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Differences between main-duct and branch-duct intraductal papillary mucinous neoplasms of the pancreas

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Abstract

In the last decade, intraductal papillary mucinous neoplasms (IPMNs) have become commonly diagnosed. From a morphological standpoint, they are classified in main-duct IPMNs (MD-IPMNs) and branch-duct IPMNs (BD-IPMNs), depending on the type of involvement of the pancreatic ductal system by the neoplasm. Despite the fact that our understanding of their natural history is still incomplete, recent data indicate that MD-IPMNs and BD-IPMNs show significant differences in terms of biological behaviour with MD-IPMNs at higher risk of malignant degeneration. In the present paper, clinical and epidemiological characteristics, rates of malignancy and the natural history of MD-IPMNs and BD-IPMNs are analyzed. The profile of IPMNs involving both the main pancreatic duct and its side branches (combined-IPMNs) are also discussed. Finally, general recommendations for management based on these differences are given.

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INTRODUCTION

In 1982, Ohhashi *et al*^[1] from Japan described four cases of pancreatic cancer characterized by overproduction of mucus, diffuse dilatation of the pancreatic ductal system and presence of bulging papilla. In the next decade, small case reports from Europe and the United States referred to this condition as "mucinous ductal ectasia"^[2-4]. Only in 1996 were these lesions defined as intraductal papillary mucinous neoplasms (IPMNs) by the World Health Organization (WHO) classification for tumors of the exocrine pancreas^[5]. Main-duct IPMNs (MD-IPMNs) are characterized by involvement of the main pancreatic duct with or without associated involvement of the branch ducts (combined IPMNs); they usually present as a dilated (≥ 1 cm) main pancreatic duct or as cystic dilation of the main duct and its branches; branch-duct IPMNs (BD-IPMNs) originate in the side branches of the pancreatic ductal system, appearing as a cystic lesion that always communicates with a non-dilated main pancreatic duct^[6].

In the last ten years, the diagnosis of IPMNs has significantly increased^[7,8]. This can be related to improved

imaging techniques, greater awareness of this condition by the gastroenterological community and incidental diagnosis among asymptomatic individuals.

The distinction among different IPMN sub-types is not only of “morphological” significance but has a practical impact on the management of patients with IPMNs. In this paper, we will review the clinico-pathological and epidemiological characteristics of IPMNs, their natural history and risk of malignancy with some guidelines for their management.

CLINICAL AND EPIDEMIOLOGICAL CHARACTERISTICS

IPMNs are typically found in elderly people. In most series, the median age of patients at the diagnosis is 65-70 years^[6,8-19]. However, while a few studies made a clear distinction between MD-IPMNs and BD-IPMNs, most series include both subgroups. We recently have analyzed the clinical and epidemiological characteristics of a large series of IPMNs who underwent surgical resection at the University of Verona and at the Massachusetts General Hospital^[20]. One hundred and fifty-nine patients had histologically confirmed BD-IPMNs while 81 had MD-IPMNs. Median age at presentation was similar in the two groups (66 and 67 years respectively) as well as a family history of pancreatic cancer (7.5% of MD-IPMNs and 11% of BD-IPMNs) and the presence of extra-pancreatic neoplasms (22% of MD-IPMNs and 20% of BD-IPMNs). The most common extra-pancreatic neoplasms were breast, colorectal, lung and prostate cancer. Other reports suggest that patients with IPMNs are at higher risk of developing extra-pancreatic tumors if compared with the general population and, in keeping with our data, colorectal cancer and adenomatous polyps are commonly found in IPMNs patients^[21-24]. Interestingly, BD-IPMNs were most commonly found in females (57%) and MD-IPMNs in males (55.5%). BD-IPMNs and MD-IPMNs were found in the proximal pancreas in 64% and 52% of cases respectively and BD-IPMNs were more frequently associated with a diffuse pattern (23% *vs* 4%)^[20].

Moreover, while BD-IPMNs are characterized by the presence of multifocal cystic lesions in different sites of the gland (sometimes with a complete involvement of the entire pancreas), MD-IPMNs spread along the main pancreatic duct, also possibly being skip lesions^[25].

