Preoperative assessment of pancreatic adenocarcinoma. Value of CT imaging

Inga Zaboriene[1], Tomas Tvarijonas[2], Gertruda Rudaityte[2] , Saulius Lukosevicius[1], Giedrius Barauskas[3], Kristina Zviniene[1]

[1]Department of Radiology, Lithuanian University of Health Sciences Kaunas, Lithuania.
[2]Lithuanian University of Health Sciences Kaunas, Lithuania.
[3]Lithuanian University of Health Sciences, Medical Academy. Department of Surgery.

ABSTRACT

Background and aim

Pancreatic adenocarcinoma is one of the most malignant cancer forms. It is fourth most common cause of cancer death worldwide, with a poor overall 5-year survival rate of only 4 %. The treatment depends upon tumour resectability at presentation. Therefore, radiological imaging is crucial in the management of the disease. In this study we evaluated the role of computed tomography in diagnosing pancreatic adenocarcinoma and CT diagnostic values in determining resectability of pancreatic.

Matherial and methods. This was a prospective randomized clinical study, in which 79 patients with resectable pancreatic cancer were studied. All the pacients underwent MDCT scan. In all CT images we analyzed location of pancreatic tumor, invasion into adjacent structures, vascular involvement and distant metastases. The results of preoperative CT staging were compared to the postoperative histological data. In order to determine diagnostic values of CT, we calculated the sensitivity, specificity, positive and negative prognostic values (PPV, NPV) as well, as accuracy. All calculations were performed using SPSS for Windows 25.0 software and Microsoft Excel 16.

Results. There was no difference in evaluating T stage pre and postoperatively X2 =74,452, df 15, p<0,001 and no statistically difference in evaluating tumor N stage pre- and postoperatively X2=8,978, df=1, p=0,003.

Overall CT sensitivity for tumor T stage was 73 %, specificity 85 %, PPV and NPV 67.1 % and 88.2 % respectively, accuracy 81.4 %. CT diagnostic values for N stage: sensitivity 75 %, specificity 59.3 %, PPV 78%, NPV 55.2% and accuracy 69.6%.

Conclusions

- CT is specific and accurate imaging modality in T stage of pancreatic adenocarcinoma.
- CT is quite sensitive, but non specific in N stage of pancreatic adenocarcinoma.

Keywords: pancreatic adenocarcinoma, resectability, CT values

INTRODUCTION

Pancreatic adenocarcinoma is one of the most malignant cancer forms. It is fourth most common cause of cancer death worldwide. Globally, about 338000 people had pancreatic cancer in 2012, making it the 11th most common cancer. The highest incidence and mortality rates of pancreatic cancer is found in developed countries. Prognosis of this cancer remains bad – 5 year survival rate is less than 5 percent. The incidence and mortality of pancreatic cancer worldwide correlated with increasing age and was slightly more common in men than in women [1,3]. Pancreatic cancer is diagnosed late in the natural history of the disease, given the few early indicators of illness, and the lack of screening tests for this disease [2]. In fact, 40% of the pancreatic cancer cases are diagnosed in late stages, when the disease has already spread far from the primary cancerous process, where as another 40% of the patients are diagnosed with locally advanced pancreatic cancer.

Early and precise diagnostics and grading are very important for further treatment and prognosis of patients. When the lesion of the pancreas is suspected, the first line diagnostic modality is computed tomography (CT). If any uncertainties occur, the following test after CT is usually magnetic resonance imaging (MRI) [2-4]. Lately, MDCT (multidetector computed tomography) became golden standard for preoperative evaluation and grading, as well as, treatment choice and observation of the pancreatic adenocarcinoma. However, when using CT as a diagnostic test, approximately 11% of the ductal adenocarcinoma‘s are missed, because density of parenchyma of the pancreas and cancerous tissue are the

same, as well as differential diagnosis between paraduodenal space pancreatitis and pancreatic cancer is complicated [4]. Moreover, it is complicated to diagnose pancreatic adenocarcinoma in the presence of chronic focal pancreatitis. In the cases mentioned above, computed tomography with perfussion and MRI are diagnostic tests of the first choice.

In this study we evaluated the role of computed tomography in diagnosing pancreatic adenocarcinoma and CT diagnostic values in determining pancreatic adenocarcinoma‘s resectability.

