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Medicine

CLINICAL PRESENTATION, DIANGOSTIC WORKUP AND THERAPEUTIC APPROACH FOR PANCREATIC CANCER IN A TERTIARY GASTROENTEROLOGY CENTER

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ABSTRACT
CANCER OF THE EXOCRINE PANCREAS IS A HIGHLY LETHAL MALIGNANCY. SURGICAL RESECTION IS THE ONLY POTENTIALLY CURATIVE TREATMENT. UNFORTUNATELY, BECAUSE OF THE LATE PRESENTATION, ONLY 15 TO 20 PERCENT OF PATIENTS ARE CANDIDATES FOR PANCREATECTOMY. THE AIM OF OUR STUDY WAS TO REVIEW THE RISK FACTORS, CLINICAL PRESENTATION, DIAGNOSTIC TOOLS AND THERAPEUTIC APPROACH OF PATIENTS WITH PANCREATIC CANCER, ADMITTED TO OUR CLINIC BETWEEN JANUARY 1ST AND DECEMBER 31ST OF 2016. WE ENROLLED TWO HUNDRED AND SIXTY EIGHT CONSECUTIVE PATIENTS. WE FOUND THAT MOST PATIENTS PRESENTED AT LEAST ONE RISK FACTOR FOR PANCREATIC NEOPLASIA, ESPECIALLY CIGARETTE SMOKING AND ALCOHOL DRINKING. MANY PATIENTS WERE DIAGNOSED IN ADVANCED STAGES OF THE DISEASE, WHEN THE TUMOR WAS LOCALLY INVASIVE OR HAD DISTANT METASTASES. THE MOST FREQUENT HISTOLOGICAL TYPE WAS ADENOCARCINOMA, FOLLOWED BY NEUROENDOCRINE TUMORS (13.36%). PATIENTS BENEFITED FROM SURGICAL, ONCOLOGICAL, AND/OR ENDOSCOPIC TREATMENT. THE MEDIAN SURVIVAL TIME WAS 8.83 MONTHS FOR ADENOCARCINOMA AND 66.34 MONTHS FOR NEUROENDOCRINE TUMORS. WE NOTED A LONGER MEDIAN SURVIVAL TIME FOR ADENOCACINOMA THAN THE EUROPEAN AVERAGE OF 4.6 MONTHS, PROBABLY DUE TO THE FACT THAN PATIENTS WERE DIAGNOSED AND TREATED BY A MULTIDISCIPLINARY TEAM, IN A TERTIARY CARE FACILITY. HOWEVER WE NEED TO DO A BETTER JOB IN IDENTIFYING HIGH RISK INDIVIDUALS AND THEN OFFERING THEM A PERSONALISED SCREENING PROGRAM, IN ORDER TO DIAGNOSE MORE PATIENTS IN POTENTIALLY CURATIVE STAGES.

KEY WORDS: PANCREAS, CANCER, RISK, TREATMENT

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INTRODUCTION

Pancreatic cancer is the fourth leading cause of cancer-related death in the United States and second only to colorectal cancer as a cause of digestive cancer-related death. Surgical resection is the only potentially curative treatment. Unfortunately, because of the late presentation, only 15 to 20 percent of patients are candidates for pancreatectomy. Furthermore, prognosis is poor, even after a complete resection. Five-year survival after margin-negative (R0) pancreaticoduodenectomy is approximately 30 percent for node-negative and 10 percent for node-positive disease[4].

The aim of our study is to investigate the risk factors, the presentation pattern, the diagnostic algorithm and the therapeutic strategy for pancreatic cancer patients in the Gastroenterology Department of the Fundeni Clinical Institute, a tertiary care center.

MAIN TEXT

A retrospective study of 443 consecutive patients with pancreatic cancer was performed. The patients were admitted to the Gastroenterology and Digestive Oncology Departments between January 1st 2015 and December 31st 2016. We analyzed data referring to risk factors, clinical presentation, diagnostic workup and therapeutic approach.

