Araştırma Makalesi / *Research Article*

İzmir Eğitim ve Araştırma Hastanesi Tıp Dergisi (Medical Journal of İzmir Hospital) 25 (3): 251-258, 2021

EVALUATION OF PREOPERATIVE COMPUTED TOMOGRAPHY IN STAGING PERITONEAL CARCINOMATOSIS PATIENTS

PERİTONEAL KARSİNOMATOZİS HASTALARININ PREOPERATİF EVRELENDİRİLMESİNDE BİLGİSAYARLI TOMOGRAFİNİN ETKİNLİĞİ

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Anahtar Sözcükler: Peritoneal carcinomatosis, preoperatif, bilgisayarlı tomografi, BT, evreleme
Keywords: Peritoneal carcinomatosis, preoperative, computed tomography, CT, staging.

Yazının alınma tarihi: 13.07.2021 Yazının Kabul tarihi: 04.08.2021 Online basım:20.09.2021

ÖZ

Giriş: *Peritoneal karsinomatozis (PK) hastalarında sitoredüktif cerrah için optimal hasta seçimi ve cerrahinin planlanması açısından preoperative evreleme çok önemlidir. Bu çalışmanın amacı preoperatif BT ile intraoperatif bulguları karşılaştırmak ve iki radyolog arasındaki korelasyonu ve uyumu araştırmaktır.*

Gereç ve Yöntem: *İki radyolog 48 PK hastasının preoperatif BT incelemelerini çift kör olarak değerlendirdi. Evreleme için lezyon boyutu ve dağılımının değerlendirildiği Sugarbaker'ın tanımladığı Peritoneal Kanser İndeksi (PKİ) kullanıldı. İntraoperatif bulgular altın standart kabul edildi. Sonuçlar Wilcoxon işaretli sıralar testi, Spearman korelasyon testi, Kendall'ın tau-b testi ve Cohen'in kappa testi kullanılarak değerlendirildi.*

Bulgular: *Ortalama toplam PKİ değeri intraoperatif 12.73 (±6.92), 1. radyolog için 11.08 (±6.34) ve 2. radyolog için 10.56 (±6.49) olarak bulundu. Her iki radyoloğun hesapladığı preoperatif PKİ değerleri ile intraoperatif PKİ değerleri arasında istatistiksel anlamlı fark saptandı (her iki radyolog için p=0.002). Her iki radyoloğun hesapladığı PKİ değerleri arasında istatistiksel anlamlı fark saptanmadı (p=0.123). Her iki radyoloğun hesapladığı PKİ değerleri ile intraoperatif skorlar arasında yüksek korelasyon saptandı (1. radyolog için r_s=0.860, p<0.001; 2. radyolog içinr_s=0.782, p<0.001). Bölgesel lezyon boyutları açısından her iki radyolog arasında anlamlı fark saptanmadı (p değerleri 0.189 ile 0.423 arasında). Her iki radyoloğun hesapladığı bölgesel PKİ değerleri arasında iyi veya mükemmel uyum (κ değerleri 0.624 ile 0.853 arasında, p<0.001) ve orta veya yüksek korelasyon izlendi (r değerleri 0.660 ve 0.894 arasında, p<0.001).*

Sonuç: *PK'nın BT ile preoperatif evrelendirilmesinde gözlemciler arası istatistiksel anlamlı bir fark saptanmamış olup; iki gözlemci arası yüksek korelasyon ve yüksek uyum saptandı. Her ne kadar BT intraoperatif skorlara göre PKİ değerlerini düşük hesaplasa da, preoperatif evrelendirmede tutarlı bir görüntüleme yöntemidir.*

SUMMARY

Introduction: *We aimed to investigate the accuracy of computed tomography (CT) and evaluate the interobserver correlation and agreement between two radiologists in preoperative staging of peritoneal carcinomatosis (PC) patients.*

