# Clinical outcomes of neoadjuvant chemotherapy and primary debulking surgery in advanced ovarian carcinoma

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**Summary**

*Background:* Primary debulking surgery (PDS) and paclitaxel-platinum chemotherapy remains the mainstay of treatment for advanced ovarian cancer. However, there is considerable morbidity and even mortality associated with this approach. The concept of primary chemotherapy followed by interval debulking surgery (IDS) has emerged for advanced stage disease with the aim of improving sensitivity to chemotherapy and improving survival. The purpose of our study was to examine the impact of IDS on clinical outcomes of patients considered unsuitable for PDS and compare them with outcomes of women that had conventional PDS followed by chemotherapy.

*Patients and methods:* A non-randomised prospective cohort study of 35 patients who underwent IDS and 29 patients treated with PDS were included. All patients had Stage IIIC or IV disease. The IDS patients were considered unresectable based on an initial laparoscopy or preoperative computed tomography findings. All patients were treated by the same lead surgeons and received the same regimen of chemotherapy.

*Results:* The median intraoperative blood loss, the incidence of pelvic lymphadenectomies, the median hospital stay and the possibility of admission to the Intensive Care Unit were significantly less in the IDS group. Optimal cytoreduction was higher in the IDS compared to the PDS group, but did not reach statistical significance.

*Conclusions:* IDS for advanced ovarian cancer may be associated with less morbidity compared to PDS and appears to require less use of hospital resources. If the ongoing randomised studies confirm that IDS does not adversely affect the long-term survival of these patients, morbidity related to ovarian cancer surgery may evolve as a crucial factor for choosing treatment options.

*Key words:* Advanced Ovarian Cancer; Interval debulking surgery; Morbidity.

## Introduction

Seventy-five percent of women with epithelial ovarian cancer present with Stage III or IV disease. Primary debulking surgery (PDS) followed by chemotherapy aims to achieve optimal cytoreduction (residual tumour < 1 cm) and is still considered the optimal treatment [1-5]. Unfortunately, it is associated with a high risk of intraoperative complications and postoperative morbidity [6-10]. Also, the true impact of PDS has never been exposed to the accepted standard of a randomised clinical trial. In fact, a systematic review of existing studies has shown that platinum-based chemotherapy rather than cytoreductive surgery may be the treatment which primarily influences survival [11, 12].

There is evidence from non-randomised studies [13-20] that interval debulking surgery (IDS) could be a feasible alternative option without any adverse effect on progression-free and overall survival. As a consequence, other factors such as perioperative morbidity and quality of life could evolve as decisive for the choice of management of these patients.

Two ongoing prospective randomised studies (CHORUS and EORTC-55971) currently recruit patients with advanced ovarian malignancies into either PDS or IDS and aim to compare treatment complications, quality of life and overall survival but the results are not expected in the near future.

The purpose of our study was to examine the impact of IDS on clinical outcomes of patients considered unsuitable for PDS (as optimal cytoreduction was not anticipated) and compare them with outcomes of women that had conventional PDS followed by chemotherapy.

## Patients and Methods

A non-randomised prospective cohort study of 35 patients who underwent IDS and 29 patients treated with PDS in two hospitals from August 2002 to March 2005. All patients had Stage IIIC or IV disease (according to the 1987 International Federation of Gynaecology and Obstetrics classification).

All women were initially considered for PDS. Exclusion criteria were extensive peritoneal involvement, paraaortic involvement above the level of the left renal vessels and/or involvement of the diaphragmatic muscle, involvement of at least two segments of the digestive tract or patients with poor performance status (World Health Organization status II or III). These patients were offered IDS. The preoperative evaluation of all patients was done either by a computed tomography (CT) scan or laparoscopy and all women that underwent IDS had histological or cytological confirmation of the disease and tumour markers before starting chemotherapy. Patients with tense ascites assigned for IDS had their ascites drained before chemotherapy was started. The decision for the mode of treatment was taken from a multidisciplinary team comprised of two accredited sub-specialist surgeons in gynaecological oncology,

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two medical oncologists, radiologists and oncology and palliative care nurses.

IDS was performed after three or four courses of platinum-based plus paclitaxel chemotherapy and was followed by post-operative chemotherapy, six cycles in total. Patients who underwent PDS received six postoperative cycles of platinum-based plus paclitaxel chemotherapy.

All patients underwent a standard procedure. At laparotomy, if optimal debulking or complete tumour resection was achievable, radical surgery was undertaken which involved midline laparotomy followed by omentectomy, salpingo-oophorectomy, total hysterectomy (if the uterus was present) and possibly pelvic and paraortic lymphadenectomy and bowel resection. A paraaortic and pelvic lymphadenectomy was performed in patients with good medical status at the end of the main debulking surgery and in those with a complete macroscopic resection or minimal residual disease (< 1 cm). In patients with a larger amount of residual disease or poor medical condition, lymphadenectomies were omitted. The same strategy applied for bowel surgery, but bowel surgery was also considered in cases where intestinal obstruction was present or deemed a serious risk.