AIM

To evaluate CT diagnostic values in determining pancreatic adenocarcinoma‘s resectability.

OBJECTIVES

1. To identify CT diagnostic values in determining the local extention of pancreatic adenocarcinoma (T stage).
2. To calculate CT diagnostic values in determining the spreading of pancreatic adenocarcinoma into regional lymph nodes (N stage).

MATHERIALS AND METHODS

This was a prospective randomized clinical study, in which 79 patients with resectable pancreatic cancer were studied.

Inclusion criteria:
1. Older than 18 year old patients with radiologically confirmed pancreatic adenocarcinoma

Exclusion criteria:
1. Patients with renal disfunction;
2. Sensitivity to iodine.
3. Refusal to participate in the study.
4. Distant metastases.

Patients were treated in clinics of surgery and gastroenterology between June year 2015 – september Year 2018. (TLK-10, C25.9). All the patients gave their written informed consent, and The Kaunas Regional Biomedical Research Ethics Committee approved the study (protocol Nr. BE-10-5, 2015 05 13).

All the patients underwent MDCT scan, using „GE light Speed Pro“ 64 CT scanner.

Native and contrast-enhanced scans were performed with non-ionic intravenous contrast, injecting 100ml of contrast media at high speed (3,5 ml/s). Arterial and venous phases were performed in 30s and 70s after the start of contrast injection, following the standard protocol, used for pancreatic imaging. If any focal liver lesions were found – late phase (after 10 minutes) was performed in order to identify the nature of those focal lesions. Axial CT images and MPR reconstructions were analysed.

According to NCCN (National Comprehensive Cancer Network) guidelines, it is recommended to use CT or MRI for grading. Decision, whether to use CT or MRI should depend on possibilities, accessibility, local practice and local experience.

Preoperative assessment is essential in identifying resectable disease, borderline resectable disease, locally advanced disease (unresectable without distant metastases) and metastatic disease (unresectable).

In our study we used NCCN guidelines version 3.2017 (pancreatic adenocarcinoma), for evaluation of resectability of the pancreatic tumor (Table 1).

During analysis of the CT images, we evaluated

Table 1. NCCN Guidelines Version 3.2017 pancreatic adenocarcinoma [15].

Arterial Evaluation		
SMA Contact	**Present**	**Absent**
Degree of solid soft-tissue contact	≤180	>180
Degree of increased hazy attenuation/stranding contact	≤180	>180
Focal vessel narrowing or contour irregularity	Present	Absent
Extension to first SMA branch	Present	Absent
Celiac Axis Contact	**Present**	**Absent**
Degree of solid soft-tissue contact	≤180	>180
Degree of increased hazy attenuation/stranding contact	≤180	>180
Focal vessel narrowing or contour irregularity	Present	Absent

CHA Contact	Present	Absent
Degree of solid soft-tissue contact	≤180	>180
Degree of increased hazy attenuation / stranding contact	≤180	>180
Focal vessel narrowing or contour irregularity	Present	Absent
Extension to celiac axis	Present	Absent
Extension to bifurcation of right/left hepatic artery	Present	Absent

Venous Evaluation

MPV Contact	Present	Absent	Complete occlusion
Degree of solid soft-tissue contact	≤180	>180	
Degree of increased hazy attenuation / stranding contact	≤180	>180	
Focal vessel narrowing or contour irregularity (tethering or tear drop)	Present	Absent	

SMV Contact	Present	Absent	Complete occlusion
Degree of solid soft-tissue contact	≤180	>180	
Degree of increased hazy attenuation / stranding contact	≤180	>180	
Focal vessel narrowing or contour irregularity (tethering or tear drop)	Present	Absent	
Extension	Present	Absent	

Arterial Evaluation

SMA Contact	Present	Absent
Degree of solid soft-tissue contact	≤180	>180
Degree of increased hazy attenuation/stranding contact	≤180	>180
Focal vessel narrowing or contour irregularity	Present	Absent
Extension to first SMA branch	Present	Absent

Celiac Axis Contact	Present	Absent
Degree of solid soft-tissue contact	≤180	>180
Degree of increased hazy attenuation/stranding contact	≤180	>180
Focal vessel narrowing or contour irregularity	Present	Absent

