Liver, Pancreas and Biliary Tract

Outcomes of intraductal papillary mucinous neoplasm with “Sendai-positive” criteria for resection undergoing non-operative management

Matteo Picicchi, Stefano Crippa, Marco Del Chiaro, Roberto Valente, Raffaele Pezzilli, Massimo Falconi, Gianfranco Delle Fave, Gabriele Capurso

Background: There are few data on the outcome of patients with intraductal papillary mucinous neoplasms of the pancreas meeting criteria for resection (Sendai-positive), and not operated.

Aim: To evaluate outcome of patients with a resectable, Sendai-positive intraductal papillary mucinous neoplasm, and not operated.

Methods: Multicentre, retrospective analysis of prospectively enrolled patients, with resectable Sendai-positive, not-operated intraductal papillary mucinous neoplasm. Overall-survival and disease-specific survival were the primary end-point, and progression-free survival secondary.

Results: Thirty-five patients (60% male, median age 77) enrolled: 40% main-duct, 60% branch-duct intraductal papillary mucinous neoplasms. In 19 patients surgery was ruled out due to comorbidities, in 7 because aged >80, 9 refused surgery. Twelve (34.3%) patients died after a mean of 32.5 months, 8 due to disease progression, 4 due to comorbidities. The median overall, disease-specific and progression-free survival were 52, 55, and 44 months respectively. Main duct involvement and age at diagnosis were associated with worse overall and progression-free survival, only main duct involvement with worse disease-specific survival (52 months main duct vs. 64 branch duct; P=0.04).

Conclusion: These results suggest that in elderly and comorbid patients with Sendai-positive intraductal papillary mucinous neoplasms, especially of the branch duct, a conservative approach could be reasonable, as associated with a relatively good outcome, and should be carefully discussed with the patients.

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1. Introduction

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are a distinct form of exocrine pancreatic neoplasm characterized by dilated ducts that are lined by a proliferation of papillary mucinous epithelium [1]. Depending on the site of the disease, IPMNs are classified as either main-duct (IPMN-MD) or branch-duct (IPMN-BD) type [2]. Mixed IPMNs, defined by a simultaneous involvement of both main pancreatic duct and its secondary branches, show close similarities with IPMN-MD in regard to clinico-pathologic and epidemiologic characteristics [3].

At the time of the diagnosis, IPMN-MD, including mixed type, have an elevated risk of malignancy, ranging from 36% to 100% in different series [4], thus requiring surgical resection [5]. On the other hand, IPMN-BD have a lower risk of malignancy, allowing the adoption of a follow-up strategy, with the aim of limiting resection to those with specific signs of malignancies [6].

On this basis, in 2006 specific criteria have been developed throughout a Consensus Conference, to define the indication for surgery in patients with IPMN. The Sendai guidelines suggest surgical resection for all patients with an IPMN involving the main pancreatic duct, and more selectively for patients with an IPMN-BD. In these latter surgery is recommended when the diameter exceeds 3 cm, in the presence of mural nodes, of specific symptoms or of positive cytology for malignant cells, or in patients who develop changes of the diameter over time [7]. These guidelines proved to have a very high sensibility in recognizing malignant IPMNs, but a lower specificity, with a high rate of patients undergoing surgery without malignancy at final pathology [8–10]. In 2012 these...
guidelines have been updated, but a similar policy in terms of indication for surgery has been maintained [4].

The Sendai guidelines suggest to limit surgery to “good surgical candidates” with a reasonable life expectancy, and to take into account patient preferences for IPMN management. However, there are few data on the outcome of patients with IPMN who meet criteria for surgical resection (Sendai positive), and are not operated upon [11].

The present study was therefore aimed at evaluating the outcome and natural history of patients with an IPMN meeting Sendai criteria for surgical resection, who, although deemed technically resectable, did not undergo surgery.

2. Patients and methods

2.1. Study design

Multicentre, retrospective analysis using institutional prospective databases.

2.2. Patients

The study included all consecutive patients seen at the participating centres (Digestive and Liver Disease Unit, University Sapienza Rome, Surgical Department Negrar, Department of Digestive Diseases and Internal Medicine, University of Bologna), who were diagnosed with an IPMN meeting Sendai criteria for surgical resection, and did not undergo surgery. All tumours were technically resectable without radiologic evidence of local infiltration or distant metastases. Patients with cystic lesions other than IPMN were excluded from the study.

