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Impact of a modified peritoneal cancer index using FDG-PET/CT (PET-PCI) in predicting tumor grade and progression-free survival in patients with pseudomyxoma peritonei

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Abstract

Objectives The peritoneal cancer index (PCI) is widely used for assessing pseudomyxoma peritonei (PMP) in surgery. The aim of this study was to evaluate the utility of a modified PCI using 18F-fluorodeoxyglucose (18F-FDG)-PET/CT (PET-PCI) for predicting pathologic grade and progression-free survival (PFS) in patients with PMP.

Methods Thirty-five patients who underwent 18F-FDG-PET/CT before cytoreductive surgery and/or hyperthermic intraperitoneal chemotherapy were enrolled. PET-PCI was determined by summing up the visually scored 18F-FDG uptake of PMP lesions in 13 specific abdominal-pelvic regions. Uptake score was defined as 0, no lesion or lesion without uptake; 1, slight uptake less than or equivalent to mediastinal blood pool; 2, moderate uptake above mediastinal but below or equal to liver; and 3, intense uptake moderately to markedly higher than liver. SUVmax of the lesion was also evaluated.

Results Pathologic diagnosis revealed 19 patients with low-grade PMP and 16 patients with high-grade PMP. Patients with high-grade PMP showed significantly higher PET-PCI and SUVmax than patients with low-grade PMP (PET-PCI 14.8 vs. 8.7, $p = 0.007$; SUVmax 3.6 vs. 2.6, $p = 0.013$). Using a cutoff PET-PCI of 12, Kaplan-Meier analyses showed a significant difference in PFS between patients with high and low PET-PCI ($p < 0.001$; hazard ratio (HR), 12.4). For SUVmax, the optimal cutoff was 2.7 and the correlation with PFS was also significant ($p = 0.008$; HR, 4.7). In multivariate Cox proportional-hazards regression, PET-PCI was independently and significantly correlated with PFS.

Conclusions PET-PCI can reflect histopathologic features and appears useful for predicting recurrence in patients with PMP.

Key Points

- *Peritoneal cancer index using 18F-FDG-PET/CT (PET-PCI) has great potential for predicting progression-free survival in patients with pseudomyxoma peritonei.*
- *PET-PCI provides higher prognostic performance than maximum standardized uptake value (SUVmax).*
- *PET-PCI shows high correlation with histopathologic grade of pseudomyxoma peritonei.*

Keywords Fluorodeoxyglucose F18 · Positron-emission tomography · Pseudomyxoma peritonei · Prognosis

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Abbreviations

CCR	Completeness of cytoreduction score
CRS	Cytoreductive surgery
HIPEC	Hyperthermic intraoperative chemotherapy
OSEM	Ordered-subset expectation maximization
PCI	Peritoneal cancer index
PFS	Progression-free survival
PMP	Pseudomyxoma peritonei
SUV	Standardized uptake value
VOI	Volume of interest

Introduction

Pseudomyxoma peritonei (PMP) is a relatively rare condition with an estimated incidence of 1 per million per year, characterized by gelatinous ascites disseminating in the peritoneum after rupture of a mucinous tumor [1–3]. The origin of the tumor is usually the appendix, but in some cases is another organ such as the ovary, colon, or pancreas [4–6]. Although the prognosis of PMP is usually poor, the introduction of cytoreductive surgery (CRS) with hyperthermic intraoperative chemotherapy (HIPEC) has brought about significant survival benefits. This therapy has recently become the standard-of-care for selected patients [7–11]. When complete CRS is not applicable (mainly due to extensive small bowel involvement), major palliative debulking is usually performed. Poor prognosis reportedly correlates with incomplete cytoreduction, absence of HIPEC, high-grade histopathologic subtype, or a high Peritoneal Cancer Index (PCI) [2, 12].

Dubreuil et al have reported that maximum standardized uptake value (SUVmax) offers a good predictor of PMP recurrence [13]. SUVmax is based on the assessment of one representative lesion, but PMP often occurs widely throughout the peritoneal space. Evaluation of the whole abdominopelvic cavity with 18F-FDG-PET/CT may thus more accurately reflect tumor burden than a single SUVmax value. The PCI is the scoring system most commonly used to quantify the extent of PMP lesions in the abdominopelvic space [14–16]. We hypothesized that PET-PCI, as an index integrating the PCI and 18F-FDG uptake, could provide a suitable marker for reflecting metabolic tumor burden and viability. The aim of this study was to evaluate the utility of PET-PCI for predicting progression-free survival (PFS) in patients with PMP as compared to SUVmax. In addition, we assessed the ability of PET-PCI to predict the histopathologic grade of PMP.

