Review

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Laparoscopic Prediction of Primary Cytoreducibility of Epithelial Ovarian Cancer

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Abstract: Ovarian cancer affects thousands of women every year and represents the female cancer with the highest mortality rate. Surgery is currently the cornerstone of the treatment of this disease and several methods have been analyzed and developed to predict the possibility of obtaining a residual tumor of 0 (RT=0). The aim of this review is to analyze the data available in the literature about minimally invasive surgical methods to predict the optimal cytoreduction of patients with advanced epithelial ovarian cancer undergoing primary debulking surgery (PDS). A review of the literature has been performed on the available data about the criteria of cytoreducibility during PDS for the surgical treatment of advanced epithelial ovarian cancer. The assessment of the extent of intra and extrabdominal pathology is essential to guide the surgeon in the most appropriate therapeutic choice for patients with ovarian cancer, so radiological methods (MRI, PET-scan and CT), surgical (mini-laparotomy, laparoscopy) and serological (CA-125, HE4) can provide a huge help for tailoring the therapeutic approach of these patients.

Keywords: ovarian cancer; gynecologic oncology; gynecologic surgery; debulking surgery; PDS; laparoscopy

1. Introduction

The most frequent ovarian malignancies are epithelial tumors. Ovarian cancer affects thousands of women every year and represents the female cancer with the highest mortality rate, with estimated 13,270 deaths in the US in 2023 [1–3]. It is most common in women over the age of 50, but it can occur at any age and its lethality is due to delayed diagnosis until advanced stages (International Federation

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of Gynecology and Obstetrics – FIGO stage III-IV). This data is also due to the actual lack of screening for early diagnosis, compared with other gynecological tumors (in particular, breast and cervical cancer) [4–9]; moreover, epithelial ovarian carcinomas clinically manifest with poor and non-specific signs and symptoms up to the most advanced stages [10,11]. The centralization of ovarian cancer care in specialized centers has been demonstrated to improve outcomes thanks to the presence of a multidisciplinary team with specialized expertise, the possibility to access to clinical trials and a streamlined approach to care, facilitating efficient and coordinated treatment plans; however, recently, the survival of patients with advanced epithelial ovarian cancer (AEOC) has radically increased and their prognosis has greatly improved [12,13]; on the one hand, the possibility of subjecting patients with increased genetic risk of developing ovarian cancer (especially with mutations of the breast cancer gene (BRCA) and homologous recombination deficiency (HRD)) to a structured screening allows a more early diagnosis; on the other hand, the introduction into our clinical practice of the use of antiangiogenic and poly-ADP ribose polymerase (PARP) inhibitors (PARPi) opened up new therapeutic scenarios [14–24].

Surgery followed by chemotherapy is currently the cornerstone of the treatment of this disease [25–31]; however, it is essential to personalize the therapeutic approach of each patient considering the tumor characteristics (especially spread and histological subtype). The goal of surgical treatment is to reduce the residual tumor load to 0 (RT=0), meaning the absence of macroscopically visible pathology. For this purpose, the surgical approach to AEOC provides two possibilities: primary surgical treatment (primary debulking surgery, PDS) or, interval debulking surgery (IDS), performing surgery after the administration of 3 or more cycles of platinum-based chemotherapy to reduce the burden of disease. Obviously, patients may not be eligible for upfront surgery not only for a high load of disease but also for the involvement of anatomical structures that cannot be removed with surgery; for the massive involvement of some organs, for example, the small and the large intestine, which would require the total or almost total removal with a consequent complete loss of function; for patient's fragility, that increase the risk of intra, peri- and post-operative complications and cause an additional risk of death [32–41]. Assessing the resectability of advanced ovarian cancer requires a multidisciplinary approach involving oncologists, gynecological surgeons, radiologists and other specialists. Several methods have been analyzed and developed to predict the possibility of obtaining residual tumor of 0 (genetic, imaging, serological, surgical), but, to date, none of them have yet been identified and can be considered the gold standard. Although laparoscopic surgery is characterized by a lower incidence of negative impact on patient well-being in the context of ovarian cancer operability analysis, it should be pointed out that, in situations where the preoperative evaluation manifests a degree of ambiguity, the surgeon might consider implementing an exploratory laparotomy. This procedure essentially consists of a surgical dissection of the abdomen that allows a direct tissue assessment. This on-site examination facilitates the accurate determination of the extent of neoplastic pathology and the subsequent feasibility of cytoreduction surgery.

