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ORIGINAL ARTICLE

Computed tomography-based diagnostics might be insufficient in the determination of pancreatic cancer unresectability

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Abstract

AIM: To inquire into a question of an overestimation of arterial involvement in patients with pancreatic cancer (PC).

METHODS: Radiology data were compared with the findings from 51 standard, 58 extended and 17 total pancreaticoduodenectomies; 9 distal resections with celiac artery (CA) excision; and 28 palliations for PC. The survival of 11 patients with controversial computed tomography (CT) and endoscopic ultrasound data with regard to arterial invasion, after R0/R1 procedures (false-positive CT results, Group A), was compared to survival after eight R2 resections (false-negative CT results, Group B) and after 12 bypass procedures for locally advanced cancer (true-positive CT results, Group C).

RESULTS: In all of the cases in group A, operative exploration revealed no arterial invasion, which was predicted by CT. The one-year survival in Group A was 88.9%, and the two-year survival was 26.7%, with a median follow-up of 22 mo. One-year survival was not attained in groups B and C, with a significant difference in survival ($P_{a\text{-}b}$ = 0.0029, $P_{b\text{-}c}$ = 0.003).

CONCLUSION: Arterial encasement on CT does not necessarily indicate arterial invasion. Whenever PC is considered unresectable, endoUS should be used. In patients with controversial CT an EUS data for peripancreatic arteries involvement radical resection might be possible, providing survival benefits as compared to R2-resections or palliative surgery.

Key words: Vascular invasion; Cancer; Pancreas; Management; Pancreaticoduodenectomy; Distal pancreatectomy; Computed tomography; Endoscopic ultrasound; Arteries; Resectability

Core Tip: Pancreatic cancer remains one of the most aggressive neoplastic processes, and the methods to manage it are constantly evolving. Resection remains the only potential cure for pancreatic cancer, and it can prolong survival in patients compared to those who do not undergo resection. However, only a minority of patients are candidates for surgery at diagnosis, and

only a minority of patients who undergo surgery survive beyond 5 years. The most important cause of an inacurate assessment of resectability is underestimation of vascular invasion. This study attempted to address the other side of the problem: overestimation of arterial involvement in patients with pancreatic cancer.

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INTRODUCTION

Pancreatic cancer remains one of the most aggressive neoplastic processes, and the methods to manage it are constantly evolving[1,2]. Despite impressive progress in the diagnosis and treatment of other-sited malignances, the resectability and 5-year survival rates for pancreatic cancer are still very poor, with survival rates for cancers of the pancreatic body and tail of 10% and 10% in North America and Western Europe, respectively, and of 34% and 18% in Japan, as well as approximately 19% for the pancreatic head[3,4]. Resection remains the only potential cure for pancreatic cancer, and it can prolong survival in patients compared to those who do not undergo resection. However, only a minority of patients are candidates for surgery at diagnosis, and only a minority of patients who undergo surgery survive beyond 5 years[5-9].

The decision "to resect or to palliate" depends on the clinical staging system, which is based on the results of pre-surgical imaging studies. In the absence of metastatic disease, assessment of vascular invasion is a key aspect in the evaluation of resectability for pancreatic cancer[4,5,10-15]. Obviously, surgical exploration with pathological examination remains the "gold standard" in terms of evaluation of resectability, especially from the point of view of vascular involvement[6,7,9]. The salient sign of unresectability in pancreatic ductal adenocarcinoma (PDAC) is encasement of the superior mesenteric and celiac arteries, indicating vascular invasion. Computed tomography (CT) is the "gold standard" for preoperative PDAC detection and for evaluation of its resectability[4,5,10-15]. Efforts have typically been focused on accurately assessing tumor resectability based on CT criteria to avoid non-therapeutic laparotomy. It is equally important, however, to ensure that no patient with a resectable tumor is denied surgery because of a false-positive evaluation of arterial invasion[10-26]. The degree of arterial involvement has been assessed by CT, with accuracy in the evaluation of pancreatic cancer (PC) resectability for single-detector row machines varying between 70% and 80%[16-18]. For modern multi-detector row computed tomography (MDCT) scanners, the accuracy of 85%-93% (sensitivity of 80%-90%, specificity of 89%-100%) is only slightly better[19-26]. The most important cause of an inaccurate assessment of resectability is underestimation of vascular invasion. This study attempted to address the other side of the problem: overestimation of arterial involvement in patients with PC.

In this study, we compared the following: (1) the instrumentally derived evidence with the findings during surgery from patients with CT-predicted circumferential tumor apposition to the peripancreatic arteries (judged unresectable in compliance with current recommendations), which proved to be uninvaded intraoperatively; and (2) these patients' survival with that of patients treated with R2 resections and palliative procedures for locally advanced pancreatic cancer.

MATERIALS AND METHODS

Patients

The institutional review board approved this retrospective study, and special patient informed consent, other than standard consent for surgery, was not required.

Data from preoperative CT and endoscopic ultrasound (EUS) reports of 163 patients consecutively operated on for ductal adenocarcinoma were compared with the findings of 51 standard, 58 extended and 17 total pancreatoduodenectomies (PDs), 9 distal resections with CA excision (DPCA) and 28 palliative bypasses for PDAC, performed between June 2005 and June 2012 (EUS-between 2008 and 2012). From all of these cases, 11 borderline-resectable patients were found who had controversial data on CT and EUS with regard to peripancreatic arterial tumor invasion (group A). They all had CT signs of arterial involvement, but curative R0/R1 procedures, with or without excision of the arteries, were performed. Survival in the above-mentioned group was compared to the survival of 8 patients who underwent R2 resections (group B) and of 12 patients with locally advanced cancer, in whom palliative bypass surgeries were performed (group C). Sixteen patients who underwent bypass procedures were not included in the study due to the presence of distant metastases. In the remaining patients, no distant metastases were detected during surgery.

The patients' historical data, including the stage of disease, level of resection, age, sex, diagnosis and site of tumor, affected vessels, mode of adjuvant chemotherapy, recurrence-free time interval (when possible) and survival, were obtained.

Methods

CT: All of the patients underwent preoperative, native and contrast-enhanced triphasic 64-slice and 256-slice multi-detector computed tomography (Phillips Brilliance). Five hundred milliliters of water was routinely administered 5-10 min before the examination to demarcate the duodenum and delineate the pancreatic head region. Each patient received 100 mL of non-ionic contrast ma-

terial with 370 mg of iodine/mL (omnipaque 350, ultravist 370, optiray 350) *via* intravenous injection at the rate of 3-5 mL/s, using an automatic power injector (OptiVantage DH (Mallinckrodt, Inc.) through an 18-gauge or 20-gauge intravenous catheter inserted into an antecubital vein. Unenhanced and triphasic (arterial phase, portal venous phase) enhanced scans were obtained. Unenhanced and enhanced scan images were obtained from the top of the diaphragm through the pelvis. Monitoring of the contrast media bolus was performed on the level of the aortic arch in all cases. The trigger threshold of density was set at 150 HU for the aortic ROI, which was placed at the center of the vessel lumen. The delay after the start of the injection was 10 s for the arterial phase and 35 s for the portal venous phase. The levels of the tracker and the starting position were the same. To estimate individual vascular trees pre-surgically, three-dimensional reconstructions of CT angiograms were acquired with the software used during routine CT examinations. All of the CT angiographic images were read by the radiologist and attending surgeon, and the arterial diameters and variants of celiaco-mesenteric arterial anatomy (according to Michels[27] criteria) were recorded.

