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TESI DI DOTTORATO

THE VALUE OF (18)FLUOR-DEOXYGLUCOSE POSITRON EMISSION
TOMOGRAPHY/COMPUTED TOMOGRAPHY (18FDG-PET/CT) IN RESECTABLE
PANCREATIC CANCER: A PROSPECTIVE STUDY

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ABSTRACT

Background and aim : Whole-body (18)fluor-deoxyglucose positron emission tomography/computed tomography (PET/CT) has emerged as a promising diagnostic modality in different tumors. The role and the utility of (18)FDG-PET/CT in resectable pancreatic cancer is debated. Aim of the present work was to assess prospectively the value of (18)FDG-PET/CT in addition to conventional imaging as a staging modality in candidates for resection of resectable pancreatic cancer. Secondary aim is to correlate (18)FDG-PET/CT results with tumor-recurrence after resection.

Material and methods : Whole-body (18)FDG-PET/CT was performed in 72 patients with pancreatic ductal adenocarcinoma who were judged resectable at high-resolution imaging. Neoadjuvant therapy was performed in the 14% of cases. Maximum standardized uptake value (SUVmax) was evaluated 60 minutes after FDG injection. PET/TC was considered "positive" for pancreatic cancer when SUV > 3.

Results : 8/72 (11%) patients were spared unwarranted resection since (18)FDG-PET/CT detected synchronous advanced lung cancer (n=1) or metastatic disease (n=7). Median CA 19.9 was 48.8 U/mL for the entire cohort and 292 U/mL for seven patients with metastases (p=0.112). In other two patients (18)FDG-PET/CT identified one colon carcinoma and a thoracic neurinoma. 15/72 (21%) patients had low metabolic activity (SUVmax<3), and 60% of these patients had undergone neoadjuvant treatment (p=0.0001). At laparotomy 3/64 (5%) patients did not undergo resection because of locally-advanced (n=1) or metastatic disease (n=2). 61 patients underwent pancreatic resections with curative intent. N1 rate was 77%, with a median of 33 resected nodes. In 8/61 (13%) patients (18)FDG-PET/CT identified metastatic lymph nodes that required an extension of lymphadenectomy. Sensitivity and specificity of (18)FDG-PET/CT for the detection of metastatic disease were 78% and 100%, respectively. Median follow-up for resected patients was 10 months and 53% of them developed recurrence. No significant correlation between SUVmax values and disease-free survival was found.

Conclusions : (18)FDG-PET/CT findings resulted in changes of therapeutic management/operative procedures in one third of patients. (18)FDG-PET/CT improves staging of patients with resectable pancreatic cancer. Neoadjuvant treatment is significantly associated with low metabolic activity limiting the value of (18)FDG-PET/CT in this setting.

ABSTRACT

Introduzione e obiettivi : La PET/TC con 18-fluoro-desossiglucosio - (18)FDG-PET/CT - si è affermata come una promettente tecnica diagnostica in diverse neoplasie. L'utilità della (18)FDG-PET/CT nel carcinoma pancreatico resecabile è dibattuto. Obiettivo di questo studio è di valutare in maniera prospettica il ruolo della (18)FDG-PET/CT in aggiunta all'imaging convenzionale per lo staging di pazienti candidati a resezione pancreatica per carcinoma. Obiettivo secondario è valutare una possibile correlazione tra (18)FDG-PET/CT e ricorrenza di malattia dopo resezione.

Materiali e metodi : (18)FDG-PET/CT è stata effettuata in 72 pazienti con adenocarcinoma pancreatico considerate resecabile all'imaging ad alta risoluzione. La terapia neoadiuvante è stata effettuata nel 14% dei casi. Il maximum standardized uptake value (SUVmax) è stato valutato 60 minuti dopo la somministrazione di FDG. La PET/TC è considerata "positiva" per carcinoma se SUV > 3.

Risultati : 8/72 (11%) pazienti non sono stati sottoposti a intervento chirurgico per l'evidenza di malattia metastatica (n=7) e di un carcinoma polmonare avanzato sincrono (n=1) alla (18)FDG-PET/CT. Il valore mediano di Ca 19.9 è stato di 48.8 U/mL per l'intera coorte e di 292 U/mL per i pazienti metastatici (p=0.112). In altri due pazienti la (18)FDG-PET/CT ha identificato un carcinoma colico e un neurinoma mediastinico. 15/72 (21%) pazienti avevano un SUVmax<3, e il 60% di questi pazienti era stato sottoposto a terapia neoadiuvante (p=0.0001). 3/64 (5%) pazienti non sono stati resecati per malattia avanzata alla laparotomia. Il 77% dei 61 pazienti resecati presentava metastasi linfonodali. Nel 13% dei casi la (18)FDG-PET/CT ha identificato metastasi linfonodali che hanno richiesto una estensione della linfoadenectomia. Sensibilità e specificità della PET/CT per malattia metastatica sono state del 78%e 100%. Il follow-up mediano dei pazienti resecati è stato di 10 mesi e il 55% di essi ha sviluppato una recidiva. Non è stata identificata alcuna correlazione significativa tra SUVmax e sopravvivenza libera da malattia.

Conclusioni : La PET/CT ha determinate un cambiamento nella strategia terapeutica del 25% dei pazienti, migliorando lo staging preoperatorio dei pazienti con carcinoma pancreatico candidati alla resezione chirurgica. Il trattamento neoadiuvante si associa ad una riduzione significativa dei valori di SUV, limitando pertanto il ruolo della PET/CT in questi pazienti.

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INTRODUCTION

Although the diagnosis and management of pancreatic cancer has improved in the last decades, its prognosis remains dismal. Surgical resection is the only treatment with potentially curative intent with a 5-year survival rate of 20-25% [1-4]. Moreover, 20 to 30% of resected patients will develop tumor-recurrence and die of disease within 12 months from resection [5]. These deaths can be related to tumors with an aggressive biological behavior with unrecognized or rapidly progressive metastatic disease [6,7]. If this subgroup of patients could be identified in the preoperative setting, neoadjuvant chemotherapy should be considered instead of upfront surgery [2,6].