The main objective of the treatment of AEOC is to balance the risks to which the patient is exposed to achieve RT=0, the surgical effort and the achievement of an optimal cytoreduction. The aim of this narrative review is to analyze the data available in the literature about minimally invasive surgical methods to predict the optimal cytoreduction of patients with AEOC undergoing PDS.

2. Materials and Methods

This is a narrative review of the available data about the criteria of cytoreducibility during PDS for the surgical treatment of AEOC. The review was reported and qualitatively assessed following the SANRA, the Scale for the Assessment of Narrative Review Articles [42]. We performed the research using a narrative review method [43]. Electronic databases PubMed (MEDLINE), Embase, Scopus, and Web of Science were searched until May 2023 (without date restriction) for relevant publications in the English language focusing on, but not limited to, the use of the following key search terms: ovarian cancer OR advanced epithelial ovarian cancer OR ovarian serous carcinoma AND cytoreduction OR cytoreducibility AND laparoscopic OR mini-invasive technique OR mini-

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invasive surgery AND primary debulking surgery OR PDS OR upfront surgery. The electronic search and the eligibility of studies were independently assessed by two authors (T.G.D and I.C.). No restrictions on the study design were applied. The first selection was based on the title, the second on the abstract, and the third on the full-text article. The bibliography was also analyzed to avoid missing potentially relevant publications. The most relevant articles for the purposes of this narrative review were included.

3. Results

In the context of advanced ovarian disease, the role of laparoscopy in mapping pathological dissemination is widely recognized. This recognition is clearly evident in authoritative sources such as the recent ESMO-ESGO consensus conference [4] and in the American guidelines issued by the National Comprehensive Cancer Network® (NCCN®) [44]. In these documents, laparoscopy is universally accepted as a reliable prediction tool for quantifying tumor burden and is also an optimal predictor for cytoreduction planning.

The first study to determine the role of diagnostic laparoscopy in detecting optimally cytoreducible patients (reported in the study as RT ≤ 1 cm) was performed by an Italian group in 2005 [45]. A total of 64 patients underwent a diagnostic LPS; in 6 cases a benign disease was diagnosed. However, in 60.9% of cases, the abdominal disease during laparoscopy was judged to be suitable to reach RT</= 1 cm. In the remaining 39.1% a mini laparotomy was performed to re-evaluate the extent of the disease and the concordance rate about an impossible optimal cytoreduction was 100%.

The use of scoring systems represents a method for comparing results and attributing them objectively to determine the most appropriate treatment for each patient. Nevertheless, this procedure is still a considerable challenge and the use of laparoscopic scoring is a potential strategy to minimize unnecessary laparotomies for the patients in question.

Interestingly, the data analysis highlighted that the pathological involvement of some anatomical structures allows to predict with good accuracy (at least 80%) the possibility of performing an optimal cytoreduction: ovarian masses, omental cake, peritoneal carcinosis, diaphragmatic carcinosis, mesenteric retraction, bowel infiltration, stomach infiltration, liver metastases and bulky lymph nodes.

These parameters were re-analyzed by the same group in a subsequent study [46]. A score including 6 of the listed anatomical districts has been proposed for the classification of patients into optimally cytoreducible and not optimally cytoreducible. The presence of ovarian masses and macroscopically pathological lymph nodes did not meet the authors' inclusion criteria for inclusion in the proposed score (specificity ≥ 75%, positive predictive value (PPV) ≥ 50%, and negative predictive value (NPV) ≥ 50%). Each parameter included in the score was assigned a value of 2 and a score was assigned to each patient. This score has been defined as “predictive index score” (PIV, also known as “*Fagotti score*”) and the cut-off≥ 8 identified patients undergoing suboptimal surgery. Subsequently, an attempt to validate this score externally was made comparing the values assigned to each variable and the overall PIV obtained in 17 centers specialized in gynecological oncological surgery with those of the center where the score was created [47]. An accuracy of more than 80% has been achieved in all centers except one.