Materials and methods

Patients

This retrospective study was approved by the institutional review board at our hospital, and the need to obtain informed consent was waived. We included patients with clinically and histologically confirmed PMP who had been scheduled for CRS and HIPEC, and underwent 18F-FDG-PET/CT before surgery between September 2012 and February 2017. Exclusion criteria for this study were (1) patients with uncontrolled diabetes, (2) patients who had a history of treatment for PMP, and (3) patients who did not undergo surgery and were treated with chemotherapy alone.

Surgery

The surgical purpose was to obtain complete cytoreduction, with residual disease nodules less than 5 mm in diameter, followed by HIPEC using mitomycin C (10 mg/m^2) at 42 °C for 60 min, and early postoperative intraperitoneal chemotherapy (EPIC) with 5-fluorouracil (15 mg/kg). Residual disease was evaluated using the completeness of cytoreduction score (CCR) (CCR-0, absence of visible residual nodules; CCR-1, absence of residual nodules ≥ 0.25 cm in diameter; CCR-2, residual nodules 0.25–2.5 cm in diameter; and CCR-3, residual nodules > 2.5 cm) [17]. When the CCR score was 0 or 1, complete resection was considered to have been achieved. If complete resection was not accomplished, HIPEC was not performed.

Follow-up

After surgery, all patients received follow-up evaluations every 3–4 months with contrast-enhanced CT and measurement of tumor markers (CEA, CA19-9, and CA125). Progression or recurrence of the tumor was determined using the combination of CT features and tumor marker values. PFS was measured from the date of CRS and/or HIPEC to the date of confirmed recurrence, progression, or death.

PET/CT examination

PET/CT images were obtained 60 min after an intravenous injection of 18F-FDG, fixed at 5.0 MBq/kg. PET/CT was performed with one of three PET/CT systems: Biograph mCT S20 (Siemens Healthineers), Biograph 16 (Siemens Healthineers), or Discovery PET/CT 600 (GE Healthcare). Each of these systems consisted of a PET scanner and a multidetector-row CT scanner (16 detectors). Low-dose CT data were acquired at 120 kVp using an auto-exposure control system with beam pitches of 0.800, 0.833, and 0.938, and slice thickness of 5.0, 5.0, and 3.8 mm from the Biograph mCT S20, Biograph 16, and Discovery PET/CT 600, respectively. Emission images were acquired in three-dimensional mode (3.0, 2.5, and 2.5 min per bed position for Biograph mCT S20, Biograph 16, and Discovery PET/CT 600, respectively). PET data were reconstructed with an ordered-subset expectation maximization (OSEM) algorithm (3 iterations, 16 subsets) for the Discovery PET/CT 600, OSEM (3 iterations, 8 subsets) for the Biograph 16, and time of flight + OSEM (2 iterations, 21 subsets) for the Biograph mCT S20.

Image analysis

All PET/CT examinations were assessed by two board-certified nuclear medicine physicians blinded to the clinical condition (R.M. and M.H., with 17 and 11 years of experience, and 10 and 4 years of expertise, respectively). When

PMP lesions were difficult to distinguish from physiological uptake of the intestine, we referred contrast-enhanced CT that had been performed before 18F-FDG-PET/CT.

In cases of disagreement, a final consensus was achieved by discussion. A volume of interest (VOI) was contoured over the PMP lesion that showed the highest uptake throughout the abdominopelvic space, and SUVmax was calculated. The mean standardized uptake value for the liver ($SUVmean_{liver}$) was also evaluated using a VOI sphere with a radius of 15 mm within the liver. The PET-PCI value was obtained by summing up visually scored 18F-FDG uptakes from PMP lesions in 13 specific abdominal-pelvic regions (0, central; 1, right upper; 2, epigastrium; 3, left upper; 4, left flank; 5, left lower; 6, pelvis; 7, right lower; 8, right flank; 9, upper jejunum; 10, lower jejunum; 11, upper ileum; 12, lower ileum) that were used when evaluating PCI at surgery [17]. The uptake score in each region was defined as follows: 0, no lesion or lesion without uptake; 1, slight uptake less than or equivalent to mediastinal blood pool; 2, moderate uptake above mediastinal but below or equal to liver; and 3, intense uptake moderately to markedly higher than liver (Fig. 1).

