ONCOLOGÍA roe-solca.ec ORIGINAL ARTICLE

Unresectability index associated with optimal cytoreduction in patients with ovarian cancer: A single-center observational study.

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Conflict of interest: The authors declare no conflict of interest.

Received: May 19, 2023
Accepted: July 20, 2023
Published: August 18, 2023
Editor: Dr. Lorena Sandoya

Cite:
Vera G, Carrasco M. Unresectability Index Associated with Optimal Cytoreduction in Patients With Ovarian Cancer: Single Center Observational Study. Revista Oncología (Ecuador) 2023;33(2):131-142.

ISSN: 2661-6653

DOI: https://doi.org/10.33821/707
SOCIEDAD DE LUCHA CONTRA EL CÁNCER

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Abstract

Introduction: The unresectability index assesses the presence of four variables (palpable abdominal mass, presence of tumor in pouch of Douglas, presence of ascites fluid, preoperative Ca 125 value greater than 1000 U/ml) before performing primary cytoreductive surgery in patients with ovarian cancer. The objective of this study was to carry out a diagnostic test of the unresectability index with the decision to perform optimal cytoreduction in patients with ovarian cancer who underwent surgery in a public hospital of national reference in Ecuador over 3 years of study.

Methodology: In the present study of diagnostic tests, women operated on for ovarian cancer were studied at the Hospital de Especialidades Eugenio Espejo (Ecuador) from September 2016 to September 2018. Patients with optimal and suboptimal cytoreduction were included. A descriptive analysis with frequencies, percentages, and averages is presented. The sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) of the unresectable index compared with cytoreduction were evaluated.

Results: A total of 148 cases were analyzed. The specificity of the index was 81%, with a positive predictive value (PV) of 77% and a negative PV of 68%. The sensitivity of ascites was 85%, and that of a palpable abdominal mass was 79%. In patients who presented CA-125 antigen values less than 1000 U/ml, the risk of obtaining optimal cytoreduction was OR: 0.15 (95% CI 0.069 - 0.307; *P*: 0.0001). The patients who presented unresectability index values between 1 and 2 points versus 3 and 4 points were OR: 7.04 (95% CI 3.33 -14.87, *P*: 0.0001).

Conclusions: The unresectability index presented a statistically significant capacity to predict optimal cytoreduction in patients with ovarian cancer operated on at the Eugenio Espejo Specialties Hospital.

Keywords:

MeSH: Cytoreduction Surgical Procedures, Ovarian Neoplasms, Surgical Procedures, Operative, CA-125 Antigen, Predictive Value of Tests.

DOI: 10.33821/707

Introduction

Ovarian cancer remains the fourth leading cause of death in women and the deadliest gynecological tumor in the world [1].

The National Institute of Cancerology of Mexico (INcan) designed a predictive index for the unresectability of ovarian cancer, which is based on clinical and laboratory parameters: palpable abdominal tumor, pouch of Douglas obliteration, presence of ascites in any amount and level of cancer antigen 125 (CA-125) equal to or greater than 1000 U/ml; a value of one point is assigned to each variable [2].

Prospectively, at this center (INcan), the index was evaluated, and the findings were as follows: 89.3% of patients with 0–2 points could be optimally cytoreduced, compared to only 36.8% of patients with 3–4 points. In patients with stage III and IV plus 3–4 points, the chance of successful surgery without morbidity and mortality is only 5.9% [2].

There are also tomographic criteria for predicting nonoptimal cytoreduction, which is a disease in the supra colic compartment, around the spleen and stomach, gallbladder fossa, tumoral disease in the superior mesenteric artery, presence of massive ascites, implants of the parietal peritoneum, and disease important part of the omentum [3].

Optimal cytoreduction has been defined in various ways. Most studies define it as the residual disease of implants not greater than or equal to two centimeters. Recently, other authors have described it as a residual disease less than or equal to one centimeter [3].

