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Surgical and survival outcomes of advanced epithelial ovarian cancer

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ABSTRACT

Background: Ovarian cancer is the 8th commonest cancer affecting females. It is usually discovered late due to lack of specific symptoms & effective screening. Prognosis is poor with advanced stages (III/IV) estimated 5-years overall survival of 15-25%. Age, stage, residual disease & histological type are the main factors affecting survival. *Aim*: To identify the surgical and survival outcomes in advanced epithelial ovarian cancer in our patient population. *Materials & methods*: Single institution prospective analysis of all cases of advanced epithelial ovarian cancer treated at our institute from September 2018 till September 2020. 56 cases were included. *Results:* 19 (33.9%) underwent primary debulking surgery whereas 37 (66.1%) had interval debulking surgery. Median age was 55.5 years (range 20-86 years). Median preoperative CA-125 level was 570 U/ml (range 145-28000 U/ml). Commonest histological subtype was serous. Complete cytoreductive surgery was fulfilled in 37 cases (66.1%). Median follow-up was 22 months (range 1-34 months). Overall survival at 1 & 2 years was 90.8% & 80% respectively while progression free survival at 1 & 2 years was 89% & 69.7% respectively. Overall survival significant factors on univariate level were CA-125 level, liver metastasis & late complications. On multivariate analysis for overall survival; only CA125 & late complications showed independent prognostic effects. For progression free survival, peritoneal invasion & late complications were significant variables on univariate level. By multivariate analysis for progression free survival, late complications only showed independent prognostic effects. *Conclusion*: CA125 level and late complications are prognostic factors for survival in advanced stage epithelial ovarian cancers.

Keywords: survival, outcomes, ovarian, cancer

1. BACKGROUND

Ovarian cancer is the 8th commonest cancer affecting females. It is responsible for the highest mortality within gynecological malignancies & usually discovered at advanced stages due to lack of specific symptoms & absence of any screening tools detecting at early stages. Despite using CA-125 level & pelvic ultrasound for monitoring & follow-up, mortality rates did not change (Bray et al., 2018; Heintz et al., 2006; Grossman et al., 2018). Epithelial ovarian

cancer (EOC) carcinogenesis is still unclear, one theory 'incessant ovulation hypothesis' proposed a protective mechanism for factors interrupting or suppressing ovulation. Another theory proposed stimulation through exposure to hormones, inflammatory mechanisms & carcinogens transport through fallopian tubes (Shana et al., 2017). Generally its prognosis is poor with an estimated 5-years overall survival (OS) of 30-45% with only 15-25% OS with advanced stages (III/IV). Identification of these prognostic factors could lead to better understanding of disease nature which would help in decisions, patient's selection for trials & evaluation of new therapeutic modalities (Engel et al., 2002; Victoria et al., 2015).

Previous studies tried to identify factors predicting survival with mixed results. The Gynecologic Oncology group (GOG) declared 5 main factors affecting survival (age, stage, grade, ascites & residuals after primary debulking surgery). Further work identified more factors (gravidity, parity, preoperative albumin level & histological type) to affect survival (Dennis et al., 2001; Omura et al., 1991). Some studies tried to identify a relation between hormonal exposure & lifestyle with prognosis of EOC. Results were inconclusive with limitations including small sample size & short follow-up period. Kim et al., (2017) studied 1421 EOC patients to identify a relation of epidemiological factors with survival. Better prognosis was associated with multiple parity & increased ovulatory cycle's number. Smoking & high BMI were associated with poor outcomes (Shana et al., 2017; Poole et al., 2016; Zhou et al., 2014). The EORTC 55971 and the CHORUS trials concluded that primary chemotherapy followed by interval debulking surgery (IDS) is associated with a similar OS as primary debulking surgery (PDS). However, the reduction in treatment associated with morbidity & mortality combined with better quality of life suggested that interval debulking surgery (IDS) is a more valid option for these patients (Vergote et al., 2010; Kehoe et al., 2015).

Recently, a new term was introduced for prognosis of advanced EOC "Peritoneal Cancer Index" (table 1). PCI quantitatively adds tumor distribution through 13 abdomino-pelvic areas with a score given according to lesion size. Two transverse lines (lower costal margin & anterior superior iliac spine) & two longitudinal lines (midclavicular) divide the abdomen into 9 regions numbered in a clockwise fashion with '0' at umbilicus & '1' beneath right hemidiaphragm. Regions (9 to 12) divide small bowel into upper '9' & lower '10' jejunum and upper '11'& lower '12' ileum. More recently, a Simplified Peritoneal Cancer Index (SPCI) was established at the Netherlands Cancer Institute (table 1) dividing the abdomen into 7 areas. This index showed survival impact following cytoreductive surgery (CRS) & hyperthermic intraperitoneal chemoperfusion (HIPEC) (Rhonda & Sugarbaker, 2005). After complete cytoreduction procedures (CRS) assessment; whether true complete cytoreduction (CC-0 or CC-1) or incomplete (CC-2 or CC-3) was reached. 'CC-0' score is given when no peritoneal seedling is seen in the operative field. 'CC-1' indicates nodules persisting <0.25cm. 'CC-2' when nodules are between 0.25 & 2.5cm, whereas 'CC-3' indicates nodules >2.5cm. The 'CC-1' size is theoretically penetrable by intracavitary chemotherapy (CTH) opening the door for complete CRS 'CC-0' if perioperative HIPEC is used (Glehen et al., 2003).

The aim of this study was to identify the surgical outcomes in advanced epithelial ovarian cancer as well as prognostic factors affecting survival in our patient population.

