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Association between High Diffusion-Weighted Imaging-Derived Functional Tumor Burden of Peritoneal Carcinomatosis and Overall Survival in Patients with Advanced Ovarian Carcinoma

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Objective: To investigate the association between functional tumor burden of peritoneal carcinomatosis (PC) derived from diffusion-weighted imaging (DWI) and overall survival in patients with advanced ovarian carcinoma (OC).
Materials and Methods: This prospective study was approved by the local research ethics committee, and informed consent was obtained. Fifty patients (mean age ± standard deviation, 57 ± 12 years) with stage III–IV OC scheduled for primary or interval debulking surgery (IDS) were recruited between June 2016 and December 2021. DWI (b values: 0, 400, and 800 s/mm^2) was acquired with a 16-channel phased-array torso coil. The functional PC burden on DWI was derived based on K-means clustering to discard fat, air, and normal tissue. A score similar to the surgical peritoneal cancer index was assigned to each abdominopelvic region, with additional scores assigned to the involvement of critical sites, denoted as the functional peritoneal cancer index (fPCI). The apparent diffusion coefficient (ADC) of the largest lesion was calculated. Patients were dichotomized by immediate surgical outcome into high- and low-risk groups (with and without residual disease, respectively) with subsequent survival analysis using the Kaplan-Meier curve and log-rank test. Multivariable Cox proportional hazards regression was used to evaluate the association between DWI-derived results and overall survival.
Results: Fifteen (30.0%) patients underwent primary debulking surgery, and 35 (70.0%) patients received neoadjuvant chemotherapy followed by IDS. Complete tumor debulking was achieved in 32 patients. Patients with residual disease after debulking surgery had reduced overall survival ($p = 0.043$). The fPCI/ADC was negatively associated with overall survival when accounted for clinicopathological information with a hazard ratio of 1.254 for high fPCI/ADC (95% confidence interval, 1.007–1.560; $p = 0.043$).
Conclusion: A high DWI-derived functional tumor burden was associated with decreased overall survival in patients with advanced OC.
Keywords: Diffusion magnetic resonance imaging; Functional peritoneal cancer index; Advanced ovarian carcinoma; Peritoneal carcinomatosis; Survival analysis

INTRODUCTION

Ovarian carcinoma (OC) is a malignant female disease with high mortality [1]. The 5-year survival rate is lower than 45%, especially in patients diagnosed with an advanced stage disease (International Federation of

Gynecology and Obstetrics [FIGO] stage III/IV) [2]. Only 15%–20% of patients will survive beyond 10 years of effective treatment [2,3].

Incomplete tumor debulking will greatly reduce the chances of survival in patients with advanced OC [4,5]. Patients with high burden of peritoneal carcinomatosis (PC) are less likely to achieve complete tumor debulking compared to patients with low burden of PC [6,7]. Additionally, the involvement of invasive and radical procedures such as liver and bowel resections to remove PC involvement at critical sites, such as at the porta hepatis and small bowel mesentery or serosa, also reduces the likelihood of achieving complete tumor debulking [8].

The surgical peritoneal cancer index (sPCI) and Fagotti score are validated prognostic scores [9,10]. However, surgical management is invasive and requires additional procedures in patients who are unsuitable for primary debulking surgery. Thus, a non-invasive method to evaluate PC burden will help guide decision-making, potentially offering patients with a heavy disease burden and poor prognosis for alternative treatment or enrolment in clinical trials.

Diffusion-weighted imaging (DWI) is useful for PC lesion detection with high sensitivity and specificity, particularly for diffuse disease [11,12]. Literature showed that apparent diffusion coefficient (ADC) could predict surgical outcome and chemotherapy response in OC [13,14]. A new scoring method for DWI that generated a new parameter called the functional peritoneal cancer index (fPCI) was shown to be significantly correlated with the sPCI [15]. fPCI could offer a semi-automated estimation of the PC burden. The combined DWI-derived fPCI/ADC can predict the likelihood of complete tumor debulking with high accuracy of 92.5% [15]. However, the association between DWI-derived fPCI/ADC and overall survival in patients with advanced OC remains unclear. We hypothesized that fPCI would be lower and ADC would be higher in patients with favorable survival outcomes.

This study aimed to investigate the association between non-invasive DWI-derived fPCI/ADC and overall survival in patients with advanced OC.

