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### Conflict of Interest

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

### Author Contributions

Conceptualization: E.A.A., S.W., M.H., M.M., M.E., S.A.A.; Formal analysis: E.D.; Funding acquisition: M.H., M.E., S.A.A.; Investigation: E.A.A., S.W., M.H., M.M., M.E., S.A.A.; Methodology: E.A.A., M.E., S.A.A.; Project administration: M.H., M.E., S.A.A.; Resources: M.H., M.E., S.A.A.; Software: E.D.; Supervision: M.H., M.E., S.A.A.; Validation: S.W., E.D.; Visualization: E.A.A., S.W., E.D., M.H., M.M.; Writing - original draft: E.A.A., S.A.A.; Writing - review & editing: E.A.A., S.W., E.D., M.H., M.M., M.E., S.A.A.

## INTRODUCTION

Epithelial ovarian cancer (EOC) is the gynecological malignancy with the highest mortality rate [1]. This may be attributed to the fact that EOC usually presents at an advanced disease stage [2]; the 5-year-survival rate for patients in stage III is reported to be 35% while in stage IV this is as low as 22% [3]. Adequate surgical cytoreduction is the most important independent factor affecting survival in EOC [4-8]. Complete tumor removal should be the aim of any primary operative treatment of EOC.

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EOC with extensive intra-peritoneal tumor growth represents a surgical challenge for the gynecological oncologist. The extent of cytoreductive surgery should be limited to standard procedures (hysterectomy, bilateral salpingo-oophorectomy, rectosigmoid resection, infragastric omentectomy, pelvic and aortic lymphadenectomy and, when applicable, appendectomy) omitting extensive radical surgical resections (multiple digestive tract resections, total abdominal peritoneum stripping, coeliac lymph node dissection, and abdominal organ resections for example splenectomy, partial gastrectomy, and liver resection) when a complete surgical cytoreduction is not attainable, as advocated by Vidal et al. [16].

It is however worth mentioning that the context of the use of PCI as a prognostic factor while dealing with colorectal and gastric cancers is different from EOC where the application of hyperthermic intraperitoneal chemotherapy (HIPEC), following complete cytoreduction including total abdominal peritoneum stripping, is an integral part of treating colorectal and gastric cancers [10-13] in contrary to the case in EOC where HIPEC is still an experimental procedure that should not be applied outside clinical trials [17,18]. This difference in the management strategy may affect the significance of PCI to play a prognostic role in EOC.

This study aimed to examine the PCI score in advanced EOC, correlating it to completeness of surgical cytoreduction, to the clinical outcome of the disease and validating a cut-off value that might have an influence on prognosis in analogy to colorectal and gastric cancers.

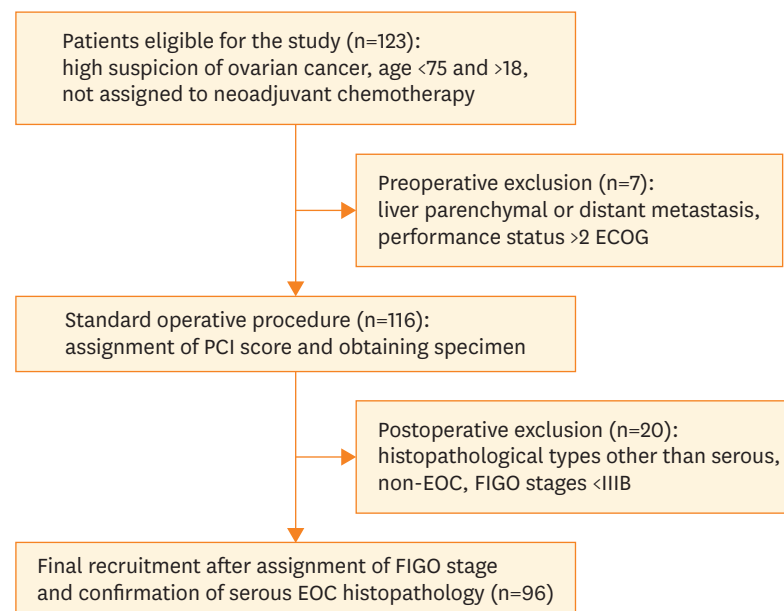
## MATERIALS AND METHODS

## 1. Ethical considerations

This was a prospective, observational cohort study that was conducted at El-Shatby Women's University Hospital, University of Alexandria, Egypt. The study was approved by the Ethics Committee, Faculty of Medicine, University of Alexandria (approval number: 160/2010). All