Regions	**Table 1** The classic PCI classification (9 areas)
'0' central	Midline abdominal incision, entire greater omentum, transverse colon
'1' right upper	Superior surface of right lobe of liver, undersurface of right diaphragm – right retrohepatic space
'2' epigastrium	Epigastric fat pad, left lobe of liver, lesser omentum, falciform ligament
'3' left upper	Undersurface of left diaphragm, spleen, tail of pancreas, anterior & posterior surfaces of stomach
'4' left flank	Descending colon, left abdominal gutter
'5' left lower	Pelvic sidewall lateral to sigmoid colon, sigmoid colon
'6' pelvis	Ovaries, tubes & uterus, bladder, Douglas pouch, rectosigmoid colon
'7' right lower	Right pelvic sidewall, cecum, appendix
'8' right flank	Right abdominal gutter, ascending colon
Small bowel '9' '10' '11' '12'	 upper jejunum lower jejunum upper ileum lower ileum
The Netherlands Simpified PCI classification (7 areas)	

'I'	Pelvis
'II'	Right lower abdomen
'III'	Greater omentum, transverse colon and spleen
'IV'	Right sub diaphragmatic area
'V'	Left sub diaphragmatic area
'VI'	Sub hepatic and lesser omental area
'VII'	Small bowel and small bowel mesentery

2. MATERIALS & METHODS

A single institution prospective analysis of all cases of advanced EOC treated from September 2018 till end of September 2020. Data collected from files at our department included patients & tumor characters (age, comorbidities, CA-125 level, stage, histological type & grade). All cases were initially stage III according to the FIGO staging system. Stages I/II, non-epithelial or borderline tumors were excluded as well as those that underwent surgery outside our institute. Patients were split into 2 groups according to intent of surgery to upfront primary debulking surgery (PDS) or interval debulking surgery (IDS) following neoadjuvant CTH. The surgical intent was debulking to no gross residual disease (complete CRS) or Optimal CRS (debulking to <1cm residual) or suboptimal CRS (debulking to >1cm residual). Surgical staging started by a midline incision, sampling of ascites or peritoneal washings for cytological examination followed by thorough inspection of abdomen & pelvis including upper viscera, diaphragm, retroperitoneal spaces. Total abdominal hysterectomy, bilateral salpingo-oophorectomy & omentectomy were performed. Pelvic & para-aortic nodes were sampled in cases with enlarged suspicious nodes. Added procedures as intestinal resections, diaphragmatic stripping, peritonectomy & splenectomy were done only if they would help cytoreduction for optimum debulking. Early complications were defined as those within 1 month of surgery, while late were those occurring >1 month after surgery or during CTH.

The CTH regimen consisted of 6 cycles of carboplatin plus paclitaxel every 3 weeks. Second line was 6 cycles' gemcitabine & carboplatin for those nonresponsive or suffering poor tolerances with severe side effects with primary protocol. Response to CTH was evaluated through physical examination, CA-125 level & CT scanning of the pelviabdominal areas. Second look surgery was offered to those with no signs of progression during CTH. Ethical clearance for the conduction of this study was obtained from our institute ethical committee with consent to participate was signed by all patients before any surgery.

Statistical methodology

Analysis of factors affecting survival was done on the whole study. Data analyzed using IBM SPSS (Statistical Package for Social Sciences) version 24 *(SPSS Inc., Chicago, IL).* Numerical data described as median & range or mean & standard deviation (SD). Qualitative data were described as number & percentage. Chi-square (Fisher's exact) test used to examine relation between qualitative variables. Multivariate analysis done for variables statistically significant on univariate level to indicate independent prognostic factors and obviate effect of confounding using logistic regression model. Survival analysis was done using Kaplan-Meier method. Comparison between two survival curves done using log rank test. Multivariate analysis was done by Cox regression model to allow testing for an independent prognostic effect of any statistically significant variables on univariate analysis and calculating hazard ratio and its 95% confidence interval. All tests were 2-tailed with p-value <0.05 considered significant. Overall survival (OS) was calculated starting from date of diagnosis until date of patient death or documented date of last follow up & Disease-free survival (DFS) was measured from the operation date until date of recurrence, date of patient death or documented date of last follow up .

3. RESULTS

A total of 56 patients were included in this study. Nineteen patients (33.9%) were treated with PDS whereas (37 cases, 66.1%) underwent IDS. Patients & tumor characteristics are shown in (table 2). Median age was 55.5 years (range 20-86 years). Five cases (8.9%) suffered chronic liver disease. The median preoperative CA-125 level was 570 U/ml (range 145-28000 U/ml). The median operative time was 153 min (range 100-180). Median blood loss was 830 cc with 51 patients (91%) receiving blood transfusion. Additional surgical procedures were required for (4 cases, 7.2%). Two (3.6%) in PDS [one (1.8%) needed intestinal resection, diaphragmatic stripping & splenectomy & the other (1.8%) needed pelvic peritonectomy. And another 2 cases (3.6%) in IDS both needed pelvic peritonectomy. Fourteen cases (25%) underwent pelvic lymphadenectomy with 2 of them had positive lymph nodes.

