Preoperative Assessment of Peritoneal Carcinomatosis in Patients Undergoing Hyperthermic Intraperitoneal Chemotherapy Following Cytoreductive Surgery

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Abstract. *The present study evaluates the accuracy of computed tomographic (CT) scan and positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET)/CT for the quantification of peritoneal carcinomatosis (PC) in patients undergoing cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC). Data were retrospectively collected for 58 patients, who were considered for CRS and HIPEC. The predictability, sensitivity, specificity and accuracy values of FDG-PET/CT and CT were tested. Preoperative CT and FDG-PET/CT failed to detect PC in 9% and 17% of cases, respectively, with a sensitivity of 91% and 82%, a specificity of 33% and 67%, an area under the curve (AUC) of 62% and 74% and a negative likelihood ratio of 0.27 (CI.95 0.07-1.09) and 0.27 (CI.95 0.11-0.62), respectively (p=0.469). Both techniques showed a high prevalence of PC extent underestimation (CT 47% and FDG-PET/CT 43% of cases). Small bowel involvement and optimal CRS had a prevalence of 60% and 76%, respectively, and both the CT and FDG-PET/CT imaging techniques were inaccurate at predicting them (AUC 53% and 52% for small bowel involvement, and 63% and 58% for optimal CRS, respectively). In conclusion both CT and FDG-PET/CT had low preoperative staging reliability for PC, and this can strongly influence the ability to implement the correct treatment strategy for patients with PC.*

Hyperthermic intraperitoneal chemotherapy (HIPEC) following cytoreductive surgery (CRS) represents, in selected patients, a powerful locoregional treatment for peritoneal carcinomatosis (PC) that increases the exposure of the cancer to anti-neoplastic agents while decreasing the systemic side- effects of chemotherapy (1). In patients treated with CRS and HIPEC, the strongest determinant of outcome is the size of the residual tumor after the CRS (2-5). CRS and HIPEC feasibility should be predicted by accurate preoperative staging to exclude patients who can not benefit from a radical treatment. The computed tomographic (CT) scan represents the most used imaging technique but has limited sensitivity and specificity for PC and a very low accuracy for detecting and quantifying very small-sized disseminated nodules (6). During the last decades, advanced imaging techniques based on cellular metabolic activity, such as positron emission tomography with ^{18}F-fluorodeoxyglucose (FDG-PET)/CT, have been suggested to replace CT-alone (7). Although FDG-PET is now potentially considered the first method of choice for staging metabolically active cancers, its accuracy may be influenced by tissue inflammation, fibrosis, vascularization and anti-blastic drugs (8-10). The main drawback of FDG-PET, which reduces its specificity and sensitivity, is the residual non-metabolic tumor tissue remaining after chemotherapy (9). Also when associated with CT, PET-CT shows conflicting results (11-14). Preoperative imaging data should be considered with caution when planning treatments for PC. Therefore, we evaluated the accuracy of imaging techniques to predict the presence of disease and to quantify the disease extent by comparing the imaging peritoneal cancer index (PCI) with the intraoperative index. Moreover, the accuracy of CT and PET-CT to predict complete CRS was tested.

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Patients and Methods

In this retrospective study, we evaluated patients with PC considered for CRS and HIPEC in our Department between 2006 and 2012. The preoperative inclusion criteria for CRS and HIPEC were as

follows: an optimal performance status (Karnofsky's index of performance status ≥90), the absence of extra-peritoneal disease or distant metastasis and an estimated PCI by preoperative staging <20. Being older than 75 years of age was not considered an absolute exclusion criterion. Indications for CRS and HIPEC included: synchronous PC stabilized or reduced in its extent by systemic chemotherapy, recurrent metachronous PC after successful systemic chemotherapy and the suspicion of neoplastic recurrence in the presence of negative preoperative imaging due to increase in tumor markers and/or significant weight loss and/or a positive peritoneal fluid cytology. Preoperative written informed consent was obtained from all participants before starting the study. All patients were preoperatively staged with the CT scan, FDG-PET/CT, or both. Only imaging examinations performed within 2 months before surgery were considered. All preoperative examinations were carried out at the Department of Radiology and Nuclear Medicine of the same third-level Hospital. Patients not eligible for CRS and HIPEC were excluded after the preoperative evaluation. Patients who were eligible for the study after this first selection step underwent an operation involving a median laparotomy and an exploration of the abdominal cavity site by site according to Sugarbaker's semiquantitative scoring system; the PCI was then calculated (1, 15). After an accurate intraoperative PC staging, the patients with unresectable hepatic metastases or an excessive PC load, exceeding a PCI of 20, were excluded from cytoreductive surgery and HIPEC but were still considered for this study. The comparison between the preoperative and intraoperative peritoneal cancer assessment concerned both the presence (qualitative criteria) and the extension (quantitative criteria) of PC. The data were classified as the presence or absence of PC in every abdominal area, according to the scheme proposed by P.H. Sugarbaker and were quantified by PCI at the time of preoperative imaging and at the intraoperative assessment. The data were considered to be in accordance when the intraoperative findings confirmed the preoperative findings or when the preoperative imaging PCI was confirmed to have adequately estimated the presence and extension of the PC by the abdominal exploration. In addition, in relation to the small bowel and its mesentery localization (Sugarbaker regions between 9 and 12) the CT scan classification proposed by Yan *et al*. was considered and adapted to compare the CT with the FDG-PET/CT scan and the intraoperative results (13). In patients who underwent the entire procedure, immediately after cytoreduction and before beginning HIPEC, the completeness of cytoreduction rate (CCR) was calculated to measure the extent of residual disease according to the following scheme: CCR0 residual disease absent, CCR1 less than 2.5 mm in maximum diameter, CCR2 residual disease between 2.5 mm and 25 mm, and CCR3 residual disease more than 25 mm in diameter (1). CCR 0-1 was defined as optimal cytoreduction. Data were analyzed by R-3.0.1 (http://cran.r-project.org/bin/linux/ubuntu/precise), considering significant $p<0.05$.

