RESEARCH ARTICLE

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The Investigation of the Risk of Malignancy in the Intraductal Papillary Mucinous Neoplasm of the Pancreas

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Objective: This study aims to investigate the risk of malignancy in the intraductal papillary mucinous neoplasm (IPMN) of the pancreas.

Materials and Methods: Between January 2015 and February 2020, a total of 42 patients who were diagnosed as IPMN radiologically were included in the study. The radiological and clinical findings were retrospectively analyzed. Magnetic Resonance Imaging (MRI), MR Cholangiopancreatography (MRCP), and Multidetector Computed Tomography (MDCT) findings were investigated.

Results: 15 of the patients were female (36%) and 27 were male (64%). The mean age was 67 (range: 45 to 81 years). (45-81). 18 cases (67%) with main duct type IPMN, 13 cases (31%) with minor duct IPMN and 11 cases (26 %) with mixed type were evaluated. In malignant cases; 3 cases (23%) diagnosed with minor branch IPMN, the mural nodule was observed. The main duct diameter was measured ≥10 mm in 10 cases (24 %). The mean cyst diameter was 12 mm (3-22 mm). The amylase level was high in all cases. Increased serum carcinoembryonic antigen (CEA) was present in 7 patients (17%) also serum carbohydrate antigen (CA 19.9) in 9 patients (21%). Positive cytology was observed in 7 cases in terms of malignancy.

Conclusion: Histological features of IPMNs range from benign adenoma to malignant invasive carcinoma. It is beneficial to predict malignant lesions, to plan before surgery. Increased pancreatic main duct dilation, increased CA 19.9 level and serum CEA, presence of enhanced mural nodule and large cyst diameter are risk factors for malignancy.

Key Words: *Pancreatic intraductal neoplasms, Multidetector computed tomography, Magnetic resonance imaging*

Pankreasın İntraduktal Papiller Müsinöz Neoplazmında Malignite Riskinin Araştırılması

Amaç: Bu çalışmanın amacı, pankreasın intraduktal papiller müsinöz neoplazmında (IPMN) malignite riskini araştırmaktır.

Gereç ve Yöntem: Ocak 2015-Şubat 2020 tarihleri arasında radyolojik olarak IPMN tanısı alan 42 hasta çalışmaya dâhil edildi. Radyolojik ve klinik bulgular retrospektif olarak değerlendirildi. Manyetik Rezonans Görüntüleme (MRI), MR Kolanjiyopankreatografi (MRCP) ve Çok Kesitli Bilgisayarlı Tomografi (ÇKBT) bulguları araştırıldı.

Bulgular: Hastaların 15'i kadın (%36), 27'si erkek (%64) idi. Ortalama yaş 67 idi (aralık: 45-81 yaş). (45-81). Ana kanal tipi IPMN'li 18 olgu (%67), minör kanal IPMN'li 13 olgu (%31) ve mikst tip tanılı 11 olgu (%26) mevcuttu. Malign olgularda; minör dal IPMN tanısı konulan 3 olguda (%23) mural nodül görüldü. Yedi hastada (%17) serum CEA değeri, 9 hastada (%21) CA-19-9 değeri artmıştı. Ana kanal çapı 10 olguda (%24) ≥10 mm olarak ölçüldü. Ortalama kist çapı 12 mm (3-22 mm) idi. Tüm olgularda amilaz seviyesi yüksekti. 7 vakada pozitif sitoloji vardı.

Sonuç: IPMN'lerin histolojik özellikleri benign adenomdan malign invaziv karsinomaya kadar değişebilmektedir. Ameliyat öncesi malign lezyonları önceden tahmin etmek, cerrahi plan açısından oldukça faydalıdır. Artmış pankreas ana kanal genişlemesi, CA 19.9 ve serum CEA seviyesi, kist içi mural nodül varlığı ve geniş kist çapı malignite açısından risk faktörleridir.