EUS: Patients underwent EUS of the pancreato-biliary system, performed by experienced endoscopists using electronic echoendoscopes EG 530 UR for radial scanning and EG 530 UT for linear scanning, supplied by an SU-7000 ultrasound processor (Fujinon, Japan) with color Doppler function. Evaluation of the superior mesenteric, portal and splenic veins and the celiac trunk could be performed with high accuracy by radial echoendoscopy. A limitation of radial scanning was incomplete visualization of the superior mesenteric artery. In such cases, we resorted to linear scanning. Endoscopy was performed under conscious sedation using intravenous midazolam. The EUS criteria for vascular invasion were: loss of the hyperechoic vessel wall/tumor interface; an irregular tumor/vessel interface; a tumor within the vessel lumen; irregularity of the vascular wall; vessel encasement; and collaterals with associated arterial narrowing or occlusion (non-visualization of major vessels)[11-13,28].

Procedures

A standard PD included the removal of the lymph nodes of the anterior and posterior pancreatoduodenal, pyloric, hepatoduodenal ligament and of the superior and inferior pancreatic head and body lymph node stations. An extended in our institution consisted of the additional removal of all of the lymph nodes from the hepatic hilum, along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery and laterally to both the renal hila, as well as clearance of the circumference of the origin of the celiac trunk and the superior mesenteric artery, with total resection of the nerve plexus around the superior mesenteric artery and the portal vein. The procedure included removal of perivascular lymphatics and nerves and retroperitoneal connective tissue.

An extended distal pancreatectomy, which we usually perform "from the right to the left", consisted of removal of the spleen and the pancreatic neck, body and tail with the splenic vessels, as well as all of the lymph nodes from the hepatic hilum, along the aorta from the diaphragmatic hiatus to the inferior mesenteric artery, and clearance of the circumference of the origin of the celiac trunk and the superior mesenteric artery, with resection of the nerve plexus to the left and right of the superior mesenteric artery. The procedure included removal of perivascular lymphatics and nerves and retroperitoneal connective tissue. If malignancy was suspected during frozen section examination of the posterior border of the specimen, a left adrenalectomy with periglandular tissue was performed. In cases of involvement of the common hepatic or celiac artery by pancreatic body cancer, a modified Appleby procedure (extended distal pancreatectomy with excision of the celiac and common hepatic arteries) was performed. The resection was considered radical if there were no tumor cells on frozen section examination, in the left resection margins for PD and in the right margins for distal pancreatectomy.

For histopathological examination of PD specimens, an axial slicing technique and circumferential resection margins studying were used. The definitions of R0 and R1 resection were based on the "1 mm clearance" rule, including lymph node assessment in case of tumor spreading beyond the lymph node capsule. We considered resection to be R0 if there were no tumor cells found within a 1 mm distance from the specimen's circumferential margins, except for the anterior surface evaluation, in which we applied the "0 mm clearance" rule[29].

Statistical analysis

Statistica software (data analysis software system, version 6.0 StatSoft, Inc. 2001; MedCalc version 11.6.0.0 of MedCalc) was used for the statistical analysis. The distributions of age at operation, postoperative hospital stays, and follow-up periods are described as medians with interquartile ranges. The numbers of the complications in the groups are expressed as integers without percentages in light of the small number of subjects. Fisher's exact test was used to analyze morbidity and mortality between the subgroups of patients. Data values are presented on a continuous scale, but distributions different from normal (*e.g.*, patient age, duration of postoperative treatment) were compared using the nonparametric analogue ANOVA and the Kruskal-Wallis test. For consistent distinction comparison, the Mann-Whitney method with Bonferroni's correction for multiple comparisons was used. Overall survival from the date of resection was estimated using the Kaplan-Meier method. The 1-and 2-year actuarial survival rates and the median survival time, with corresponding 95%CI, are presented. Disease-free survival could not be calculated in all of the patients because of the retrospective nature of the study. The end of the follow-up period for the patients who survived was in December 2012. Patients alive at the last follow-up were censored and are

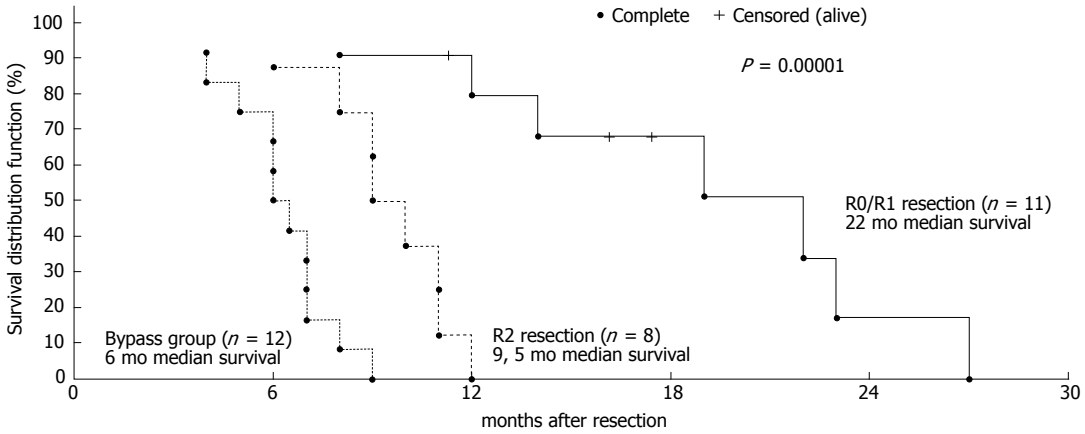

Figure 1 Differences in survival between the groups were significant. The explanation is in the text.

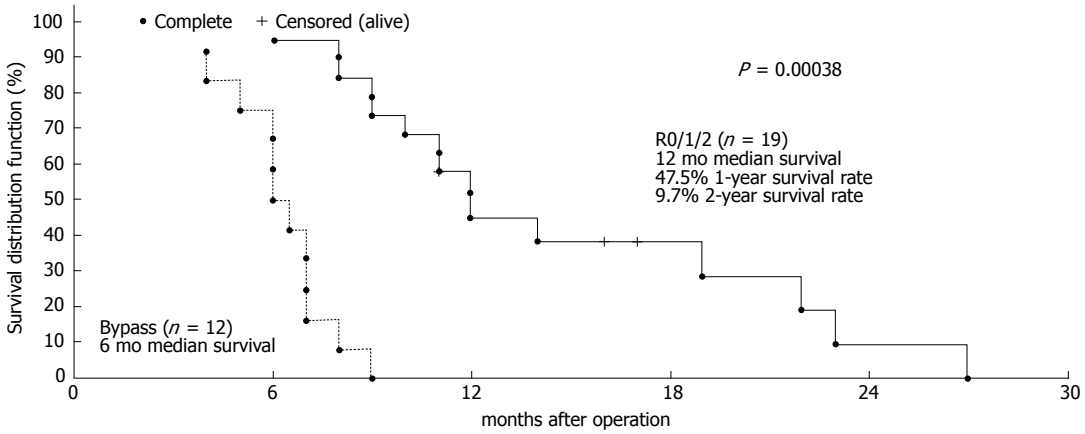

Figure 2 Median survival following palliative operations was 6 mo (95%CI: 5-7 mo) and there was a significant difference in survival between the palliative group (C) and the united resection group (group A + group B).

marked in Figures 1 and 2. The log-rank test was used to compare survival curves. Two-sided *P* values were always computed, and an effect at a *P* value <0.05 was considered statistically significant.