We presented data as mean±standard deviation (SD), median (with interquartile range – IQR), prevalence value, or odds ratio (OR). Where appropriate, also 95% confidence interval (95% CI) was presented. Univariate analysis was performed by *t*-test, or Wilcoxon test in case of continuous variables, chi-square test or Fisher exact test in case of categorical variables. Also univariate and multivariate logistic regression was performed. The accuracy of imaging techniques to find disease presence (gold standard intraoperative findings) was evaluated by calculating the sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, positive predictive value, and negative predictive value. Moreover, receiver operator characteristic (ROC) curves were drawn and areas under the curve (AUC) were compared with DeLong's test. The ROC curves and AUCs were also considered to analyze the accuracy to predict optimal cytoreduction or small bowel involvement by CT or FDG-PET/CT examination before surgery. Furthermore, the preoperative PCI estimation was evaluated to correlate the prognostic value of the imaging PCI for PC staging. Accordingly, the PCI was divided into four classes: class 0=absence of disease; class 1-10=minimal PC extent; class 10-20=median extent of disease; and class >20=high PC extent. Then, the accordance between the preoperative imaging techniques and surgical results was evaluated. The Pearson's rho with its related *p*-value was also adopted to assess the concordance between preoperative and intraoperative PCI (16).

Results

We considered 77 patients for this study. After the preoperative imaging work-up, 19 patients were excluded from the treatment protocol and data analysis; 11 patients had distant organ metastases (unresectable hepatic and lung metastases), and 8 patients had excessive planned surgical risk. Fifty-eight patients were finally considered for CRS and HIPEC, with a mean age of 61.4±11.5 years. The primary tumors were: 26 colorectal cancers, 21 ovarian cancers, 8 gastric cancers and 3 pseudomyxoma peritonei. Preoperatively, 11 patients underwent only CT scan, and 47 underwent both CT and FDG-PET/CT. Among the 58 patients who underwent CT, 51 (88%) were diagnosed with PC, while 7 (12%) were apparently disease-free. Among the 47 patients who underwent FDG-PET/CT, 35 (74%) were diagnosed with PC, while 12 (26%) were apparently disease-free. Following surgical exploration, further 14 patients were excluded from treatment: 8 were excluded due to an unresectable hepatic intraperitoneal tumor and 6 were excluded due to unresectable metastases. Forty-four patients (76%) underwent CRS and HIPEC, and optimal cytoreduction (CCR 0 or 1) was obtained in 76% (44/58) of patients. After intraoperative staging, 33 (57%) patients showed disease persistence and 18 (31%) showed recurrence. The remnant 7 patients (12%) were completely disease-free. The positive likelihood ratio to detect any carcinomatosis lesion (PCI>0 at surgical exploration) by CT and FDG-PET/CT was respectively 1.37 (0.76-2.44) and 2.47 (0.79-7.73) and the negative likelihood ratio was respectively 0.27 (0.07-1.09) and 0.27 (0.11-0.62). General AUC of CT and FDG-PET/CT was 62% and 74%, respectively, with a sensitivity of 91% and 82% and a specificity of 33% and 67%, but these differences were not significant ($p=0.469$). The site-by-site specific accuracy was evaluated in every abdominal region according to the Sugarbaker' scheme to predict presence of disease. The FDG-PET/CT was more accurate to predict the presence of disease in region 3 (left upper) with an AUC of 68% *vs*. 62% for CT ($p=0.085$). Both techniques appeared to have low accuracy for the prediction of the

