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Laparoscopic prediction of primary cytoreducibility of epithelial ovarian cancer

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To the Kind Attention of the Editor and Reviewers,
Minerva Obstetrics and Gynecology.

Thank you for giving us the opportunity to submit a revised draft of our manuscript titled "Laparoscopic prediction of primary cytoreducibility of epithelial ovarian cancer" (Minerva Obstet Gynecol-5452). We appreciate the time and effort that you and the reviewers have dedicated to providing your valuable feedback on our manuscript. We are grateful to the reviewers for their insightful comments on our paper. We have been able to incorporate changes to reflect most of the suggestions provided by the reviewers that you can find highlighted within the manuscript.
Here is a point-by-point response to the reviewers' comments and concerns.

According to the Editor's suggestions:
We thank the authors for having submitted it to this journal. Two of the referees expressed major concerns on this article. We recommend to largely revision of the article before resubmitting but given this initial evaluation we cannot guarantee the future acceptance of the article.

We are grateful for the careful review of our manuscript, the positive comments, and the precious suggestions to improve it.

According to the Reviewer #1's suggestions:
Thanks for the submission. It is an important subject. It would help if you summarized the included papers in a table including the type of studies and main results.

Thank you for these relevant suggestions. We have included a table accordingly.

The language and flow need serious revision if not complete re-writing.

Thank you for your valuable suggestion. A native English speaker was involved in the revision of the entire manuscript to correct grammar and readability.

Consider commenting on the quality of the papers included in the study.

As suggested, we have reported in the table comments on the quality of the studies included.

If re-written, kindly ensure clarity of ideas.

Thanks for highlighting this important point. We decided to revise the entire manuscript to improve its clarity.

According to the Reviewer #2's suggestions:

No changes

We are grateful and honored for your appreciation.

According to the Reviewer #3's suggestions:

Authors attempted to bring a review of the literature regarding the role of laparoscopic evaluation and prediction in advanced ovarian cancer surgery, however, the presented article reflects a chapter of a book further than a review article. The paper in its current fashion does not add to the literature and does not serve as a review to the readers. I would recommend rejecting the article, however, It could be considered in a special issue or as a chapter of a special book on the topic.

We thank the reviewer for the precise comments. The goal of our review is to summarize the data currently available on the laparoscopic prediction of primary cytoreducibility of epithelial ovarian cancer. We think that this review adds a broad-based view on the subject, which remains an important topic.

Actually, the paper handles this issue comprehensively, however, long conversations and discussions should be shortened and repetitions should be avoided.

Thank you for this consideration. We have revised the entire manuscript to improve its clarity and readability.

For review articles there is a strong need for summarizing tables which obviously shorten the article. A statistical method to summarize the discussed articles and their results in tables should be incorporated.

Thank you for these relevant suggestions. We have included a table accordingly.

Novel methods and scores such as the Cukurova score should be considered and referenced.

Thank you for this important suggestion. We have included this novel and interesting score in the discussions.

In addition to the above comments, all spelling and grammatical errors pointed out by the reviewers have been corrected. We hope that the new version of the manuscript can be considered in line with the high-quality standards of the Journal. We look forward to hearing from you in due time regarding our submission and to respond to any further questions and comments you may have.

Sincerely,

On behalf of the co-authors,

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Manuscript title: Laparoscopic prediction of primary cytoreducibility of epithelial ovarian cancer

Running title: Laparoscopic score of cytoreducibility in 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. Effectively, it is a severe disease that requires a multidisciplinary approach for optimal treatment. Surgery currently is the cornerstone of its treatment and numerous methods have been analyzed and developed to predict the possibility of obtaining a residual tumor of 0 (RT=0). Th is review aims to analyze the available data in the literature about minimally invasive surgical methods to predict an RT=0 in patients

with advanced epithelial ovarian carcinoma undergoing primary debulking surgery. An accurate review of the literature has been performed on the available data about the surgical criteria of cytoreducibility during primary debulking surgery . An accurate assessment of the extent of intra- and extra-abdominal pathology is essential to guide the surgeon in the most appropriate therapeutic choice for patients with ovarian cancer and multidisciplinary approaches that combine different methodologies such as radiological methods (magnetic resonance imaging, positron emission tomography and computed tomography), surgical (mini-laparotomy, laparoscopy) and serological (CA-125, HE4) data provide a complete picture in determining the extent of the tumor and an enormous aid in personalizing the therapeutic approach.