Table 2 Patient and Tumor characteristics (56 cases, 100%)	
Groups: PDS IDS	 19 cases, 33.9% 37 cases, 66.1%
Age: ≤55 years >55 years	 31 cases, 55.4 % 25 cases, 44.6%
Comorbidities: Chronic liver disease Diabetes Hypertension	 5 cases, 8.9% 3 cases, 5.4% 3 cases, 5.4%
CA-125 level: ≤ 500 U/ml >500 U/ml	 18 cases, 32.1% 38 cases, 67.9%
Surgical procedures: Formal staging (FS) FS + pelvic peritonectomy Oophorectomy Omentectomy FS+intestinal resection+diaphragmatic stripping+splenectomy	 49 cases, 33.9% 3 cases, 66.1% 2cases, 3.6% 1 case, 1.8% 1 case, 1.8%
Complications: Early (within 1 month of surgery) Late (>1 month)	 16 cases, 28.5% 20 cases, 35.7%
Pathological stage: IIIB IIIC IVB	 23 cases, 41.1% 27 cases, 48.2% 6 cases, 10.7%
Histological type: Serous Non-serous	 42 cases, 75% 14 cases, 25%
Lymphadenectomy: (14 cases, 25%): Positive Negative	 2 cases, 3.6% 12 cases, 21.4%
Grading: High grade Low grade	 33 cases, 58.9% 23 cases, 41.1%
R resection: R0 R1 R2	 37 cases, 66.1% 5 cases, 8.9% 14 cases, 25%

Early complications occurred in 16 cases (28.6%) with wound infection being the most common (25%). Other early complications included bladder tear, paralytic ileus, small intestinal injury, ureteric injury, burst abdomen, deep vein thrombosis, external iliac artery injury and faecal fistula. Late complications occurred in 20 cases (35.7%) and 25% of these complications were incisional hernias. Other late complications included intractable nausea with hyperemesis, paraparesis, adhesive intestinal obstruction, deep vein thrombosis, disturbed conscious level, severe and chronic calcular cholecystitis with obstructive jaundice. The most common

final pathologic stage was IIIC (48.2%), followed by stage IIIB (41.1%), and finally stage IVB (10.7%). Complete CRS was fulfilled in (37 cases, 66.1%), optimal CRS were done in (5 cases, 8.9%). Fourteen cases (25%) underwent sub-optimal CRS. The median length of hospital stay was 6 days (range 3-21 days). Median follow-up time was 22 months (range 1-34 months). During follow-up (14 cases, 25%) developed recurrence or metastases (figures 1 – 8).

Survival analysis

The median time of follow-up was 22 months ranging (1-34). The cumulative overall survival (OS) for the whole study at 1 & 2 years was 90.8% & 80% respectively while cumulative progression free survival (PFS) at 1 & 2 years was 89% & 69.7% respectively. By studying relations of different prognostic factors with OS on univariate level, statistically significant factors were CA-125 level, liver metastasis & occurrence of late complications (Table 3). OS for CA-125 levels <500 were 100% at 1 year & 96.2% at 2 years (p-value =0.001). Cases without liver metastasis, OS was 93.8% at 1year & 84% at 2 years (p-value=0.007). Finally, cases without late complications; OS was 100% at 1year & 79.9% at 2 years (p-value=0.004) (table 3).

After doing multivariate analysis to obviate effect of confounding & interaction between variables on univariate level, the only independent prognostic effect for OS was for CA125 & occurrence of late complications. For the CA-125 level, hazard ratio for levels >500 was nearly 11 times more than that <500, (p-value=0.021, CI [1.4-88.5]). For late complications, hazard ratio with late complications was nearly 4 times more than that without (p-value=0.034, CI [1.1-16.1]) (table 4).

Table 3 Overall survival & its relation to prognostic factors

Prognostic factors	No.	No. of events	Cumulative survival % at 12 months	Cumulative survival % at 24 months	p-value
Whole group	56	11	88.8	80.0	
PDS	19	6	77.0	71.1	0.119
IDS	37	5	94.4	83.9	0.119
Age (years)					
<55	28	3	92.3	88.1	0.096
>55	28	8	85.4	71.7	
Chronic liver disease					
Yes	5	2	60.0	60.0	0.224
No	51	9	91.7	81.9	
Radiological staging					
IIIB	41	8	87.4	81.8	0.854
IIIC	15	3	93.3	78.8	
CA-125 level					
<500 U/ml	30	1	100.0	96.2	0.001
>500 U/ml	26	10	75.4	62.2	
Ascites					
No	6	1	100.0	75.0	0.770
Yes	50	10	87.4	80.5	
PCI					
<8	33	14	93.8	86.8	0.198
>8	23	16	86.4	72.7	
Operative time (min)					
<150	37	7	88.7	79.2	0.941
>150	19	4	88.9	82.5	
Blood transfusion					
Yes	50	9	89.6	59.2	0.344
No	6	2	83.3	93.8	

Hospital stay (days) <6 >6	36 20	7 4	88.1 90.0	80.1 79.4	0.836
Liver metastasis Yes No	5 51	3 8	40.0 93.8	40.0 84.0	0.007
Pathological type Serous Non serous	42 14	8 3	92.6 78.6	80.4 78.6	0.863
Omental invasion Yes No	40 16	8 3	89.5 87.5	76.3 87.5	0.667
Peritoneal invasion Positive Negative	42 14	21 6	88.6 94.5	53.2 93.4	0.232
Lymph node status Positive Negative	2 54	0 11	100 88.4	100 79.2	0.638
Grade High Low	33 23	10 1	84.2 95.5	69.4 95.5	0.15
R status R0 R1 R2	37 6 13	5 1 5	94.1 83.2 76.9	87.6 83.3 60.6	0.225
CTH cycles <6 >6	6 31	1 4	83.3 97.7	83.3 97.7	0.824
Late Complications Yes No	20 36	8 3	70.0 100.0	80.4 79.9	0.004

Table 4 Multivariate analysis (cox regression hazard model) of OS

Independent prognostic factor	Beta coefficients	Standard Error	P-value	HR	95% CI for HR	Beta coefficients
					Lower	Upper
CA-125 level	2.420	1.052	0.021	11.246	1.430	88.445
Late complications	1.444	0.681	0.034	4.236	1.115	16.088

Again studying the relation of the same prognostic factors with PFS, the only significant variable was peritoneal invasion & occurrence of late complications. The cumulative PFS for cases without peritoneal invasion was 100% & 92.3% at 1 & 2 years respectively (p-value = 0.022) while cumulative PFS for cases without late complications was 100% & 78.9% at 1 & 2 years respectively (p-value=0.002). By multivariate analysis of PFS, the only independent prognostic effect again was occurrence of late complications where hazard ratio of cases suffered late complications was nearly 3 times those that did not (p-value = 0.004, CI [1.4-6.1]) (table 5 & 6).

