NOWOTWORY Journal of Oncology • 2004 • volume 54
Number 6 • 555–559

The clinical value of imaging modalities (USG, EUS, CT) in pancreatic carcinoma staging

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Aim. to assess the clinical value of endoscopic ultrasound in the staging of pancreatic carcinoma as opposed to ultrasonography and CT
Material and methods. We evaluated 42 patients (18 F, 24 M; mean age 61.3) operated on for pancreatic carcinoma between 1991 and 2002 analysing accuracy, sensitivity, specificity, PPV and NPV of routine and doppler ultrasonography, CT and EUS.
Results. EUS showed the best accuracy in local tumour staging – 93.1%, vascular infiltration – 90%, and lymph node assessment – 87.5%. Routine USG was the least accurate: 82.5%, 67.5% and 72.5%, respectively. The accuracy of both CT and doppler USG were similar: 88.1%, 82.5% and 80.0%.
Conclusions. EUS is the most accurate method available to stage pancreatic cancer in the pre-operative period. However, the advantage of EUS as opposed to CT and USG does not justify its routine use due to the costs, its low availability and invasiveness.

Wartość kliniczna badań obrazowych (USG, EUS, KT) w ocenie zaawansowania raka trzustki

Cel pracy. Ocean wartości klinicznej ultrasonografii endoskopowej w ocenie zaawansowania raka trzustki jako metody konkurencyjnej dla USG i tomografii komputerowej.
Materiał i metody. Badaniu poddano 42 chorych (18 K, 24 M), średni wiek: 61,3) operowanych z powodu raka trzustki w latach 1991–2002. Przeanalizowano trafność diagnostyczną, czułość, swoistość, PPV i NPV USG tradycyjnego, doplerowskiego, KT i EUS.
Wyniki. Najwyższą dokładność w ocenie zaawansowania miejscowego, naciekania naczyń krwionośnych oraz przerzutów do węzłów wykazała EUS – odpowiednio 93,1%, 90%, 87,5%. Najmniejszą trafność wykazało rutynowe badanie USG: odpowiednio 82,5%, 67,5% i 72,5%. Trafność KT i doplerowskiego USG była zbliżona: 88,1%, 82,5% oraz 80,0%.
Wnioski. Najbardziej precyzyjną metodą w przedoperacyjnej ocenie miejscowego zaawansowania raka trzustki jest endoskopowa ultrasonografia. Wydaje się jednak, że z powodu kosztu, małej dostępności i inwazyjności nie może ona zastąpić w rutynowej diagnostyce raka trzustki metod ultrasonograficznych i tomografii komputerowej.

Key words: pancreatic cancer, ultrasound, doppler ultrasound, EUS, computed tomography, accuracy
Słowa kluczowe: rak trzustki, badanie ultrasonograficzne, ultrasonografia doplerowska, EUS, tomografia komputerowa, trafność diagnostyczna

Introduction

Pancreatic cancer is one of the leading causes of death in the USA. Mortality rates place this neoplasm fourth as far as morbidity is concerned [1, 2]. Prognosis is very poor, with the one-year mortality rate exceeding 80% and the overall 5-year survival rates not exceeding 5%. Detection of early pancreatic cancer is of great importance because this type of carcinoma is potentially resectable. However, early detection is extremely difficult due to the scarcity of symptoms.

The choice of treatment in pancreatic cancer depends mostly on correct diagnosis and staging. Accurate diagnosis enables the most appropriate method of surgical and multimodal treatment and avoids unnecessary laparotomy (which in advanced disease does not improve survival nor quality of life and exposes patients to increased suffering at the same time generating high treatment costs).

Endoscopy, computed tomography, MRI and ultrasonography are the most common methods used to today in order to evaluate pancreatic carcinoma. Computed

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tomography, considered to be the "gold standard" in many countries, achieves a 95% accuracy in detecting and staging pancreatic carcinoma. Routine ultrasonographic techniques are slightly less efficient, with an accuracy ranging from 67% to 85% [3-5]. Some authors report that Doppler imaging can improve those results, even up to 95% [3, 6, 7].

