

ORIGINAL PAPER

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Defining the Ca 125 value to predict optimal cytoreduction in patients with epithelial ovarian cancer

Definir el valor de Ca 125 para predecir citorreducción óptima en pacientes con cáncer epitelial de ovario

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ABSTRACT

Objective: To define the Ca 125 value to predict optimal cytoreduction in patients with epithelial ovarian cancer. **Methods:** Observational, analytical and retrospective study of 52 consecutive patients who had surgical intervention for clinical stage III and IV epithelial ovarian cancer and who did not receive preoperative chemotherapy. These patients were attended between January 2014 and December 2018 in the Gynecology Service of the Carlos Alberto Seguí Escobedo Hospital, Arequipa, Peru. Sensitivity, specificity, positive and negative predictive value, and the area under the ROC curve of the most appropriate Ca 125 cutoff point for optimal cytoreduction were determined. **Results:** The patients were on average 58 years old, the serous histologic subtype was the most frequent with 73.1%; clinical stage IIIC corresponded to 65.4% of cases and optimal cytoreduction was achieved in 61.5% of patients. The ROC curve reached 78% with Ca 125 of 716.7 U/mL as the best cut-off point for predicting optimal cytoreduction, with sensitivity of 75%, specificity 75%, positive predictive value 82.8% and negative predictive value 65.2%. **Conclusion:** The tumor marker Ca 125 was useful in the prediction of optimal cytoreduction in patients who underwent surgery for epithelial ovarian cancer, with the best cut-off point being 716.7 U/mL.

Key words: Ovarian diseases, Ovarian neoplasms, Cytoreduction surgical procedures, ROC curve

RESUMEN

Objetivo. Definir el valor de Ca 125 para predecir citorreducción óptima en pacientes con cáncer epitelial de ovario. **Métodos.** Estudio observacional, analítico y retrospectivo de 52 pacientes consecutivas intervenidas de cáncer de ovario epitelial en estadio clínico III y IV y que no recibieron quimioterapia preoperatoria, entre enero de 2014 y diciembre del 2018 en el Servicio de Ginecología del Hospital Carlos Alberto Seguí Escobedo, Arequipa, Perú. Se determinó sensibilidad, especificidad, valor predictivo positivo y negativo, y el área bajo la curva ROC del punto de corte de Ca 125 más adecuado para citorreducción óptima. **Resultados.** Las pacientes tuvieron en promedio 58 años de edad, el subtipo histológico seroso fue el más frecuente con 73,1%, el estadio clínico IIIC correspondió a 65,4% de casos y se logró citorreducción óptima en 61,5% de las pacientes. La curva ROC alcanzó 78% con Ca 125 de 716,7 U/mL como el mejor punto de corte de predicción de citorreducción óptima, con sensibilidad de 75%, especificidad 75%, valor predictivo positivo 82,8% y valor predictivo negativo 65,2%. **Conclusión.** El marcador tumoral Ca 125 resultó útil en la predicción de citorreducción óptima en pacientes intervenidas de cáncer de ovario epitelial, siendo el mejor punto de corte 716,7 U/mL.

Palabras clave. Enfermedades del ovario, Neoplasias ováricas, Procedimientos quirúrgicos de citorreducción, Curva ROC

INTRODUCTION

Epithelial ovarian cancer ranks fourth in worldwide incidence among gynecological malignancies, after breast, cervical and endometrial cancers, but it is the leading cause of death from gynecological cancer⁽¹⁾. In Peru, ovarian cancer ranks third among gynecological neoplasms, after cervical and breast cancer⁽²⁾. In Colombia, each year there are 8.7 new cases of ovarian cancer per 100,000 women, with more than 800 deaths⁽³⁾.