CHA Contact	Present	Absent
Degree of solid soft-tissue contact	≤180	>180
Degree of increased hazy attenuation/stranding contact	≤180	>180
Focal vessel narrowing or contour irregularity	Present	Absent
Extension to celiac axis	Present	Absent
Extension to bifurcation of right/left hepatic artery	Present	Absent

Venous Evaluation

MPV Contact	Present	Absent	Complete occlusion
Degree of solid soft-tissue contact	≤180	>180	
Degree of increased hazy attenuation/ stranding contact	≤180	>180	
Focal vessel narrowing or contour irregularity (tethering or tear drop)	Present	Absent	

SMV Contact	**Present**	**Absent**	**Complete occlusion**
Degree of solid soft-tissue contact	≤180	>180	
Degree of increased hazy attenuation/ stranding contact	≤180	>180	
Focal vessel narrowing or contour irregularity(tethering or tear drop)	Present	Absent	
Extension	Present	Absent	
Other			
Thrombus within vein (tumor, bland)	**Present:** MPV SMV SplenicVein	**Absent**	
Venous collaterals	**Present:** Around pancreatic head Porta hepatis Root of the mesentery Left upper quadrant	**Absent**	

* SMA – superior mesenteric artery, CHA – common hepatic artery, MPV – main portal vein, SMV – superior mesenteric vein

homogenicity of the tumor, density of cancerous tissue in comparison with normal pancreatic parenchyma, relation with the surrounding vessels. For extrapancreatic evaluation we looked for distant liver metastases, peritoneal and omental nodules, ascites, suspicious lymph nodes and other extrapancreatic disease (invasion of adjacent structures).

After preoperative radiological evaluation, all the patients underwent radical surgical treatment with further histopathological examination of obtained specimens. The results of CT scans were compared with results of surgery and histopathological examination. Pathologic TNM staging system of pancreatic cancer in the 8th edition of UICC cancer staging system is presented in Table 2.

Table 2 . TNM staging of pancreatic cancer (7th edition of the AJCC (The American Joint Committee on Cancer) stage system) [16].

CLINICAL	STAGE CATEGORY DEFINITIONS	PATHOLOGIC
Extent of disease before any treatment		Extent of disease through completion of definitive surgery
y clinical – staging completed after neoadjuvant therapy but before subsequent surgery		y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery

	PRIMARY TUMOR (T)	
Tx	Primary tumor cannot be assessed	Tx
T0	No evidence of primary tumor	T0
Tis	Carcinoma in situ*	Tis
T1	Tumor limited to the pancreas, 2cm or less in greatest dimension	T1
T2	Tumor limited to the pancreas, more than 2 cm in greatest dimension	T2
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery	T3
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)	T4
	**Note: This also includes the "PanInIII" classification*	
	REGIONAL LYMPH NODES (N)	
Nx	Regional lymph nodes cannot be assessed	Nx
N0	No regional lymph node metastasis	N0
N1	Regional lymph node metastasis	N1
M0	DISTANT METASTASIS (M)	M1
	No distant metastasis (no pathologic M0; use clinical M to complete stage group	
M1	Distant metastasis	

ANATOMIC STAGE & PROGNOSTIC GROUPS			
		CLINICAL	
GROUP	T	N	M
0	Tis	N0	M0
IA	T1	N0	M0
IB	T2	N0	M0
IIA	T3	N0	M0
IIB	T1	N1	M0
	T2	N1	M0
III	T3	N1	M0
IV	T4	Any N	M0
Stage unknown	Any T	Any N	M1

STATISTICAL ANALYSIS

Quantitative values were presented as mean values and standard deviation. Chi-square test was performed to evaluate correlation between Qualitative values. Statistically significant value was considered when $p < 0,05$. To determine pancreatic adenocarcinoma's local spreading and resectability, we calculated CT prognostic values. We calculated accuracy, the sensitivity, and specificity of this investigation, as well as positive and negative prognostic values. Calculations were performed using formulas [5]:

Accuracy of diagnostic method (percentage) = a + d / a + b + c + d x 100
Sensitivity of diagnostic method (percentage) = a / (a +c) x 100
Specificity of diagnostic method (percentage) = d / (b + d) x 100
Positive predictive value = a / (a + b) x 100
*Negative predictive valu*e (percentage) = d / (c + d) x 100
Where: a – fairly positive cases, b – false positive cases, c – false negative values, d – fairly negative values.

Statistical analysis was performed using IBM SPSS Statistics 25.0 software and Microsoft Excel 16.

