

Original Article



A triage strategy in advanced ovarian cancer management based on multiple predictive models for R0 resection: a prospective cohort study

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ABSTRACT

Objective: To present the surgical outcomes of advanced epithelial ovarian cancer (AEOC) since the implementation of a personalized approach and to validate multiple predictive models for R0 resection.

Methods: Personalized strategies included: 1) Non-invasive model: preoperative clinico-radiological assessment according to Suidan criteria with a predictive score for all individuals. Patients with a score 0–2 were recommended for primary debulking surgery (PDS, group A), or otherwise were counseled on the choices of PDS, neoadjuvant chemotherapy (NAC, group B) or staging laparoscopy (S-LPS). 2) Minimally invasive model: S-LPS with a predictive index value (PIV) according to Fagotti. Individuals with a PIV <8 underwent PDS (group C) or otherwise received NAC (group D). Intraoperative assessment (with Eisenkop, peritoneal cancer index [PCI], and Aletti scores) and surgical results were prospectively collected.

Results: Between September 2015 and August 2017, 161 pathologically confirmed epithelial ovarian cancer patients were included. A total of 52 (32.3%) patients had a predictive score of 0–2, and 109 (67.7%) patients had a score ≥3. Among these individuals, 41 (25.5%) patients received S-LPS. Finally, 110 (68.3%) patients underwent PDS (A+C), and 51 (31.7%) patients received NAC (B+D). The R0 resection rates in PDS and NAC patients were 56.4% and 60.8%, respectively. The area under the curve (AUC) of Suidan criteria was 0.548 for group (A+C). The AUC of Fagotti score was 0.702 for group C. The AUC of Eisenkop, PCI, and Aletti scores were 0.808, 0.797, and 0.524, respectively.

Conclusion: The Suidan criteria were not effective in these AEOC patients. S-LPS was helpful in decision-making for PDS and should be endorsed in the future.

Keywords: Predictive Model; Scoring Method; Surgical Outcomes; Perioperative Complications; R0 Resection; No Residual Disease

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: F.Z., W.H., W.X.; Data curation: F.Z., W.H., J.X., C.X., X.L.; Formal analysis: F.Z., W.H., J.Z., L.S., J.X., C.X., X.L., X.J.; Funding acquisition: W.X.; Investigation: F.Z., W.H., J.Z., L.S., X.J., B.R.; Methodology: F.Z., W.H., J.Z., L.S., X.J., W.X.; Project administration: W.X.; Resources: F.Z., W.H., J.X., C.X., X.L.; Software: F.Z., W.H., J.Z., L.S., X.J.; Supervision: W.X.; Validation: F.Z., W.H., J.X., C.X., X.L., B.R.; Visualization: J.X., C.X., B.R., W.X.; Writing - original draft: F.Z., W.H.; Writing - review & editing: J.Z., L.S., J.X., C.X., W.X.

INTRODUCTION

Ovarian cancer (OC) is one of the most common and lethal diseases among females worldwide. Approximately two-thirds of all patients are of advanced stage at diagnosis, with widespread intraabdominal disease [1,2]. The standard treatment for OC includes staging/debulking surgery and individual platinum-based adjuvant chemotherapy.

Several studies have reported that residual disease after primary debulking surgery (PDS) could independently influence patient survival. Individuals in the complete cytoreduction (no residual disease) group achieved the best prognosis among advanced epithelial ovarian cancer (AEOC) patients [3-8]. Currently, the primary goal of PDS has been changed to R0 resection.

However, not all patients could afford extensive surgical procedures to achieve complete cytoreduction. Two randomized trials (European Organisation for Research and Treatment of Cancer [EORTC] 55971 and CHemotherapy OR Upfront Surgery [CHORUS]) have shown non-inferior prognosis with lower postoperative adverse events in neoadjuvant chemotherapy (NAC) groups compared with PDS groups of AEOC patients [9-11]. Although the NAC group had higher R0 resection rates compared with those of the PDS group, the complete cytoreduction rates in both groups are lower compared with other studies [8,12]. Patients debulked to no gross RD in the PDS group had the best prognosis in both studies [9,11]. Thus, NAC has been proposed as an alternative in AEOC patients with low performance status, underlying morbidity, older age or disseminated unresectable disease. Additionally, clear selection criteria for different approaches are urgently required for the personalized management of AEOC patients.

