Role of computer tomography and endoscopic ultrasonography in assessing portal and superior mesenteric vessels invasion in cephalo-pancreatic adenocarcinoma

Ann. Ital. Chir., 2017 88, 4: 336-341
pii: S0003469X17027129

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AIM: *The aim of this study is to evaluate the information given by contrast-enhanced computer tomography (CECT) and ultrasound endoscopy (EUS) regarding vascular involvement of cephalo-pancreatic cancer, data compared with intraoperative findings.*
MATERIAL AND METHODS: *We choose to analyze the most often interested vessels by tumor development, such as superior mesenteric artery (SMA), superior mesenteric vein (SMV) and portal vein (PV). The patients included in the study (n=425) had a cephalo-pancreatic tumor diagnosed in our Institute and a positive histology for pancreatic adenocarcinoma. The exclusion criteria were: tumors in sites other than the head of the pancreas (including metastases); tumor involvement of common hepatic artery, celiac trunk, inferior cava vein or aorta; CECT or EUS diagnosis performed in another center; and a delay of more than 35 days between the diagnostic imaging and surgery.*
RESULTS: *In diagnosing SMA invasion CECT had an accuracy of 84,92% and EUS had an accuracy of 87,39%. In diagnosing PV and SMV involvement, CECT had an accuracy of 84,83% and EUS had an accuracy of 92,17%. The accuracy of the two combined examinations in diagnosing vascular invasion was 93%.*
CONCLUSONS: *Both types of examination have showed good accuracies in diagnosing vascular invasion separately. A combination of the two may be used when the CECT result is uncertain as it provides a higher chance of a correct diagnosis.*

KEY WORDS: Pancreatic cancer, Resectability criteria, Vascular invasion

Introduction

Pancreatic cancer is the fourth most common cause of cancer related mortality worldwide with an incidence rate of 10/100,000 persons per year equaling that of its mortality rate [1-4].

The 5-year relative survival rate has remained a constant 4% over the last 50 years [5] with a 5-year overall survival rate after curative resection of 20%. Early diagnosis although crucial is difficult to perform due to the fact that there are hardly any symptoms few and non-specific.

Only 20% of patients who are diagnosed with pancreatic cancer are candidates for curative resection and just

Pervenuto in Redazioone Aprile 2017. Accettato per la pubblicazione Maggio 2017
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7% of pancreatic cancers are localized in the organ, without regional spread or metastases [6].
Moreover 30% of the patients who undergo surgery develop early recurrence as a result of misdiagnosed aggressive tumors and die within one year after surgery [7]. Improvement of the long-term survival can be achieved with advances in cancer therapy and a better patient selection for radical surgery.

Objective

The goal of this study was to evaluate the accuracy of our Institute's contrast enhanced computed tomography (CECT) and endoscopic ultrasound (EUS) examinations in detecting vascular tumor invasion (portal vein – PV –, superior mesenteric vein – SMV – and superior mesenteric artery – SMA) in patients with cephalo-pancreatic cancer.

Material and Methods

Between March 2009 and December 2014 there were 1125 cases of pancreatic cancer admitted to the Surgery Clinic of the Regional Gastoenterology and Hepatology Institute of Cluj-Napoca, Romania. The patients included in the study had a tumor of the head of the pancreas diagnosed by either CECT or EUS in our Institute and a positive histology for pancreatic adenocarcinoma. The exclusion criteria were: tumors in sites other than the head of the pancreas (including metastases); tumor invasion of the celiac trunk, common hepatic artery, inferior cava vein or aorta; CECT or EUS diagnosis performed in other center prior to admission; and a delay of more than 35 days between the diagnostic imaging and surgery. The final study population comprised 425 subjects of which 239 (56.2%) were males and 186 (43.8%) were females, all of them between 28 and 88. One hundred fifty nine (37.4%) patients underwent cephalic pancreatico-duodenectomy, while 266 (62.6%) patients had palliative surgery (Table I). Palliative surgery was indicate if the patients were symptomatic (jaundice or vomiting) and they had metastases or local vascular invasion (arterial involvement or more than 180 of venous circumference invaded), founded at the time of operation. As palliative surgery we performed billiary and digestive by-pass of the tumor, such as colangio-jejunal or cholangio-duodenal anastomosis and gastro-jejunal anastomosis. The patients have been assigned to three groups: A, B and C. Group A included patients that had received a CECT diagnosis (N=358), group B included patients that had received a EUS evaluation (N=230) and group C included patients that had received a diagnosis after undergoing first CECT and then EUS examination (N=161).