The major risk factors for pancreatic cancer are: cigarette smoking, high body mass and lack of physical activity, nonhereditary chronic pancreatitis and pancreatic cysts. Hereditary risk factors have also been described, such as hereditary pancreatitis, other highly penetrating conditions caused by germline mutations in known cancer-causing genes and familial pancreatic cancer, for which a specific genetic abnormality has not yet been identified. Other potential risk factors, with weaker association include: A blood group, recent onset diabetes mellitus, Helicobacter pylori infection, hepatitis B and C viral infection, alcohol consumption. Data regarding the impact of alcohol ingestion on the risk of pancreatic cancer have been conflicting. Two pooled analyses suggest if there is an effect of alcohol consumption, it is small and limited to heavy drinkers. The relationship between alcohol use and pancreatic cancer is confounded by cigarette smoking[5].

We documented all the risk factors mentioned above. The mean age at diagnosis was 63.54 years, ranging between 32 and 89 years old. The male to female sex ratio was 1.31:1. Cigarette smokers represented 37.12% of all patients, alcohol consumption was found in 40.46% of all cases, diabetes mellitus in 30.26 % of subjects, frequently type 2 (98.81%). Fifteen per cent of individuals had evidence of present or past hepatitis B or C virus infection. A personal history of acute or chronic pancreatitis was noted in 7.19% of patients and a personal history of other neoplasia in 3.68%. A large number of patients presented with more than one risk factor: two factors – 23.18%, three risk factors – 10.94%, four risk factors –1.83% and five risk factors – 0.52%. Cigarette smoking was frequently associated with alcohol consumption (66.54%). Average tobacco consumption was: 13.30% under 15 pacs/year, 46.27% between 16 and 30 pacs/year and 40.53% more than 30 pacs/year.

[4] Allen PJ et al. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. Ann Surg 2017; 265:185.

[5] Lowenfels AB, et al. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. *Med Clin North Am* 2000; 84:565

Diabetes mellitus as a risk factor was found to be frequently type II, the average age at diagnosis being 65.86 years. The pancreatic neoplasia was diagnosed after an average duration of 4.73 years after the onset of diabetes mellitus. Computed tomography (CT) screening of all older subjects with new onset diabetes in order to discover a small number of pancreatic cancers is not feasible. Identification of those features that differentiate pancreatic cancer-associated diabetes from other cases with new-onset diabetes would help direct efforts to the subset of individuals who would most benefit from screening CT, but these factors have not yet been established. At present, screening is only carried out for high-risk individuals who have familial syndromes predisposing them to pancreatic cancer[6].

The most common presenting symptoms in patients with exocrine pancreatic cancer are pain, jaundice, and weight loss. The initial presentation of pancreatic cancer varies according to tumor location. Compared with tumors in the body and tail of the gland, pancreatic head tumors more often present with jaundice, steatorrhea, and weight loss. The pain associated with pancreatic cancer is usually insidious in onset, and has been present for one to two months at the time of presentation. Jaundice, which is usually progressive, is most often due to obstruction of the common bile duct by a mass in the head of the pancreas, causing hyperbilirubinemia. It may be accompanied by pruritus, darkening of the urine, and pale stools. Jaundice is a relatively early sign in tumors arising from the pancreatic head, and pancreatic tumors that present with painless jaundice have been ascribed a relatively more favorable prognosis compared with those that present with pain and obstructive jaundice. Signs of metastatic disease may be present at presentation. Metastatic disease most commonly affects the liver, peritoneum, lungs, and less frequently, bone[7].

Out of our patients, at presentation, 64.41% had abdominal pain or discomfort, lasting for an average of 5.3 months prior to hospital admission, 78.14% had weight loss - an average of 6.57 kg during the last 2.38 months. Jaundice was present initially in 50.22% of the patients with tumors located in the pancreatic head and in 44.71% patients with body or tail tumors. Other documented symptoms were: diarrhea (13.25%), fever (6.87%) and uncontrolled diabetes mellitus (5.73%). In 5.63% of cases the pancreatic cancer was an incidental finding, in asymptomatic individuals who underwent imaging of the abdomen for various indications.