RESULTS

79 patients were enrolled in this study: 33 (41.8%) males and 46 (58.2%) females. Patient's age distribution was normal. There was no significant difference between male and female age.
After CT imaging in 82.3 % of all cases, pancreatic adenocarcinoma was diagnosed at stage T3 and T4 disease and only 17.7 % in stage T1 and T2.
After surgery there were 74,7 % T3 and T4 disease and 20,2 % of T1 and T2 disease. There was no difference in evaluating T stage pre and postoperatively X2 =74,452, df 15, p<0,001. More detailed characterstics of radiological and postoperative staging are presented in Table 3.
Based on CT scan results, stage N1 was the most common (63.3% of all the cases, n=50) and stage N0 was found in 36.7% of the cases (n=29). After surgery stage N1 was found in 52 of all cases (65,8 %) and stage N0 in 27 of all cases (34,2%). There was no statistically difference in evaluating tumor N stage pre and postoperatively X2=8,978, df=1, p=0,003
Postoperative histological evaluation revealed adenocarcinomas in 76 cases (96,2%), 1 case was confirmed as metastases and two cases were proven to be pancreatic inflamatory changes (n=3, 3,8 %)

Table 3. Radiological and postoperative characteristics of TNM staging of the study.

	T radiologically					T postoperatively						
	T1	T2	T3	T4	Total	T1	T2	T3	T4	Ca in situ	Non tumor	Total
Frequency	3	11	58	7	79	5	11	54	5	1	3	79
Percent	3.8	13.9	73.4	8.9	100	6.3	13.9	68.4	6.3	1.3	3.8	100

Table 4 shows accuracy, sensitivity, specificity, positive prognostic value (PPV), negative prognostic value (NPV) and accuracy of T and N staging, using MDCT.

Table 4. Sensitivity, specificity, PPV, NPV and accuracy of T and N staging, using MDCT, of our study.

	HISTOLOGICAL STAGING				
T stage	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**	**Accuracy %**
CT T1+T2	62.5	94.4	42.9	93	88.6
CT T3	83.3	48	77.6	57.1	72.2
CT T4	60	94.6	42.9	97.2	92.4
T overall	73	85	67.1	88.2	81.4
N stage	**Sensitivity %**	**Specificity %**	**PPV %**	**NPV %**	**Accuracy %**
CT N0	59.3	75	55.2	78	69.6
CT N1	69.2	48.1	72	44.8	62
N overall	75	59.3	78	55.2	69.6

DISCUSSION

Detection and accurate staging of pancreatic carcinoma is essential for providing optimal therapy for the patients; MDCT is the most commonly used imaging modality for diagnosing and staging pancreatic adenocarcinoma. It allows pancreatic imaging with a very high spatial and temporal resolution within a short breath-hold and is still considered the gold standard for evaluation of pancretic solid tumors [6]. A complete and accurate assesment of the primary tumor, it's relationship with adjacent vascular structures and distant metastatic disease is required for accurate characterization of disease as resectable, borderline resectable or unresectable. The

resection criteria include: no invasion into major arteries; short segment of SMV (superior mesenteric vein) and portal vein involvement (in order to allow venous reconstruction) and absence of distant metastases.

The overall sensitivity of CT in the detection of pancreatic adenocarcinoma according to the literature has improved over the recent years, ranging between 75 and 100 %, with specificity of 70-100 % [7-9,11]. CT is considered to be the most reliable technique for evaluating unresectable tumor, with reported sensitivity and specificity of 79-94 % and 82-89 % respectively [10,11].

According to our study results, CT sensitivity of determining T1/T2 stage tumors was quite low - 62.5 %; specificity 94.4 %, positive predictive value 42.9 % (TPV) and negative predictive value 93 % (NPV). But the sample of T1/T2 groups is very small, so the results should be interpreted with caution.

T3 tumors were detected in 68.4% of all cases. CT sensitivity and specificity for T3 were 83.3% and 48% respectively and TPV and NPV were 77.6% and 57.1% respectively. Figure 1 demonstrates CT image of T2 disease.

T4 stage was detected in 6.3% of cases. CT sensitivity and specificity in T4 disease were 60% and 94.6% respectively and TPV and NPV - 42.9% and 97.2% respectively. These results should be interpreted with caution as well due to a small sample size. Figure 2 demonstrates an example of T4 disease.