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

TEXT

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 an estimated 13,270 deaths in the US in 2023 [1-3]. It is most common in women over the age of 50 and its lethality is due to delayed diagnosis until advanced stages (International Federation of Gynecology and Obstetrics – FIGO stage III-IV) and to the actual lack of screening programs for an 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 until 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 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 of antiangiogenic and poly-ADP ribose polymerase (PARP) inhibitors (PARPi) opened up new therapeutic scenarios [14-24].

Currently, s urgery followed by systemic therapy is the cornerstone of the treatment of AEOC [25-31]; however, it is essential to personalize the therapeutic approach considering patients and tumor characteristics . The goal of the 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 3 or more cycles of platinum-based chemotherapy to reduce the burden of disease. Patients may not be eligible for upfront surgery for a high load of disease and/or for the involvement of anatomical structures that cannot be excised with surgery, for the massive involvement of 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 increases the risk of intra, peri- and post-operative complications and cause an additional risk of death [32-41]. Assessing the extent 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 RT=0 (genetic, imaging, serological, surgical), but, to date, none of them can be considered the gold standard. Despite the known advantages of laparoscopic surgery in minimizing patient morbidity, in cases of uncertain operative status, an exploratory laparotomy may be strategically considered. 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. Th is narrative review aims 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 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-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 this narrative review were included.

3. Results

The role of laparoscopy in mapping advanced ovarian disease dissemination is widely recognized. This is 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], where laparoscopy is accepted as a reliable prediction tool for quantifying tumor burden and it is an optimal predictor for cytoreduction planning.

The studies included are summarized in Table 1.

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 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 and to minimize unnecessary laparotomies.

Interestingly, the pathological involvement of some anatomical structures allows predicting 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 to classify patients into optimally 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, 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 an alternative modified score evaluating 6 variables: (1) massive peritoneal involvement and/or a miliary pattern of distribution for parietal peritoneal carcinomatosis; (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 they demonstrated that a PIV >10 correlated with the impossibility 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 in 2006 demonstrated 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 able to tolerate major surgery (4/87 patients; 4.6%) or due to the detection 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 fragile or with advanced disease), with RT=0 in the PDS group of 96% and in the IDS group of 86%, finding only 2 metastases localized at the 5 mm trocar's access. Moreover, 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 debulking surgery was performed only in 61% of cases (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] including 201 patients with epithelial ovarian cancer (EOC). Thanks to the use of a minimally invasive technique the rate of not optimal cytoreduction (RT>1 cm) 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 principally 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 by 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, right and left hypochondrium, epigastrium, right and left flank, mesogastrium, right and left iliac fossa and hypogastrium. 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 laparotomic PI (Area under the ROC Curve (AUC) = 0.75) and the laparoscopic PCI (AUC= 0.87) were associated with the best accuracy in RT=0 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 revealed that the peritoneal carcinomatosis indicator proved to be the strongest predictor, regardless of the surgical approach employed (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.

The R3 and R4 models are alternative predictive models to assess suitability for surgical cytoreduction for advanced ovarian cancer [53]. Overall, 110 patients with advanced ovarian cancer were included. The data extracted from the cohort were used to develop two separate predictive models. Clinical, pathological and surgical data were collected and submitted for analysis 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 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, contributing to an overall maximum score of 39. If more than one lesion was found within a single region, the largest was included in the score calculation. Complete cytoreduction was categorized as the macroscopic absence of tumor residual; optimal cytoreduction was defined as

the presence of a residual tumor with a diameter of less than 1 centimeter; suboptimal cytoreduction was established in the presence of a residual tumor greater than 1 centimeter. 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] analyzed the prognostic performance of these models, comparing them with the Fagotti model, 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 for advanced ovarian cancer, although they were most reliable in predicting complete surgical cytoreduction. Model R4 demonstrated superior efficacy compared to the others by the inclusion of laparotomic assessment of the peritoneal carcinomatosis index.

4. Discussion

After 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 benefit from, according to the molecular status (mutations in BRCA and HRD genes) and 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].

At present, obtaining an absent residue of disease is the main goal of the surgical approach; indeed, an RT=0 is a breakpoint 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 and its accurate assessment is essential. 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 results in a limitation in anatomical imaging, which may be a major determinant of tumor surgical unresectability. 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 and there is a need for advanced and specific imaging methodologies to conduct an accurate analysis of these anatomical regions. This approach is a crucial tool to minimize the adoption of unnecessary laparotomies[65].