Therefore, detection of distant metastases and identification of aggressive tumors at diagnosis is of paramount importance when deciding if an operation should be performed for pancreatic carcinoma. Despite significant advances of high-resolution imaging techniques, the appropriate assessment of resectability of pancreatic cancer is still challenging [8-11]. Particularly, the diagnosis of small metastases can be problematic even in the setting of contrast-enhanced, multi-detector computed tomography (MDCT) [12,13].

Whole body 2-(fluorine-18)fluoro-deoxy-D-glucose-positron emission tomography in combination with computed tomography (FDG-PET/CT) has emerged as a promising imaging modality in the management of cancer patients [14]. (18)F-FDG PET can image tumoral cells thanks to their accelerated glucose metabolism. These functional information are then combined with the anatomical details of CT scan. (18)F-FDG PET/CT has demonstrated significant efficacy in the staging and detection of occult metastases in a number of malignancies, including oesophagogastric carcinomas, small and non-small cell lung cancer (NSCLC), breast cancer and lymphoma [15-19]. Furthermore, (18)F-FDG PET/CT has been identified as a prognostic factor for tumor

recurrence after surgery in gastric cancer, NSCLC and gynaecological cancers [20-22].

The role of (18)F-FDG PET/CT in patients with potentially resectable pancreatic cancer is still debated. In this setting, while some authors have reported a high sensitivity rate for identifying occult metastatic disease [12,23-25] , others did not favor PET/CT over MDCT for properly staging pancreatic cancer [26,27]. Moreover, few studies have evaluated if (18)F-FDG PET/CT could be a prognostic indicator of tumor-recurrence and survival after resection of pancreatic cancer [28,29].

The primary end point of the present study was to prospectively evaluate the role of (18)F-FDG PET/CT for detecting occult metastatic disease and its impact on the management of patients with resectable pancreatic cancer after conventional staging based on high-resolution imaging techniques. Secondary end points included i) assess the accuracy of (18)F-FDG PET/CT in the identification of lymph node metastases; ii) evaluate a possible prognostic role of (18)F-FDG PET/CT for tumor-recurrence in patients undergoing pancreatic resection.

MATERIALS AND METHODS

The study population was represented by all consecutive patients with potentially resectable pancreatic ductal adenocarcinoma who prospectively underwent (18)F-FDG PET/CT at Ospedale Sacro Cuore-Don Calabria, Negrar, Italy between May 2011 and July 2012

Preoperative staging and surgical resectability were based on abdominal MDCT and/or magnetic resonance imaging (MRI) and chest X-ray. Chest CT scan and pancreatic endoscopic ultrasound (EUS) were performed on selected cases. MDCT or MRI performed outside our Hospital were reviewed by a multidisciplinary team to assess the quality of these examinations. In doubtful situation, preoperative staging was performed at our hospital and it was based on contrast-enhanced, multi-detector (2.5 mm slice thickness) abdominal computed tomography with pancreas protocol.

The preoperative radiological diagnosis of potentially resectable pancreatic cancer was based on the following criteria: 1) absence of abutment/encasement of portal vein, superior mesenteric vein, hepatic artery, superior mesenteric artery, celiac trunk; 2) absence of infiltration of peripancreatic organs with the exception of common bile duct and duodenum; 3) absence of distant metastases.

Exclusion criteria included: 1) age less than 18 years; 2) presence of locally-advanced or metastatic pancreatic cancer; 3) presence of poor general conditions or of severe comorbidities that precluded patients from undergoing surgery; 4) patients with pancreatic tumors other than ductal adenocarcinoma (i.e. intraductal papillary mucinous neoplasms). Patients with an initial diagnosis of "borderline-resectable" or locally-advanced pancreatic cancer who underwent neoadjuvant treatment and who showed tumor-downstaging to potentially resectable disease were included in the study.

All patients underwent (18)F-FDG PET/CT two or three day before the planned admission to the Hospital. They were asked to fast for at least 6 hours before the examination. The blood glucose level of each patient was determined before the examination. Scanning of patients with diabetes mellitus was not performed until the blood glucose level was less than 140 mg/dL. All examinations were carried out by a single, highly experienced, nuclear medicine physician (MS). All the tests were performed using a hybrid PET/CT scanner (Siemens mCT Biograph, Germany). The whole-body CT scanning was performed using a continuous spiral technique on a 64-slice helical CT, and the PET scanner had three detector rings. No contrast medium was administered during CT scanning. After CT scan, an emission scan was performed from the head to the thigh after the intravenous injection of 0.08 mC/kg (2.96 MBq/kg) FDG. PET scanning is performed with a 16 cm bed for about 7/8 bed per patient. CT and PET scan data were co-registered. The standardized uptake value (SUV) was acquired using the attenuation-corrected images, the amount of injected FDG, the body weight of the patient, and the cross-calibration factors between PET and the dose calibrator. Maximum SUV (SUVmax) was evaluated 60 minutes after FDG injection and a value of SUVmax of more than 3 being indicative of malignancy. Medium

Patients' demographics, clinical presentation, serum carbohydrate antigen (CA 19.9) levels, operative and postoperative data, complications, pathology and follow-up data were prospectively collected. Formal pancreatic resections were carried out if intraoperative exploration confirmed 1) the absence of metastatic disease; 2) no involvement of celiac trunk, hepatic artery or superior mesenteric artery; 3) no involvement of portal vein/superior mesenteric vein or encasement < 180° of these vessels. Standard lymphadenectomy was commonly performed as described elsewhere [30].

Classification of pancreatic ductal adenocarcinoma was based on the WHO 2010 classification of digestive tumors [31]. Quality of resection was determined according to the R-classification by the International Union Against Cancer. Tumor (T), nodal status (N) and grade (G) were determined using standard TNM classification according to AJCC classification [32]. Histopathologic grading of pancreatic ductal adenocarcinoma included [31]: (1) G1, well-differentiated neoplasms; (2) G2, moderately differentiated neoplasms; (3) G3, poorly differentiated neoplasms. Intraoperative evaluation of the resection margins was performed routinely, and when positive, the resection was extended whenever possible.

Adjuvant treatment was considered in all patients who experienced a good recovery within 8 weeks from operation.

The follow-up schedule was described elsewhere [5]. Recurrence was defined as the presence of locoregional disease (ie, recurrence in the pancreatic remnant, peripancreatic tissue, or lymph nodes metastases) or of metastatic disease (ie, liver metastases, peritoneal carcinomatosis) by radiologic imaging techniques. Tumor recurrence was confirmed histologically whenever possible. Follow-up was updated on February 2013.