Pathological analysis

The pathologic diagnosis was performed by board-certified pathologists using surgically resected specimen. PMP lesions were classified into the following categories: low grade, high grade, and high grade with signet cells. Low- and high-grade PMP are considered synonymous with disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis, respectively [18].

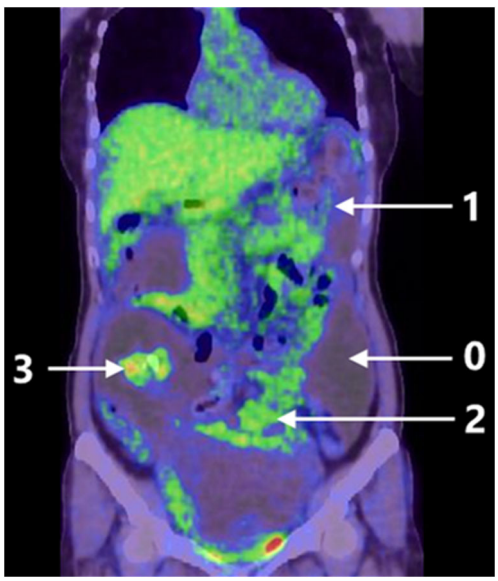

Fig. 1 Coronal 18F-FDG-PET/CT. Arrows (0–3) indicate lesions of pseudomyxoma peritonei. For calculating PET-PCI, the degree of 18F-FDG uptake in 13 regions was visually scored using a 0–3 point grading system: 0 = no lesion or lesion without uptake (arrow 0), 1 = slight uptake less than or equivalent to mediastinal blood pool (arrow 1), 2 = moderate uptake above mediastinal but below or equal to liver (arrow 2), 3 = intense uptake moderately to markedly higher than liver (arrow 3)

Statistical analysis

Student's *t* test was used to compare PET-PCI, SUVmax, and $SUVmax/SUVmean_{liver}$ between low- and high-grade PMP. Kaplan-Meier analysis with the log-rank test was performed to evaluate the correlation of PET-PCI, SUVmax, and $SUVmax/SUVmean_{liver}$ with PFS. A receiver operating curve analysis was used to determine optimal cutoff values for PET-PCI, SUVmax, and $SUVmax/SUVmean_{liver}$ when addressing survival analysis. Cox hazard ratio (HR) regression was performed for univariate and multivariate analyses. Two-tailed p values < 0.05 were regarded as significant. The R software package was used for statistical purposes.

Results

Forty patients met the study inclusion criteria. Of these, three patients underwent chemotherapy without surgery, and two patients were not treated in our hospital. A final total of 35 patients were thus included in the analysis. Patient characteristics are shown in Table 1. Complete cytoreduction was not

Table 1 Demographic characteristics of patients

No. of patients	35
Sex	M 12, F 23
Mean age, years (SD)	56.7 (13.7)
CEA (μg/L)	
Median (min–max)	20 (1.8–4908)
CA19-9 (U/mL)	
Median (min–max)	32 (0–3352)
CA125 (U/mL)	
Median (min–max)	55.7 (12.5–278.1)
Histological grade	
Low grade	19
High grade	10
High grade with signet cells	6
PCI	
0–10	0
11–20	0
21–30	14
31–39	12
N/A	9
CCR	
0–1	28
2–3	7

M male, *F* female, *PCI* peritoneal cancer index, *N/A* not applicable, *CCR* completeness of cytoreduction score

possible for seven patients and HIPEC was therefore not performed. Mean follow-up was 18.2 ± 9.1 months. Twenty patients showed recurrence during the follow-up (mean time to recurrence, 16.5 ± 10.6 months) and seven died from PMP. Twenty patients underwent PET/CT with the Discovery PET/CT 600, 12 patients with the Biograph 16, and three patients with the Biograph mCT S20.

Histopathologic correlation

Pathologic diagnosis revealed 19 PMP patients with low-grade PMP, 10 with high-grade PMP, and six with high-grade PMP with signet cells. PET-PCI was greater for patients with high-grade PMP (14.8 ± 5.0) than for those with low-grade PMP (8.7 ± 6.1, $p = 0.007$). Patients with high-grade PMP showed significantly higher SUVmax (3.6 ± 1.3) than patients with low-grade PMP (2.6 ± 1.0; $p = 0.013$) (Fig. 2). SUVmax/SUVmean$_{liver}$ was also higher in high-grade PMP than in low-grade PMP (1.7 ± 0.6 vs. 1.2 ± 0.5, $p = 0.011$).