Anahtar Kelimeler: *Pankreatik intraduktal neoplazm, Multidedektör bilgisayarlı tomografi, Manyetik rezonans görüntüleme*

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Introduction

There are neoplastic and non-neoplastic cystic pathologies in the pancreas. With the proliferation of cross-sectional imaging methods, the detection of these lesions has increased significantly. In asymptomatic individuals, the prevalence of pancreatical cystic lesions are reported to be 8% (1). The lesions are usually asymptomatic and benign. However, more than half of the benign lesions have the potential to become malignant. Therefore, its accurate identification and radiological characterization are a very important for patient management and follow-up. Morphology of the cystic pancreatic lesions, fluid content, and relationships with the pancreatic duct can be evaluated in detail by imaging methods (2). Intraductal papillary mucinous neoplasia (IPMN) is an epithelial tumor originating from the pancreatic duct, causing cystic

dilatation, characterized by mucin production. It is seen in older men and women. Usually, it is located at the head part of the pancreas (1). It has three subtypes: main duct IPMN, minor duct IPMN, and mixed type IPMN (MT-IPMN). Its characteristic finding is the expansion in the main pancreatic duct. Multicystic appearance secondary to enlargement in the lateral branches of the pancreatic duct and intraductal papillary solid lesions can be observed (3). IPMN cases have the potential for malignancy. They can be found in a wide spectrum ranging from a slow-growing local lesion to invasive and metastatic tumors. According to their biological behavior, lesions were grouped into 3 groups as IPMN adenoma, borderline IPMN, and intraductal papillary mucinous carcinoma (4). Carcinomas are also grouped as in situ carcinoma and invasive carcinoma. Predicting the development of high-grade dysplasia to invasive carcinoma in IPMN is very useful in planning before surgery, predicting the prognosis of patients, and also in postoperative follow-up. There are not enough studies in the literature on this subject. This study aims to investigate the risk of malignancy in pancreatic IPMN.

Materials and Methods

This research was done following the principles of the Declaration of Helsinki. This research was done following the approval from the Non-Interventional Clinical Research Ethics Committee from the Firat University (date; 14/05/2020, Number; 392147)..

Between January 2015 and February 2020, a total of 42 patients who were diagnosed as IPMN radiologically were included in the study. The radiological and clinical findings were retrospectively analyzed. Magnetic Resonance Imaging (MRI), MR Cholangiopancreatography (MRCP), and Multidetector Computed Tomography (MDCT) findings were investigated. Significant clinical and laboratory findings related to current pathology were noted. The location, type, main canal diameter, minor brunch cyst dimensions, and enhancement features of pancreatic lesions were noted. The cyst sizes of the patients with follow-up were evaluated comparatively. Histopathological features and radiological findings were compared in operated cases.

MDCT Examination: Patients were examined by MDCT using a Toshiba Aquilion 64 slice CT scanner, (Medical Systems, Japan). The scanning area was identified between the diaphragm and the iliac crest. Images were of kVp 120, mAs 150-200 value, and 0.5 mm collimated cross-section thickness, 0.3 mm reconstruction interval, diameter FOV (30 cm), and with a pitch value between 1-1.5. Investigations were initiated one hour before the examination every 15 min, following 1000–1500 mL oral consumption of water. All examinations were performed with the patients in the supine position and automatic injection of 100 mL iopromide or 100 mL iohexol at a rate of 3 mL/sec through the right antecubital vein, through single breath-holding at 65 sec.

MRI Examination: 1.5T MRI device was used (Ingenia, Philips). Patients were analyzed by the 32-channel body coil with respiratory monitoring. The following parameters were used in MR images: Matrix: 288x251, FOV: 40x35 cm NEX: 1.0, space between cross-sections: 0.5 mm, cross-sectional thickness: 5 mm, TE: 80 ms, TR: 441 ms. Diffusion MRI was performed with the b 0, 400, and b 1000 values. ADC mappings were obtained. The parameters of the DW images: NEX: 2.0, Matrix: 132x114, FOV: 40x35 cm, TR, and TE: minimum. Diffusion direction: All directions. A dynamic series performed of pre-contrast series followed by early arterial, late arterial and portal phase imaging with 32-second intervals for the start of each phase imaging.

MRCP Examination: After 6 hours of fasting, MRCP images were obtained in the supine position, with Phased-array coil, without using contrast agent, monitoring breathing. MRCP images were as follows. Axial T2A, axial heavy T2A (3-5 mm), coronal T2A (MIP), SSFSE.

Statistical analysis: Statistical analysis was performed using the Statistical Package (SPSS) for Windows© software, version 22.0 (NY, Armonk, USA). All data were analyzed. Data were expressed as mean and standard deviation, distribution frequencies, median (min-max), and percentages, as appropriate.