## 2. Patient population, assessments, and treatment

All patients underwent the standard institutional therapy for ovarian cancer, namely primary surgical cytoreduction, which involved explorative laparotomy, abdominal hysterectomy with bilateral salpingo-oophorectomy omentectomy, peritoneal sampling and eventually stripping if needed, systematic pelvic and para-aortic lymphadenectomy and bowel resection, as recommended by the German Workgroup for Gynecological Oncology (AGO) [20]. Lymphadenectomy and bowel resections were exclusively reserved for patients in whom a



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	Regions	LS score	LS
0	Central	LS 0	No tumor seen
1	Right upper	LS 1	Tumor up to 0.5 cm
2	Epigastrium	LS 2	Tumor up to 5 cm
3	Left upper	LS 3	Tumor bigger than 5 cm or confluence
4	Left flank		
5	Left lower		
6	Pelvis		
7	Right lower		
8	Right flank		
9	Upper jejunum		
10	Lower jejunum		
11	Upper ileum		
12	Lower ileum		
	PCI		

**Fig. 2.** Score sheet for calculating PCI score [9].  
LS, lesion size; PCI, peritoneal cancer index.

complete surgical cytoreduction seemed attainable. The PCI was obtained and registered intraoperatively (**Fig. 2**). Complete surgical cytoreduction is defined as complete removal of all tumor tissue without any macroscopic residues and is assigned R0. Optimal cytoreduction is defined as incomplete removal of all tumor tissues leaving microscopic or macroscopic tumor residues that are smaller than 1 cm in maximal diameter and assigned R1, while suboptimal cytoreduction is defined as leaving tumor residues larger than 1 cm in maximal diameter and assigned R2. This is based on the final histopathology report. Finding microscopic tumor residues at the resection edge was assigned as R1. Postoperatively, all patients received 6 chemotherapy cycles that comprised a combination of paclitaxel (175 mg/m<sup>2</sup> body surface area) and carboplatin (area under the curve [AUC]=5/6), both of which were administered intravenously every 3 weeks as standard adjuvant therapy as recommended by the AGO [20]. The treatment was considered complete after the chemotherapy had finished. A CT scan was performed at completion of chemotherapy in all patients. All patients were followed up for 24 months after chemotherapy completion. The follow-up was in the form of quarterly visits, in which general and gynecological clinical examinations, a transvaginal to detect local recurrences in the pelvis and an abdominal ultrasound to monitor ascites were performed. At clinical suspicion or suggestive symptoms, a CT scan was performed, and compared to the final CT findings at completion of chemotherapy, in order to confirm or exclude a recurrence. This was performed according to recommendations by leading bodies [20]. Patients lost to follow-up were excluded from the statistical analysis. The survival data were registered.

### 3. Statistical analyses

The data were tabulated using Microsoft Excel (Microsoft Corporation, Redmond, WA, USA) and analyzed using IBM® SPSS® for Windows, version 21.0 (IBM Corporation, Armonk, NY, USA). The normality of the data was tested using the one-sample Kolmogorov-Smirnov test. The  $\chi^2$  test was used to test the associations between categorical variables. Different cut-off points were tested by receiver operator characteristic (ROC) curves to determine the most meaningful cut-off point. Significant variables entered into Logistic regression model using the Forward Wald statistical technique to predict the most significant determinants and to control for possible interactions and confounding effects. The Kaplan-Meier test was used for the survival analysis, and the statistical significance of the differences between the curves was assessed using





for patients with PCI >13 this was 5.6 months (95% CI=2.8–8.3);  $p \leq 0.001$ . The median OS for patients with PCI  $\leq 13$  was 22.2 months (95% CI=21.2–23.1) while for patients with PCI >13 was 17.9 months (95% CI=14.9–20.8;  $p=0.004$ ).