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 [66].

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 demonstrating any statistically significant correlation[62,68,69].

In this same line of research, Gerestein et al. conducted a study including of 115 patients to develop a nomogram based on predictive parameters that may facilitate the prediction of suboptimal cytoreduction [70]. 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% cases. However, further external validation studies are needed to confirm the reliability and applicability of this tool in clinical practice.

Moreover, gene expression analysis emerges as a constantly developing field of research. This discipline focuses on understanding and utilizing genetic information to prescribe the most appropriate therapeutic strategy for patients with malignancies. This approach assumes that the genetic profile of tumors may condition the response to specific treatments and assumes a key role in determining whether surgical action is warranted, as well as outlining the appropriate timing and extent of surgery. 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. 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, 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]. 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]. 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. Many 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, suggesting 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].

Finally, the Cukurova score was recently proposed for stratifying patients who may benefit from primary debulking surgery [83]. This score integrates the performance status of each patient with laparoscopic and video-assisted thoracic surgery parameters, clinical parameters and anticipated surgical procedures with imaging. The authors showed that a cut-off ≤ 12 can predict in over 96% of cases a complete cytoreduction rate at primary debulking surgery for AEOC, moreover, a score >12 correlated with post-operative complication rates and higher mortality [83].

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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Conflicts of interest

The authors declare no conflict of interest.

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Authors' contributions

Conceptualization and writing—review and editing, T.C.D.; methodology and software, I.C.; E.D.A.; validation, V.D.D., L.M. and O.D.; formal analysis, V.C.; investigation, S.C.; resources, A.R.B.; data curation, A.S.L.; writing—original draft preparation, A.F.; L.M.; visualization, G.B.; supervision, A.G. and D.C.; project administration, V.D.D. All authors have read and agreed to the published version of the manuscript.

Table legend

Table 1. Summary of studies included.

Table 1. Summary of studies included.

Author	Year	Type	N pat	Score	Objective	Results	Conclusion
Fagotti [45]	2005	Prospective	64	Fagotti score	Optimal cytoreduction	Accuracy rate of laparoscopy was 90%.	Laparoscopy can be considered imposable to standard longitudinal laparotomy in identifying not optimally resectable
Fagotti [46]	2006	Prospective	64	Fagotti score	Optimal cytoreductive surgery	A predictive index score >=8 identified patients undergoing suboptimal surgery with a specificity of 100%	The reliability of laparoscopy in assessing the chance of optimal cytoreduction can be improved by using a simple scoring system.
Fagotti [47]	2013	Prospective	120	Fagotti score	Optimal cytoreduction	All but 1 satellite center, reached an accuracy rate of 80% or greater for both single parameters and overall score	LPS allows an accurate and reliable assessment of intraperitoneal diffusion of disease
Jean-Luc Brun [48]	2008	Retrospective	55	Modified score of Fagotti score	Optimal cytoreductive surgery	A modified score of >or=4 was associated with suboptimal cytoreduction.	This simplified laparoscopy-based score was at least as accurate as the Fagotti score to predict resectability
M Petrillo [49]	2015	Prospective	234	Laparoscopy-based predictive index model	Incomplete cytoreduction	At a Laparoscopy-based predictive index model ≥ 10 the chance of achieving complete Primary debulking surgery was 0, and the risk of unnecessary laparotomy was 33.2%.	Staging laparoscopy is confirmed as an accurate tool in the prediction of complete Primary debulking surgery
Roberto Angioli [50]	2006	Prospective	87	Diagnostic open laparoscopy	Optimal primary cytoreductive surgery	Diagnostic laparoscopy allows to select patients for optimal primary cytoreductive surgery.	Diagnostic open laparoscopy could be considered a valid diagnostic tool in evaluating the extent of disease
Marianne J Rutten [51]	2012	Randomized	200	Additional diagnostic laparoscopy	Suboptimal cytoreductive surgery	Patients who have disease considered to be resectable to less than one centimeter	Laparoscopy before starting treatment for ovarian cancer can be an additional diagnostic tool to predict the outcome of primary debulking surgery