A modified score was proposed in 2008 by Brun et al. including, among the parameters to be evaluated during diagnostic laparoscopy, only 4 of the 8 anatomical structures identified by Fagotti et al.: diaphragmatic carcinosis, mesenteric retraction, stomach infiltration and liver metastases [48]. Each of the listed parameters is assigned a value of 2 if macroscopically involved by the disease and a cut-off ≤ 4 was identified to consider the patient optimally cytoreducible. The authors concluded that the use of this modified score allowed the detection of patients not optimally cytoreducible with sensitivity, specificity, PPV, NPV, and accuracy of 35%, 100%, 100%, 43%, and 56% respectively.

Petrillo et al., identifying 2 variables as "absolute criteria of unresectability" (miliaric carcinomatosis on the serosa of the small bowel and mesenterial retraction), proposed another modified score by assigning a score of 2 points to each of the 6 variables included: (1) massive peritoneal involvement and/or a miliary pattern of distribution for parietal peritoneal carcinomatosis;

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(2) widespread infiltrating carcinomatosis, and/or confluent nodules to the most of the diaphragmatic surface; (3) tumor diffusion along the omentum up to the large stomach curvature; (4) possible large/small bowel resection (excluding, recto-sigmoid involvement, giving its pelvic localization and since posterior exenteration is considered a standard surgical procedure in AEOC); (5) obvious neoplastic involvement of the stomach, and/or lesser omentum, and/or spleen; and (6) liver surface lesions larger than 2 cm [49]. After retrospectively applying this score to 234 patients with AEOC who underwent a diagnostic laparoscopy and subsequent primary cytoreduction, they have demonstrated that a PIV >10 correlated with the possibility of obtaining an optimal cytoreduction (RT< 1 cm) with a positive predictive value of 100%; moreover, this PIV value was associated with a high (85.7%) rate of postoperative complications (Clavien/Dindo 5-6).

Another Italian group has demonstrated in an article published in 2006, that the use of laparoscopy allowed to selection of patients eligible for optimal cytoreduction based on the intrabdominal extension of disease [50]. Eighty-seven patients have undergone a diagnostic laparoscopy and 37 of them received neoadjuvant chemotherapy because they were not considered to be able to tolerate major surgery (4/87 patients; 4.6%) or because the detection during laparoscopy of at least one of the following (30/34; 88,2%): extended visceral peritoneal metastases, large involvement of upper abdomen, extended small bowel involvement, multiple liver metastases, heavily bleeding tumoral tissue. Due to the use of a minimally invasive technique, the authors found a low rate of major complications in both groups (only 1 case in the group of patients considered more fragile or with advanced disease), with RT=0 in the group subjected to PDS of 96% and in the group subjected to IDS of 86%, finding only 2 metastases localized at the 5 mm trocar's access. One of the most interesting points is that the authors compared the data obtained with those obtained before the introduction of laparoscopy as a technique to guide the therapeutic path of patients with ovarian cancer; indeed, although only 61% of patients undergoing debulking surgery (obtaining any residual disease), much lower than 95% in the previous period, the optimal debulking rate was increased from 46% to 96%.

The first multicentric randomized controlled trial (RCT) on this topic was published in 2017 by Rutten et al. [51]. Two hundred and one patients with epithelial ovarian cancer (EOC) were included in this trial. Due to the use of a minimally invasive technique the rate of not optimal cytoreduction (RT>1 cm) in the group that used this approach was significantly reduced compared to the counterpart (10% vs 39%, relative risk [RR], 0.25; 95% CI, 0.13 to 0.47; p=0.001). The parameters used to predict the non-cytoreducibility during laparoscopy were mainly the extensive involvement of the diaphragmatic peritoneum and the presence of diffuse intrabdominal disease. No significant differences were found in overall survival (OS) and progression-free survival (PFS) between the groups analyzed.