Statistical analysis

Distributions of continuous variables are reported as median and minimum/maximum range. Categorical variables are presented as numbers and percentages. The comparison between subgroups was performed with the Student t test or Mann-Whitney U test for continuous variables. Qualitative data were compared by the χ^2 test or Fisher exact test when necessary. Disease-free survival (DFS) was defined as the time from resection to tumor-recurrence and was censored at the last follow-up date if no events had occurred. Patients who eventually died of postoperative complications were excluded from survival analysis. Cut-off points were calculated

around the median for continuous variables. Survival probability was estimated according to the Kaplan-Meier method. Statistical analyses were performed in SPSS 16.0 for Windows software (SPSS Inc, Chicago, IL). P values were considered significant when less or equal than .05.

RESULTS

Seventy-two consecutive patients were prospectively included in the study. The main patient characteristics are reported in Table 1

Table 1. Patient characteristics.

	N	%
Sex	72	
Male	36	50
Female	36	50
Median age, years (range)	65	39-81
Symptomatic patients	64	89
Presence of diabetes	15	21
Symptoms		
Jaundice	47	65
Weight loss	32	44.5
Pain	30	41.5
Bowel obstruction	4	5.5
Pancreatitis	1	1.5
Tumoral markers		
CEA, ng/ml, median (range)	1.80	0.5-19.9
CA19-9, U/ml, median (range)	64.4	0.8- 3547
Neoadjuvant treatment	14	19
Chemotherapy	7	9.5
Chemoradiation	7	9.5

Fourteen patients (19%) underwent neoadjuvant treatment because of locally-advanced (n=7) or borderline resectable pancreatic cancer (n=7). In all these patients, re-staging after neoadjuvant therapy showed the presence of a potentially resectable disease.

SUVmax < 3 was found in 15 patients (21%) while in the 79% of patients (18)F-FDG PET/CT was positive for malignancy (SUVmax >3). The 60% of patients with SUVmax < 3 had undergone neoadjuvant treatment compared to a rate of neoadjuvant therapy of 10.5% in the group with SUVmax > 3 (P= 0.0001). Median SUVmax value was 5.9 (range 2.5-24.5) in the entire cohort and 6.7 (range 2.5-24.5) in all patients but those who underwent neoadjuvant therapy.

Figure 1 shows the results of (18)F-FDG PET/CT with patients management. Eight out of 72 patients (11%) were spared surgical resection because of (18)F-FDG PET/CT findings. In seven patients occult distant metastases were found, and they were histologically/cytologically confirmed after fine-needle aspiration.

Figure 1. Flow chart showing the results of (18)F-FDG PET/CT with patients management
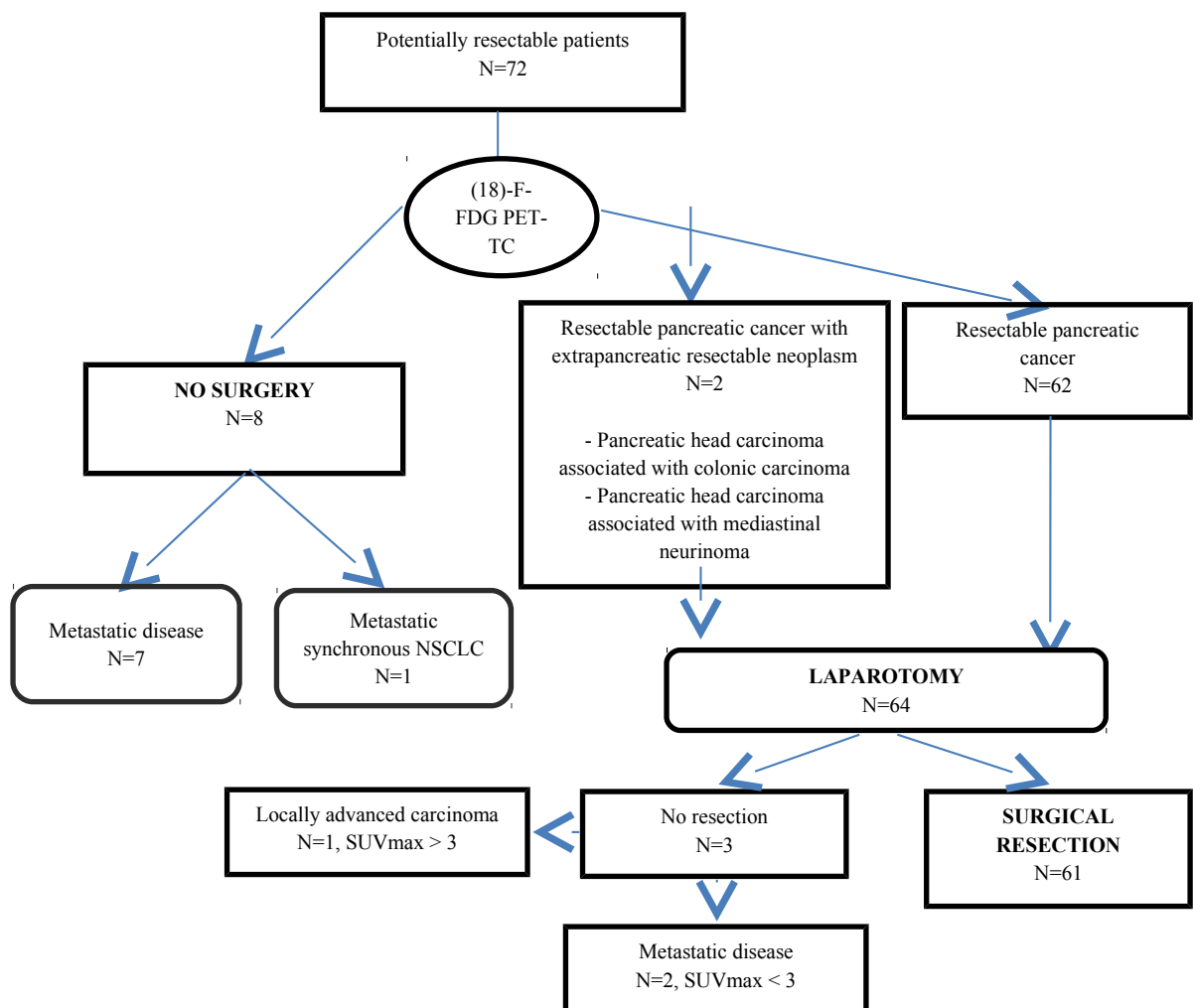
In the remaining patient (18)F-FDG PET/CT showed the presence of a synchronous NSCLC with mediastinal lymph node metastases. In patients with occult metastatic disease, median CA 19.9 value was 292 U/ml (range 47- 3547) compared to 48.8 U/mL (range 10-256) of the remaining patients (P= 0.112).