Inclusion criteria were: (i) a certain or highly probable diagnosis of IPMN. The diagnosis of IPMN was considered as certain in the presence of one of the following criteria: (1) histological diagnosis obtained by endoscopic ultrasound (EUS) fine-needle aspiration (EUS FNA) or biopsy (EUS FNAB); (2) cytological diagnosis obtained by EUS FNA. A highly probable diagnosis of IPMN was based on the presence of one or several of the following accepted criteria: presence of one or several main pancreatic duct and/or branch duct dilatation(s) and/or pancreatic cystic lesions communicating with pancreatic ducts at CT, magnetic resonance cholangiopancreatography with secretin stimulation (S-MRCP), endoscopic retrograde cholangiopancreatography (ERC) or EUS. (ii) The patients had to at least one Sendai criteria for surgical resection (size > 30 mm, mural nodules, involvement of main duct, symptoms) and were deemed resectable. (iii) The patients did not undergo surgery and underwent observation without other treatments. Due to the study design, clinical approaches were not standardized, and thus patients underwent follow-up examinations at different intervals (at least every 6 months, or at shorter intervals if necessary) by means of different imaging procedures.

The research protocol has been approved by the ethics committee of each participating centres, and informed consent has been obtained from patients.

2.3. Data analysis

All data were prospectively collected at the centre where the patient had been initially observed. A unique computerized datasheet was created, and data regarding the main demographic, clinic, and pathological features were retrospectively analyzed.

Data on clinical history, tumour localization and ductal involvement were recorded at enrolment.

Data on disease progression (DP) and patients’ outcome were prospectively collected at control visits.

The main end points considered were overall survival (OS), and disease-specific survival (DSS), whereas progression-free survival (PFS) was considered as secondary end points. OS was defined as the time between diagnosis of IPMN with criteria for a surgical resection and the decision not to undergo surgery (which coincided with time of presentation at the centres) and date of death due to any cause. DSS was defined as the time between diagnosis and death due to IPMN. PFS was defined as the interval between the diagnosis of IPMN and the time of DP, or patient death, if it occurred before documented radiological progression. DP was defined as the appearance of new lesions or an increase in size associated with the appearance of a solid component or with signs of local or vascular invasion.

For survival analysis, data were censored if the patient was alive, or lost at follow-up (censoring date was the date of the last adequate tumour assessment). PFS, as well as OS analysis, were performed using the Kaplan–Meier method, and the results were compared by using a log-rank test. Risk factors were expressed as hazard ratio (95% confidence interval, CI). The analysis of risk factors for prediction of progression during follow-up was performed by univariate and multivariate analysis using a Cox proportional hazards model. The multivariate model was constructed by ‘enter’ method, after including all variables which had resulted significant at the univariate analysis.

3. Results

3.1. Patients’ characteristics

Thirty-five patients meeting the inclusion criteria were enrolled at the participating centres. Demographics and general features of these subjects are detailed in Table 1. These patients were selected analyzing a database of 387 IPMN patients seen at the participating Units, with a certain (histological) diagnosis in 77 cases (20%) and a highly probable diagnosis in 310 (80%). The included 35 patients therefore accounted for 9% of all the initial IPMN population.

Most of these neoplasms (23/35, 65.7%) were asymptomatic at diagnosis, incidentally diagnosed in the course of radiological examinations performed for reasons unrelated to the pancreas. The remaining 12 patients had either recurrent abdominal pain (5/12, 41.7%), acute pancreatitis (3/12, 25%), jaundice (2/12, 16.7%), weight loss and steatorrhea (2/12 16.7%). The indication for surgery according to Sendai criteria are resumed in Table 1. Fourteen (40%) patients had a main duct involvement and 21 (60%) a branch duct IPMN, with a median size of 40 mm (range 27–80 mm).

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Total (n = 35)</th>
<th>MD-IPMN (n = 14)</th>
<th>BD-IPMN (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>77 (43–87)</td>
<td>80 (63–87)</td>
<td>77 (43–86)</td>
</tr>
<tr>
<td>Male sex</td>
<td>21 (60%)</td>
<td>10 (71.4%)</td>
<td>11 (52.3%)</td>
</tr>
<tr>
<td>Indication for surgery*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td>12 (34.3%)</td>
<td>9 (64.2%)</td>
<td>3 (14.2%)</td>
</tr>
<tr>
<td>MD involvement</td>
<td>14 (40%)</td>
<td>14 (100%)</td>
<td></td>
</tr>
<tr>
<td>BD-IPMN ≥ 30 mm</td>
<td>20 (57.1%)</td>
<td></td>
<td>20 (95.2%)</td>
</tr>
<tr>
<td>Mural nodules</td>
<td>13 (37.1%)</td>
<td>7 (50%)</td>
<td>6 (28.6%)</td>
</tr>
<tr>
<td>Potential curative surgical intervention</td>
<td>18 (51.4%)</td>
<td>10 (71.4%)</td>
<td>8 (38.1%)</td>
</tr>
<tr>
<td>PD</td>
<td>4 (11.4%)</td>
<td>4 (28.6%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>DP</td>
<td>13 (37.1%)</td>
<td>5 (35.7%)</td>
<td>8 (38.1%)</td>
</tr>
</tbody>
</table>