EUS is an imaging technique, which combines both endoscopy and ultrasonography, and thus possesses advantages of both modalities (exclusion of acoustic barriers and higher picture resolution). It is thought that EUS is one of the best methods for detecting small, early pancreatic neoplasm [8-10].

The aim of the study was to assess the clinical value of endoscopic ultrasound in detecting and staging pancreatic carcinoma compared to more routine imaging methods.

Material and methods

The study was designed as a retrospective clinical trial involving 42 patients (18 women and 24 men; mean age 61.3; range 37-81 years) operated on for pancreatic tumour (with suspicion of carcinoma) at the 1st Department of General and GI Surgery, Jagiellonian University of Cracow, between January 1991 and December 2002. All subjects gave informed consent.

Using routine color and power Doppler ultrasonography, helical computed tomography and EUS, multiple analyses of diagnostic accuracy, sensitivity, specificity, and positive as well as negative prognostic values (PPV and NPV) were made. The stage of the cancer was consistently classified using WHO TNM classification. Siemens Sonoline AC and Hitachi EUB 555 and 6000. Ultrasonographic equipment was used to perform ultrasound examinations. Helical, dual-scan computed tomography was performed using Elscint and Siemens Sommatom Sensation 10 approx. three hours after the administration of oral contrast (1000 ml 2.0% Urographin, Schering AG) and additional administration of intravenous contrast (Uropolinum or Omipaque, Polpharma and Nycomed, respectively). Endoscopic ultrasound examinations were made using Pentax FG-38UX and Olympus EXU-M3 with Siemens Sonoline AC and Hitachi EUB 555 and 6000. Examinations were performed in the lateral position, after infusion of pharmaceutical pre-medication (Dolargan and Buscolisinum i.v.). All results were collected as prints, *.jpeg, *.tiff files (MO and HD).

All examinations were performed according to the same protocol, which included the evaluation of pancreatic neoplasm, its local and regional staging, as well as the assessment of all other abdominal organs, in order to determine the presence of dissemination and distant metastases. To verify the accuracy of diagnostic imaging, the following methods were used:
- intraoperative surgeon's evaluation,
- histopathological examination of the tumor and specimens,
- intraoperative ultrasound findings.

Statistical evaluation was performed using Statistica™ software. Student's T test was used to determine significant differences.

Results

The study included 42 patients, 27 of which underwent pancreatic resection (11 Kausch-Whipple procedures, 9 pylorus-preserving resections, 4 total pancreatectomies, and 3 distal resections). Only 15 palliative procedures (due to unresectable cancer) were performed.

In 37 of 42 patients who underwent surgery, the diagnosis of pancreatic ductal carcinoma was made. In 3 patients, endocrine neoplasm (insulinoma) was found and in 2 patients – non-cancerous lesions (chronic pancreatitis) were diagnosed. The most common, local stage of cancer according to the TNM classification was T4, found in 11 patients (29.7%). Less frequent stages were T2 and T3, found in 10 patients (27.0%) and 9 patients (24.3%), respectively. The least common stage diagnosed was early carcinoma, T1, detected in 7 patients (18.9%). Complete analysis of diagnostic accuracy of EUS, CT and ultrasonographic methods was carried out in 37 patients with pancreatic ductal adenocarcinoma; the other cases (endocrine and non-carcinomatous tumours) were omitted from study.

Although full statistical analysis was not possible in the group with T1 stage cancer, due to small group size (n=7), it is worth mentioning that the most accurate modality to assess early cancer was EUS (6 correct diagnoses and 1 false negative). There were 4 false negative results with routine USG and 3 false negatives with CT and doppler-USG combined. Detailed data is shown in Table I.