Although Fagotti's index is mostly used as the tool of choice among gynecological oncology specialists in Europe for predicting surgical cytoreduction, laparoscopic predictive models used for ovarian cancer analysis also include the peritoneal carcinosis index, originally described by Sugarbaker [52]. The abdominal cavity is divided into nine anatomical regions, which include the right hypochondrium, epigastrium, left hypochondrium, right flank, mesogastrium, left flank, right iliac fossa, hypogastrium and left iliac fossa. In addition, four specific subdivisions corresponding to the gastrointestinal tract are delineated: the upper jejunum, the lower jejunum, the upper ileum and the lower ileum. Each area is evaluated according to a scoring system in which it is assigned: 0 with no evidence of tumor; 1 when the tumor is less than 0.5 cm; 2 when the tumor is between 0.5 and 5 cm; 3 when the tumor exceeds 5 cm or merges with other lesions.

The total score varies between 0 and 39, with a 'cut-off' value between 10 and 20 to determine the adequacy of surgical cytoreduction [53-54].

Recently, Di Donna et al. suggested that the laparoscopic score assessment had high accuracy for optimal cytoreduction in AOEC patients undergoing PDS or IDS [55]: in particular, in patients undergoing PDS, the laparoscopic Predictive Index (PI) and the laparotomic Peritoneal Cancer Index (PCI) had the best accuracies for complete cytoreduction (R0); in women undergoing IDS, the

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laparotomic PI (Area under the ROC Curve (AUC) = 0.75) and the laparoscopic PCI (AUC= 0.87) were associated with the best accuracy in R0 prediction.

A comparative analysis of the scores developed by Sugarbaker and Fagotti, aimed at assessing their efficacy in predicting complete debulking, performed by either laparoscopic or laparotomic approaches, was conducted within a non-randomized retrospective study conducted by Climent et al [56]. This study involved a cohort of 34 patients who met the eligibility criteria, 85.3% of whom had peritoneal carcinomatosis of ovarian origin. The analysis clearly revealed that the peritoneal carcinomatosis indicator developed by Sugarbaker proved to be the strongest predictor, regardless of the surgical approach employed, whether laparoscopic or laparotomic.

The results of the analysis indicated that when the Peritoneal Carcinomatosis Score (PCI) ≥ 20, the test achieved a sensitivity and specificity of 43% and 88%, respectively. The overall accuracy of the index was 79%, with positive and negative prediction values of 50% and 86%, respectively.

These results emphasized that the peritoneal carcinomatosis index described by Sugarbaker constitutes a valid diagnostic tool that possesses considerable prognostic value in the evaluation of peritoneal carcinomatosis of gynecological origin.

Among the various predictive models used to assess suitability for surgical cytoreduction for advanced ovarian cancer are the R3 and R4 models, analyzed in the study by Llueca et al [53]. A group of 110 patients with advanced ovarian cancer was included in the study. The data extracted from the cohort were used to develop two separate predictive models. Clinical, pathological and surgical data were diligently collected and submitted for analysis in order to determine the Peritoneal Tumor Load Index (PCI) and the Lesion Size Relative Score. The R3 model score is a measure of the severity of the bowel obstruction, based on preoperative imaging, surgical findings, and clinical symptoms. The R4 model score adds operative PCI to the R3 model score, which may provide a more accurate assessment of the severity of the obstruction and the risk of complications. Lesions were scrupulously evaluated in 13 different anatomical regions within the abdomen and pelvis, with subsequent transposition of the respective dimensions into a numerical scale ranging from 0 to 3, thus contributing to an overall maximum score of 39. In the situation where more than one lesion was found within a single region, the lesion with the largest size was selected for inclusion in the score calculation. About the cytoreduction result, the following definition was adopted: complete cytoreduction was categorized as the absence of any residual macroscopic presence of tumor, while optimal cytoreduction was defined as the presence of a residual tumor with a diameter of less than 1 centimeter. In contrast, suboptimal cytoreduction was established in the presence of a residual tumor greater than 1 centimeter in diameter. Each model presented a tripartite stratification of risk score and proved capable of predicting both suboptimal or complete and optimal surgical cytoreduction eligibility, with a sensitivity of 83% (R4 model) and 69% (R3 model), respectively. A PCI > 20 was found to be a significant risk factor for surgical unresectability.