Sensitivity and specificity of (18)F-FDG PET/CT for the detection of occult metastatic disease in the entire cohort of 72 patients were 78% and 100%, respectively. Sensitivity and specificity were 87.5% and 100%, respectively, excluding those 14 patient who underwent neoadjuvant treatment, as SUVmax was < 3 in 2/3 of these patients.

Exploratory laparotomy was planned in 64 patients (89%). In two of them, (18)-F-FDG PET/CT confirmed the presence of a pancreatic head cancer and showed the presence of an associated extrapancreatic synchronous tumor, in the left colon and in the posterior mediastinum, respectively. The first patient underwent colonoscopy with biopsy that confirmed the presence of a colonic carcinoma. The second patient underwent thoracoscopy with resection of a mediastinal neurinoma. Both patients subsequently underwent pancreaticoduodenectomy, associated with left colectomy in the first patient.

A pancreatic resection was carried out in 61/64 (95%) patients who underwent laparotomy. The remaining three patients (Figure 1) did not undergo pancreatectomy because of unresectable locally-advanced (n=1) and a metastatic disease (n=2). The two patients with intraoperative evidence of metastatic disease had a SUVmax < 3. In one of these two cases laparotomy was carried out after neoadjuvant chemoradiation for a locally-advanced tumor of the pancreatic tail with radiological down-staging. Table 2 shows operative procedures and postoperative complications. In keeping with anatomic location, pancreaticoduodenectomy was the most common surgical

procedures (80%). There was one postoperative death (1.5%) due to sepsis after pancreatic fistula with intra-abdominal abscess and late bleeding.

Table 2. Operative procedures and postoperative complications

	N	%
Pancreatic resection		
Pancreaticoduodenectomy	49	80
Left pancreatectomy and	7	12
splenectomy	5	8
Total pancreatectomy	14	23
Vascular resection		
	1	1.5
Postoperative mortality		
	28	46
Overall morbidity	11	18
Pancreatic fistula	10	16
Abdominal collection	7	11.5
Sepsis	6	10
DGE	5	8
Bleeding	4	6.5
Chilous fistola		

Pathological data are reported in Table 3. The histological diagnosis of pancreatic ductal adenocarcinoma was confirmed in all 61 patients who underwent resection. The patient who underwent colonic resection had a T3N1 colonic adenocarcinoma associated with pancreatic cancer.50% of patients had a G3 tumor, and lymph node metastases were found in 77% of the cases. There was no any significant correlation between SUVmax values and any of the following pathological parameters: grading, tumor size, nodal status, R status, presence of perineural or microvascular invasion.

(18)F-FDG PET/CT showed an increased FDG uptake in the abdominal lymph nodes in 11/61 patients (18%) who underwent surgical resection. Particularly, (18)F-FDG PET/CT identified in 8/11 patients suspected nodal metastases in lymph node stations outside the area of standard lymphadenectomy. Therefore in these eight patients an

extension of lymphadenectomy was required, and lymph nodes along celiac trunk and superior mesenteric artery and around the abdominal aorta (para-aortic nodes) were removed. Final histological examination showed the presence of lymph node metastases in 10/11 patients with PET/CT findings of nodal metastases, and in 7/8 patients who required an extension of lymphadenectomy.

Table 3. Pathology data in 61 patients who underwent pancreatic resection

	N	%
Median tumor size (mm), range	25	8-50
Grading		
G1	0	0
G2	31	51
G3	30	49
Microvascular invasion	57	93
Perineural invasion	55	90
R status		
R0	52	85
R1	9	15
R2	0	0
T stage		
T1	1	1.5
T2	1	1.5
T3	59	97
N status		
N0	14	23
N1	47	77

Sensitivity and specificity of (18)F-FDG PET/CT for detecting lymph node metastases in 61 resected patients were 21% and 93%, respectively. Median number of resected nodes in patients who underwent standard lymphadenectomy was 32 (range 10-52) compared to 44 (range 28-91) nodes when an extended lymphadenectomy was carried out (P=0.235).

(18)F-FDG PET/CT modified the clinical and therapeutic management of 18/72 patients (25%) who were deemed to undergo pancreatic resection for resectable pancreatic cancer. (18)F-FDG PET/CT diagnosed advanced disease in eight patients (11%), identified synchronous, extra-pancreatic, resectable tumors in two (3%), and identified another eight patients (11%) who required an extension of lymphadenectomy. Excluding patients who underwent neoadjuvant treatment (n=14), (18)F-FDG PET/CT changed the management of 18/58 patients (31%).

Median follow-up for resected patients was 10 months (range 4-20). 53% of them developed tumor recurrence. Of these patients, 24 (75%) had distant metastases whereas 8 (25%) loco-regional recurrence. Twelve patients died of disease. Median disease-free survival was 12 months (Figure 2). The 6-month and 1-year DFS for all resected patients were 80% and 49% respectively. Median SUVmax was 3.25 in patients without recurrence versus 3.4 in those with recurrence (P=NS). Considering all resected patients, median DFS was 10 months for those with SUVmax>6 and it was not reached for patients with SUVmax<6. The 6-month and 1-year DFS were 79% and 40% for SUVmax>6 and 80% and 58% for SUVmax<6, respectively (P=0.148, Figure 3).

Excluding patients who underwent neoadjuvant treatment (n=14), median SUVmax was 3.3 in patients without recurrence versus 3.8 in those with recurrence (P=NS). In this subgroup of patients, median DFS was 10 months for those with SUVmax>6 and it was not reached for patients with SUVmax<6. The 6-month and 1-year DFS were 78% and 39% for SUVmax>6 and 84% and 65% for SUVmax<6, respectively (P=0.076, Figure 4).