Epithelial ovarian cancer is a heterogeneous disease that includes several histological subtypes, with different prognosis⁽¹⁾. This neoplasm represents 90% of malignant ovarian neoplasms⁽⁴⁾, the most frequent histological subtype being serous, followed by mucinous, endometrioid, clear cell, Brenner's tumor and undifferentiated neoplasms⁽⁵⁾. Overall survival at 5 years is 40%, being higher than 80% in stages I and II. In locally advanced stages III and IV the overall mortality is high, because approximately 70% involve the upper abdomen⁽⁶⁾.

Until 2010, the trend in the surgical treatment of advanced epithelial ovarian cancer was to achieve optimal cytoreduction. But, with the publication of the EORTC trial⁽⁷⁾ and later in 2015 of CHORUS⁽⁸⁾, neoadjuvant chemotherapy followed by interval surgery was shown to be not inferior to optimal primary cytoreduction (PC) in progression-free survival and overall survival. It also offers lower treatment-induced morbidity and mortality⁽⁹⁾.

The selection of a cut-off point of Ca 125 could allow the identification of a group of patients with advanced disease who could benefit from neoadjuvant chemotherapy and subsequent interval surgery, with decreased risks of morbidity and mortality due to aggressive surgery. The aim of the present study was to define the value of the tumor marker Ca 125 in predicting optimal primary cytoreduction in patients operated on for epithelial ovarian cancer.

METHODS

The present observational, analytical, and retrospective study included patients operated on for clinical stage III and IV epithelial ovarian cancer by non-probabilistic consecutive sampling in the Gynecology Service of the Carlos Alberto Seguí Escobedo National Hospital (HNCASE) of Arequipa, Peru, between January 2014 and December 2018. Patients underwent primary cytoreduction and preoperative Ca 125 dosing one month before.

Patients who received chemotherapy, or who had borderline tumors, non-epithelial ovarian cancer, chronic liver disease, endometriosis, synchronous endometrial cancer or with gestation were excluded. Ca 125 was determined in serum and plasma with the Elecsys CA 125 II-Roche in vitro immunological test (normal value < 35 IU/mL).

Data were collected in 2019 from the medical records of patients diagnosed with ovarian cancer exposed to cytoreduction between 2014-2018. Subsequently, the data of patients who met the inclusion criteria were recorded on a data collection sheet. Age, Ca 125 value, histological type, tumor stage were included and according to the operative report 2 subgroups were defined: one of optimal cytoreduction -when the residual tumor volume was less than 1 cm- and another of suboptimal cytoreduction, if the residual tumor was greater than 1 cm. To reduce selection bias, data were collected by a single investigator, the Ca 125 measurement and operative specimen evaluation were done in the same laboratory, and the surgical interventions were performed by only 2 surgeons.

Descriptive statistics were used to determine absolute and relative frequencies. The relationship between the variables cytoreduction and Ca 125 at different cut-off points was determined, with sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), confidence intervals (CI) and odds ratio for positive test.

Receiver operator curve (ROC) calculation was performed to measure the predictive accuracy of the tumor marker, and the optimal cutoff point was determined with the Youden index. The area under the ROC curve (AUC) was calculated to quantify the accuracy of Ca 125 in discriminating optimal cytoreduction (OC) from suboptimal cytoreduction (SOC). The statistical package SPSS version 20.0 for Windows was used for statistical analyses.

Regarding ethical aspects, this study was considered safe and was approved by the Health Research Ethics Committee of the Carlos Alberto Seguí National Hospital, corresponding to the Gynecology section.

RESULTS

Initially 64 patients were included, of which 12 were excluded: in 8 cases because in the final pathology result they corresponded to non-epithelial tumors, 3 because they were staging surgeries and not cytoreduction surgeries, and in 1 case because of association of epithelial ovarian cancer with gestation at term.



At the time of diagnosis of epithelial ovarian cancer, the average age of the patients was 58 years, with standard deviation 13.1 years and an age range of 34-84 years. 48.0% of the women were in the 46-60 age group. The most frequent histologic subtype was serous with 38 patients (73.0%) and the least common was mucinous with 1 patient (Table 1).