Table 5 Progression free survival & its relation to prognostic factors

Prognostic factors	No.	No. of events	Median survival time (months)	Cumulative survival % at 12 months	Cumulative survival % at 24 months	p-value
Whole group PDS IDS	56 19 37	30 12 18	29.05 25.03 29.05	90.8 83.6 94.4	69.7 61.3 74.1	 0.444 0.444
Age (years) <55 >55	29 27	12 18	30.99 25.03	92.7 88.9	73.5 65.8	0.133
Chronic liver disease Yes No	5 51	5 25	29.97 29.05	80 91.8	80 68.5	0.510
Radiological Staging IIIB IIIC	41 15	20 10	29.05 29.97	89.5 93.8	67.4 75	0.951
CA-125 level <600 >600	30 26	13 17	29.97 26.02	100 80.1	74.5 64.1	0.350
Ascitis No Yes	6 50	2 27	25 29.97	100.0 89.8	66.7 68.6	0.321
PCI <8 >8	33 23	5 6	29.97 26.02	93.8 82.2	86.8 72.1	0.340
Operative time (min) <150 >150	36 20	20 11	29.05 29.97	91.2 90	69.5 70	0.976
Blood transfusion Yes No	50 6	28 2	29.05 NR	91.7 83.3	70 66.7	0.870
Hospital stay (days) <6 >6	36 20	18 12	29.97 26.02	91.3 90	73.1 63.8	0.280
Liver metastases Yes No	5 51	2 28	29.97 26.02	100 88.7	88.9 64.8	0.680
Pathological type Serous Non-serous	41 15	22 8	30.99 29.05	95 78.6	89.4 71.4	0.728
Omental invasion Yes No	39 17	8 3	24 6	92.2 87.5	67.2 75	0.189
Peritoneal invasion Positive Negative	42 14	27 3	25.3 29.97	87.9 100	62.1 92.3	0.022
Lymph node status Positive Negative	2 54	0 30	//// ////	100 90.4	100 68.5	0.631
Grade High Low	33 23	19 11	26.02 30.99	87.2 95.5	63.2 77.3	0.780
R status R0 R1 R2	37 6 13	16 3 11	29.97 24.01 25.03	94.3 84.6 83.3	83.4 70.2 61.5	0.363

CTH cycles <6 >6	 6 31	 3 21	 31.08 29.06	 92.5 76.7	 82.8 67.9	0.690
Late Complications Yes No	 20 36	 8 3	 24.0 30.1	 75.0 100	 53.8 78.9	0.002

Table 6 Multivariate analysis (cox regression hazard model) of PFS

Independent prognostic factor	Beta coefficients	Standard Error	P value	HR	95% CI for HR	
					Lower	Upper
late complication (Yes versus No)	1.076	0.370	0.004	2.934	1.421	6.057

