ANTICANCER RESEARCH *40*: 3925-3929 (2020)
doi:10.21873/anticanres.14383

Primary and Interval Debulking Surgery Provide Similar Survival and Platinum Sensitivity Outcomes in Advanced Ovarian Cancer: A Retrospective Study

OLIVER GLOVER[1], VIREN ASHER[1], ANISH BALI[1], SUMMI ABDUL[1], ANNA COLLINS[2] and ANDREW PHILLIPS[1]

[1]*Derby Gynaecological Cancer Centre, University Hospitals of Derby and Burton, Derby, U.K.;*
[2]*University Hospitals of Leicester NHS Trust, University of Leicester - Infirmary Square, Leicester, U.K.*

Abstract. *Background/Aim: CHORUS and EORTC55971 trials demonstrated that neoadjuvant chemotherapy followed by interval debulking surgery (IDS) or primary debulking surgery (PDS) offered the same survival rates. These trials have since been criticised due to poor surgical complexity. We compared overall (OS), progression free (PFS), and platinum sensitivity in advanced ovarian cancer (AOC) patients undergoing IDS or PDS, who had received either intermediate or high complexity surgery to achieve complete cytoreduction. Patients and Methods: All patients with AOC treated between February 2014 and May 2019 obtaining complete cytoreduction with intermediate/high surgical complexity were included. Recurrence was defined according to GCIG criteria on radiological findings and/or CA125 levels. Results: Seventy-one patients (38 PDS and 33 IDS) with full recurrence data were identified. No statistical difference was seen between groups in OS, PFS or platinum sensitive interval. Conclusion: PDS or IDS were both acceptable treatment options for AOC, showing similar survival and platinum sensitivity outcomes in patients undergoing intermediate or high complexity surgery.*

Ovarian cancer (OC) is the eighth commonest female cancer worldwide. The prognosis for OC is poor as 60-70% of patients are diagnosed with advanced (stage 3 or 4) ovarian cancer (AOC), at presentation (1, 2). Standard treatment consists of cytoreductive surgery, with the aim of complete resection of all macroscopic disease (3-5), combined with platinum-based chemotherapy.

Correspondence to: Andrew Phillips, Derby Gynaecological Cancer Centre, University Hospitals of Derby and Burton, Derby, DE22 3NE, U.K. Tel: +44 1332785088, e-mail: Andrew.phillips6@nhs.net

Key Words: Ovarian cancer, debulking surgery, PDS, IDS, surgical complexity.

Traditionally, primary debulking surgery (PDS) with adjuvant chemotherapy has been the standard treatment (6). However, recent trials demonstrated that neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) may be an equally effective alternative approach (7). Both EORTC55971 and CHORUS trials showed that NACT followed by IDS was not inferior to PDS in patients with AOC (7, 8). Whilst results of EORTC55971 and CHORUS have not suggested any difference in survival outcomes following PDS or IDS, a retrospective study of patients undergoing high complexity surgery found that avoiding PDS in favour of NACT and IDS results in a shorter platinum sensitive interval (PSI) and a higher percentage of platinum resistant recurrences (9). However, the findings of this study have not been reproduced. A recent meta-analysis by Chiofalo *et al*. demonstrated no differences in OS or PFS between PDS or IDS; however, a reduction in surgical complexity score and post-operative complications were seen in the IDS cohort (10).

In view of the conflicting evidence and ambiguity regarding the most efficacious treatment for AOC, the present retrospective study aimed to identify differences in overall survival (OS), progression free survival (PFS) and platinum sensitivity interval (PSI) between AOC patients undergoing PDS or IDS, where complete cytoreduction is achieved *via* intermediate or high complexity surgery.

Patients and Methods

Patients. We performed a review of prospectively recorded patients diagnosed with stage 3 or 4 epithelial, ovarian, tubal or peritoneal cancer (hereafter referred as AOC) diagnosed and treated between February 4th 2014 and May 15th 2019 at the University Hospitals of Derby and Burton NHS Trust (UHDB), a tertiary cancer referral centre in the United Kingdom.

At UHDB, our standard approach for ovarian cancer is PDS with the intention to remove all macroscopic disease, followed by 3-6 cycles of platinum-based adjuvant chemotherapy. Neo-adjuvant

chemotherapy (NACT) is also used for patients with stage 4 disease (beyond isolated hepatic or splenic metastasis), poor performance status (11), and large volume ascites with low-albumin levels. NACT is given with the intention of enhancing the feasibility of radical interval debulking surgery (IDS) and improving the nutritional and performance status of the patient.

