Predictors of Malignancy in Pancreatic Intraductal Papillary Mucinous Neoplasms and Applicability of Current Guidelines

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ABSTRACT

Introduction: Pancreatic intraductal papillary mucinous neoplasms (IPMN) are recognized as pre-malignant lesions, corresponding to less than 3% of all pancreatic exocrine neoplasms. The study objectives were: to evaluate the surgical results of our institution, to identify factors predicting malignancy in IPMN and to assess the validity of recently introduced IPMN guidelines in our population.

Methods: A single center, retrospective study in patients submitted to surgical resection for IPMN was conducted, between 1/2008-6/2016, to identify predictive factors for malignancy, and to evaluate the surgical results.

Results: Thirty-nine patients were submitted to a surgical resection. The median age was 68 years (61.5% females). Adenocarcinoma and high-grade dysplasia were present, in 7 and 4 patients, respectively. A significant association was identified with the phenotype and the degree of atypia ($p = 0.001$), and duct origin and degree of atypia ($p = 0.026$). Malignant transformation was associated with intestinal or pancreatic-biliary subtypes.

Discussion and Conclusions: Applying the European guidelines, all adenocarcinoma would have undergone surgical resection, but 1 with high-grade dysplasia would not be resected. If we applied the American guidelines, 1 patient with adenocarcinoma and 3 with high-grade dysplasia wouldn't be submitted to resection. The decision in patients with these lesions requires multidisciplinary teams and a tailored based approach.

Key words: carcinoma, pancreas, pancreatic cancer, pancreatic cyst, pancreatic ductal, pancreatic surgery

INTRODUCTION

Pancreatic IPMN is a tumor arising from the pancreatic duct with malignant potential, corresponding to 1-3% of all pancreatic exocrine neoplasms. It was first described by Ohashi et al. in 1982 but only recognized by the World Health Organization in 1996 (1-2).

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Pancreatic IPMN can be divided according to its origin in the pancreatic duct, with lesions of the main duct (MD), the branch ducts (BD) or mixed-type. These lesions are characterized by the proliferation of pancreatic ductal epithelium (often with papillary aspect), hypersecretion of mucin and cystic dilation (1).

The incidence of pancreatic cystic neoplasms has been reported to be rapidly increasing over the past two decades, mainly due to the incidental finding in routine computed tomography (CT) and ultrasonography (US) scans (3).

They can be diagnosed in a wide age range, although most prevalent between the 6th and 7th decades of life, with no gender predominance (1).

The diagnosis, characterization and treatment decisions are difficult and require a multidisciplinary approach (4).

The study aims were: to evaluate the surgical results in our institution, to identify factors predicting malignancy in IPMN and to assess the validity of recently introduced IPMN guidelines in our population.

MATERIAL AND METHODS

Retrospective and single-center study (tertiary hospital), reviewing the files of patients submitted to surgical resection for pancreatic IPMN, between January 2008 and June 2016. Demographic, operative, postoperative and histological data were collected. Patients were all studied by CT and/or magnetic resonance imaging (MRI) and some underwent endoscopic US (EUS) evaluation with EUS-guided fine needle aspiration (FNA). Data was analyzed by chi-square test and Kruskal-Wallis test (SPSS®22), and was considered statistically significant when $p < 0.05$.

RESULTS

During the study period, 39 patients were submitted to a surgical resection for IPMN. The median age was 68 years (range – 45 to 81 years-old) with a predominance of the female gender (61.5% - 24 females).

Surgical procedures are listed in *table 1*. In 17 patients (43.6%) a laparoscopic approach was used, with a conversion rate of 29.4% (5/17). The reasons for conversion to open surgery were hemorrhage (2 cases) or technical difficulties (3 cases).