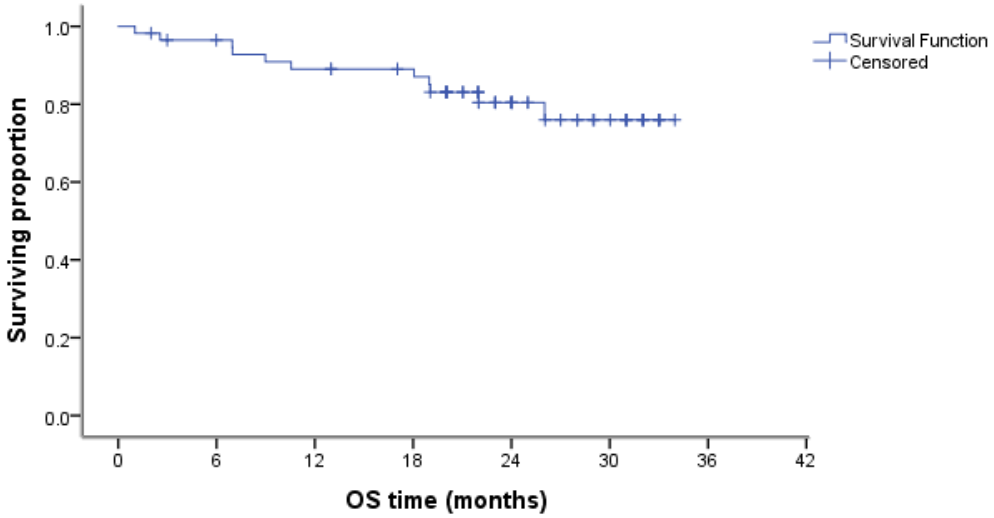

Figure 1 OS for the whole study

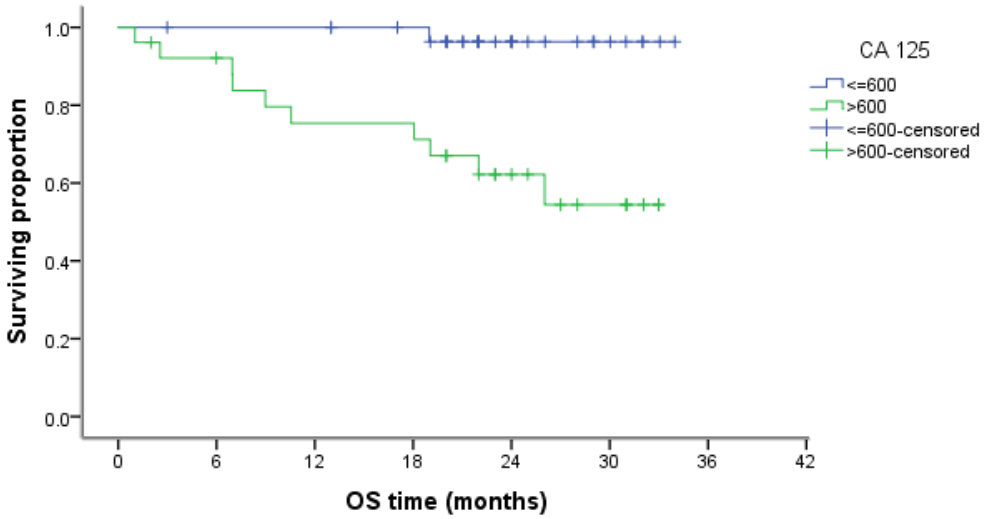

Figure 2 OS & its relation to CA125

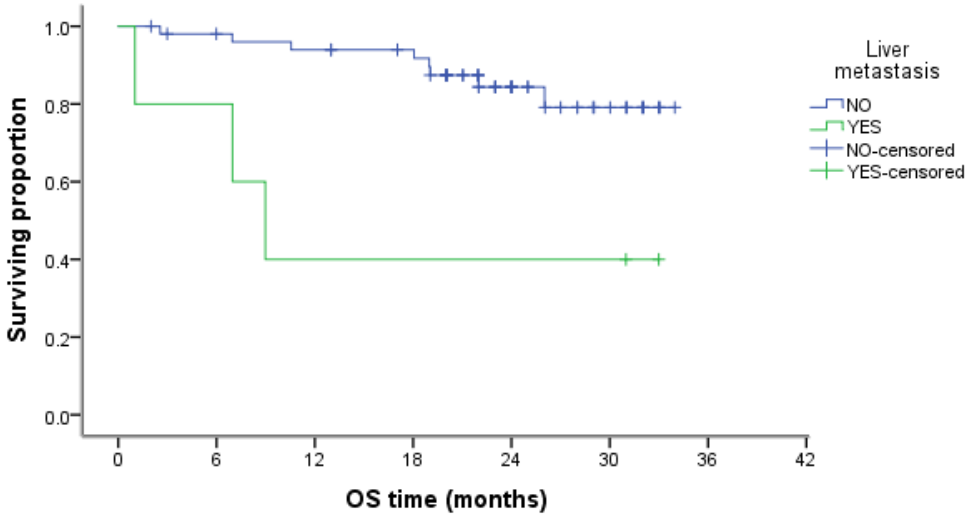

Figure 3 OS & its relation to liver metastasis

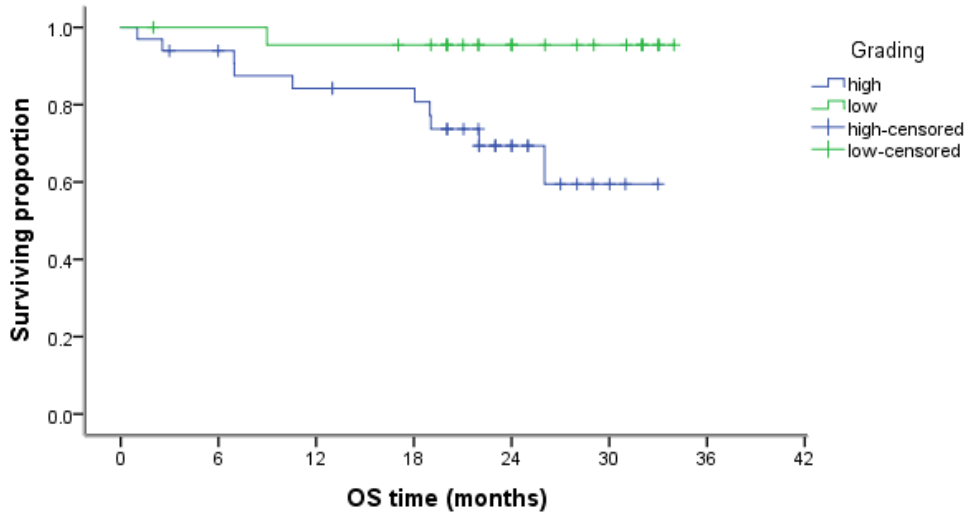

Figure 4 OS & its relation to grading

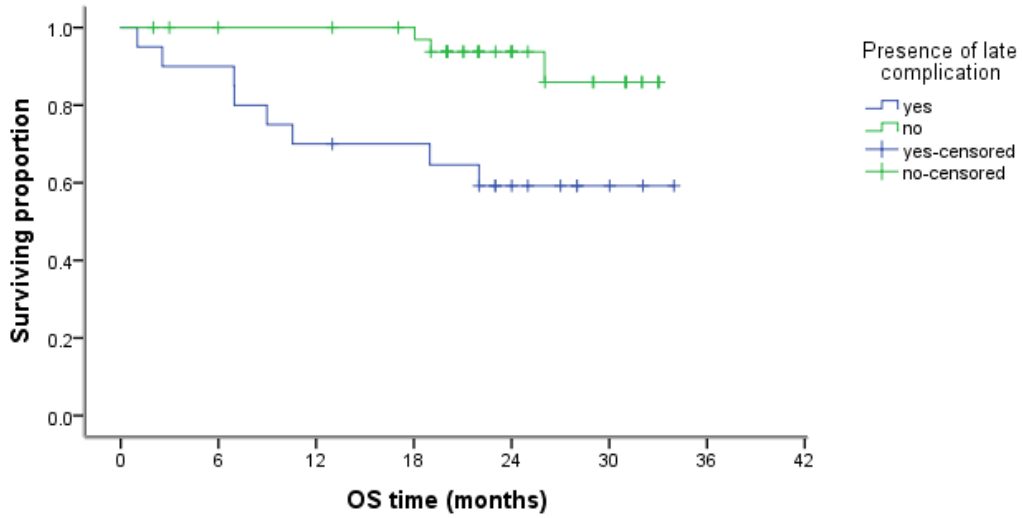

Figure 5 OS & its relation to presence of late complications

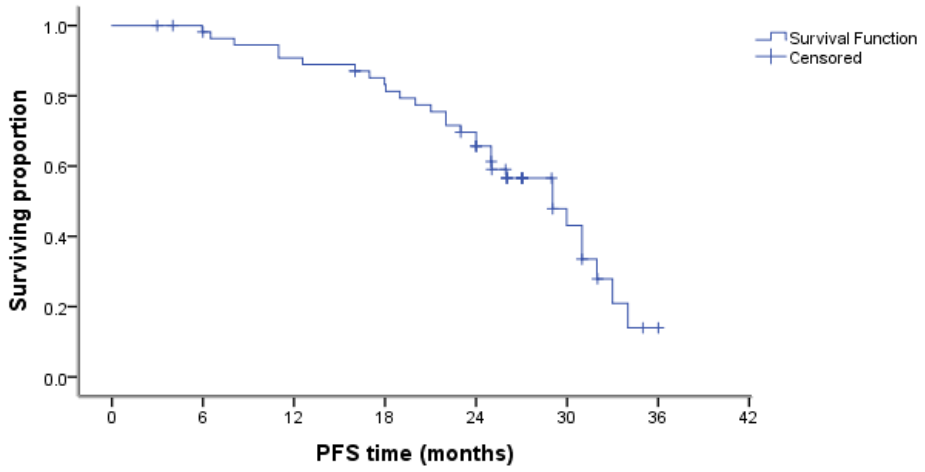

Figure 6 PFS for the whole study

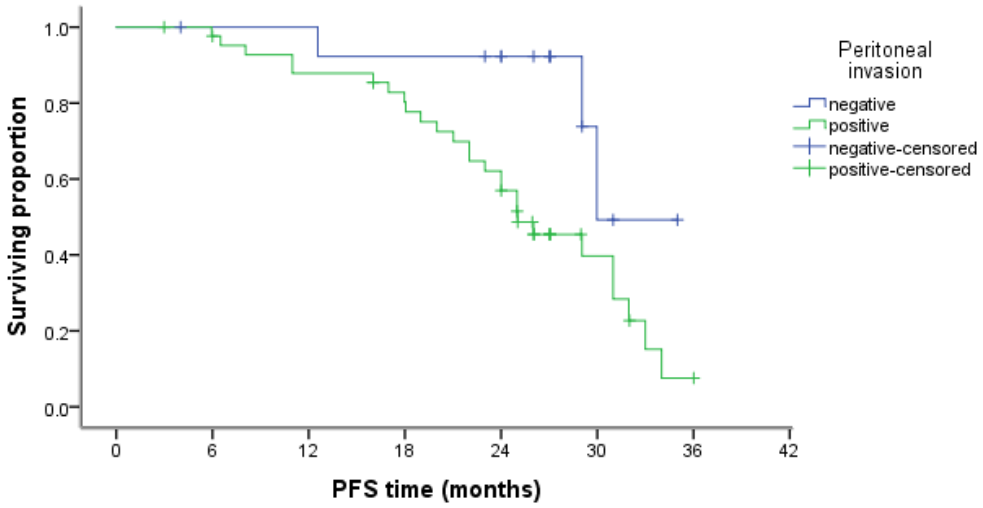

Figure 7 PFS & its relation to peritoneal invasion

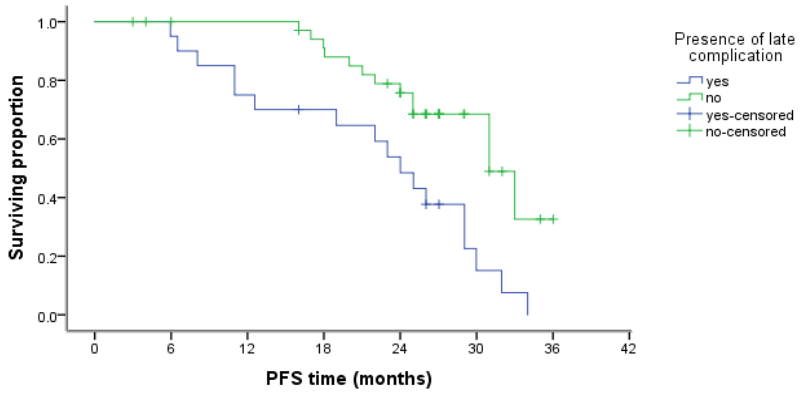

Figure 8 PFS & its relation to late complications

4. DISCUSSION

This study included patients with advanced stage epithelial ovarian cancer (stage III/IV) treated by either primary debulking surgery followed by adjuvant CTH or interval debulking surgery following neoadjuvant CTH. We found no statistically significant difference regarding survival between cases of PDS or IDS among OS (p-value=0.119) or PFS (p-value=0.444). This result was in line

with the 2 main trials comparing PDS & IDS. The EORTC 55971 trial included 718 cases with stage III/IV disease who were randomized to PDS or IDS. Results showed comparable OS between both treatments. The median OS for PDS was 30 months versus 29 months for IDS. Again the CHORUS randomized 550 cases to undergo PDS versus IDS. Results also showed no difference in OS between both arms with median OS of 22.6 months in PDS & 24.1 months for IDS (Vergote et al., 2010; Kehoe et al., 2015).

