

Original Article



The impact of interval between primary cytoreductive surgery with bowel resection and initiation of adjuvant chemotherapy on survival of women with advanced ovarian cancer: a multicenter cohort study

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ABSTRACT

Objective: Our aim was to determine if the time interval between bowel resection and initiation of adjuvant chemotherapy impacts survival in advanced ovarian cancers.

Methods: This was a retrospective cohort study using data from two cancer centers, Princess Margaret Cancer Centre in Toronto, Ontario, Canada and Samsung Comprehensive Cancer Center in Seoul, South Korea. Patients with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV ovarian cancer that underwent large bowel resection during primary cytoreductive surgery (PCS) were included.

Results: Ninety-one women were eligible of which the majority (90.1%) were diagnosed with high-grade serous cancer. The median interval from PCS to chemotherapy for all patients was 21 days (7–86 days). Patients were stratified into 3 groups: 1) Interval ≤ 14 days, 32 (35.2%) patients; 2) Interval between 15–28 days, 27 (29.6%) patients; and 3) Interval between 29–90 days, 32 (35.2%) patients. Surgical procedures and postoperative outcomes were similar between groups. Multivariate analysis indicated that PCS to chemotherapy interval of 2–4 weeks, younger age, and completion of 4 or more adjuvant chemotherapy cycles were independent prognostic factors of favorable overall survival.

Conclusion: Initiation of adjuvant chemotherapy between 2 to 4 weeks after PCS with bowel resection may improve survival outcomes in women with advanced ovarian cancer by maximizing the benefit of PCS plus adjuvant chemotherapy.

Keywords: Epithelial Ovarian Cancer; Cytoreductive Surgery; Large Bowel Resection; Time; Survival; Progression-Free Survival

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: L.Y.Y., M.T.; Data curation: M.T., K.S.R.; Formal analysis: L.Y.Y., M.T.; Methodology: L.Y.Y., M.T.; Supervision: M.T., B.T.; Writing - original draft: L.Y.Y., M.T.; Writing - review & editing: K.S.R., K.A., B.T., M.T.

Synopsis

Optimal waiting time for adjuvant chemotherapy after bowel resection during surgery in advanced ovarian cancer is unclear. Two to 4 weeks after surgery showed best survival outcomes which is similar in colorectal cancer. Stoma formation and intraperitoneal chemotherapy are associated with delayed waiting time.

INTRODUCTION

Advanced epithelial ovarian cancer (EOC) is a lethal disease with a dismal 5-year survival rate of less than 35%. The degree of residual disease after surgery and the response to adjuvant chemotherapy are the two most important determinants of survival [1,2]. Therefore, maximal cytoreduction with the goal of residual disease of less 1–9 mm or ideally 0 mm is highly recommended when feasible [3]. Since the pelvic tumor in advanced EOC often directly involves the bowels such as the rectosigmoid colon, terminal ileum, and cecum, bowel resections are often necessary to achieve optimal or complete cytoreduction in advanced EOC [4]. The current treatment algorithm following primary cytoreductive surgery (PCS) includes adjuvant systemic chemotherapy to treat any macroscopic or microscopic residual disease [5].

Several retrospective studies in advanced EOC have reported a wide variation in the time interval between primary cytoreduction and initiation of adjuvant chemotherapy, with an average interval reported at 28 days (range, 4–158 days) [6]. These studies have also reported variable survival outcomes associated with delayed initiation of adjuvant chemotherapy [7,8]. This variability is likely due to the lack of clear definition of ‘optimal’ cytoreduction in these studies, the heterogeneity of cytoreductive outcomes and amount of residual disease across the studies [6]. We have recently reported on superior overall survival (OS) in patients who had shorter interval between PCS and the first cycle of adjuvant chemotherapy [9]. This suggests that delaying the delivery of first cycle of adjuvant chemotherapy leads to a negative impact on survival in this cohort. This concept has been demonstrated in other cancer sites. A meta-analysis of patients with colorectal cancers showed that longer intervals between bowel resections and initiation of adjuvant chemotherapy were associated with worse survival [10]. Similarly, in early breast and lung cancers, a shorter interval between cancer surgery and subsequent initiation of adjuvant chemotherapy was also associated with improved OS [11,12].