MATERIALS AND METHODS

Study Population

The local Institutional Research Ethics Committee approved this prospective study, and all patients provided written informed consent (IRB No. HKU/HA HKW IRB UW 15-536). The data in this study were partially (44/50 patients) included in another study published by European Radiology on May 13, 2020 [15]. The inclusion criteria were as follows: 1) FIGO stage III/IV OC confirmed by histology, 2) local multidisciplinary meeting recommendation for primary debulking surgery or neoadjuvant chemotherapy (NACT) followed by interval debulking surgery (IDS) according to the European Society of Gynaecological Oncology guidelines on surgery for OC [8], 3) DWI performed before debulking surgery, and 4) a minimum of 18 months of follow-up. The exclusion criteria were 1) poor imaging quality for diagnosis on DWI, 2) non-gynecological malignancy or benign ovarian masses, and 3) any previous history of other malignant diseases, except for OC. All patients' clinical and pathological characteristics, including age, FIGO stage, pre-surgical CA-125 level, and histological subtype, were documented. CA-125 levels were tested within 14 days of debulking surgery. Histological confirmation was based on surgical specimens or biopsy samples acquired during surgery.

Surgical Evaluation

All patients were evaluated by a local multidisciplinary team according to the European Society of Gynaecological Oncology guidelines [8]. Patients who were not suitable for primary debulking were given 3–6 cycles of NACT followed by IDS.

During surgery, the tumor burden and extent of PC were assessed using sPCI. There were 13 arbitrary regions in the abdominopelvic cavity, each assigned a score (score 0–3) depending on the size of the largest lesion within the region. Therefore, the sum of the scores, denoted as sPCI, varies between 1 and 39 [16].

At the end of the debulking surgery, through visual inspection and systematic palpation, the immediate surgical outcome was dichotomized into complete (without residual disease) and incomplete tumor debulking (irrespective of the size and location of the residual disease).

MRI Examination and Evaluation

All MRI examinations were scheduled before debulking surgery on a 3 Tesla (T) MRI platform (Achieva TX, Philips Healthcare). All patients were required to fast for 6 hours before MRI examination. To allow for optimal bowel distension, patients drank 1.5–2.0 L of the Metamucil mixture (The Proctor & Gamble Co. 2 mL/kg mixed with

Table 1. Summary of MRI Scanning Parameters

Sequences	Sagittal T2WI	Coronal T2WI	Axial T2WI	Contrast-Enhanced 3D T1WI	DWI
Coverage	Pelvis	Diaphragm to the groin	Diaphragm to the groin	Diaphragm to the groin	Diaphragm to the groin
TR/TE, msec	4654/80	2800/100	622/10	3/1.4	1210/53
FOV, mm^2	800 x 800	768 x 768	1200 x 1200	640 x 640	480 x 480
Matrix size	480 x 300	316 x 298	580 x 438	248 x 245	160 x 157
Slice thickness, mm	4	4	4	3	4
Receiver bandwidth, kHz	217	152	218	724	3004

DWI = diffusion-weighted imaging, FOV = field of view, TE = echo time, TR = repetition time, T1WI = T1 weighted imaging, T2WI = T2 weighted imaging

water, 50 g/L) 2 hours before image acquisition. All patients received 20 mg intravenous hyoscine butylbromide (Buscopan, Boehringer Ingelheim) immediately before MRI examinations to decrease intestinal peristalsis. Standard MRI sequences (sagittal T2WI, coronal T2WI, axial T2WI, and contrast-enhanced 3D T1WI) and DWI (3 b values: 0, 400, and 800 s/mm^2) were acquired with a 16-channel phased-array torso coil. For the upper abdomen, breath-hold or respiratory-triggered techniques were used to minimize motion artifacts, while for the pelvis, all sequences except T1WI were acquired during free breathing. One case with poor imaging quality was excluded after consensus reading by the two reviewers. The scanning parameters are listed in Table 1.

All images were reviewed by two board-certified radiologists in consensus (1st radiologist with 3 years' experience in cross-sectional imaging and 2nd radiologist with more than 10 years' experience in cross-sectional imaging with a special interest in gynae-oncological imaging).

fPCI Calculation

The derivation of functional tumor burden, denoted as fPCI, has been described previously [15,17]. Two radiologists first visually identified all lesions in consensus on b = 800 s/mm^2 images, with reference to standard MRI sequences and co-registered ADC maps. Then, they manually drew volumes of interest (VOIs) to include the entirety of all lesions on all slices in which the lesions existed but did not require strict delineation. VOIs were automatically transferred to the ADC map for quantification. This set of VOIs was aimed at calculating the fPCI and was denoted as VOI$_{fPCI}$ (Fig. 1). For diffuse thickening, the VOI$_{fPCI}$ was placed over the areas involved, which might include normal or benign tissues, and subsequently, K-means clustering was

used to identify the tumor component.