Many patients undergo surgical exploration with an attempt at primary staging cytoreduction, which is of little use and in which a diagnostic biopsy is performed exclusively; this procedure is called diagnostic exploratory laparotomy [4].

Few retrospective studies answer the question of predicting which patients will be unlikely to have optimal debulking, such that these patients would receive neoadjuvant chemotherapy as initial treatment and subsequently undergo interval surgery [2].

Typically, these patients undergo diagnostic exploratory laparotomy with attempted staging and primary cytoreduction; however, optimal cytoreductive surgery is achieved in less than 50% of them, and approximately 50% present complications secondary to the procedure, with the consequent delay at the start of the chemotherapy cycle [2].

It is necessary to prospectively evaluate the predictors of optimal cytoreduction previously studied by other authors and thus determine the best treatment strategy for each patient, avoiding unnecessary procedures that entail significant morbidity, delay in definitive treatment, and deterioration in the quality of life [2].

The most important independent prognostic factor for overall survival was the absence of residual tumors after primary or interval debulking surgery [5].

An alternative approach for women with unresectable stage III or IV is neoadjuvant chemotherapy with subsequent surgical debulking (interval surgery), which can potentially avoid aggressive surgery in women with “unresectable” advanced diseases with a poor prognosis. Neoadjuvant chemotherapy may increase the optimal debulking ratio in interval surgery [5].

Currently, few retrospective studies answer the question of predicting in which patients with epithelial ovarian cancer it is possible to perform optimal primary cytoreduction so that in these patients, neoadjuvant chemotherapy can be chosen as the initial treatment and subsequently. Perform interval surgery [2].

The National Institute of Cancerology of Mexico (INcan) designed a predictor index for the unresectability of ovarian cancer, which is based on clinical and laboratory parameters such as a palpable abdominal tumor, pouch of Douglas obliteration on vaginal exploration, presence of ascites in any quantity and preoperative level of cancer antigen 125 (CA-125) greater than 1,000 U/ml. A value of one point is subsequently assigned to each variable to calculate this index [6]. The findings were as follows: optimal cytoreduction was achieved in 89.3% of patients with 0–2 stitches, compared to only 36.8% of patients with 3–4 points [2].

It is estimated that in less than 50% of patients diagnosed with ovarian cancer in whom an exploratory laparotomy is performed, the objective of staging and primary cytoreduction is

achieved; in addition, 50% present complications secondary to the procedure, with the consequent delay in initiation of chemotherapy treatment [2].

Due to these antecedents, it is necessary to retrospectively evaluate the predictors of optimal cytoreduction that other authors have previously studied and thus determine the best treatment strategy for each patient, avoiding unnecessary procedures that entail significant morbidity, delay of definitive treatment, and deterioration in the quality of life [2].

The objective of this study was to analyze the validity of the Unresectability Index with the decision to perform optimal cytoreduction in patients with ovarian cancer who underwent surgery at the Hospital de Especialidades Eugenio Espejo, September 2016 – September 2018.

Materials and methods

Study design
The study is a diagnostic test with cross-sectional sampling from a retrospective source.

Study Area
The study was carried out in the surgery service of the Eugenio Espejo Specialty Hospital of the Ministry of Public Health in Quito-Ecuador. The study period was from September 1, 2016, to September 30, 2018.

Universe and Sample
The universe comprised all the cases registered in the institution that corresponded to 223. The sample size was probabilistic, with a confidence level of 95%, a margin of error of 5%, and Z value=1.96 with a formula for a population defined with 0.5 probability of success and 0.5 probability of failure. The calculated size was 141 patients.

Participants
Cases of women aged ≥18 years with postsurgical histological confirmation of epithelial ovarian cancer who underwent primary cytoreduction were included. Patients diagnosed with ovarian cancer with histological types other than epithelial ovarian cancer, such as ovarian germ cell cancer tumors derived from germ cells and ovarian stromal tumors, were excluded from the study. Incomplete medical records that did not contain the four study parameters for measuring the unresectability index were excluded. Clinical histories that did not describe in their postoperative protocol the surgical findings that allowed the classification of optimal or suboptimal cytoreduction were excluded. Medical records with postsurgical histological diagnosis of benign adnexal masses were excluded.