Bowel resections are often required to achieve optimal or complete cytoreduction in advanced EOC and represent the most commonly performed extra-uterine procedures conducted during a cytoreductive surgery. Eisenkop et al. [13] reported that 52.1% and 19.6% of patients with advanced EOC had pelvic and extra pelvic bowel resections, respectively, during PCS to achieve optimal cytoreduction. Our previous work has demonstrated that in patients who undergo PCS with bowel resection, there is often a delay in initiation of chemotherapy [7]. The aim of this study was to investigate whether time intervals between PCS with bowel resection and subsequent initiation of adjuvant chemotherapy have an impact on peri-operative complication rates and OS in patients with advanced EOC.

MATERIALS AND METHODS

This was a retrospective cohort study using data from two cancer centers, Princess Margaret Cancer Centre, Toronto, Ontario, Canada (between January 1, 2002, and December 31, 2012)

and Samsung Comprehensive Cancer Center, Seoul, South Korea (between January 1, 2002, and December 31, 2015). Ethics approval was obtained from the Research Ethics Boards at both institutions (15-8740-CE and 2014-05-083, respectively).

We included patients who were diagnosed with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV primary EOC, fallopian tube, or primary peritoneal cancer and who had any type of large bowel resection during PCS. Types of large bowel resection in this cohort included low-anterior resection of the rectosigmoid colon, anterior resection of the descending or sigmoid colon, transverse colectomy and right hemi-colectomy. All patients had primary circular or side-to-side re-anastomoses. Patients with EOC patients with FIGO stage I or II, neoadjuvant chemotherapy, and synchronous malignancies were excluded. Treatment interval of more than 90 days were excluded since we considered there is no role of adjuvant chemotherapy for curative intent as previously described [14]. Clinicopathologic and survival data were obtained from the medical records at each hospital. Residual disease less than 10 mm after PCS was defined as optimal cytoreduction. The treatment interval was defined as the period between the date of PCS and the date of the first cycle of adjuvant chemotherapy measured in days. All patients had platinum-based combination chemotherapy.

Three groups were defined according to the time interval between PCS and first cycle of adjuvant chemotherapy, based on previous studies. First, a meta-analysis in colorectal cancer demonstrated that a 4-week increase in time to initiation of adjuvant chemotherapy was associated with a significant decrease in OS [10]. Considering all patients in our study population had any type of large bowel resections, it seemed reasonable to follow this time frame in the current study. Second, a recent analysis showed that shorter intervals were associated with significant improvement in OS in patients with advanced EOC who had optimal PCS and the positive survival impact started as early as 1 to 2 weeks after PCS [9]. Taking all these into account, we grouped our patients into: 14 days or less (group 1), 15 to 28 days (group 2), and 29 to 90 days (group 3) from PCS and initiation of adjuvant chemotherapy.

Statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA). Descriptive statistics included median (range) for continuous variables, and number (percentage) for categorical variables. Clinical data were compared by using χ^2 test or Fisher exact test for categorical variables, and Student's t-test or Wilcoxon rank sum test for continuous variables. OS was defined as the time from surgery to the date of death or the date of last follow-up, and was calculated by the Kaplan-Meier method.

RESULTS

In total, 91 patients (32 treated at Princess Margaret Cancer Centre and 59 at Samsung Comprehensive Cancer Center) were identified who met inclusion criteria. The median follow-up period was 43.0 months (range, 2–128 months). During the study period, 20 (22.0%) women died. The median OS was therefore not reached during the follow up period and the 5-year OS was 71.0%.

