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Evaluation of imaging techniques and CA 19-9 in differential diagnosis of carcinoma and other focal lesions of pancreas

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ABSTRACT

BACKGROUND: *Ultrasonography and magnetic resonance imaging are the most important imaging techniques in the diagnostics of pancreatic carcinoma and disease staging; they are also very useful in monitoring and follow-up of treatment efficacy. The problems with imaging diagnostics arise in certain cases of pancreatic focal lesions - for example in the differentiation of focal chronic pancreatitis and pancreatic carcinoma. Our objectives were the evaluation of ultrasonography and magnetic resonance imaging reliability and determination of the importance of tumor antigen CA 19-9 in the diagnostics of pancreatic carcinoma.*

METHODS: *Our investigation included patients with pancreatic focal mass suspected of malignancy. All patients were examined by ultrasonography, MR, and ultrasound-guided needle biopsy. Cytopathologic examination of biopsied samples was used to diagnose the disease. Oncomarker levels CA 19-9 were assayed in all patients.*

RESULTS: *Magnetic resonance imaging and ultrasonography examination made possible the correct diagnosis of carcinoma in case of 17 patients; in three patients with focal chronic pancreatitis the diagnosis was false positive. No case of false-negative diagnosis was found. The tumor antigen CA 19-9 in serum was determined and it was clearly positive (above 45U/ml) in all patients (17) with pancreatic cancer.*

CONCLUSION: *Imaging techniques gave good results in the evaluation of pancreatic pathology. However, when using imaging techniques differential diagnosis between focal chronic pancreatitis and pancreatic carcinoma seems to be major problem. Correlation of imaging technique and determination of tumor antigen CA 19-9 has an important role in the diagnostics of pancreatic carcinoma. Imaging techniques and identification of tumor antigen CA 19-9 are complementary methods in the examination and diagnostics of pancreatic carcinoma and they allow better precision of diagnosis of pancreatic focal lesions.*

KEY WORDS: *Diagnostic Imaging; Pancreatic Neoplasms; Pancreatic Diseases; Diagnosis, Differential*

INTRODUCTION

Pancreatic cancer is an aggressive disease. The survival rate has only slightly increased during the last 20 years, the majority of patients die within one year after diagnosis (1). The prevalence of pancreatic cancer in the general population is extremely low (0.01%), but this cancer is highly lethal disease historically, with few reports of 5-year survivors and with a median survival of approximately 3 months (2,3). The descriptive epidemiology of this disease presents a uniformly unfavorable, seemingly unchanging pattern. Most cases and most deaths occur in developed countries (approximately two thirds) (4). Pancreatic cancer (2% of all cancer diagnoses) is one of the most common and most lethal cancers in the Western world (1). Today, pancreatic cancer has been ranged among first five death causes in the Western world, and has a similar epidemiology in USA and Western Europe (5). In the year 2002 reported about 29 700 cancer deaths in USA. Despite worldwide variations in incidence and mortality similar figures are reported in Western Europe with about 30 000 deaths in the European Community every year (2). Despite improvements in therapeutic strategies including surgical techniques, local and systemic chemotherapies, pancreatic cancer remains one of the leading causes of cancer death in industrialized countries. Incidence rates and mortality rates are virtually identical (1).

Pancreatic cancer is still a difficult diagnostic and therapeutic challenge. Its prognosis is extremely poor because the disease is generally recognized at a very advanced stage and its clinical course is very rapid. Chronic pancreatitis has also been linked with pancreatic cancer. Pancreatitis may also appear both as a secondary condition induced cancer and as a predisposing factor (6). Accurate characterization and staging of malignancies have become increasingly important for cancer patients to avail themselves of the increasing advances in treatment options. Imaging techniques ultrasonography (US) and magnetic resonance imaging (MRI) play an important role in the diagnostic evaluation and manage-

ment of cancer patients (7-12). With further advances in imaging technology and an ever-increasing variety of diagnostic options, such as computed tomography (CT) and MRI, a greater precision in the verification of pancreatic lesions has been achieved (12,13). Recognition of unusual lesions and differentiation of chronic pancreatitis from a carcinoma is still a difficult clinical problem (14,15). Imaging studies may also reveal similar features. The complexity of differential diagnosis is enhanced because pancreatic cancer is frequently associated with secondary inflammatory changes (14). Modern imaging of pancreatic cancer remains a daily challenge both for detection and staging. Precise localization of disease process has made possible percutaneous biopsies of pancreatic cancer or other focal lesions (16,17). Most biopsies in oncology patients are performed to confirm malignancy in an imaging suspicious lesion or to obtain a tissue diagnosis in an in determinate lesion. Ultrasound is an ideal guidance modality for interventional procedures for various reasons (16). Some possible indications for tumor markers appear to be of clinical value: diagnosis, monitoring course of disease/response to therapy and detection of relapse, prognosis and screening. The use of serologic tumor markers, such as tumor antigen CA 19-9, is important in diagnosis and monitoring of patients with pancreatic carcinoma (18,19). This marker is useful in following of disease and in assessing the adequacy of resection (20,21). CA 19-9 is thought to be the most reliable marker for the diagnosis of pancreatic cancer (6), and its prognostic value for the evaluation of patients with inoperable adenocarcinoma of the pancreas is important (21). However, high levels of CA 19-9 are also present in patients with other cancers. Elevated serum levels of CA 19-9 are observed in 1%-4% of benign disease. It may also be useful for screening patients at high risk, such as men over the age of 60 years, smokers, black population, or resent-onset diabetics (2).

Algorithm of the diagnostic procedures sequence of focal pancreatic lesions has become a must in the process of diagnostic examination of the patient suspected of pancreatic cancer (9). Algorithm of diagnostic examination of pancreatic focal lesions starts with ultrasonography. If the obtained results are not clear whether the lesion is benign or malignant CT or MRI examination should be additionally performed. The results obtained by these techniques should be confirmed by fine needle biopsy and histopathologic analysis (22). If ultrasound finding is suspected of malignancy it is necessary to perform fine-needle biopsy for the purpose of diagnosis confirmation. Further surgical treatment, chemotherapy or radiotherapy could be performed only after histopathologic confirmation of malignancy. The gold standard in diagnosis of pancreatic cancer or chronic pancreatitis is histopathologic evidence of inflammation or malignancy (16). Our objectives were the evaluation of ultrasonography and magnetic resonance imaging reliability and determination of the importance of CA 19-9 level in the diagnostics of pancreatic carcinoma.

PATIENTS AND METHODS

The study was conducted at the Clinic for Internal Oncology and Diagnostic Imaging Center of the Institute of Oncology Sremska Kamenica during the period 2001-2003.

Patients

A total number of 31 patients with malignant diseases (17 patients) and benign pancreatic diseases (14 patients) were included in the study. In the group of patients with pancreatic carcinoma there were 11 men (64.7%) and 6 women (35.2%) (sex ratio, 1.8:1). The mean age of the patients with pancreatic carcinoma was 59.3 years (range, 42-79 years). In the group of patients with chronic pancreatitis there were 9 men (64%) and 5 women (35%) The mean age of the patients with chronic pancreatitis was 51 years (range, 31-62 years). Patients with suspected symptomatology to pancreatic disease were included in the study. All patients were clinically examined and underwent ultrasonography of the pancreas. The patients were divided into two groups.

One group consisted of patients suspected of benign pancreatic disease and the other group comprised of patients suspected of malignant pancreatic disease. On the basis of ultrasonography findings a group of patients diagnosed with focal pancreatic lesion suspected of malignant pancreatic neoplasm was separated.

Methods

Ultrasonography

All patients were examined by ultrasonography (US) in Diagnostic Imaging Center of the Institute of Oncology in Sremska Kamenica. We used the ultrasound device (Siemens Sonoline SL-200) with a sector probe of 3.5 MHz. Ultrasonography criteria for establishing suspect of benign an/or malignant pancreatic lesions are: echosonographic (ultrasonographic) image of pancreatic lesion, i.e. its size, contours, shape and echostructure (7-9). Ultrasonographic image of the pancreatic lesion is most often presented as an enlargement of a part (segment) of the pancreas, irregularly or clearly infiltrated contours, and hypoechogenic echostructure of the lesion. Echostructure of the tumor of the pancreas may have inhomogeneous, homogeneous or so-called target pattern, or "bull's-eye" pattern; the presence of calcification in the pancreas can also be identified by ultrasonography examination (1,7,8,11). Besides mentioned criteria other ultrasonographic signs were also observed: the appearance and diameter of the pancreatic duct, bile duct, cholecyst appearance, and other signs that may indicate either benign or malignant pancreatic disease.

Ultrasound-guided fine-needle biopsy

To establish precise diagnosis we performed ultrasound-guided fine-needle biopsy of the tumor mass in pancreas suspected of malignancy (16,17). We used the ultrasound device with a sector probe of 3.5 MHz, and fine-needles of 0.7-0.8 mm in diameter and 20 cm in length, for ultrasound guided fine-needle biopsy. Ultrasound-guided fine-needle biopsy of the pancreatic lesions was made for histopathologic confirmation of the diagnosis (1,22).

Magnetic resonance imaging

Magnetic resonance examinations (Magnetom SP 63-4000, Siemens, Erlangen) of the pancreas and abdomen were done in case of patients with unclear ultrasonographic findings in Diagnostic Imaging Center of the Institute of Oncology in Sremska Kamenica. MR examination of pancreatic cancer includes the imaging of topography and size of pancreatic tumor, and its locoregional spread (9,11-13,23,24).

Tumors are presented as hypointense lesions on T1W sequences and as hyperintense lesions on T2W sequences. Primary adenocarcinoma of the pancreas manifests lower signal intensity on MRI T1W images than does the normal pancreas tissue (23,25). However, MRI T2W images show variable signal intensity because of different degree of desmoplasia, presence of inflammation, and hemorrhage (25). Effective techniques useful for imaging of pancreas (are fat suppression and breath-hold. By means of fat suppression it is possible to enhance the contrast between pancreatic tumor and normal pancreatic tissue (13). MR examination also demonstrates necrotic areas in tumor and postgadolinium signal enhancement in the carcinoma of the pancreas. The basic principle of contrast media effectiveness is chemical alteration of relaxing time. The contrast media potential for reducing relaxing time depends on the concentration of the medium in tissue and on tissue relaxing time. Gadolinium is an effective relaxing enhancer (13,25).

Tumor antigen CA 19-9

The levels of oncomarker CA 19-9 were determined in all patients by IRMA-mat method. Reference value of tumor antigen Ca 19-9 was 45 U/ml. Serum carbohydrate antigen 19-9 (CA 19-9) has been identified as a useful tumor marker in patients with pancreatic cancer. The increased level of CA 19-9 is registered in patients with pancreatic carcinoma (19,20,26).

Statistics

For the evaluation of applied methods we used following parameters: sensitivity, specificity, and accuracy of the tests. Wilcoxon rank sum test was used for statistical data processing of CA 19-9 level in serum for two groups of patients: patients with malignant pancreatic lesions vs. patients with benign pancreatic lesion (27).

RESULTS

Pancreatic disease was diagnosed in 31 patients: 17 patients had malignant disease (pancreatic adenocarcinoma) and 14 were diagnosed with benign pancreatic disease (chronic inflammation). Twenty patients out of the total number who were examined by both imaging techniques had focal lesion of the pancreas suspected of malignancy; among them three patients were diagnosed with focal chronic pancreatitis. After complete examination of all 20 patients (imaging techniques, tumor antigen CA 19-9, and histopathologic analysis of biopsied focal mass of the pancreas) we confirmed malignant disease of pancreas in 17 and chronic focal pancreatitis in three patients. The findings of ultrasound examination showed suspectible malignancy in 14 of total 31 patients. The US findings were not clear about benign or malignant pancreatic lesions in 5 patients, and they were examined by MR. The findings of MR examination cleared up the final diagnosis in 2 patients, but it did not clear up dilemma between malignant and benign disease in case of three of 5 patients. MR imaging and US examination made possible the correct diagnosis of carcinoma in 17 patients (17/20); in three patients (3/20) with focal chronic pancreatitis the diagnosis established using imaging techniques was false positive (Table 1,2). No case of false-negative diagnosis was found.

Table 1. CA 19-9 serum levels

	Number of patients	
Pancreatic disease	Focal lesion	Total
Pancreatic carcinoma	17	17
Chronic pancreatitis	3	14
Total	20	31

Table 2. Ultrasound and magnetic resonance imaging findings

	Imaging	CA 19-9	Positive finding Imaging + CA 19-9
Pancreatic carcinoma	20	17	17
Focal pancreatitis	0	3	0

Table 3. Combined findings of imaging examination (US and MRI) and CA 19-9 assay

	CA 19-9			
Patients	<45U/ml	45-150U/ml	>150U/ml	>1000U/ml
Malignant disease	0	1	7	9
Benign disease	13	1	0	0

Ultrasound-guided fine-needle biopsy of pancreatic was performed only in case of patients suspected of pancreatic tumor lesions provided that they gave written consents (19/20). Histopathologic analysis of the sample obtained by biopsy confirmed the diagnosis of pancreatic carcinoma in all patients except 4. Patients whose diagnosis was not cytopathologically confirmed underwent surgical exploration. In spite of all analyses and fine-needle biopsy that had been done in a number of patients it was not possible to establish a precise diagnosis; those patients were surgically treated to obtain a final confirmation of malignancy. Surgery was also performed in a small number of patients although they were finally diagnosed. Figure 1 shows ultrasonographic image of pancreatic head carcinoma - hypoechoic lesion (arrow); Figure 2 is an ultrasonographic image of ultrasound-guided fine-needle biopsy with the point of the needle in the center of the pancreatic lesion (arrow); Figure 3 (A, B) is MR imaging of pancreatic body carcinoma (arrow) with hepatic metastases (arrow); A- with gadolinium, B - without gadolinium.

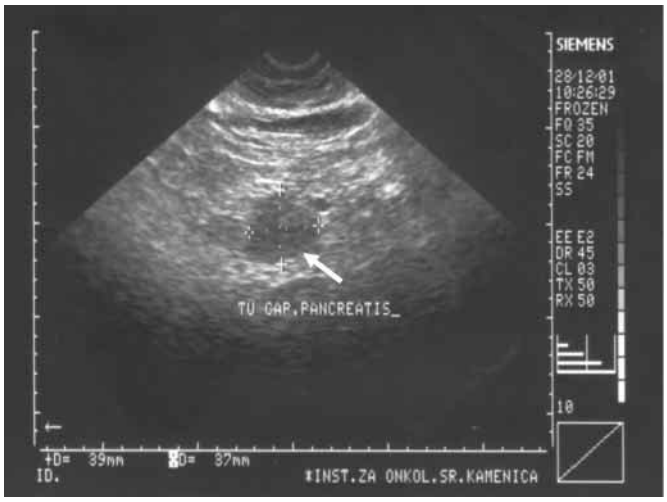

Figure 1. Pancreatic head carcinoma; ultrasound demonstrates a hypoechoic lesion

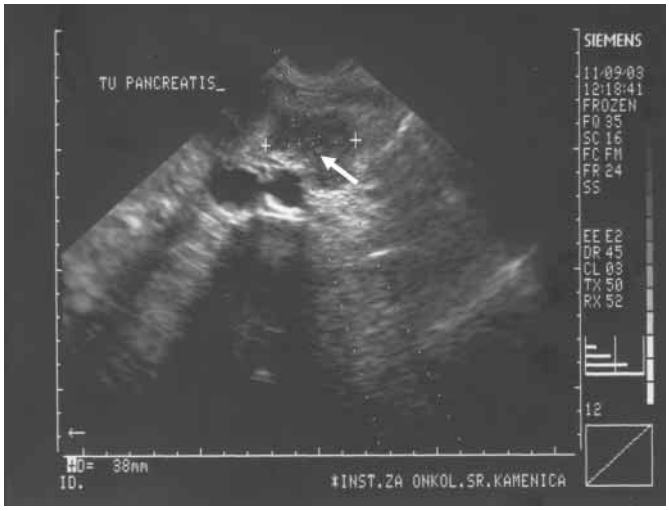

Figure 2. Percutaneous ultrasound-guided fine-needle biopsy pancreatic carcinoma

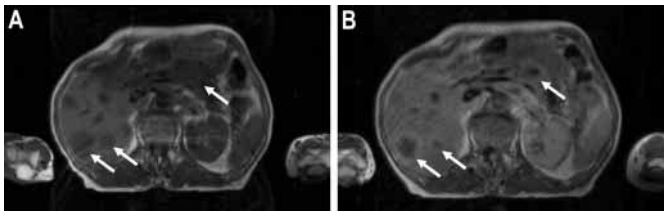

Figure 3. MR imaging of the pancreas - pancreatic body carcinoma with hepatic metastases; A- with gadolinium, B - without gadolinium

The serum levels of CA 19-9 were clearly elevated in all 17 patients with pancreatic carcinoma (>45U/ml). CA 19-9 serum levels above 150 U/ml were found in 16 patients (16/17); 9 patients (9/17) had CA 19-9 serum levels above 1000 U/ml; only one patient (1/17) had CA19-9 serum levels up to 150 U/ml, which still within the ranges of malignancy (Table 3). Serum level of CA 19-9 was normal in 13 patients diagnosed with pancreatitis (13/14 patients) except for one patient (1/14) with serum level above 45 U/ml but less than 150 U/ml. Statistical significance of the difference of the levels of CA 19-9 in serum between patients with malignant disease and patients with benign pancreatic lesions was determined by rank sum test. The difference between the two groups was statistically significant ($z=4.82$, $p< 0.001$). Suspected malignant focal lesions of the pancreas in 17 patients were finally diagnosed as pancreatic adenocarcinoma (17 out of 20 cases), and in 3 patients the final diagnosis was focal chronic pancreatitis (3 out of 20 cases).

In all 20 cases, US an MRI revealed hypoechogenic and hypodense focal pancreatic areas, 17 patients with pancreatic carcinoma. The sensitivity of imaging techniques US was 70%, and MRI 82%. Sensitivity of combined use US, MR and tumor marker CA 19-9 in pancreatic cancer diagnosis increases to 94%. The specificity of US was 64% and MRI 78,5%. The CA 19-9 was elevated in 17 patients with pancreatic carcinoma, and in 1 patient with benign pancreatic disease. The CA 19-9 was negative in 3 patients with suspected malignant lesions found by US and MRI but the final diagnosis in those patients confirmed benign disease - focal pancreatitis.

DISCUSSION

The differentiation between chronic pancreatitis and pancreatic cancer is difficult. In patients with a longstanding history of chronic pancreatitis, misdiagnosis of malignant lesion arising in the pancreas is potential pitfall leading to delay of treatment (26,28). Few imaging methods have been successful at distinguishing the mass effect of chronic pancreatitis from carcinoma (14,15). Ultrasound is used as the first-step examination for patients suspected of pancreatic carcinoma (1,2). Ultrasonography is low-cost, less invasive (no oral or intravenous contrast), and is usually the technique for initial evaluation. Imaging approaches utilize US, CT, MRI, and other techniques (7,10,11,22,29). Advances in technology for CT and MRI have improved the ability to detect pancreatic carcinoma (10,12,13). CT or MR imaging gives better information about local or distant metastases (30, 31). This is important for pre-operative investigation and surgical treatment of pancreatic carcinoma. But it is less accessible and more costly. CT is the most frequently used imaging modality for the initial diagnosis, staging, assessment of response to therapy and evaluation of medical complications related to pancreatic cancer (22). MRI are rapidly evolving modalities for the detection, staging and surgical assessment of pancreatic cancer (6). Magnetic resonance imaging has a large potential for detecting parenchymal changes in pancreatic carcinoma. Findings in several studies have suggested that MR imaging may be superior to CT in pancreatic lesion detection and preoperative staging (30,31).

Nonetheless, with both CT and MR imaging findings are not specific to cancer and can occur in chronic pancreatitis (28). The differentiation of focal, chronic pancreatitis and pancreatic cancer poses a diagnostic dilemma. Both conditions may present with the same symptoms and signs, and similar imaging pattern. The differential diagnosis between focal chronic pancreatitis and pancreatic adenocarcinoma can therefore be considered the major pitfall of MR imaging in the diagnosis of focal lesions (14,15,28). The use of serologic tumor markers for pancreatic carcinoma, such as CA 19-9 has an important role in diagnosis and monitoring of patients with pancreatic malignancies. Serum elevations of CA 19-9 with highest incidence rates are reported for pancreatic carcinoma (1,20,32).

In patients with focal pancreatic mass, hypoechogenic or hypodense lesions detected by US, CT or MR, and elevated CA 19-9 level are important in the diagnostic strategy. Combined use of serum CA 19-9 antigen test and imaging diagnoses result in greater diagnostic precision. In our study, in all patients with pancreatic cancer the results of imaging examinations showed tumor mass, and CA 19-9 levels were higher than 45 U/ml (above 150 U/ml, and in 6 patients above 1000 U/ml). Our results show that all patients with pancreatic cancer were detected with tumor mass by US and MR examination, and had elevated CA 19-9 values over 45 U/m. A number of patients from this group had CA 19-9 values over 150 U/ml, and 6 of them even over 1000 U/ml.

Our results correlate with the results obtained by other authors. For example, Riker et al. report patients with pancreatic cancer showing that imaging techniques (US, CT, MRI) and fine needle aspiration cytology may detect a pancreatic mass, which can be interpreted as a pancreatic tumor, as can also be suggested by the CA 19-9 value (33). Very high CA 19-9 levels usually indicate the advanced stage of pancreatic cancer (19, 21). The results reported by Ziske et al. (21), Barclay et al. (19) and Furukawa et al. (6) also confirm the importance of prognostic value of CA 19-9 in the diagnosis of pancreatic cancer. Diagnostic precision in differential diagnosis of pancreatic cancer is enhanced with combination of imaging methods (US CT, MR) and tumor antigen CA 19-9 (6,34-36).

The diagnostic precision was proved in our group of 17 patients with pancreatic cancer and our results are similar to the results presented by other authors. Our group of examined patients was small to perform a more detailed statistical analysis concerning specificity and sensitivity of applied methods. The combination of imaging techniques and CA 19-9 enhanced the sensitivity of diagnosis establishing to 90% (26) or according to some authors even to 95.2% (37). According to published results, CA 19-9 and imaging techniques offer the best accuracy in the diagnosis of pancreatic cancer. Bottger et al. show that 96% of patients with pancreatic carcinoma imaging techniques are adequate for diagnosis (38). Their study presents differentiation between malignant lesions of pancreas and chronic pancreatitis by means of imaging techniques, CA 19-9 values, and percutaneous aspiration biopsy cytology). In our study, we presented the importance of imaging techniques in the combination with CA 19-9 serum levels for differential diagnosis of focal pancreatic lesions. However, in spite of the use of costly imaging techniques sometimes it is not possible to establish clear and final diagnosis. In such cases, ultrasound-guided fine-needle biopsy is required for obtaining definite diagnosis of pancreatic disease. Ultrasound, being the most simple and the most inexpensive imaging technique, is available in almost all medical institutions, but in differential diagnosis of unclear pancreatic lesions CA 19-9 serum levels should be also assayed.

We presented that the use of ultrasound, as the simplest and the most available imaging technique, which in other institutions is more and more replaced by other, more sophisticated techniques, is important in the diagnostics of pancreatic cancer and in addition reduces the costs and time of diagnostic procedure; this certainly has far-reaching effects for all patients suffering from this aggressive and highly lethal malignant disease. A prospective study comparing CA 19-9, imaging techniques, US-guided fine-needle biopsy exhibited positive predictive rates (29). However, there is not a single test or imaging technique that can reliably discriminate between chronic pancreatitis and pancreatic cancer (35). Although claimed to correlate with pancreatic carcinoma, the finding of elevated tumor markers in the blood, such as CA 19-9, is not a full proof (35). Correlation of imaging technique and identification of CA 19-9 has an important role in the diagnostics of pancreatic carcinoma, but there is not a single test or imaging technique that can reliably differentiate chronic pancreatitis from pancreatic cancer. Although these results are only partially satisfying, they represent a significant step forward in the diagnosis of pancreatic cancer. Serum test CA 19-9 and imaging diagnoses have been tried in attempt to improve the precision of differential diagnosis between focal pancreatic lesions. In modern imaging we possess both the requisite technology and the clinical expertise to do a great deal for our patients. There is, however, a third factor to be considered, the so-called "cost-benefit" equation for patient and society. The cost element of this concept is not based only on the financial impact of imaging techniques, but also on the risks of ionizing radiation for both the patient and the population as a whole (10).

In addition to these considerations the cost-benefit ratio of imaging in financial terms is a constant reminder that we do not live in utopia and in the nonindustrialized world major epidemiological factors usually tend to direct resource allocation away from high technology medicine. These issues are, if anything, even more important now than when they were first

raised. Ultrasonography is used as a first-step examination for patients suspected of pancreatic carcinoma with respect to convenience, risks, availability, and costs. Ultrasonography is the simplest and the most available imaging technique and, when combined with fine-needle biopsy, it makes possible a fast diagnosis of tumor or other pancreatic lesions, and excludes the use of expensive techniques. Ultrasound is used as initial imaging investigation with CT or MRI as additional techniques. The diagnosis of chronic pancreatitis or pancreatic cancer is based on clinical presentation and imaging studies. Imaging techniques give good results in the evaluation of pancreatic pathology. However, when using imaging techniques differential diagnosis between focal chronic pancreatitis and pancreatic carcinoma seems to be major problem. Finally, none of imaging techniques gives a "histological" diagnosis of pancreatic lesions. Thus, to confirm the diagnosis it is necessary to do ultrasound-guided fine-needle biopsy (15).

CONCLUSION

A well-designed imaging strategy is an implicit component of the approach to a patient with pancreatic cancer. Algorithm of diagnostic procedures has become essential in clinical practice. Ultrasound is used as the first-step examination for patients suspected of pancreatic carcinoma. CT or MR is additional method used in case of unclear results. In patients with pancreatic cancer the diagnostic precision is greater with combined imaging methods and determination of CA 19-9 levels. Ultrasound-guided fine-needle biopsy is necessary in differential diagnosis of pancreatic lesions verified by some of imaging techniques. We can conclude that imaging techniques and identification of tumor marker CA 19-9 are complementary methods in the examination and diagnostics of pancreatic carcinoma and they allow better precision of diagnosis of pancreatic focal lesions.

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