Results

Among all patients, 15 were female (36%), and 27 were male (64%). The mean age was 67 years (range: 45 to 81 years). There were 18 cases (67 %) with main duct IPMN, 13 cases with minor duct IPMN (31%), and 11 cases (26%) with mixed type IPMN. Eleven cases (61%) diagnosed with the main duct IPMN were located at the head of the pancreas, and 7 cases (39%) were located in the body (Figure 1a, b). In 9 cases (69%) diagnosed with minor duct IPMN, cystic enlargements were located at the pancreatic head and uncinate process, and in 4 cases (31%) in the body and tail (Figure 2a, b, Table 1). In 3 cases (23%) diagnosed with minor duct IPMN, a millimeter-sized mural nodule was observed in the cyst wall (Figure 3). The main duct diameter was measured ≥10 mm in 10 cases (24%). The mean cyst diameter was 12 mm (range 3 to 22 mm) in all cases. The radiological findings are summarized in Table 2. The 7 patient with minor duct IPMN, no significant increase was observed in the cysts followed in the 2-years. In all cases, the amylase level was increased (>100 U/L). In the cyst fluid analysis by endoscopic ultrasonography (EUS), amylase value was found high in 7 cases. The increased Carcinoembryonic antigen (CEA) in 7 cases (17%) and carbohydrate antigen (CA 19-9) in 9 cases (21%) were found. Laboratory findings of the patients are summarized in Table 3. In terms of malignancy, positive cytology was present in 11 cases (26%). At the time of diagnosis, diabetes mellitus (DM) in 3 cases and acute pancreatitis in 4 cases were accompanied. A total of 15 cases (36%)

were operated, with the main duct diameter of ≥10 mm, positive cytology, increased CA 19-9, and mural nodules. histopathological diagnosis was reported as in situ carcinoma in 6 cases (14%) and invasive carcinoma in 9 cases (21%). The other 27 patients who could not be followed with a significant risk factor for malignancy were included in the annual follow-up program.

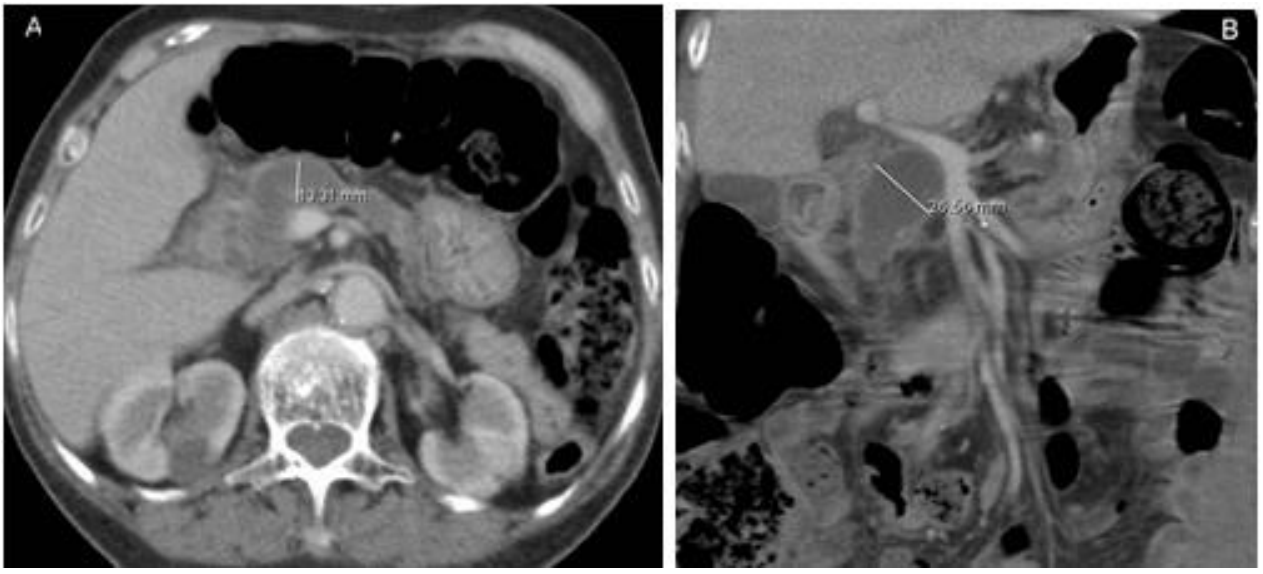

Figure 1. Enhanced upper abdomen MDCT revealed the main duct IPMN were located in the head and body of the pancreas in axial (a) in the head of the pancreas in coronal views (b)