Table I - *Demographic data and outcome of the patients.*

	N	%
GENDER		
Male	239	56,2
Female	186	43,8
AGE		
Min	22	
Max	82	
Mean	63,7	
OUTCOME		
Improved	345	81,2
Stationary	51	12
Deteriorated	3	0,7
Deceased	26	6,1
TYPE OF OPERATION		
PD	159	37,4
Palliative	266	62,6

The CECT examinations were performed with the Siemens Sensation 16 (Siemens Medical Solutions, Forchheim, Germany). Patients were examined after at least 2 hours of fasting for solids. They were administered 500 ml of oral hypodense contrast (water) 15 minutes prior to the examination and another 100 ml during the examination. An iodine-based hypo-osmolar contrast medium (Ioversol, Optiray^{TM}350, Covidien, Germany) was administered intravenously (120 ml) through a peripheral vein by an automated serynge (OptiVantage^{TM} DH, Malinckrodt) with a flow of 3 ml/s followed by 35 ml of saline. The collected data consisted of tumor size (in milimeters), site of the pancreatic mass, Wirsung and biliary duct dilations, and signs of extrapancreatic invasion (lymph nodes, blood vessels, neighboruring organs, metastases). Out of these we chose to focus on blood vessel invasion. Venous invasion was defined by the following criteria: tangential contact or less than 180° of the vessel circumference invaded on a length bigger than 2 cm, invasion of less than 180° of the vessel circumference on a length lesser than 2 cm with parietal irregularities (the teardrop sign), envelopment of the vein by the tumor with possible stenosis or occlusion, and venous thrombosis. Arterial invasion was declared if the circumferential invasion surpassed 180° or in the case of total envelopment, luminal irregularrities, stenosis or occlusion.
For the EUS diagnosis the patients were examined using the GF-UCT140-AL5 linear echo-endoscope (Olympus, Japan) in conjunction with the Aloka Alpha 5 ultrasound unit (Aloka, Japan) under light sedation with intravenous midazolam. All the EUS were performed by two examiners (A.S. and R.S.-I.). The examination gathered the following data: pancreatic mass size (maximum diameter), site of the pancreatic mass, pancreatic morphology, vascularization of focal pancreatic lesions (using power Doppler), invasion of the great vessels, surrounding

lymph node appearance, and left hepatic lobe structure. The typical appearances of vascular invasion are loss of the sonic interface between the echogenic vessel and the parenchyma, a tumor within the vessel lumen, or the presence of collateral circulation.

The role of exploratory surgery was to determine the resectability of the tumor. We considered unresectable tumors to have hepatic or peritoneal metastases discovered during surgery, involvement of a major artery or venous involvement for more than 180 with venous thrombosis. Tangent invasions of PV or SMV underwent wedge resection whereas the more severe invasions underwent segmental venous resection with termino-terminal suture reconstruction. None of the subjects needed a graft interposition for the venous reconstruction. The assessment of vascular invasion was done through dissection. The intraoperative findings regarding the involvement of the SMA, SMV and PV were later compared with the CECT and EUS diagnoses.

Data collection was done using Microsoft Excel (http://products.office.com/ro-ro/Excel). R v3.1.2 (http://www.r-project.org/about.html) was used for the statistical analysis. The Chi squared test, confidence intervals, and probabilities were computed in order to compare the statistical accuracy of the CECT and EUS versus the intraoperative findings.

Results

Venous Invasion

In group A the data provided by CECT concerning SMV and PV invasion was in agreement with intraoperative findings in 304 cases (84,92%). Ninety-six (88,07%) of the 109 cases reported to have invasion on the CECT were confirmed intraoperatively and of the 249 cases which were diagnosed with non-invasive tumors 208 (83,53%) were found to have non-invasive tumors intraoperatively.

For group B EUS diagnoses were concordant with intraoperative findings in 201 (87,39%) cases. Sixty-three (90%) of the 70 cases diagnosed with venous invasion were confirmed intraoperatively and of the 160 cases diagnosed with non-invasive tumors 138 (86,25%) were found to have non-invasive tumors intraoperatively.

Table II shows the specificity, sensibility, positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of the two imaging examinations in assessing tumor invasion in the SMV and PV.

Arterial Invasion

The CECT findings regarding SMA invasion coincided with the intraoperative findings in 302 (84.83%) group A subjects. Sixty-two (81,58%) of the 75 cases diagnosed with invasion were confirmed during surgery, and 240 (85.71%) of the 280 cases diagnosed with non-invasive tumors were found to have non-invasive tumors intraoperatively.

The data rendered by EUS was in agreement with intraoperative findings in 212 (92.17%) group B subjects. Of these 63 (86,3%) out of 73 cases had an intraoperatively confirmed arterial invasion and 149 (94,90%) out of 157 were found to have non-invasive tumors intraoperatively.

