Intraductal Papillary Mucinous Neoplasms: The Bologna Experience

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ABSTRACT

Background In the last decades, the attention to Intraductal Papillary Mucinous Neoplasms (IPMNs) has risen due to the increase of their incidental diagnosis. The aim of the present study was to evaluate which factors influenced survival in population affected by intraductal papillary mucinous neoplasms. **Methods** A retrospective study on a prospective database of 357 patients observed at our Institute from January 2007 to December 2016 was conducted. Pre-, intra- and postoperative data were collected. Patients managed conservatively were compared with those who underwent surgery as regards demographic, clinical data, radiological work up, features of the cysts and overall and disease specific survival. Multivariate analyses were carried out in order to assess factors related to patient's management as well as those related to overall survival. **Results** Multivariate analysis showed that the factors strongly related to surgery were: site (tail of the pancreas-OR 4.48; P=0.011), presence of mural nodules (OR 15.39; P<0.001), Wirsung duct size >5 mm (OR 8.55; P<0.001), Wirsung duct size ≥ 10 mm (OR 133.75; P<0.001), positive citology (OR 19.81; P=0.008) and acute pancreatitis (OR 16.7; P<0.001); conversely, age was independently related to the follow up strategy (OR 0.93; P=0.001). Furthermore, parameters that significantly influenced overall survival were: age (HR 1.07; P<0.001), jaundice (HR 7.67; P<0.001) and the presence of mural nodules (HR 2.03; P=0.019). **Conclusions** Despite the limitations of the study, the main factors related to OS in our experience were age, jaundice and the presence of mural nodules within the cyst.

INTRODUCTION

The management of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas represents an important challenge in referral centres for pancreatic diseases [1, 2] expecially in the last years for the increase of their incidental diagnosis. The consensus conferences held, first, in Sendai in 2006 [3] and, secondly, in Fukuoka in 2010 [4], recognized risk factors to help surgeons and gastroenterologists in the choice of a proper management of the different types of IPMNs because they are considered a precursor lesion of pancreatic cancer via adenoma-carcinoma sequence [5]. Recent meta-analyses [6, 7, 8] and large cohort studies [9, 10, 11, 12] have provided informations regarding the accuracy of radiological features in IPMNs in order to detect in situ (high-grade dysplasia) or invasive carcinomas and to establish their proper management. The present study reports the experience of a tertiary referral centre regarding the management of IPMNs according Sendai and Fukuoka consensus conferences with the aim of evaluating the factors that influenced overall survival of patients who underwent to surgical approach compared to those who were followed-up.

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Abbreviations BD branch duct; CEA carcinoembryogenic antigen; CT computed tomography scan; ERCP endoscopic retrograde cholangiopancreatography; EUS endoscopic ultrasound; FNA fine needle aspiration; HGD: high-grade dysplasia; IPMN intraductal papillary mucinous neoplasm; LGD low-grade dysplasia; MD main duct; MRI magnetic resonance imaging; PAC: pancreatic adenocarcinoma; PCN pancreatic cystic neoplasm; PD pancreatic duct
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PATIENTS AND METHODS

With the approval of the Ethic Committee of S.Orsola-Malpighi Hospital and patient informed consent, all patients with diagnosis of IPMN observed in our Department of Surgery from January 2007 to December 2016 were collected in a prospective database. Diagnostic work-up included abdominal ultrasonography (US), magnetic resonance cholangiopancreatography (MRCP), endoscopic ultrasonography (EUS) with or without fine needle aspiration and /or fine needle biopsy, serum CA 19-9 value and, in selected cases, multidetector computed tomography (MDCT). Cystic lesions not resected were classified as likely IPMNs if there were one or more pancreatic cysts >5 mm in diameter communicating with the main pancreatic duct (MPD) [3, 4] and divided in IPMN type I-II or III in relation to their morphological characteristics. According Fukuoka Consensus guidelines