The median hospital stay was 13 days (range – 4 to 74 days). The most common surgical complication was intra-abdominal collection in 7 cases, 5 of which required percutaneous drainage. Morbidity was

Table 1 – Surgery type

Surgery type	Number of patients
Pancreatoduodenectomy	11
Distal Pancreatectomy	8
Distal Pancreatectomy with spleen preserving	7
Subtotal Distal Pancreatectomy	5
Central Pancreatectomy	4
Total Pancreatoduodenectomy	3
Enucleation	1

Table 2 – Morbidity according to Clavien-Dindo classification⁵

Clavien-Dindo classification	Number of patients
I	2
II	10
IIIa	5
IIIb	4
IVa	0
IVb	0
V	1

classified according to the Clavien-Dindo classification (5) (*table 2*). Ninety day mortality was 2.6% (1 case – septic shock). The median follow-up was 52 months (range – 2 to 121 months).

Regarding histological data, all resection margins were disease-free (R0). The median lesion size was 27 mm (range – 6 to 60 mm). We did not find a statistically significant association between cyst size and degree of atypia ($p = 0.121$). In 7 patients (17.9%) IPMN was associated with invasive carcinoma, and these lesions exhibited intestinal or pancreatic-biliary phenotypes. Low-grade and high-grade dysplasia were documented in 61.5% (24 patients) and 10.3% (4 patients), respectively, of the remainder IPMNs.

In our study, there was a statistically significant association between the phenotype and the degree of atypia ($p = 0.001$). Gastric phenotype was associated with absent or mild dysplasia; intestinal phenotype was associated high-grade dysplasia or malignant transformation; pancreatic-biliary or mixed phenotypes exhibited either low-grade dysplasia or malignant transformation.

Concerning the duct origin, a significant association with the degree of atypia ($p = 0.026$) was also found. Only 1 case of BD (5.3%) had high-grade dysplasia; in MD IPMN, 42.9% had high-grade dysplasia or adenocarcinoma.

DISCUSSION

IPMN are diagnosed more often by the increased use of imaging exams, namely CT scan and MRI. MD or mixed-type lesions are at higher risk of malignancy, when compared to the BD type (40-92% vs. 5-30%). However, symptomatic BD IPMN have a higher risk of malignancy than asymptomatic lesions (30% vs. 5%) (6).

In 2006, a panel of experts convened in Sendai, and published consensus guidelines for the management of IPMNs. According to these experts, MD or mixed-type IPMNs should be resected, as should BD IPMNs that are symptomatic, larger than 3 cm, with more than 6 mm dilation of MD, with the presence of a solid component or positive cytology for malignancy (6).

The Sendai guidelines were widely adopted worldwide and reported to be safe, with a high negative predictive value. With time, however, these guidelines were recognized as having limitations, and, in 2012, new guidelines were established in Fukuoka, but their utility has not yet been validated. These guidelines consider that MD or mixed-type lesions continue to have surgical indication. However, in cases of BD IPMNs a watch and wait strategy is reasonable in asymptomatic patients without high risk (HR) stigmata (main pancreatic duct >10 mm in size, rapid growth of lesions, presence of mural nodules or cytological atypia) (3,6-10). The Fukuoka consensus guidelines stratify IPMN into HR, worrisome risk (WR), and low risk (LR). Stratification of IPMN into HR and WR groups resulted in a higher positive predictive value (PPV) in the HR group, but a similarly low PPV when compared with the 2006 consensus criteria, with some malignant IPMN potentially missed (8).

The European Guidelines (2013) also consider that MD or mixed-type IPMNs are an indication for resection. In BD IPMNs, imaging surveillance is reasonable in asymptomatic patients (without obstructive jaundice, diabetes or acute pancreatitis) with lesions smaller than 4 cm, and without high risk stigmata (mural nodules, more than 6 mm dilatation of the MD or cytological atypia). Additionally, elevated serum carbohydrate antigen (CA) 19.9 levels or a growth rate of more than 2mm/year, are relative risk factors that should be considered in the evaluation of these patients (4,7,10). Applying the European guidelines to our patients, the 7 patients with adenocarcinoma would have undergone surgical resection, but 1 of the 4 tumors with high-grade dysplasia would not be resected (*table 3*).

