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RESEARCH ARTICLE

Current State of The Problem of Resectability Prediction and Personalized Treatment Selection in Advanced Ovarian Cancer (Literature Review)

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Abstract

Ovarian cancer remains one of the leading causes of mortality among gynecological malignancies: more than 70% of patients present with FIGO stage III–IV disease, and five-year survival in advanced disease does not exceed 30–40%. Complete (R0) cytoreductive surgery is the strongest independent prognostic factor, whereas current preoperative methods of resectability assessment — computed tomography, diagnostic laparoscopy, and tumor/inflammatory biomarkers — show limited and heterogeneous accuracy. This review summarizes current literature on the epidemiology and clinicopathological features of advanced ovarian cancer, the role of cytoreductive surgery as the principal prognostic factor, radiologic (R.E. Bristow index) and laparoscopic (A. Fagotti Predictive Index Value, PIV; Peritoneal Cancer Index, PCI) methods of resectability assessment, the role of CA-125, HE4 and the ROMA algorithm, systemic inflammatory markers (NLR, PLR, SII), molecular factors of the tumor microenvironment (VEGF, HIF-1α, CD8+, CD68+, PD-L1), the results of randomized trials comparing primary cytoreduction with neoadjuvant chemotherapy (EORTC-NCIC 55971, CHORUS, JCOG0602), and the prospects of machine learning and the TRIPOD framework for multiparametric predictive modeling. Most existing tools rely on a single diagnostic modality, while studies integrating clinical, laboratory, radiologic, endoscopic, morphological and molecular predictors into a single, properly validated quantitative model remain scarce. The development and validation of such multiparametric models is substantiated as a promising direction for personalizing surgical strategy in advanced ovarian cancer.

KEYWORDS

Ovarian cancer; cytoreductive surgery; resectability; Bristow index; laparoscopic Predictive Index Value; Peritoneal Cancer Index; CA-125; HE4; ROMA; systemic immune-inflammation index; VEGF; HIF-1α; PD-L1; neoadjuvant chemotherapy; machine learning; predictive model.

INTRODUCTION

Ovarian cancer occupies one of the leading positions in the structure of mortality from malignant neoplasms of the female

reproductive system, second in aggressiveness of course only to a few tumor localizations of the pelvic organs. The absence of specific clinical symptoms in the early stages of the disease leads to the fact that more than 70% of patients seek medical help already at stage III–IV according to the International Federation of Gynecology and Obstetrics (FIGO) classification, when the tumor is characterized by widespread peritoneal carcinomatosis, presence of ascites, involvement of the omentum, regional, and distant lymph nodes [19]. Despite significant progress in drug therapy and surgical techniques, five-year survival of patients with advanced ovarian cancer remains low and does not exceed 30–40%, defining this pathology as one of the most unresolved issues in modern gynecologic oncology.

The key factor determining the prognosis of the disease and patient overall survival is the ability to perform complete (R0) or optimal cytoreductive surgery. Numerous studies over recent decades have demonstrated that the absence of residual tumor after cytoreduction is the most significant independent factor of favorable prognosis, surpassing even disease stage and histological tumor type in its impact on survival [10]. However, existing preoperative methods for assessing resectability — imaging modalities, diagnostic laparoscopy, intraoperative staging — possess limited accuracy and largely depend on the subjective experience of the operating surgeon and radiologist. Consequently, a significant proportion of exploratory laparotomies still occurs, alongside the unjustified assignment of potentially resectable patients to neoadjuvant chemotherapy, which underscores the relevance of this review.

1. Epidemiology and Clinicopathological Features of Advanced Ovarian Cancer

Ovarian cancer represents a heterogeneous group of malignant neoplasms differing in histogenesis, molecular profile, and clinical course. According to modern concepts [20], epithelial ovarian tumors are classified into serous, mucinous, endometrioid, clear cell, and undifferentiated forms, with high-grade serous carcinoma accounting for the largest share among advanced stages and demonstrating the most aggressive behavior with early intraperitoneal dissemination.

The lack of effective early diagnostic screening tools leads to late detection: in the majority of patients, the tumor is diagnosed at stage III–IV according to FIGO [21], when the process is characterized by dissemination across the parietal and visceral peritoneum, omental involvement, ascites, and regional lymph node involvement. Stage IV, defined by distant metastases including pleural effusion with cytologically confirmed malignant cells or parenchymal metastases, is associated with the least favorable prognosis. The natural course of advanced ovarian cancer is primarily characterized by intraperitoneal dissemination forming multiple implantative foci on the peritoneum, omentum, intestinal loops, and diaphragm, which dictates the surgical complexity of the intervention and justifies the necessity of precise preoperative assessment of disease burden.

