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CT-Based Fagotti Scoring System for Non-Invasive Prediction of Cytoreduction Surgery Outcome in Patients with Advanced Ovarian Cancer

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Objective: To construct a CT-based Fagotti scoring system by analyzing the correlations between laparoscopic findings and CT features in patients with advanced ovarian cancer.

Materials and Methods: This retrospective cohort study included patients diagnosed with stage III/IV ovarian cancer who underwent diagnostic laparoscopy and debulking surgery between January 2010 and June 2018. Two radiologists independently reviewed preoperative CT scans and assessed ten CT features known as predictors of suboptimal cytoreduction. Correlation analysis between ten CT features and seven laparoscopic parameters based on the Fagotti scoring system was performed using Spearman's correlation. Variable selection and model construction were performed by logistic regression with the least absolute shrinkage and selection operator method using a predictive index value (PIV) ≥ 8 as an indicator of suboptimal cytoreduction. The final CT-based scoring system was internally validated using 5-fold cross-validation.

Results: A total of 157 patients (median age, 56 years; range, 27–79 years) were evaluated. Among 120 (76.4%) patients with a PIV ≥ 8, 105 patients received neoadjuvant chemotherapy followed by interval debulking surgery, and the optimal cytoreduction rate was 90.5% (95 of 105). Among 37 (23.6%) patients with PIV < 8, 29 patients underwent primary debulking surgery, and the optimal cytoreduction rate was 93.1% (27 of 29). CT features showing significant correlations with PIV ≥ 8 were mesenteric involvement, gastro-transverse mesocolon-splenic space involvement, diaphragmatic involvement, and para-aortic lymphadenopathy. The area under the receiver operating curve of the final model for prediction of PIV ≥ 8 was 0.72 (95% confidence interval: 0.62–0.82).

Conclusion: Central tumor burden and upper abdominal spread features on preoperative CT were identified as distinct predictive factors for high PIV on diagnostic laparoscopy. The CT-based PIV prediction model might be useful for patient stratification before cytoreduction surgery for advanced ovarian cancer.

Keywords: *Ovarian cancer; Residual tumor; Cytoreductive surgery; Laparoscopy; Multidetector computed tomography*

INTRODUCTION

Primary debulking surgery (PDS) followed by platinum-based chemotherapy is a conventional treatment approach for advanced ovarian cancer (AOC). Many studies have demonstrated that the extent of residual tumor following debulking surgery is the only modifiable and the strongest independent prognostic factor in AOC [1-5]. Therefore, the surgical goal should be complete removal of all macroscopic tumors, that is, complete cytoreduction (R0). When this is infeasible, surgical attempts should be made to achieve optimal cytoreduction, which is now generally accepted

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as a residual tumor size of < 1 cm, as many studies have reported that a debulking surgery has limited benefit if the residual disease cannot be reduced to less than 1 cm [5,6]. Neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) offers an alternative treatment option for patients with bulky stage IIIC or IV ovarian cancer. This is supported by two prospective randomized studies, the EORTC 55971 trial and the CHORUS trial, demonstrating comparable survival and less surgical morbidity of NAC/IDS compared to PDS [7,8].

Accurate preoperative prediction of the probability of optimal cytoreduction is important to avoid unnecessary PDS and establish personalized management. CT is a widely used for preoperative staging of ovarian cancer. Many CT-based models to predict the outcome of PDS have been suggested using various radiographic features, such as peritoneal thickening, ascites, para-aortic lymphadenopathy, and bowel involvement [9-18]. Although each study showed good predictive performance in its dataset, cross-validations were largely unsuccessful. Some researchers have also assessed the laparoscopic evaluation of resectability. Fagotti et al. [19] designed a laparoscopy-based scoring system consisting of seven parameters based on intra-abdominal distribution of the disease via laparoscopic visualization. The additive sum of scores is defined as a predictive index value (PIV), and a PIV of ≥ 8 demonstrated the best accuracy in predicting suboptimal cytoreduction. In such cases, NAC should be considered as an initial treatment instead of PDS. The Fagotti scoring system showed good predictive performance even in an independent external cohort and prospective validation [19-21]. However, the laparoscopic scoring system is fundamentally invasive and requires additional general anesthesia.

Thus, we hypothesized that a non-invasive prediction model using CT with good reproducibility might be achieved by considering the characteristics of the laparoscopic scoring in the CT prediction. This study aimed to construct a CT-based Fagotti scoring system for predicting suboptimal cytoreduction in AOC by identifying CT features with high laparoscopic PIV.