To more precisely quantify the intraabdominal extent of OC, multiple predictive models and ranking systems have been proposed [13-17]. For non-invasive methods, Suidan et al. [17] proposed a model with high predictive ability (area under the curve [AUC]=0.72), containing 3 preoperative clinical and 8 radiological criteria, for complete cytoreduction. However, the external validation has not been confirmed. Minimal invasive approaches, such as laparoscopy, are recommended according to the guidelines. Based on previous studies, we hypothesized that applying suitable predictive models can better classify patients into different treatment approaches with elevated radical surgery rate and acceptable morbidity.

In September 2015, the specialized OC unit at our institution implemented a personalized surgical approach for the treatment of all suspected AEOC. The aim of the present study was to present surgical outcomes for AEOC since implementation of a personalized approach and to validate the performance of multiple predictive models for R0 resection.

MATERIALS AND METHODS

1. Data collection

This study was conducted according to the Declaration of Helsinki and was approved by the Committee at Fudan University Shanghai Cancer Center (FUSCC, approval number: 050432-4-1212B). All individual participants consented to the use of their medical records for research purposes. The clinical data were prospectively collected from patients referred to FUSCC for suspicious AEOC. All patients included in this group did not receive any disease treatment prior to referral. The histological diagnoses were based on World Health Organization criteria, and patients with other malignancies according to pathological

reports were excluded. Between September 1, 2015 and August 31, 2017, a prospective cohort containing 161 patients with pathologically confirmed epithelial ovarian cancer was included in the analysis. The data included the demographics, preoperative labs and radiological findings, preoperative medical evaluation, intraoperative findings, and surgical outcomes and complications for the patient.

2. Predictive models and strategies

A summary of the present strategy for patients with suspicious AEOC is shown in **Fig. 1**. We have validated 2 predictive models.

1) Non-invasive model

All patients had computed tomography scans within 2 weeks before treatment. Two experienced gynecological radiologists had preoperative radiological assessment according to the Suidan criteria for R0 resection with a predictive score for all individuals (**Supplementary Table 1**) [17]. Patients with a score 0–2 were recommended for PDS (group A), while the other individuals with a score ≥ 3 were counseled on the choices of PDS (group A), NAC (group B), or an optional staging laparoscopy (S-LPS).

2) Minimally invasive model

S-LPS with a predictive index value (PIV) according to Fagotti (**Supplementary Table 2**) [15]. PIV was evaluated by 2 experienced gynecological oncologists. Individuals with a PIV <8 underwent PDS (group C), or otherwise received NAC (group D).

3. Intra- and postoperative findings

Intraoperative assessments of tumor burden (with Eisenkop [14] and Peritoneal cancer index [PCI] score [16]) were recorded by 2 experienced gynecological oncologists (**Supplementary Tables 3 and 4**). The Aletti score was used for ranking surgical complexity (**Supplementary**