2. Cytoreductive Surgery as a Key Prognostic Factor

The concept of cytoreductive surgery as the cornerstone of treatment for advanced ovarian cancer has developed over the past four decades and remains a central element of the therapeutic algorithm. The volume of residual tumor following surgical intervention is the single most important independent prognostic factor determining progression-free and overall survival, exceeding stage, histological type, and grade in predictive power. A pooled analysis of three prospective randomized AGO-OVAR trials demonstrated that achieving macroscopically complete resection is associated with optimal survival outcomes regardless of initial tumor burden [10].

In accordance with modern terminology, surgery is categorized into complete cytoreduction (absence of macroscopically visible residual tumor, R0), optimal cytoreduction (residual lesions ≤ 1 cm), and suboptimal cytoreduction (residual lesions > 1 cm) [9]. The surgical complexity of achieving complete cytoreduction in advanced cases, combined with the risk of perioperative complications during extensive procedures (bowel resections, diaphragmatic peritonectomy, splenectomy, liver resections), necessitates accurate preoperative prediction of the likelihood of achieving a radical surgical outcome.

3. Preoperative Resectability Assessment Methods

3.1. Computed Tomography Criteria

Multidetector computed tomography remains the baseline preoperative imaging tool for staging disease extent. R.E. Bristow and colleagues developed and validated a predictive index based on CT features associated with a high probability of suboptimal cytoreduction: mesenterial involvement, multiple diaphragmatic implants, porta hepatis and omental

disease, as well as retroperitoneal lymphadenopathy; the area under the ROC curve (AUC) for this model was 0.969 [1]. Subsequent multi-institutional studies, including work by R.S. Suidan et al., confirmed the clinical utility of combining CT criteria with CA-125 levels, yet showed moderate reproducibility of exact cut-off thresholds when applied to external cohorts [23]. A limitation of CT criteria remains their moderate sensitivity in detecting intraoperative unresectability, restricting their standalone application for definitive surgical decision-making.

3.2. Laparoscopic Resectability Index

A major step forward in preoperative evaluation was the implementation of diagnostic laparoscopy. A. Fagotti et al. developed a laparoscopic Predictive Index Value (PIV), assessing peritoneal and diaphragmatic carcinomatosis, mesenteric infiltration, and involvement of the stomach, intestine, liver, and spleen; at a PIV ≥ 8, the positive predictive value for incomplete cytoreduction approached 100% [2]. Scoring these parameters allows prediction of the likelihood of optimal cytoreduction before laparotomy, reducing exploratory procedure rates. Limitations include its invasive nature and a degree of intraoperative observer subjectivity.

3.3. Peritoneal Cancer Index

To quantitatively measure peritoneal dissemination extent, the Peritoneal Cancer Index (PCI) — originally developed by P.H. Sugarbaker for gastrointestinal malignancies [3] — was adapted for ovarian cancer. The index divides the abdominal cavity into anatomical regions with lesion size scores assigned to each; the total PCI score correlates with the probability of complete cytoreduction and serves as a key intraoperative/laparoscopic predictor of resectability and postoperative complication risk.

3.4. Clinical and Functional Scoring Systems

Besides imaging and endoscopic tools, clinical models combining age, functional status, CA-125, and CT features are utilized for selecting primary cytoreduction candidates, alongside the AGO score (ECOG 0, absence of severe ascites, anticipated complete resection feasibility), originally developed for selecting recurrent disease candidates in the DESKTOP trial series [11]. A common limitation of these tools remains their reliance on a restricted set of predictors predominantly from a single diagnostic modality, leading to variable accuracy across different cohorts.

4. Tumor Markers and Systemic Inflammatory Indices

The tumor marker CA-125 remains the most widely used laboratory test in ovarian cancer diagnosis and monitoring; its serum concentration correlates with tumor burden, ascites volume, and peritoneal dissemination extent. Insufficient specificity of CA-125 prompted the search for complementary biomarkers, among which Human Epididymis Protein 4 (HE4) gained the highest clinical value. R.G. Moore et al. proposed the Risk of Ovarian Malignancy Algorithm (ROMA), integrating CA-125 and HE4 levels with menopausal status [12], the diagnostic accuracy of which was subsequently confirmed in prospective validation studies [13]. Combining markers yields higher malignancy risk stratification accuracy than either biomarker alone, although evidence regarding their independent predictive value for surgical resectability remains less consistent than for diagnostic triage.

In recent years, considerable attention has focused on the prognostic significance of systemic inflammatory response markers. Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic immune-inflammation index (SII: Platelets×NLR/Lymphocytes) have shown strong associations with tumor burden and surgical outcomes. Systematic reviews and meta-analyses show that an elevated SII is independently associated with worse overall survival (HR 2.35; 95% CI 1.56–3.55) and progression-free survival (HR 2.51; 95% CI 1.71–3.67) [14, 15], providing justification for incorporating such indices into comprehensive resectability models.