VOI$_{fPCI}$ was segmented into three clusters based on ADC values using K-means clustering. In short, the intracluster variance between the voxel and its surrounding voxels was initially calculated. Then, the voxel was assigned to the cluster with the lowest intra-cluster variance. The same step was repeated until the lowest intracluster variance was achieved. Only the intermediate ADC cluster was regarded as a solid tumor component with high cellularity and was used for the subsequent fPCI calculation. The highest ADC cluster, considered as having normal or cystic tissues, and the lowest ADC cluster, considered to contain fibrous or fat tissues, were disregarded. All the segmentation and calculations were performed using MATLAB (ver. 2020b, The MathWorks, Inc.) using in-house written scripts [15].

Similar to sPCI, fPCI was calculated based on the sum of all scores in the 13 arbitrarily divided abdominopelvic regions, determined by the volume of the largest lesion within each region. To incorporate the importance of critical sites on the feasibility of achieving complete tumor debulking, three extra scores were assigned to the involvement of these sites, namely the mesentery, bowel serosa, or porta hepatis [8]. Thus, the fPCI scores varied between 1 and 42.

ADC Measurement

The largest primary or PC lesion was selected as the target lesion for the ADC quantification. Another set of VOIs based on strict delineation on b = 800 s/mm^2 with careful exclusion of air, fat, and normal tissues, aimed at measuring ADC, was denoted as VOI$_{ADC}$ (Fig. 1). The average ADC was measured using VOI$_{ADC}$.

Statistical Analysis

As fPCI and ADC have antagonistic effects, we anticipated
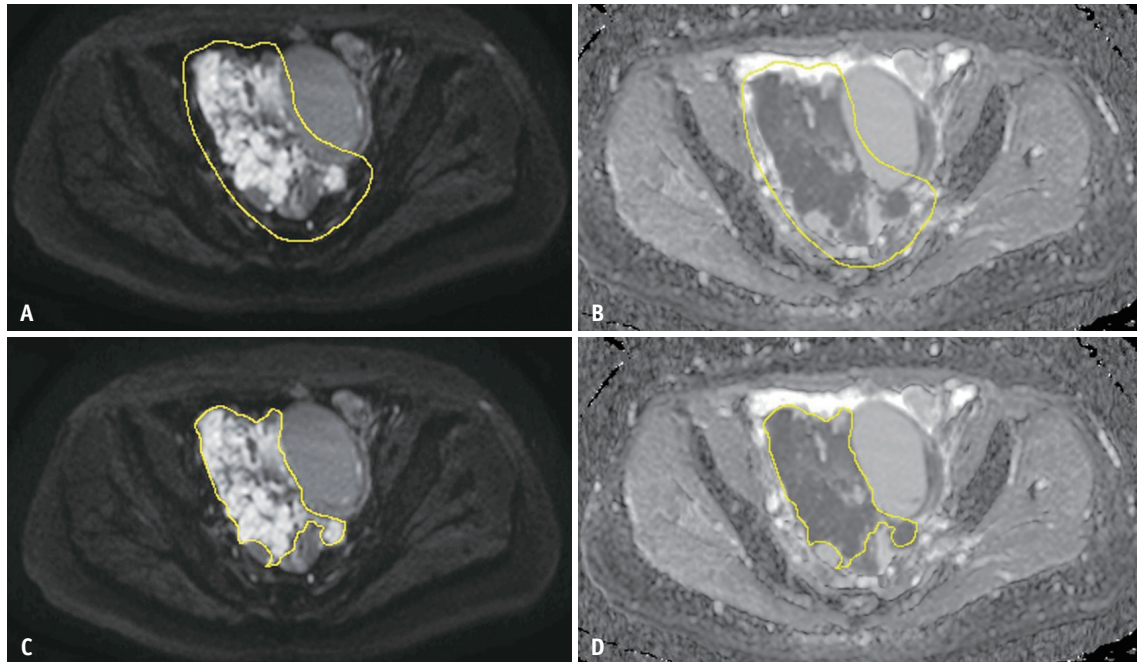
Fig. 1. An exemplary placement of VOIs.
A. The VOI$_{fPCI}$ was placed on all lesions but careful exclusion of air, fat, or normal tissues was not required. **B.** Segmentation of the VOI$_{fPCI}$ on corresponding ADC map to only include the intermediate ADC cluster. **C.** The VOI$_{ADC}$ was strictly drawn on the largest lesion with careful exclusion of air, fat, or normal tissues. **D.** The VOI$_{ADC}$ was transferred to the ADC map to measure ADC. ADC = apparent diffusion coefficient, fPCI = functional peritoneal cancer index, VOI = volume of interest