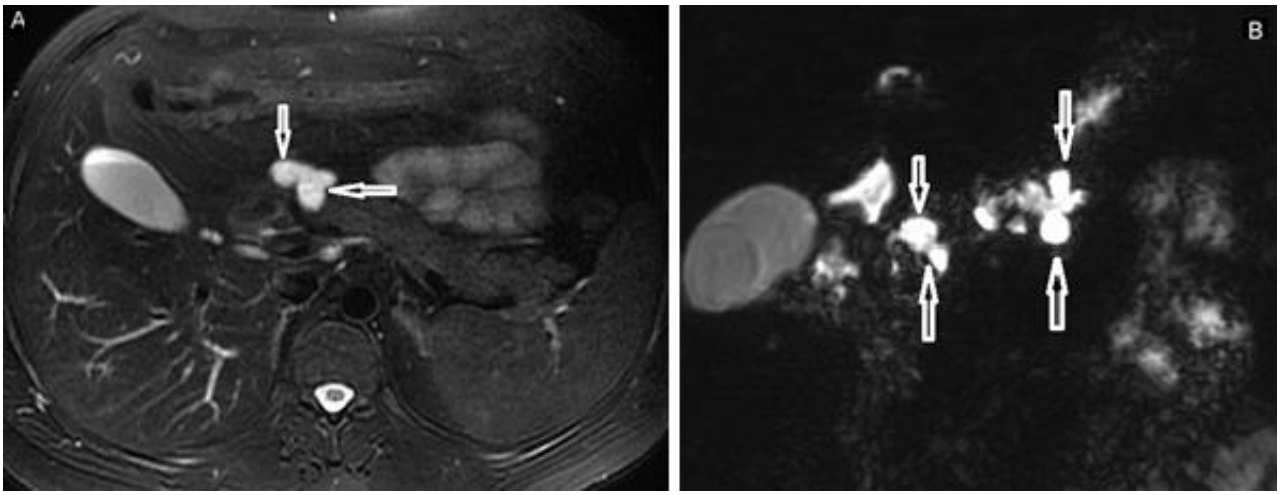

Figure 2. Axial fat-satured T2W upper abdomen MRI showed that cystic enlargements with minor duct IPMN were located at the head of pancreas (arrows) (a) MRCP image demonstrates multiple cystic enlargements in the body and tail of the pancreas (arrows) (b)

Table 1. The types of IPMN and their localizations

Main duct IPMN	n:18 (67%)	Pancreas head: n:11 (61%) Pancreas body: n:7 (39%)
Minor duct IPMN	n:13 (31%)	Pancreas head: n:9 (69%) Pancreas body: n:4 (31%)
Mixed type IPMN	n:11 (26%)	

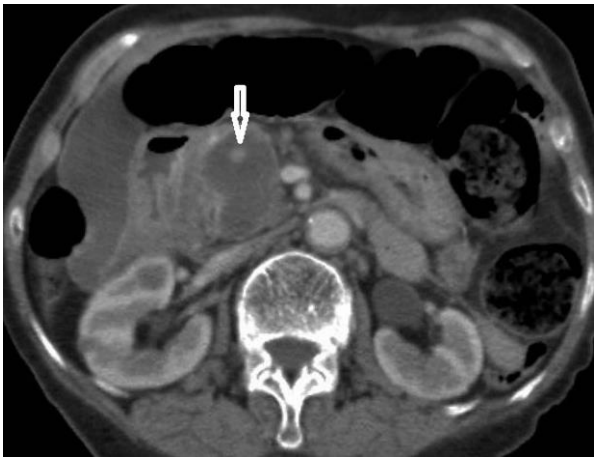

Figure 3. Enhanced upper abdomen MDCT showed that mural nodule in the cyst (arrow)

Table 2. Radiological findings of IPMN

Main duct diameter	≤10 mm (5.5±3.8)	n: 32 (76%)
	≥10 mm (12.5±2.6)	n: 10 (24%)
Cyst diameter	≤10 mm (6.2±2.4)	n: 4 (31%)
	≥10 mm (13.1±5.2)	n: 7 (54%)
	≥20 mm (22±1.8)	n: 2 (17%)
Mural nodule	(4.5±2.2 mm)	n: 3 (23%)

Table 3. Incidence of clinical and laboratuary findings

Increased amylase level	n: 42 (100%)
Increased CEA	n: 7 (17%)
Increased CA19-9	n: 9 (21%)
Positive cytology	n: 11 (26%)
Diabetes mellitus	n: 3 (7%)
Acute pancreatitis	n: 4 (9%)

Discussion

Epithelial tumors characterized by papillary proliferation of pancreatic duct epithelium and mucin production leading to cystic dilatation are called IPMN. IPMNs are 21% to 30% of all cystic pancreatic masses. Most of the lesions (60%) are seen in the male. It occurs mostly in the 6th to 7th decade (5). It is characterized by an increase in mucin cells producing mucus with different degrees of atypia. In the analysis of cyst fluid obtained by aspiration with EUS, increased amylase level is detected. Because they are associated with the pancreatic duct. If CA 19-9, CEA or CA 72.4 levels are increased, this suggests that it contains a malignant component (6).