[4], type I-III have more probability to be or to became over the time a malignant tumor (70% of cases) respect on IPMN type II (20-25% of cases). Thus, IPMN type I-III need a surgical approach while IPMN type II need a surgical approach only in presence of specific features. Surveillance protocol was made according Italian consensus guidelines of cystic pancreatic neoplasms [13] using MRCP [14], while MDCT was reserved for selected patients in whom MRCP was not possible. In all patients who underwent pancreatic resection, the pathological diagnosis of IPMN type I-II and III was reported with their grade of dysplasia: low/moderate dysplasia, in situ (high-grade dysplasia) or invasive carcinoma. Types of surgical procedures and their postoperative outcomes were reported (mortality and morbidity rates). For each patient the following data were collected: age at diagnosis, sex, presence of major comorbidities, imaging strategy (weak= ultrasonography and/or MDCT scan; suboptimal=ultrasonography and/or CT scan plus EUS or MRCP; optimal=plus EUS and MRCP), serum CA 19-9 value, cysts size, number and location, presence of high risk stigmata (contrast enhanced mural nodules, jaundice, main pancreatic duct size >10 mm), positive cytology for carcinoma or high grade dysplasia and presence of worrisome features (acute pancreatitis, cysts size >30 mm, thickened walls/septa, main pancreatic duct size 5-9 mm). Finally, we recorded the length of follow-up of the entire cohort of patients and we calculated overall survival (OS) and disease specific survival (DSS). Patients who underwent surveillance and those who underwent pancreatic resection were evaluated and compared.

STATISTICAL ANALYSIS

Medians, standard deviations and frequencies were used to describe the data. Medians and 95% confidence intervals of survival were estimated using the Kaplan-Meier method and were compared between the two groups of patients using the log-rank test. Univariate analyses were carried out using the Fisher's exact test and the Student's test. Multivariate analyses were carried out using logistic regression. All statistical analyses were carried out by running Microsoft Excel and IBM SPSS for Windows (version 22.0) on a personal computer. Two-tailed P values less than 0.05 were considered statistically significant.

RESULTS

Three-hundred and fifty-seven patients affected by IPMNs were observed at our Department of Surgery, Sant'Orsola- Malpighi Hospital, University of Bologna, from January 2007 to December 2016. The characteristics of the entire population and comparison between patients who underwent surveillance (n=271) and those who underwent surgical therapy (n=86) were summarized in **Table 1**. Briefly, the population was mainly elderly (median 70.9 years), female (59.9%) with comorbidities (66.4%). At multivariate analysis, the factors significantly different between patients followed and resected were: age (72.2 versus 69.7 years; P=0.001); cystic size between 11-20 mm (82.6% versus 17.4%; P=0.047), 21-30 mm (72.3% versus 27.7%; P=0.031), >30 mm (32.1% versus 67.9%; P<0.001); among high risk stigmata, contrast enhanced mural nodules (20.9% versus 79.1%; P<0.001), MPD>10 mm (10% versus 90%; P<0.001), positive citology (12.5% versus 87.5%; P=0.008); among worrisome features, acute pancreatitis (30.4% versus 69.6%; P<0.001), MPD between 5 and 9 mm (43.3% versus 56.7%; P<0.001). In the patient who underwent surgical treatment the following operations were performed: 31 distal pancreatectomies, 33 pancreaticoduodenectomies and 22 total pancreatectomies. Postoperative mortality rate was 2.3% (2 cases) and major complications (Clavien-Dindo 3-4) 15.1% (13 cases). Among the 86 patients who underwent surgical treatment, 67(77.9%) were IPMNs type I or III and 19(22.1%) IPMNs type II. The pathological diagnosis of IPMNs type I-III showed in 20 cases (29.8%) a low/moderate dysplasia; in the remaining 47(70.2%) a severe dysplasia or invasive carcinoma; in IPMNs type II there was a low/moderate dysplasia in 10 cases(52.6%) and a severe dysplasia or invasive carcinoma in 9 cases(47.4%). There was no statistical difference between IPMN type I-III and IPMN type II regarding pathological diagnosis (P=0.100), even if IPMNs type I-III were more frequently malignant than IPMN type II (70.2% versus 47.4%). The patients followed were mainly affected by IPMN type II (250 cases-92.2%), while 21 patients (7.8%) were diagnosed as IPMN type I-III and refused surgical treatment.

The median follow-up of the entire cohort of patients was 37.5 months (range 1-138). Patients surgically treated had a median follow-up of 39.7 months (1-138), 23 (26.7%) died (2 postoperative death), 13(15.1%) for the disease. Patients who underwent surveillance (n=271) had a median follow-up of 36.8 months (range 1-136), 10 (3.7%) underwent pancreatic resection during follow-up; 43 (15.9%) died, only 2 (0.7%) for pancreatic cancer.