Baseline patients' characteristics are shown in **Table 1**. All women had PCS for EOC or fallopian tube cancer with FIGO stage III (n=81, 89.0%) or stage IV disease (n=10, 11.0%). All patients had at least one large bowel resection during PCS. Mean age was 57.3 years and high-

Table 1. Patient demographics (n=91)

Characteristics	Values
Mean age (yr)	57.3±9.9
Pre-operative CA125 (U/mL)	793 (0–15,887)
FIGO stage	
III	81 (89.0%)
IV	10 (11.0%)
Primary sites	
Epithelial ovarian cancer	87 (95.6%)
Fallopian tube cancer	4 (4.4%)
Histology	
High grade serous	82 (90.1%)
Endometrioid	3 (3.3%)
Transitional	2 (2.2%)
Clear cell	1 (1.1%)
Mucinous	1 (1.1%)
Undifferentiated	2 (2.2%)
PCS	91 (100.0%)
Any type of large bowel surgeries during PCS	91 (100.0%)
Residual disease	
<1 mm (microscopic)	56 (61.5%)
1–9 mm (optimal)	35 (38.5%)
Interval* (days)	21 (7–86)
Group 1: ≤14 days	32 (35.2%)
Group 2: 15–28 days	27 (29.6%)
Group 3: 29–90 days	32 (35.2%)
IP chemotherapy	14 (15.4%)
Number of adjuvant chemotherapy cycles	
1–3 cycles	5 (5.5%)
4 cycles or more	86 (94.5%)

Values are expressed as mean±standard deviation, median (range), or number (%).

FIGO, International Federation of Gynecology and Obstetrics; IP, intraperitoneal; PCS, primary cytoreductive surgery.

*Intervals refers to days between surgery and the first cycle of adjuvant chemotherapy.

grade serous was the most common histologic subtype (n=82, 90.1%). At the conclusion of PCS, 56 patients (61.5%) had complete cytoreduction with no visible residual disease, and 35 (38.5%) had optimal cytoreduction with 1–9 mm visible residual disease. None of the patients had suboptimal cytoreduction with visible residual disease equal or larger than 10 mm. The median interval from PCS to chemotherapy for all patients was 21 days, with a range of 7 to 86 days. When stratified into predesignated time interval groups, 32 (35.2%) of patients were in group 1 (within 2 weeks or fewer), 27 patients (29.6%) in group 2 (between 2–4 weeks), and 32 (35.2%) of patients in group 3 (between 4 weeks–90 days). Greater than 90% of patients completed 6 cycles of adjuvant chemotherapy after PCS.

Of the entire cohort (n=91), multiple large bowel resections were performed in 11 patients (12.1%) and diverting stoma was made in 17 patients (18.7%). Among 91 patients, 102 large bowel resections were done. Low anterior resection was the most common procedure and was performed in 90 patients (88.2%) followed by ileocectomy in 6 patients (5.9%) then large bowel resection with anastomosis in the descending colon, transverse colon and ascending colon in 3 (2.9%), 2 (2.0%), and 1 (1.0%) patients, respectively. Other complex procedures performed included diaphragmatic peritonectomies in 29 patients (31.9%), liver resections in 6 patients (6.6%), and splenectomy in 15 patients (16.5%). The rates of postoperative complications were similar among groups as shown in **Table 2**. The perioperative mortality rate was zero. Among clinical parameters, stoma formation (p=0.030) and intraperitoneal (IP) chemotherapy (p=0.003) had an impact on delayed interval (data not shown).

Wait times in ovarian cancer after bowel surgery
Table 2. Surgical procedures during primary cytoreductive surgery and related peri-operative complications

Variables	Entire cohort (n=91)	Group 1 (n=32)	Group 2 (n=27)	Group 3 (n=32)	p-value
Intervals*	21 (7–86)	10 (7–14)	21 (15–28)	39 (29, 86)	<0.001
FIGO stage IV	10 (11.0%)	5 (15.6%)	2 (7.4%)	3 (9.4%)	0.700
Mean age (yr)	57.3±9.9	55.6±8.6	56.7±10.4	59.6±10.6	0.262
Small bowel resection	9 (9.9%)	2 (6.2%)	3 (11.1%)	4 (12.5%)	0.682
Large bowel resection	91 (100.0%)				0.120
Single	80 (87.9%)	31 (96.9%)	23 (85.2%)	26 (81.2%)	
Multiple	11 (12.1%)	1 (3.1%)	4 (14.8%)	6 (18.8%)	
Stoma creation	17 (18.7%)	2 (6.2%)	4 (14.8%)	11 (34.4%)	0.013
Diaphragm peritonectomy	29 (31.9%)	6 (18.8%)	10 (37.0%)	13 (40.6%)	0.135
Liver resection	6 (6.6%)	3 (9.4%)	3 (11.1%)	0	0.154
Splenectomy	15 (16.5%)	4 (12.5%)	9 (33.3%)	2 (6.2%)	0.020
Residual disease (1–9 mm)	35 (38.5%)	13 (40.6%)	12 (44.4%)	10 (31.2%)	0.556
IP chemotherapy	14 (15.4%)	0	5 (18.5%)	9 (28.1%)	0.003
Postoperative complications					
Deep SSI†	12 (13.2%)	3 (9.4%)	4 (14.8%)	5 (15.6%)	0.794
Others	31 (34.1%)	8 (25.0%)	9 (33.3%)	14 (43.8%)	0.285

