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Feasibility of Complete Cytoreduction in Advanced Epithelial Ovarian Cancer

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Abstract

Objective: Complete resectability of all visualized tumor implants at debulking surgery for advanced epithelial ovarian cancer is confirmed to be the single most important prognostic factor. This study aims to develop preoperative predicting score based on clinical, biological, and radiological criteria of epithelial ovarian cancer to assess the feasibility of complete cytoreduction. **Study Design:** A retrospective record-based study. **Patients and Methods:** The study was conducted upon 50 consecutive patients managed for epithelial ovarian cancer with FIGO stage III. Patients' data were collected from records of the Gyne-Oncology Clinic of El Shatby University Maternity Hospital affiliated to Alexandria University. **Results:** Many parameters were significantly associated with completeness of resectability in univariate analysis; including age, BMI, CA125, albumin, pre-albumin, PCI, mesenteric, and right copula of diaphragm affection by CT scan (p value < 0.05). A 100-point predictability score was developed, 10 for BMI ≥ 35 kg/m^2, 25 points for Pre albumin < 14.5 mg/dl, 35 points for mesenteric affection, and 30 points for affection of Rt. copula of diaphragm. The overall accuracy of the score was 92%. **Conclusion:** In advanced ovarian cancer, pre-operative predicting score (including clinical, biological, and radiological criteria) can be used as a roadmap for prediction of feasibility of complete resectability. However, more research is needed on larger sample sizes.

Keywords

Cytoreduction, Ovarian Carcinoma, Predictive Score

1. Introduction

Almost two-thirds of ovarian cancer patients at diagnosis are of advanced stage [1] [2]. The standard treatment for epithelial ovarian cancer includes cytoreduc-

tive surgery in addition to chemotherapy [3] [4].

The size of the residual tumor tissue is considered to be the major prognostic factor in patients with advanced epithelial ovarian cancer. The purpose of cytoreductive surgery is to achieve complete cytoreduction which is defined as resection and removal of all macroscopic tumor implants upon completion of the surgery (CC0). Complete cytoreduction is considered to have a dramatic overall benefit as well as progression free survival benefit [4]-[9].

Therefore, it is essential in the management of ovarian cancer to identify surgically resectable cases and those who will benefit from primary complete cytoreductive surgery and other unresectable cases for whom primary complete resection is unattainable and better to be referred first for receiving neoadjuvant chemotherapy. Hence, predicting the resectability of advanced epithelial ovarian neoplastic cases to reach complete cytoreduction is of utmost seriousness and paramount.

Laparoscopic assessment using Fagotti and Fagotti-modified laparoscopic scores is considered to be the most common technique to evaluate tumor spread and resectability [10] [11] [12] [13]. Yet, laparoscopic assessment, still, has some restrictions and might undervalue the degree of intraperitoneal spread of the disease in some cases [14] [15].

The goal of this study was to assess the feasibility of complete cytoreduction in advanced epithelial ovarian cancer, and to develop preoperative predicting score for the degree of resectability of all macroscopic peritoneal tumor implants based on clinical, biological, and radiological criteria of epithelial ovarian malignancy.

2. Patients and Methods

A retrospective record-based study was conducted upon patients managed for epithelial ovarian cancer at El Shatby Main University Maternity Hospital. Data were collected from all records of the Gyne-Oncology Clinic of the hospital (duration from January 2016 to June 2018). The study was approved by Faculty of Medicine Alexandria University Ethics Committee.

All records retrieved summed up to a sample size of 50 patients with FIGO stage III epithelial ovarian cancer. Only data collected on the preliminary assessment of the extent of the disease was used. This included clinically, biologically, radiologically and the operative data retrieved from the initial cytoreductive surgery.

The sample excluded patients with non-epithelial or borderline ovarian cancer, patients who received neoadjuvant chemotherapy, those with recurrent ovarian cancer, and those who did not have primary exploratory surgery. Also, patients with incomplete data were excluded from the study.