Since ultrasonography (US) is an easily accessible, inexpensive, and repeatable test, it is often the first preferred imaging method in the evaluation of the pancreas. The pancreas can be imaged with the US in 75-90 % of cases when appropriate techniques and imaging parameters are used (7). Color Doppler US also contributes significantly to the diagnosis. Besides, US Elastography, and the contrast-enhanced US are useful other modalities (8).

The most important radiological modality in the evaluation of pancreatic pathologies is MDCT. This examination enables high spatial resolution and rapid multiplane imaging in inflammatory and neoplastic diseases of the pancreas. The distinction between normal and pathological pancreatic tissue can often be made safely in contrast-enhanced MDCT. The ductal system is also evaluated. In pancreatic tumors, it is aimed to the evaluation of lesion, arterial and venous system involvement, metastatic changes in the liver and peritoneum, lymph nodes, dilatation that can be observed in the biliary tract and pancreatic duct (9)

MRI is used as a problem-solving method by imaging pancreatic parenchyma, pancreatic, and biliary anatomy, peripancreatic soft tissues. The addition of sequences such as diffusion-weighted imaging (DWI), MRCP facilitates differential diagnosis of neoplasia and inflammatory processes. The detailed evaluation of both glandular function and pancreatic ducts can be made with the Secretin-stimulated MRCP (10, 11). With MRCP, it is possible to detect malignant stenosis of the pancreatic duct and cystic lesions of the pancreas, to characterize and to show the relationship of the cyst with the duct. It is necessary to distinguish the main duct enlargement due to IPMN from the dilatation of the duct caused by chronic pancreatitis. The transition point from the enlarged duct to the normal duct should be evaluated. The main duct in IPMN is progressively thinner without a focal transition point. In chronic pancreatitis, there is a focal stricture at the transition point. Atrophy can be seen around the dilated ductal segment secondary to occlusion and in the pancreatic parenchyma (5, 6).

Minor duct IPMNs cause cystic dilation. The main pancreatic duct is normal. They are seen at the head of the pancreas or in the uncinate process (60%) (5). There may be lobulation at the contour and septa in the cyst. It is important to identify their relationship with the main duct in distinguishing it from other cystic lesions in the pancreas (4, 5). In the US, the connection of the duct with the main canal cannot be seen. In such cases, MRI and MRCP imaging are required for further evaluation. If present, nodular components or wall thickening may show contrast enhancement after gadolinium injection (5, 12). The presence of mural nodules in IPMN is a significant indicator of malignancy. Increased activity can be detected in the cyst wall in IPMNs with high dysplasia in FDG PET-MR (13). Mixed type IPMNs have display features of both main duct IPMNs and minor duct IPMNs (12).

In our study, patients whose main canal diameter was measured ≥10 mm, mural nodules, cyst diameter was measured ≥20 mm, and patients with positive cytology, increased CEA and CA 19-9 values were operated considered as significant risk factors for malignancy. Histopathological diagnosis supported the risk factors of malignancy correlated with the literature (14).

In the literature, the presence of a cyst of ≥30 mm, a positive predictive value is between 25% and 35% for

malignancy (15). Also, an increase of more than 2 mm in the cyst diameter during the year, it has been reported that the risk of malignancy development is 45-50 % in 5-year (16).

This study has several limitations. MDCT and MRI images could not be obtained optimally in every patient secondary to respiratory and movement artifact. The main duct and cyst diameter measurements may have a minimal mistake in some patients for this. Cytological examination and tumor markers were not examined in all cases. There were a few patients that did not accept surgery or could not be operated due to additional diseases. So there is a need to research with larger patient series and additional parameters.

In conclusion MDCT, MRI and MRCP are used in the diagnosis and follow-up of IPMN. In selected cases, EUS can also be used for follow-up. Routine follow-up is recommended for patients with IPMN without indication of operation. Cyst size is important in follow-up if there is no risk factor. In the first year 6-month follow-up is sufficient (17). A 6-month follow-up is recommended for patients with relative risk factors for surgery, the elderly and those with severe comorbidity. Also, in patients undergoing partial pancreatectomy for IPMN, follow-up should be done throughout life.

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