A univariate logistic regression analysis of the factors associated with recurrence in this cohort showed that a PCI score above 13 (odds ratio [OR]=9.104; 95% CI=2.502–33.132;  $p \leq 0.001$ ), suboptimal surgical cytoreduction (OR=16.361; 95% CI=4.501–59.470;  $p \leq 0.001$ ), and advanced FIGO stage, namely FIGO IIIC and IVA (OR=5.750; 95% CI=2.287–14.456;  $p \leq 0.001$ ), had statistically significant impacts on the probability of recurrence. A multivariate analysis determined that, of the factors that had a significant impact on recurrence in the univariate analysis, suboptimal surgical cytoreduction was the only independent predictive factor for recurrence in this cohort (OR=7.548; 95% CI=1.473–38.675;  $p=0.015$ ).

A univariate logistic regression analysis of the factors that can possibly be associated with death in this cohort, namely PCI score >13, suboptimal surgical cytoreduction, FIGO stage and tumor grading showed that suboptimal surgical cytoreduction (hazard ratio [HR]=2.24; 95% CI=1.23–4.09;  $p=0.005$ ), and PCI score >13 (HR=2.18; 95% CI=1.22–3.89;  $p=0.012$ ) were the factors that had a statistically significant impact on OS. A multivariate analysis determined that only suboptimal surgical cytoreduction (HR=2.33; 95% CI=0.616–8.795;  $p=0.005$ ), but not PCI score >13 (HR=1.289; 95% CI=0.329–5.046;  $p=0.716$ ), was an independent predictive factor of survival.

## DISCUSSION

Predictors of survival in EOC have not changed much in the last few decades despite expanding knowledge about the disease. A complete surgical cytoreduction with removal of all macroscopic detectable tumor tissue remains the most important independent risk factor predicting survival. PCI was thought to be a possible predictor of survival, in analogy to gastric and colorectal cancers. In a recent report on a retrospective cohort, Gasimli and co-workers [21] concluded that PCI is not adequate as an independent predictor of survival, although their data found a significant impact on DFS in the multivariate analysis. In another recent report, PCI was concluded to be a reliable predictor of the completeness of surgical cytoreduction. Its ability to predict survival was not, however, reported in this study [22].

Complete surgical cytoreduction may not be attainable in advanced EOC cases. A possible option for such patients may be neoadjuvant chemotherapy followed by interval debulking, which was proved non-inferior to primary debulking surgery in randomized controlled trials [23,24]. Moreover, a work group from Leuven University suggested selection criteria according to which neoadjuvant chemotherapy and interval debulking are offered to the patients. These criteria are poor general condition of the patient, tumors larger than 2 cm around the superior mesenteric artery or behind porta hepatis, multiple liver metastasis or extra abdominal metastasis, extensive serosal invasion of the intestine necessitating a resection of more than 1.5 m of bowel length and patients who cannot receive a complete surgical cytoreduction under reasonable conditions (more than 1 bowel resection, operative time more than 4 hours) [25].

In analogy to colorectal and gastric cancer and based on the findings that chemotherapeutic agents administered intraperitoneally at high temperatures have more cytotoxic effect [26,27], some authors reported a role for HIPEC combined with complete surgical

cytoreduction after extensive surgical procedures in providing patients with primary and recurrent EOC an improvement in overall and in DFS in comparison with the standard of care namely primary surgical cytoreduction followed by adjuvant systemic chemotherapy [28-31]. The available data regards this therapeutic modality is heterogenous and cannot offer solid ground to consider HIPEC as a standard treatment option for EOC patients [17,32].

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The PCI score may help predicting complete surgical cytoreduction as seen in published data [22], these needs, however, to be further assessed in larger prospective studies. Possible drawbacks of this study are the fact that 34.4% of the patients were FIGO stage IIIB and that in 64.6% of the patients a complete surgical cytoreduction was possible. Moreover, the maximum PCI score in our cohort was only 19, whereas the absolute maximum PCI score is 39. This could raise claims that this cohort included patients with EOC that was not very advanced, representing a selection bias. This bias is due to the inclusion of patients with FIGO stage IIIB that is postoperatively assigned that have been probably intraoperatively assigned as FIGO stage II leading to recruiting cases that are not advanced enough leading to a low PCI score in this cohort. The PCI score was determined intraoperatively while the FIGO stage was assigned postoperatively.

We conclude from this study that the PCI score is a reliable tool helping to assess the extent of disease intraoperatively in advanced serous EOC patients. PCI score may also help predict complete surgical cytoreduction, however, a PCI cut-off score that has prognostic significance could not be extrapolated from this cohort. The findings of this study should be further validated in prospective studies including a larger cohort of patients with longer follow-up periods.

## REFERENCES

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