						should undergo primary debulking surgery to improve prognosis.	
Antoni Llueca [53]	2019	Prospective, analyzed retrospectively	110	R4 model (included operative PCI), R3 model	Suboptimal and optimal cytoreductive surgery and	Sensitivity of 83% (R4 model) Sensitivity of 69% (R3 model)	PCI>20 was a major risk factor for unresectability
Antoni Llueca [54]	2018	Retrospective	80	PCI score	evaluate the prognostic value of PCI	PCI was significantly associated with suboptimal surgery	PCI may provide important information for surgical planning
Mariano Catello Di Donna [55]	2023	Retrospective	100 (69 underwent PDS 31 underwent NACT and IDS)	Predictive Index score Peritoneal Cancer Index score	Complete cytoreduction	In patients undergoing PDS, the laparoscopic PI and the laparotomic PCI had the best accuracies for complete cytoreduction (R0) In the IDS group, the laparotomic PI were associated with the best accuracy in R0 prediction	Laparoscopic score assessment had high accuracy for optimal cytoreduction in patients undergoing PDS or IDS.
María Teresa Climent [56]	2021	Retrospective	34	Fagotti's index Sugarbaker's peritoneal cancer index	Optimal and suboptimal surgery	The rate of complete cytoreductive surgery was 79.4% The highest sensitivity was obtained with a PCI > 20.	The best diagnostic method to classify patients with peritoneal cancer is the PCI
Antoni Llueca [57]	2021	Prospective, analyzed retrospectively	103	Fagotti R3 models R4 models	Suboptimal cytoreductive surgery	The three models were able to predict suboptimal cytoreductive, but they were more reliable for predicting complete cytoreductive surgery.	The R4 model discriminated better because it includes the laparotomic evaluation of the peritoneal carcinomatosis index.

Manuscript title: Laparoscopic prediction of primary cytoreducibility of epithelial ovarian cancer

Running title: Laparoscopic score of cytoreducibility in 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. Effectively, it is a severe disease that requires a multidisciplinary approach for optimal treatment. Surgery currently is the cornerstone of its treatment and numerous methods have been analyzed and developed to predict the possibility of obtaining a residual tumor of 0 (RT=0). Th is review aims to analyze the available data in the literature about minimally invasive surgical methods to predict an RT=0 in patients with advanced epithelial ovarian carcinoma undergoing primary debulking surgery. An accurate review of the literature has been performed on the available data about the surgical criteria of cytoreducibility during primary debulking surgery . An accurate assessment of the extent of intra- and extra-abdominal pathology is essential to guide the surgeon in the most appropriate therapeutic choice for patients with ovarian cancer and multidisciplinary approaches that combine different methodologies such as radiological methods (magnetic resonance imaging, positron emission tomography and computed tomography), surgical (mini-laparotomy, laparoscopy) and serological (CA-125, HE4) data provide a complete picture in determining the extent of the tumor and an enormous aid in personalizing the therapeutic approach.

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

TEXT

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 an estimated 13,270 deaths in the US in 2023 [1-3]. It is most common in women over the age of 50 and its lethality is due to delayed diagnosis until advanced stages (International Federation of Gynecology and Obstetrics – FIGO stage III-IV) and to the actual lack of screening programs for an 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 until 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 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 of antiangiogenic and poly-ADP ribose polymerase (PARP) inhibitors (PARPi) opened up new therapeutic scenarios [14-24].

Currently, s urgery followed by systemic therapy is the cornerstone of the treatment of AEOC [25-31]; however, it is essential to personalize the therapeutic approach considering patients and tumor characteristics . The goal of the 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 3 or more cycles of platinum-based chemotherapy to reduce the burden of disease. Patients may not be eligible for upfront surgery for a high load of disease and/or for the involvement of anatomical structures that cannot be excised with surgery, for the massive involvement of 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 increases the risk of intra, peri- and post-operative complications and cause an additional risk of death [32-41]. Assessing the extent 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 RT=0 (genetic, imaging, serological, surgical), but, to date, none of them can be considered the gold standard. Despite the known advantages of

laparoscopic surgery in minimizing patient morbidity, in cases of uncertain operative status, an exploratory laparotomy may be strategically considered. 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. Th is narrative review aims 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 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-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 this narrative review were included.

3. Results

The role of laparoscopy in mapping advanced ovarian disease dissemination is widely recognized. This is 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], where laparoscopy is accepted as a reliable prediction tool for quantifying tumor burden and it is an optimal predictor for cytoreduction planning.