The diagnostic gold standard used to validate the resectability of peritoneal carcinomatosis was surgical Medline exploratory laparotomy for evaluation of the feasibility of complete cytoreductive surgery and resection of all macroscopic

intraperitoneal tumor implants.

Patients were classified as "resectable" when primary cytoreductive surgery was complete (CC0) with complete removal of all macroscopic tumor implants by median laparotomy. Patients who experienced incomplete cytoreductive surgery were classified as "Unresectable" where the final residual tumor was more than CC0 due to the extent of peritoneal carcinomatosis or comorbidities of the patient.

Statistical analysis

Data entry and statistical analysis were performed using statistical package for social science (SPSS version 20.0). Patients were compared in two groups "resectable" and "unresectable". Qualitative variables were described using frequency and percent while quantitative variables were described using mean and standard deviation for normally distributed variables while median and (minimum-maximum) were used for skewed data. For univariate analysis, chi-squared test was used for categorical variables (Fisher Exact Test and Monte Carlo Test were used when the sample was too small). However, for normally distributed data, comparison between two independent population means was done using independent t-test while more than two population means were compared using F-test (ANOVA). As to skewed data, comparison was done using Mann Whitney test. Significance test results were quoted as two-tailed probabilities. Significance of the obtained results was judged at the 5% level.

Variables significantly associated with incomplete cytoreduction were dichotomized on either side of the best cutoffs identified by receiver-operating characteristic (ROC) curves (Figure 1). Multiple logistic regression cannot be done,

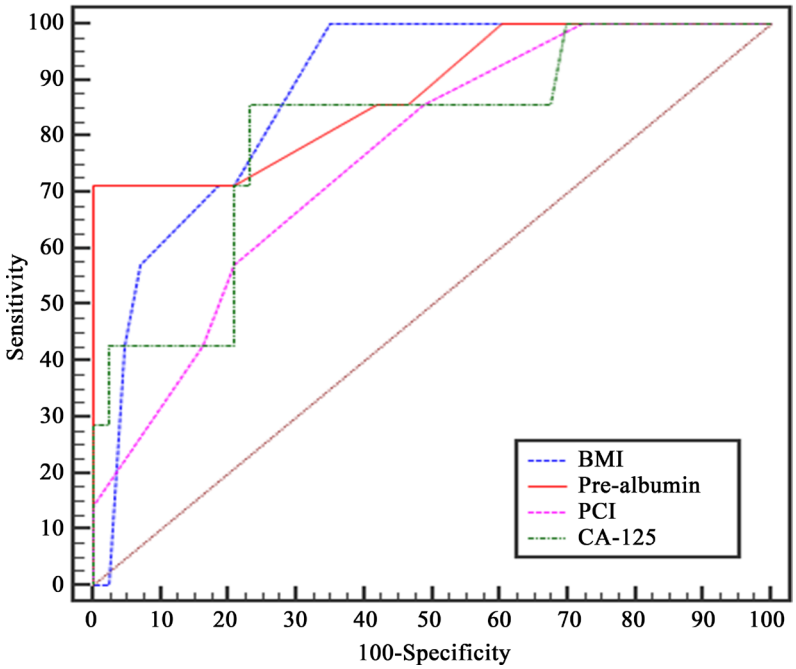

Figure 1. ROC curve for different parameters to predict unresectable versus resectable cases.

because the "unresectable" group included only 7 cases. Multivariate linear regression analysis of significant independent variables was used to predict a pre-operative resectability score. Values of standaradized coefficients (Beta) of the significant variables were used to assign the weights for each variable used in the predictability score. The sum of the 4 coefficients was transformed into a 100 point score and each variable weighed according to the value of its standardized coefficient (Beta).

3. Results

Complete cytoreduction was achieved in 43 cases (86%), whereas 7 cases (14%) had non-complete surgery.