MATERIALS AND METHODS

Patient Selection

Our human research committee approved this study and waived the need for individual written informed consent (IRB No. 2020-0922-001). This retrospective cohort study included consecutive patients diagnosed with ovarian cancer between January 2010 and June 2018. A total of 172 patients were enrolled according to the following inclusion criteria: 1) International Federation of Gynecology and Obstetrics (FIGO) stage III and IV ovarian cancer; and 2) patients who underwent diagnostic laparoscopy with Fagotti score available in our electronic medical record system. We excluded 15 of 172 patients initially enrolled for the following reasons: 1) unavailable preoperative CT (n = 10); 2) unacceptable CT image quality or lack of contrast-enhanced phase (n = 2); and 3) incomplete medical records (n = 3). Finally, 157 patients with stage IIIC and IV ovarian cancer who underwent diagnostic laparoscopy were included in the analysis.

Diagnostic Laparoscopy

The following seven laparoscopic parameters were assessed intraoperatively by surgeons, and each was assigned a score of 2: peritoneal carcinomatosis, diaphragmatic carcinomatosis, mesenteric retraction, omental cake, bowel and/or stomach infiltration, and superficial liver metastasis. For patients whose PIV < 8 or optimal cytoreduction was deemed feasible regardless of PIV, the procedure was subsequently converted to an open laparotomy, and maximal surgical effort was attempted. The standard laparotomy included the removal of tumor masses, total hysterectomy, bilateral salpingo-oophorectomy, appendectomy, omentectomy, peritonectomy, radical pelvic/para-aortic lymphadenectomy, and additional surgery (bowel resection, diaphragm stripping, liver resection, and splenectomy) if needed. In contrast, when PIV ≥ 8 or suboptimal cytoreduction was expected regardless of PIV, surgeons ended the laparoscopy, and patients underwent NAC. Details of laparoscopy-based scores and management after diagnostic laparoscopy were available in each patient's medical records.

CT Imaging Techniques

Preoperative CT was performed with various CT scanners, and detailed information for scanners is available in Supplementary Material 1. Each patient was intravenously administered a contrast material (iopromide, Ultravist 300, Schering) via an antecubital vein using a mechanical injector (140 mL at 2.3 mL/s). All patients underwent CT examination in the supine position, with both arms elevated. Scanning began at 70 seconds or 80 seconds after the start of IV contrast injection (from the lower thorax to

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the lower pelvis). The following CT parameters were used: a tube voltage of 100 kVp or 120 kVp, a detector array of 16-256 channels, a beam pitch of 0.6–0.984, and 3-mm thickness with a 3-mm interval for image reconstruction.

Image Analysis

Preoperative CT scans of each patient were independently reviewed by two radiologists (with 3 years and 20 years of experience in gynecological imaging, respectively) who were blinded to the laparoscopic findings and surgical outcomes. Investigators reviewed axial and coronal reformation during the portal phase of preoperative CT scans after contrast injection and assessed the following ten CT features: c1, ascites; c2, pelvic and/or low abdominal peritoneal involvement; c3, mesenteric involvement; c4, omental cake; c5, upper abdomen involvement (c5-1, porta hepatis; c5-2, Morrison's pouch; c5-3, gastro-transverse mesocolon-splenic (GTS) space; c5-4, lesser curvature); c6, diaphragmatic involvement; c7, pelvic wall extension; c8, parenchymal involvement (distant metastasis); c9, lymphadenopathy; and c10, liver surface involvement.

These CT features were selected by combining conventional CT predictors of suboptimal cytoreduction and imaging findings related to the Fagotti score system parameters [12,13]. c5-3 (GTS space) was defined arbitrarily on axial images as the space between the greater curvature of the stomach and the splenic hilum, superior to the level of the transverse mesocolon. Each CT feature was rated according to the presence of tumor nodules, tumor extent, or the largest size of the tumor nodule. The detailed scoring criteria are provided in Supplementary Table 1. The sum of scores was defined as the CT-based peritoneal cancer index (PCI). Delineation and classification of intra-abdominal lesions were determined by consensus between the two radiologists when there was a discrepancy between them.

Statistical Analysis

Spearman's correlation was used to assess correlations between CT features and laparoscopic parameters. In addition to the seven laparoscopic parameters, PIV ≥ 8 was added as an independent variable. PIV ≥ 8 is a comprehensive indicator of suboptimal cytoreduction. For multivariable analysis of CT features and laparoscopic parameters, logistic regression was used with the least absolute shrinkage and selection operator (LASSO) method. The final CT-based scoring system was internally validated using 5-fold cross-validation. Statistical analyses were performed using R software (version 3.4.3, R Foundation for Statistical Computing).