Values are expressed as mean±standard deviation, median (range), or number (%).

FIGO, International Federation of Gynecology and Obstetrics; IP, intraperitoneal; SSI, surgical site infection.

*Median intervals between PCS and chemotherapy in days; †Deep SSI includes anastomotic site leak, fistula, and abscess formation. Other complications refers to superficial surgical site infections, wound problem, post operation ileus, and thrombo-embolic events.

The median time interval between PCS and chemotherapy initiation was 21 days (range, 7–86 days) in entire cohort (**Table 2**). The rates of small bowel resections, multiple large bowel resections, diaphragm peritonectomy, FIGO stage IV, and residual disease after PCS were similar among the 3 groups. OS rates were not significantly different among the 3 groups as shown in **Fig. 1**; however, there was a trend towards better survival favoring group 2 compared to group 1 or group 3 (p=0.242). Five patients who had 3 cycles or less of adjuvant chemotherapy experienced worse survival (p<0.001). A multivariate Cox analysis was performed controlling for variables that were significantly different between the groups, including stoma formation, splenectomy, and IP chemotherapy. Other prognostic factors included in the Cox model analysis included age, residual disease status, and FIGO stage. The results indicated that group 2 (interval between 2 to 4 weeks), younger age, and completion of 4 or more adjuvant chemotherapy cycles were independent prognostic factors of favorable OS (**Table 3**).

Table 3. Cox model for overall survival

Variables	Univariate			Multivariate		
	HR	95% CI	p-value	HR	95% CI	p-value
Interval*						
Group 1	1			1		
Group 2	0.367	0.097–1.387	0.140	0.119	0.021–0.687	0.017
Group 3	1.012	0.390–2.627	0.981	0.533	0.153–1.860	0.324
Age (yr)	1.049	1.007–1.093	0.021	1.067	1.016–1.121	0.010
RD status						
<1 mm	1			1		
1–9 mm	2.593	1.068–6.292	0.035	2.248	0.738–6.850	0.154
No. of CTx cycles						
1–3	1			1		
≥4	0.058	0.019–0.170	<0.001	0.042	0.009–0.193	<0.001
FIGO stage						
III	1			1		
IV	0.357	0.048–2.667	0.315	0.406	0.051–3.229	0.395
IP chemotherapy	0.033	0.000–3.096	0.141	0	0.000–NA†	0.967

CTx, adjuvant chemotherapy; FIGO, International Federation of Gynecology and Obstetrics; IP, intraperitoneal; NA, not applicable; PCS, primary cytoreductive surgery; RD, residual disease.

*Intervals between PCS and chemotherapy; †No death in patients with IP chemotherapy (n=14).