RESULTS

The diagnosis of ductal adenocarcinoma of the pancreas was histologically proved in all of the cases. In all of the cases in group A, the arteries involved on CT were considered intact during surgery (Figures 3-7). There were no differences between the groups regarding age or sex. The tumor size was significantly larger in the bypass group (Table 1), although real tumor size in these patients could not be measured because the tumors were not removed, and they were assessed during surgery only approximately.

Attempts at PD or distal pancreatectomy in Group A were chosen as a result of the obvious discrepancies between the CT evidence and EUS findings: in each of these cases, the CT imaging features displayed were consistent with the peripancreatic arteries (Table 2) being completely encased by the tumor, while the EUS appearance was suggestive of the tumor merely abutting the arteries. In group B, palliative PDs were performed as motivated by the equivocal CT findings regarding tumor resectability and surgeon-disclosed superior mesenteric artery (SMA) and/or CA tumoral involvement after gland transection, that is, after having crossed "the point of no return".

In group A (Table 2), the tumor was located in the pancreatic head and body in 5 and 5 cases, respectively, and in 1 case, the pancreas was completely involved. No CT-presumed encasement of the peripancreatic arteries by the tumor was noted in the surgical records to have been discovered during surgery in group A (Figures 3-7). Under microscopy, in cases 2, 3, 7, 9 and 10, tumor cells were detected in the periarterial nerve plexus to the left of the artery of interest, while the right side of the plexus was free of tumor. In cases 1, 5, 6, 8 and 11, tumor cells were detected in the periarterial nerve plexus to the right of the artery of interest, and the left side of the plexus was free of tumor. In case 4, tumor cells were detected in the periarterial nerve plexus to the right and to the left of the SMA. In all of the cases, the artery of interest was definitely uninvolved (Figures 3-7).

In all but one of the cases, the level of an R1 resec-

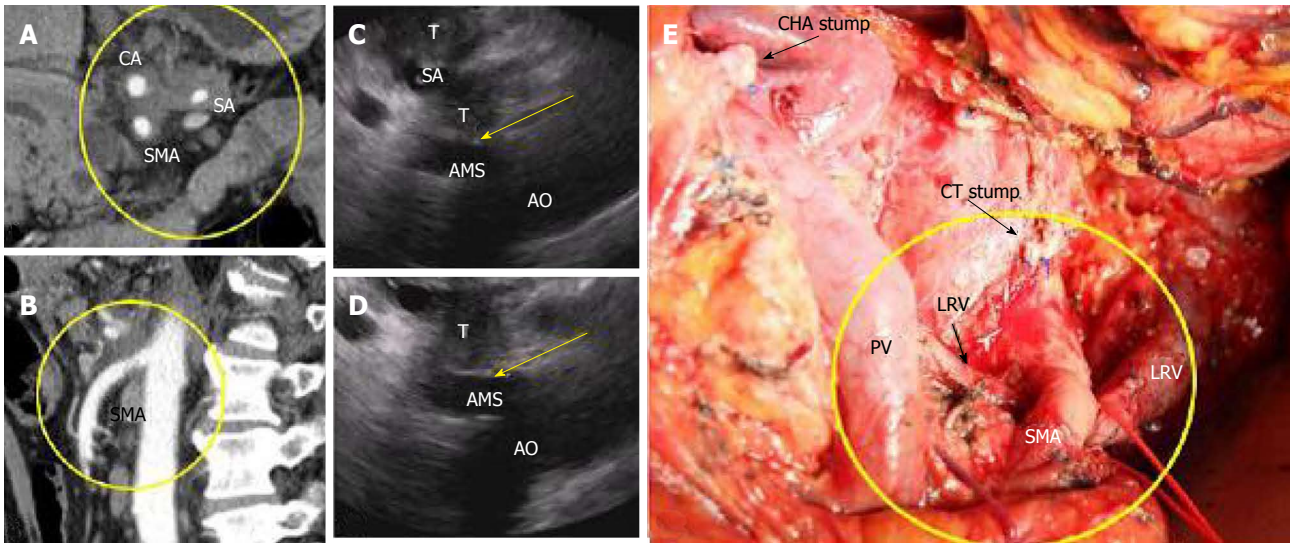

Figure 3 In this 65-year-old man (case #10), pancreatic body DAC with 360° celiac (CA), splenic (SA) and superior mesenteric artery (SMA) encasement was established on CT (A, B), but endoUS data did not confirm this conclusion, finding a plane between the tumor and the SMA (C, D, arrows). AMS: Arteria mesenterica superior, AO: Aorta, T: Tumor. Distal pancreatectomy with excision of the celiac artery (CA) and left adrenalectomy were performed, and no SMA involvement was identified during surgery (E). The level of resection was R1 because of the contact of the SMA with the tumor. CHA: Common hepatic artery; CT: Celiac trunk; LRV: Left renal vein; PV: Portal vein.

Table 1 The demographic findings and tumor size in groups

	R0/R1 resection (*n* = 11)	R2 resection (*n* = 8)	Bypass (*n* = 12)	$P_{Kruskal-Wallis}$
Age (yr)	61 (59-65)	69 (65-72)	62 (60-68)	0.122
Male/female	5/6	4/4	3/9	-
Tumor size (cm)	4 (4-4.5)	4 (3.9-4.2)	5 (4.5-5.5)[1]	0.001

[1]Tumor size was measured without tumor removal.

tion was secured as required by the artery-tumor contact; in 1 case an R0 resection was achieved. The status of a negative resection margin of the pancreas and clear soft tissues to the left of the SMA during PD and to the right of the SMA during distal pancreatectomy were histologically confirmed during surgery in each of these cases. In three cases a classical PD was performed, in two cases - pylorus-preserving PD, in one case - a pylorus-preserving total duodenopancreatectomy, and in five cases we performed distal PD with CA excision (the modified Appleby procedure). Three PDs were added by pancreatic body resection and portal vein (PV) or superior mesenteric vein (SMV) resection. Based on the CT data in all the cases, the tumor extents were clinically staged as T4, with regional spread suspected in five cases. In all the cases, CT revealed the unresectable tumors: in six cases it was caused by involvement of the SMA, in one case - of the SMA and CA, in one case - of the CA and left hepatic artery (LHA), in one case - of the common hepatic artery (CHA), and in the last two cases the unresectability on CT were caused by replaced right hepatic artery (rRHA) and gastroduodenal artery (GDA) involvement respectively.

In the R2 group (B, Table 3), the neoplasm was observed in the pancreatic head in 7 cases and in the body of the pancreas in 1 case. In 2 cases, the classical version of standard PD was performed, and in 6 cases, its pylorus-preserving variation was performed. In one case, the modified Appleby operation was performed. In all of the cases, the tumor extent was intraoperatively assigned as T4, owing to SMA invasion, and all of the patients were found to have regional metastases (Table 3). Five patients in this group were examined by endoUS, which showed SMA involvement in one case and CA involvement in one case, and in three cases, the report was equivocal because of technical difficulties.