Cytoreductive outcome was defined as: complete (R0); <1 cm (R1); and >1 cm (R2), as per du Bois (12). Only patients who had undergone either PDS or IDS, with intermediate or high complexity surgery, as graded by Aletti *et al*. (13), where complete cytoreduction (R0) was achieved at surgery, were selected for inclusion.

Data. For each patient, the data gathered included: age, date of diagnosis, date of surgery, site of tumour, histology, grade, stage (FIGO classification), surgical procedure, surgical complexity score (SCS) (13), level of cytoreduction, chemotherapy, lowest serum CA 125 level after completion of treatment, date of recurrence and overall survival.

Date of recurrence was defined according to Gynecological Cancer Intergroup criteria as any radiological evidence (computed tomography scans) of recurrence, according to RECIST criteria, or serum CA 125 showing a doubling from lowest recorded (nadir) value (14). Recurrent disease was categorized as either platinum-resistant (<6 months) or platinum-sensitive (>6 months) (15).

Statistical analysis. Categorical variables were compared with the chi-squared test and continuous variables were compared with the Kruskal–Wallis test. All tests were two-sided and a *p*-value of less than 0.05 was regarded as being statistically significant. The Kaplan–Meier method was used to estimate survival using IBM SPSS statistics version 23.

Table I. *Demographic and clinicopathological characteristics of the patients (N=71).*

	PDS	IDS	*p*-Value (Chi squared)
Number of patients, n	38	33	
Age at diagnosis, (years), mean±SD	64±13.8	65±8.5	>0.05
Site of tumour origin, n (%)			0.004
Ovarian	22 (57.9%)	13 (39.4%)	
Tubal	5 (13.2%)	16 (48.5%)	
Peritoneal	11 (28.9%)	4 (12.2%)	
Histological type, n (%)			>0.05
Serous	34 (89.5%)	30 (90.9%)	
Endometroid	1 (2.6%)	0	
MMMT	3 (7.9%)	1 (3.0%)	
Other	0	2 (6%)	
Clear cell		1 (3.0%)	
Adenocarcinoma		1 (3.0%)	
Grade, n (%)			>0.05
I	4 (10.5%)	1 (3.0%)	
II	3 (7.9%)	0	
III	31 (81.6%)	31 (93.9%)	
Unknown		1 (3.0%)	
FIGO stage, n (%)			>0.05
III	12 (31.6%)	19 (57.6%)	
IV	26 (68.4%)	14 (42.4%)	
Surgical complexity score, median (IQR)	6.5 (5-10)	7 (5-9)	>0.05

MMMT: Malignant mixed mullarian tumour; FIGO: International Federation of Gynecology and Obstetrics; IQR: interquartile range.

Results

Between 4th February 2014 and 15th May 2019, 71 patients were identified with full recurrence data available. All patients were diagnosed with AOC and received either PDS or IDS with NACT achieving complete cytoreduction (R0) following intermediate or high-complexity surgery. The patients were divided into two groups with 38 patients undergoing PDS and 33 patients undergoing IDS. The majority of patients across both groups had Stage 3 high grade serous cancer of tubo/ovarian origin. There were no significant differences between the mean age of the two groups (64±13.8 and 65±8.5 years for PDS and IDS group, respectively). More patients were identified as having ovarian primaries in those that underwent PDS (57.9%) compared to IDS (39.4%). Conversely, the fallopian tube was the most common site of origin in the IDS patients (48.5%) compared to PDS patients (13.2%) (p=0.004). No difference was seen in histological subtype, grade or stage (Table I).

Unsurprisingly, within a cohort selected by complete cytoreduction obtained with intermediate or high complexity surgery, median SCSs were elevated (median SCS 6.5 and 7 for PDS and IDS respectively). However, no significant difference in complexity of surgery was seen between those patients undergoing PDS or IDS.

Recurrences were detected through radiological evidence on computed tomography (CT) scan or by a doubling of the lowest CA 125 value post treatment. In both groups, around half of the recurrences were detected by a doubling of CA 125 and the other half through CT scans. Patients diagnosed by CA 125 were later confirmed by CT.