Clinical stage IIIC was the most frequently diagnosed with 65% of cases (34 patients), followed by stages IIIA and IIIB, each with 7 patients (13.4%). The clinical stage was documented in all patients because they were all treated at our institution. Optimal cytoreduction treatment considering residual tumor smaller than 1 cm was achieved in 32 patients (61.5%), and in 20 patients (38.4%) suboptimal cytoreduction was performed because of mesentery involvement, extensive infiltration of the lesser omentum and liver metastasis in 1 case (Table 1).

The best cut-off point for Ca 125 was 700 IU/mL. With this value, a sensitivity of 75.0% (95% CI 55.7-93.3) and specificity of 75.0% (95% CI 55.7-93.3), PPV of 82.7% and NPV of 65.2% were achieved. And it presented the highest odds ratio value for positive test (LR+) 3.0 (95% CI 1.31-6.58), which means that a patient with Ca 125 less than 700 IU/mL has a 3 to 1 chance of OC in relation to patients with Ca 125 > 700 IU/mL (Table 2).

Applying the ROC curve to achieve the highest sensitivity and specificity, the most appropriate cutoff point was 716 IU/mL for the Ca 125 marker, which presented a Youden index of 0.5, with sensitivity of 75% and specificity of 75% (Table 3). The AUC was 0.78, 95% CI 0.65-0.91, meaning that a patient randomly selected from the OC group would have Ca 125 < 700 in 78% of cases (Figure 1).

DISCUSSION

A total of 52 patients operated on for primary cytoreduction were included, with an average age of 58 years and 48.1% between 46-60 years (Table 1). These data are similar to those found by Saygili⁽¹⁰⁾, who reported an average age of 56 years. Acosta described that the age group above 50 years is the one with the highest risk of ovarian cancer⁽¹¹⁾.

TABLE 1. CLINICAL CHARACTERISTICS OF WOMEN WITH EPITHELIAL OVARIAN CANCER.

Variable	Absolute frequency N = 52	Relative frequency N = 100%
Age		
31 – 45 years	16	30.8
46 – 60 years	25	48.1
> 60 years	9	21.2
Histologic subtype		
Serous	38	73.1
Transitional cell	4	7.7
Clear cell	3	5.8
Endometrioid	3	5.8
Undifferentiated	3	5.8
Mucinous	1	1.9
Clinical stage		
III A	7	13.5
III B	7	13.5
III C	34	65.4
IV	4	7.7
Cytoreduction		
Optimal	32	61.5
Suboptimal	20	38.5

TABLE 2. UTILITY OF CA 125 AS A PREDICTOR OF OPTIMAL CYTOREDUCTION IN WOMEN WITH EPITHELIAL OVARIAN CANCER.

Ca 125 IU/mL	OC* N	SOC + N	Se ‡ %	Sp § %	PPV %	NPV ¶ %	LR + **	95% CI § LR +
< 400	14	4	43.7	80.0	77.7	47.0	2.1	0.8-5.7
< 500	18	4	56.2	80.0	81.8	53.3	2.8	1.1-7.1
< 600	23	5	71.8	75.0	82.1	62.5	2.8	1.3-6.3
< 700	24	5	75.0	75.0	82.7	65.2	3.0	1.3-6.5
< 800	25	8	78.1	60.0	75.7	63.1	1.9	1.1-3.4
< 900	26	6	81.2	70.0	81.25	70.0	2.7	1.3-5.4

* OC: optimal cytoreduction; † SOC: suboptimal cytoreduction; ‡ Se: sensitivity; § Sp: Specificity; || PPV: Positive predictive value; NPV: Negative predictive value; ** LR +: positive likelihood ratio

The most frequent histological subtype of ovarian cancer was serous, with 73.1% of cases, followed by the transitional cell subtype with 7.7%, similar to the 81.9% of the serous subtype in Li-yuan Feng's study⁽¹²⁾. Table 1 also shows that 65.4% of patients were found in clinical stage IIIC, similar to the 67.4% described by Vorgias⁽¹³⁾ as the most frequent stage of initial presentation of epithelial ovarian cancer.