In all cases, the lead surgeon was one of the two accredited sub-specialists (SBM or AT). Characteristics of debulking surgery, surgical procedures, intraoperative complications, admission rates to the Intensive Care Unit (ICU), blood transfusion rates and postoperative morbidity rates were recorded and analysed.

## Results

*Interval debulking surgery group*

This comprised 35 patients. The mean age was 62.7 years (range 32-76 years).

Twenty-five women (71.4%) were in Stage IIIC and ten (28.6%) Stage IV (Table 1). All patients had preoperative histological or cytological diagnoses.Twenty-eight patients were operated on after three cycles of chemotherapy and the remaining seven after four cycles.

Optimal cytoreduction (residual tumour < 1 cm) was achieved in 29 patients (82.9%) and suboptimal in six (17.1%). All patients had omentectomies and salpingoophorectomies. Seven patients had had previous hysterectomies; the rest underwent hysterectomies as part of the debulking procedure. One patient had an intraoperative bowel injury. Details of the sur-gical procedures performed are listed in Table 2.

The mean intraoperative blood loss was 924 ml (range 150-10000 ml). Two patients (5.7%) were admitted to the ICU and the mean hospital stay was seven days (range 4-25).

Table 1. — *Distribution of patient characteristics in the group of patients with interval debulking surgery (IDS) and the group with primary debulking surgery (PDS).*

| Parameter | IDS group | PDS group | p value | Test |
|---|---|---|---|---|
| Sample size (n) | 35 | 29 | – | – |
| Age | 62.7 (32-76) | 59.5 (32-86) | 0.317 | Student's t-test |
| Stage IIIC | 25 (71.4%) | 26 (89.7%) | 0.071 | Chi-square |
| Stage IV | 10 (28.6%) | 3(10.3%) | 0.071 | Chi-square |

Details of early postoperative complications (less than 10 days after surgery) are listed in Table 3. There were no late postoperative complications.

*Primary debulking surgery group*

This comprised 29 patients. The mean age was 59.5 years (range 32-86 years).

Twenty-six women (89.7%) were in Stage IIIC and three (10.3%) Stage IV (Table 1).

Optimal cytoreduction (residual tumour < 1 cm) was achieved in 18 patients (62.1%) and suboptimal in 11 (37.9%). All patients had omentectomies and salpingoophorectomies. Three patients had had previous hysterectomies; the rest had hysterectomies as part of the debulking procedure. Five patients had intraoperative bladder or bladder injuries and one patient had a permanent enterostomy. Details of the sur-gical procedures performed are listed in Table 2.

The mean intraoperative blood loss was 1.520 ml (range 100-3000 ml). Fourteen patients (48.3%) were admitted to the ICU and the mean hospital stay was eight days (range 6-17).

Details of early postoperative complications (less than 10 days after surgery) are listed in Table 3. Late complications (more than 10 days after surgery) were: one vault haematoma (drained vaginally), one thrombosis of the left internal jugular vein, one wound dehiscence and a necrotic abscess four months after the initial laparotomy (required repeat laparotomy).

One patient died two days after surgery from multiple organ failure.

Table 2. — *Distribution of surgical procedures and intra-operative complications in each group (%).*

| Parameter | IDS group | PDS group | p-value | Test |
|---|---|---|---|---|
| Optimal cytoreduction | 82.9% | 62.1% | 0.061 | Chi-square |
| Hysterectomy | 20% | 10.3% | 0.060 | Chi-square |
| Paraaortic lymphadenectomy | 8.6% | 20.7% | 0.165 | Chi-square |
| Appendicectomy | 17.1% | 37.9% | 0.061 | Chi-square |
| Bowel injury | 2.9% | 13.8% | 0.105 | Chi-square |
| Bladder injury | 0% | 3.4% | 0.453 | Fishers |
| Bowel resection | 11.4% | 17.2% | 0.505 | Chi-square |
| Permanent enterostomy | 2.9% | 3.4% | 1.0 | Fishers |
| Pelvic lymphadenectomy | 20% | 58.6% | 0.001 | Chi-square |

Table 3. — *Median blood loss, admission to the Intensive Care Unit (ICU), median hospital stay and early postoperative morbidity in each group.*

| Parameter | IDS group | PDS group | p value | Test |
|---|---|---|---|---|
| Median blood loss (range) | 500 (100-3000) | 1,000 (150-10,000) | 0.043 | Mann-Whitney |
| ITU admission | 5.7% | (14) 48.3% | < 0.001 | Chi-square |
| Median hospital stay (range) | 7 (4-25) | 8 (6-17) | 0.005 | Mann-Whitney |
| DVT/PE | 2 (5.7%) | 1 (3.4%) | 1.0 | Fishers |
| Early postop. infection (chest/urinary) | 8 (22.9%) | 6 (20.7%) | 0.835 | Chi-square |

*Comparison between groups*

The results that are statistically significant are: risk of ICU admission ($p < 0.001$), median hospital stay ($p = 0.005$) and intraoperative blood loss ($p = 0.043$). They are all in favour of the IDS group. Also, the occurrence of pelvic lymphadenectomy was significantly lower in the IDS group ($p = 0.001$). There was no statistical difference in all the other parameters studied.