At the time of analysis, 17 of the 38 PDS patients and 20 of the 33 IDS patients had recurred. Of these recurrences, 2/17 (12%) PDS patients had an early/refractory platinum-resistant recurrence within 3 months, compared with 5/20 (25%) in those treated with IDS (p>0.05). The corresponding number of platinum-resistant recurrences within 6 months were 5/17 (29%) and 11/20 (55%), (p>0.05) and for all recurrences by 12 months were 11/17 (65%) and 16/20 (80%) in PDS and IDS respectively (p>0.05). There was no statistically significant difference in platinum sensitivity interval between the two groups.

The CA 125 levels at the completion of adjuvant chemotherapy were similar for both groups, with 28 patients (74%) in the PDS group and 23 patients (70%) in the IDS group with normalised CA 125 levels. Both groups showed comparable numbers of recurrences at 6, 12 and >12 months,

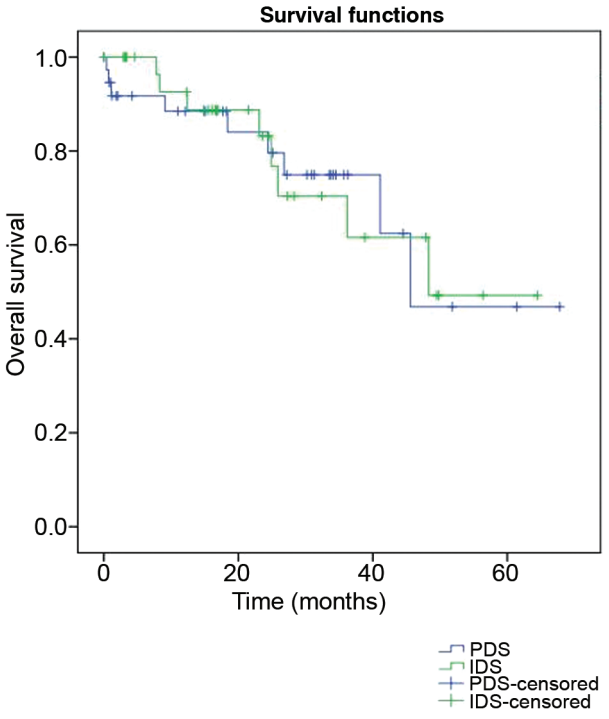

Figure 1. *Kaplan-Meier plot of overall survival (OS) in patients who have undergone either primary debulking surgery (PDS) or interval debulking surgery (IDS).*

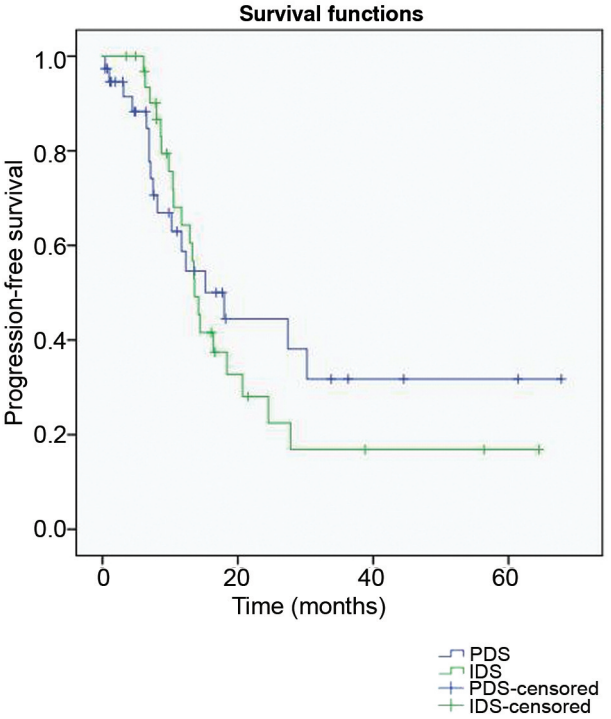

Figure 2. *Kaplan-Meier plot of progression-free survival (PFS) in patients who have undergone either primary debulking surgery (PDS) or interval debulking surgery (IDS).*

with the PDS group showing a non-significant tendency to recur later relative to the IDS group.

No differences were observed between patients undergoing PDS or IDS with regards to OS, with a mean of 47.5 (±5.4) and 46.5 (±4.9) (median OS of 45.6 and 48.3, respectively) (Figure 1). In contrast, although no significant difference was observed in PFS between PDS and IDS patients, there was an elevated median PFS in PDS (18.0 months; IQR=9.2-26.8) compared to IDS patients (13.6 months; IQR=11.7-15.5) (Figure 2).