Material and Method: *Two blinded radiologists retrospectively evaluated preoperative CT scans of 48 patients with PC. According to the Sugarbaker classification, the peritoneal cancer index (PCI) was scored based on lesion size and distribution. Intraoperative findings were regarded as the gold standard. The results were analyzed by the Wilcoxon signed-rank, Spearman's correlation, Kendall's tau-b, and Cohen's kappa tests.*

Results: *The mean PCI score was 12.73 (±6.92) for surgery, 11.08 (±6.34) for Radiologist 1, and 10.56 (±6.49) for Radiologist 2. A comparison of total PCI scores showed a significant difference between surgical PCI scores and preoperative CT PCI scores (for both radiologists p=0.002). There was no significant difference between the two radiologists' total scores (p=0.123) with a very strong correlation (r_s=0.921, p<0.001). Both radiologists strongly correlated with intraoperative PCI (r_s=0.860, p<0.001; r_s=0.782, p<0.001). There was no significant difference between the two radiologists' regional lesion sizes (p values range from 0.189 to 0.423). There were substantial to almost perfect agreements (κ=0.624-0.853, p <0.001) and moderate to strong correlations (τ_b=0.66-0.83, p<0.001) between two radiologists' regional PCI scores.*

Conclusion: *CT is a consistent imaging technique in the preoperative staging of PC patients with its high interobserver correlation and agreement, although it underestimates intraoperative findings.*

INTRODUCTION

Peritoneal carcinomatosis (PC) is described as the peritoneal cavity's infiltration by malignant cells from non-peritoneal tissues. Gastrointestinal (stomach, colon, rectum, appendix, and pancreas), ovarian, breast, lung, and endometrial cancers can metastasize to the peritoneum and cause peritoneal carcinomatosis (1). In large case series involving PC cases, 55% of cases were diagnosed during the initial diagnosis of the primary carcinoma, and 45% of cases were diagnosed on follow-up imaging studies (1).

Until the near past, patients with PC were considered to be terminal; however, this has changed with novel and emerging treatment options. If not treated, patients with PC have an overall median survival of 6 months (2). Sugarbaker suggested that PC should be considered as a locoregional disease rather than a metastasis, leading to the multimodal treatment package involving cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC), which is widely accepted as the almost only curative therapy for PC (3).

It is of great importance to determine the spread of the disease radiologically, thus the clinical stage, to create a treatment plan and decide if cytoreductive surgery and HIPEC could be successfully performed (4). Surgical evaluation is currently the gold standard for peritoneal carcinomatosis staging. However, preoperative laparoscopic surgical staging is rarely performed. Computed tomography (CT), magnetic resonance imaging (MRI), or F-Fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) are used to stage PC preoperatively, but CT is still the primary imaging modality in the evaluation of peritoneal carcinomatosis (5, 6).

Created by Sugarbaker, peritoneal cancer index (PCI) is the most commonly used method to stage PC, select patients for cytoreductive surgery and HIPEC, and evaluate the treatment results (Figure 1) (7-8). Previous studies showed that preoperative PCI carries prognostic value for optimal cytoreductive surgery, and it is a useful staging system to determine operability and foresee postoperative prognosis (9). For instance, cytoreductive surgery and HIPEC is not recommended to patients with PCI score higher than 20 (10). PCI score is calculated by radiologists preoperatively as well as intraoperatively by oncologic surgeons via inspection and palpation (11).

This study aims to evaluate the diagnostic accuracy of preoperative CT by using intraoperative staging as a gold standard. Also, the preoperative CT staging of two different radiologists will be compared, and interobserver correlation and agreement will be assessed.

MATERIALS AND METHODS

Patient Inclusion Criteria

This study was conducted with the approval of the institutional review board. Our study focused on patients diagnosed with PC who had cytoreductive surgery and HIPEC in our institution between December 2005 and January 2018. Patients' CT scans were retrospectively scanned at the same Picture Archiving and Communication System (PACS) stations. Patients 18 years old and above who had an abdominopelvic CT scan with intravenous contrast within the two months before the operation and an intraoperatively calculated PCI score were included in the study. Each patient's age, sex, primary carcinoma, and intraoperative PCI score were retrospectively scanned and recorded.