that patients with poor survival would have high fPCI and low ADC. Hence, a combined DWI-derived metric, fPCI/ADC, was developed and evaluated.

Survival time was measured from the date of diagnosis until death from any cause or by censored time (December 2021). Patients were dichotomized into high- and low-risk groups based on immediate surgical outcomes (with and without residual disease, respectively). The Mann-Whitney U test was used to compare differences in sPCI and fPCI/ADC between the two risk groups. Kaplan-Meier curves and log-rank tests were conducted to compare the patients' overall survival in these two groups. Multivariable Cox proportional hazards models were constructed with sPCI, immediate surgical outcome, and clinicopathological information (age, FIGO stage, pre-surgical CA-125, histological subtypes, treatment strategy, whether patients had primary debulking surgery or NACT followed by IDS) or with fPCI/ADC, immediate surgical outcome, and clinicopathological information. Hazard ratios (HR) of the significant determinative features were calculated.

All statistical analyses were performed using SPSS Statistics (ver. 22.0, IBM Corp.), and MedCalc (ver. 11.4, MedCalc Software Ltd.). Statistical significance was set at $p < 0.05$.

RESULTS

Patients' Characteristics

Fifty patients enrolled between June 2016 and December 2021 were included in the study with an average age ± standard deviation of 57 ± 12 years old, and a median pre-surgical CA-125 level of 137.8 U/mL (range: 12.7–7116.5 U/mL). Fifteen (30.0%) patients underwent primary debulking surgery, and 35 (70.0%) patients underwent NACT followed by IDS. There were 28 (56.0%) patients with FIGO stage III and 22 (44.0%) patients with FIGO stage IV disease. Thirty-seven (74.0%) patients were histologically proven as high-grade serous carcinoma (HGSC), and 13 (26.0%) patients were histologically proven as non-HGSC (mucinous carcinoma = 3, clear cell carcinoma = 4, endometrioid carcinoma = 4, squamous cell carcinoma = 1, Mullerian origin carcinoma = 1). The median time interval between the MRI and debulking surgery was 14 days (range: 1–63 days). Complete tumor debulking was achieved in 32 (64.0%) patients.