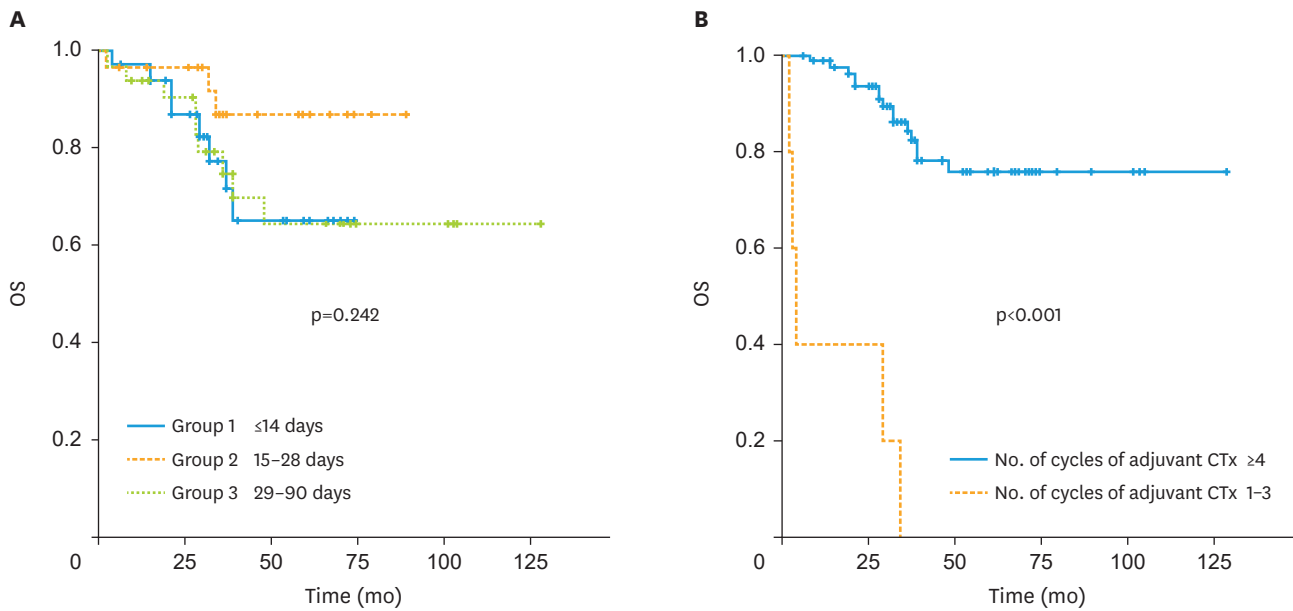


Fig. 1. OS according to interval from surgery to initiation of chemotherapy (A) and number of adjuvant CTx cycles received (B). CTx, chemotherapy; OS, overall survival.

DISCUSSION

To our knowledge, this is the first study addressing the timing between PCS and initiation of adjuvant chemotherapy that focuses only on patients with advanced EOC who had PCS with bowel resection. Our results demonstrate that the optimal timing of initiation of adjuvant chemotherapy following bowel resection/PCS is between 2 and 4 weeks in advanced EOC.

The concept of accelerated growth of residual tumors after incomplete surgical resection has long been described. One possible mechanism may relate to increased levels of angiogenic cytokines and growth factors in serum [15,16] and wound fluid during the perioperative period [17]. This accelerated growth of residual cancer may contribute to the worse oncologic outcomes seen in our study and others (Ref). For example, a case series was reported in 1980 observing sudden and dramatic exacerbation of residual tumors of the germ cell testicular cancer after cytoreductive surgery [18]. In vivo studies also demonstrate increased proliferation of residual or metastatic tumor cells after surgery [19-21]. For example, Fisher et al. used metastatic heterotopic mouse model with mammary adenocarcinoma and found that early (peri-operative) chemotherapy prevented surgery-induced accelerated tumor growth and led to improved survival as compared with delayed initiation of chemotherapy [20]. Furthermore, in patients with breast cancer, delayed initiation of adjuvant chemotherapy following surgery was associated with worse survival [22]. Interestingly, surgery-induced accelerated residual tumor growth may be affected by the amount of operative damage following cancer surgery. Concentrations of angiogenic cytokines and growth factors in the systemic circulation or local wound fluid were detected at higher levels in large surgical wounds (e.g., laparotomy) as compared to smaller surgical wounds (e.g., laparoscopy) in preclinical [23,24] and clinical studies [16]. In a randomized clinical trial of non-metastatic colon cancer patients, laparoscopic approach showed better survival than laparotomy [25].

In EOC, there is conflicting evidence regarding the impact of delayed initiation of adjuvant chemotherapy after PCS on survival outcomes. A recent meta-analysis failed to show any association between the time from surgery to chemotherapy and survival outcomes due to heterogeneity of the included study results [8]. Of the seven studies included in the meta-analysis, two included all FIGO stages (I through IV) and five studies included advanced stage disease only (III and IV). Poor survival outcomes were only noted in patients with FIGO stage III or IV EOC and incomplete or non-curative surgery [21]; in other words, delayed initiation of adjuvant chemotherapy was associated with worse survivals in advanced EOC (FIGO stage III or IV) [26] but not in early stage EOC (FIGO stage I or II) [27].