RESULTS

A total of 157 consecutive patients were enrolled in this study. Of these, 120 patients had PIV ≥ 8, and 37 patients had PIV < 8 on diagnostic laparoscopy. There was no significant difference in median age between the two

Table 1. Characteristics of Patients

Characteristics	Total (n = 157)	PIV ≥ 8 (n = 120)	PIV < 8 (n = 37)
Age, years			
Median (range)	56 (27–79)	57 (27–79)	56 (35–78)
ECOG performance status			
1	63 (40.1)	44 (36.7)	19 (51.4)
2	73 (46.5)	57 (47.5)	16 (43.2)
3	21 (13.4)	19 (15.8)	2 (5.4)
FIGO stage			
IIIA	4 (2.5)	2 (1.7)	2 (5.4)
IIIB	26 (16.6)	17 (14.2)	9 (24.3)
IIIC	70 (44.6)	53 (44.2)	17 (45.9)
IV	57 (36.3)	48 (40)	9 (24.3)
Preoperative CA-125, U/mL			
Median (range)	1166.7 (3.5–23918.5)	1459.7 (3.5–23918.5)	516.3 (31.0–16251.9)
Triage			
NAC	113 (72.0)	105 (87.5)	29 (78.4)
PDS	44 (28.0)	15 (12.5)	8 (21.6)
Histology			
Serous	139 (88.5)	110 (91.7)	29 (78.4)
Mucinous	4 (2.5)	2 (1.7)	2 (5.4)
Endometrioid	1 (0.6)	1 (0.8)	0 (0)
Clear cell	8 (5.1)	5 (4.2)	3 (8.1)
Carcinosarcoma	3 (1.9)	1 (0.8)	2 (5.4)
Others	2 (1.3)	1 (0.8)	1 (2.7)
Grade			
1	5 (3.2)	4 (3.3)	1 (2.7)
2	16 (10.1)	10 (8.3)	6 (16.2)
3	134 (85.4)	105 (87.5)	29 (78.4)
Unknown	2 (1.3)	1 (0.8)	1 (2.7)
CT PCI			
0–16	152 (96.8)	115 (95.8)	37 (100)
>16	5 (3.2)	5 (4.2)	0 (0)

Data are number of patients with % in parentheses, unless specified otherwise. CA-125 = cancer antigen 125, CT PCI = CT-based Peritoneal Cancer Index, ECOG = Eastern Cooperative Oncology Group, FIGO = International Federation of Gynecology and Obstetrics, NAC = neoadjuvant chemotherapy, PDS = primary debulking surgery, PIV = predictive index value

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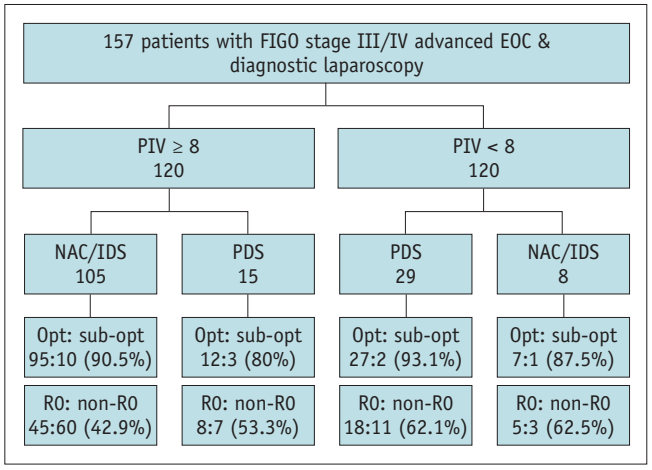

Fig. 1. Flow diagram shows treatment allocation and surgical outcome. EOC = epithelial ovarian cancer, FIGO = International Federation of Gynecology and Obstetrics, IDS = interval debulking surgery, NAC = neoadjuvant chemotherapy, Opt = optimal cytoreduction, PDS = primary debulking surgery, PIV = predictive index value, R0 = complete cytoreduction, sub-opt = suboptimal cytoreduction

groups (PIV ≥ 8 group, 57 years, range 27–79 years; PIV < 8 group, 56 years, range 35–78 years). The median baseline serum CA-125 level was higher in patients with PIV ≥ 8 (PIV ≥ 8 group, 1459.7 U/mL, range: 3.5–23918.5 U/mL; PIV < 8 group, 516.3 U/mL, range: 31.0–16251.9 U/mL). The most common histological type was high-grade serous carcinoma. Patient characteristics at initial diagnosis, triage, and final pathology are presented in Table 1.