Clinically, BD-IPMNs were more frequently discovered in asymptomatic individuals (34.5% *vs* 13.5%). Abdominal pain was common in both MD-IPMNs and BD-IPMNs but in many cases it was an aspecific symptom. On the other hand, more specific and objective symptoms such as jaundice and weight loss were significantly associated with the presence of MD-IPMNs^[20]. The main features of both IPMNs are briefly summarized in Table 1.

NATURAL HISTORY AND RISK OF MALIGNANCY

Our knowledge of the natural history of IPMNs is still

incomplete but a better awareness of the distinction between the main and branch duct variants have contributed to a better understanding. It is well known that IPMNs can show a series of dysplastic changes from adenoma to invasive carcinoma and that different degrees of dysplasia can be found within the same lesion^[5,6,26,27]. The frequency of malignancy (*in-situ* and invasive carcinoma) in MD-IPMNs is high, ranging between 60% and 92% with a mean of 70%^[6,10,16-19]. The largest published series on MD-IPMNs combines the experience of Massachusetts General Hospital and University of Verona with 140 resected patients^[18]. In this study, we found that patients with malignant MD-IPMNs were significantly older by 6.4 years than those with benign ones. The experiences from Johns Hopkins^[10] and Indiana University^[16] confirmed this observation, showing that patients with MD-IPMNs with invasive cancer are older than those with noninvasive neoplasms by 5 years. These findings suggest that most, if not all, MD-IPMNs can progress to malignancy.

By contrast, in BD-IPMNs the frequency of malignancy is significantly lower (between 6% and 46%, with a mean of 25%) and that of invasive cancer ranges from 0 to 30% (mean of 15%)^[6,8,9,10-16]. In the combined experience of Massachusetts General Hospital and University of Verona, 145 patients underwent surgical resection for BD-IPMNs^[9]. Of these, 32 (22%) had malignancy but there was invasive carcinoma in only 11% (16 patients) with no age difference between benign and malignant tumors (66 years *vs* 67.5 years). Schmidt *et al*^[16] and Peleaz-Luna *et al*^[13] reported a rate of malignancy of only 19% and 12% in their series of 103 and 77 patients who underwent surgery for BD-IPMNs. Levy *et al*^[2] calculated the longitudinal risk of malignant transformation since the first clinical or radiological sign in a series of 106 patients with histologically proven IPMNs or probable IPMN (30 patients with a radiological diagnosis of BD-IPMNs). Overall ten year actuarial risk of occurrence of IPMNs with low-grade dysplasia, high-grade dysplasia and invasive cancer was 67%, 49% and 29% respectively. Five year actuarial risk of malignancy was 15% for BD-IPMNs and 63% for MD-IPMNs ($P < 0.001$).

THE PROFILE OF COMBINED-INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

Combined-IPMNs are characterized by an involvement of both the main pancreatic duct and the branch-ducts of the pancreas by the tumor. Combined-IPMNs have historically been considered as an extension of MD-IPMNs into the side branches of the ductal system^[6,18]. However, it is unclear if combined-IPMNs represent a progression of MD-IPMNs, a progression of multifocal BD-IPMNs or if they represent a disease itself with a specific profile. In this light, we have recently compared the clinical and epidemiological characteristics of 159 patients with BD-IPMNs, 81 MD-IPMNs and 149 combined-IPMNs in order to elucidate differences among the three groups^[20].

Table 1 Epidemiological and clinicopathological characteristics of patients with main-duct, branch-duct and combined intraductal papillary mucinous neoplasms *n, %*

	Main duct IPMNs (<i>n</i> = 81)	Branch duct IPMNs (<i>n</i> = 159)	<i>P</i> value, MD vs BD
Median age, yr (range)	67 (37-85)	66 (35-90)	n.s.
Sex			
Female	36 (44.5)	91 (57)	0.04
Male	45 (55.5)	68 (43)	
Positive family history of pancreatic cancer	6 (7.5)	16 (11)	n.s.
Positive History of other neoplasm	18 (22)	32 (20)	n.s.
Tumor site			
Proximal	52 (64)	82 (52)	n.s.
Distal	26 (32)	40 (25)	n.s.
Diffuse	3 (4)	37 (23)	0.0001
Entire pancreas along MPD	3 (4)	0	
Multifocal lesions	0	37 (23)	
Incidental diagnosis	11 (13.5)	55 (34.5)	0.0001
Abdominal pain			
Yes	45 (53)	72 (45)	n.s.
No	38(47)	87 (55)	
Presence of other symptoms ^a			
Yes	59 (73)	72 (45)	0.0001
No	22 (27)	87 (65)	
Jaundice	14 (17)	7 (5)	0.001
Diabetes	10 (12)	14 (9)	n.s.
Weight loss	41 (50.5)	37 (23)	0.0001
Acute pancreatitis	14 (17)	27 (17)	n.s.
Pathology			
Adenoma	9 (11)	71 (44)	0.0001
Borderline	17 (21)	54 (34)	0.05
Carcinoma <i>in situ</i>	16 (20)	17 (11)	n.s.
Invasive carcinoma	39 (48)	17 (11)	0.0001
Presence of lymph node metastases ^b	13 (33)	4 (23.5)	n.s.