Table I. Overall accuracy of ultrasonographic modalities, EUS and CT in local staging of pancreatic cancer (n=37)

	Routine USG	NS/S	Doppler USG	NS/S	EUS	NS/S	CT
T1 (n=7) Correct diagnosis	3/7		4/7		6/7		4/7
T2 (n=10) Accuracy	77.5	S	85.0	S	92.5	S	85.0
T3 (n=9) Accuracy	77.5	S	85.0	S	90.0	S	85.0
T4 (n=11) Accuracy	85.0	S	90.0	S	92.5	S	90.0

Statistical analyses of T2-T4 stages were made separately with a combined T1-T4 stage analysis. The most accurate assessment of T2 stage was made with EUS (overall accuracy 92.5%), and the sensitivity, specificity, PPV and NPV are all presented together with the parameters of the other methods in Table I. The accuracy of routine ultrasound, Doppler ultrasound and CT were 77.5% and 85.0%, respectively.

EUS was also determined to be the best method used to assess T3 and T4 stages (90.0% and 92.5%, respectively). The difference between EUS and the other imaging tests used was significant ($p<0.05$). Routine USG used to assess stages T3 and T4 achieved accuracy scores of only 77.5% and 85.0%, respectively; but both doppler-USG and CT improved the results to 85.0% and 90.0% accuracy, respectively [Figures 1-4].

General analysis of local advancement of pancreatic carcinoma (stages T1 – T4) proved that EUS was the most efficient method, with a diagnostic accuracy of

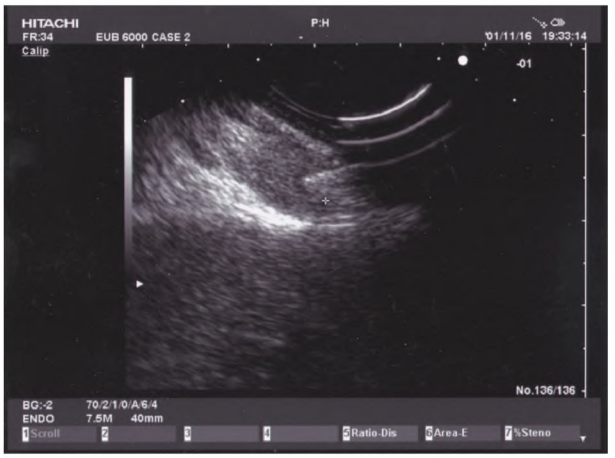

Figure 1. Pancreatic cancer – EUS

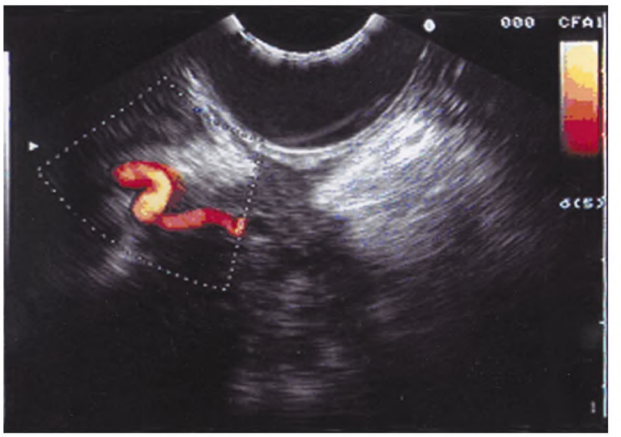

Figure 2. Pancreatic cancer – EUS + Doppler technique – no signs of vessel infiltration