Among the 37 patients with PIV < 8 on diagnostic laparoscopy, 29 underwent PDS. Optimal debulking was achieved in 27 patients (93.1%). Among 120 patients with PIV ≥ 8, 105 patients were assigned to NAC, and the optimal cytoreduction rate was 90.5% in IDS (Figs. 1-3).

There was no significant correlation between CT and laparoscopic diagnostic findings, even between relevant findings (e.g., peritoneal involvement, diaphragmatic disease, mesenteric disease, and omental disease) (Fig. 4). Table 2 shows the LASSO regression coefficients between

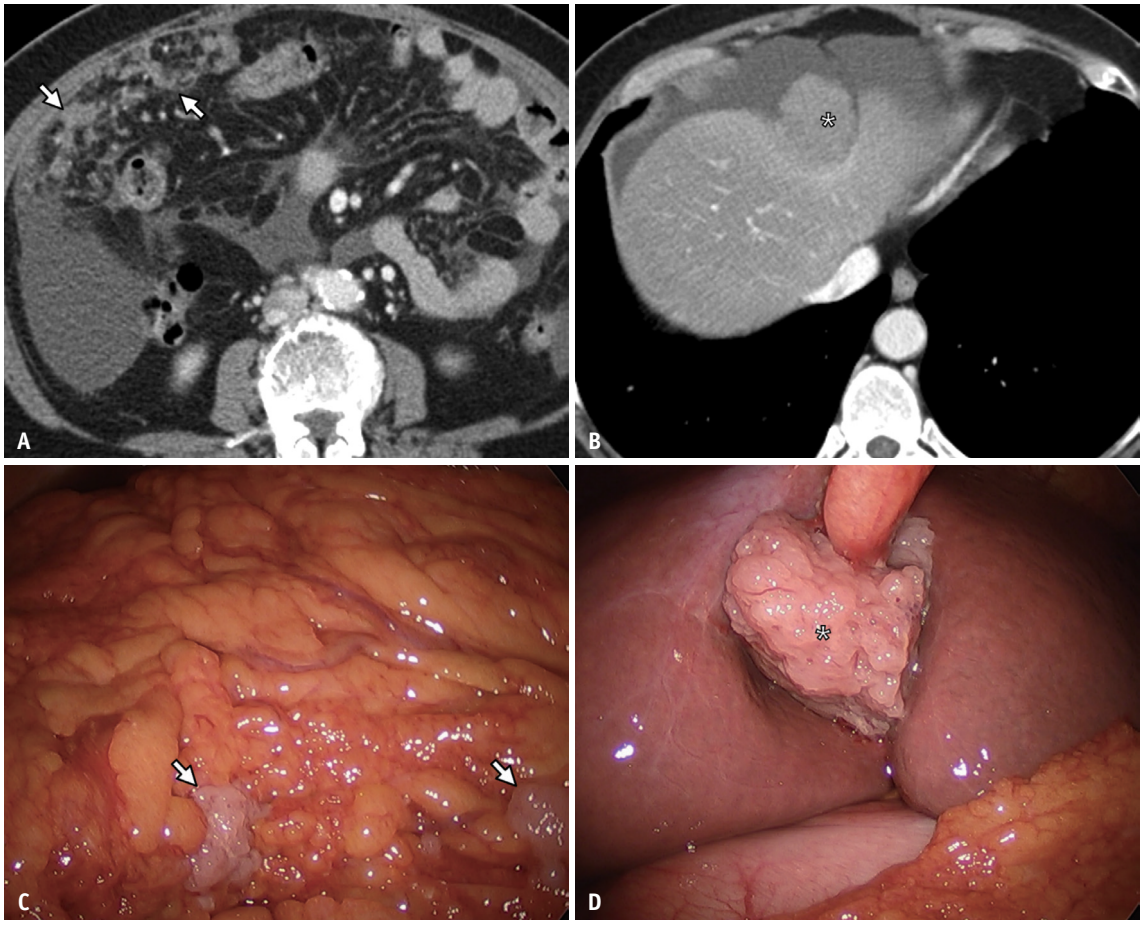

Fig. 2. 56-year-old female with stage IV ovarian cancer.
A, B. Axial contrast-enhanced portal phase CT scans show seeding nodules on the omentum, mesentery (arrows), and liver surface near the falciform ligament (asterisk). **C, D.** In laparoscopy, there were corresponding lesions; omental disease (arrows), and superficial liver metastasis (asterisk). The predictive index value is 8 (superficial liver metastasis, stomach infiltration, peritoneal carcinomatosis, and diaphragmatic disease).