In the bypass group (C, Table 4), the tumor was located in the pancreatic head and body in 9 and 2 cases, respectively, and in 1 case, the entire gland was affected. In all of the cases, CT identified the spread of the malignancy as T4 due to SMA alone or both the SMA and CA together being involved in 7 and 5 cases, respectively. Regional spread was proved in 5 cases. In the other patient, pancreas biopsy was performed, while biopsy of the lymph nodes was not performed.

Gemcitabine chemotherapy is a standard postsurgery treatment in pancreatic cancer, and it was performed in 23 cases. Eight patients in group A, 6 in group B and 8 in group C received and/or are receiving gemcitabine chemotherapy. One patient with pancreatic body cancer from group A was administered gemcitabine and eloxatin neoadjuvant chemotherapy. Five patients (1 from group A, 1 from group B and 3 from group C) refused chemotherapy, and in three cases (1 case from each group), chemotherapy was canceled because of bad physical performance.

Perioperative characteristics were only compared in groups A and B because there was no significant blood loss or ICU stays in the bypass group (C). There were no differences between operating time (P_{MW} = 0.368),

Table 2 The characteristics of patients who underwent radical (R0-1) surgery for pancreatic ductal adenocarcinoma with circular arterial involvement on computed tomography (group A)

Stage	R factor	PDAC location	Artery involved on CT	ChT	DFS (mo)	Survival (mo)
cT4NxM0	pT3N1M0(R1)	Head	rRHA	+	17	19
cT4NxM0	pT3N1M0(R1)	Body	SMA	+	20	27
cT4NxM0	pT3N1M0(R1)	Body	SMA	+	19	22
cT4N1M0	pT3N1M0(R1)	Head	SMA	+	17	23
cT4NxM0	pT3N0M0 (R1)	Total	CHA	-	12	14
cT4NxM0	pT3N1M0(R1)	Head	SMA + SMA[2]	+	NA	17[1]
cT4N1M0	pT2N0M0 (R0)	Body	CA and LHA	+	16	16[1]
cT4N1M0	pT3N1M0(R1)	Head	SMA	+	10	12
cT4N1M0	pT3N1M0(R1)	Body	GDA	-	6	8
cT4NxM0	pT4N1M0(R1)	Body	SMA	+	NA	11[1]
cT4N1M0	pT3N1M0(R1)	Head	SMA and CA	+	10	11[1]

[1]Alive; [2]In case 6 there were two SMA segments involved on CT. SMA: Superior mesenteric artery; rRHA: Replaced right hepatic; LHA: Left hepatic; CA: Celiac artery; GDA: Gastroduodenal artery; PDAC: Pancreatic ductal adenocarcinoma.

Table 3 The characteristics of patients who underwent R2 resections for pancreatic ductal adenocarcinoma (group B)

Stage		PDAC location	Artery involved	ChT	Distant mets (mo)	Survival (mo)
cT3NxM0	pT4N1M0	Head	SMA	+	7	10
cT3NxM0	pT4N1M0	Body	SMA	-	3	6
cT3N1M0	pT4N1M0	Head	SMA	+	NA	11
cT3NxM0	pT4N1M0	Head	SMA	+	8	12
cT3N1M0	pT4N1M0	Head	SMA	+	7	11
cT3NxM0	pT3N1M0	Head	SMA	+	NA	9
cT3NxM0	pT4N0M0	Head	SMA	-	NA	9
cT3NxM0	pT4N1M0	Head	SMA	+	6	8

SMA: Superior mesenteric artery; PDAC: Pancreatic ductal adenocarcinoma; NA: Not available; ChT: Chemotherapy.

Table 4 The characteristics of patients who underwent bypass procedures for locally advanced pancreatic ductal adenocarcinoma (group C)

Stage	PDAC location	Artery involved	ChT	DFS (mo)	Survival (mo)
cT4N1M0	Head	SMA and CA	-	3	4
cT4NxM0	Head	SMA	-	NA	7
cT4NxM0	Head	SMA	+	4	7
cT4NxM0	Head	SMA	+	4	6,5
cT4NxM0	Head	SMA	+	NA	6
cT4N1M0	Body	SMA and CA	+	2	5
cT4NxM0	Total	SMA and CA	-	NA	4
cT4NxM0	Head	SMA	+	5	7
cT4NxM0	Head	SMA	+	5	9
cT4N1M0	Head	SMA and CA	+	NA	6
pT4N1M0	Body	SMA and CA	-	NA	6
pT4N1M0	Head	SMA	+	4	8

ChT: Chemotherapy; SMA: Superior mesenteric artery; CA: Celiac artery; GDA: Gastroduodenal artery; LHA: Left hepatc artery; CHA: Common hepatic artery; rRHA: Replaced right hepatic artery; DFS: Disease-free survival.

blood loss (P_{MW} = 0.47) and length of ICU stay (P_{MW} = 0.409) between groups A and B. The overall hospital stay time was approximately the same (P_{KW} = 0.165) in all three groups (Table 5). Postoperative complications are shown in Table 6. Three pancreatic fistulas appeared after Appleby procedures, as well as one after a Whipple procedure.

There were significant differences in survival among the groups (P = 0.0001). One-year survival was not attained in groups B and C, notwithstanding the difference in survival between groups B and C being considerable (P = 0.003). The median survival for group B was 9.5 mo (95%CI: 8.5-11 mo). The one-year survival rate in group A was 79.5% (95%CI: 54.5%-100%), and the two-year survival rate was 17% (95%CI: 0.00%-47.5%), with a median follow-up period of 16 mo (95%CI: 11-22 mo) and median survival of 22 mo (95%CI: 14-23 mo). The difference in survival between groups A and B was significant ($P_{log\text{-}rank}$ = 0.00001) (Figure 1). The actuarial one-year survival in the united resection group (group A + group B), *i.e.*, in resections with non-mettering factor R, was as high as 45% (95%CI: 21%-68%), while two-year survival was 9.7% (95%CI: 0.00%-27.5%), with median survival of 12 mo (95%CI: 10-22 mo). The median survival following palliative operations was 6 mo (95%CI: 5-7 mo), and there were significant differences in survival among the groups (Figure 2).

The sensitivities of CT (147 patients) and EUS (87 patients) for the detection of arterial involvement were 60% and 78.5%, respectively, with specificities of 78.5% and 98.6%, respectively. Sixteen patients were excluded because of distant spread confirmed by CT and during surgery.

DISCUSSION

Vascular involvement was found in 21%-64% of patients with pancreatic carcinoma, most often with involvement of the superior mesenteric artery, due to its location, and errors associated with evaluation of arterial invasion were frequent[19-26]. Currently, it is believed that involvement of the PV or SMV is not a criterion of unresectability for pancreatic carcinoma[4,5,8,9,30,31]. In half of the cases, only fibrotic changes were found during the histologic

Table 5 The perioperative characteristics in groups

ME (25%-75%)	R0/R1 resection (*n* = 11)	R2 resection (*n* = 8)	Bypass (*n* = 12)
Operation time, min	570 (470-630)	540 (390-600)	Ne
Blood loss, mL	700 (450-1500)	1000 (600-1500)	Ne
ICU, d	2 (2-3)	3 (2-8)	Ne
Postoperative hospital stay, d	16 (13-26)	13 (12-19)	12 (11-17)

Ne: Not evaluated; ICU: Intensive care unit.