Table 1 shows that 61.5% of 52 patients had optimal cytoreduction, which differs from the findings of Zlatko Topolovec⁽¹⁴⁾ who achieved optimal cytoreduction (residual tumor <1 cm) in 49.2% of 126 patients. This difference could be due to the fact that the latter study included more patients with supraumbilical disease and that the context in which it was performed is different from ours.



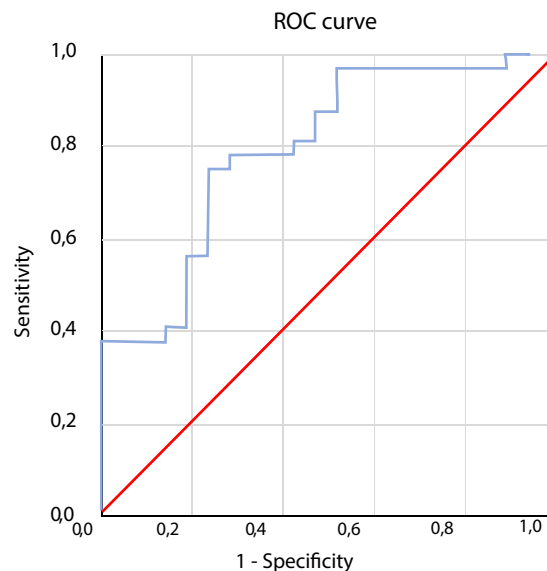
TABLE 3. ROC CURVE COORDINATES.

Cut-off point	Sensitivity	1-Specificity	Youden's index
110.65	0.18	0.00	0.19
123.10	0.21	0.00	0.22
139.50	0.25	0.00	0.25
164.95	0.28	0.00	0.28
195.60	0.31	0.00	0.31
210.90	0.34	0.00	0.34
229.50	0.37	0.00	0.38
287.50	0.37	0.05	0.33
341.15	0.37	0.10	0.28
368.05	0.37	0.15	0.23
381.40	0.40	0.15	0.26
383.90	0.40	0.20	0.21
398.60	0.43	0.20	0.24
427.70	0.46	0.20	0.27
458.90	0.50	0.20	0.30
480.15	0.53	0.20	0.33
493.25	0.56	0.20	0.36
503.85	0.56	0.25	0.31
514.55	0.59	0.25	0.34
531.35	0.62	0.25	0.38
544.40	0.65	0.25	0.41
548.85	0.68	0.25	0.44
624.50	0.71	0.25	0.47
716.70	0.75	0.25	0.50
737.70	0.75	0.30	0.45
749.52	0.78	0.30	0.48
774.62	0.78	0.35	0.43
895.50	0.78	0.40	0.38
1,076.50	0.78	0.45	0.33
1,176.50	0.81	0.45	0.36
1,218.50	0.81	0.50	0.31
1,240.00	0.84	0.50	0.34
1,292.00	0.87	0.50	0.38
1,345.00	0.87	0.55	0.32
1,353.00	0.90	0.55	0.36
1,397.00	0.93	0.55	0.39
1,444.50	0.96	0.55	0.42

Table 2 shows that with a Ca 125 cutoff point of 700 IU/mL, 75% sensitivity and specificity, PPV of 82% and NPV of 65% are achieved. This cut-off point would be the optimal value, because it presents a higher positive likelihood ratio; it means that it is 3 times more likely that a patient with OC obtains Ca 125 < 700 IU/mL in relation to a patient with SOC.

In the analysis with ROC (receiver operating characteristic) curves⁽¹⁵⁾, Table 3 shows some

FIGURE 1. ROC CURVE FOR DIFFERENT Ca 125 CUT-OFF POINTS AS A PREDICTOR OF OPTIMAL CYTOREDUCTION.



Source: Prepared by the authors from the results of the study.

cut-off points generated in the SPSS program to establish the optimal cut-off point for Ca 125 as a predictor of OC. According to the Youden index, the highest value was obtained when the Ca 125 value was 716.7. At this cutoff point, the sensitivity is 75%, and the specificity is 75%; therefore, it constitutes the optimal value for predicting OC.