Figure 2. Disease-free survival for the entire cohort of 60 patients who underwent surgical resection for pancreatic cancer.
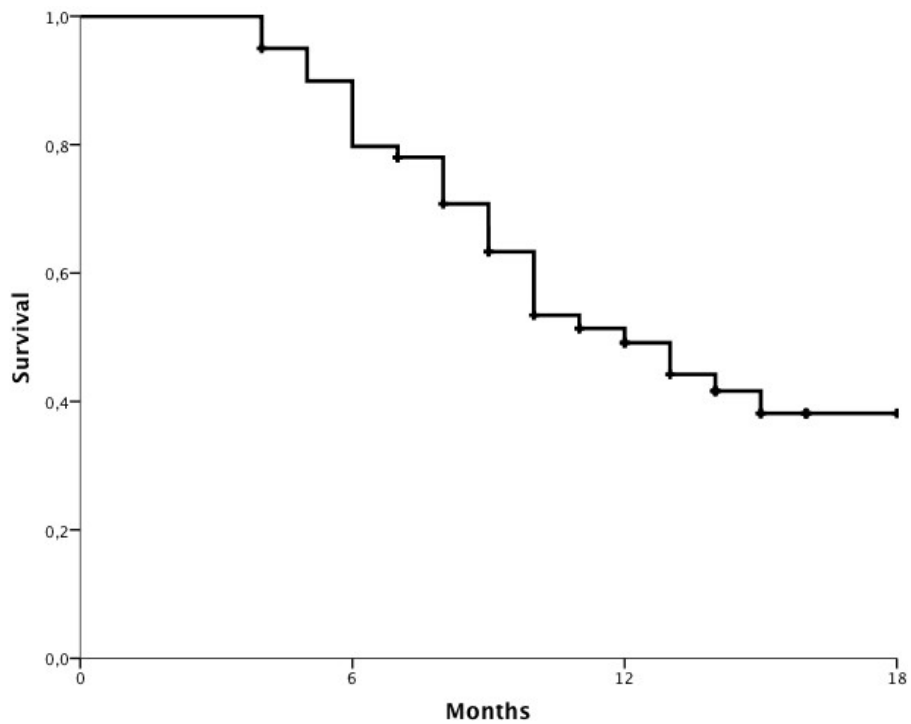
Figure 3. Disease-free survival for the entire cohort of 60 patients who underwent surgical resection for pancreatic cancer according to SUVmax value < 6 (n=31) and > 6 (n=29).
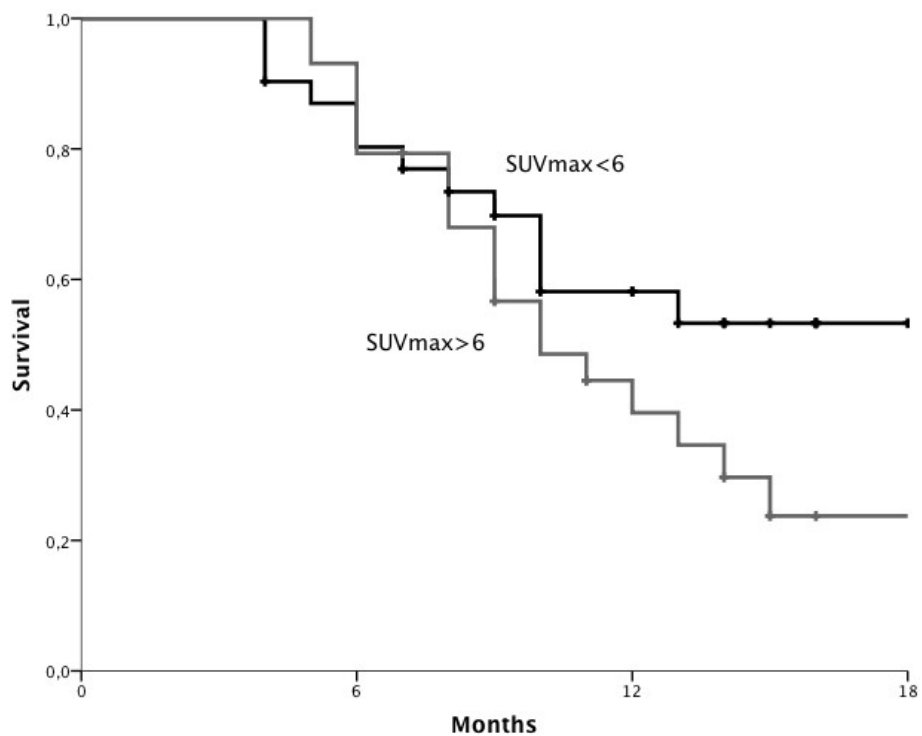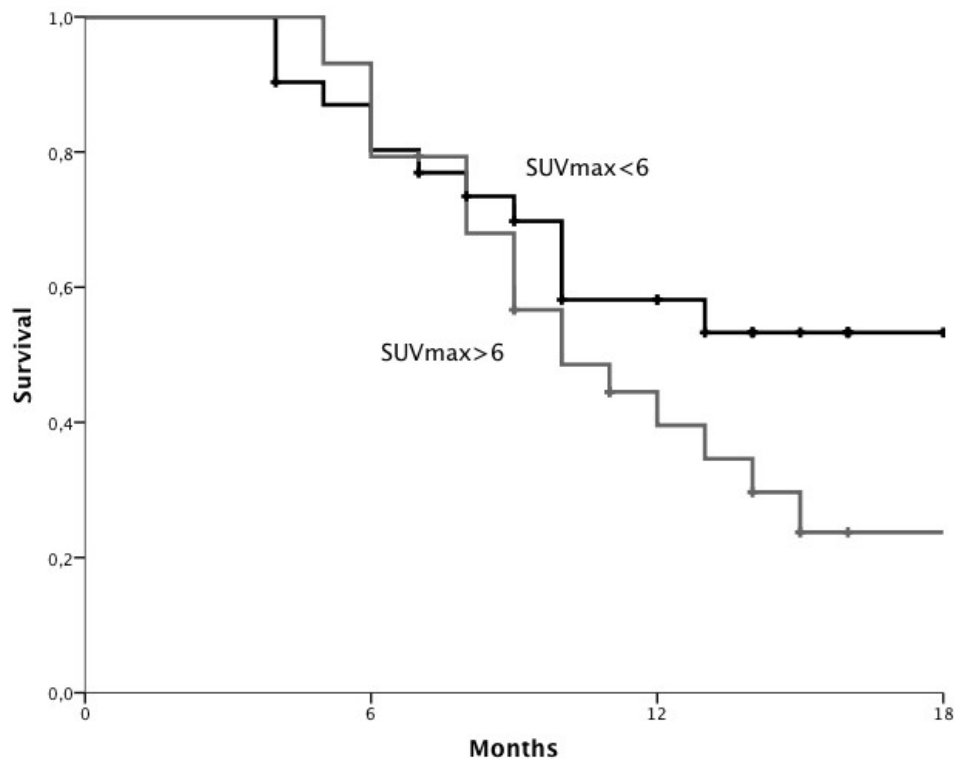