Exclusion Criteria

Patients without an intraoperatively calculated PCI score, without an abdominal CT scan with contrast within the two months before the operation, and below 18 years of age were excluded from this study.

Interpretation of CT Scans

CT images were interpreted retrospectively by two radiologists separately in two separate PACS stations. One radiologist had 27 years, and the other had four years of radiology experience. Radiologists calculated PCI scores blindly without knowing patients' clinical status or intraoperative PCI scores. Results were saved in a Microsoft Office Excel form by the radiologists.

Peritoneal thickening, plaque-like appearance, nodular appearance, mass-like thickening in a small bowel wall, omental thickening, and omental cake findings were considered positive on patients' CT scans (Figure 2) (12).

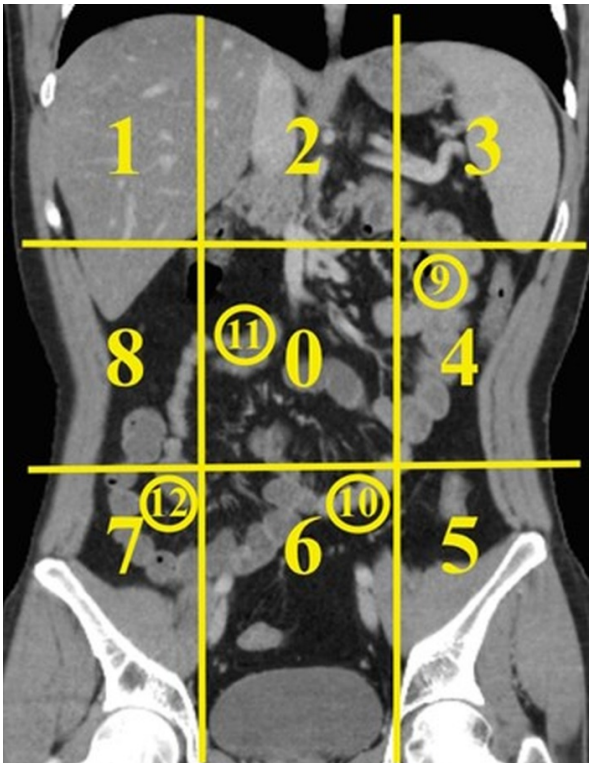


Figure 1. Abdominopelvic regions in the peritoneal cavity, according to PCI. 0-8: abdominopelvic regions, 9-12: small bowel regions. The score is given based on the largest implant size in each region. No lesion: 0 point, 0.1-0.5 cm: 1 point, 0.6-5.0 cm: 2 points, >5.0 cm:3 points.

CT Scan Parameters

Patients' CT scans included arterial and portal phase images, obtained via 64 channeled and 16 channeled multi-slice computerized tomography (CT) machines (Brilliance, Philips Medical Systems) in our Radiology Department and using KVP:120, mA: 280-400, 2 mm thickness, FOV: 385-410 mm, matrix: 512 x 512, and pitch: 1-1.5 parameters. Axial plane images were interpreted collaboratively with coronal and sagittal reformatted images.

Iodine-based contrast agents were used in our study. Contrast material was injected from a peripheral vein with a 3-5 mL/s pace. After contrast injection, the images were obtained in the late arterial and portal venous phases 15-20 seconds and 50-60 seconds after bolus tracking, respectively. Negative oral contrast was used to increase the detection rate of subtle peritoneal and small bowel implants.

Statistical Analysis

Data were summarized with mean (+/- standard deviation) and median values. Kolmogorov-Smirnov test was used for distributional analysis. As the data from the study were not normally distributed, non-parametric tests were used for analysis. Intraoperative and radiologically calculated total PCI scores were compared by the Wilcoxon matched-pairs signed-rank test to interrogate a difference. Correlation between intraoperative and radiologic total PCI scores was evaluated with Spearman's rank-order correlation (r_s). The Wilcoxon test evaluated the difference between the largest size of the regional PC implants measured by each radiologist. Spearman's rank-order coefficient assessed the interobserver correlation of the largest regional implant sizes (mm) between two radiologists. A Kendall's tau-b (r_b) correlation was run to determine the relationship between regional PCI scores amongst two radiologists. Interobserver agreement of regional PCI scores was analyzed by the Kappa test (κ).