The mean overall and disease specific survival of the entire cohort of patients was 103.8±3.7 and 129.5±2.3 months, respectively. The 5-year overall survival of patients who underwent surveillance and surgery was 94.7±1.4% and 75.2±5.7%, respectively **(Figure 1)**. There was no statistical differences in the OS between patients who underwent surveillance and those to surgical treatment (P=0.452). At multivariate analysis the factors related to OS were the following: increasing age (HR 1.07-1.03-1.10; P<0.001); contrast enhanced mural nodules (HR 2.03-1.12-3.69; P=0.019) and jaundice (HR 7.67-2.94-19.98; P<0.001) **(Table 2)**.

DISCUSSION

Currently, the management of IPMNs remains controversial because their natural history is still unknown, even if they are considered a precursor lesion of pancreatic cancer via adenoma-carcinoma sequence [5]. The Sendai and Fukuoka consensus findings [3, 4] suggested a surgical approach only in the presence of predictive factors for

Table 1. Characteristics of the entire cohort of patients affected by intraductal papillary mucinous neoplasms (n=357) and comparison between patients who underwent surveillance (n=271) and those who underwent surgical therapy (n=86).

Parameters	Total n=357(%)	Surveillance n=271(%)	Surgery n=86(%)	Univariate analysis OR (95 %CI)	P value	Multivariate Analysis OR (95 %CI)	P value
Sex							
Male	143(40.1)	101(70.6)	42(29.4)	0.62(0.38-1.01)	0.058	1.14(0.50-2.61)	0.742
Female	214(59.9)	170(79.4)	44(20.6)				
Age (years; median, range)	70.9 (40.5-93.3)	72.2 (40.5-93.3)	69.7 (40.6-82.9)	0.97 (0.95-1.00)	0.088	0.93 (0.90-0.97)	0.001
Comorbidities							
No	120(33.6)	96(80)	24(20)	1.41(0.83-2.41)	0.200	**	**
One or more	227(66.4)	175(73.8)	62(26.2)				
Imaging strategy							
Weak	80(22.4)	54(67.5)	26(32.5)	Referent	<0.001	Referent	Referent
Suboptimal	221(61.9)	183(82.8)	38(17.2)	2.31(1.29-4.16)	0.005	0.41(0.15-1.09)	0.075
Optimal	56(15.7)	34(60.7)	22(39.3)	0.32(0.16-0.61)	0.001	0.68(0.19-2.36)	0.550
CA 19-9 (U/mL; median, range)	21.5 (0.8-2888)	12.1 (0.8-2888)	31 (1.0-1824)	1.01 (0.99-1.03)	0.108	**	**
Size							
0-10	87(24.4)	83(95.4)	4(4.6)	Referent	<0.001	Referent	Referent
11-20	149(41.7)	123(82.6)	26(17.4)	0.22(0.07-0.67)	0.008	3.50(1.01-12.09)	0.047
21-30	65(18.2)	47(72.3)	18(27.7)	0.55(0.27-1.09)	0.091	4.68(1.15-19.09)	0.031
>30	56(15.7)	18(32.1)	38(67.9)	0.18(0.08-0.39)	<0.001	47.71(11.68-194.77)	<0.001
Site (mm; median and range)							
Diffuse	147(41.2)	116(78.9)	31(21.1)	Referent	0.023	Referent	Referent
Head	127(35.6)	96(75.6)	31(24.4)	1.57(0.66-3.72)	0.302	0.44(0.16-1.20)	0.112
Body	47(13.2)	39(83)	8(17)	0.25(0.09-0.70)	0.008	1.53(0.44-5.36)	0.498
Tail	36(10.0)	20(55.6)	16(44.4)	2.99(1.38-6.45)	0.005	4.48(1.40-14.25)	0.011
Number of lesions							
Single	176(49.3)	131(74.4)	45(25.6)	0.85(0.52-1.3)	0.520	**	**
Multiple	181(50.7)	140(77.3)	41(22.7)				
High risk stigmata							
CE mural nodules	43(12.0)	9(20.9)	34(79.1)	19.03(8.61-42.05)	<0.001	15.39(4.56-51.93)	<0.001
Jaundice	7(2.0)	0	7(100)	*	<0.001	*	0.750
MPD>10 mm	20(5.6)	2(10)	18(90)	35.60(8.06-157.16)	<0.001	133.75(15.77-1134.12)	<0.001
Positive citology	16(4.5)	2(12.5)	14(87.5)	26.15(5.81-117.71)	<0.001	19.81(2.19-179.25)	0.008
Worrisome features							
Acute pancreatitis	23(6.4)	7(30.4)	16(69.6)	8.62(3.41-21.77)	<0.001	16.70(4.35-64.09)	<0.001
Cyst size >30 mm	63(17.5)	25(39.7)	38(60.3)	7.79(4.31-14.08)	<0.001	0.32(0.05-1.86)	0.206
Thickened wall/septa	90(25.2)	52(57.8)	38(42.2)	3.33(1.97-5.62)	<0.001	0.82(0.29-2.27)	0.700
MPD 5-9 mm	60(16.8)	26(43.3)	34(56.7)	7.83(4.18-14.63)	<0.001	8.55(3.12-23.46)	<0.001

