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Risk factors for malignant progression of intraductal papillary mucinous neoplasms

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ABSTRACT

Background: Intraductal papillary mucinous neoplasms of the pancreas are increasingly diagnosed. Due to their malignant potential, greater understanding of their nature is required.
Aims: Define risk factors for malignancy in intraductal papillary mucinous neoplasms.
Methods: An international, multicentre study was performed in Europe and the United States. Clinical databases were reviewed for patients with intraductal papillary mucinous neoplasms diagnosis.
Results: Of 1126 patients, 84 were diagnosed with invasive carcinoma/high-grade dysplasia and were compared to the rest of the cohort. Multivariate logistic analysis showed a statistically significant association between cancer/high-grade dysplasia and the variables smoking history (OR 1.9, 95% CI [1.1–3.1]), body mass index (OR 1.1, 95% CI [1–1.1]), symptoms (OR 3.4, 95% CI [1.9–6]), jaundice (OR 0.1, 95% CI [0–0.3]), and steatorrhea (OR 0.3, 95% CI [0.1–0.8]). Univariate analysis showed no association between malignancy and the cyst number/location ($p = 0.3$ and $p = 0.5$, respectively) although a strong association was shown for cyst size ($p < 0.001$). The presence and size of nodules ($p < 0.01$) and main duct involvement ($p < 0.001$) were also strongly related with malignancy.
Conclusion: The presence of jaundice and steatorrhea, smoking, high body mass index, and imaging features such as cyst size, main duct involvement, and the presence and size of mural nodules are associated with high-grade neoplasia in intraductal papillary mucinous neoplasms.

1. Introduction

Since its first consideration as an independent entity in 1996 [1], intraductal papillary mucinous neoplasms (IPMN) of the pancreas have been diagnosed with increasing frequency [2]. Detection and resection of IPMN offer a unique opportunity to cure and prevent adenocarcinoma of the pancreas, an otherwise highly lethal disease. The main clinical concern related to IPMN is its wide-ranging potential for malignancy from low-risk indolent lesions to those with high incidence of malignant degeneration. It is well-established that this malignant progression varies based on the morphological subtypes [3–6]. The current methods of predicting malignant potential are limited to clinical, morphological, and cyst fluid cytology and biomarker data.

To address these limitations, the aim of the present study is to identify and define the risk factors for malignancy progression in IPMN.

2. Materials and methods

The ethics committee at each of the participating centres approved collection of the registry data.

2.1. Study design and population

This was an international, multicentre study that included four centres. One centre in the USA (Mayo Clinic [Jacksonville, FL]) and

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three in Italy (San Rafaelle Scientific Institute [Milano], Azienda Universitario-Ospedaliera San Giovanni Battista [Torino], and University of Bologna/Hospital of Imola [Bologna]).

We conducted a retrospective descriptive study. Every patient with a clinical suspicion of an IPMN following the actual guidelines criteria [7–10], who also had a high resolution imaging technique (MRI, CT scan, or endoscopic ultrasound [EUS]) performed as a baseline examination, was included in the study. Once in the registry, each patient was prospectively updated with the corresponding follow-up visits until August 2014.

2.2. Epidemiological variables

One demographic standardised data form was completed per patient. All variables were filled with the information available at the time of the diagnosis.

Two environmental factors were also included in this data form: smoking history and alcohol consumption. To assure the absence of bias when comparing smoker groups, the amount and duration of smoking were also collected. These two variables were afterwards merged into one called "pack-years" that was defined as the product of packs smoked per day and the years smoking.

Due to the size difference between the Mayo Clinic and the Italian group cohorts, demographic characteristics were also analysed separately to evaluate possible confounding by centre.

2.3. Visit information

A second, different standardised data form was also filled with the information regarding symptoms, cyst features, imaging tests, and surgery if present. These data was extracted from the clinical charts of each of the follow-up visits performed. For the analysis results presented here, we collected only the information contained in the initial visit, i.e., when the cyst was first diagnosed. This way, a homogeneous criterion was used independently of the final outcome.

For the cyst features, a suspicious diagnosis of IPMN was made when a dilated main pancreatic duct ([MPD] ≥5 mm) or a cystically dilated branch duct (≥5 mm) was recognised. If there was involvement of both main and branch ducts, these patients were placed in the main duct group for the analysis. In case of multiple cysts, the features of the biggest cyst were reported. The cyst size was determined by the maximum dimensions measured in both the major and the minor axes. Mural nodules were considered present if described in the final imaging report. As patients with main duct involvement are almost always referred for surgery, we also performed a secondary analysis of the cyst features to look separately at those patients with isolated side branch involvement. The imaging technique used for the data collection (MRI, CT scan, or EUS) depended on which one was performed in the initial visit. If more than one was performed in the same visit, the order of preference was firstly EUS (as other variables EUS-dependent were also registered in the questionnaire), then MRI, and finally CT scan.