Variables
The variables were cytoreduction, presence of ascites, palpable abdominal tumor, pouch of Douglas obliteration, and tumor marker Ca125.

Procedure, techniques, and instruments.
The information regarding the study variables obtained from each electronic medical record through the HOSVITAL computer system of the Eugenio Espejo Specialties Hospital was compiled in a data collection sheet; this information was entered and tabulated in a data sheet. Excel calculation version 16.0.

Diagnostic and intervention procedures: As a retrospective study of information review, the diagnosis and procedures were already performed on the patients. Therefore, no additional diagnostic tests or direct intervention procedures were performed on the study population.

The presence of the unresectability index was estimated, and the presence of the four study variables was identified. Each one was given a value of one point, so the index's total value was calculated on four points according to the presentation of the variables. It was compared with optimal or suboptimal cytoreduction surgery performed in patients with ovarian cancer.

The following parameters included in the unresectability index were identified in this study:

- Palpable abdominal mass on physical examination (1 point).
- Pouch of Douglas obliteration on vaginal exploration
- Presence of ascitic fluid in any quantity described in the surgical protocol. (1 point)
- Preoperative CA value – 125 greater than 1000 U/ml (1 point).

Avoidance of bias

To avoid study bias, the registration of clinical histories in a Microsoft Excel database was guaranteed, as well as a double checklist to include only those cases from the surgery service that met the study variables.

Statistical analysis

The information was stored in a database in Excel version 16.0, whose characteristics allowed us to carry out quality control and filtering of the information and transfer them to the computer software SPSS version 25.0 (Service Solution Statistics Product), in which a descriptive analysis of the variables under study was carried out through frequencies, percentages, and averages.

As it is a diagnostic test validation study design, it allows the evaluation of validity, that is, how close a measurement is to the actual value it intends to measure. They are procedures that make it possible to determine whether an individual has a particular disease (or other characteristic).

For this, the following parameters were calculated:

a) Sensitivity (S) or proportion of true positives as the probability that the test is positive conditional on the individual being sick.

b) Specificity (E) or proportion of true negatives as the probability that the test is negative provided that the individual is not sick.

c) Positive Predictive Value (PPV): proportion of individuals with a “positive” result who truly have the disease.

d) Negative Predictive Value (NPV): proportion of individuals with a “negative” result who genuinely does not have the disease.

Sensitivity and specificity represent the validity of the diagnostic test. The positive and negative predictive values represent the diagnostic test's safety. In this sense, we can classify a diagnostic test in the parameters above as excellent (greater than or equal to 95%), good (between 80% and 94%), fair (between 50% and 79%), and poor (less than 50%) through contingency tables with a confidence interval of 95% and a significance level of $P < 0.05$.

Results

Participants

A total of 148 patients were included in the study.

Demographic characterization

In 87% (n=129) of the population, palpation of the abdominal mass was positive, while tumor presence in the pouch of Douglas on vaginal examination was positive in 51% (n=75). The presence of ascites in the evaluated group reached 90% (n=133). Regarding the value of the tumor marker CA-125, 60% (n=89) reported values below 1000 U/ml. This is described in Table 1.

With the previous results, the value of the unresectability index was qualified according to the variables presented in the described population. A total of 14.9% (n=22) obtained a score of 4, 44.6% (n=66) of the group received a score of 3, 33.8% (n=50) obtained a score of 2, and 6.8% (n=10) obtained a score of 1 (Table 1).

Table 1 . Distribution of patients diagnosed with ovarian cancer, operated according to the variables analyzed in the index of unresectability

Variable	Frequency (n=148)	Percentage (%)
Mass abdominal palpable	129	87.2%
Tumor in POD touch vaginal	75	50.7%
Ascites	133	89.9%
CA-125 > 1000 units/ml	59	39.9%
Unresectability Index		
1 criteria	10	6.8%
2 criteria	50	33.8%
3 criteria	66	44.6%
4 criteria	22	14.9%

POD: pouch of Douglas.