Progression-free survival

Using a cutoff PET-PCI of 12, Kaplan-Meier analyses showed a significant difference in PFS between patients with high and low PET-PCI (log-rank test $p < 0.001$), with a HR of 12.4 (95% confidence interval (CI) 2.9–54.0, $p < 0.001$) (Fig. 3a). For SUVmax, the best cutoff was 2.7 and the correlation with PFS was also significant (log-rank test, $p = 0.008$) with a HR of 4.7 (95% CI, 1.4–16.6; $p = 0.015$) (Fig. 3b). For SUVmax/SUVmean$_{liver}$, the optimal cutoff was 1.3, and it was significantly correlated with PFS (log-rank test, $p = 0.007$; HR, 4.2 (95% CI, 1.4–13.2)). In univariate Cox analysis, CEA (cutoff, 14.8 μg/L), CA19-9 (cutoff, 56.0 U/mL), CA125 (cutoff, 38.8 U/mL), and pathologic grade (low vs. high) were all significant prognostic factors for PFS with HRs of 3.8 (95% CI, 1.1–13.1; $p = 0.034$), 3.7 (95% CI, 1.4–9.6; $p = 0.006$), 5.1 (95% CI, 1.2–22.0; $p = 0.030$), and 3.5 (95% CI, 1.3–9.4; $p = 0.011$), respectively. The absence of HIPEC showed no significant difference in predicting PFS (log-rank test, $p = 0.34$; HR, 1.6 (95% CI, 0.6–4.4)). In multivariate Cox proportional-hazards regression analysis using clinically important factors, PET-PCI was independently and significantly correlated with PFS, whereas other factors including SUVmax were not significant (Table 2). Representative cases are shown in Figs. 4 and 5.

Discussion

The purpose of this study was to investigate whether PET-PCI is more helpful than SUVmax for predicting PFS in patients with PMP. Although both PET-PCI and SUVmax correlated with PFS in univariate analysis, only PET-PCI was independently significant in multivariate analysis, and the HR was higher for PET-PCI than for SUVmax.

PET-PCI showed a high correlation with PFS as compared to SUVmax. This is probably because PET-PCI can reflect both tumor metabolic activity and spread into the abdominal space, whereas SUVmax represents metabolism only within a limited area. In the case of localized lesions, PET-PCI tends to