Table III shows the specificity, sensibility, PPV, NPV and diagnostic accuracy of the two imaging examinations in assessing tumor invasion in the superior mesenteric artery.

Arterial and Venous Invasion

In group C (N=161), 27 (16,77%) cases had a preoperative vascular invasion diagnosis which was confirmed intraoperatively and 112 (69,57%) cases had preoperative diagnoses that excluded vascular invasion, once again found to have non-invasive tumors intraoperatively. There was a 93% (95% CI, 88-98%; p=0,05) probability that the invasion diagnosis set by both examinations coincided with the intraoperative findings and a 97% (95%CI, 96-99; p=0,02) probability that a diagnosis of non-invasiveness set by the two examinations would be found to be non-invasive intraoperatively. In 22 (13,66%) cases the CECT and EUS results did not coincide. Four subjects had an invasive diagnosis on the CECT and a non-invasive diagnosis on the EUS, 2 of

Table II - *Comparison between CECT and EUS in venous invasion diagnosing*

	CECT		EUS	
Parameter	**Value**	**CI 95%***	**Value**	**CI 95%***
Accuracy	0.849	0.809 -0,878	0,874	0,824-0,906
Sensibility	0.701	0.648-0,739	0,741	0.674-0.785
Specificity	0.941	0.909-0.965	0,952	0,912-0,977
PPV	0.881	0,815-0,929	0,900	0.818-0.953
NPV	0.835	0.807-0.865	0,863	0.827-0.886

*95% confidence interval

Table III - *Comparision between CECT and EUS in arterial invasion diagnosing*

	CECT		EUS	
Parameter	**Value**	**CI 95%***	**Value**	**CI 95%***
Accuracy	0.848	0.809-0.878	0.922	0.875-0.953
Sensibility	0.608	0.539-0.660	0.887	0.812-0.938
Specificity	0,945	0,917-0,966	0,937	0.904-0.960
PPV	0.816	0.724-0,886	0.863	0.790-0.912
NPV	0.857	0.832-0.876	0.949	0.915-0.972

*95% confidence interval

which were diagnosed with vascular invasions intraoperatively. The CECT findings diagnosed non-invasive tumors in 18 subjects, data that contradicted the EUS findings for these patients. The probability of issuing a CECT diagnosis that predicted the intraoperative findings was 28% (95% CI, 17-39; p=0.11) in this case. The resecability in our study population was 37,41%.

Discussion

For the moment a preoperative examination with 100% sensibility and specificity in diagnosing vascular invasion in pancreatic adenocarcinomas has yet to be discovered. The slight decrease of these parameters in reality can be caused by the fact that peritumoral inflammation sometimes simulates true tumor infiltration. Up to 50% of tumors thought to have vascular invasion intraoperatively have been subsequently found to only possess inflammatory adhesions to the portal vein after the histologic examination [7-9]. The management of a suspicious tumor adhesion to a vessel is one of the most important challenges when envisioning a pancreatico-duodenectomy. In such cases the surgeon is confronted with three options: either to leave the tumor attached to the vessel resulting in a grossly positive resection margin, to try separating the tumor from the vessel with a considerable hemorrhage risk, or to perform a partial or segmental resection of the portion of invaded vessel with consecutive reconstruction.

The unresectability criteria for pancreatic adenocarcinomas in our Institute are the presence of metastasis, the arterial invasion and the venous invasion with venous thrombosis. A large body of evidence has showed that even though the pancreatico-duodenectomy is a technical possibility it does not influence postoperative survival in these cases. This is because artery involvement implies a more aggressive tumor biology [10-12]. In a systematic review, Mollberg [13] analyzed the role of arterial resection in pancreatectomies performed on borderline resectable tumors. The perioperative morbidity rates were found to be between 17% and 100% (median: 53.6%) for patients with arterial resection the median mortality rate being of 12% (range: 0%-45.5%) compared to 2.6% for standard pancreatic resections. This shows that arterial resection pancreatectomies increase mortality risks fivefold without significant advantages in terms of long-term survival.

Venous invasion as opposed to its arterial counterpart can be operated. Surgical techniques differ according to the severity of the invasion. Tangent invasions can benefit from wedge resection whereas larger invasions can be treated with vascular resection followed by termino-terminal vascular anastomosis. This study did not include cases in which a graft was used in the venous reconstruction.