Patients were dichotomized into low- (n = 32) and high-risk (n = 18) groups for survival analyses based on immediate surgical outcomes. The mean sPCI in low- and high-risk groups were 5.78 vs. 11.78 ($p < 0.001$), and the
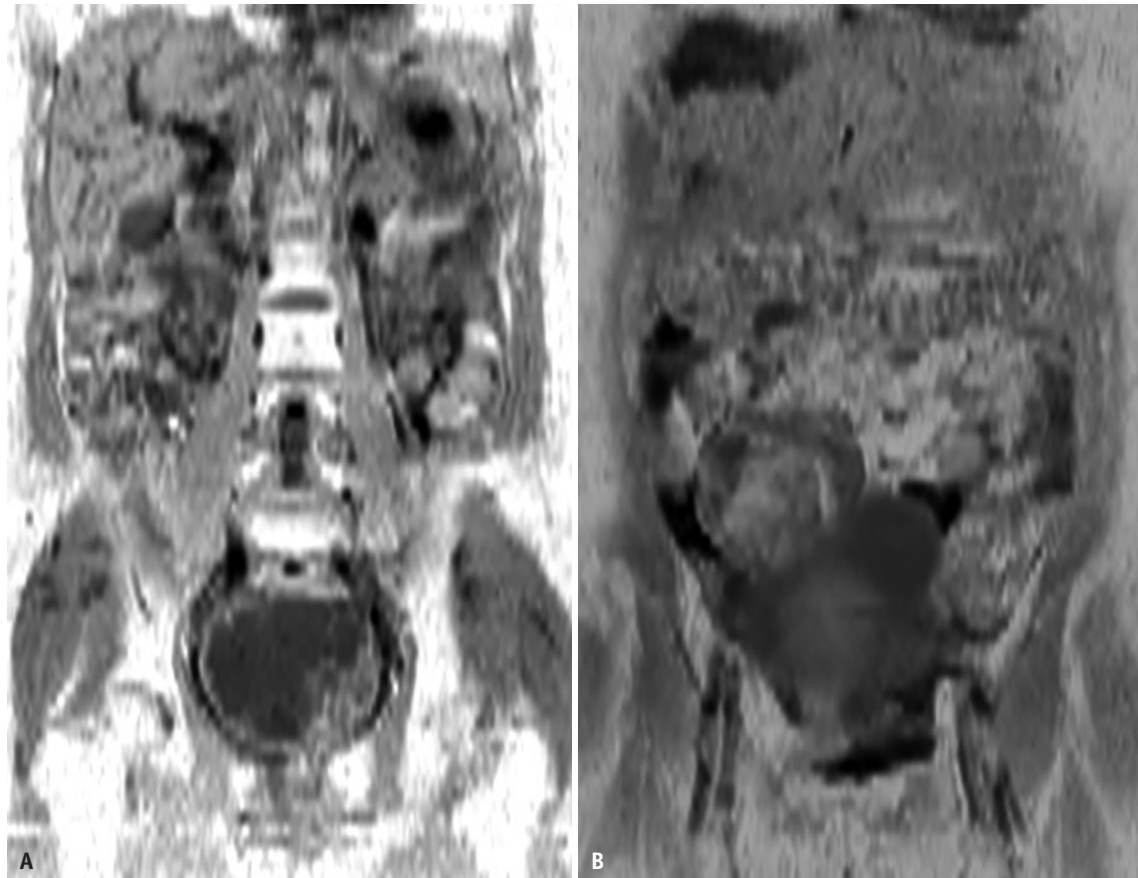
Fig. 2. Comparison of tumor burden between low- and high-risk groups.
A. A case in low-risk group (without residual disease) showing low tumor burden with large pelvic mass on MIP image of DWI. **B.** A case in high-risk group (with residual disease) showing high tumor burden on MIP image of DWI. Apart from disease in the pelvis extending to the right iliac fossa, a right subdiaphragmatic disease was present. DWI = diffusion-weighted imaging, MIP = maximum intensity projection
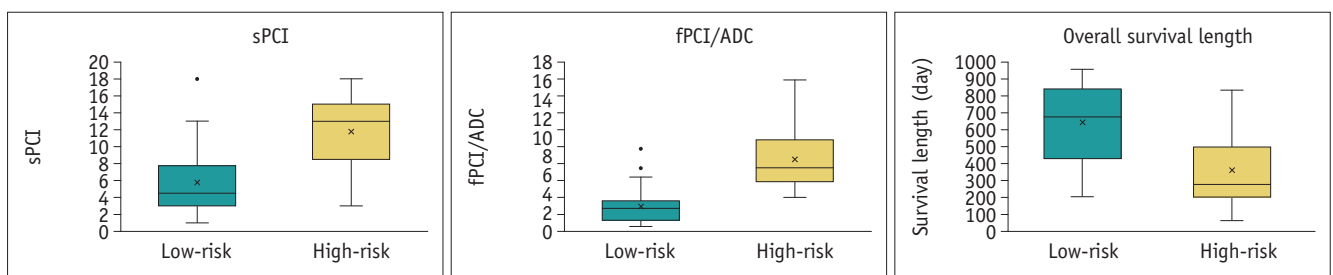

Fig. 3. sPCI, fPCI/ADC, and overall survival length between high- and low-risk groups (with and without residual disease, respectively). ADC = apparent diffusion coefficient, fPCI = functional peritoneal cancer index, sPCI = surgical peritoneal cancer index

mean fPCI/ADC in low- and high-risk groups were 2.68 vs. 7.89 ($p < 0.001$), respectively (Figs. 2, 3).