Comparison between the two groups (Table 1) showed that there was no statistically significant difference between the two studied groups concerning the pathological type (Table 1). However, univariate analysis showed that other parameters were significantly associated with completeness of resectability. Those factors included age, BMI, CA125, albumin, pre-albumin, peritoneal carcinomatosis index (PCI), mesenteric, and right copula of diaphragm affection by CT scan (p value < 0.05). Using the results of the univariate analysis, a scoring system was developed for the unresectable group and was used to construct a linear regression analysis model to detect the predictability of incomplete cytoreduction. Affection of small bowel mesentery and the right copula of diaphragm, prealbumin level, and BMI were the most significant predictors of incomplete resectability (Table 2 & Table 3).

A 100-point predictability score was developed for prediction of non-complete cytoreduction. This score was based on four criteria that were independently associated with incomplete cytoreduction those include; one clinical; BMI ≥35 kg/m^2 (10 points), one biological; pre-albumin value < 14.5 mg/dl (25 points), and two radiological; small bowel mesenteric affection (35 points), and right copula of diaphragm affection (30 points). The overall accuracy of the score was 92% (Table 4).

4. Discussion

The current study developed a score for prediction of the feasibility of complete cytoreductive surgery. The score was based on four criteria; BMI ≥ 35 kg/m^2, pre-albumin value < 14.5 mg/dl, affection of the small bowel mesentery and affection of the right copula of the diaphragm.

In the current work, obesity with increased BMI > 35 kg/m^2 as a clinical parameter was associated with significant high prediction of unresectability with 42.86% sensitivity, 95.35% specificity, 60.0% PPV, 91.11% NPV and 87% AUC. These results were in accordance with Chesnais *et al.* study who concluded that BMI > 30 kg/m^2 was also associated with high risk of incomplete cytoreduction [16]. That might be due to the surgical difficulties that could face the surgeon during retroperitoneal dissection and adequate removal of all macroscopic lesions.

Table 1. Comparison between the two studied groups according to different parameters.

	Total (n = 50) No. (%)	Resectable group (n = 43) No. (%)	Unresectable group (n = 7) No. (%)	Test of sig.	p
Age (years)	51.9 ± 9.7	53 ± 9.7	45.1 ± 7.1	t = 2.037*	0.047*
≤60	40 (80%)	33 (76.7%)	7 (100%)	χ^2 = 2.035	0.154
>60	10 (20.0%)	10 (23.3%)	0 (0%)		
KPS (%)	79.6 ± 7.6	80 ± 7.6	77.1 ± 7.6	t = 0.927	0.358
Previous surgery					
Free	21 (42%)	19 (44.2%)	2 (28.6%)		
GYN	14 (28%)	12 (27.9%)	2 (28.6%)	χ^2 = 0.961	^{MC}p = 0.784
Non GYN	15 (30%)	12 (27.9%)	3 (42.9%)		
BMI (kg/m^2)	31.1 ± 3.1	30.6 ± 3	34.4 ± 1.8	t = 4.671*	0.001*
<35	44 (88%)	41 (95.3%)	3 (42.9%)	χ^2 = 0.961	^{MC}p = 0.002*
≥35	6 (12%)	2 (4.7%)	4 (57.1%)		
CA-125 (IU/ml)	242.5 (14.9 - 2250)	190 (14.9 - 1900)	800 (90 - 2250)	U = 58.50*	0.010*
Albumin (mg/dl)	3.2 ± 0.3	3.3 ± 0.3	3 ± 0.4	t = 2.827*	0.007*
Pre-albumin (mg/dl)	16 ± 1.5	16.3 ± 1.2	14 ± 1.5	t = 3.709*	0.007*
Ascetic fluid amount					
No	9 (18%)	7 (16.3%)	2 (28.6%)		
Mild	12 (24%)	11 (25.6%)	1 (14.3%)	χ^2 = 4.058	^{MC}p = 0.208
Moderate	19 (38)	18 (41.9%)	1 (14.3%)		
Severe	10 (20%)	7 (16.3%)	3 (42.9%)		
PCI	15.5 ± 1.9	15.3 ± 1.8	17.1 ± 1.7	t = 2.524*	0.015*
Pathological type					
Serous	37 (74%)	31 (72.1%)	6 (85.7%)	χ^2 = 0.581	^{FE}p = 0.660
Mucinous	5 (10%)	5 (11.6%)	0 (0%)	χ^2 = 0.904	^{FE}p = 1.000
Endometriosis	4 (8%)	3 (7%)	1 (14.3%)	χ^2 = 0.437	^{FE}p = 0.464
Brenner	1 (2%)	1 (2.3%)	0 (0%)	χ^2 = 0.166	^{FE}p = 1.000
Clear cell carcinoma	2 (4%)	2 (4.7%)	0 (0%)	χ^2 = 0.339	^{FE}p = 1.000
Serous + Mucineous	1 (2%)	1 (2.3%)	0 (0%)	χ^2 = 0.166	^{FE}p = 1.000
Grade					
I	5 (10%)	4 (9.3%)	1 (14.3%)		
II	14 (28%)	14 (32.6%)	0 (0%)	χ^2 = 3.389	^{MC}p = 0.150
III	31 (62%)	25 (58.1%)	6 (85.7%)		
Porta hepatis	1 (2%)	0 (0%)	1 (14.3%)	χ^2 = 1.098	^{FE}p = 0.140
Right copula of diaphragm	3 (6%)	0 (0%)	3 (42.9%)	χ^2 = 13.136*	^{FE}p = 0.002*
S.B. mesenteric metastasis	3 (6%)	0 (0%)	3 (42.9%)	χ^2 = 13.136*	^{FE}p = 0.002*
L.N	22 (44%)	18 (41.9 %)	4 (57.1%)	χ^2 = 0.566	^{FE}p = 0.362
Omental cakes	44 (88%)	38 (88.4%)	6 (85.7%)	χ^2 = 0.04	^{FE}p = 0.84