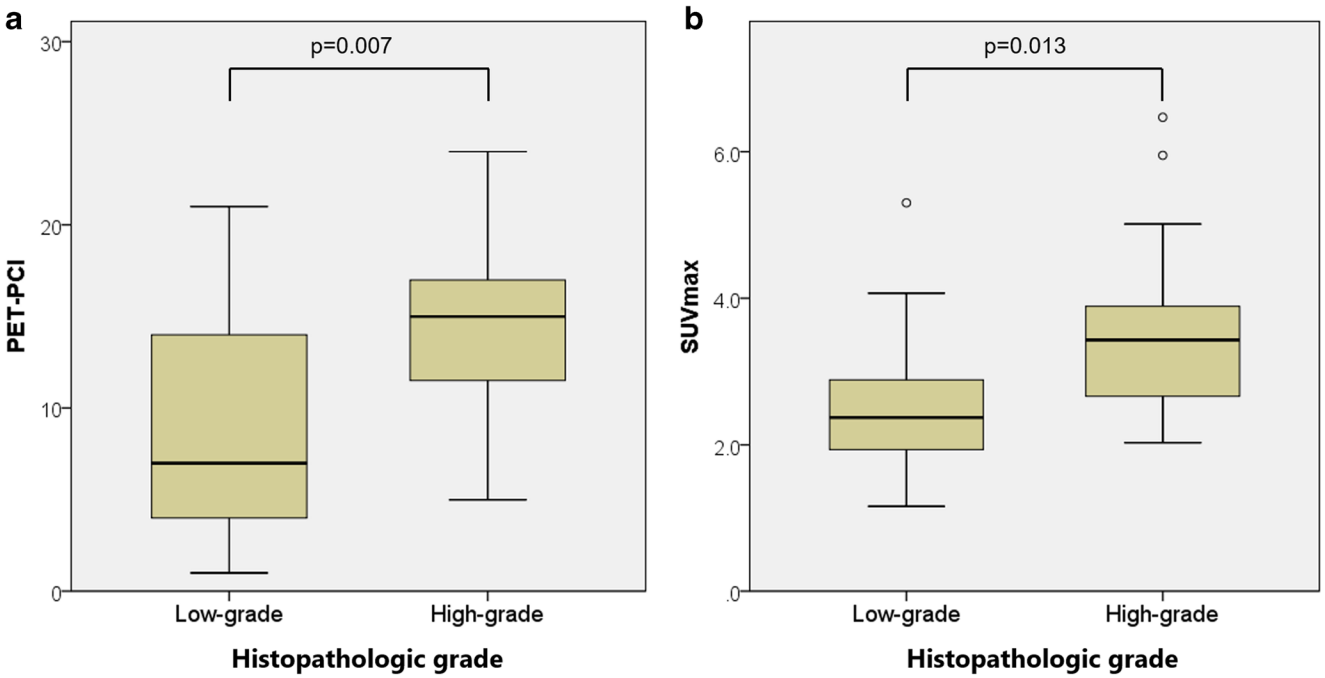

Fig. 2 Comparison of PET-PCI (**a**) and SUVmax (**b**) between low- and high-grade pseudomyxoma peritonei. Error bars show 95% confidence intervals

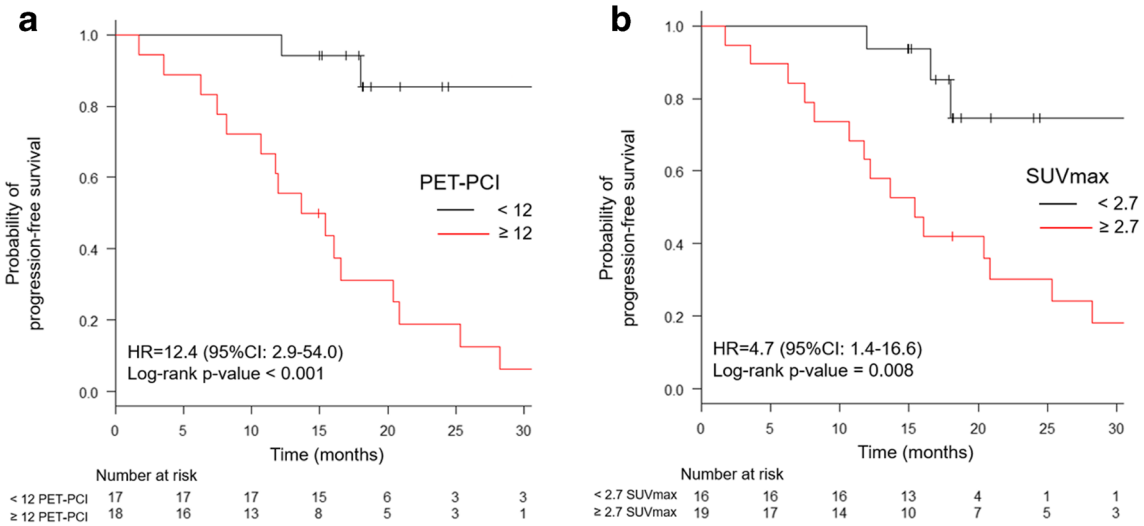

Fig. 3 Kaplan-Meier curves for progression-free survival of patients with PET-PCI < 12 versus PET-PCI ≥ 12 (**a**) and patients with SUVmax < 2.7 versus SUVmax ≥ 2.7 (**b**). HR, hazard ratio

be low, even if SUVmax is high. If the lesion is confined, complete resection of the lesion may be achievable. On the other hand, if the lesion has spread widely into the abdominopelvic space, especially into multiple segments of small bowel, complete resection is difficult to accomplish [14]. This is in line with why high PCI (≥ 20) is associated with poor prognosis and is occasionally considered as the criterion for the resectability of PMP [12, 19, 20]. Higher PCI is associated with a broader extent of lesions. To assess the extent of PMP lesions preoperatively, the utility of CT has been reported [21–23]. Indeed, radiologic PCI obtained by CT correlates strongly with actual PCI score, which can be improved by using contrast media [14]. When distinguishing PMP lesions in PET/CT is difficult because of the relatively low resolution, referencing contrast-enhanced CT, which is typically taken before PET/CT, is helpful, and this method was used in our study. Adding 18F-FDG-PET information (i.e., metabolic activity) to anatomical features obtained from CT will increase the diagnostic ability to evaluate the precise tumor burden.