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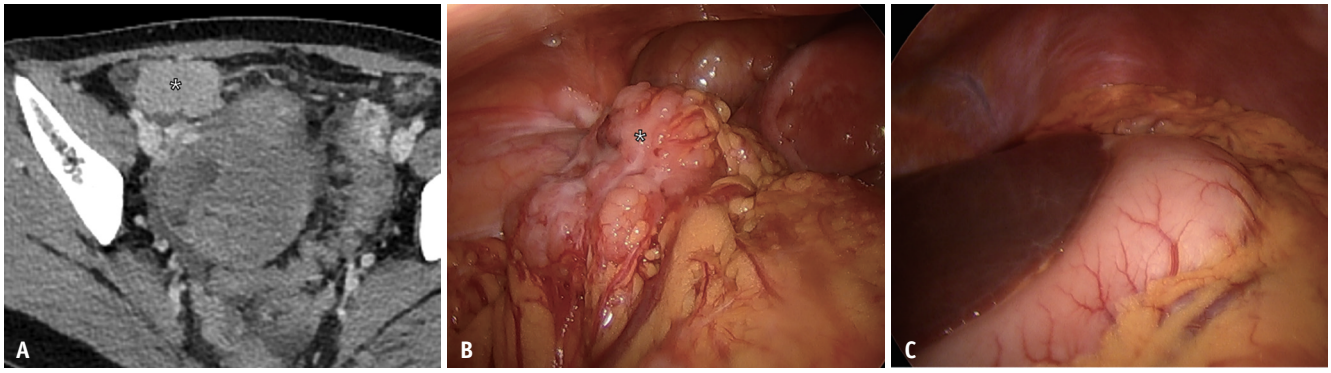

Fig. 3. 38-year-old female with stage IV ovarian cancer.
A. Axial contrast-enhanced portal phase CT scan show a large seeding mass on pelvic peritoneum (asterisk). Omentum and mesentery involvement are also noted. There is no evidence of metastasis in the upper abdomen, including the liver surface and the diaphragm. **B.** In laparoscopy, there are corresponding seeding lesions on the omentum, mesentery, and pelvic peritoneum (asterisk). **C.** Surgeons assess the upper abdomen as free of cancer. The predictive index value is 6 (mesenteric disease, omental disease, and peritoneal carcinomatosis).

Table 2. LASSO Regression Coefficient Values between CT Features and Laparoscopic Parameters

	PIV ≥ 8	f1	f2	f3	f4	f5	f6	f7
Intercept	-0.137342	1.86524	-0.940962	-0.446572	0.294049	-0.328299	-1.387497	-1.324321
c1	0.248974	0	0.478254	0.080678	0.038997	-0.010394	0	0.045549
c2	-0.481101	0	0	-0.171475	-0.580115	0.132048	0	-0.040411
c3	0.433991	0	0.048093	0.587358	0.906637	-0.459610	0	0
c4	0.235492	0	0.705333	0.041992	0.862485	0.153107	0	-0.021202
c5_1	0.381149	0	0	-1.148632	0	-1.278703	0	0
c5_2	0.056804	0	0.276472	0.705908	0	0	0	0
c5_3	0.795926	0	0	0.892640	0.802890	0.609752	0	0
c5_4	-0.087859	0	0	-1.303490	0	-0.881452	0	0
c5	0.314009	0	0.031612	0.920170	0.069904	0.327369	0	0
c6	1.325737	0	0.083123	0.577082	1.468862	0.284149	0	0.675801
c7	0	0	0	2.723917	0	0	0	0
c8	0	0	0	-0.825299	0.294766	-0.131674	0	0
c9	0.399030	0	-0.096902	-0.125698	0.079032	0.507221	0	-0.091882
c10	0.242446	0	0	-0.282185	-1.335076	0.247273	0	0.385527