The American Gastroenterological Association (2015) restricted indications for surgery to both a solid component and a dilated pancreatic duct and/or

Table 3 – Patients submitted to surgery that fills surgical indications according to the different guidelines

Guidelines	Adenocarcinoma (n=7)	High-grade dysplasia (n=4)
European 2013	7	3
American 2015	6	1
Sendai 2016	7	2

concerning features on EUS and FNA, and recommended to stop surveillance if no significant change had occurred in a pancreatic cyst after five years surveillance (7,11). If we applied the American guidelines, 1 patient with adenocarcinoma and 3 with high-grade dysplasia would not be submitted to resection (*table 3*).

A new panel of experts convened in 2016, again in Sendai, and a new consensus was proposed, concerning prediction of invasive carcinoma and high-grade dysplasia, surveillance, and postoperative follow-up of IPMN (7). For MD tumors, this group strongly recommended surgical resection for all surgically fit patients with MD ≥ 10 mm (dilation of 5-9 mm should be considered as one WR), jaundice or mural nodules ≥ 5 mm (11). In BD IPMN, if cytology positive for high-grade dysplasia and the presence of mural nodules ≥ 5 mm, patients should undergo resection in fit patients without further testing. If WR was present (cyst of ≥ 3 cm, enhancing mural nodule < 5 mm, thickened/enhanced cyst walls, MD size of 5–9 mm, abrupt change in the MD caliber with distal pancreatic atrophy, lymphadenopathy, elevated serum level of CA19-9 and a rapid rate of cyst growth > 5 mm / 2 years) patients should be evaluated by EUS to further stratify the lesion. If mural nodules ≥ 5 mm, suspicious MD involvement and suspicious or positive for malignancy cytology were EUS documented, surgery should be proposed (11). With this new recommendation, all of our patients with adenocarcinoma would be submitted to resection, but 2 with high-grade dysplasia would not (*table 3*).

Histological subtypes also have clinical implications. Gastric subtype (38.5% of our cases; literature 35.5 to 46.1%) is typically associated with low-grade dysplasia, as can be seen in our series, but when there is malignant transformation, tumors tend to be more aggressive (tubular type) (6,12-13). The pancreaticobiliary subtype (35.9% of our cases; literature 11.3 to 14.6%) is less well characterized and when carcinoma develops, is also more aggressive (11-12). On the other hand, the intestinal subtype (10.3% of our patients; literature 26.6 to 34.6%) is most often associated with high-grade dysplasia or malignant transformation, but has an indolent behavior (6,12). In our series, all cases

of intestinal subtype had MD origin, which is according to the literature. Malignant transformation was associated with intestinal or pancreatic-biliary subtypes: 50% of intestinal and 21.4% of pancreatic-biliary subtype tumors presented with malignant transformation. The pre-operative identification of the BD IPMN subtypes would, therefore, be an important tool to more accurately decide between surgical resection or imaging follow-up (12).

CONCLUSION

In conclusion, IPMN have for a long time been recognized as pre-malignant lesions (14), and its surgical excision remains recommended in MD or mixed-type (15-16). In contrast, in BD type, in the absence of HR stigmata, imaging follow-up is acceptable (6,11,16-17).

Pancreatic resection surgery, whatever its extent, is still associated with a high rate of post-operative complications and mortality between 1 and 3% in reference centers (6,18). A multidisciplinary, tailored based approach, considering the risk of malignancy, clinical condition and cyst location is mandatory.

Our study presents the limitations of a single-center, retrospective series with a relatively small caseload, more studies being required to evaluate the applicability of the different guidelines.

Ethical approval

The terms of the Helsinki Agreement have been respected.

Author contribution

All of author had contributed to this article. All authors approved the final manuscript.

Conflicts of Interest and Source of Funding

Authors have no conflict of interest to declare.