The studies included are summarized in Table 1.

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 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 and to minimize unnecessary laparotomies.

Interestingly, the pathological involvement of some anatomical structures allows predicting 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 to classify patients into optimally 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, 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 an alternative modified score evaluating 6 variables: (1) massive peritoneal involvement and/or a miliary pattern of distribution for parietal peritoneal carcinomatosis; (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 they demonstrated that a PIV >10 correlated with the impossibility 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 in 2006 demonstrated 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 able to tolerate major surgery (4/87 patients; 4.6%) or due to the detection 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 fragile or with advanced disease), with RT=0 in the PDS group of 96% and in the IDS group of 86%, finding only 2 metastases localized at the 5 mm trocar's access. Moreover, 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 debulking surgery was performed only in 61% of cases (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]including 201 patients with epithelial ovarian cancer (EOC). Thanks to the use of a minimally invasive technique the rate of not optimal cytoreduction (RT>1 cm) 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 principally 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 by 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, right and left hypochondrium, epigastrium, right and left flank, mesogastrium, right and left iliac fossa and hypogastrium. 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 laparotomic PI (Area under the ROC Curve (AUC) = 0.75) and the laparoscopic PCI (AUC= 0.87) were associated with the best accuracy in RT=0 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 revealed that the peritoneal carcinomatosis indicator proved to be the strongest predictor, regardless of the surgical approach employed (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.

The R3 and R4 models are alternative predictive models to assess suitability for surgical cytoreduction for advanced ovarian cancer [53]. Overall, 110 patients with advanced ovarian cancer were included. The data extracted from the cohort were used to develop two separate predictive models. Clinical, pathological and surgical data were collected and submitted for analysis 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 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, contributing to an overall maximum score of 39. If more than one lesion was found within a single region, the largest was included in the score calculation. Complete cytoreduction was categorized as the macroscopic absence of tumor residual; optimal cytoreduction was defined as the presence of a residual tumor with a diameter of less than 1 centimeter; suboptimal cytoreduction was established in the presence of a residual tumor greater than 1 centimeter. 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] analyzed the prognostic performance of these models, comparing them with the Fagotti model, 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 for advanced ovarian cancer, although they were most reliable in predicting complete surgical cytoreduction. Model R4 demonstrated superior efficacy compared to the others by the inclusion of laparotomic assessment of the peritoneal carcinomatosis index.

4. Discussion

After 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 benefit from, according to the molecular status (mutations in BRCA and HRD genes) and 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].

At present, obtaining an absent residue of disease is the main goal of the surgical approach; indeed, an RT=0 is a breakpoint 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 and its accurate assessment is essential. 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 results in a limitation in anatomical imaging, which may be a major determinant of tumor surgical unresectability. 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 and there is a need for advanced and specific imaging methodologies to conduct an accurate analysis of these anatomical regions. This approach is a crucial tool to minimize the adoption of unnecessary laparotomies[65].

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 [66].

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 demonstrating any statistically significant correlation[62,68,69].

In this same line of research, Gerestein et al. conducted a study including of 115 patients to develop a nomogram based on predictive parameters that may facilitate the prediction of suboptimal cytoreduction [70]. 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% cases. However, further external validation studies are needed to confirm the reliability and applicability of this tool in clinical practice.

Moreover, gene expression analysis emerges as a constantly developing field of research. This discipline focuses on understanding and utilizing genetic information to prescribe the most appropriate therapeutic strategy for patients with malignancies. This approach assumes that the genetic profile of tumors may condition the response to specific treatments and assumes a key role in determining whether surgical action is warranted, as well as outlining the appropriate timing and extent of surgery. 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. 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, 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]. 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]. 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.

Many 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, suggesting 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].

Finally, the Cukurova score was recently proposed for stratifying patients who may benefit from primary debulking surgery [83]. This score integrates the performance status of each patient with laparoscopic and video-assisted thoracic surgery parameters, clinical parameters and anticipated surgical procedures with imaging. The authors showed that a cut-off ≤ 12 can predict in over 96% of cases a complete cytoreduction rate at primary debulking surgery for AEOC, moreover, a score >12 correlated with post-operative complication rates and higher mortality [83].

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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Conflicts of interest

The authors declare no conflict of interest.