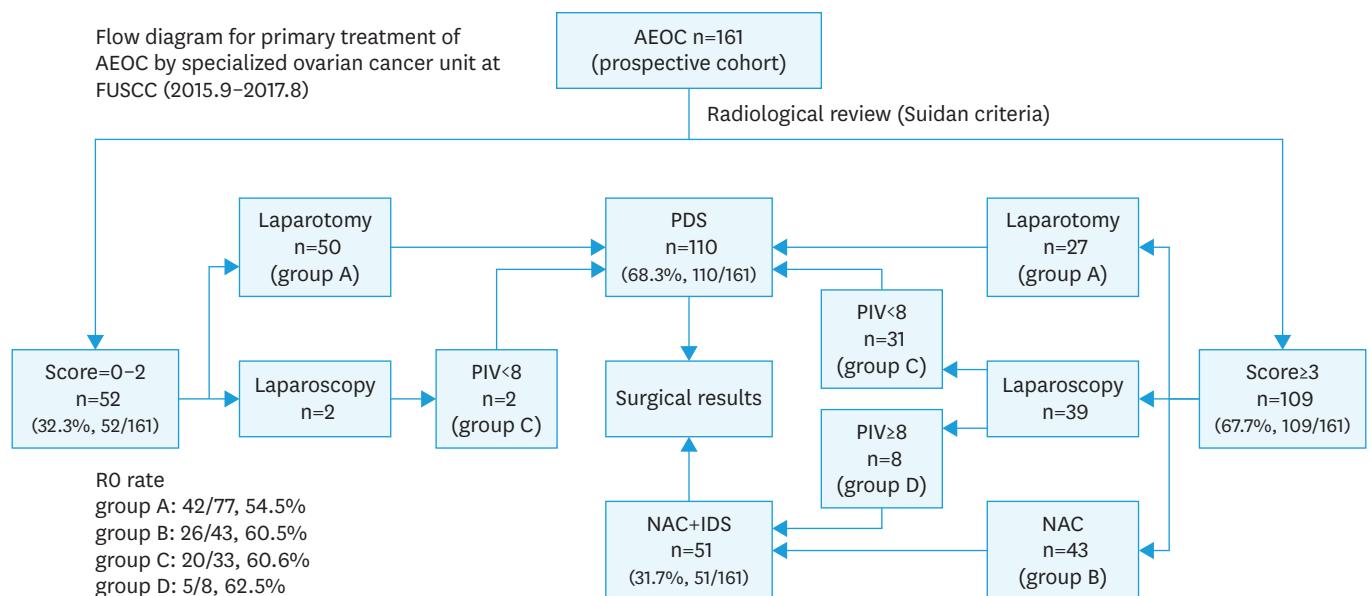


Fig. 1. Flow diagram for primary treatment of AEOC by specialized ovarian cancer unit at FUSCC (2015.9–2017.8). Group A: PDS; Group B: NAC+IDS; Group C: LP+PDS; Group D: LP+NAC+IDS.

AEOC, advanced epithelial ovarian cancer; FUSCC, Fudan University Shanghai Cancer Center; IDS, interval debulking surgery; LP, laparoscopy; NAC, neoadjuvant chemotherapy; PCI, peritoneal cancer index; PDS, primary debulking surgery; PIV, predictive index value.

Table 5) [13]. Residual disease after surgery was reported as R0, R1, and R2. R0 was defined as no macroscopic residual disease. R1 and R2 were defined as macroscopic residual disease with a maximal diameter of <1 cm and >1 cm, respectively. The optimal resection was defined as the combination of R0 and R1. Surgical morbidity was determined according to the Clavien-Dindo Classification [18]. Complications > grade 2 requiring clinical intervention were reported.

4. Statistical analyses

SPSS statistical software (version 21.0; IBM Inc., New York, USA) was used for the statistical analyses. Descriptive statistics were used for the demographic data and summarized as medians with ranges or frequencies with percentages. The categorical data were compared with χ^2 or Fisher's exact tests as appropriate. Continuous outcomes were compared by using Student's t-test. ROC curve analysis was used to assess the ability of the pre- and intra-operative ranking systems to identify patients who were most likely to have complete surgical resection. The AUC was used as an indicator for predictive accuracy. The $p < 0.05$ was considered statistically significant, and all reported p-values were 2-sided.

RESULTS

1. Patient characteristics

The patient characteristics are summarized in **Table 1**. A total of 161 OC patients were included in the analysis. The median (range) age was 57 (27–77) years old. The median cancer antigen 125 was 1,062 IU/mL. The majority (158/161, 98.1%) of patients were of advanced International Federation of Gynecology and Obstetrics stage, including 128 patients with stage III and 30 patients with stage IV diseases, and 81.4% of patients were high-grade serous OC.