P-values of less than 0.05 were regarded as statistically significant. All the statistical analysis was conducted using SPSS 22.0 software.

RESULTS

Forty-eight patients from 286 were included in our study after the exclusion criteria were applied

(Figure 3). The median age was 52.9 (+/- 13.4). There were 34 (71%) female and 14 male (29%) patients (Table 1). The primary malignancies were originating from the ovaries (20 patients, 42%), colon (18 patients, 38%), rectum (6 patients, 12%), and appendix (1 patient, 2%). Two patients (4%) had pseudomyxoma peritonei, and one patient's (2%) primary malignancy was unknown (Table 1). The median interval between CT scan and surgery was 12.5 days (1-60 days, mean 18.4 days).

The mean intraoperative total PCI score was 12.73 (+/-6.92), the first radiologist's mean total PCI score was 11.08 (+/-6.34), and the second radiologist's mean total PCI score was 10.56 (+/-6.49) (Figure 4). A statistically significant difference was observed between the first radiologist's and intraoperative total PCI scores (Z=3.163, p=0.002). Similarly, the difference between the second radiologist's and intraoperative total PCI scores was also statistically significant (Z=3.076, p=0.002). In addition, a strong positive correlation was observed between the first radiologist's and intraoperative total PCI scores (r_s=0.860, p<0.001) and between the second radiologist's and intraoperative total PCI scores (r_s=0.782, p<0.001).

There was no statistically significant difference between the two radiologists' total PCI scores (Z=1.543, p=0.123) (Figure 4). The correlation between the two radiologists' total PCI scores was very strongly positive (r_s=0.921, p<0.001).

Regional lesion sizes and PCI scores calculated by each radiologist were compared to assess interobserver correlation and agreement (Figure 5). Interobserver correlation and agreement analysis of the 9th, 10th, 11th, and 12th regions were unable to be performed since data distribution was not suitable for analysis.

Table 1. Patient demographics.

Characteristic		N=48	(%)
Age (years)			
	Median	53	
	Range	22-79	
Sex			
	Female	34	71
	Male	14	29
Primary malignancy			
	Ovarian	20	42
	Colon	18	38
	Rectum	6	12
	Pseudomyxoma peritonei	2	4
	Appendix	1	2
	Unknown	1	2

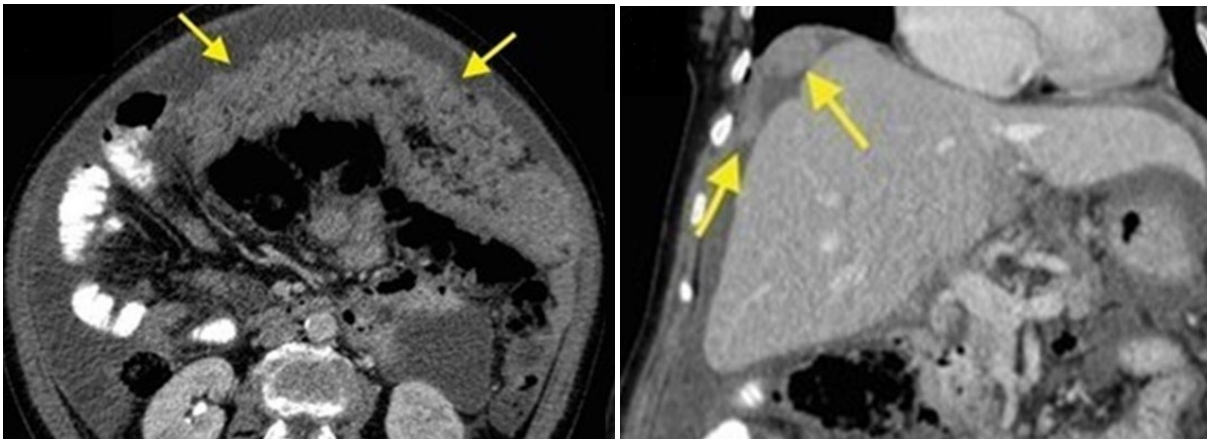


Figure 2. Peritoneal carcinomatosis secondary to ovarian serous cystadenocarcinoma. (A) Axial IV and PO contrast-enhanced CT scan shows omental cake appearance (arrows). (B) Coronal reformatted contrast-enhanced CT scan demonstrates two peritoneal implants in the right subphrenic space.