CA 19-9 Carbohydrate Antigen; CEContrast Enhanced; MPD main pancreatic duct

*not computable

** not included

malignancy while in the absence of these risk factors the consensus proposed a follow-up period. However, these consensus guidelines are still under debate probably because an "ideal risk factor" capable of recognising all malignant IPMNs has not been identified. The present study, reported the management, according Sendai and Fukuoka guidelines, and the overall and disease specific survival of a cohort of 357 patients affected by IPMNs.

First of all, in the present study we noted that surgical treatment was limited to about 20% of the entire cohort of patients. In addition, patients who underwent to surveillance were mainly elderly patients (median age, 72 years), affected by small IPMN type II that had an overall and disease specific survival similar to those patients who underwent surgery. Finally only 0.7% died for pancreatic cancer. These data allows to hypothesize that IPMN type II could be considered a disease of the elderly people, usually indolent and benign, rarely with a malignant behavior. Second, the indications for surgery were mainly due to the presence of "high risk stigmata", less frequently to the presence of "worrisome features". In particular, a surgical approach was significantly preferred to surveillance in younger patients (median age, 69 years) with the presence of CE mural nodule, MPD>10 mm, or between 5 to 9 mm in size, positive cytology and symptoms referred to pancreatitis. However, these factors were not always related to malignancy. In fact, in situ or invasive carcinoma was diagnosed in 65.1% of the patients (56 out of 86) who underwent pancreatic resection without significant difference between IPMN type I-III and IPMN type II (P=0.100). These data allowed two considerations: 1) a percentage of patients will undergo surgery without in situ or invasive carcinoma, even in the presence of risk parameters; 2) as we know from Sendai and Fukuoka guidelines, IPMNs type I-III were considered more frequently malignant than IPMNs type II. However,