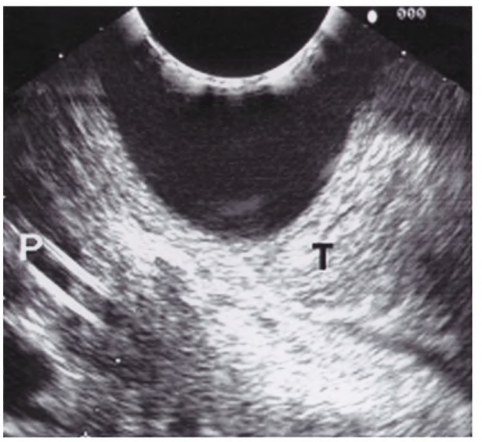

Figure 3. Advanced pancreatic cancer (T 4) – EUS

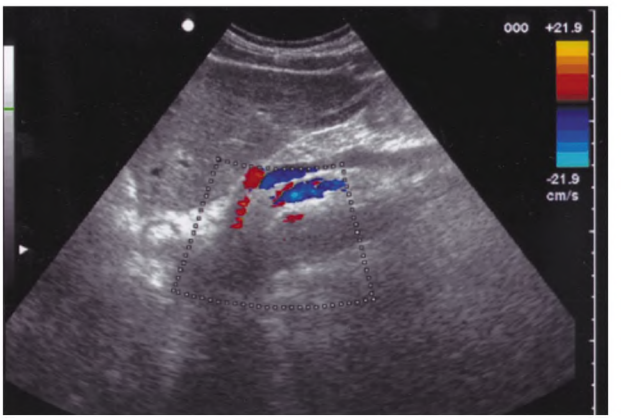

Figure 4. Pancreatic cancer: USG – color-Doppler – no infiltration of large vessels

93.1% and a sensitivity, specificity, PPV and NPV of 82.5%, 96.6%, 89.1% and 95.1%, respectively. These results were significantly better than the other methods, all of which are shown in Table I.

The evaluation of ultrasound and CT techniques to assess vascular carcinomatous infiltration was the next aim of the study. Such data is essential when planning surgery. Each ultrasound and CT exam included the evaluation of the following vessels: the superior mesenteric vein and artery, the portal vein, the inferior vena cava, the aorta and the celiac trunk [Figures 5, 6].

Routine ultrasound procedure achieved a relatively low accuracy of 67.5% (sensitivity: 74.0%, specificity: 53.8%, PPV: 76.9% and NPV: 53.8%) and color-doppler imaging improved the accuracy up to 82.5% (sensitivity, specificity, PPV and NPV 88.8%, 69.2%, 85.7% and

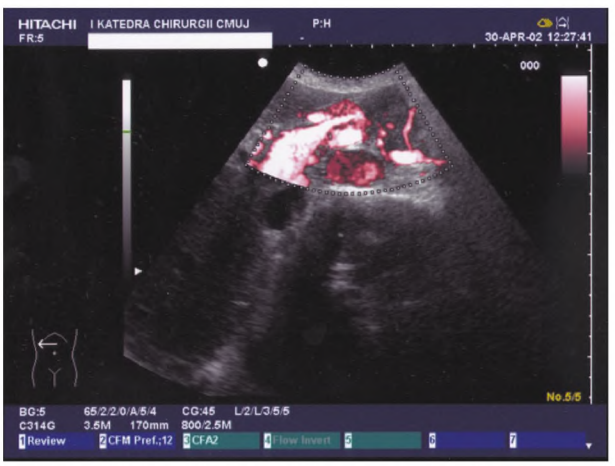

Figure 5. Pancreatic cancer: USG – power-Doppler – infiltration of the portal vein

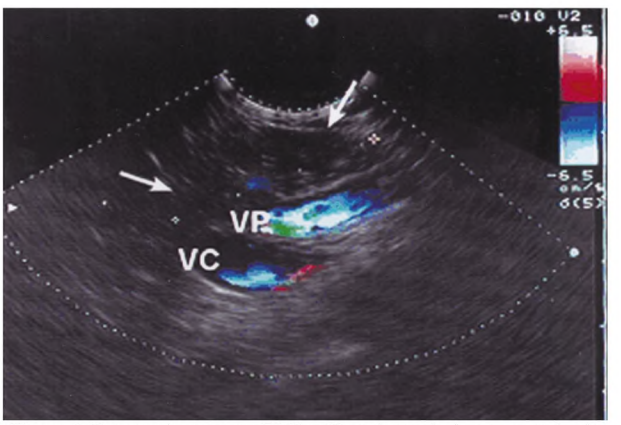

Figure 6. Pancreatic cancer – EUS + Doppler technique – portal vein infiltration

75.0%, respectively). The same results were obtained with CT. EUS was the most accurate method with an overall rate 90.0%, and sensitivity, specificity, PPV and NPV of 96.1%, 84.6%, 92.0%, and 84.6%, respectively. These results were significantly higher than the other obtained.