2.4. Criteria for consolidation of groups

Once the whole data was entered in the registry, the final sample was divided into two groups. The first group comprised patients who underwent surgery and had a pathological confirmation of malignancy in the surgical specimen. We included in this group patients with both high-grade dysplasia ([HGD] formerly carcinoma *in situ*) and invasive carcinoma.

On the other hand, the control group included those patients who either underwent surgical resection and the pathological report was consistent with intermediate-grade dysplasia (IGD) or low-grade dysplasia (LGD), or those who had a high clinical suspicion of a non-malignant lesion and, therefore, were included in an observational follow-up programme.

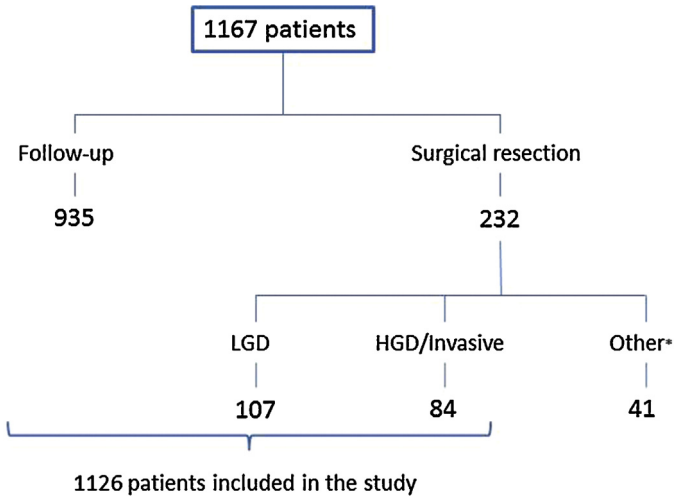

Fig. 1. Patients selected for the final analysis. **Other*: 7 Serous cystadenoma, 9 benign cysts, 1 chronic pancreatitis, 3 neuroendocrine tumours, 12 mucinous cystic neoplasms, 2 other malignant tumours, 7 unknown. LGD, low-grade dysplasia intraductal papillary mucinous neoplasms; HGD, high-grade dysplasia intraductal papillary mucinous neoplasms.

2.5. Statistical analysis

Study data were collected and managed using REDCap (Research electronic Data Capture hosted at Mayo Clinic) database. The Stata 13 software for Mac OS X Lion (Stata Inc., College Station, TX) was used for the analysis. Categorical variables were compared using a χ^2 test or Fischer's exact test and continuous variables were analysed with a two-tailed Student's *t* test or a Wilcoxon rank-sum test when appropriate. Multivariate logistic analysis was performed with the demographical and clinical variables. Imaging variables were not included in the analysis as it would have eliminated a large proportion of patients with missing values and significant loss of power. All variables that had a *p* value of <0.20 in the univariate analysis were considered candidates for the initial model. A backward elimination procedure was used to obtain the final optimal model. Due to the different biological behaviour between BD-IPMNs and MD-/mixed-IPMNs, we also performed two different subanalyses in these populations.

All statistical tests were two-sided and considered significant when *p* values were less than 0.05. Bonferroni correction was not used for variables *a priori*.

3. Results

A total of 1167 patients with a clinical suspicion of an IPMN were included from October 1997 until November 2013. This included 972 patients from Mayo Clinic, 95 from San Raffaele Hospital, 87 from San Giovanni Battista Hospital, and 13 from Imola Hospital.

From this cohort, 41 patients were finally excluded from the analysis due to a pathological diagnosis different from IPMN after surgical resection, leading to a final study sample of 1126 patients (Fig. 1). Overall, the median age was 70.6 years, the median BMI was 25.9, and females were slightly predominant (61%). Eighty-one percent of the study cohort had a EUS performed in their initial visit, followed by MRI (5%) and CT (3%). Two hundred fifty-four patients (23%) had a FNA-based IPMN diagnosis in their first visit. A total of 84 patients (7.5%) were diagnosed with either HGD or IPMN-derived invasive carcinoma (29 cases [2.5%] and 55 cases [4.7%], respectively). The mean time of the incidental cases (>3 months