Both PET-PCI and SUVmax were higher for high-grade PMP than for low-grade PMP. Patients with high-grade PMP reportedly display poorer prognosis than patients with low-grade PMP [2]. Patients with high PET-PCI and SUVmax are therefore considered to have poor prognosis, consistent with our results. Dubreuil et al reported no correlation between SUVmax and histopathology of PMP [13]. One possible explanation is that the pathologic classification in our study is based on the World Health Organization (WHO) classification [24], whereas their study used a three-grade Ronnet classification [25]. Previous investigations have generally used the Ronnet classification, but this method was not without controversy. One drawback of the Ronnet classification is that the intermediate group of peritoneal mucinous carcinomatosis is prone to show no significant difference from other groups [18, 26]. Based on this background, the WHO published a classification that divided PMP into low and high grades in 2010, allowing better categorization of patients [27]. This appropriate histopathologic classification may have contributed to the significant differences in PET-PCI and SUVmax between tumor grades in our study.

PET-PCI was useful for predicting prognosis and pathologic grade in patients with PMP. In addition to PMP, PET-PCI can be adapted to other tumors spreading into the peritoneal cavity, such as peritoneal mesothelioma, peritoneal sarcomatosis, and peritoneal disseminated tumors (e.g., gastric, pancreatic, colorectal, and ovarian cancers). Metabolic tumor volume and total lesion glycolysis have been widely used to assess tumor burden on PET [28–31]. However, as with PMP, calculating these volumetric parameters precisely is challenging given the difficulty determining the VOI. PMP lesions generally have the density of water and show minimal 18F-FDG uptake, and are frequently widespread into the abdominal space. These unique features represent obstacles to separating

Table 2 Multivariate Cox regression analysis for progression-free survival in patients with pseudomyxoma peritonei who received surgery

Factor	Hazard ratio	95% CI	*p* value
PET-PCI (≤ 12 vs. > 12)	9.7	2.1–45.9	0.004
SUVmax (≤ 2.7 vs. > 2.7)	1.6	0.4–6.4	0.47
CCR (0–1 vs. 2–3)	1.6	0.5–4.5	0.41
Pathologic grade (low vs. high)	2.3	0.8–6.7	0.13

PCI peritoneal cancer index, *CCR* completeness of cytoreduction score

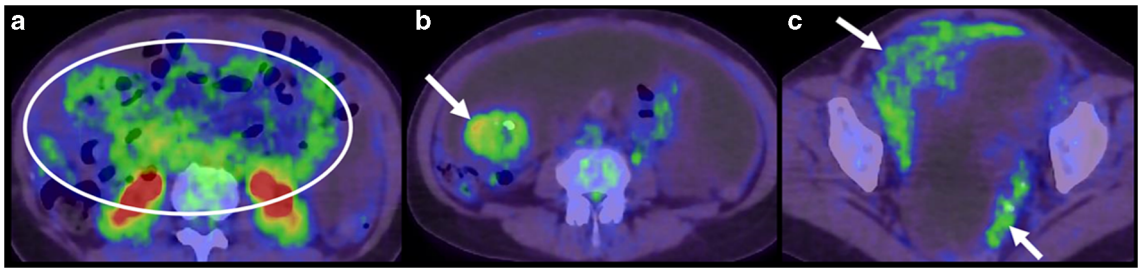

Fig. 4 A 55-year-old woman with high-grade pseudomyxoma peritonei (PMP). 18F-FDG-PET/CT images (**a**–**c**) show PMP lesions with 18F-FDG uptake on mesentery (**a**: circle), enlarged appendix (**b**: arrow), and peritoneum (**c**: arrows) of the pelvic space. The appendix lesion shows the highest SUVmax (4.0), suggesting appendiceal origin. PET-PCI is high, at 21, representing widespread PMP lesions with high metabolic activity. Although cytoreductive surgery and hyperthermic intraperitoneal chemotherapy were performed, tumor recurrence was observed 15.6 months after surgery

the lesions from other organs, particularly the intestine, and thus cause volumetric analysis to show low reproducibility between operators. In contrast, PET-PCI, which potentially reflects tumor volume and extent, can be obtained without determining a VOI and requires no specific image-analysis tools or algorithms. Given the simplicity of the method, PET-PCI can be applied to other tumors that spread into the abdominal cavity and for which the precise contours are usually difficult to determine.