2. Personalized surgical triage

All patients referred to the institution with a suspicious AEOC were initially evaluated by the multidisciplinary unit. For radiological assessment, 52 (32.3%) patients had a predictive

Table 1. Patient characteristics (n=161)

Characteristics	Value
Age	57 (27–77)
FIGO stage	
Early	3 (1.9)
Advanced	158 (98.1)
Stage III	128 (79.5)
Stage IV	30 (18.6)
Family history	
Yes	54 (33.5)
No	107 (66.5)
CA-125 (IU/mL)	1,062 (39.19→5,000)
Radiological score	4 (0–12)
Histology	
High-grade serous	131 (81.4)
Low-grade serous	4 (2.5)
Endometrioid	1 (0.6)
Clear cell	6 (3.7)
Carcinosarcoma	1 (0.6)
Undifferentiated	11 (6.8)
Regression	7 (4.3)

Values are presented as median (range) or number (%).

CA-125, cancer antigen 125; FIGO, International Federation of Gynecology and Obstetrics.

R0 resection model for ovarian cancer

Table 2. Patient characteristics and surgical variables according to the stratification groups

Parameters	Group A	Group B	Group C	Group D
No. of patients	77	43	33	8
Radiological score	2 (0–7)	6 (3–12)	5 (0–10)	6 (3–9)
Eisenkop	7 (1–14)	6 (0–12)	9 (0–12)	8 (2–11)
PCI	13 (2–31)	11 (0–22)	18 (3–30)	13 (4–24)
Aletti				
Low (0–3)	15 (19.5)	18 (41.9)	3 (9.1)	3 (37.5)
Intermediate (4–7)	22 (28.6)	6 (14.0)	15 (45.5)	1 (12.5)
High (≥8)	40 (51.9)	19 (44.2)	15 (45.5)	4 (50.0)
Residual disease				
R0	42 (54.5)	26 (60.5)	20 (60.6)	5 (62.5)
R1	21 (27.3)	13 (30.2)	10 (30.3)	2 (25.0)
R2	14 (18.2)	4 (9.3)	3 (9.1)	1 (12.5)

Values are presented as median (range) or number (%). Group A: PDS; Group B: NAC+IDS; Group C: LP+PDS; Group D: LP+NAC+IDS. IDS, interval debulking surgery; LP, laparoscopy; NAC, neoadjuvant chemotherapy; PCI, peritoneal cancer index; PDS, primary debulking surgery.

score of 0–2, almost all (50/52, 96.2%) received PDS, except that 2 patients had subsequent S-LPS. One hundred nine (67.7%) patients had a score ≥3. Among them, 27 patients (24.8%) insisted on PDS, 43 (39.4%) patients received NAC, and the rest 39 (35.8%) had S-LPS. In total, 41 of 161 (25.5%) patients received S-LPS, and 33 out of 41 (80.5%) were then submitted to PDS. Finally, 110 (68.3%) patients underwent PDS (A+C), and 51 (31.7%) patients received NAC (B+D) (**Fig. 1**). For NAC patients, scores at interval surgery (Eisenkop, PCI, and Aletti scores) were also collected. Detailed surgical variables according to the stratification groups are shown in **Table 2**.

3. Performance of the predictive models for R0 resection

Complete resection (R0) was achieved in 56.4% of the PDS cases (54.5% in group A and 60.6% in group C, respectively). The AUC of the clinico-radiological predictive score was 0.548 in the PDS group (A+C). The values for the AUC of the Eisenkop, PCI, and Aletti scores were 0.808, 0.797, and 0.524, respectively (**Fig. 2**). The AUC of the Fagotti score was 0.702 in group C (**Fig. 3**).