REFERENCES

- Barreiro P, Pinto-Marques P, Chagas C, Couto G, Ramos S, Brito M et al. Neoplasia mucinosa papilar intraductal do ducto principal e dos ductos secundários pancreáticos: a propósito de 2 casos clínicos. *GE J Port Gastrenterol*. 2012;19(6):312-7.
- Fong ZV, Fernández-Del Castillo C. Intraductal Papillary Mucinous Neoplasm of the Pancreas. *Surg Clin North Am*. 2016;96(6):1431-45.
- Goh BK. International guidelines for the management of pancreatic intraductal papillary mucinous neoplasms. *World J Gastroenterol*. 2015;21(34):9833-7.
- Del Chiaro M, Verbeke C, Salvia R, Klöppel G, Werner J, McKay C et al. European experts consensus statement on cystic tumours of the pancreas. *Dig Liver Dis*. 2013; 45(9): 703-11.
- Dindo D, Demartines N, Clavien PA. Classification of Surgical Complications, A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey. *Ann Surg*. 2004; 240: 205-13.
- Tanaka M, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatol*. 2012; 12(3):183-97.
- Vege SS, Ziring B, Jain R, Moayyedi P and the Clinical Guidelines Committee. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts. *Gastroenterology* 2015; 148: 819-22.
- Goh BK, Lin Z, Tan DM, Thng CH, Khor CJ, Lim TK et al. Evaluation of the Fukuoka Consensus Guidelines for intraductal papillary mucinous neoplasms of the pancreas: Results from a systematic review of 1,382 surgically resected patients. *Surgery* 2015; 158:1192-202.
- Yan L, Siddiqui AA, Laique SN, Saumoy M, Kahaleh M, Yoo J et al. A large multicenter study of recurrence after surgical resection of branch-duct intraductal papillary mucinous neoplasm of the pancreas. *Minerva Gastroenterol Dietol*. 2017; 63(1):50-4.
- Del Chiaro M, Ateeq Z, Hansson MR, Rangelova E, Segersvärd R, Kartalis N et al. Survival Analysis and Risk for Progression of Intraductal Papillary Mucinous Neoplasia of the Pancreas (IPMN) Under Surveillance: A Single-Institution Experience. *Ann Surg Oncol*. 2017; 24(4): 1120-6.
- Tanaka M, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatol*. 2017; 17(5): 738-53.
- Koh YX, Zheng HL, Chok AY, Tan CS, Wyone W, Lim TK et al. Systematic review and meta-analysis of the spectrum and outcomes of different histologic subtypes of noninvasive and invasive intraductal papillary mucinous neoplasms. *Surgery* 2015;157: 469-509.
- Koh YX, Chok AY, Zheng HL, Tan CS, Goh BK. Systematic review and meta-analysis comparing the surgical outcomes of invasive intraductal papillary mucinous neoplasms and conventional pancreatic ductal adenocarcinoma. *Ann Surg Oncol*. 2014; 21(8): 2782-800.
- Scheiman JM, Hwang JH, Moayyedi P. American gastroenterological association technical review on the diagnosis and management of asymptomatic neoplastic pancreatic cysts. *Gastroenterology* 2015; 148: 824-48.
- Sugimoto M, Elliott IA, Nguyen AH, Kim S, Muthusamy VR, Watson R et al. Assessment of a Revised Management Strategy for Patients With Intraductal Papillary Mucinous Neoplasms Involving the Main Pancreatic Duct. *JAMA Surg*. DOI:10.1001/jamasurg.2016.3349.
- Marsoner K, Haybaeck J, Csengeri D, Waha JE, Schagerl J, Langeder R et al. Pancreatic resection for intraductal papillary mucinous neoplasm—a thirteen-year single center experience. *BMC Cancer* DOI 10.1186/s12885-016-2887-8.
- Nguyen A, Toste PA, Farrell JJ, Clerkin BM, Williams J, Muthusamy VR et al. Current recommendations for surveillance and surgery of intraductal papillary mucinous neoplasms may overlook some patients with cancer. *J Gastrointest Surg*. 2015; 19(2): 258-65.
- Kimura K, Amano R, Ymazoe S, Ohira G, Nishio K, Hirakawa K et al. The Clinical Indications for Limited Surgery of Intraductal Papillary Mucinous Neoplasms of the Pancreas. *World Journal of Surgery* 2017;41(5):1358-65.