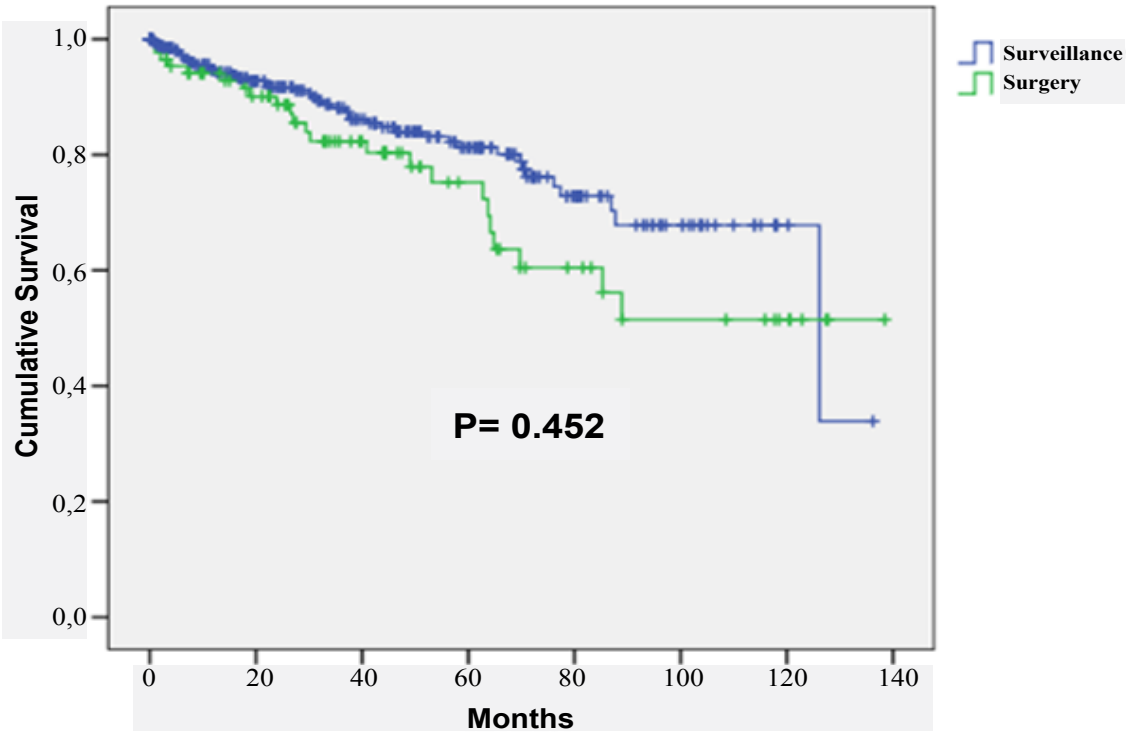

Figure 1. Non -malignant Ecc.

Risk Factors	Multivariate analysis HR (CI 95%)	P value
Sex (M/F)	0.58(0.35-0.95)	0.032
Age (years)	1.07(1.03-1.10)	<0.001
Size (/mm)		
1-10	Referent	
11-20	1.39(0.67-2.89)	0.376
21-30	0.83(0.33-2.06)	0.317
>30	1.96(0.79-4.87)	0.647
Site		
Diffuse	Referent	Referent
Head	0.99 (0.54-1.84)	0.986
Body	1.46 (0.69-3.06)	0.317
Tail	0.77 (0.25-2.33)	0.647
High risk stigmata		
CE mural nodules	2.03 (1.12-3.69)	0.019
Jaundice	7.67 (2.94-19.98)	<0.001
MPD>10 mm	2.21 (0.94-5.22)	0.069
Positive cytology	0.53 (0.14-1.93)	0.337
Worrisome features		
Acute pancreatitis	1.43 (0.59-3.48)	0.426
Cyst >30 mm	1.55 (0.42-5.69)	0.509
Thickened wall/septa	0.73 (0.41-1.31)	0.299
MPD 5-9 mm	1.61 (0.91-2.85)	0.096
Surgery	0.74 (0.34-1.62)	0.452

CE contrast enhanced; CI confidence interval; HR hazard ratio; MPD main pancreatic duct

in patients who underwent surgical treatment, IPMNs type II with specific morphological characteristics can be considered with a similar behavior of IPMNs type I-III. Thus, surgical option is justified.

Results from long-term outcomes, overall and disease specific survival reinforced the hypothesize that IPMNs are rarely malignant. In patients followed, mainly elderly patients affected by small IPMN type II, in fact, only about 4% of patients underwent pancreatic resection and only 0.7% died for pancreatic cancer. It means that the biological behavior of these tumors seem to be indolent and the type of treatment was properly choosen. Nevertheless, it is important to underline that the morphological findings at the time of diagnosis represents only a static picture of the disease, thus its surveillance become mandatory. Overall and disease specific survival were very long and similar between patients resected and those followed. In addition, the disease-specific survival, calculated for the entire population, resulted higher than overall survival. This means that rarely patients dead for the disease, more frequently dead for other reasons, often related to the elderly age. However, factors related to overall survival resulted to be increasing age, contrast enhanced mural nodules and jaundice. The datum that increasing age is related to overall survival confirmed that these patients died not for the disease but for other diseases related to elderly age. On the contrary, the relation between jaundice and contrast enhanced mural nodules and overall survival could be explained by the fact that these factors are strongly related to the malignancy of the disease.

CONCLUSION

In conclusion, despite the limitations related expecially to the retrospective design of the study, it seems reasonable to suggest that IPMNs should be treat as a benign and indolent disease, rarely malignant. Surgical option is rarely performed and only in patients with "high risk stigmata", strongly related to malignancy; in other cases, surveillance is preferred. Overall survival is very long and it is related mainly to elderly patients and to risk factors related to malignancy as well as jaundice and contrast enhanced mural nodules. However, additional multicentric studies are needed in order to identify risk factors (probably including genetic factors) related to overall and disease specific survival.

Conflict of Interest

Riccardo Casadei and the other co-authors have no conflict of interest.

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