Table 6 The postoperative complications in groups (according to Clavien-Dindo classification)

	R0/R1 resection (*n* = 11)	R2 resection (*n* = 8)	Bypass (*n* = 12)
Grade 2	3	2	3
Lymphorrhea	3	2	-
Diarrhea	2	-	-
Delayed gastric emptying Grade 3a	-	-	3
Pancreatic fistula[1]	3 (grade B)	1 (grade B)	-

[1]According to ISGPF classification.

evaluation of resected veins due to a suspicion of tumor intergrowth[30,31]. According to the existing TNM classification, involvement of the main peripancreatic arteries by pancreatic adenocarcinoma is considered a contraindication for pancreatic resection[4,5]. Nevertheless, the concept of arterial invasion remains a matter for discussion and gradual changes, which is supported by recently adopted National Comprehensive Cancer Network guidelines for borderline resectable pancreatic adenocarcinoma[5]. In particular, it happens because reconstruction of arteries is not a technical problem anymore[32-34], and resection of the celiac and common hepatic arteries during distal pancreatectomy usually does not require reconstruction[35,36]. Histologic results, similar to those for veins, have shown that invasion of resected arteries occurs in only half of cases[37-39].

The criteria for assessing the accuracy of resectability prior to surgery and, in particular, vascular involvement remain surgical exploration with pathohistological evaluation, although intraoperative diagnostics for arterial invasion can require aggressive actions, resulting in incomplete resection and remains subjective[37-40]. Frequently, invasion of the arteries is found when the pancreas has already been cut and the "point of no return" passed[40]. Palpation of the superior mesenteric artery and celiac artery, even after mobilization and cutting of the pancreas, cannot be considered an accurate method of detection of arterial invasion, especially after radiotherapy, during reoperations, or in cases of large tumors and accompanying pancreatitis[2,6,7,37-40]. For example, in our research, according to data on only intraoperative revisions, none of the tumors was considered resectable in group A, and none of the tumors was considered unresectable in group B before transection of the pancreas.

Today, CT scanning is considered the method of choice for suspected pancreatic carcinoma, allowing for diagnosis and for determining the localization, size, dissemination and staging of tumors during one noninvasive examination[10-15]. The adoption of CT criteria for arterial involvement in pancreatic cancer (absence of a fat plane between the tumor and vessels, vessels surrounding the tumor by more than 50% of its circumference, occlusion of vessels with development of collaterals) can be significantly aided by 3D and multiplanar reconstructions[22-24], 3D CT-angiography[41,42] and the technique of thin pancreatic slices, which reveals fine details of the vessel walls[10,19,43-45].

Two meta-analyses of CT's ability to reveal arterial involvement in pancreatic carcinoma showed sensitivities of 91% and 68% and specificities of 85% and 93%[25,26]. Loyer *et al*[46] noted that the presence of a fat plane (type A) or normal pancreatic tissue between the tumor and vessels (type B) is a good prognostic sign, as resectability in these situations reached 95%. Phoa *et al*[15] discovered that in vessel embedment into the tumor (type D) or the vessel's circular encasement (type E), the rate of vessel invasion was nearly 88%, and potential resectability was 7% for type D and 0% for type E. It was noted that the sensitivity of CT for the detection of unresectability of pancreatic carcinoma reached 60%, and specificity reached 90% if contact of a vessel with tumors of type D or E was noted over at least 90° degrees of its circumference[15]. A relatively reliable sign of vein intergrowth by a tumor is contact of more than 5 mm in length (78% for PV and 81% for SMV). This sign was not proved for arteries; however, it was shown that surrounding of the vascular wall by more than 180° of the tumor's circumference was correlated with unresectability, with a sensitivity of 84%, specificity of 98%, positive predictive value (PPV) of 95%, and negative predictive value (NPV) of 93%[23]. A high risk of invasion has been recognized by several authors due to pronounced narrowing of the arteries on CT, although involvement of the arterial wall is possible, even if its diameter is normal[15,19,47].

The criteria developed by Li *et al*[47] for arterial invasion during pancreatic carcinoma are embedment of vessels in the tumor or a combination of the tumor surrounding no less than a half of a vessel's circumference with stenosis of the artery (sensitivity of 79%, specificity of 99%) or with irregularity of the arterial wall (sensitivity of 45%, specificity of 99%). House *et al*[48], using 3D CT for detection of arterial invasion, showed sensitivity of 86%-87% and specificity of 97%-99%. The accuracy of CT for the detection of arterial invasion by pancreatic carcinoma is shown in Table 7.

The accuracy of MRT for the detection of arterial invasion in pancreatic carcinoma was equal to the accuracy of CT[25,26,49,50] and EUS[51], while the accuracy of angiography was relatively low (sensitivity of 21%-84%[11,14,52], specificity of 50%-100%[14,52], PPV of > 60%[11,52] and NPV 50% of 83%[52]) compared to other diagnostic modalities. The capability of CT angiography to delineate the celiaco-mesenteric architecture with high accuracy