Saygili⁽¹⁰⁾ included 92 patients in clinical stage IIIC to investigate the predictive value of CA 125. He achieved OC considering residual tumor smaller than 1 cm in 48 patients (52%) and the ROC curve showed that the most adequate cut-off value was 500 IU/mL, with a sensitivity and specificity of 75%. Optimal cytoreductive surgery was performed in 36 cases (77%). Li-yuan Feng⁽¹²⁾ published a Ca 125 of 313 IU/mL as the best cut-off point but considered OC with zero residual tumor (R=0). This difference with our results may be due to the heterogeneity of stage IIIC in ovarian cancer, ranging from a 2 cm tumor in omentum to a massively infiltrated cake omentum, or a peritoneum with multiple infiltrates.

In a cohort study, Vorgias⁽¹³⁾ included 426 women with stage III-IV ovarian carcinoma, achieving optimal cytoreduction in 177 patients (41.5%). He found that the level of 500 IU/mL has the highest predictive power for OC, with Ca 125 sensitivity of 78.5% and specificity of 89.6%. This difference may be explained by the greater number of cases in more advanced stages included in this study and by the actual experience of each indi-



vidual surgeon, which may vary significantly.

In Mexico, Treviño⁽¹⁶⁾ in 94 patients found 427.81 IU/mL as the optimal cut-off point, while Guillén⁽¹⁷⁾ in the city of Trujillo, Peru, reported a preoperative Ca 125 level of 500 IU/mL to predict OC with sensitivity of 63%, specificity of 91%, PPV of 87% and NPV of 71%. It is observed that the scope and period of the study is similar to ours, but it should be considered that the institution where it was carried out contains a greater number of oncologic patients than in the institution of the present study.

To determine the capacity of Ca 125 to distinguish cases of OC versus SOC, the area under the ROC curve was quantified⁽¹⁸⁾, which was 0.78, as shown in Figure 1, i.e., a patient in the OC group would have a 78% probability of having lower Ca 125 compared to the SOC group. Arab found 420 IU/mL as the best cut-off point according to Youden's index, with AUC of 0.75 to predict OC (19), values similar to ours which show that Ca 125 is a good predictor of optimal cytoreduction and that it could also be useful to assess interval cytoreduction after chemotherapy⁽²⁰⁾.

A limitation of the present study is that it is retrospective and therefore susceptible to reporting bias. The sample size was smaller due to the exclusion of 12 patients. In addition, we should mention that among the Ca 125 values found, although most of them were in ranges lower than 500 IU/mL, in two cases they were higher than 700 IU/mL and optimal cytoreduction was performed. This may have influenced the Ca 125 cut-off point calculated at 700 IU/mL to be higher in comparison with other similar studies.

The strength of the study is that no similar work has been found in our city, so there is certainty of having a reference cut-off point according to the Elecsys CA 125 II test to achieve optimal cytoreduction. This will make it possible to identify which patients may have resectable disease prior to their surgical intervention and reduce the number of patients who enter laparotomy 'blind'. In addition, it could facilitate the selection of patients with unresectable disease for diagnostic laparoscopy, neoadjuvant chemotherapy and then interval cytoreduction, with reduced morbidity.

CONCLUSIONS

The predictive accuracy of the tumor marker Ca 125 in patients operated on for epithelial ovarian cancer for optimal cytoreduction was 0.78. The value of 716.7 IU/mL was the best cut-off point found for the Ca 125 marker in predicting optimal cytoreduction, with a sensitivity of 75% and specificity of 75%. The best cut-off point for Ca 125 for optimal cytoreduction was 700 IU/mL, with a positive predictive value of 82.7% and a negative predictive value of 65.2%. In practice this means that a patient with ovarian cancer with Ca 125 marker greater than 716 IU/mL may not be a candidate for primary cytoreduction surgery.

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