The presence of nodal spread of pancreatic carcinoma is very valuable information from the surgeons' point of view, as it is always associated with a poor prognosis. In this study the accuracy of imaging methods was evaluated in a group of 40 patients (only the patients who underwent resection were enrolled). Histopathological examinations showed the incidence of nodal metastases to be 16 (40%).

The study showed that EUS is the most precise diagnostic tool to determine lymph node metastases; EUS accuracy reached 87.5%, while the efficacy of routine ultrasound was 72.5%, ultrasound with doppler technique 80.0% and CT 82.5%. The differences were significant ($p<0.05$).

Discussion

Modern approach to pancreatic cancer treatment requires individual strategy and is mostly depended on diagnostic tools, as correct diagnosis and staging determine further tactics. Although endoscopy, computed tomography, MRI and ultrasound are most often used to evaluate pancreatic carcinoma, there is still a need to find the most optimal diagnostic method for its staging.

Correct assessment of early pancreatic carcinoma (T1 stage according to WHO) proves most valuable in pre-operative diagnosis. Innocenti et al. and Pichler et al. have reported that the accuracy of routine ultrasonography in T1 evaluation does not exceed 67.0% – 72.3%, and Doppler technique increases it to 87.4% [11, 12]. The accuracy of CT, according to Freeny et al., Gress et al. and Legman et al., reaches 67.0% [13-15]. Rosch et al. and Shoup et al. showed accuracy of 90.0% – 99.0% in early pancreatic cancer staging with EUS, documenting its value in detecting endocrine tumors smaller than 15 millimeters in diameter [15, 16]. The same high efficacy was observed in advanced stages: Mertz et al., Rosch et al. and Shoup et al. reported an accuracy of 93.0% – 100% in stages T2 – T4 [15-17].

The efficiency of imaging methods in advanced cancer stages is far better than in other methods; according to Pichler et al. and Howard et al., the accuracy of routine ultrasound at stages T2 – T4 was 85.0% – 90.0%, while Doppler technique increased it to 91.2% [12, 18]. At the same stage, CT showed an efficacy of 95.0%, reported by Bluemke, Calculli, Legman and Rosch et al. This opinion was, however, questioned by Chen et al. and Gorelick et al [3, 5, 15, 19, 20, 21].

Our research confirmed that EUS plays a leading role in local staging assessment. In the early stage, we observed only one false negative result out of seven cases. Accuracy of 92.5%, 90.0 and 92.5% was observed in stages T2, T3 and T4, respectively. The efficiency of routine and Doppler ultrasound and CT was poorer.

The presence of large vessel involvement caused by pancreatic cancer is important information when planning surgery. The efficiency of routine ultrasound for determining local vascular invasion is variable and can be poor. A majority of authors judge it to be about 60.0% [1, 8]. Modern ultrasound techniques improve the accuracy, increasing it to even 84.0% – 96.0% [6, 22, 23]. According to Calculli et al., Legman et al. and Ueno et al., CT is considered to be of similar effectiveness, reaching up to 100%, while others report values higher than 80.0% to be unlikely [3, 5, 14, 20, 22, 24].

Opinions vary as to the accuracy of EUS; Baarir et al. have shown it to be 95.0 %– 96.0%, but Howard et al. have questioned these outcomes, reporting the accuracy to be 76.0% [18, 25].

In our study the accuracy of routine ultrasound was 67.5%. 82.5% accuracy was achieved with Doppler-ultrasound and computed tomography combined. EUS was the best method to evaluate vascular involvement, with a correct diagnosis in 90.0% of cases. Our research concurred with the majority of reports regarding EUS, however, the accuracy of CT was lower than that reported by Calculli, Legman and Ueno [3, 5, 23].