Previous studies discussed the prognostic value of age for EOC. Generally, young (<40y) ages show high incidence of borderline & well-differentiated tumors & optimally cytoreduced compared with ages >40 years (Duska et al., 1999; Thigpen et al., 1993). Analysis of 18,191 cases with EOC (2,560 cases aged 45 years) in the SEER Program demonstrated that 5 year OS for cases <45 years (45%) was better compared ages >85 years. Older women also face more risk of recurrence & death may be due to different tumor biology, immunity compromise, multiple comorbidities or hesitance & reluctance of oncologists treating older ages aggressively (Ries, 1993).

Our results showed that age didn't have a statistical significance on a univariate level. Despite this, the OS for <55years was better than >55 years at 1 & 2 years respectively (92.3% & 88.1% versus 85.4% & 71.7%; p-value=0.096). Similarly, PFS for <55years was better than >55 years at 1 & 2 years respectively (92.7% & 73.5% versus 88.9% & 65.8%; p-value=0.133). Younger ages <55 years predominated our work (31 cases, 55.4 %). Median age for the whole study was 55.5 years (range 20-86 years). The exact reason for this decade being younger than median age in other studies is unknown. It may reflect the demographic profile of Egyptian population with a relatively younger population than the West (Vergote et al., 2010; Kehoe et al., 2015; Ries, 1993).

Studies always described the relation between histology & prognosis. Non-serous histologies (mucinous & clear cell) are associated with worse OS & PFS compared with serous. Clear cell type is always referred to as the worst unfavorable EOC due to specific genomic expression pattern that differs clear cell from serous, suggesting different biologic phenotype. As a result of rarity of mucinous EOC, its molecular alterations detection is limited. However, its association with dismal prognosis suggests an aggressive biologic activity. Studies also suggest 7% of EOC are actually deposits from occult mucinous gastrointestinal primary. Despite this fact, no assessment of gastrointestinal tract prior to treatment was justified by any protocol. Recently, genomic markers assisted in distinguishing primary ovarian from primary colonic cancers (Dennis et al., 2001; Zorn et al., 2003).

In our cohort, serous histology predominated (42 cases, 75%). Although it was not associated with any statistical significance on univariate or multivariate levels, still OS analysis for serous histology was better than non-serous at 1 & 2 years respectively (92.6% & 80.4% versus 78.6% & 78.6%; p-value=0.863). Also, PFS for serous histology was better than non-serous at 1 & 2 years respectively (95% & 89.4% versus 78.6% & 71.4%; p-value=0.728). In our study CA125 level turned out to be a significant prognostic factor after multivariate analysis (p-value=0.001) with a cut off value of 500 U/mL. The hazard ratio for the group of patients more than 500 was nearly 11 times more than the hazard ratio for the group of patients with CA 125<=500 (p-value= 0.021,CI1.4 to 88.5).

Cooper et al., (2002) conducted a study where 78.8% of cases were stage III/IV divided into 5 groups according to preoperative CA-125 level. After multivariate analysis adjusting existing covariates, the joint effect of CA-125 level was statistically significant (p-value=0.03). Another work by Geisler et al., (1996) found that decreased survival was related to preoperative elevated CA-125 level as cases survived >5 years had mean CA-125 level of 899 U/mL (SD +/- 1.880 U/mL) while those survived <5 years had mean CA-125 level of 1.978 U/ml (SD +/- 1.852 U/mL). Other studies found no relation between CA-125 level & survival. Muallem et al., (2017) conducted a study that included 277 patients with serous EOC to investigate CA-125 level as predictor of outcome. Cut-off values of 252 & 475 U/ml were used for survival analysis (highest sensitivity & specificity) & cases divided into 3 groups (<252 U/ml), between (252-475 U/ml) & (>475 U/ml). No significant survival difference among PFS & OS appeared in any group.

Grading has always been a significant factor for early stages (I & II) EOC. However, with advanced stages it seems not related to poor outcomes. Most studies concluded that CRS is not affected by grade, besides; response to platinum-based regimens in the International Collaborative Ovarian Neoplasm Collaborators trial shows no relation with grading. Although our work showed high grades (grade III) to predominance (33 cases, 58.9%), it was not significant on univariate or multivariate levels. Yet OS analysis for high grades was worse than low grades at 1 & 2 years respectively (84.2% & 69.4% versus 95.5% & 95.5%; p-value = 0.15). Similarly, PFS for high grades was worse than low grades at 1 & 2 years respectively (87.2% & 63.2% versus 95.5% & 77.3%; p-value=0.728) (Vergote et al., 2001; ICON 3 group, 2002). Although 5 of our cases (8.9%) had parenchymatous liver deposits (stage VIB), they underwent PDS as these liver lesions were not apparent on preoperative imaging. By studying effects of liver deposits on univariate levels for OS & PFS. Only OS for cases without liver deposits were statistically significant & better than those with liver deposits at 1 & 2 years respectively (93.8% & 84% versus 40% & 40%; p-value = 0.007). These cases would have benefited from IDS if they were properly diagnosed as reported in an analysis by Van Meurs et al., (2013) of the results of The EORTC 55971 trial.