A subsequent study conducted by Llueca A et al. [57] conducted an analysis of the prognostic performance of these models, comparing them with the Fagotti model, in order to predict suboptimal surgical cytoreduction in a cohort of 103 patients with advanced ovarian cancer. The results showed that the three models were able to satisfactorily predict suboptimal surgical cytoreduction situations for advanced ovarian cancer, although they were most reliable in predicting complete surgical cytoreduction. Model R4 demonstrated superior efficacy compared to the others by virtue of the inclusion of laparotomic assessment of the peritoneal carcinomatosis index.

4. Discussion

Due to the introduction into clinical practice of maintenance therapies (in particular Vascular endothelial growth factor (VEGF) inhibitors and PARPi(s)), ovarian epithelial carcinomas can be considered a chronic disease [4,17,19–21,58]. Therefore, although relapse rates change according to the type of maintenance therapy that each patient can use, based on their molecular status (mutations in BRCA and HRD genes) and on the County's reimbursement policy, the course of the disease is predominantly influenced by the radicality of the surgical treatment (primary or after neoadjuvant chemotherapy) [19–23,59].

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At present obtaining an absent residue of disease is the main goal of the surgical approach; indeed, an RT=0 is a watershed to direct each patient toward a first-instance surgery or its revaluation after 3 or more cycles of platinum-based chemotherapy [60–63].

The ability to perform optimal cytoreduction is a crucial aspect of cancer surgery. It is primarily tied to the extent of the disease, a parameter that is of considerable importance. An accurate assessment of the extent of the tumor is essential to determine whether it is possible to completely remove the disease without compromising the functionality of the surrounding organs. However, it should be noted that the main challenge in this context is the validation of predictive models. For this reason, several authors have proposed surgical and non-surgical models aimed at assessing the feasibility and success of optimal cytoreduction of advanced ovarian cancer [52-53, 64].

The complexity of laparoscopy in advanced ovarian carcinoma is intrinsically related to its limited ability to exhaustively explore deep abdominal cavities. This inherent restriction of laparoscopic methodology results in a limitation in anatomical imaging, which, consequently, may be a major determinant of surgical unresectability of the tumor. Specifically, anatomical regions such as the hepatic pedicle, the retrohepatic region and the retroperitoneal space may be under-represented or even completely inaccessible by the laparoscopic approach. In view of this, there is a need for advanced and specific imaging methodologies to conduct an accurate analysis of these anatomical regions with high precision. This approach is a crucial tool with a view to minimizing the adoption of non-core laparotomies, ultimately reducing the rate of suboptimal cytoreduction, in line with optimizing surgical practice and increasing therapeutic efficacy [65]. For this reason, Llueca et al. described two models combining both laparoscopic and radiological images (model R3) and, subsequently, laparotomic findings (model R4) [53].

Several authors have reported promising results in predicting the suitability for optimal cytoreduction using radiological imaging alone; however, it is imperative to emphasize that these results have not yet been universally validated in various medical institutions [66]. Therefore, it is essential to exercise due caution in the use of preoperative radiological signs as a preeminent decision-making tool for the targeting of cytoreduction strategies, particularly when considered exclusively in the decision-making context regarding the outcome of the cytoreductive procedure.

Axtell et al. analyzing the data of 65 patients with AEOC subjected to PDS have identified 2 predictors of suboptimal cytotoxicity evaluable with CT scan: the presence of diaphragmatic disease and the involvement of the intestinal mesentery (risk ratio 5.69 e 6.07, respectively) [67]. However, the authors suggest using such predictors critically in the decision between upfront surgery and IDS.

Other authors have hypothesized a role of the massive ascitic effusion in predicting an optimal cytoreduction, however, without being able to demonstrate any statistically significant correlation [62,68-69].

In this same line of research, Gerestein et al. conducted a study to develop a nomogram based on predictive parameters that may facilitate the prediction of suboptimal cytoreduction, making it a useful clinical practice tool [70].

In this study, a sample of 115 patients was enrolled. The analysis identified that preoperative platelet count (p=0.1990), diffuse peritoneal thickening (p=0.0074), and the presence of ascites in at least two-thirds of the CT scan sections were predictive of residual disease greater than 1 centimeter after cytoreduction. This nomogram accurately predicted the surgical outcome in 74% of the patients.