CT features on rows: c1 = ascites, c2 = pelvic and/or low abdomen peritoneal involvement, c3 = mesenteric involvement, c4 = omental cake, c5 = upper abdomen involvement (c5-1 = porta hepatis, c5-2 = Morrison's pouch, c5-3 = gastro-transverse mesocolon-splenic complex, c5-4 = lesser curvature), c6 = diaphragmatic involvement, c7 = pelvic wall extension, c8 = parenchymal involvement, c9 = lymphadenopathy, and c10 = liver surface involvement. Laparoscopic parameters on columns: f1 = peritoneal carcinomatosis, f2 = diaphragmatic disease, f3 = mesenteric disease, f4 = omental disease, f5 = bowel infiltration, f6 = stomach infiltration, f7 = liver metastasis. LASSO = least absolute shrinkage and selection operator, PIV = predictive index value

the CT features and laparoscopic parameters. The following CT features were significantly correlated with PIV ≥ 8: mesenteric involvement (c3), upper abdomen involvement (c5), especially c5-1 porta hepatis and c5-3 GTS complex, diaphragmatic involvement (c6), and lymphadenopathy (c9).

The probability of PIV ≥ 8 was calculated with the formula shown below:

$$\text{Probability (PIV} \geq 8) = \frac{\exp\,(\text{equation})}{1 + \exp\,(\text{equation})}$$

exp (equation) = -0.137342 + 0.248974 x c1 - 0.481101 x c2 + 0.433991 x c3 + 0.235492 x c4 + 0.235492 x c5 + 0.381149 x c5_1 + 0.056804 x c5_2 + 0.795926 x c5_3 - 0.087859 x c5_4 + 1.325737 x c6 + 0.39903 x c9 + 0.242446 x c10

The area under the receiver operating curve (AUC) of the final model for predicting PIV ≥ 8 was 0.72 (95% CI: 0.62–0.82) (Fig. 5).

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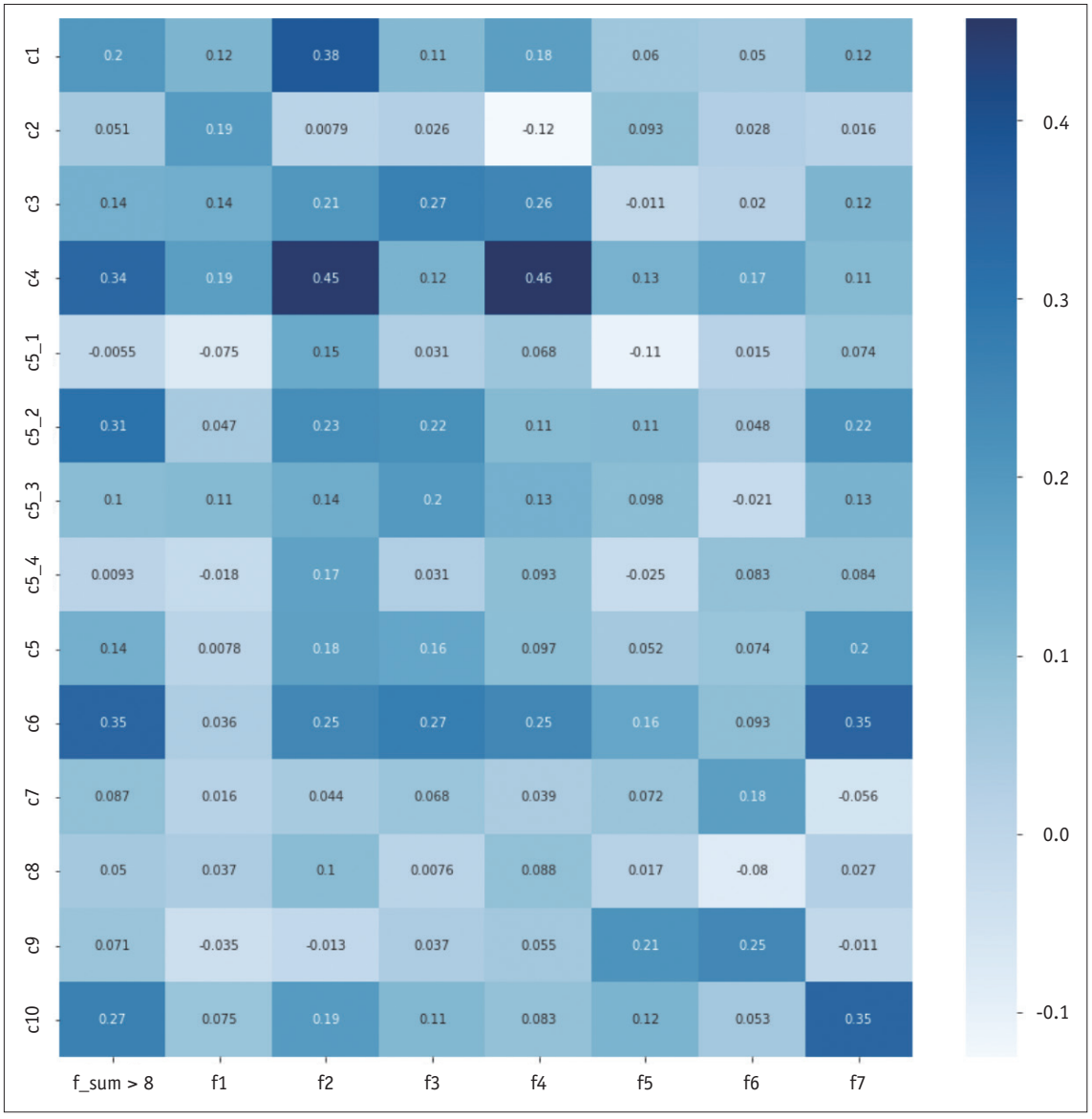