χ^2: Chi square test; FET: Fisher Exact test; MC: Monte Carlo; t: Student t-test. U: Mann Whitney test; p: p value for comparing between the studied groups; *: Statistical significance at p ≤ 0.05; PCI: Peritoneal carcinomatosis index; L.N.: Lymph nodes; K.P.S: Karnofsky performance score; S.B. Mesentery metastasis: Small bowel mesenteric metastasis.

Table 2. Agreement (sensitivity, specificity) for different parameters to predict unresectable versus resectable cases.

	AUC	p	95% C.I	Cut off	Sensitivity	Specificity	PPV	NPV
BMI	0.879*	0.001*	0.772 - 0.985	>35	42.86	95.35	60.0	91.11
CA-125	0.806*	0.010*	0.626 - 0.985	>550	71.43	76.74	33.3	94.3
Pre-albumin	0.879*	0.001*	0.722 - 1.035	<14.5#	71.43	100.0	100.0	95.6
PCI	0.764*	0.026*	0.592 - 0.936	>16	57.14	79.07	30.8	91.9

#: Cut off for Youden; AUC: Area under the curve; p value: Probability value; CI: Confidence Intervals; NPV: Negative predictive value; PPV: Positive predictive value; BMI: body mass index; PCI: peritoneal carcinomatosis index; *: Statistically significant at $p \leq 0.05$.

Table 3. Univariate and multivariate linear analysis for the parameters affecting (unresectable) group.

	Univariate		#Multivariate	
	B(95%C.I)	p	B (95%C.I)	p
CA125 (>550)	0.346* (0.154 - 0.537)	0.001*	0.028 (-0.051 - 0.106)	0.480
Pre albumin (≤14.5)	0.956* (0.766 - 1.145)	<0.001*	0.470* (0.309 - 0.632)	<0.001*
Diaphragm	0.915* (0.584 - 1.245)	<0.001*	0.598* (0.385 - 0.812)	<0.001*
S.B mesentry	0.915* (0.584 - 1.245)	<0.001*	0.617* (0.438 - 0.796)	<0.001*
BMI (>35)	0.511* (0.210 - 0.812)	0.001*	0.139* (0.007 - 0.270)	0.040*
PCI (>16)	0.227* (0.007 - 0.447)	0.044*	−0.027 (−0.107 - 0.053)	0.502
		$R^2 = 0.917$		

Beta: Standardized Coefficients; C.I: Confidence interval; #: All variables with $p < 0.05$ was included in the multivariate; *: Statistically significant at $p \leq 0.05$.