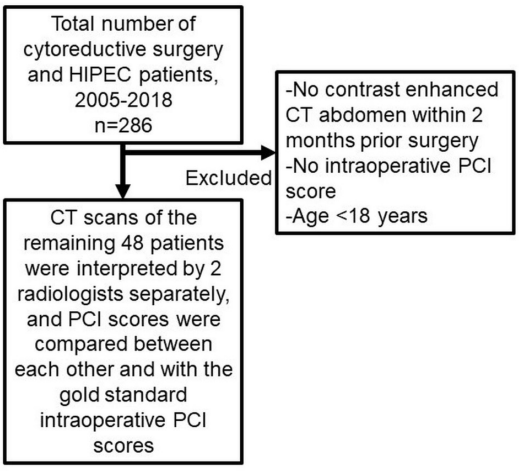


Figure 3. Flowchart of the study.

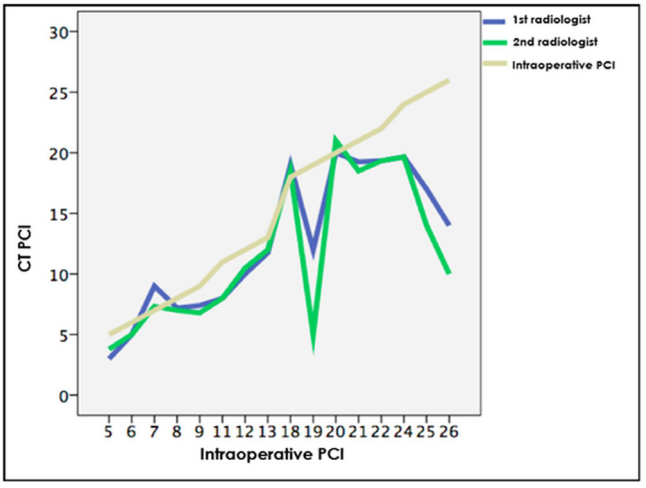


Figure 4. Comparison between intraoperative PCI and two radiologists' CT PCI scores.