Discussion

Our study supports the findings of two previous randomised controlled trials (7, 8) and a recent meta-analysis (10) that there is no difference in OS between patients treated with PDS and IDS when the same surgical effort is applied to achieve complete cytoreduction. However, consistent with the findings of Petrillo (9), the results are suggestive of a prolonged progression-free survival and increased rate of patients remaining recurrence-free at 5 years following PDS. Additionally, when patients received PDS there was a trend in our cohort towards platinum-sensitive recurrences compared to patients undergoing IDS. However, the suggestion of an improved recurrence pattern following PDS needs to be confirmed in a larger study and the results of the upcoming TRUST trial will be important to inform future care.

Our study is limited by its retrospective nature. Additionally, whilst the number of patients in our study is limited compared to larger studies, all patients underwent intermediate/high complexity surgery and achieved complete cytoreduction. This contrasts with CHORUS, where only 17% of PDS and 39% of IDS patients achieved R0, and only 20% received any upper abdominal surgery (16). It is likely that the proportion of intermediate/high complexity patients in their study was limited. Similarly, in the EORTC-55971 trial only 19.2% of the PDS and 51.2% of the IDS patients received R0 resections (7). Also in this trial the utilisation of upper abdominal procedures was limited (diaphragmatic surgery 16% PDS and 16% IDS, splenectomy 7% PDS and 4% IDS). Therefore, the proportion receiving intermediate or high complexity surgery compared to our cohort was likely to be limited. Indeed, CHORUS explicitly comments that, with a similar surgical ethos as EORTC-55971, it does not address the difference between standard and radical surgery in advanced ovarian cancer (8). Conclusions drawn from CHORUS and EORTC-55971

regarding non-inferiority of PDS or IDS may not be applicable in patients receiving high complexity surgery, and are likely to have included comparatively few patients with our entry criteria. In fact, our study population includes more patients with complete surgery than the upcoming SCORPION trial (25 and 30 R0 patients in the initial PDS and IDS arms) (17). Our study therefore addresses some of the concerns highlighted by Chiofalo (10) regarding the limited complexity of surgery in patients undergoing IDS and suggest that overall survival in patients undergoing intermediate or high complexity surgery is similar in those receiving IDS or PDS.

A second limitation of our study was the relatively short follow-up period after treatment for those who had more recently finished their treatment. The difference between the PFS and recurrence findings in comparison to the similar OS figures between the two arms are likely to be due to our small sample size and duration of follow-up. Fifty-five percent of PDS and 40% of IDS patients had not had a recurrence at the time of analysis, and as such the 15% difference in recurrence rate may not be sufficient to significantly influence the OS, while patients are still under follow-up. However, we would expect that with further follow-up the difference in survival between both arms would emerge in view of the greater number of recurrences and worse recurrence characteristics in the IDS arm.

Whilst our results echo the findings of Petrillo *et al*. with respect to more early recurrences following IDS (9), there are certain differences between our two cohorts. Firstly, whereas 74% of the Petrillo cohort were aged ≤65, only 49% of the current cohort were. Additionally, we saw a lower rate of lower grade disease (11% grade 1 or 2 compared to 22%) and more stage 4 disease (37% compared to 20%).

As such, our cohort represents an older cohort with more aggressive and advanced disease, and this may explain some of the differences in survival seen between these studies. Additionally, it implies that an improved recurrence rate may be achieved with utilisation of PDS in younger patients with stage 3C disease and potentially in older patients, if they are fit for primary surgery. However, further investigation with a larger study is required to confirm these findings.

The final difference between the UHDB and Petrillo *et al*. (9) cohorts was that although all patients achieved R0, different approaches were used to assess disease volume. Tumour load as determined by Aletti *et al*. (13) with 4-cm plaques on diaphragm or mesentery was required for entry into the Petrillo study, whereas we used a SCS of 4 or more as a surrogate marker of tumour load. Since both methods of assessing the extent of disease yield similar findings, we suggest that surgical effort is a potential marker of tumour burden. Further research into objective measures of intra-abdominal disease such as the Peritoneal Cancer Index (18), as well as other descriptors of intra-abdominal tumour load and their correlation with surgical complexity to achieve R0 is worthy of investigation.