Fig. 4. Heat map depicting absolute values of Spearman correlation coefficient between ten imaging features and laparoscopic parameters. The color intensity increases proportionally with the magnitude of correlation coefficient. Ten CT features lie on the y-axis: c1 = ascites, c2 = pelvic and/or low abdomen peritoneal involvement, c3 = mesenteric involvement, c4 = omental cake, c5 = upper abdomen involvement (c5-1 = porta hepatis, c5-2 = Morrison's pouch, c5-3 = gastro-transverse mesocolon-splenic complex, c5-4 = lesser curvature), c6 = diaphragmatic involvement, c7 = pelvic wall extension, c8 = parenchymal involvement, c9 = lymphadenopathy, and c10 = liver surface involvement. Laparoscopic parameters lie on x-axis: f sum ≥ 8 = predictive index value over 8, f1 = peritoneal carcinomatosis, f2 = diaphragmatic disease, f3 = mesenteric disease, f4 = omental disease, f5 = bowel infiltration, f6 = stomach infiltration, f7 = liver metastasis

DISCUSSION

In the present study, we attempted to assess correlations between CT features and Fagotti scoring system parameters to construct an improved CT-based prediction model for suboptimal cytoreduction that would be both non-invasive and reproducible. Although some CT-based prediction models using the PCI have been suggested, none is widely used in clinical settings due to unsuccessful cross-validation [22]. Their poor results were mainly caused by overlooking surgeon factors, such as surgeons' capability and philosophy. In addition, these CT-based models could not fully reflect the surgical difficulty for the anatomic location of the lesion. Moreover, laparoscopy-based prediction of suboptimal cytoreduction is used by many surgeons because it reflects the surgeon factor with an overall accuracy of 75% [19]. A similar predictive performance was identified in an independent external cohort, showing good

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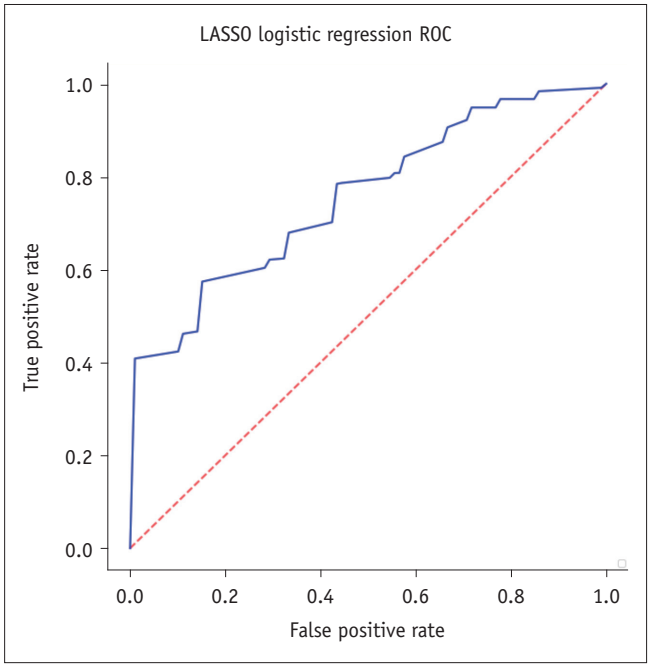

Fig. 5. The ROC curve of CT-based Fagotti scoring system (blue line). The area under the ROC curve was 0.72 (95% confidence interval: 0.62–0.82). Reference: dashed red line. LASSO = least absolute shrinkage and selection operator, ROC = receiver operating characteristic

reproducibility [20]. However, laparoscopic evaluation has its limitations: it is an invasive procedure under general anesthesia, accompanied by the risk of postoperative complications and increased costs. In addition, it tends to underestimate the disease extent because some areas are difficult to visualize using laparoscopy, especially in the retroperitoneum, retrohepatic space, and porta hepatis.