Cytoreduction

Regarding the result of the cytoreduction performed on the patients of the investigated group, optimal cytoreduction was obtained in 74 women, corresponding to 50% of the population, and suboptimal cytoreduction was obtained in 74 women, corresponding to the remaining 50%. (Table 2).

Table 2. Distribution according to the result of cytoreduction performed in patients with ovarian cancer.

No.=148	Frequency n=148	Percentage (%)
Optimal	74	50%
Suboptimal	74	50%

* Optimal cytoreduction: not to leave any visible cancer or tumors that measure more than 1 cm.

Inferential analysis

It was found that in patients who presented CA-125 antigen values less than 1000 U/ml, the risk of obtaining optimal cytoreduction was 76% higher compared to those patients with a higher value (OR: 0.15; 95% CI 0.069–0.307; *P*: 0.0001). It was also identified that in the patients who presented unresectability index values between 1 and 2 points, the benefit for optimal cytoreduction was seven times more significant compared to those with scores between 3 and 4 (OR: 7.04; 95% CI 3.333 -14.872; *P*: 0.0001). The following table shows that all the parameters improve the predictive capacity of optimal cytoreduction (Table 3).

Table 3. Relationship between the analyzed variables of the unresectability index with the result of the cytoreduction done in the patients with ovarian cancer

Mass abdominal palpable					
	Yes	No	OR	CI 95%	*P*
CR-Optimum	63	eleven	0.69	0.262 – 1,839	0.463
sub optimal	6	8			
Tumor in bottom of sack of Douglas to the Vaginal Touch					
	Yes	No	OR	CI 95%	*P*
CR-Optimum	33	41	0.61	0.320 – 1,174	0.139
Sub optimal	42	32			
Ascites					
	Yes	No	OR	CI 95%	*P*
CR-Optimum	59	15	NN	NN	NN
Sub optimal	74	0			
Worth Preoperative of AC – 125					
	> 1000 U/ml	*< 1000 U/ml*	*OR*	*CI 95%*	*P*
CR-Optimum	14	60	0.15	0.069 – 0.307	0.0001
Sub optimal	46	28			
Worth index _ of unresectability					
	1 to 2 points	*3 to 4 points*	*OR*	*CI 95%*	*P*
CR-Optimal	46	28	7.04	3,333 – 14,872	0.0001
Sub optimal	14	60			

CR: Cytoreduction.

Assessment of predictive diagnostic indices and criteria for unresectability

Sensitivity for palpation of the tumor mass from abdominal assessment and ascites presented important values of 85% and 79%, respectively; however, they presented inferior positive predictive values (48% and 44%, respectively), while regarding the specificity (ability to measure false negatives among healthy subjects), of this group of parameters, in none of them was it higher than 50%, being for those described above, palpable abdominal mass and ascites, of 11% and 0%, respectively, with negative predictive values of 42% and 0%, respectively (Table 4).

Table 4. Diagnostic tests for cytoreduction in patients with ovarian cancer

	Optimal	*Sub optimal*	*S%*	*AND%*	*VP+*	*VP-*	*VR+*	*RV-*
Mass abdominalpalpable	63	66	85.1%	10.8%	48.8%	42.1%	0.95	1.38
Tumor in FSD atvaginal touch.	33	42	44.6%	43.2%	44.0%	43.8%	0.79	1.28
Ascites	59	74	79.7%	0.0%	44.4%	0.0%	0.80	NN
CA-125 >1000 U/ml	14	46	18.9%	38.4%	23.7%	31.8%	0.31	2.11
Index of unresectability 1 to 2	46	14	62.2%	81.1%	76.7%	68.2%	3.29	0.47

S: Sensitivity. E: specificity. PV: predictive value.