The questions around whether primary debulking surgery or neo-adjuvant based approaches are more efficacious in AOC are therefore still unclear. Whilst our data is suggestive of an improved recurrence profile with primary debulking surgery, these findings have not been demonstrated significantly with respect to PFS and show no difference with respect to OS. Himoto *et al*. have demonstrated a difference in the distribution pattern of recurrent disease dependent on treatment approach, identifying that patients treated with IDS were more likely to develop recurrences in operated regions than patients treated with PDS who tended to recur in new anatomical sites (19). This suggests that that trends towards an improved recurrence pattern with PDS in our data may be related to the nature of recurrent disease following PDS. This study however predominantly included PDS patients with only 54 patients undergoing IDS. These findings contrast with a larger study of 193 IDS patients who found no such difference in recurrence in operated fields (20). The results of the ongoing TRUST (21) trial into high complexity surgery in AOC are keenly awaited.

In conclusion, similar survival outcomes are observed in AOC patients undergoing PDS or IDS, when intermediate or high complexity surgery is performed to achieve complete cytoreduction. This is in consistence with previous data from studies that included patients treated with less extensive surgery. However, PDS appears to be suggestive of a better recurrence pattern. Further studies on larger population samples and long-term outcomes following both treatment approaches are warranted to improve surgical management of patients with AOC.

Conflicts of Interest

All Authors have no conflicts of interest to disclose.

Authors' Contributions

Conception was developed by AP, VA, AB and SA. Planning was performed by AP and VA. Data was collected by OG, AC and AP. Analysis and Manuscript preparation was performed by OG, AC, AP, VA and AB.

References

1 Bray F, Ferlay J, Soerjomataram I, Siegel R, Torre L and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68*: 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492

2 Maringe C, Walters S, Butler J, Coleman M, Hacker N, Hanna L, Mosgaard B, Nordin A, Rosen B, Engholm G, Gjerstorff M, Hatcher J, Johannesen T, McGahan C, Meechan D, Middleton R, Tracey E, Turner D, Richards M and Rachet B: Stage at diagnosis and ovarian cancer survival: Evidence from the International Cancer Benchmarking Partnership. Gynecol Oncol *127*: 75-82, 2012. PMID: 22750127. DOI: 10.1016/j.ygyno.2012.06.033

3 Ledermann J, Raja F, Fotopoulou C, Gonzalez-Martin A, Colombo N and Sessa C: Newly diagnosed and relapsed epithelial ovarian carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol *24*: vi24-vi32, 2013. PMID: 24078660.DOI: 10.1093/annonc/mdt333

4 Bristow R: Survival effect of maximal cytoreductive surgery for advanced ovarian carcinoma during the platinum era: A meta-analysis. J Clin Oncol *20*: 1248-1259, 2002. PMID: 11870167. DOI: 10.1200/JCO.2002.20.5.1248

5 Phillips A, Balega J, Nevin J, Singh K, Elattar A, Kehoe S and Sundar S: Reporting 'Denominator' data is essential for benchmarking and quality standards in ovarian cancer. Gynecol Oncol *146*: 94-100, 2017. PMID: 28411948. DOI: 10.1016/j.ygyno.2017.04.007

6 Eisenkop S, Spirtos N, Friedman R, Lin W, Pisani A and Perticucci S: Relative influences of tumor volume before surgery and the cytoreductive outcome on survival for patients with advanced ovarian cancer: a prospective study. Gynecol Oncol *90*: 390-396, 2003. PMID: 12893206. DOI: 10.1016/s0090-8258(03)00278-6

7 Vergote I, Tropé C, Amant F, Kristensen G, Ehlen T, Johnson N, Verheijen R, van der Burg M, Lacave A, Panici P, Kenter G, Casado A, Mendiola C, Coens C, Verleye L, Stuart G, Pecorelli S and Reed N: Neoadjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. N Engl J Med *363*: 943-953, 2010. PMID: 20818904. DOI: 10.1056/NEJMoa0908806

8 Kehoe S, Hook J, Nankivell M, Jayson G, Kitchener H, Lopes T, Luesley D, Perren T, Bannoo S, Mascarenhas M, Dobbs S, Essapen S, Twigg J, Herod J, McCluggage G, Parmar M and Swart A: Primary chemotherapy *versus* primary surgery for newly diagnosed advanced ovarian cancer (CHORUS): an open-label, randomised, controlled, non-inferiority trial. Lancet *386*: 249-257, 2015. PMID: 26002111. DOI: 10.1016/S0140-6736(14)62223-6

9 Petrillo M, Ferrandina G, Fagotti A, Vizzielli G, Margariti P, Pedone A, Nero C, Fanfani F and Scambia G: Timing and pattern of recurrence in ovarian cancer patients with high tumor dissemination treated with primary debulking surgery *versus* neoadjuvant chemotherapy. Ann Surg Oncol *20*: 3955-3960, 2013. PMID: 23838915. DOI: 10.1245/s10434-013-3091-6

10 Chiofalo B, Bruni S, Certelli C, Sperduti I, Baiocco E and Vizza E: Primary debulking surgery vs. interval debulking surgery for advanced ovarian cancer: review of the literature and meta-analysis. Minerva Medica *110*: 330-340, 2019. PMID: 31081304. DOI: 10.23736/s0026-4806.19.06078-6

11 Oken M, Creech R, Tormey D, Horton J, Davis T, McFadden E and Carbone P: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol *5*: 649-656, 1982. PMID: 7165009.