CECT is considered to be the golden standard in diagnosing pancreatic tumors. A meta analysis published in 2012 by Zhang [14] that contains 8 studies and 296 patients reports a pooled sensitivity of computed tomography (CT) in diagnosing vascular involvement of 71% (95% CI, 64-78) and a pooled specificity of 92% (95% CI, 89-95). The overall accuracy of this type of resectability assessment varies from 70% to 100% [15-17]. CT is the most frequently used examination for the preoperative staging of pancreatic tumors in our Institute. It has a diagnostic accuracy of 85% (95%CI, 81-88%) for all three main vessels (superior mesenteric artery and vein, portal vein). The specificity is slightly higher in diagnosing vein invasion while the sensibility is relatively the same for artery and vein invasion. Some of the particularities of this study are the fact that CECT was used instead of multiple detector CT (MDCT) and that there were more than one designated examiner. The examiner's experience is a determining factor in establishing a correct tumor staging. For example, Pawlik [11] analyzed 203 patients with CT examinations that revealed locally advanced/unresectable disease (35%), metastatic disease (18%), and locally advanced disease with metastasis (1%). After an accurate review of the imaging, the clinical stage of the disease was modified in 19% of patients. Forty-eight out of the 203 (24%) patients benefited from a subsequent change in the management of their pathology.

EUS has been shown to be accurate in diagnosing and staging pancreatic cancer [18], with the help of fine needle aspiration, with 96.6% sensitivity, 99.0% specificity, 96.2% NPV, and 99.1% PPV [19]. Sugiyama, et al [20] reported that EUS is more accurate than CT, US, and angiography in the detection of portal vein invasion; similar findings were shown in other series [21,22]. Arterial invasion is assessed with more difficulty by EUS [22-24]. Globally, the sensitivity is 50%-100%[25-27], the specificity 58%-100% [27,28], the PPV 28%-100% [28,29], and the NPV 18%-93% [18,23]. Giovannini [30] reports a 55-94% sensibility and a 85-100% specificity of EUS in assessing vascular involvement.

In our Institute the tendency is to demand a EUS when there are doubts concerning the presence of a pancreatic tumor or when the vascular involvement is uncertain. The diagnostic accuracy of this examination is 87% (95% CI 82-90) for veins and 92% (95% CI, 88-95) for the SMA. Its sensibility is higher for artery invasion while the specificity is roughly the same for both types of vessel invasion. For the current study, the EUS was performed with a linear endoscope mostly by the same examiner (A.S.).

What we have gathered from studying group C is that combining CECT with EUS (in this order) will significantly elevate the statistical accuracy of a diagnosis when the two results coincide raising the probability of a correct diagnosis to 93-97%. This finding is significant for patient management because it lowers the need for exploratory laparotomies and augments resecability.

Conclusion

Performing an EUS in the preoperative assessment is a legitimate action when there is suspicion of pancreatic cancer. As for vascular invasion detection, EUS has shown good accuracy. This accuracy augments if the combination between CECT and EUS is used.

Institutional review board statement: The Ethics Committee of Regional Institute of Gastroenterology and Hepatology Cluj, Romania, approved this study.

Informed consent statement: Informed consent was acquired from all the enrolled patients.

Conflict-of-interest statement: The authors declare that no conflicts of interest exist.

Riassunto

Con questo studio ci siamo proposti di valutare le informazioni fornite dalla angio-TAC (CECT)e dalla ecografia endoscopica (EUS) circa il coinvolgimento vascolare da parte del cancro pancreatico in sede cefalica, paragonando i risultati con i rilievi intraoperatori.

L'indagine è stata rivolta nei confronti dei vasi più frequentemente coinvolti dallo sviluppo neoplastico, come l'arteria mesenterica superiore (SMA), la vena mesenterica superiore (SMV) e la vena porta (PV). I 425 pazienti considerati in questo studio erano affetti da cancro cefalo-pancreatico diagnosticati nel nostro Istituo con conferma istologica di adrnocarcinoma del pancreas. I criteri di esclusione sono stati la localizzazione del cancro in sedi diverse dall'area cefalica (comprese le metastasi), l'infiltrazione dell'arteria epatica comune, del tronco celiaco, della vena cava inferiore o dell'aorta; i pazienti diagnosticati con CECT o EUS in altra sede, e quelli con intervallo superiore a 35 giorni tra la diagnostica per immagini e l'intervento chirurgico.

È risultato che nel diagnosticare l'invasione della SMA la CECT ha una accuratezza del 84,92% e la EUS una accuratezza del 97,39%. Nel diagnostica l'invasione della Vena Porta e della Vena Mesenterica Superiore la CECT ha una accuratezza del 84,83% e la EUS una accuratezza del 92,17%. La combinazione di entrambe le metodiche raggiunge una accuratezza del 93% nel diagnosticare l'invasione vascolare.

Possiamo concludere che entrambe le metodiche, usate separatamente, dimostrano entrambe una buona accuratezza nel diagnosticare una invasione vascolare, ma la combinazione dei due metodi può essere adottata quando la CETC fornisce dati incerti perché offre una maggiore possibilità di una diagnosi corretta.

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