## Discussion and Conclusion

Our IDS group was comprised of women that were deemed to be very unlikely to undergo optimal debulking with a primary surgical procedure, either due to the extent of the disease or poor performance status. Our selection criteria for IDS were not the same as described by other researchers [21-24] and that complicates the comparison of different studies. Obviously it would be ideal if selection criteria for IDS were standardised [25], so results from different centres could be more meaningful.

Our decision for choice of treatment was based on either CT or laparoscopy. We consider laparoscopy to be the most sensitive test to assess resectability as it is able to detect small volume tumours (< 8 mm) which are not detected with CT [10]. CT remains extremely useful however in assessing larger volume tumour deposits, particularly in the upper abdomen and thorax and within the parenchyma of the liver and spleen. CT was mainly used for very unfit patients or when laparoscopy was considered particularly hazardous (i.e. multiple previous laparotomies, solid masses in the upper abdomen). However, CT has been used extensively by other authors with good results [26, 27]. The theoretical advantage of using CT is that chemotherapy may start very soon afterwards while recovery from laparoscopy may delay the first course of chemotherapy for a few days. In our experience this has not been a problem for our patients, as our Histology Department required a few days to provide us with the diagnosis, by which time the post-laparoscopy patients were fit to receive chemotherapy. In the UK, delays may occur while waiting for CT cross-sectional imaging and often laparoscopy is quicker.

We routinely used povidone iodine to clean the port sides following laparoscopy in order to prevent infection in our group of IDS women. We did not routinely close trocar sites < 10 mm. Other authors have suggested closure of the peritoneum to reduce the risk of metastatic seeding on the trocar sites [28, 29].

Clinical examination, CT findings and CA125 levels were used to assess response to chemotherapy after three cycles of treatment. IDS was performed after cycle 3 (or cycle 4 in very advanced stage disease).

All patients that had neo-adjuvant chemotherapy were found to have less extensive disease at IDS than what was described by the initial CT or staging laparoscopy. However, not all patients respond well to neoadjuvant chemotherapy. This is not a disadvantage of IDS but conversely rather beneficial as it spares aggressive surgery in women with chemoresistant disease, who have a poor outcome regardless of treatment [30].

Our results demonstrate that patients treated with IDS for advanced stage 'unresectable' ovarian cancer, suffer less intraoperative blood loss, are less likely to be admitted to the ICU and stay fewer days in the hospital. Apart from the benefits of avoiding the small risk of transmission of infective diseases associated with blood transfusion, sparing ICU and ward beds has a considerable financial and resource benefit.

In our series, there was no statistically significant difference in optimal cytoreduction rates between the two groups (62.1% in the PDS group vs 82.9% in the IDS group). Despite the relatively small number of patients, this reflects good preoperative selection preventing patients from undergoing PDS if they were unlikely to be optimally debulked. Nonetheless, other studies with a similar number of patients have shown better rates of optimal debulking in patients that had IDS [31]. One suspects that if our selection of patients had been randomised, the PDS group would have had a significantly lower rate of optimal debulking. We await the results of the two randomised controlled trials with interest.

The rates of bowel or bladder injury or resection were similar in the two groups. Again, this may reflect an efficient preoperative selection that did not allow 'inoperable' cases to enter the PDS group. The rate of pelvic lymphadenectomies was significantly lower in the PDS group and this could be one of the reasons that the IDS group had lower intraoperative blood loss and quicker recovery.

Our results strengthen the evidence presented by other researchers [10, 31-33] that IDS for advanced ovarian cancer may be associated with less morbidity compared to PDS. If these results are confirmed by the ongoing randomised studies, the place of PDS as a gold standard strategy for advanced ovarian cancer should be reconsidered and morbidity related to ovarian cancer surgery may evolve as a crucial factor for choosing treatment options. At present, there is no evidence that IDS adversely affects the progression-free interval and overall survival [10, 33-34] and hopefully the ongoing studies will reinforce this finding.

Our series has the advantage over other studies that all the operations were either done or directly supervised by two specialist gynaecological oncology surgeons and therefore we can not attribute any difference of results to variation in surgical skills. We have now stopped recruiting patients into our study, as we are participating in the CHORUS trial. However, as our results were communicated to our patients, we have faced some difficulty recruiting patients into CHORUS, as patients are attracted to the lower morbidity offered by IDS and neoadjuvant chemotherapy.

Despite excellent radiology and the benefits of a multidisciplinary team approach, we were only able to optimally debulk 62.1% of those selected for PDS. Hopefully, analysis of the two ongoing trials and other studies will help to refine the process and criteria for the best selection of cases for PDS.

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