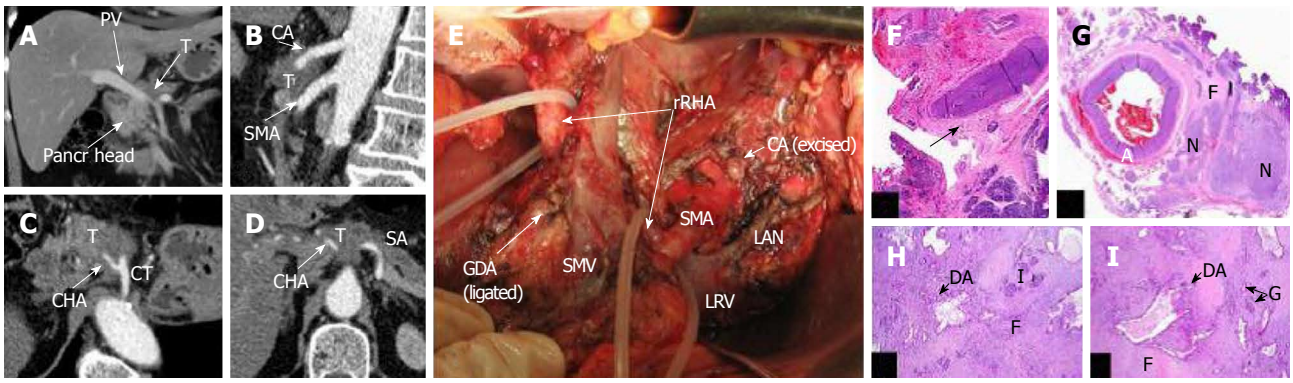

Figure 4 In this 64-year-old woman (case 7), circular encasement of the celiac, common hepatic, left gastric, left hepatic and splenic arteries by PDA on the background of aberrant arterial anatomy; a replaced right hepatic artery (rRHA, Michels, type VIIIb) was identified on CT (A-D). E. Photograph of operating field after distal pancreatectomy (R0 resection), with excision of the celiac, common, left gastric, left hepatic arteries and gastroduodenal artery resection in the absence of any evidence for major arterial invasion, either during surgery or on histopathology; the blood supply to the stomach was routed from the SMA *via* pancreaticodudenal arcades and then through the GDA with the latter's proximal segment being resected and ligated. F-I: Removed specimen under microscope. The tumor (DA) was smaller than 2 cm and was surrounded by a thick layer of fibrotic tissue (H,I). There were no signs of involvement of the major peripancreatic (CHA, GDA, LHA) arteries; H: CHA section obtained from close to the point of its transection (white arrow) in the fibrotic zone (black arrow) along the pancreas margin. No evidence of tumor growth x 5. G: Celiac plexus and trunk area of diffuse fibrosis (F) x 5; A: Artery; N: Nerve plexus with large ganglion; H: Pancreatic tissue with apparent diffuse fibrosis (F), groups of islets remaining (I) and groups of glandular formations of ductal adenocarcinoma (DA) of the pancreas x 50. d: Structures of DA throughout the fibrotic tissue (F) containing remnants of pancreatic tissue (atrophic islets and ductules) x 50, hematoxylin + eosin. PV: Portal vein; T: Tumor; CA: CT-celiac artery (celiac trunk); SMA: Superior mesenteric artery; GDA: Gastroduodenal artery; rRHA: Replaced right hepatic artery; PDA: Pancreato-duodenal arcade; LRV: Left renal vein; PV: Portal vein; SMV: Superior mesenteric vein; LAV: Left adrenal vein.

has practically excluded angiography from the diagnostic algorithm for patients with pancreatic tumors[41,42].

EUS is an operator-dependent (especially in the hepatopancreatobilliary zone) and expensive method[11-13,28,53-61], the sensitivity of which for staging of pancreatic carcinoma (with fine-needle aspiration) is 96.6%, with accuracy of 99.0%, NPV of 96.2% and PPV of up to 100%[11-13,28,56-61]. It was shown that endoscopic ultrasound is a more accurate method for the diagnosis of venous invasion, compared to CT, conventional ultrasound and angiography[54,57]. Evaluation of arterial involvement is a more complicated task for EUS: sensitivity is from 50% to 100%, with specificity from 58 to 100%, PPV from 28% to 100% and NPV between 18% and 93%[28,53,55,56-61].

A comparison of EUS, MDCT, magnetic resonance imaging (MRI) and selective angiography for the evaluation of periampullary tumors showed that EUS was more accurate than CT and MRI for the evaluation of local tumor spread, although this accuracy decreased from 84% to 72% in the presence of transpapillary biliary stents[62]. The accuracy of resectability evaluations by laparoscopic ultrasound is close to that as with endoUS[63]. Transvenous ultrasound is only used for the evaluation of venous invasion, and there are no data on arterial invasion assessments using this method[64].

The low accuracy of CT in the evaluation of the resectability of pancreatic carcinoma was shown by the results of pathohistological evaluations of resected peripancreatic arteries[37-39] as without previous treatment, so as after neoadjuvant radio- and chemoradiotherapy[65,66]. Our observations showed that none of described arterial invasion CT criteria[15,47-49], or even their combination, was absolutely reliable (Figures 3-7). At the same time, combined use of radial and convex EUS transducers allowed for the detection of a space between the tumor and artery (Figure 3), despite the pressing of previously accepted CT data showing circular artery involvement.

It is possible that peritumoral desmoplasia or an inflammatory reaction is indistinguishable from tumor infiltration on CT evaluation. These histopathological findings appear to be a reason for CT false-positive conclusions regarding arterial involvement in pancreatic carcinoma. When considering the accuracy of CT and other diagnostic modalities in assessing arterial invasion by pancreatic cancer, it is noteworthy that the problem of false-positive results of CT in the evaluation of arterial involvement is discussed very little. As mentioned previously, it is accepted now that without distant spread, the resectability of pancreatic carcinoma can be determined by the involvement of the SMA and CA[4,5]. At the same time, according to the literature, patients who underwent pancreatic resection, even with positive margins, lived significantly longer than patients after palliative surgery[67-71], especially taking into consideration recent data that most pancreatic cancer resections are R1 resections[72]. Considering that the tactics for pancreatic carcinoma treatment are based primarily (and often only) on data from CT, the long-term survival rates and patients' fates are extremely CT-dependent. With this connection, cases of CT false positivity regarding arterial invasion (when involvement of the artery, predicted by CT, is not confirmed during surgery) acquire a special meaning. There are only two ways to confirm or refute arterial invasion: to resect and examine a specimen or to perform circular skeletonization and determine that there is no involvement. The mystery is that neither one nor the other is recommended by existing guidelines[4,5], and most HPB departments follow these recommendations. Nevertheless, many pub-

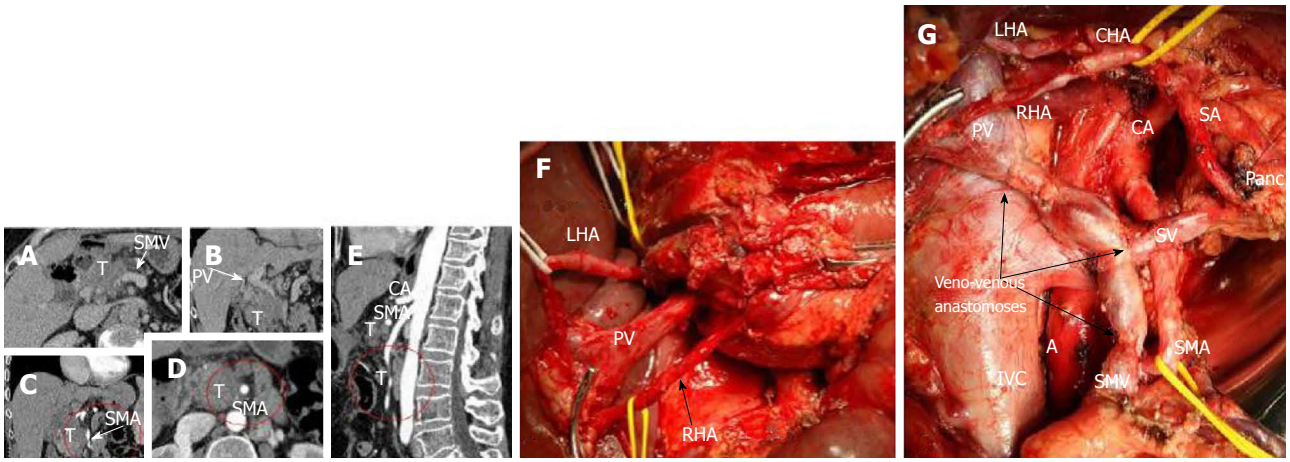

Figure 5 In this 61-year-old woman (case 6), 260° and 360° pancreatic ductal adenocarcinoma encasement of SMA segments was diagnosed on computed tomography (A-E), while endoUS data described only tumor abutment with the superior mesenteric artery. A, B: Venous phase. Sagittal view. Computed tomography provided evidence of circumferential involvement of the SMV and PV; C, E: Arterial phase. Sagittal view. The distal SMA segment (6-7 cm from the origin) presented circumferential adjacency to pancreatic head ductal adenocarcinoma. The celiac artery (CA) was unaffected; D: Arterial phase. Axial image. At least 260° of the proximal SMA segment (2.5-3 cm from the origin) was circumscribed by tumor. An extended Whipple procedure with pancreatic body, portal, splenic and superior mesenteric vein resection was performed with the use of a superficial femoral vein autograft (F, G). Notwithstanding "organoleptic" signs of unresectability (both hepatic arteries were embedded in the tumor) (F), there were no signs of superior mesenteric artery (SMA) or hepatic artery involvement during surgery (G). The level of resection was R1 because of the contact of the SMA with the tumor. A: Aorta; CHA: Common hepatic artery; RHA: Right hepatic artery; LHA: Left hepatic artery; SA: Splenic artery; SMV: Superior mesenteric; PV: Portal vein; LRV: Left renal veins; T: Tumor; Pancr: Pancreatic tail stump.