Discussion

Worldwide, ovarian cancer is the seventh most frequent cause of cancer, with approximately 238,700 new cases in 2012, and it is the eighth cause concerning cancer-associated mortality, with 151,900 deaths, being the one with the worst prognosis among the gynecologic neoplasms [7]. The incidence and mortality rates of ovarian cancer present differences according to the geographical region but mainly according to the level of development, seeing greater affectation in areas with better economic conditions, such as North America and Europe, which may be related to a higher prevalence of several established risk factors, such as nulliparity/low parity, use of menopausal hormone therapy, familial predisposition, and a lower prevalence of a vital protective factor, the use of oral contraceptives [8].

At diagnosis, 15-20% of women have stage I disease, according to the FIGO classification. Surgical staging in this group provides relevant prognostic information and advice on adjuvant chemotherapy. In this context, surgical staging classically required exploratory laparotomy to perform procedures recommended by FIGO, such as peritoneal lavages, bilateral salpingo-oophorectomy, hysterectomy, multiple peritoneal biopsies, infracolic omentectomy, appendectomy in case of mucinous histology, and lymph node pelvic dissection and paraaortic lymphatics to the renal veins [9].

Regarding cytoreduction surgery, its indication is established for those patients with stage III or IV disease, representing approximately 80% of diagnosed cases of epithelial ovarian cancer [10]. This percentage is close to the number of patients included in our study, representing 67.26% of the patients treated for this neoplasm.

Between 15 and 50% of cancer patients develop ascites, which is more frequent in carcinomas of the ovary, breast, endometrium, colon, stomach, pancreas, and bronchi. Additionally, approximately 10% of cases with ascites are associated with malignancy. Thirty-five percent of patients with ovarian cancer present ascites at diagnosis, and 60% present ascites at the time of death [11]. These figures contrast our results, where we found evidence of ascites in nearly 90% of our patients. This could be explained because our study group included patients with ovarian cancer in advanced stages, requiring cytoreductive surgery [12].

Although the results presented by different studies are contradictory, the serum level of CA125 has been associated with a robust prognostic factor for overall survival and progression-free survival in ovarian cancer, such that a decreasing level generally indicates a positive response to therapy, including cytoreductive surgery [13].

Cruickshank's study in Aberdeen found no correlation in survival when studying CA 125 ≥ 35 U/ml as a presurgical predictor of suboptimal response [14]. Three subsequent studies using the preoperative value of CA 125 ≥ 65 U/mL associated with poor survival demonstrated that patients with CA 125 < 65 U/mL had better postoperative outcomes [15, 16].

When analyzing higher cutoff points to compare survival, studies have been published with conflicting results, such as Makar AP in Norway and Buller R in the USA, as well as Osman N in Limerick, which found that levels of CA 125 ≤ 150 and ≤ 500, respectively, did not have a favorable prognostic value in survival [17, 18]. In contrast, Cooper BC in the USA and Gadducci An in Italy found that CA 125 levels ≥ 160 and ≥ 500, respectively, had a worse preoperative prognosis [19, 20].

At INcan in Mexico, an optimal cytoreduction unresectability predictor index was designed through the use of clinical parameters that include the presence of a palpable abdominal tumor, pouch of Douglas obliteration, ascites, and the same CA-125 level. or greater than 1000 U/ml, with a point assigned for each variable. Through a prospective analysis with this index, it was possible to demonstrate that in patients with less than two points, an optimal cytoreduction of approximately 100% was achieved; when two parameters were present, the optimal cytoreduction was 62%, and with three or more, it decreased to less than 32%, and it was concluded that the index predicts suboptimal cytoreduction with a specificity of 89.3% and sensitivity of 84.2%, together with a positive predictive value of 84.2% and a negative predictive value of 89.3% [2]. Martínez-Saíd et al., when reviewing the INcan data regarding advanced ovarian cancer through univariate and stratified analysis of 15 different parameters, found four variables significantly related to a lower probability of optimal cytoreduction: CA

125 > 1000 U/ml, palpable abdominal tumor, and Douglas sac with tumor occupation demonstrated by vaginal and rectal examination and ascites; with them, they were able to determine that in those patients with one variable or less, a tumor residual <2 cm was achieved in 62%; in contrast to the group of patients with 2 to 4 variables, optimal cytoreduction was obtained in only 32% [21]. These findings were also corroborated in our study, which showed optimal cytoreduction, especially in the group of patients with two factors or less.