Patients who present with jaundice or epigastric pain and weight loss often undergo right upper quadrant transabdominal ultrasound (US) initially to evaluate for dilated bile ducts or a pancreatic mass. While the reported sensitivity for US in diagnosing pancreatic cancer is 95 percent for tumors >3 cm, it is much less for smaller tumors. If a suspicion of pancreatic cancer is raised by the US, the next step is a CT or MRI for confirmation and staging. A mass within the pancreas is the most common CT finding of pancreatic cancer, although enlargement of the whole gland is sometimes seen. Sensitivity of CT for pancreatic cancer depends on technique and is highest (89 to 97 percent) with triple-phase, helical multidetector row CT[8]. Local unresectability is usually (but not always) due to vascular invasion. Endoscopic ultrasonography is another

[6] Michaud DS et al. Dietary sugar, glycemic load, and pancreatic cancer risk in a prospective study. *J Natl Cancer Inst* 2002; 94:1293
[7] Mujica VR, Barkin JS, Go VL. Acute pancreatitis secondary to pancreatic carcinoma. Study Group Participants. *Pancreas* 2000; 21:329
[8] Bronstein YL et al. Detection of small pancreatic tumors with multiphasic helical CT. *AJR Am J Roentgenol* 2004; 182:619.

effective method to assess tumor extent and vascular invasion. Histologic confirmation is required to establish a diagnosis of pancreatic cancer. Biopsy of a pancreatic mass can be accomplished through percutaneous or endoscopic approaches.

All the patients in our study were investigated by abdominal CT or MRI and 31.08% had an endoscopic ultrasound (± fine needle aspiration). The TNM stage at presentation was: T1 – 5.61%, T2 – 22.09%, T3 – 29.96 % and T4 – 42.32; 56.92% of patients were N1 (nodes positive) and 51.31% already had distant metastases. The tumors were located at the level of the pancreatic head in 55.98% of patients, 24.74% in the body and 19.28% in the tail.

Resectable disease was established in 27.30% of cases, 21.39% of tumors were locally advanced and 51.31% were metastatic at diagnosis. The percentage of early stage, resectable tumors, is higher than the literature data (15-20%), probably due to the vast experience of our multidisciplinary team in investigating patients with pancreatic disorders.

Histology was available in 80.97% of cases and it was obtained through EUS in 38.72% of cases, surgical biopsy – 35.33% and percutaneous biopsy from liver metastases in 25.94% of patients. The histological types of cancer were: 82.94% adenocarcinomas, 13.36% neuroendocrine tumors (NETs), 1.38% gastrointestinal stromal tumors (GISTs), 0.92% mixed adeno-neuroendocrine carcinomas (MANECs), one pancreatic intraepithelial neoplasia (PanIN), one mucinous cystic neoplasm and one solid-pseudopapillary tumor.

In literature, ductal adenocarcinoma accounts for 85% of pancreatic exocrine neoplasms. Pancreatic intraepithelial neoplasia (PanIN) refers to a small (generally <5 mm) intraductal noninvasive lesion that is formed by metaplasia and proliferation of ductal epithelium. Most ductal adenocarcinomas are considered to arise from PanIN, presumably developing as a result of a series of genetic events. However, although PanIN is considered to represent a precursor lesion to invasive ductal adenocarcinoma, it appears that only a small fraction of low-grade PanIN progress to invasive cancer[9].

Pancreatic pancreatic NETs, also known as islet cell tumors, are rare neoplasms that arise in the endocrine tissues of the pancreas. They can secrete a variety of peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP), resulting in a variety of clinical syndromes. They account for 3% to 5% of pancreatic malignancies and overall have a better prognosis than the more common pancreatic exocrine tumors. Five-year survival is about 55% when the tumors are localized and resected but only about 15% when the tumors are not resectable. Overall 5-year survival rate is about 42%[10].

Out of the 121 patients deemed resectable after initial staging, 105 turned out to be resectable during surgery: 77 had douodenopancreatectomy, 25 had distal pancreatectomy and 3 had total pancreatectomy. The remaining 322 patients were considered to be initially unresectable. However, 74 of them had palliative surgery: 41 had biliary bypass, 15 had enteral bypass, 10 had bilioenteral bypass and 8 had splanhnicetomy as pain therapy.

For obstructive jaundice, 37 biliary stents were placed endoscopically (28 metal and 9 plastic). When endoscopic retrograde cholangiopancreatography was not technically feasible, external biliary drainage was performed, under CT guidance.

[9] Hruban RH et al. An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 2004; 28:977

[10] Ries LAG et al. SEER Survival Monograph: Cancer Survival Among Adults: U. S. SEER Program, 1988-2001, Patient and Tumor Characteristics. Bethesda, MD: National Cancer Institute, 2007. *NIH Pub*. No. 07-6215

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The available evidence from randomized trials suggests that systemic chemotherapy provides a significant survival benefit over best supportive care alone, both for first-line and second-line treatment.