The developed nomogram has the potential to be used in estimating surgical outcomes and identifying patients who might benefit from alternative therapeutic approaches. However, further external validation studies are needed to confirm the reliability and applicability of this tool in clinical practice.

In the context of prospective strategies for determining the appropriateness of cytoreduction in advanced ovarian cancer, gene expression analysis emerges as a constantly developing field of research. This discipline focuses on understanding and utilizing genetic information in order to prescribe the most appropriate therapeutic strategy for patients with malignancies. This approach is based on the assumption that the genetic profile of tumors may condition the response to specific treatments, and therefore allows the therapeutic decision on optimal cytoreduction to be guided by

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the analysis of the tumor's genetic signatures. The prediction perspective thus obtained assumes a key role in determining whether surgical action is warranted, as well as outlining the appropriate timing and extent of surgery itself. This is achieved through the application of sophisticated methodologies for analyzing the genetic profile of tumors, such as transcriptomic analysis of messenger RNA and genomic investigation of genetic mutations. In a study conducted by Reem Abdallah et al. involving a sample of 124 female patients, an initial analysis was carried out involving over 12,000 genes. This investigation revealed that 58 of these genes had a predictive accuracy for cytoreduction of 69% ($p = 0.005$). In a second in-depth analysis, 220 genes emerged as predictors of cytoreduction accuracy in 74% of cases. Unfortunately, it must be emphasized that these patterns were not uniformly confirmed in independently conducted gene expression experiments [71].

Furthermore, several tumor markers have been proposed to predict the cytoreductivity of malignant ovarian tumors: Angioli et al. proposed a value of the serum tumor marker Human epididymis protein 4 (HE4) ≤ 262 pmol/L as predictive of RT≤ 1 cm; studies on the use of pre-operative cancer antigen 125 (CA125) values are conflicting about the possibility of its use as a predictor of surgical radicality [72]. Obviously, the association of different parameters has been considered to propose an accurate score without having reached this goal until now [73–75]. Interestingly, further therapeutic targets are under evaluation [76-80]. The adoption of those new strategies would potentially improve response to treatments and patients' outcomes [76-80]. Prediction of optimal cytoreduction through gene and marker expression is an evolving field that could have a significant impact on personalizing treatments for cancer patients.

Similarly, we are able to extend this not only to the context of predicting suboptimal or optimal cytoreduction but also to the anticipation of tumor sensitivity to chemotherapeutic agents and to the prognostic estimation of patients, allowing the delineation of therapeutic outcomes before treatment initiation. Regarding the latter, radiomic nomograms based on MRI image analysis were developed, demonstrating a remarkable accuracy, sensitivity, and specificity of 85.0%, 87.0%, and 80.0%, respectively, in the context of the validation groups. These results suggest that MRI-based radiomic nomograms may be a reliable tool to guide therapeutic decisions and improve the accuracy in predicting therapeutic outcomes in patients with advanced ovarian cancer [81 82].

In conclusion, the assessment of the extent of intra- and extra-abdominal pathology is of paramount importance in the management of patients with AEOC. By using a multidisciplinary approach that combines radiological methods such as MRI, PET and computed tomography, surgical techniques such as mini-laparotomy and laparoscopy, and genetic and serological markers such as CA-125 and HE4, it is possible to customize the therapeutic approach for these patients. The use of advanced imaging methods such as MRI and PET allows for a more detailed assessment of the extent of the disease, identifying possible metastases and involvement of surrounding tissues. Mini-LPTM and LPS surgical techniques offer less invasive options for the removal of ovarian tumors while reducing recovery time and potential side effects. Genetic markers such as CA-125 and HE4 can provide further information on the presence and severity of the tumor. In addition, these markers can be used to monitor response to treatment and disease recurrence. The multidisciplinary approach described is essential to improve the outcomes of patients with AEOC, allowing the most appropriate treatment to be adopted according to the severity and extent of the disease. This holistic approach aims to improve the quality of care and provide personalized treatment to people facing the challenges of advanced epithelial ovarian cancer.

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