Figure 4. Disease-free survival for resected patients excluding those who underwent neoadjuvant treatment according to SUVmax value < 6 (n=19) and > 6 (n=27).

DISCUSSION

Preoperative evaluation of the extent of pancreatic adenocarcinoma is crucial in order to decide the most appropriate treatment options and to avoid futile laparotomies. In recent years advances in high-resolution imaging techniques have significantly improved the quality of preoperative tumor-staging. MDCT, eventually associated with other procedures such as endoscopic ultrasound (EUS), can give accurate data regarding the invasion of peripancreatic structures (T stage) and thus "local resecability" [8-13,33]. However, the identification of distant metastases may be more problematic, especially for small metastatic lesions. In this setting, in 10 to 15% of patients deemed to be resectable after conventional imaging staging, surgical resection cannot be performed because of locally advanced tumors or occult metastatic disease [8-14,]. Another 20% of patient who undergo resection will develop tumor recurrence and die of disease within 12 months after surgery [2,5]. These "early recurrences" can be attributed to occult metastatic disease. Better diagnostic tools are needed to improve preoperative patient selection in order to offer surgery to those who are likely to benefit from it.

(18)F-FDG PET/CT has been shown to be an accurate examination for the preoperative staging, identification of occult metastatic disease and of early tumor-recurrence, and evaluation of treatment response in different tumors [14-22]. Nowadays PET/CT imaging is a standard practice in staging of lung and esophageal carcinoma [15,16].

On the other hand, the role of (18)F-FDG PET/CT in the management of pancreatic cancer patients is controversial. While some authors have reported a significant clinical impact of this technique in the staging of patients with resectable pancreatic cancer, others showed a limited value, even in the detection of metastases [23-29].

In this prospective study we demonstrated that whole body (18)F-FDG PET/CT significantly improves patients selection by changing the oncological management of 25% of a cohort of patients with resectable pancreatic cancer. Farma et al. and Heinrich et al. showed that PET/CT modified the management of 11% and 16% of their patients, respectively, with a specific focus on the differentiation between benign and malignant pancreatic tumors and preoperative staging [12,23]. The 25% rate of our study is particularly high, considering that all these patients underwent preoperative high-resolution imaging. In our experience, patients management was modified not only because of the detection of occult metastases but also for the identification of synchronous extra-pancreatic tumors or lymph node metastases that required an extension of the lymphadenectomy at laparotomy.

Of note, if we do not consider patients who underwent (18)F-FDG PET/CT after neoadjuvant treatment and characterized by a SUVmax < 3 in most cases, the impact of this diagnostic technique on patients management rises from 25 to 31%. Nineteen per cent of the 72 patients included in this study underwent neoadjuvant chemotherapy/chemoradiation for a locally-advanced or borderline resectable pancreatic cancer. Neoadjuvant treatment was significantly associated with the lack of an increased FDG uptake at PET/CT (SUVmax < 3). Therefore neoadjuvant chemotherapy/chemoradiation induces a decrease of FDG uptake capability by tumors. These finding are confirmed by other studies. Kittada and colleagues, in a cohort of 40 patients with locally advanced pancreatic cancer, found a significant decrease of median SUVmax value from 4.7 to 2.2 after chemoradiation [34]. Similarly Topkan et al. reported a significant SUVmax decrease after chemoradiation (from a 14.5 to 3.9, pre and postchemoradiation median values) [35]. Recent data suggest that a reduction > 50% in FDG uptake after neoadjuvant treatment compared to baseline values is associated with better treatment response and improved clinical outcomes [34-36]. Therefore, in patients who undergo neoadjuvant therapy it is

mandatory to perform a pre-treatment, baseline evaluation with PET/CT in order to evaluate a "metabolic treatment response".

In this study (18)F-FDG PET/CT excluded from surgical exploration 11% of patients scheduled for laparotomy because of the presence of metastatic disease. Sensitivity and specificity of PET/CT for the identification of metastases were 78 and 100%, respectively, and remarkably sensitivity rate was 87.5% considering patients who did not undergo neoadjuvant treatment. In previous series, sensitivity of PET/CT for the diagnosis of metastatic disease ranged between 68 and 91%, while specificity was in between 64 and 95% [23-26,36-40]. Frohlich and colleagues showed that sensitivity of (18)F-FDG PET/CT in detecting liver metastases was 97% for lesions greater than 1 cm in size but it was only 43% if the size was less than 1 cm, underlying that even for PET/CT tumor size is an important parameter [40]. On the other hand the diagnosis of peritoneal metastases can be problematic. Diederisch et al. Reported a PET/CT sensitivity of only 25% for the detection of peritoneal disease [37]. More recently a study by Panagiotidis E et al. indicated a high incidence of peritoneal implants revealed by (18)F-FDG PET/CT in a number of malignancies including pancreatic cancer, with an overall accuracy of 91% [41].

Since PET/CT is an expensive diagnostic tool, the identification of subgroup of patients that may benefit from PET/CT after conventional staging work-up could be of clinical interest. It has been suggested that serum perioperative CA 19.9 levels can correlate with tumor burden and tumor spread in resectable pancreatic cancer. A preoperative CA 19.9 level > 200 U/mL is associated with early recurrence and poor survival after pancreatectomy for pancreatic cancer [5,42]. In the present study we found that median CA 19.9 level was higher in patients with metastatic disease showed at PET/CT (292 versus 49 U/mL). The difference was not statistically significant likely because of the low number of metastatic patients. However, the

performance of (18)F-FDG PET/CT should be highly recommended in patients with resectable pancreatic cancer at high resolution imaging but with CA 19.9 > 200 U/mL.