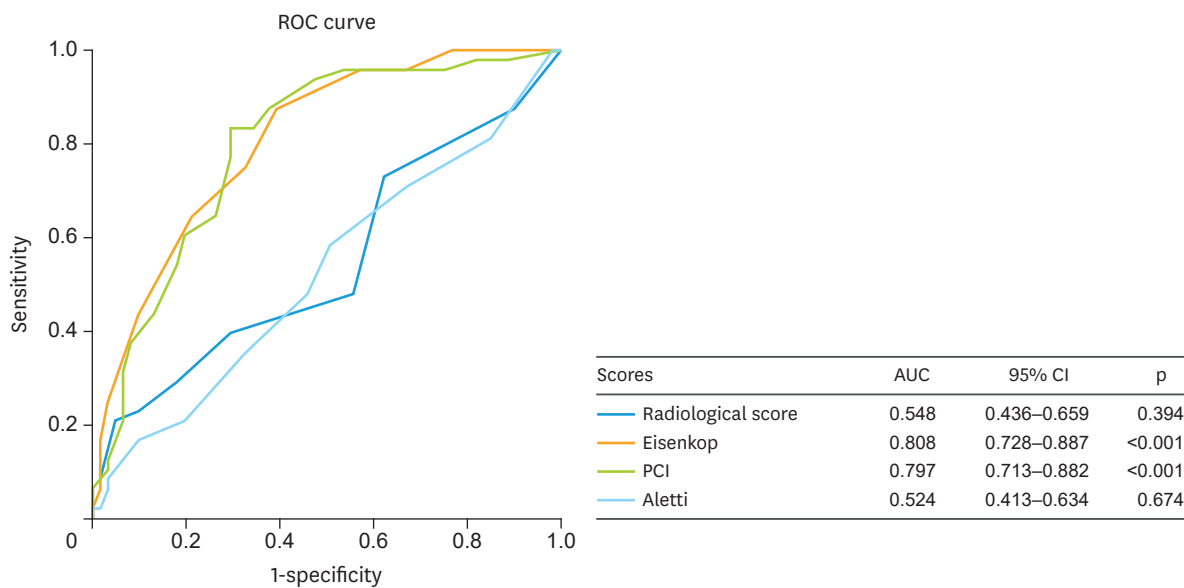


Fig. 2. Discriminatory power of radiological and intraoperative scores for complete resection. AUC, area under the curve; CI, confidence interval; PCI, peritoneal cancer index; ROC, receiver operating characteristics.