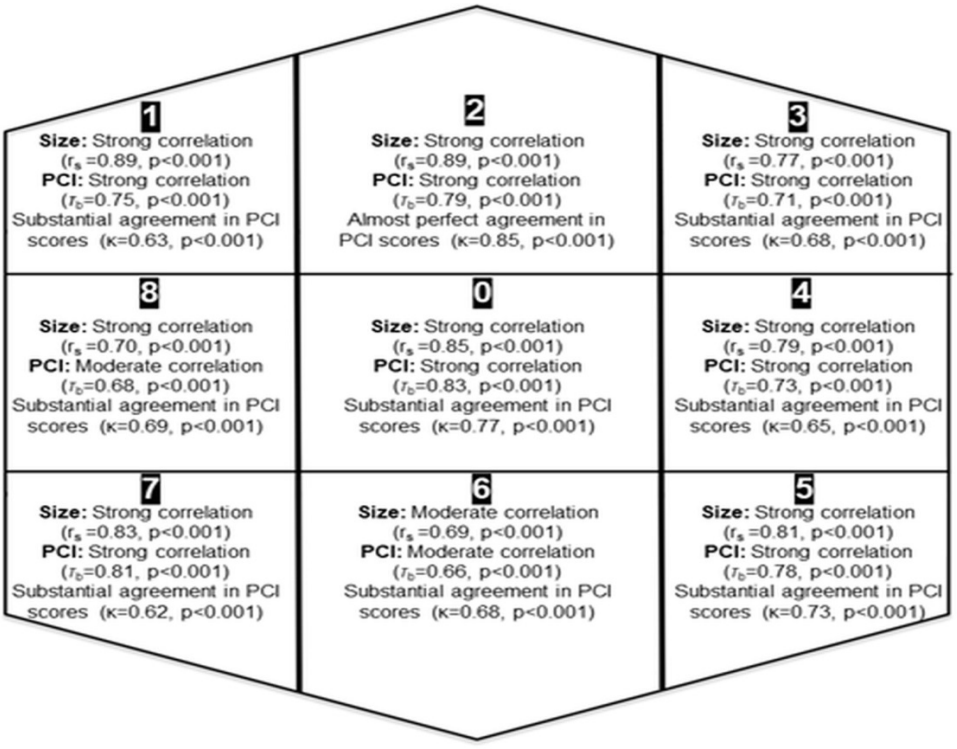


Figure 5. Interobserver correlation analysis between two radiologists' regional largest implant size and interobserver correlation and interobserver agreement analysis of two radiologists' regional PCI scores.

There was no statistically significant difference for lesion sizes in any of the 13 regions described (Z score between -2.517 and -0.801, p=0.19-0.42). Correlational analysis for the largest regional implant sizes between the two radiologists revealed a moderate positive correlation (r_s=0.69, p<0.001) for the 6th region and a strong positive correlation (r_s=0.70-0.83, p<0.001) for the other eight regions. Calculated regional PCI scores were compared between the two radiologists, and it showed a moderate positive correlation for the 6th (r_b=0.68, p<0.001) and 8th regions (r_b=0.66, p<0.001) and a strong positive correlation (r_b=71-0.83, p<0.001) for the

remaining regions. Interobserver agreement analysis between the regional PCI scores of the two radiologists indicated almost perfect agreement (κ=0.853, P<0.001) for the 2nd region and substantial agreement (κ=0.624-0.773, p<0.001) for the rest of the regions.

DISCUSSION

Numerous imaging modalities are being used to diagnose and stage PC. Although CT scan is one of the preferred imaging studies for evaluating peritoneal tumors, it is suggested to be insufficient in detecting tumor volumes (12-14). We also observed no statistically significant difference between the two radiologists' PCI scores (Z=-1.543, p=0.123). CT scan has a sensitivity ranging from 25-90% for detecting peritoneal carcinomatosis, depending on the size, localization, and morphology of the tumor deposits (14). In a previous study by Esquivel et al., preoperative PCI scores were statistically significantly lower than the intraoperative PCI scores (mean intraoperative PCI score=12.9, mean preoperative CT PCI score=8.7, p=0.003) (11). Another study by Koh et al. demonstrated similar statistically significant lower preoperative PCI scores (p<0.001, mean intraoperative PCI score=12.47, mean preoperative CT PCI score=6.68) (15). They suggested that the sensitivity of CT to detect peritoneal implants was affected by lesion size, and false negativity decreased with increased lesion size. They reported an 11% detection rate for nodules under 5 mm, while over 5 cm had 94%. In a study by De Bree et al., CT had a 59-67% sensitivity for detecting tumor implants larger than 5 cm, while CT's sensitivity dropped to 9-24% for tumor implants smaller than 1 cm (14). Coakley et al. reported a statistically significant lower sensitivity of CT for tumor implants smaller than 1 cm (25-50%) compared to the general sensitivity (85-93%) of CT (p<0.05) (16). Specifically, detection of small bowel involvement (regions 9,10,11, and 12) with CT was repeatedly reported significantly lower than the other abdominal regions in the literature with a sensitivity as low as 8-17% (15).

On the other hand, Pfannenberg et al. reported CT's overall sensitivity for detecting peritoneal implants as 84%, whereas they claimed a 65% detection rate for lesions <5 mm (17). They attributed the better sensitivity of detecting smaller lesions than literature to 3 factors: Firstly, all studies were interpreted by an experienced gastrointestinal radiologist. Secondly, all studies were performed with thin slices and interpreted with multiplanar sagittal and coronal reformat images. Lastly, patients were imaged with spasmolytic agents, oral and rectal contrast to detect bowel involvement.