Figure 1. CT images of T2 disease Our case of T3 stage disease; contrast enhanced CT image, axial plane, venous phase; hypodense mass in the head of the pancreas abutting the superior mesenteric vein (arrow); no narrowing of the vessel is seen.

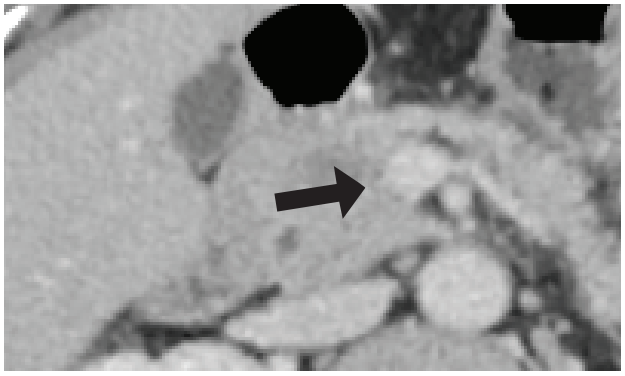


Figure 2. CT images of unresectable T4 stage disease. The patient with pancreatic head adenocarcinoma with duodenal obstruction and dilatation of the stomach a) axial contrast enhanced CT image, arterial phase; an illdefined hypodense mass in the head of the pancreas (arrow) with circumferential surrounding of SMA b) portal venous phase of the same patient shows involvement of SMV (arrow).

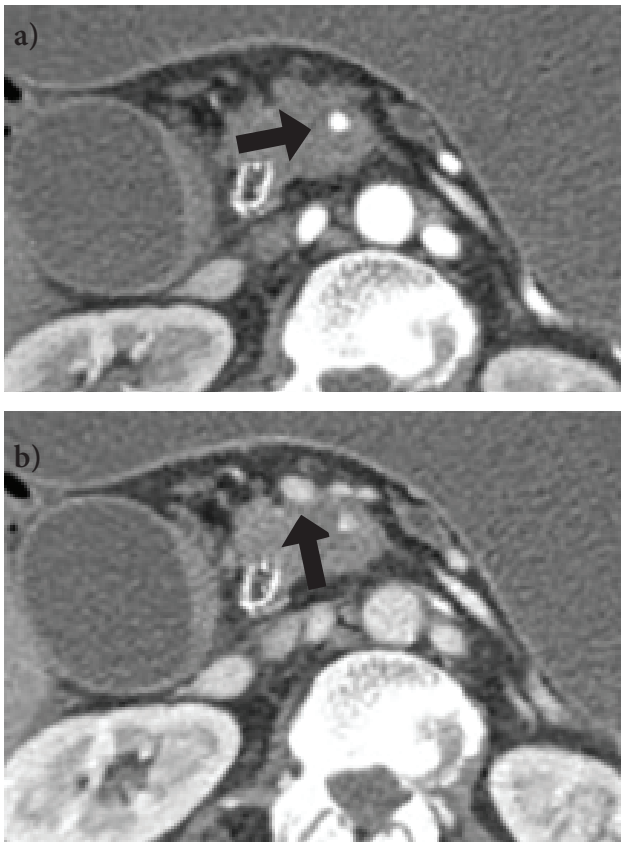
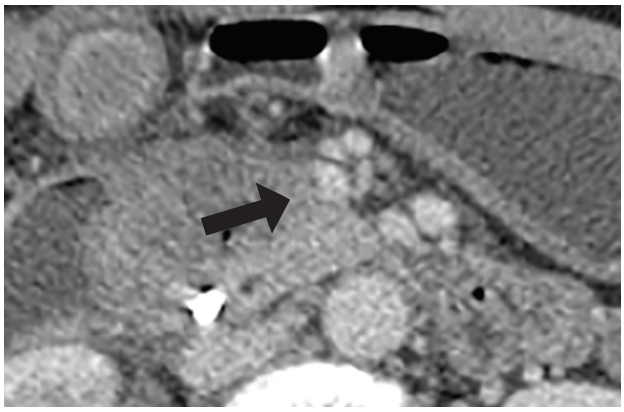


Figure 3. CT image of T4 stage disease with „tear drop deformity" of SMV. Axial contrast enhanced CT image; venous phase; a hypodense mass in the head of the pancreas involving SMV with teardrop deformity (arrow).