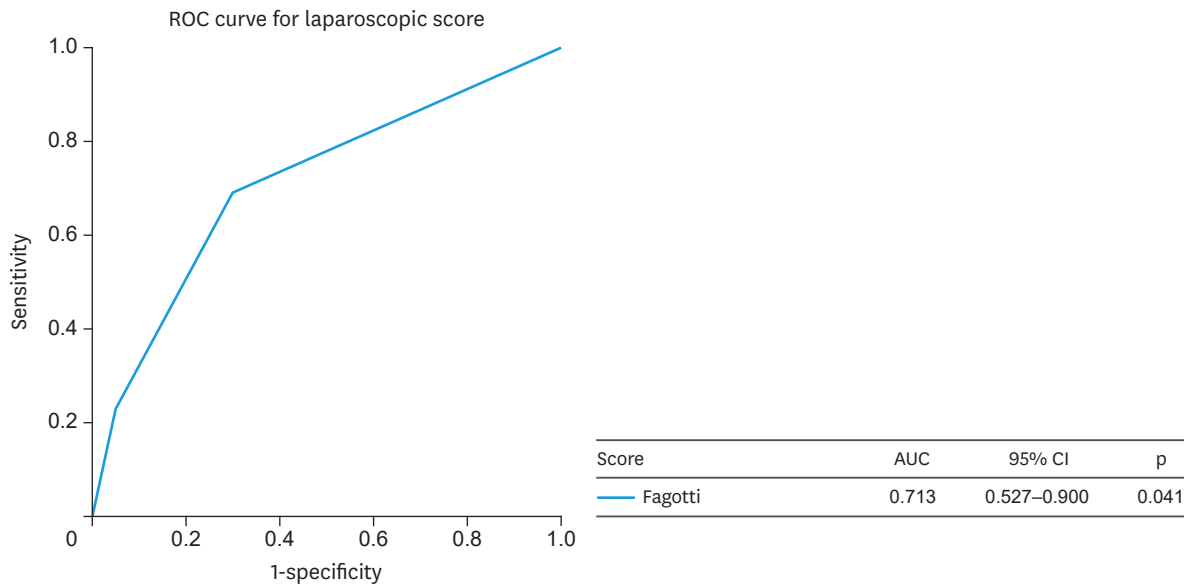


Fig. 3. ROC curve analysis for S-LPS score. AUC, area under the curve; CI, confidence interval; ROC, receiver operating characteristics; S-LPS, staging laparoscopy.

4. Surgical outcomes between PDS and NAC groups

Compared with PDS, interval-debulking surgery required a significantly shorter operation time (202 [83–454] vs. 166 [72–316] minutes, $p=0.019$). The optimal resection rates in PDS and NAC patients were 84.5% (56.4% R0 and 28.2% <1 cm) and 90.2% (60.8% R0 and 29.4% <1 cm), respectively. More patients in the PDS group received more extensive surgery and had high complexity surgery scores compared with those in the NAC group ($p=0.001$). The intraoperative complication rates were low in both groups, without significant difference ($p=0.506$). PDS patients experienced more postoperative complications compared with NAC patients (32.7% vs. 13.7%, $p=0.013$), and longer median (range) hospital stay (12 [6–61] vs.

Table 3. Surgical results stratified by PDS and NAC groups

Parameters	PDS Group A+C	NAC+IDS Group B+D	p
No. of patients	110	51	
Residual disease			0.622
R0	62 (56.4)	31 (60.8)	
R1	31 (28.2)	15 (29.4)	
R2	17 (15.5)	5 (9.8)	
Aletti			0.001
Low (0–3)	18 (16.4)	21 (41.2)	
Intermediate (4–7)	55 (50.0)	23 (45.1)	
High (≥ 8)	37 (33.6)	7 (13.7)	
Operative time (min)	202 (83–454)	166 (72–316)	0.019
Intraoperative complication			0.506
No	102 (92.7)	49 (96.1)	
Yes	8 (7.3)	2 (3.9)	
Postoperative complication			0.013
No	74 (67.3)	44 (86.3)	
Yes	36 (32.7)	7 (13.7)	
Postoperative stay (day)	12 (6–61)	8 (6–24)	<0.001

Values are presented as median (range) or number (%). Complications were classified according to the Clavien-Dindo Classification. Group A: PDS; Group B: NAC+IDS; Group C: LP+PDS; Group D: LP+NAC+IDS.

IDS, interval debulking surgery; LP, laparoscopy; NAC, neoadjuvant chemotherapy; PDS, primary debulking surgery.

8 [6–24] days, $p < 0.001$) (**Table 3**). In the PDS group, postoperative complication rates were correlated with surgical complexity (low vs. intermediate vs. high, 5.6% vs. 29.1% vs. 51.4%, $p = 0.001$). The complication rates also increased with increasing surgical complexity, but remained below 30% in all groups (low vs. intermediate vs. high, 4.8% vs. 17.4% vs. 28.6%, $p = 0.224$). Details of perioperative complications are shown in **Supplementary Table 6**.

DISCUSSION

The present study validated multiple predictive models for R0 resection in a large prospective patient cohort treated by a specialized surgical team. The Suidan criteria were not effective for the present AEOC patients. S-LPS was helpful for PDS decision-making with a high AUC. Patients in the PDS group had similar R0 rate compared with those in the NAC group. Applying suitable predictive models can better triage patients into different treatment approaches with elevated radical surgery rates and acceptable morbidity.

The volume of residual disease is inversely correlated with the prognosis of the AEOC patient, and the definition of optimal debulking has changed over the years [3-5]. Since complete cytoreduction achieved the best prognosis among AEOC patients, the primary goal of PDS has been changed to R0 resection [6-8]. In a previous study, we showed a complete resection rate of 31% OC patients at our institution between 2005 and 2013 [19]. Since the implementation of a personalized surgical approach, the R0 rate improved to 56.4% in the PDS group. These results are comparable to those in other studies, reporting R0 rates ranging from 41% to 67.8% [20-22].