Comparison of Survival Outcomes between Risk Groups

Twenty-one patients died during the follow-up period (until December 2021). Ten patients died in the low-risk group compared with 11 patients in the high-risk group. The median survival time was 561 days (677 and 279 days for the low- and high-risk groups, respectively). The

Kaplan-Meier curves are shown in Figure 4. Overall survival was significantly shorter in patients with residual disease after debulking surgery than in those without residual disease ($p = 0.043$).

Multivariable Survival Analysis: Cox Proportional Hazards Models

Multivariable Cox proportional hazards analysis was conducted, including sPCI or fPCI/ADC (Table 2), along with

residual disease and clinicopathological information (age, pre-surgical CA-125, FIGO stage, histological subtypes, and treatment strategy) to predict patients' overall survival. The combined fPCI/ADC was a significant independent factor with an HR for high fPCI/ADC = 1.254 (95% confidence interval, 1.007-1.560; p = 0.043).
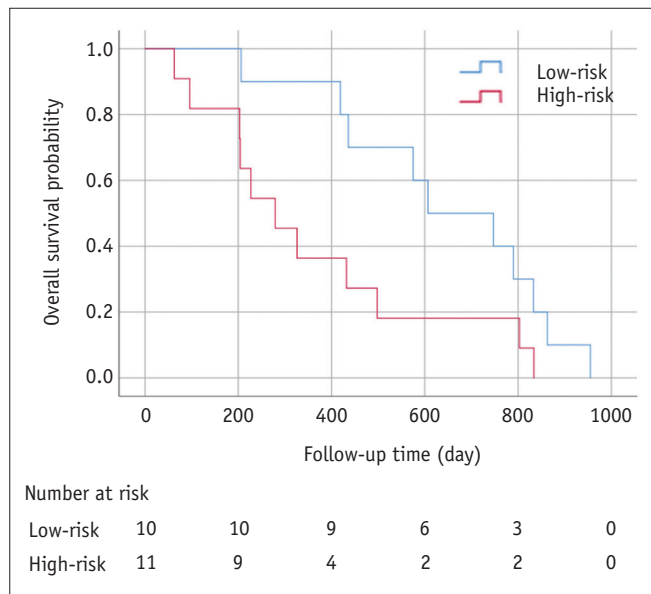

Fig. 4. Kaplan-Meier curves dichotomized by high- and low-risk groups (with and without residual disease, respectively).

DISCUSSION

In the present study, high DWI-derived combined fPCI/ADC was correlated with decreased overall survival in patients with advanced OC who underwent primary debulking surgery or NACT with IDS, indicating that the novel non-invasive DWI-derived parameters might have potential prognostic value for advanced OC. This may reveal opportunities for adjuvant treatment escalation and a more aggressive follow-up regimen for patients with high fPCI/ADC ratios.

Complete tumor debulking is one of the most important factors determining patient survival in advanced OC [14]. Our results showed that patients with residual disease had significantly reduced overall survival compared to patients without residual disease after debulking surgery, which was in concordance with a previous study [14]. However, in a multivariate analysis, the difference was not significant. This could be due to potential collinearity with other clinical information.

However, the prognostic value of sPCI in patients with advanced OC remains controversial. A previous study found that sPCI could not serve as an independent prognostic factor for long-term survival [18], while another study found that sPCI was related to a 5-year survival [19].

Table 2. Multivariable Cox Proportional Hazards Analysis Based on sPCI or fPCI/ADC Incorporated with Residual Disease and Clinicopathological Information to Predict Patients' Overall Survival

Variables	sPCI		Variables	fPCI/ADC	
	HR (95% CI)	P		HR (95% CI)	P
sPCI, unit = 1	0.904 (0.757–1.080)	0.267	fPCI/ADC, unit = 1	1.254 (1.007–1.560)	0.043
Age, year	0.974 (0.901–1.053)	0.505	Age, year	0.991 (0.912–1.077)	0.836
CA-125, U/mL	1.001 (1.000–1.002)	0.053	CA-125, U/mL	1.001 (1.000–1.002)	0.072
FIGO stage			FIGO stage		
III	Reference		III	Reference	
IV	3.080 (0.876–10.838)	0.080	IV	1.940 (0.614–6.126)	0.259
Histology			Histology		
Non-HGSC	Reference		Non-HGSC	Reference	
HGSC	0.415 (0.118–1.455)	0.169	HGSC	0.225 (0.060–0.839)	0.026
NACT status			NACT status		
Without NACT	Reference		Without NACT	Reference	
With NACT	1.364 (0.324–5.735)	0.672	With NACT	1.122 (0.246–5.109)	0.882
Risk			Risk		
Low-risk	Reference		Low-risk	Reference	
High-risk	3.031 (0.470–19.531)	0.243	High-risk	0.823 (0.180–3.766)	0.802