In our experience (18)F-FDG PET/CT was poorly sensitive for the detection of lymph node metastases. In fact sensitivity and specificity for nodal involvement were 21 and 93%, respectively. These data are in keeping with the current literature [23-26,36-40]. There are several possible causes that may explain these disappointing results. Firstly, pancreatic cancer is commonly associated with a high rate of lymph node metastases (70/80%) [2,3]. Secondly, most metastatic nodes are in the peripancreatic tissue, close to the primary tumor. Thirdly, metastatic nodes are commonly small in size (diameter < 1 cm). Based on these findings, (18)F-FDG PET/CT poorly sensitive in distinguishing between primary pancreatic cancer and its peripancreatic metastatic nodes. An interesting and new finding from our study is the capability of (18)F-FDG PET/CT to identify lymph node metastases in nodal stations that are not comprised in the area of standard lymphadenectomy. In eight of the 61 resected patients (13%) lymphadenectomy was extended to lymph nodes along the superior mesenterica artery, celiac trunk and to para-aortic nodes. Nodal metastases were found at histological examination in seven of these eight patients (87.5%). Para-aortic and celiac trunk lymph node metastases are associated with poor prognosis in pancreatic cancer [43,44]. The preoperative identification of nodal metastases at these sites could represent an indication for neoadjuvant treatment, but accurate preoperative diagnosis is difficult [45]. In this light (18)F-FDG PET/CT, characterized by a high specificity for nodal metastases, may represent a new diagnostic tool for the proper identification of these patients that should be considered for neoadjuvant chemotherapy instead of upfront surgery.

We aimed to evaluate a possible correlation between preoperative SUVmax values and tumor-recurrence. Okamoto et al. in a series of 56 patients who underwent pancreatic resection for pancreatic cancer, showed that preoperative SUVmax was

significantly higher in patients who experienced tumor –recurrence, and that SUVmax was the only independent predictor of early recurrence [29]. However, our results failed to demonstrate a significant difference in SUVmax values among patients with and without recurrence. One-year DFS was better for patients with SUVmax < 6 but the difference was not statistically significant (P=0.148) likely because the relatively short follow up time of this cohort. Of note, excluding patients who underwent neoadjuvant therapy, the DFS difference between patients with SUVmax > and < 6 improved, but again without reaching significance (P=0.076). An ultimate conclusion regarding the correlation between SUVmax and DFS cannot be drawn. Therefore a longer follow-up is needed to obtain definitive results.

CONCLUSIONS

(18)FDG-PET/CT findings resulted in changes of therapeutic management/operative procedures in one third of patients. (18)FDG-PET/CT improves staging of patients with resectable pancreatic cancer, particularly for the detection of occult metastatic disease. Although (18)FDG-PET/CT has limited value in characterizing the N status, it was helpful to detect loco-regional nodal metastases that required an extension of the lymphadenectomy or a neoadjuvant treatment. Neoadjuvant treatment is significantly associated with low metabolic activity limiting the value of (18)FDG-PET/CT in this setting. Longer follow-up data are needed to evaluate a possible correlation between SUVmax and disease-free survival. Based on these results, **(**18)FDG-PET/CT should be considered as part of the preoperative staging of patients with resectable pancreatic cancer after high-resolution imaging, especially in those with high CA 19.9 serum levels.

REFERENCES

1) Oettle H., Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 2007;297:267-277

2) Crippa S, Partelli S, Zamboni G, et al. Poorly differentiated resectable pancreatic cancer: is upfront resection worthwhile? Surgery 2012;153 (3 Suppl 1):S119-119

3) Hartwig W, Hackert T, Hinz U, et al. Pancreatic cancer surgery in the new millennium: better prediction of outcomes. Ann Surg 2011;254:311-319

4) Huguet F, Girard N, Guerche CS. et al. Chemioradiotherapy in the management of locally advanced pancreatic carcinoma: a qualitative systemic review. J Clin Oncol 2009;27:2269-2277

5) Barugola G, Partelli S, Marcucci S, et al. Resectable pancreatic cancer: who really benefits from resection? Ann Surg Oncol 2009;16:3316-3322

6) Crane CH, Varadhachary G, Wolff RA, et al. The argument for pre-operative chemoradiation for localized, radiographically resectable pancreatic cancer. Best Res Clin Gastroenterol 2006;20:365-382

7) Evans DB, Varadhachary GR, Crane CH, et al. Preoperative gemcitabine-based chemoradiation for patients with resectable adenocarcinoma of the pancreatic head. J Clin Oncol 2008;26:3487-3495

8) Wong JC, Lu DS. Staging of pancreatic adenocarcinoma by imaging studies. Clin Gastroenterol Hepatol 2008;6:1301-1308

9) Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol 2009;16:1727-1733

10) House MG, Yeo CJ, Cameron JL, et al. Predicting resectability of periampullary cancer with three-dimensional computed tomography. J Gastrointest Surg 2004;8:280-288

11) Zhang Y, Huang J, Chen M, Jiao LR. Preoperative vascular evaluation with computed tomography and magnetic resonance imaging for pancreatic cancer: a meta-analysis. Pancreatology 2012;12:227-233

12) Farma JM, Santillan AA, Melis M, et al. PET/CT fusion scan enhances CT staging in patients with pancreatic neoplasms. Ann Surg Oncol 2008; 15:2465-2471

13) Kaneko OF, Lee DM, Wong J, et al. Performance of multidetector computed tomographic aniography in determining resectability of pancreatic head adenocarcinoma. J Comput Assist Tomogr 2010;34:732-738

14) Zafra M, Ayala F, Gonzalez-Billalabeitia E, et al. Impact of wholebody 18F-FDG PET on diagnostic and therapeutic management of Medical Oncology patients. Eur J Cancer 2008;4:1678–1683

15) Lordick F, Ott K, Krause BJ. New trends for staging and therapy for localized gastroesophageal cancer: the role of PET. Ann Oncol 2010; 21 Suppl 7:294-299