Interestingly, the amount of residual disease may impact the significance of the time interval between surgery and initiation of adjuvant chemotherapy in EOC [8]. Our group has previously demonstrated that the interval from surgery to chemotherapy has a more pronounced impact in patients with EOC who underwent PCS with residual disease of 1–9 mm as compared to patients with 0 mm or ≥ 10 mm residual disease [9]. Alternatively, Tewari and colleagues [26] showed a significant effect of the interval from surgery to chemotherapy in patients with stage IV EOC following complete cytoreduction to 0 mm residual disease, but not in FIGO stage III disease with any gross residual disease after PCS.

In aggressive surgical cytoreduction with bowel resection, the level of surgical trauma might be higher than that of studies that included early stage disease where surgery would include surgical staging or less complex cytoreduction. Chan et al. examined the association of timing of chemotherapy initiation in patients with stage I and II EOC [27]. They categorized patients into 3 groups based on the interval from surgery to first cycle of chemotherapy (<2 weeks, 2–4 weeks, and ≥ 4 weeks). No survival difference was observed among the groups. In contrast, our study examined a higher risk patient population with advanced stage disease requiring resection of bowel as a component of cytoreductive surgery, which achieved optimal debulking. The surgical complexity and associated surgical trauma may partly explain the negative impact of delayed chemotherapy on survival in our study population [10,28].

Notably, our data showed no difference between the 3 study groups in terms of peri-operative complications, including the rates of deep surgical site infections. Similarly, Kolb et al. [29] showed that the timing of adjuvant chemotherapy did not increase the risk of wound complications after PCS in advanced EOC. In particular, the performance of bowel resection did not adversely influence the risk of infection and hence the authors recommended that chemotherapy for advanced EOC should not be delayed solely because of concern for wound healing. Although stoma formation and IP chemotherapy delayed the initiation of chemotherapy independently in our study, starting chemotherapy between 2–4 weeks after PCS may give surgeons sufficient time to observe for possible complications before initiation of chemotherapy.

There is limited evidence regarding the optimal timing of adjuvant chemotherapy initiation. In an animal model of breast cancer, chemotherapy on the same day as surgery showed superior survival when compared with chemotherapy 1 week after surgery [20]. In a preclinical study conducted by our group to investigate the optimal timing of adjuvant chemotherapy in EOC model [30], cisplatin was given on one of three time points including the same day as surgery, 1 week, or 4 weeks after surgery. We demonstrated that the administration of cisplatin 1 week after surgery was more effective than cisplatin administration on the same day of surgery or 4 weeks after surgery. Importantly, the expression of the chemo resistant substance survivin [31,32] was noted to increase as early

as 6 hours after surgery and reach pre-operative levels within 1 week [24]. This finding may explain the inferior survival outcomes noted in this study when chemotherapy was administered within 2 weeks of surgery as compared to chemotherapy that's administered 2-4 weeks post-operatively.

The 5-year OS outcome was 71% in this cohort. This relatively high survival rate in patients with advanced EOC may be accounted for by selection of patients with favorable factors including tumor distribution amenable to primary surgery, good performance scores to allow for aggressive PCS and relatively low per-operative complications allowing for timely initiation of systemic chemotherapy. More on that, our study is also limited by its retrospective nature and the confounders associated with this study design. In addition, the reasons for timing of initiation and cessation of chemotherapy were not available in this database which limited interpretation of the results. The strengths of this study include its multicenter nature.

In conclusion, initiation of adjuvant chemotherapy between 2 to 4 weeks after PCS with bowel resection may increase survival outcomes in women with EOC by maximizing the benefit of PCS plus adjuvant chemotherapy. Although stoma formation and use of IP route were independent factors that delay initiation of adjuvant chemotherapy, efforts need to be made to initiate adjuvant chemotherapy within 2–4 weeks following PCS. A prospective study is warranted to prove this association.

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