ADC = appreant diffusion coefficient, CA-125 = cancer antigen-125, CI = confidence interval, FIGO = International Federation of Gynecology and Obstetrics, fPCI = functional peritoneal cancer index, HGSC = high grade serous carcinoma, High-risk = patients with residual disease after debulking surgery, HR = hazard ratios, Low-risk = patients without residual disease after debulking surgery, NACT = neo-adjuvant chemotherapy, sPCI = surgical peritoneal cancer index

Another retrospective study performed a multivariate analysis in 80 patients with primary advanced OC, showing that sPCI was significantly associated with progress-free survival (p = 0.005) but not with overall survival (p = 0.162) [20]. In the aforementioned study, only patients who underwent complete debulking surgery were included, which might have resulted in a selection bias. A later study that included 80 patients with advanced OC who underwent primary debulking surgery reported a cutoff value of 15 for poor survival [21]. Our study found that patients with a high sPCI had reduced overall survival, but this was not significant in the multivariate analysis. This could be due to the inclusion of both patients who underwent primary debulking surgery and those who underwent IDS after NACT, resulting in a relatively low sPCI in our study.

A previous study showed that DWI-derived fPCI demonstrated high correlation with sPCI, and both were predictive of the immediate surgical outcome in advanced OC, in terms of complete and incomplete tumor debulking [15]. Other studies have shown that changes in ADC reflect changes in tumor cellularity following treatment [22]. After one treatment cycle, an increase in ADC was associated with improved progression-free survival in patients with disease relapse [13]. We found that the combined parameter, fPCI/ADC, reflected both tumor burden and tumor cellularity and was negatively correlated with patients' overall survival.

Our study has several limitations. The sample size was small with inhomogeneous cohorts, including patients who underwent primary debulking surgery or NACT followed by IDS, which could potentially affect the intraoperative evaluation of sPCI and the immediate surgical outcome, as NACT could alter the appearance of PC and induce fibrosis and adhesions in the abdominopelvic cavity [23]. However, in the Cox proportional hazards models, the use of NACT was not a significant factor influencing survival. This is in agreement with a previous study that showed the non-inferiority of NACT followed by IDS compared to primary debulking surgery in advanced OC [24]. Second, the decision to perform debulking surgery might be affected by imaging results, as clinicians were not blinded to these, but fPCI was not disclosed. Nevertheless, all treatment decisions were made by the same local multidisciplinary team according to the European Society of Gynecological Oncology guidelines. Third, the results were from a single unit and would require further cross-center validation and multi-institutional participation. Fourth, the MRI evaluation was based on consensus reading by two radiologists, which may not reflect usual clinical practice, and the decision may potentially be overweighed by opinion from a more experienced radiologist. Fifth, VOI$_{ADC}$ was manually drawn on DWI with a relatively low spatial resolution compared to standard MRI sequences, which might not be precise. However, the use of the K-means clustering method in the derivation of fPCI would help partially overcome this drawback. Finally, a minimum of 18 months of follow-up might not be sufficient and could result in truncation of survival.

In conclusion, a high DWI-derived functional tumor burden is associated with decreased overall survival in patients with advanced OC.

Availability of Data and Material

The datasets generated or analyzed during the study are not publicly available due to sensitivities with patient-related clinical information but are available from the corresponding author on reasonable request.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Author Contributions

Conceptualization: He An, Elaine YP Lee. Data curation: Hextan YS Ngan, Elaine YP Lee. Formal analysis: Keith WH Chiu, Edward S Hui, Elaine YP Lee. Investigation: Mandy MY Chu, Siew Fei Ngu, Hextan YS Ngan, Elaine YP Lee. Methodology: He An, Jose AU Perucho, Elaine YP Lee. Project administration: Elaine YP Lee. Resources: Mandy MY Chu, Siew Fei Ngu, Hextan YS Ngan, Elaine YP Lee. Software: He An, Jose AU Perucho. Supervision: Elaine YP Lee. Validation: He An, Jose AU Perucho. Visualization: He An, Elaine YP Lee. Writing—original draft: He An. Writing—review & editing: all authors.

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