The correlation shows the strength of the relationship between the relative changes in the two variables. We observed a strong correlation between both radiologists'PCI scores and intraoperative PCI scores (1st radiologist rs=0.860, p<0.001; 2nd radiologist rs=0.782, p<0.001) along with a very strongly correlated total PCI score between two radiologists (rs=0.921, p<0.001). The regional analysis also demonstrated moderate or strong correlations between two radiologists' PCI scores along with substantial or almost perfect agreements. A study by Duhr et al. revealed a strong correlation between the CT PCI and intraoperative PCI scores (r_s=0.887) (18). A very strong correlation (r_s=0.913, p<0.001) was shown between the two radiologists' mean PCI scores in the same study. Another study by Mazzei et al. also reported strongly correlated CT and intraoperative PCI scores (12).

There are several studies indicating MRI may be superior to other modalities (19-21). While being useful for small intraperitoneal tumors and distinguishing lesions from the intestines, MRI may have significant artifacts caused by gut peristalsis and respiration. Additionally, it is more expensive and less available than CT, which leads CT to be an essential component in diagnosing and staging PC in daily practice (21). Specifically, for small bowel involvement (regions 9-12), Low et al. reported CT's sensitivity as 55%, whereas 95% with MRI (20). Whilst a meta-analysis by Laghi et al. concluded that CT should be the preferred imaging modality for detecting PC, another meta-analysis by van't Sant et al. recommended MRI with diffusion-weighted imaging (DWI) as the preferred imaging method to evaluate PC (22, 23). In conclusion, DWI and postcontrast T1 weighted imaging are recommended in the literature, particularly to assess PC involvement of small bowel, mesenteric root, falciform ligament, hepatic

hilum, gallbladder fossa, uterine surface, and bladder dome that may be decisive upon patient selection for surgery (19).

Although many studies in the literature have demonstrated the superior accuracy of 18F-FDG PET/CT comparing CT alone, given the already high effectivity of CT, large multicenter studies are still required to confirm the statistical proof of 18F-FDG PET/CT being preferable to CT (24). Pfannenberg et al. reported mean PCI values as 18.6 for intraoperative, 18.2 for CT, and 18.5 for 18F-FDG-PET/CT (17). A very strong correlation was demonstrated for both CT (r_s=0.919) and 18F-FDG-PET/CT (r_s=0.951). Another study by Pasqual et al. demonstrated higher sensitivity of CT in comparison with 18F-FDG-PET/CT (91% with CT and 82% with FDG-PET/CT), although both modalities underestimated the intraoperative findings (25). Besides, low specificity (affected by inflammation, fibrosis, and necrosis) is another limitation of 18F-FDG-PET/CT, particularly in pre-treated patients (25). Overall, an avid implant in a close relationship with bowel loops might be recognized with better sensitivity with 18F-FDG-PET/CT, while low-grade metabolically active tumors (e.g., mucinous tumors) and necrotic implants might be demonstrated more thoroughly by contrast-enhanced CT.

This study has some limitations. Firstly, the study design was retrospective. Secondly, patients with different primary malignancies were included. Thirdly, because intraoperative PCI scores were recorded as a total score rather than regional, the comparison between regional preoperative and intraoperative scores was unable to be done; specificity, sensitivity, negative predictive, and positive predictive values were unable to be calculated. Also another limitation of the study was limited number of the patients.

Our study showed no difference between two radiologists in the staging of peritoneal carcinomatosis with contrast-enhanced CT, along with a very strong interobserver correlation and substantial to almost perfect agreement. However, although preoperative staging with CT was strongly correlated with intraoperative findings, the total PCI score was underestimated, likely because of the low sensitivity of CT to detect small implants and small bowel involvement. Since cytoreductive surgery and HIPEC is not recommended for cases with extensive small bowel involvement and high PCI (>20), further evaluation with MRI or 18F-FDG-PET/CT in selected patients should be recommended.

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