12 du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I and Pfisterer J: Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: A combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials. Cancer *115*: 1234-1244, 2009. PMID: 19189349. DOI: 10.1002/cncr.24149

13 Aletti G, Eisenhauer E, Santillan A, Axtell A, Aletti G, Holschneider C, Chi D, Bristow R and Cliby W: Identification of patient groups at highest risk from traditional approach to ovarian cancer treatment. Gynecol Oncol *120*: 23-28, 2011. PMID: 20933255. DOI: 10.1016/j.ygyno.2010.09.010

14 Rustin G, Vergote I, Eisenhauer E, Pujade-Lauraine E, Quinn M, Thigpen T, du Bois A, Kristensen G, Jakobsen A, Sagae S, Greven K, Parmar M, Friedlander M, Cervantes A and Vermorken J: Definitions for Response and Progression in Ovarian Cancer Clinical Trials Incorporating RECIST 1.1 and CA 125 Agreed by the Gynecological Cancer Intergroup (GCIG). Int J Gynecol Cancer *21*: 419-423, 2011. PMID: 15026475. DOI: 10.1093/jnci/djh081

15 Eisenhauer E, Vermorken J and van Glabbeke M: Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: A multivariate analysis of 704 patients. Ann Oncol *8*: 963-968, 1997. PMID: 9402168. DOI: 10.1023/a:1008240421028

16 Kang S: Neoadjuvant chemotherapy for ovarian cancer: do we have enough evidence? Lancet *386*: 223-224, 2015. PMID: 25364394. DOI: 10.1177/1758834014544891

17 Fagotti A, Ferrandina G, Vizzielli G, Fanfani F, Gallotta V, Chiantera V, Costantini B, Margariti P, Gueli Alletti S, Cosentino F, Tortorella L and Scambia G: Phase III randomised clinical trial comparing primary surgery *versus* neoadjuvant chemotherapy in advanced epithelial ovarian cancer with high tumour load (SCORPION trial): Final analysis of peri-operative outcome. Eur J Cancer *59*: 22-33, 2016. PMID: 26998845. DOI: 10.1016/j.ejca.2016.01.017

18 Sugarbaker P and Jablonski K: Prognostic features of 51 colorectal and 130 appendiceal cancer patients with peritoneal carcinomatosis treated by cytoreductive surgery and intraperitoneal chemotherapy. Ann Surg *221*: 124-132, 1995. PMID: 7857141. DOI: 10.1097/00000658-199502000-00002

19 Himoto Y, Cybulska P, Shitano F, Sala E, Zheng J, Capanu M, Nougaret S, Nikolovski I, Vargas HA, Wang W and Mueller JJ: Does the method of primary treatment affect the pattern of first recurrence in high-grade serous ovarian cancer? Gynecol Oncol *155*: 192-200, 2019. PMID: 31521322. DOI: 10.1016/j.ygyno.2019.08.011

20 Phillips A, Sundar S, Pounds R, Elattar A, Nevin J, Kehoe S, Balega J, and Singh K: Has the 'paradigm shift' in the management of advanced ovarian, tubal and primary peritoneal cancer altered the locations of recurrence? Eur J Gynaecol Oncol *39*: 365-371, 2018. DOI: 10.12892/ejgo4183.2018

21 Reuss A, du Bois A, Harter P, Fotopoulou C, Sehouli J, Aletti G, Guyon F, Greggi S, Mosgaard B, Reinthaller A, Hilpert F, Schade-Brittinger C, Chi D and Mahner S: TRUST: Trial of Radical Upfront Surgical Therapy in advanced ovarian cancer (ENGOT ov33/AGO-OVAR OP7). Int J Gynecol Cancer *29*: 1327-1331, 2019. PMID: 31420412. DOI: 10.1136/ijgc-2019-000682

Received April 20, 2020
Revised May 21, 2020
Accepted June 2, 2020