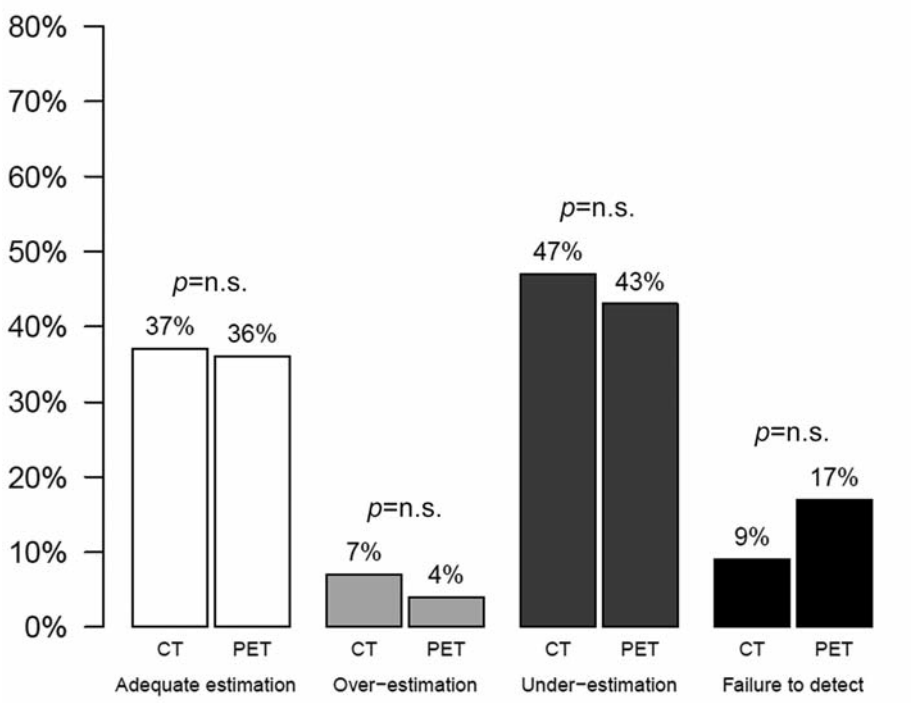

Figure 1. *Concordance between imaging and surgery. CT: computed tomography scan; PET: ^{18}F-fluorodeoxyglucose positron emission tomography.*

presence of disease in regions between 9 and 12 (small bowel), being the AUC in these regions only slightly greater than 50%. The small bowel involvement prevalence was 60%, and the performance of the imaging techniques to detect this type of disease was low, with an AUC of 53% for CT and 51% for FDG-PET/CT. Furthermore, the sensitivity was 14% and 11% for CT and FDG-PET/CT, respectively, and the specificity was 91% and 91%, the negative likelihood ratio was 0.94 (0.78-1.13) and 0.97 (0.82-1.15), and the positive likelihood ratio was 1.64 (0.42-6.42) and 1.31 (0.34-5.14), respectively.

Three different analyses to check the accordance of the preoperative CT and FDG-PET/CT PCI data with the intraoperative PCI findings were performed. First, we analyzed the correlation between preoperative and intraoperative PCI, and for both imaging techniques the Pearson test was statistically significant ($p<0.05$). Second, a test to assess the accuracy of the diagnostic test when the gold standard is continuous (intraoperative PCI) was used and we found that CT and FDG-PET/CT had a 69% and 71% accuracy, respectively, but this difference was not significant ($p=0.415$). Third, the correspondence between preoperative imaging and surgical second-look PC assessment was evaluated according to the subdivision of the PCI into four classes (0, 1-10, 10-20, >20). The CT and FDG-PET/CT adequately estimated the intraperitoneal cancer extension in 37% and 36% of the cases, respectively). In 9% (5/58) (CT scan) and 17% (8/47) (FDG-PET/CT scan) of cases, the imaging failed to detect intraperitoneal cancer (false-negative), and 7% (4/58) and 4% (2/47) of cases were false-positive, respectively (Figure 1). In addition, intraoperative PCI higher than 20 was not detected in 19% (11/58) of cases by CT scan imaging or in 15% (7/47) of cases by FDG-PET/CT scan imaging ($p=0.582$). In this case, the Pearson's rho was 0.128 ($p=0.323$) for the CT scan and 0.125 ($p=0.381$). The prediction of complete CRS by imaging PCI was analyzed, and no significant differences were found between the AUC values of the PCI obtained from the CT or the FDG-PET/CT scan ($p=0.365$) (Figure 2). The factors significantly predictive of CRS were tested, and only a low intraoperative PCI (0-10) value appeared to be significantly predictive of complete CRS by uni- and multivariate logistic regression analysis ($p<0.05$) (Table I).