In the retrospective case series study conducted by Alcarraz et al., which included Peruvian women treated with neoadjuvant chemotherapy with carboplatin (AUC 6 mg/ml/min) and paclitaxel (80 mg/m^2 weekly) followed by surgery after an interval of cytoreduction, thirty-four patients (82.9%) achieved optimal cytoreduction and five (14.7%) achieved pathological complete response, results that contrast with our work in which optimal primary cytoreduction was obtained in 50% of patients [22].

This pattern is also evident in prospective phase III trials such as the EORTC study, the Japan Clinical Cancer Group (JCOG) study, and the CHORUS study, which evaluated the efficacy of neoadjuvant chemotherapy with carboplatin and paclitaxel at conventional doses followed by surgery. interval debulking compared with primary debulking surgery, presenting optimal debulking rates of 80.6%, 72%, and 40%, respectively [23].

Primary cytoreductive surgery is currently a very relevant therapeutic strategy in managing ovarian cancer in advanced stages. However, conditions specific to each patient may indicate that this is suboptimal or optimal. In this sense, in this study, we sought to validate the score developed by the INcan of Mexico, having shown that it has a statistically significant capacity to predict optimal cytoreductive surgery in patients with epithelial ovarian cancer at the Hospital de Especialidades Eugenio Espejo.

One of the limitations of this study was the finding of incomplete medical records, such as the lack of information obtained from the physical examination, the lack of reporting of imaging and laboratory tests, and the need for more protocolization in reporting surgical findings. described in the surgical protocol and the heterogeneity of the medical specialists who performed the surgical interventions. New studies should resolve these weaknesses.

Conclusions

All the parameters improved the predictive profile of optimal cytoreduction with a high specificity of 81%, a positive predictive value (PPV) of 77%, and a negative predictive value (NPV) of 68%. Both ascites and a palpable abdominal mass had good sensitivity, 85%, and 79%, respectively, for predicting optimal debulking surgery. In patients who presented CA-125 antigen values less than 1000 U/ml, the risk of obtaining optimal cytoreduction was 76% higher than in patients with a higher value (OR: 0.15; 95% CI 0.069 – 0.307; *P*: 0.0001). For the patients who presented values of the unresectability index between 1 and 2 points, the benefit for optimal cytoreduction was 7 times greater compared to those with scores between 3 and 4 (OR: 7.04; 95% CI 3.333 -14.872; P: 0.0001). The Unresectability Index presented a statistically significant capacity to predict optimal cytoreduction in patients with ovarian cancer operated on at the Eugenio Espejo Specialty Hospital. This demonstrates its validity for decision-making in performing optimal cytoreduction.

Abbreviations

S: Sensitivity.

E: specificity.

PV: predictive value.

Administrative information

Additional Files

None declared by the authors.

Acknowledgments

We thank the directors and staff of the Teodoro Maldonado Carbo Hospital of the Ecuadorian Institute of Social Security, where the study was conducted.

Author contributions

Geovanny Fernando Vera Pardo, Conceptualization, formal analysis, research, project management, resources, software.

Maria Lucila Carrasco Guerra: Conceptualization, methodology, validation, visualization, writing review, and editing.

All the authors have read and approved the final version of the manuscript.

Financing

The researchers funded the study. The authors did not receive any financial recognition for this research work.

Availability of data and materials

Data are available upon request to the corresponding author. No other materials are reported.

Statements

Ethics committee approval

No studies of databases or medical records were needed.

Consent for publication

It is not required when images, resonances, or tomographic studies of specific patients are not published.

Conflicts of interest

The authors declare that they have no conflicts of competence or interest.

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