Table 4. Preoperative score for prediction the feasibility of complete cytoreduction.

Variables	Cut off value	Point
BMI	>35 kg/m^2	10.0
Pre albumin	<14.5 mg/dl	25.0
Rt. Copula of diaphragm	+/−	30.0
small bowel mesentery	+/−	35.0

Regarding the biological biomarkers for prediction of resectability, the current study found that in multivariate analysis pre-albumin with cutoff point ≤ 14 mg/dl came former as a biological predictor of resectability than CA125, with sensitivity 71.43%, specificity 100%, PPV 100%, NPV 95.6%, and AUC 87.9%. Geisler *et al.* also concluded that extremely malnourished ovarian cancer patients (prealbumin < 10 mg/dl) may be better managed by neoadjuvant chemotherapy with interval cytoreductive surgery if nutrition improves [17]. Memarzadeh *et al.* concluded that CA125 value was a weak positive and negative predictor of complete cytoreductive surgery in patients with advanced epithelial ovarian cancer [18].

The current study showed by multivariate analysis that the presence of diaph-

ragmatic and mesenteric affection by CT-scan had a powerful weight in prediction of complete resectability more than the entire PCI. That was in accordance with Rosendahl *et al.* study, who selected small intestine and hepatoduodenal ligament as precise PCI regions corresponding to complete resection than the total PCI [19].

The score constructed in the present study showed partial agreement with Chesnais M. *et al.* who developed 100-point score to predict the resectability of peritoneal carcinomatosis. Their score depended also on four criteria, one clinical, one biological, and two radiological; BMI ≥ 30 kg/m^2, CA125 > 100 IU/ml, omental and/or diaphragmatic metastasis by CT-scan, and positive parenchymal metastasis. However, their score was settled from all stages of epithelial ovarian cancer whether early, advanced, primary, interval, and recurrent epithelial ovarian cancer [16]. The current study also used different corner stones, and different cut off points; their BMI had lower cut off level (≥30 kg/m^2), and they gave it double the weight given in the present study: (20 point versus 10).

Dessapt AL *et al.* study constructed a 10-point score based on clinical, radiological and laparoscopic criteria: which are age > 60 years, diaphragmatic involvement by CT and PCI > 10. However, their overall accuracy was 76% compared to 91% reported in the present study [20].

There are other various studies that developed a score for predicting surgical resectability of ovarian cancers. These previously developed scores were mainly based on laparoscopic criteria which were considered invasive and operator dependent, carrying the risk of tumor upstaging, trocar site metastasis, anesthetic complications in addition to many obstructs considered in laparoscopic surgery. However, the current obtained score was intended to be a noninvasive predictor model of complete cytoreduction feasibility (upstream of laparoscopy) [10] [11] [14] [15] [20].

Though the current study has provided valuable information concerning predictability of complete cytoreduction, yet, it was faced several limitations. Firstly, though data was collected over 2 years, yet the sample size was small and logistic regression analysis was not feasible because of the small number of the unresectable group (7 cases). However, results were comparable to and in accordance with similar studies developing similar scores. It is highly recommended to repeat the study on larger samples and include studies in a meta-analysis. Secondly, no difficulty to preform external validation of the model which was developed and evaluated on the same group with optimistic performance. Thirdly, being a record based retrospective study, some of the data were missing for some patients who were subsequently excluded from the study decreasing the sample size.

5. Conclusion

In advanced ovarian cancer, pre-operative predicting score (including clinical, biological, and radiological criteria) could be used as a roadmap for prediction of

surgery completeness feasibility. However, more research is needed on larger sample sizes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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