Discussion

Abdominal CT, MRI and FDG-PET/CT are currently the most utilized imaging techniques during preoperative work-up to diagnose PC (7, 17). In our study, both CT and FDG-PET/CT presented low preoperative staging reliability for advanced intraperitoneal cancers, and this can strongly influence the ability to implement the correct treatment

Table I. *Predictive factors for complete cytoreductive surgery at uni- and multivariate logistic regression analysis. PCI: peritoneal cancer index; CT: computed tomography scan; FDG-PET: ^{18}F-fluorodeoxyglucose positron emission tomography.*

	OR (95% CI)	*p*-Value
Intra-operative PCI	0.86 (0.78-0.95)	<0.05
CT-scan PCI	0.92 (0.79-1.08)	0.303
FDG-PET/CT scan PCI	0.89 (0.72-1.09)	0.264
Interpretative scan classification of small bowel and its mesentery		
CT-scan		
Normal appearance	Referral	
Ascites only	0.81 (0.2-3.27)	0.770
Tumor up to 0.5 cm	0.25 (0.01-4.51)	0.348
Tumor >0.5 cm	0.25 (0.03-2.1)	0.202
FDG-PET/CT scan		
Normal appearance	Referral	
Ascites only	0.58 (0.15-2.19)	0.421
Tumor up to 0.5 cm	-	-
Tumor >0.5 cm	0.24 (0.03-2.02)	0.190

The reported values are the odds ratio (OR) and the 95% confidence interval (95% CI).

strategy for patients with PC. The CT sensitivity for PC varies from 60% to 90%, depending on the disease extent and the single nodule size (18-20). A multi-Institutional study of colorectal PC found no correlation between the PCI obtained by CT (mean PCI value 8.6) and the intraoperative PCI (mean PCI value 13.2) (21). Peritoneal carcinomatosis localization may also limit CT sensitivity, which is very low for mesenteric deposits (22). FDG-PET associated with CT can increase the sensitivity and specificity of CT for PC detection (11, 23, 24). Unfortunately, the identification of micrometastases, lesions in specific anatomical areas, such as the small bowel and its mesentery, lesions smaller than 6 mm, and a low specificity for FDG (influenced by fibrosis, inflammation, not viable tumors and previous multischeduled chemotherapy) are still limitations of this combined procedure (9, 22, 25), particularly in strongly pre-treated patients (8, 11, 12, 23, 24, 26). In our population, both techniques were predictive of disease presence (intraoperative PCI >0) and the AUCs of the CT and FDG-PET/CT were 62% (41%-83%) and 74% (53%-96%), respectively, but no significant difference was observed between the accuracy of these two techniques. In particular, we found a higher sensitivity (91% with CT and 82% with FDG-PET/CT) than previously published studies (12, 24), but this result was in accordance with recent literature (23). Significant correlations between the preoperative PCI based on imaging findings and the intraoperative PCI were found, but both techniques significantly underestimated the intraoperative PCI values and failed to adequately assess all the cases with a PCI value higher than 20; this was mainly due to the lack of accuracy in predicting small bowel involvement (22). No significant difference was found between the CT and FDG-PET/CT scan for preoperative staging, and both techniques were lacking in disease quantification, thus being insufficient for adequate surgical planning. Therefore, in our opinion, the most convenient instrumental examination (either CT scan or FDG-PET/CT scan) should be chosen based on the locally available resources. Promising results from staging laparoscopy should

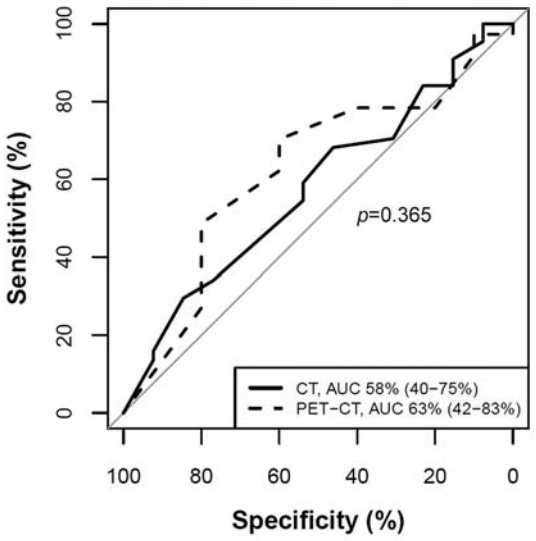

Figure 2. *Receiver operator characteristic (ROC) curves and relative areas under the curve (AUC) showing the accuracy to predict optimal cytoreduction by computed tomography scan (CT), and ^{18}F-fluorodeoxyglucose positron emission tomography/CT (PET/CT), respectively. p-Value obtained using the DeLong's test.*

be taken into consideration (27, 28). If this goal is achieved, it would help maximize the CRS and HIPEC results (29).

In conclusion, both CT and FDG-PET/CT have low preoperative staging reliability for PC, and this can strongly influence the ability to implement the correct treatment strategy for patients with PC.

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