16) Fischer B, Lassen U, Mortesen J, et al. Preoperative staging of lung cancer with combined PET-CT. N Engl J Med 2009;361:32-39

17) Fischer BM, Mortesen J, Langer SW, et al. A prospective study of PET/CT in initial staging of small-cell lung cancer: comparison with CT, bone scintigraphy and bone marrow analysis. Ann Oncol 2007;18:338-345

18) Ruers TJ, Langenhoff BS, Neeleman, et al. Value of positron emission tomography with [F-18]fluorodeoxyglucose in patients with colorectal liver metastases: a prospective study. J Clin Oncol 2002;20:388-395

19) Pommier P, Dussart S, Girinsky T, et al. Impact of 18F-fluoro-2-deoxyglucose positron emission tomography on treatment strategy and radiotherapy planning for stage I-II Hodgkin disease: a prospective multicenter study. Int J Radiat Oncol Biol Phys. 2011;79;823-828

20) Kim K, Kim SJ, Kim IJ, Kim YS, Pak K, Kim H. Prognostic value of volumetric parameters measured by F-18 FDG PET/CT in surgically resected non-small-cell lung cancer. Nucl Med Commun 2012;33:613-620

21) Rockall AG, Cross S, Flanagan S, Moore E, Avril N. The role of FDG-PET/CT in gynaecological cancers. Cancer Imaging 2012;12:49-65

22) Lee JW, Lee SM, Lee MS, Shin HC. Role of 18F-FDG PET/CT in the prediction of gastric cancer recurrence after curative surgical resection. Eur J Nucl Med Mol Imaging 2012;39:1425-1434

23) Heinrich S, Goerres GW, Schafer M, et al. Positron emissiontomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness. Ann Surg. 2005;242:235-243

24) Kauhanen SP, Komar G, Seppanen MP, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed

tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. Ann Surg. 2009;250:957-963

25) Asagi A, Ohta K, Nasu J, et al. Utility of contrast-enhanced FDG-PET/CT in the clinical management of pancreatic cancer: impact on diagnosis, staging, evaluation of treatment response, and detection of recurrence. Pancreas 2013;42:11-19

26) Kim MJ, Kwang HL, Kyu TL, et al. The value of Positron Emission Tomography/Computed Tomography for evaluating metastatic disease in patients with pancreatic cancer. Pancreas 2012;41:897-903

27) Izuishi K, Yamamoto Y, Sano T, et al. Impact of 18-fluorodeoxyglucose positron emission tomography on the management of pancreatic cancer. J Gastrointest Surg 2010;14:1151-1158

28) Sperti C, Pasquali C, Bissoli S, Chierichetti F, Liessi G, Pedrazzoli S. Tumor relapse after pancreatic cancer resection is detected earlier by 18-FDG PET than by CT. J Gastrointest Surgery 2010;14:131-140

29) Okamoto K, Koyama I, Miyazawa M, et al. Preoperative 18[F]-fluorodeoxyglucose positron emission tomography/computed tomography predicts early recurrence after pancreatic cancer resection. Int J Clin Oncol 2011;16:39-44

30) Pedrazzoli S, DI Carlo V, Dionigi R, et al. Standard versus extended lymphadenectomy associated with pancreaticoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy study group. Ann Surg 1998;228:508-517

31) Hruban R, Boffetta P, Hiraoka N. Ductal adenocarcinoma of the pancreas: WHO classification of tumours of the digestive system. Lyon, IARC, 2010, pp 279-291

32) AJCC Cancer Staging Manual, 7th ed. New York (NY): Springer-Verlag; 2010

33) Tellez-Avila FI, Chavez-Tapia NC, Lopez-Arce G, et al. Vascular invasion in pancreatic cancer: predictive value for endoscopic ultrasound and computed tomography imaging. Pancreas 2012;41:636-638

34) Kittada H, Hidenori T, Hiroaki O, et al. Role of 18F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography in Predicting the Pathologic Response to Preoperative Chemoradiation Therapy in Patients With Resectable T3 Pancreatic Cancer. World J Surgery 2013;37:169-178

35)   Topkan E, Parlak C, Kotek A, et al Predictive value of metabolic 18FDG-PET response on outcomes in patients with locally advanced pancreatic carcinoma treated with definitive concurrent chemoradiotherapy. BMC Gastroenterology 2011;11:123

36) Smyth EC, Shaha MA. Role of (18F) 2-fluoro-2-deoxyglucose positron emission tomography in upper gastrointestinal malignancies. World J Gastroenterol 2011;17:5059-5074

37) Diederichs CG, Staib L, Vogel J, et al. Values and limitations of 18F-fluorodeoxyglucose positron emission tomography with preoperative evaluation of patients with pancreatic masses. Pancreas 2000;20:109–116

38) Koyama K, Okamura T, Kawabe J, et al. Diagnostic usefulness of FDG PET for pancreatic mass lesions. Ann Nucl Med 2001;15:217–224

39) Nishiyama Y, Yamamoto Y, Yokoe K, et al. Contribution of whole body FDG-PET to the detection of distant metastases in pancreatic cancer. Ann Nucl Med 2005;19:491–497

40) Frohlich A, Diederichs CG, Staib L, et al. Detection of liver metastases from pancreatic cancer using FDG PET. J Nucl Med 1999; 40:250–255

41) Panagiotidis E, Datseris IE, Exarhos D, et al. High incidence of peritoneal implants in recurrence of intra abdominal cancer revealed by 18F-FDG PET/CT in patients with increased tumor markers and negative findings on conventional imaging. Nucl Med Commun 2012;33:431-438

42) Ferrone CR, Finkelstein DM, Thayer SP, et al. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. J Clin Oncol 2006;24:2897-2902

43) Kanda M, Fujii T, Nagai S, et al. Pattern of lymph node metastasis spread in pancreatic cancer. Pancreas 2011;40:951-955

44) Murakami Y, Uemura K, Sudo T, et al. Prognostic impact of para-aortic lymph node metastasis in pancreatic ductal adenocarcinoma. World J Surg 2010;34:1900-1907

45) Imai H, Doi R, Kanazawa H, et al. Preoperative assessment of para aortic lymph node metastasis in patients with pancreatic cancer. Int J Clin Oncol 2010;15:294-300