NAC could also improve the R0 rate of AEOC patients compared with PDS according to 2 randomized trials (EORTC 55971 and CHORUS) [9,11]. However, the R0 rates in the PDS group were below 20%, much lower compared with those in other studies [8,12], and it is not clear whether maximal efforts were made during PDS. Although patients in the NAC group showed non-inferior prognosis compared with those in the PDS groups, the patients in the PDS group with no residual disease subgroup had the best prognosis. Thus, NAC has been proposed as an alternative treatment strategy for advanced AEOC patients with low performance status, underlying morbidity, older age or disseminated unresectable disease. Additionally, clear selection criteria to triage surgical candidates are urgently required for the personalized management of AEOC patients.

As the extent of the disease determines the ability to perform complete cytoreduction, several predictive models have been proposed [12,15,17,23-26]. Clinico-radiological assessment is non-invasive, convenient and cost-effective. Mono-institution studies have reported the high predictive accuracies of radiological models. However, these findings could not be confirmed in cross-validation studies, and these studies did not aim at R0 resection prediction [23,24,27]. Suidan et al. [17] first proposed a predictive model for complete cytoreduction composed of 3 preoperative clinical and 8 radiological criteria with high predictive ability (AUC=0.72) based on post hoc analysis of a prospective non-randomized multicenter trial. However, the AUC of the Suidan criteria was only 0.548 in the present cohort, which is not as effective as that in the training cohort. This result indicated that in contemporary situations, preoperative radiological predictors should be used with caution, and there are still no universal applicable criteria.

Minimal invasive approaches, such as laparoscopy, are recommended according to international guidelines. The laparoscopic predictive score, the Fagotti score, has been well recognized, with a negative predictive value of 100% [15,28]. In the S-LPS group, we reported an AUC of 0.713, compared with 0.66 in Fagotti et al.'s study [12]. Thus, S-LPS could be used for decision-making in PDS. However, some patients did not receive S-LPS for economic or invasive reasons, while almost all patients underwent preoperative radiological scans. Thus, it is valuable to develop a strategy for incorporating minimally invasive laparoscopic assessment into routine mandatory non-invasive radiological assessment, which is more convenient and cost-effective in daily practice. Multi-center co-operation is required to establish the general criteria for disease evaluation, and each institution could validate their own cutoffs based on their respective clinical practices.

According to the present selective algorithm, the patients were triaged into PDS or NAC group. Consistent with previous studies, the present study has also found the benefit of NAC and interval debulking surgery (IDS) compared with PDS, such as shorter operative time, shorter hospital stays, and lower postoperative complication rates. Notably, half of the patients in the PDS group with high surgical complexity suffered postoperative complications, and in the NAC group, the patients with surgical complexity had acceptable complication rates under 30%. Different from previous studies, there was no difference in the R0 resection rates between PDS and NAC groups. This finding may be due to the selected approach used in the present study, and patients in the NAC group had a higher tumor burden than those in the PDS group. Moreover, the determination for residual disease after IDS was subjective because of the fibrosis and adhesion in the peritoneal cavity after NAC. Since the present personalized approach was initiated in 2015, prognosis comparison needs further follow-up.

In conclusion, we demonstrated a personalized surgical approach to AEOC based on multiple predictive models for R0 resection. This algorithm needs further modification to better define the best candidates for different treatment approaches, and multi-center cooperation is required to establish the general criteria.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1

The Suidan criteria for R0 resection [17]

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Supplementary Table 2

Fagotti score [15]

[Click here to view](#)

Supplementary Table 3

Eisenkop score [14]

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Supplementary Table 4

PCI [16]

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Supplementary Table 5

Aletti score [13]

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Supplementary Table 6

Perioperative complications among PDS and NAC groups

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