primary treatment for all women with advanced ovarian cancer is questionable, based on our small historical cohort study, and a number of large prospective randomized control trials. Such findings are important and an attempt to move towards personalised therapeutic protocol whereby individuals receive tailored therapeutic regimens based on individual patient and tumour characteristics is now felt to be an achievable goal [11]. In this context side effect profiles and quality of life are becoming more pertinent as ovarian cancer management moves towards a chronic disease scenario.

The five-year survival figures among the various groups in our study are comparable with international results. We find no evidence that paclitaxel confers any additional advantage in women with no macroscopic or small volume residual disease, but it may increase overall survival in women with residual disease >2cm. The results of this study have not changed the medical management of ovarian cancer in our unit, but our findings agree with a number of large prospective randomised trials and suggest that selective use of paclitaxel needs to be considered in appropriately designed trials as it may significantly reduce patient morbidity and cost.

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Comments: