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DOCTORAL THESIS

**CONTRIBUTION TO THE PANCREATIC TUMORS
DIAGNOSE BY IMAGING AND
MORPHOPATHOLOGY METHODS**

ABSTRACT

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CONTENTS

CONTENT.....	1
ABBREVIATIONS.....	IV
INTRODUCTION.....	1
KNOWLEGE STAGE.....	4
CHAPTER I DESCRIPTIVE ANATOMY OF THE PANCREAS.....	5
History	6
Embryogenesis	6
Descriptive anatomy.....	8
Pancreas structure	11
CHAPTER II PANCREATIC TUMORS GENERAL PRESENTATION.....	15
Demographic trends	16
Pathogenesis of pancreatic tumors	17
CHAPTER III DIAGNOSTIC PRINCIPLES IN PANCREATIC TUMORS.....	20
Clinical diagnostic elements	21
Morphopathology	34
Histopathology of the primary tumor	39
PERSONAL CONTRIBUTION.....	47
CHAPTER IV MATERIAL AND METHODS.....	48
Study objectives	49
Studied material	49
CHAPTER V CLINICAL STUDY.....	67
Patients age	68
Patients sex	69
Patient environment	70
Subjective clinical signs	70
Localization	71
Incidence	71
CHAPTER VI.....	73
IMAGING STUDY.....	73
CHAPTER VII MORPHOLOGICAL STUDY.....	74
Macroscopic evaluation.....	95
Microscopic evaluation	95
RESULTS AND DISCUSSIONS.....	106
C-O-N-C-L-U-S-I-O-N-S	110
BIBLIOGRAPHY.....	113

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INTRODUCTION

Pancreatic cancer is one of the most aggressive forms of neoplasia, being the 5th cause of death by cancer after gastric cancer, breast cancer, bronchopulmonary cancer and prostate cancer.

The goal of this study is the evaluation of the accuracy of imagistic investigations in the diagnostic of pancreatic tumors and in the establishment of the real track record of the tumoral extension; the diagnostic of the pancreatic duct adenocarcinoma, the most frequent type of neoplasia seen during our study, being interpreted at the histopathological exam. In the case of neuroendocrine tumors (insulinoma) the histopathological exam was completed with immunohistochemistry.

STATUS OF KNOWLEDGE

Cancer is a multistage affection, in its evolution were seen more stages of development determined by genetic and epigenetic modifications.

Initiation

Purely genetical event which headquarters can be constituted as well in normal tissues as in those tissues which presented before different kind of lesions susceptible of becoming malign.

The morphological traits of the neoplasia are represented by the growth and the abnormal cellular differentiation.

Promotion and development

It appears as following the action of a promoting agent on the initial cell. It is an epigenetic phenomenon that implies alterations of the genetic expression, without DNA modifications, with the proliferation of the initial cells and the cloning selection of those cells. The promotion can be reversible. The result consists in the transformation of the normal cell in malign cell.

The development takes place through the growing of the cancerous cells number in the tissue of origin. Characteristic is the atypical severe epithelial, polarity loss and basal membrane integrity. The external factors have a small influence being conditioned by internal factors (for example: hormonal factors). The duration is

variable, from a few months to 5-10 years. The number of cells grows without signs or disease symptoms. The tumor is avascular, not exceeding the basal membrane. Macroscopically: the aspect is uncharacteristic; sometimes we can observe an erosion area or a small ulceration. Microscopically it is characterized by architectural and cytological anomalies in the presence of an intact basal membrane.

Progression

Between the carcinoma locally and the clinical one manifest there is the microcarcinoma phase – with certitude only histological diagnostic (from 105 to 109 cells).

Macroscopically it is similar to the “local” carcinoma. Microscopically though, next to the modifications described before, adds to it the rupture of the basal membrane and the minimal invasion in the subject’s conjunctive tissue (3-5mm), where we observe an inflammatory infiltrate of the lymfo-plasmocyte type.

Metastasization

The process of dissemination of malign cells from the primary tumor to other compartments (organs, tissues, humors) of the organism or the transfer of the malign disease from an organ to another organ or tissue with which it is not in anatomical rapport.

For the classification of the pancreas cancer are used many more systems, the most satisfactory one being considered the classification/ conditionalization TNM (Tumor, Node, Metastases), which is made up at the proposal of UICC (Union Internationale Contre le Cancer) and the AJCC (American Joint Commission of Cancer), with 3 elemental components. With the fact that the certitude diagnostic in tumoral pathology is offered by the histopathological exam of the affected tissue, the most satisfactory classification remains the classification on a morphological central criteria.

PERSONAL CONTRIBUTIONS

OBJECTIVES OF THE RESEARCH STUDY

The research topic is of great interest because it explores and improves recent discoveries in the field of the pancreatic tumors, relying in particular on the complex evaluation of imaging (CT, MRI 3T, ultrasound and EUS) followed by minimally invasive sampling performed by puncture and fine aspiration together with histopathology and immunohistochemistry examination

Main objectives

- demographic particularities evaluation of patients with pancreatic tumor pathology;
- the evaluation of the patients based on diagnostic algorithms including, on the one hand by the computer tomography examination, the magnetic resonance and high performance EUS, on the other hand by making fine puncture aspiration and immunohistochemical analysis;
- testing the role of the imaging methods, including CT and 3T MRI with sequences of diffusion in the diagnosis of pancreatic tumors;
- histological and immunohistochemical identification of the most commonly encountered in practice in patients with pancreatic formations.

MATERIAL AND METHODS

Radiology and Medical Imaging, Imaging Department of the Center for Research in Gastroenterology and Hepatology, histopathology and immunohistochemistry laboratory of the Department of Pathology in the UMF Craiova, aiming to have prospective nature .

The study consisted in 201 patients, who were individualized in 3 groups:

- Group I consisting in 170 patients with pancreatic cancer who were studied from the demographic, clinical and imaging point of view;
- Group II consisting in 2 patients with islet pancreatic cancer and 30 patients with EUS evaluated with the use of contrast substance (SonoVue);
- Group III consists of 35 patients divided as follows: pancreatic adenocarcinoma (28 patients), islet (2 patients) and pancreatic metastases (5 patients) who underwent histopathology and immunohistochemistry examinations.

Transabdominal ultrasounds were performed using an ultrasound system HITACHI 8500 HITACHI and EUB PREIRUS. The examination was made á jeun with the patient lying down and / or left lateral decubitus position using frequency convex transducer of 3.5-5 MHz or 2.5 MHz in overweight patients, and performing axial, oblique and sagittal sections.

CT scanning (CT) was performed using a device SIEMENS SOMATOM 16 turns. Exploration by CT imaging were performed sequentially, native and non-ionic iodinated contrast medium is administered orally and intravenously (iv). Gastrografin oral

contrast was used to study postcontrast using Iopamiro 370 and Ultravist 370, iv, the bolus dose administered was 1 ml / kg.

CT examination began with a topogram on which it was defined an area of interest, and continued conducting axial sections using 5mm slices with 5mm pitch, where small lesions had 3mm slice with 3mm pitch. The images obtained with three-dimensional and multiplanar reconstructions in the coronal and sagittal plane were stored on DVDs, and in some cases printed also on radiological films.

Magnetic resonance imaging exam (MRI) was performed with a Philips INGENIA 3 Tesla. This was done by using an antenna of "phased-array" with the patient supine, both native and after injection of paramagnetic contrast substance. The advantage of such antennas is to obtain a better ratio signal / noise ratio and thus a higher quality image.

The dye used was gadolinium chelate dose of 0.1mmol / kg. Purchases were performed in the axial plane, sagittal and coronal, with the slice thickness of 2-3 mm.

Histopathology (HP) – the operators pieces were processed by histochemical technique which consisted of: determining fragments in neutral 10% formalin, paraffin embedding, effecting microscopic sections of 5 microns and usual coloring of hematoxylin-eosin.

RESULTS

CLINICAL PROFILE

The analysis of clinical parameters evaluation results showed that pancreatic adenocarcinoma was met predominantly in men coming from the urban areas, the peak incidence is around an average age of 68 years.

The main location of adk pancreatic was at the cephalic level, followed in descending order by location at the corporeal and then caudal level. It was also observed a annual growth trend of the pancreatic cancer.

IMAGING PROFILE

Transabdominal ultrasonography

Screening, non-invasive method that has been used as a "screening" for all the cases in the studied group.

The ultrasound examination had as a purpose to observe:

- the location and size of the tumor - where pancreatic adenocarcinoma could be seen at ultrasound, they were presented as hypoechogenic formations,

poorly defined, irregular outline, sometimes showing peripheral hyperechoic halo caused by the peritumoral sclerosis; most malignancies being highlighted at the cephalic level. In small tumors located at the cephalic level, difficult to be observed by the abdominal US it was necessary to perform EUS and / or CT, MR with MRCP sequences;

- Intrahepatic biliary tract and duct Wirsung dilation;
- The presence of liver metastases and those of the lymph nodes;
- The presence or absence of ascites.

In 31.32% of patients ultrasound revealed no exploration of pancreatic tumor so the transabdominal ultrasound sensitivity in the pancreatic tumor process of visualization is 67.66%.

Examination by CT

Optimal sequences were obtained during the arterial and portal phases. The portal phase, portal vein, superior mesenteric vein and peripancreatic veins show maximum contrast thus facilitating the identification of tumor, and also hypovascular liver metastases can be better viewed in this phase due to the maximum contrast of the hepatic parenchyma. By using volumetric acquisitions, arterial tridimension and upper abdomen reconstructions were performed, useful in evaluating the direct relationship between the neoplastic process and peripancreatic vessels.

During the CT scanning TNM staging of the tumor was performed, identifying the causes of nonresectability of the lesion, as well as the fat plan disappearance around the celiac trunk or the superior mesenteric artery.

In terms of the localization of the tumor formations, results of the computed tomography exploration were similar to those revealed by the transabdominal ultrasound examination, most malignancies being dealt with in the pancreatic head.

Unlike abdominal ultrasonography, only in 10.5% of the patients it was not visualized the primary pancreatic tumor, the diagnostic accuracy of CT being 88.35%.

When CT examination results were inconclusive or relevant in part (because very small size of the neoplastic formations or insignificant differences in density between them and adjacent structures) it was decided completion with RM examinations with sequences MRCP and / or EUS.

Nuclear magnetic resonance

MR examination with MRCP sequences was useful both to the evaluation and characterization of the pancreatic adenocarcinomas and their staging.

It was observed:

- The presence of signal changes occurring in the tumor process, hyposignal ascertaining in the T1-weighted sequences, iso/hypersignal in T2 weighted sequences due to necrosis or cystic degeneration, appearing T1 hyposignal in paramagnetic postcontrast;
- Wirsung duct changes.

Ecoendoscopy

In cases where CT and MRI investigations have failed to illustrate all the details necessary for a complete diagnosis, it was tried to obtain the necessary information by using EUS. This proved to be useful in staging pancreatic tumors and it has also allowed the differentiation of the cystic solid tumors from those neuroendocrine and papilar ones. The main advantage of the method was the possibility of making guided puncture aspiration. At 4.9% of patients the EUS exploration revealed no pancreatic tumor, thing correlated with the majority of the studies in the field which ranges EUS sensitivity as over 92%.

MORPHOLOGIC PROFILE

The analysis of the sections made from fragments of the pancreas and stained with hematoxylin and eosin showed that the histopathologic predominant form was the ductal adenocarcinoma poorly differentiated (G3).

CONCLUSIONS

From our study, which included both an individual and a comparative analysis of a set of imaging and pathology parameters several important and applicable conclusions resulted in the approach of the pancreatic adenocarcinoma:

1. Pancreatic cancer is a devastating disease with a poor prognosis, an important factor of morbidity and mortality, in our study we observed an annual growth trend of this one.
2. It is stressed the environment of origin and the socio-economic status, the incidence of pancreatic cancer being higher in men from classes with high economic status and education, with a mean age of 68 years;
3. The topography of the primary tumor revealed a predominance for pancreatic cephalic region, followed in a decreasing order by the localization at the corporeal and caudal level;
4. The large number of patients that entered this prospective study, conducted over a period of 5 years has enabled a thorough statistical analysis on imaging methods for exploration. The cutting-edge explorations carried out (CT, MR diffusion 3T, immunohistochemistry, computerized and automated data analysis) proved outstanding qualities and capabilities of diagnostic in the reference centers;
5. If the US is the "screening" examination in evaluating the pancreatic pathology directing to the diagnosis, the next-generation imaging allows highly accurate characterization of the lesion process and of the evolutionary status;
6. The computed tomography plays a major role in exploring the hepato-biliary pancreatic region, the multislice spiral CT being used largely for the appearance of the pancreatic tumors. This technology allows to scan the entire abdomen during only one breathing stop for analyzing the pancreas including the secondary damages and in particular the pancreatic metastases;
7. In the case of the pancreatic tumor lesions, regardless of their origin imaging examination also allows to establish the real loco-regional extension or at a distance, with important prognostic repercussions and decision regarding the therapeutic approach;

8. CT and EUS correlated with RM shows sensitivity and increased specificity in the detection of the pancreatic tumor pathology having in the same time the advantage of the concurrent exploration of the other abdominal parenchymal organs;
9. The current imaging methods are complementary, but appealing to several investigations is the prerogative of uncertain cases requiring complex exploration;
10. The main limitations of the imaging test are their high cost and the equipment availability;
11. A milestone in the diagnostic and therapeutic algorithm in the diagnosis of the pancreatic cancer is generated by the morphopathology diagnoses. The study of the histological forms showed that the histopathology predominant form of the pancreatic cancer was the ductal adenocarcinoma poorly differentiated.