^aSome patients complained of more than 1 symptom; ^bRate of lymph node metastases was calculated considering only patients with invasive intraductal papillary mucinous carcinomas. IPMNs: Intraductal papillary mucinous neoplasms; MD: Main-duct; BD: Branch-duct.

All these patients underwent surgical resection and therefore a histological diagnosis was available. Interestingly, combined-IPMNs showed close overlapping similarities with MD-IPMNs with regard to clinico-pathological and epidemiological characteristics. For example we found that MD-IPMNs and combined-IPMNs have the same sex ratio (female 44%, male 54%) opposite to that of BD-IPMNs. While the median age at presentation was similar in the three groups, patients with MD-IPMNs and combined-IPMNs with invasive cancer were significantly older than those with noninvasive neoplasms, suggesting tumor progression. As previously described, BD-IPMNs were more likely asymptomatic whereas the majority of patients with MD-IPMNs and combined-IPMNs were symptomatic. Finally, most patients with BD-IPMNs had an adenoma (44%) with a low prevalence of cancer (overall malignancy 22%, invasive cancer 11%). On the other hand, MD-IPMNs and combined-IPMNs contained malignant elements in 68% and 62% respectively, with invasive cancer present in 48% and 42%. Considering all these findings, we conclude that combined-IPMNs can be considered a sub-group of MD-IPMNs. The presence of an age difference between non-invasive and invasive tumors and the high frequency of malignancy in MD-IPMNs and combined-IPMNs^[10,18,20] suggest that these IPMNs subtypes share an aggressive biology characterized by progression to invasive cancer.

ADVANCES IN PATHOLOGY

Based on morphological criteria and mucin expression, IPMNs can be classified in four subtypes including gastric, intestinal, pancreatobiliary and oncocytic types^[6,27]. Ban *et al.*^[28] evaluated the features of 80 gastric-type IPMNs and of 30 with intestinal-type. They showed that gastric-type IPMNs were mostly BD-IPMNs (98%) and were associated with high-grade dysplasia or invasive cancer in only 8% of cases whereas the intestinal-type IPMNs were usually MD-IPMNs (73%) and had malignancy in 80% of cases. They also showed that intestinal-type IPMNs were characterized by MUC2 expression and that low-grade PanIN complexes were typical features of gastric-type IPMNs. These authors concluded that gastric and intestinal-type IPMNs have distinct histopathological features and mucin profiles, perhaps suggesting that they follow different biological pathways. This in turn may account for the clinical differences between BD-IPMNs and MD-IPMNs.

Unfortunately, specific genetic analysis in order to elucidate differences in the biological behavior among MD-IPMNs, BD-IPMNs and combined-IPMNs has not been published yet.

DIFFERENCES IN MANAGEMENT

Briefly, the differences in clinical-pathological characteris-

tics, risk of malignancy and biological behavior between MD-IPMNs (including the combined-type) and BD-IPMNs have a strong impact on their clinical management. Considering the high prevalence of malignancy/invasive carcinoma in MD-IPMNs and the lack of clinical and radiological parameters predictive of malignancy, all of these lesions in surgically fit patients have to be resected^[6,10,16-19]. On the other hand, several studies demonstrated that BD-IPMNs less than 3 cm in size, without nodules and with no symptoms can be carefully managed in a surveillance program whereas surgical resection is indicated for any symptomatic lesion, for BD-IPMNs with a median diameter more than 3 cm and in the presence of nodules because these parameters are more frequently associated with a potential risk of malignancy^[6,8,9,10-15].

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