The evaluation of nodal spread, which is an important prognostic factor, is one of the most difficult tasks to assess. Gorelick et al. and Pichler et al. have reported routine ultrasound to have an accuracy of 76.6% – 78.3%, but Chen et al. have questioned this opinion, because in their study sensitivity did not exceed 33% [12, 20, 21]. Both Bunk et al. and Innocenti et al. indicate that Doppler techniques can improve the efficacy, increasing it to 82.5% [11, 22]. CT, which is thought to be the "gold standard" in local assessment of pancreatic cancer, is also helpful in nodal status evaluation. Chen et al., Grees et al., Legman et al., van Hoe et al. and Tomazic et al. demonstrated its accuracy to be 50.0% – 85.0% with CT, which was not confirmed by Chen et al. and Yeo et al. (accuracy of 50.0%) [5, 7, 20, 26, 27]. The efficiency of EUS is also variable; Howard et al., and Gress et al. observed an accuracy of 72.0% – 75.0%, while Chen et al., and Yeo et al. reported only 47.0% – 62.0% [14, 18, 20, 27].

Our results have confirmed the relatively low accuracy of routine ultrasonography (72.5%), doppler-ultrasonography (80.0%) and CT (82.5%). Again, EUS proved to be the most efficient, with an accuracy exceeding 87.0%.

Our study demonstrated that endoscopic ultrasonography is the most accurate method of assessing not only local tumor stage, but also vascular and nodal status. The efficiency of EUS was the highest in all categories, but only in the case of early carcinoma did the difference achieve statistical significance. In the other categories this difference was not so obvious. Thus EUS is an expensive, invasive technique with a low availability and creating the possible need to re-examine the patient. Therefore, it should not be the routine method of choice in each case, but should be used only when the diagnostic problems cannot be solved with ultrasound or CT.

Conclusions

1. EUS is the best method to diagnose early pancreatic cancer (6 out of 7 patients); the same diagnosis was made in only 3 and 4 of these same 7 cases when USG or CT were used, respectively.
2. The general local staging accuracy of EUS exceeded 93.1%, routine ultrasound reached 82.5%, and Doppler USG and CT reached 88.1%.
3. The accuracy of vascular involvement detection was 67.5% with routine USG, 82.5% with CT and Doppler USG, and 90.0% with EUS.
4. The accuracy of EUS is also the highest in lymph node assessment (87.5%).
5. Endoscopic ultrasonography is the most accurate method to diagnose and stage pancreatic carcinoma in the pre-operative period.
6. EUS is invasive, expensive and of limited availability as compared to routine or Doppler USG; therefore, it should be used in selected cases, especially when early pancreatic carcinoma is suspected.