One of the possible staging tools for advanced EOC is laparoscopy. Fagotti et al., (2013) described a scoring system using staging laparoscopy to help identify patients with high tumor load and aid in the decision whether to undergo PDS or IDS. None of our cases was staged using laparoscopy. Prognostic effect on residual disease volume has been also highlighted in an analysis of

prospectively randomized multicenter trials that included a total of 3388 patients diagnosed with advanced stage epithelial ovarian cancer. Division of patients into 3 subgroups was made according to the extent of residual disease: Group A (complete resection), group B (residual disease ≤ 1cm) and group C (residual disease ≥ 1 cm). Multivariate analysis demonstrated that group A had a superior overall and progression free survival in comparison to groups B and C (p-value<0.001). Other studies also demonstrated that complete debulking was a significant factor for improved survival (Dennis et al., 2001; Omura et al., 1991; Andreas du bois et al., 2009).

In this cohort, most cases (37 cases, 66.1%) received R0 resection successfully (complete CRS with no gross or microscopic residuals). Although R0 resection compared to R1 (microscopic residual) or R2 (gross residual <1cm) was not significant on univariate or multivariate levels, still OS for R0 resections was better than R1& R2 resections at 1 & 2 years respectively (94.1% & 87.6% versus 83.2% & 83.3% versus 76.9% & 60.6%; p-value=0.15). Similarly, PFS for R0 resections was better than R1 & R2 resections at 1 & 2 years respectively (94.3% & 83.4% versus 84.6% & 70.2% versus 83.3% & 61.5%; p-value=0.363). Extent of CRS was always considered as the most important factor affecting outcome in advanced EOC.

Ghisoni et al., (2018) reported that PCI score >16 was associated with non-complete response & poor outcome than PCI <16. Other work including 246 cases with advanced EOC demonstrated that completeness of CRS had significant impact over OS & PFS in cases with limited peritoneal carcinomatosis (PCI <10) while it had no impact on either OS or DFS with extensive peritoneal carcinomatosis (PCI >10). This was higher than our cut-off (PCI >8) in this cohort where PCI >8 increased risk of non-complete response. Our results showed cases with PCI <8 predominating (33 cases, 58.95). Although PCI didn't significantly affect OS & DFS yet our analysis showed PCI <8 were having better OS results than PCI >8 at 1 & 2 years respectively (93.8% & 86.8% versus 86.4% & 72.7%; p-value=0.198). Also, PCI <8 were associated with better PFS than PCI >8 at 1 & 2 years respectively (93.8% & 86.8% versus 82.2% & 72.1%; p-value=0.340) (Bakrin et al., 2012; Dennis et al., 2009).

This non-significant correlation between PCI & survival might be explained by the fact that PCI is less objective depending on assessment of operating surgeons making it more subjective in assessment of peritoneal disease extension. Moreover, PCI depends on size of peritoneal nodules & number of affected abdomino-pelvic regions rather than which region is affected (for example affection of small intestine & its mesentery is worse & had lower respectability potentiality than anterior abdominal wall or pelvic peritoneum affection). This makes PCI inaccurate in prediction of CRS (that depend mainly on location of peritoneal disease rather than number of affected regions or peritoneal nodules size), surgical extent & postoperative morbidity & mortality. Regarding completeness of CRS, extensive upper abdominal procedures resulted in increased optimal CRS rates & significantly improved PFS & OS (Ghisoni et al., 2018; Dennis et al., 2009).

For lymphadenectomy, no evidence exists regarding the role of complete pelvic & para-aortic lymphadenectomy in advanced EOC apart from complete CRS of clinically suspicious nodes. Management of clinically suspicious nodes worldwide is very heterogeneous. LION trial is a phase III randomized controlled trial which included 657 cases with EOC staged IIB to IV who had undergone complete CRS & had pre & intraoperative negative nodes. Authors concluded that pelvic & paraaortic lymphadenectomy of clinically negative nodes with complete CRS neither improved OS nor PFS despite detecting & removing silent nodal metastases in 56% of cases. In our work, lymphadenectomy was done in (14 cases, 25%) found suspicious intraoperatively & removed as a part of complete CRS. 6 cases (10.7%) from PDS group had 2 positive cases (3.6%) & 8 cases (14.3%) from IDS group with none were positive. No significant correlation found between nodal sampling & outcome (Harter et al., 2017).

5. CONCLUSION

Although our study was prospective with accurate data collection, yet we acknowledge the presence of limitations to our study, mainly the relatively small sample size and short follow up period. After analysis of 20 clinico-pathological variables to identify their prognostic effect on survival in locally advanced epithelial ovarian cancer. On multivariate analyses, CA125 level was a significant prognostic factor for OS, peritoneal invasion was a significant prognostic factor for PFS. Late complications were a significant prognostic factor for both OS and PFS.

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Author Contributions

Ahmed El-sayed Fathalla designed the study. Sayed Shaker Sheier And Hala Aziz Shokralla recruited patients and collected clinical data. Tamer M. Manie drafted the manuscript. Ahmed El-sayed Fathalla revised the manuscript. All authors read and approved the final manuscript.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Ethical Approval

This work was approved by the Medical Ethical Committee (Institutional Review Board-IRB) of the National Cancer Institute-Cairo University. IRB No: IRB00004025, FWA No: FWA00007284, Organization No: IORG0003381. Consent to participate was signed by the patients before surgery.

Conflicts of interest

The authors declare that they have no conflict of interest.

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Data and materials availability

All data associated with this study are present in the paper.

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