Some limitations to this study must be considered. First, although PMP is a rare disease and our center is a core hospital for surgery for PMP in our country, the investigation was still a single-center study with a relatively small cohort. Second, three different PET/CT scanners were used in this study, which may have affected the reproducibility of the semi-quantitative analyses, including SUVmax. As a qualitative analysis, however, PET-PCI should have been basically unaffected by small differences in scanners. Third, our study included both patients with and without HIPEC. However, patients without HIPEC showed no statistical inferiority in PFS in our study, possibly due to the small number of patients without HIPEC.

In conclusion, PET-PCI and SUVmax are useful for predicting recurrence in patients with PMP, and correlate with histopathologic type. PET-PCI can provide higher prognostic performance than SUVmax. PET-PCI represents tumor activity and the extent of PMP, and appears promising as a factor for evaluating tumor burden. PET-PCI can be used as a selection marker for high-risk patients, and may have a large impact on treatment strategy.

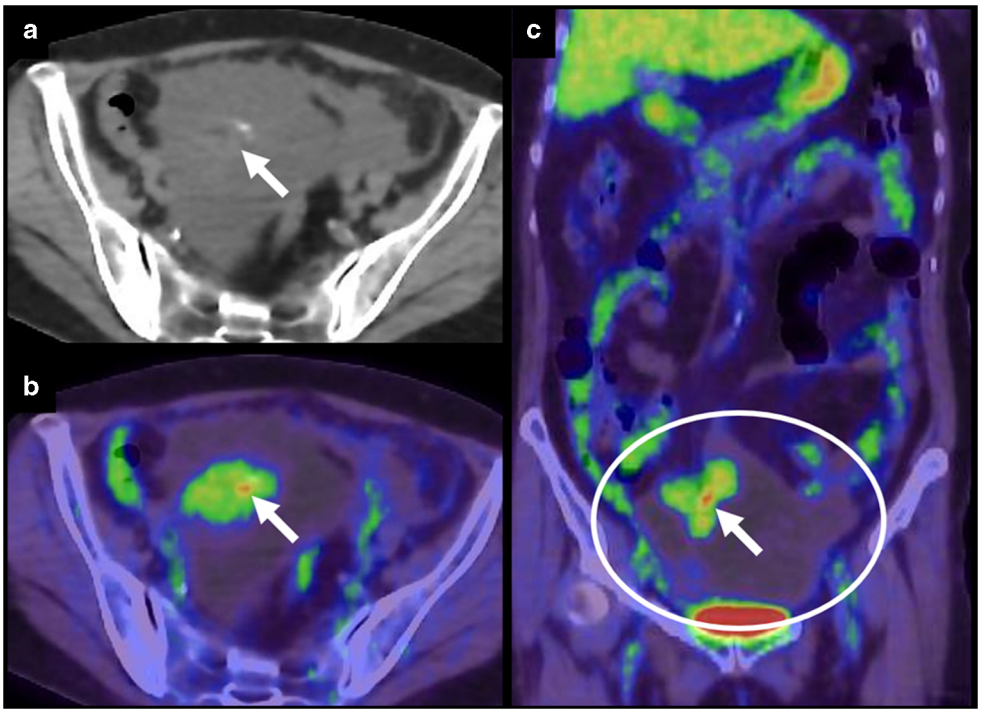

Fig. 5 A 58-year-old woman with high-grade pseudomyxoma peritonei (PMP). Axial CT image (**a**) depicts an ileocecal soft-tissue mass (arrow) contained within pelvic space fluid. Axial (**b**) and coronal (**c**) 18F-FDG-PET/CT images show uptake (SUVmax = 5.0) into the ileocecal lesion (**b**, **c**: arrow), suggesting high-grade PMP with appendiceal origin. In contrast to high SUVmax, PET-PCI was as low as 5, reflecting the localized lesion within the pelvic space (**c**: circle). The patient underwent cytoreductive surgery plus hyperthermic intraperitoneal chemotherapy. No recurrence has been observed for more than 3 years after surgery

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Compliance with ethical standards

Guarantor The scientific guarantor of this publication is Ryogo Minamimoto.

Conflict of interest The authors declare that they have no competing interests.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the institutional review board.

Ethical approval Institutional review board approval was obtained.

Methodology
- Retrospective
- Diagnostic or prognostic study
- Performed at one institution

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