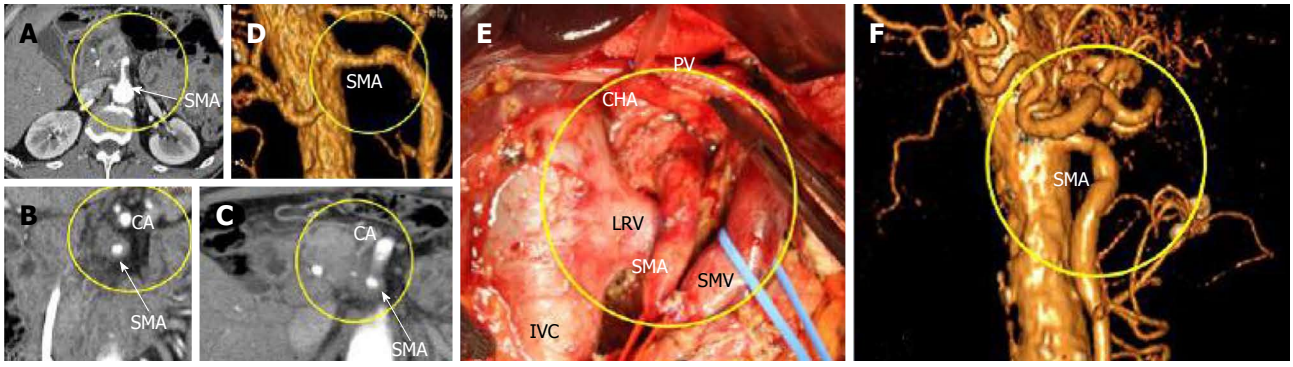

Figure 6 In this 59-year-old man (case 4), 360°pancreatic ductal adenocarcinoma encasement of the superior mesenteric artery was diagnosed on computed tomography (A-D), while endoUS data described only tumor abutment with the superior mesenteric artery. A-C: Computed tomography (CT), Arterial phase, Axial images. CT showed circumferential infiltration of the SMV. The CA was intact; D: CTA. Local narrowing of the SMA at the site at which it was circumscribed by the tumor; E: Intraoperative photograph. An extended Whipple procedure was performed. There were no signs of SMA involvement during surgery. The level of resection was R1 because of the contact of the SMA with the tumor; F: CT angiography. Three months postsurgery. No relapse and no narrowing of the SMA. SMA: Superior mesenteric artery; SMV: Superior mesenteric; PV: Portal; IVC: Inferior caval; LRV: Left renal veins; CA: Celiac artery.

lications comparing different methods of detection of arterial invasion in carcinoma have reported a number of false-positive results different from zero and, accordingly, a PPV different from 100% (Table 7).

This problem generates a number of questions: (1) What is/are the culprit/s in false-positive CT results of arterial invasion assessment in pancreatic cancer? How can surgeons appraise these results intraoperatively? Would mere palpation suffice for the surgeon to determine? (2) What makes a surgeon revise the arteries (primarily the CA and SMA, which are rather tedious to revise) after CT has shown them to be involved? (3) How can the surgeon ascertain that the artery (especially the SMA and CA) is intact, if he/she does not resect it or does not perform extended pancreatectomy, implying circumferential skeletonization of the CA and SMA? (This question is of greater concern in light of it being most hospitals' (including high-volume hospitals) policy not to resort to extended pancreatic resection because they are considered oncologically unwarranted[1,73,74].

The standard answer to these questions is "We do not perform pancreatic resections if CT discovers circular arterial infiltration, indicating arterial and/or periarterial neural invasion, which is associated with poor prognosis. That is why we do not have false-positive results." However, lack of research on this subject, data from a number of authors regarding the long-term survival of patients after pancreatic resections compared to a palliative surgery, the existence of false-positive results on CT (Table 7), and data from our work indicate that not all is

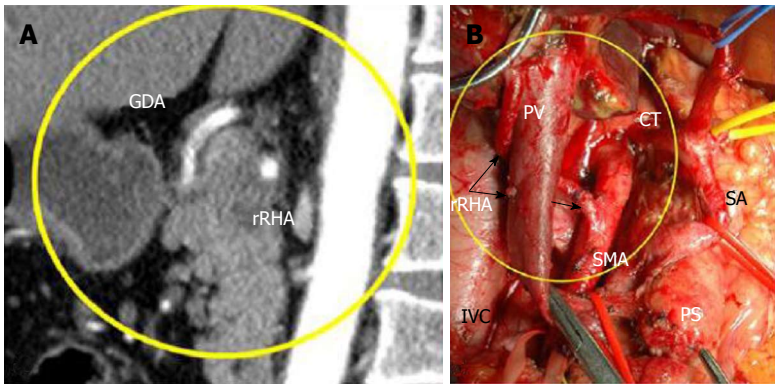

Figure 7 In 75-year-old woman (case 1), 360° PDAC encasement of the replaced right hepatic artery was diagnosed on computed tomography (A), while endoUS data described only tumor abutment with the artery. Arterial phase, Sagittal images: CT showed circumferential infiltration of the rRHA, B: Intraoperative photograph. An extended Whipple procedure was performed. There were no signs of rRHA or SMA involvement during surgery (arrows). The level of resection was R1 because of the contact of the rRHA with the tumor. SMA: Superior mesenteric artery; rRHA: Replaced right hepatic; LHA: Left hepatic; RGEA: Right gastro-epiploic arteries; CT: Celiac trunk; SMV: Superior mesenteric; PV: Portal; LRV: Left renal vein; T: Tumor; PS: Pancreatic stump.