To overcome the limitations of both CT and diagnostic laparoscopy, the investigators of this study first analyzed the correlations between CT-based PCI parameters and laparoscopic parameters of the Fagotti scoring system. However, Spearman correlation analysis between them did not show any strong head-to-head correlation, even between corresponding findings such as c2 vs. f1 (peritoneal involvement), c6 vs. f2 (diaphragmatic involvement), c3 vs. f3 (mesenteric disease), and c4 vs. f4 (omental disease). This might be due to the lower resolution and larger coverage of CT than laparoscopy. Some laparoscopic findings, such as sheet-like or miliary nodules, infiltrative organ involvement, and mesenteric retractions, are invisible or poorly delineated on the corresponding CT section. Instead, they present as subtle wall thickening or indirect findings, such as haziness or ascites on CT. Unlike laparoscopic parameters, CT features included almost all intraperitoneal locations; thus, it is expected that there would be no strong correlation. Because a surgeon's decision mainly depends on the laparoscopic PIV (sum of each score), we constructed a prediction model for PIV using all CT parameters. The final model revealed that diaphragmatic involvement (c6), GTS space involvement (c5-3), mesenteric involvement (c3), and lymphadenopathy (c9) on preoperative CT were distinct predictive factors for PIV ≥ 8, which are known to have a high risk for suboptimal cytoreduction.

Our study has several limitations. First, the final model did not show a strong predictive power, with an AUC of 0.72. Prior CT-based prediction models showed wide range of AUC, from 0.64 to 0.96 [10-12,14,23]. The difference in AUC might be attributed to different sets of CT parameters, as well as clinical features (e.g., CA-12 and performance status) and operative findings. Furthermore, we predicted PIV ≥ 8 as an indicator of suboptimal cytoreduction, while other studies predicted surgical outcomes directly. To improve the predictability of the CT-based Fagotti scoring system, it is necessary to reconstruct CT parameters tailored to laparoscopy with further analysis using a combination of selected CT features with significant correlation values. In addition, the scoring system for each CT parameter should be updated with an adjustment of the threshold. The CT-based PCI system can be fundamentally restructured using a multidisciplinary approach. Second, external validation of the final model has not yet been performed. A larger population study in different groups of surgeons might be necessary for further validation. Third, the association between the CT-based Fagotti scoring system and patient prognosis needs to be investigated in a future study.
The CT-based Fagotti scoring system can be a useful tool for predicting suboptimal cytoreduction in AOC patients because it has the advantages of both modalities: noninvasiveness and reproducibility.

In conclusion, central tumor burden (mesenteric involvement, involvement of the gastrosplenic and gastrocolic ligament, and para-aortic lymphadenopathy) and upper abdominal spread, including diaphragm involvement on preoperative CT, were identified as distinct predictive factors for high PIV on laparoscopy. This CT-based PIV prediction model may be useful for patient stratification before cytoreduction surgery for AOC.

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Supplement

The Supplement is available with this article at https://doi.org/10.3348/kjr.2020.1477.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: Dae Chul Jung, Jung Yun Lee, Na Young Kim. Data curation: Dae Chul Jung, Jung Yun Lee, Na Young Kim. Funding acquisition: Dae Chul Jung. Investigation: Dae Chul Jung, Jung Yun Lee, Na Young Kim. Methodology: Dae Chul Jung, Jung Yun Lee, Na Young Kim, Kyung Hwa Han. Project administration: Dae Chul Jung. Resources: Dae Chul Jung, Jung Yun Lee, Na Young Kim. Supervision: Dae Chul Jung, Jung Yun Lee, Young Taik Oh. Validation: Dae Chul Jung, Jung Yun Lee, Na Young Kim, Kyung Hwa Han. Writing—original draft: Dae Chul Jung, Na Young Kim. Writing—review & editing: Dae Chul Jung, Jung Yun Lee, Na Young Kim, Kyung Hwa Han.

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