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References

1. American Gastroenterological Association Medical Position Statement: Epidemiology, Diagnosis, and Treatment of Pancreatic Ductal Adenocarcinoma. *Gastroenterol* 1999; 117: 1463-1482.
2. Puchalski Z. Chirurgia trzustki. *Medycyna praktyczna – Chirurgia* 1999; 8: 135-8.
3. Calculli L, Casadei R, Diacono D et al. Role of spiral computerized tomography in the staging of pancreatic carcinoma. *Radiologia Medica* 1998; 95: 344-8.
4. Kulig J et al. Wartość badania ultrasonograficznego w rozpoznawaniu guzów trzustki. *Przegl Lek* 1987; 59: 917-921.
5. Legman P, Vignaus O, Dousser B et al. Pancreatic tumors: comparison of dual-phase helical CT endoscopic sonography. *Am J Radiol* 1998; 170: 1315-22.
6. Casadei R, Ghigi G, Gullo L et al. Role of color Doppler ultrasonography in the preoperative staging of pancreatic cancer. *Pancreas* 1998; 16: 26-30.
7. Tomazic A, Pegan V.: Preoperative staging of periampullar cancer with US, CT, EUS and CA 19-9. *HepatoGastroenterology* 2000; 47: 1135-7.
8. Midwinter MJ, Beveridge CJ, Wilsdon JB et al. Correlation between spiral computed tomography, endoscopic ultrasonography and findings at operation in pancreatic and ampullary tumours. *Brit J Surg* 1999; 86: 189-93.
9. Queneau PE, Sauve G, Koch S et al. The impact on clinical practice of endoscopic ultrasonography used for the diagnosis and staging of pancreatic adenocarcinoma. *JOP* 2002; 2: 98-104.
10. Taylor AM, Roberts SA, Manson J. Experience with laparoscopic ultrasonography for defining tumour resectability in carcinoma of the pancreatic head and periampulary region. *Brit J Surg* 2001; 88: 1077-83.
11. Innocenti P, Falchini M, Stecco A.: Ultrasonography of pancreatic neoplasm. *Tumori* 1999; 85: 11-3.
12. Pichler W, Frank W, Jantsch H et al. Sonographic staging of pancreatic cancer. Report of 100 cases. *Rofo: Fortschrichtte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin*. 1989; 150: 241-5.
13. Freeny P. Computed tomography in the diagnosis and staging of cholangiocarcinoma and pancreatic carcinoma. *Ann Oncol* 1999; 10: 12-7.
14. Gress F, Hawes R, Savides T et al. Role of EUS in the preoperative staging of pancreatic cancer: a large single-center study. *Gastrointest Endoscopy* 1999; 50: 786-9.
15. Rosch T, Lorenz R, Braig C et al. Endoscopic ultrasound in pancreatic tumor diagnosis. *Gastrointest Endoscopy* 1991; 37: 342-7.
16. Shoup M, Hodul P, Aranha GV et al. Defining a role for endoscopic ultrasound in staging periampullary tumors. *Am J Surg* 2000; 179: 453-6.
17. Mertz HR, Sechopouolos P, Delbeke D et al. EUS, PET and CT scanning for evaluation of pancreatic carcinoma. *Radiol* 2000; 52: 367-71.
18. Howard T.J., Chin A.C., Streib E.W et al. Value of helical computed tomography, angiography and andoscopic ultrasound in determining respectability of periampullary carcinoma. *Am J Surg* 1997; 174: 237-41.
19. Bluemke DA, Cameron JL, Hruban RH. et al. Potentially resectable pancreatic adenocarcinoma: spiral CT assessment with surgical and pathologic correlation. *Radiol* 1995; 197: 381-385.
20. Chen CH, Tseng LJ, Yang CC et al. Preoperative evaluation of periampullary tumors by endoscopic sonography, transabdominal sonography and computed tomography. *J Clin Ultrasound* 2001; 29: 313-2.
21. Gorelick AB, Scheimann JM, Fendrick AM. Identification of patients with resectable pancreatic cancer: at what stage are we? *Am J Gastroenterol* 1998; 93: 1995-6.
22. Bunk A, Pistorius S, Konopke R et al. The value of color duplex sonography in the assessment of surgical resectability of pancreatic tumors. *Ultraschall in der Medizin* 2001; 22: 265-73.
23. Ueno N, Tomiyama T, Tano S et al. Color Doppler ultrasonography in the diagnosis of portal vein invasion in patients with pancreatic cancer. *Journal of Ultrasound in Medicine* 1997; 16: 825-30.
24. Lu DS, Reber HA, Krasny R et al.: Local staging of pancreatic cancer: criteria for unresectability of major vessels as revealed by pancreatic-phase, thin-section helical CT. *Am J Radiol* 1997; 168: 1436-43.
25. Baarir N, Amouyal G, Faintuch JM et al. Comparison of color Doppler ultrasonography and endoscopic ultrasonography for preoperative evaluation of the mesenteric-portal axis in pancreatic lesions. *Chirurgie* 1998; 123: 445-9.
26. Van Hoe L, Baert AL. Pancreatic cancer: applications for helical computed tomography. *Endoscopy* 1997; 29: 539-60.
27. Yeo C. Pancreatic cancer: 1998 update. *J Am College Surg* 1998; 187: 429-42.

Paper received: 1 March 2004
Accepted: 30 March 2004