Table 7 The celiac trunk accuracy for assessment of arterial invasion in pancreatic cancer

Reference	*n*	Sensitivity	Specificity	PPV	NPV
Soriano *et al*[14]	62	67%	94%	89%	80%
Li *et al*[47]	54	79%	99%	-	-
House *et al*[48]	115	86% SMA, 87% CA	97% SMA, 99% CA	83% SMA ,93% CA	98% SMA, CA
Squillaci *et al*[52]	50	97%	100%	100%	95%
Gress *et al*[53]	151	15%	100%	100%	60%
Buchs *et al*[57]	153	54.5%	91.2%	66.7%	86.1%
Tellez-Avila *et al*[59]	50	66.7%	90%	60%	92.3%
Pietrabissa *et al*[63]	50	82%	53%	-	-

SMA: Superior mesenteric artery; CA: Celiac artery; PPV: positive predictive value; NPV: Negative predictive value.

clear. In particular, our research showed the following: (1) Diagnostics for arterial invasion in pancreatic carcinoma remains a complex problem requiring a complex approach; (2) There is a group of patients in which pancreatic carcinoma can be considered unresectable according to the CT criteria for arterial invasion, while during surgery (group A), the tumor is found to be resectable. The detection of such patients is also important because after chemoradiation and restaging, they can remain in the group of unresectable locally advanced tumors due to insignificant changes on CT images[59,60]. If a surgeon has results of EUS that disagree with CT data with regard to local tumor extent, then this disagreement can justify pancreatic resection as an initial attempt, as well as an attempt of surgery with curative intent after neoadjuvant therapy. Our retrospective analysis showed that long-term survival after pancreatic resection, regardless of surgical radicalism, is significantly better than that after palliative surgery. Herewith, patients lived significantly longer after R0-R1 resection than after R2 resection, which is consistent with the findings of other authors[36,65,66]; (3) According to our results, EUS has advantages over CT in the detection of local tumor spread, even in large tumors, which is in agreement with the findings of some authors[59] and in disagreement with those of others[60]. CT should be aided by endoscopic ultrasound if unresectability of pancreatic carcinoma as a result of arterial involvement is suspected. In some cases, it allows for the exclusion of arterial invasion, which is important because in cases of rejection of pancreatectomy, patients move to palliative treatment, with a significantly lower survival rate; (4) In our research, intraoperative exploration, including visualization, palpation and even transection of the pancreas, was not a reliable method of evaluation of arterial intergrowth. Out of 19 observations, described in groups A and B, 100% of the cases of operative revision only led or would have led to tactical mistakes, and this finding is reflected in publications[6,7,37-39]. That is, preoperative diagnosis of arterial involvement by pancreatic carcinoma must include not only CT but also endoscopic ultrasound, and a decision regarding the unresectability of a tumor cannot be based only on the results of operative revision and palpation. Such an approach, in our opinion, will allow for the reduction of the number of false-positive and false-negative observations. With regard to the latter aspect, knowing that the detection of arterial involvement in large tumors by palpation is unreliable and considering the difficulties of forthcoming resection, one must bear in mind that it is easier for a surgeon (especially one with a lack of experience) to say "no", that is, to recognize arteries as involved and a tumor as unresectable, even if CT shows the opposite; (5) In light of CT-dependent tactics and the survival prognosis of patients with nonmetastatic large pancreatic carcinomas, it is interesting to analyze the dependence of CT accuracy on arterial involvement from the standpoint of surgical aggressiveness. Aggressiveness leads to an increased number of false-positive results (the artery is involved on CT but not involved during surgery), decreasing specificity, decreasing the number of false-negative results (when the artery is not involved on CT but is considered involved at surgery), and increasing the sensitivity

of the method. This fact means that in every surgical department, the value of CT for the detection of arterial involvement is unique and depends on that department's surgical ideology.

Despite the limitations of this research, including its retrospective nature and small number of patients, we believe that it has demonstrated the need for combined use of CT and EUS for the detection of arterial involvement by pancreatic cancer. This combination allows for the expansion of the group of patients with borderline resectable tumors who could benefit from pancreatic resection. False positivity on CT in the diagnosis of arterial invasion in pancreatic cancer remains a problem for surgeons, radiologists and gastroenterologists, and it requires further research.

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COMMENTS

Background

Decision "to resect or to palliate" pancreatic cancer depends on clinical staging system, which is based on the results of pre-surgical imaging studies. In the absence of metastatic disease, assessment of vascular invasion is a key aspect in the evaluation of resectability for pancreatic cancer. The salient sign of pancreatic ductal adenocarcinoma (PDAC) unresectability is the superior mesenteric and celiac arteries encasement, signaling vascular invasion and computed tomography is the "gold standard" for preoperative evaluation of arteries involvement. Efforts have typically been focused on accurately assessing tumor resectability based on computed tomography (CT) criteria in order to avoid non-therapeutic laparotomy and it is equally important to ensure that no patient with resectable tumor is denied surgery because of a false-positive evaluation of arterial invasion. The most important reason for inaccurate assessment of resectability is underestimation of the vascular invasion. In contrast, this study addresses the overestimation of arterial involvement in patient with pancreatic cancer.

Research frontiers

Diagnostics of arterial invasion in pancreatic carcinoma remains a complex problem requiring a complex approach. There is a group of patients in which pancreatic carcinoma can be considered unresectable according to CT criteria of arterial invasion, while at surgery a tumor is resectable. The detection of such patients is also important because after chemoradiation and restaging they can remain in a group of irresectable locally advanced tumors due to insignificant postradiation changes of CT picture. If surgeon has results of endoscopic ultrasound controversial to CT data in regards to local tumor extent, this can justify pancreatic resection as an initial attempt, as well as an attempt of surgery with curative intent after neoadjuvant therapy. The authors retrospective analysis showed that long-term survival after pancreatic resection, regardless of surgical radicalism, significantly better than that after palliative surgery. Herewith, patients lived significantly longer after R0-R1 resection than after R2 resection which is consistent with other authors. According to the results, EUS has advantages over CT in detection of local tumor spread even in large tumors. CT should be aided by endoscopic ultrasound if irresectability of pancreatic carcinoma as a result of arterial involvement is suspected. In some cases it allows to exclude arterial invasion, which is important because in case of rejection of pancreatectomy patients move to a group of palliative treatment with significantly lower survival rate. In the research, intraoperative exploration, including visualization, palpation and even transection of the pancreas were not reliable methods of evaluation of arterial intergrowth. Out of 19 observations described in 100% of cases operative revision only has led or would have led to tactical mistakes. That is, preoperative diagnostics of arterial involvement by pancreatic carcinoma must include not only CT, but endoscopic ultrasound as well, and a decision regarding irresectability of tumor cannot be based only on results of operative revision and palpation. Such an approach, in our opinion, will allow to reduce a number of false-positive as well as false-negative observations. As regards to the last aspect, knowing that detection of arterial involvement in large tumors by palpation is unreliable and, considering difficulties of forthcoming resection, one has to have in mind that it is easier for surgeon (especially with the lack of experience) to say "no", that is, recognize arteries as involved and a tumor as irresectable even if CT shows the opposite.

Innovations and breakthroughs

The study of CT and EUS accuracy for assessment of arteries involvement in borderline-resectable pancreatic cancer by comparison their conclusions with intraoperative findings shows that we have to double-check CT data if they say about unresectability of pancreatic cancer.

Applications

The research shows the possibility of extraction of patients with pancreatic cancer Stage II (who benefit from radical surgery) from Stage III group (treated by palliation) in which they have to be included according to present regulations if we use only CT (and this is general practice) for diagnostics of arterial involvement. Further application of the tactics introduced by authors may prolong survival of the patients with pancreatic cancer. The authors believe that the topic of false-positivity in CT diagnostics of vascular involvement in pancreatic cancer is of special interest because it was discussed very little.

Terminology

Pancreatic cancer: one of the most deadly cancers which treatment is still experimental and mainly palliative; arterial encasement - involvement by tumor of more than 180° or more than 50% of the vessel circumference; arterial abutment - involvement by tumor of less than 180° or les than 50% of the vessel circumference. Resectability-possibility to remove tumor and regional lymphatics (as potential site of tumor spread) within the borders of uninvolved tissues.

Peer review

This paper is informative and interesting, describing important and contradictory points for surgery of pancreatic cancer.

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