In the adenocarcinoma group, 275 patients (68%) received chemotherapy, out of which 68% with palliative intent, 30% with adjuvant intent and 2% as neoadjuvant therapy. First line therapy was based on a gemcitabine containing regimen in 88.7% of cases, the remaining adenocarcinoma patients receiving FOLFIRINOX – 10.2% or other therapies – 3.1% (eg. Carboplatin). We were able to evaluate the best response to chemotherapy in 234 patients: 23.5% had complete response, 10.3% partial response, 23.9% stable disease and most (42.3%) had progressive disease.

Patients with metastatic pancreatic cancer should be offered aggressive treatment for pain and other symptoms related to the cancer. Patients with an Eastern Cooperative Oncology Group (ECOG) PS ≥3 or poorly controlled comorbid conditions should be offered systemic chemotherapy only on an individualized, case-by-case basis; supportive care should be emphasized[11].

Overall survival data was available for 264 patients with adenocarcinoma and 34 patients with neuroendocrine tumors. The median survival time was 8.83 months for adenocarcinoma and 66.34 months for neuroendocrine tumors.

The median survival time in our study was longer than the European average of 4.6 months, this being linked also with the fact that more patients were diagnosed in early stages, compared to literature data. We think that this positive outcome is due to the multidisciplinary treatment and large clinical expertise with pancreatic cancer patients in our clinic.

CONCLUSION

A large number of patients with pancreatic cancer present one ore more of the well-studied risk-factors for the occurrence of the disease. However, a large proportion of patients are diagnosed in advanced stages, when curative treatment is no longer an option. We need to be able to identify high risk individuals and then offer them a personalized screening program.

[11] Sohal DP et al. Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016; 34:2784

REFERENCES

1. **Allen PJ, Kuk D, Castillo CF, Basturk O, Wolfgang CL, Cameron JL, Lillemoe KD, Ferrone CR, Morales-Oyarvide V, He J, Weiss MJ, Hruban RH, Gönen M, Klimstra DS, Mino-Kenudson M**. Multi-institutional Validation Study of the American Joint Commission on Cancer (8th Edition) Changes for T and N Staging in Patients With Pancreatic Adenocarcinoma. *Ann Surg* 2017; 265:185.;
2. **Lowenfels AB, Maisonneuve P, Whitcomb DC**. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. *Med Clin North Am* 2000; 84:565;
3. **Michaud DS, Liu S, Giovannucci E, Willett WC, Colditz GA, Fuchs CS.** Dietary sugar, glycemic load, and pancreatic cancer risk in a prospective study. *J Natl Cancer Inst* 2002; 94:1293;
4. **Mujica VR, Barkin JS, Go VL**. Acute pancreatitis secondary to pancreatic carcinoma. Study Group Participants. *Pancreas* 2000; 21:329;
5. **Bronstein YL Loyer EM, Kaur H, Choi H, David C, DuBrow RA, Broemeling LD, Cleary KR, Charnsangavej C.** Detection of small pancreatic tumors with multiphasic helical CT. *AJR Am J Roentgenol* 2004; 182:619.*;*
6. **Hruban RH, Takaori K, Klimstra DS, Adsay NV, Albores-Saavedra J, Biankin AV, Biankin SA, Compton C, Fukushima N, Furukawa T, Goggins M, Kato Y, Klöppel G**, **Longnecker DS, Lüttges J, Maitra A, Offerhaus GJ, Shimizu M, Yonezawa S.** An illustrated consensus on the classification of pancreatic intraepithelial neoplasia and intraductal papillary mucinous neoplasms. *Am J Surg Pathol* 2004; 28:977;
7. **Ries LAG, Young JL, Keel GE, Eisner MP, Lin YD, Horner M-J**. SEER Survival Monograph: Cancer Survival Among Adults: U. S. SEER Program, 1988-2001, Patient and Tumor Characteristics. Bethesda, MD: National Cancer Institute, 2007. NIH Pub. No. 07-6215;
8. **Sohal DP, Mangu PB, Khorana AA, Shah MA, Philip PA, O'Reilly EM, Uronis HE, Ramanathan RK, Crane CH, Engebretson A, Ruggiero JT, Copur MS, Lau M, Urba S, Laheru D.** Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2016; 34:2784.