5. Molecular Mechanisms of Tumor Progression and Microenvironment

Ovarian cancer progression and peritoneal carcinomatosis formation are heavily driven by the biological features of the tumor microenvironment, including angiogenesis, hypoxia, and local immune responses. Vascular Endothelial Growth Factor (VEGF) is a key mediator of tumor angiogenesis; its overexpression correlates with ascites formation and peritoneal dissemination, forming the theoretical framework for anti-angiogenic therapies. Hypoxia-Inducible Factor 1-Alpha (HIF-1α) acts as a central cellular regulator under hypoxic conditions, driving transcription of genes responsible for angiogenesis, metabolic adaptation, and invasive capacity; its upregulation correlates with aggressive disease and chemotherapy resistance.

The cellular composition of the tumor microenvironment is equally critical. Tumor-infiltrating CD8+ cytotoxic T-lymphocytes are recognized as favorable prognostic markers linked to superior survival in high-grade serous carcinoma [16]. Conversely, accumulation of CD68+ M2-phenotype macrophages, which possess pro-inflammatory and pro-angiogenic properties, is associated with accelerated disease progression. PD-L1 expression on tumor and immune cells reflects local immune suppression and, as reported by J.R. Webb et al., correlates with both T-cell infiltration density and favorable outcomes in high-grade serous carcinoma [16], pointing to its utility as a potential predictor for ongoing immunotherapeutic evaluations.

6. Primary Cytoreductive Surgery versus Neoadjuvant Chemotherapy

An intense scientific debate continues regarding the optimal sequencing of surgical and systemic treatment in advanced ovarian cancer. Results from the landmark randomized EORTC-NCIC 55971 trial (I. Vergote et al.) showed comparable overall survival between primary cytoreduction and neoadjuvant chemotherapy followed by interval debulking surgery [4]. Similar conclusions were drawn in the British CHORUS trial (S. Kehoe et al.) [5], and a pooled individual patient data meta-analysis of both trials confirmed equivalent overall and progression-free survival between both strategies [8]. Conversely, the Japanese JCOG0602 trial failed to confirm non-inferiority of the neoadjuvant strategy regarding overall survival, though it demonstrated reduced treatment invasiveness and lower perioperative morbidity [6, 7], suggesting population and surgical expertise variations across trial regions.

These findings shifted the clinical debate from deciding which strategy is universally superior to accurately selecting individual patients in whom primary cytoreduction carries a high likelihood of complete resection. Selection criteria proposed by D.S. Chi et al., derived from primary debulking outcomes during the EORTC-NCIC 55971 era [9], along with the AGO score [11], form the foundation of current clinical guidelines; however, they lack systematic integration of laboratory and molecular biomarkers, limiting individual predictive precision. Ongoing investigations, including interim outputs from the TRUST trial, highlight the ongoing challenge of patient selection and variations in regional surgical expertise that directly influence achievable complete resection rates [17].

7. Predictive Modeling and Artificial Intelligence in Gynecologic Oncology

Advances in computational modeling and big-data aggregation have accelerated the deployment of machine learning algorithms in oncology. Random Forest, Gradient Boosting (XGBoost), and Artificial Neural Networks can uncover complex non-linear and multidimensional interactions among predictors that escape traditional regression methods, offering superior accuracy in predicting clinical endpoints, including resectability.

However, implementing artificial intelligence in clinical workflows demands rigorous methodological discipline: robust internal and external validation adhering to the TRIPOD (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis) guidelines [18], algorithmic interpretability via explainable AI techniques (e.g., SHAP feature importance analysis), and clinical utility confirmation using Decision Curve Analysis (DCA). Adherence to these standards is essential for transitioning predictive algorithms from statistical artifacts to clinically viable decision-support systems.

CONCLUSION

The literature review demonstrates an extensive evidence base regarding individual aspects of predicting resectability in advanced ovarian cancer — including radiologic, laparoscopic, laboratory, and molecular-biological predictors — as well as strategies for choosing between upfront surgery and neoadjuvant therapy. Each reviewed tool — the R.E. Bristow index, A. Fagotti laparoscopic index, Peritoneal Cancer Index, ROMA algorithm, systemic inflammatory markers, and tumor microenvironment biomarkers — possesses established, yet moderate and cohort-dependent, predictive accuracy when applied individually.

However, there is a lack of broadly validated studies in the literature that integrate the complete spectrum of clinical, laboratory, radiologic, endoscopic, morphological, and molecular parameters into a unified quantitative predictive model using modern machine learning methods and rigorous multi-stage validation according to TRIPOD guidelines. This gap highlights a crucial direction for future research: the development and clinical validation of multiparametric resectability models capable of offering an objective,

reproducible, and personalized approach to treatment selection in advanced ovarian cancer across routine clinical environments.

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