We also evaluated overall CT values for N staging of panreatic adenocarcinoma: 69.6% sensitivity and specificity was 75% and 59.3% respectively, TPV and NPV 78% and 55.2% respectively.
According to different authors, CT accuracy of N staging varies from 44 to 75 % and is not very accurate [11, 12]. In our study sensitivity of N staging based on CT scans is not very high, as well as accuracy and specificity. Although, we had cases when no pathological lymph nodes were visible on CT scans (CT N0 disease), however histological study revealed stage N1 disease. But in general, preoperative detection of peritumoral lymph nodes was estimated as not essential for assessing the resectability of pancreatic adenocarcinoma, because these lymph nodes are resected together with the primary tumor;
In conclusion, contrast enhanced CT is the primary imaging modality for the detection and staging of pancreatic adenocarcinoma; and our study results of preoperative assessment of pancreatic cancer T and N staging are very similar to those reported in the literature.
In the assesment of vessel invasion, the „teardrop vein sign" is a diagnostic sign of unresectable cancer [13, 14]. So, in our study we considered this sign as sign of unresectable disease (Figure 3).

CONCLUSIONS

• CT is specific and accurate imaging modality in T stage of pancreatic adenocarcinoma.
• CT is quite sensitive, but non specific in N stage of pancreatic adenocarcinoma.

REFERENCES

1. Evans db, george B, Tsai S. Non metastatic pancreatic cancer: resectable, borderline resectable, and locally advanced-definitions of increasing importance for the optimal delivery of multimodality therapy. Ann SurgOncol. 2015;22 (11):3409-13

2. Lu DS, Reber HA, Krasny RM, Kadell BM, Sayre J. Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancretaic –phase, thin section helical CT. AJR Am J Roentgenol. 1997;168(6):1439-43.

3. Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J. Preoperative / neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PloS Med. 2010;7(4):e1000267

4. Ishikawa O, Ohigashi H, Imaoka S, Furukawa H, Sasaki Y, Fujita M, et al. Preoperative indications for extended pancreatectomy for locally advanced pancreas cancer involving the portal vein. Ann Surg. 1992:215 (3): 231-6,

5. https://onlinecourses.science.psu.edu/stat507/node/71/

6. Katz MH, Marsh R, Herman JM, SHI Q, Collison E, Venook AP, et al. Borderline resectable pancreatic cancer: need for standartization and methods for optimal clinical trial design. Ann Surg Oncol. 2013;20(8):2787-95.

7. Bronstein YL, Loyer EM, Kaur H et al (2004) detection of small pancreatic tumors with multiphasic helical CT. AJR Am J Roentgenol 182:619-623

8. De Witt J, Devereaux B, Chriswell M et al (2004) Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med 141:753-763.

9. Fusari M, Maurea S, Imriaco M et al (2010 Comparison between multislice CT and MR imaging in the diagnostic evaluation of patients with pancreatic masses. Radiol Med 115:453-466)

10. Karmazanovsky G, fedorov V, Kubyshkin V et al (2005) Pancretaic head cancer: accuracy of CT in determination of resectability. Abdom Imaging 30:488-500

11. Mirko D'Onofrio, Paola Capelli, Paolo Pederzoli (2015) Imaging and pathology of Pancreatic Neoplasms; a pictorial Atlas.

12. Roche CJ, hughes ml, garvey CJ et all (2003) CT and pathologic assessment of prospective nodal staging in patients with ductal adenocarcinoma of the head of the pancreas. AJR Am J Roentgenol 180:1311-1323

13. Hough TJ, Raptopoulos V Siewert B, Matthews JB (1999) teardrop superior mesenteric vein: CT sign for unresectable carcinoma of the pancreas. AJR Am J Roentgenol 173:1509-1512

14. Fuhrman GM, Leach SD, Staley CA et al (1996)Rationale for en bloc vein resection in the treatment of pancreatic adenocarcinoma adherent to the superior mesenteric-portal vein confluence. Pancreatic tumor study group. Ann surg 223:154-162.

15. https://www.nccn.org/professionals/physician_gls/default.aspx

16. NCCN Clinical Practice Guidelines in Oncology (NCCN GUIdelines). Pancreatic Adenocarcinoma. Version 3.2017 – September 11, 2017; NCCN.org