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Authors' contributions

Conceptualization and writing—review and editing, T.G.D.; methodology and software, I.C.; E.D.A.; validation, V.D.D., L.M. and O.D.; formal analysis, V.C.; investigation, S.G.; resources, A.R.B.; data curation, A.S.L.; writing—original draft preparation, A.F.; L.M.; visualization, G.B.; supervision, A.G. and D.C.; project administration, V.D.D. All authors have read and agreed to the published version of the manuscript.

Table legend

Table 1. Summary of studies included.

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Author	Year	Type	N pat	Score	Objective	Results	Conclusion
Fagotti [45]	2005	Prospective	64	Fagotti score	Optimal cytoreduction	Accuracy rate of laparoscopy was 90%.	Laparoscopy can be considered imposable to standard longitudinal laparotomy in identifying not optimally resectable
Fagotti [46]	2006	Prospective	64	Fagotti score	Optimal cytoreductive surgery	A predictive index score >=8 identified patients undergoing suboptimal surgery with a specificity of 100%	The reliability of laparoscopy in assessing the chance of optimal cytoreduction can be improved by using a simple scoring system.
Fagotti [47]	2013	Prospective	120	Fagotti score	Optimal cytoreduction	All but 1 satellite center, reached an accuracy rate of 80% or greater for both single parameters and overall score	LPS allows an accurate and reliable assessment of intraperitoneal diffusion of disease
Jean-Luc Brun [48]	2008	Retrospective	55	Modified score of Fagotti score	Optimal cytoreductive surgery	A modified score of >or=4 was associated with suboptimal cytoreduction.	This simplified laparoscopy-based score was at least as accurate as the Fagotti score to predict resectability
M Petrillo [49]	2015	Prospective	234	Laparoscopy-based predictive index model	Incomplete cytoreduction	At a Laparoscopy-based predictive index model ≥ 10 the chance of achieving complete Primary debulking surgery was 0, and the risk of unnecessary laparotomy was 33.2%.	Staging laparoscopy is confirmed as an accurate tool in the prediction of complete Primary debulking surgery
Roberto Angioli [50]	2006	Prospective	87	Diagnostic open laparoscopy	Optimal primary cytoreductive surgery	Diagnostic laparoscopy allows to select patients for optimal primary cytoreductive surgery.	Diagnostic open laparoscopy could be considered a valid diagnostic tool in evaluating the extent of disease
Marianne J Rutten [51]	2012	Randomized	200	Additional diagnostic laparoscopy	Suboptimal cytoreductive surgery	Patients who have disease considered to be resectable to less than one	Laparoscopy before starting treatment for ovarian cancer can be an additional diagnostic tool to predict the outcome of primary debulking surgery

						centimeter should undergo primary debulking surgery to improve prognosis.	
Antoni Llueca [53]	2019	Prospective, analyzed retrospectively	110	R4 model (included operative PCI), R3 model	Suboptimal and optimal cytoreductive surgery and	Sensitivity of 83% (R4 model) Sensitivity of 69% (R3 model)	PCI>20 was a major risk factor for unresectability
Antoni Llueca [54]	2018	Retrospective	80	PCI score	evaluate the prognostic value of PCI	PCI was significantly associated with suboptimal surgery	PCI may provide important information for surgical planning
Mariano Catello Di Donna [55]	2023	Retrospective	100 (69 underwent PDS 31 underwent NACT and IDS)	Predictive Index score Peritoneal Cancer Index score	Complete cytoreduction	In patients undergoing PDS, the laparoscopic PI and the laparotomic PCI had the best accuracies for complete cytoreduction (R0) In the IDS group, the laparotomic PI were associated with the best accuracy in R0 prediction	Laparoscopic score assessment had high accuracy for optimal cytoreduction in patients undergoing PDS or IDS.
María Teresa Climent [56]	2021	Retrospective	34	Fagotti's index Sugarbaker's peritoneal cancer index	Optimal and suboptimal surgery	The rate of complete cytoreductive surgery was 79.4% The highest sensitivity was obtained with a PCI > 20.	The best diagnostic method to classify patients with peritoneal cancer is the PCI
Antoni Llueca [57]	2021	Prospective, analyzed retrospectively	103	Fagotti R3 models R4 models	Suboptimal cytoreductive surgery	The three models were able to predict suboptimal cytoreductive, but they were more reliable for predicting complete cytoreductive surgery.	The R4 model discriminated better because it includes the laparotomic evaluation of the peritoneal carcinomatosis index.