Data are expressed as median (range). MD, main duct; BD, branch duct; IPMN, intraductal papillary mucinous neoplasm; PD, pancreaticoduodenectomy; DP, distal pancreatectomy; TP, total pancreatectomy.

* Some patients had more than one indication.
In relation with the site and distribution of the lesions, the potential curative surgical approach would have been a pancreatec-
doduodenectomy (PD) in 18 (51.4%), a distal pancreatectomy (DP)
in 4 (11.4%) and a total pancreatectomy (TP) in 13 (37.1%) patients.

3.2. Reasons for not undergoing surgery

In 19 of 35 subjects (54.3%) surgery was ruled out due to the
presence of one or multiple relevant comorbidities determining an
American Association of Anaesthetists (ASA) score ≥ 3, and/or of
synchronous neoplasms as detailed in Table 2. Seven other patients
had an ASA score < 3, but they were older than 80 years (median
age 84, range 81–86), and surgery was deferred, opting for a close
follow-up, as the risk of surgery, which would have been a total
pancreatectomy or a pancreatectoduodenectomy, was considered
to outbalance that of rapid tumour progression. The remaining 9
patients (median age 72, range 43–78), with an ASA score < 3,
refused surgery after being informed regarding their disease (BD
lesions in all cases), and about the indication for surgical resection
(total pancreatectomy or pancreatectoduodenectomy in all but one
case) and risks.

3.3. Outcome of patients and survival analysis

A total of 12 out of 35 patients (34.3%) died after a mean follow-
up of 32.5 months (95%CI 25.9–39.1). Eight of these patients died
due to progression of the disease at a mean time of 36.3 months
(95%CI: 19.9–52.8) from diagnosis (Table 3), while four died due to
other significant comorbidities (other cancer, heart failure, pneu-
monia with sepsis and stroke) at a mean of 30.7 months from
diagnosis (95%CI: 1.7–63.2). Accordingly, the median OS estimate
at the Kaplan–Meier curve was of 52 months with a 5-year OS rate of
35.2%. The median DSS was 55 months (Fig. 1), with a disease-
specific 5-year survival rate of 48.5%. The median PFS was of 44
months (Fig. 2), and the median 5-year PFS was not reached.

The variables considered as risk factors for survival were ana-
yzed using univariate and multivariable analysis as summarized in
Table 4. The only factors associated with worse OS were age at
diagnosis (HR 1.26; 95%CI: 1.03–1.5 per year; P = 0.006)
and involvement of the main pancreatic duct (HR 3.29; 95%CI:
0.96–11.3; P = 0.053). Only age was confirmed as a significant
factor associated with worse OS at the multivariate analysis (HR 1.23;
95%CI: 1–1.5; P = 0.009).

The only factor associated with worse DSS was the involvement
of the main pancreatic duct (HR 4.7; 95%CI: 0.91–24.4; P = 0.048).
Accordingly, the median DSS, estimated at Kaplan–Meier analysis,
Table 2
Reasons for not undergoing surgery in the 35 patients with patients with intraductal papillary mucinous neoplasm with positive Sendai criteria for surgical resection.

<table>
<thead>
<tr>
<th>ASA score ≥ 3&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Total (n = 35)</th>
<th>MD-IPMN (n = 14)</th>
<th>BD (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>16 (45.7%)</td>
<td>11 (68.7%)</td>
<td>5 (31.3%)</td>
</tr>
<tr>
<td>Chronic respiratory failure</td>
<td>6 (17.1%)</td>
<td>1 (16.6%)</td>
<td>5 (83.4%)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>5 (14.3%)</td>
<td>4 (80%)</td>
<td>1 (20%)</td>
</tr>
<tr>
<td>synchronous neoplasm</td>
<td>2 (5.7%)</td>
<td>1 (50%)</td>
<td>1 (50%)</td>
</tr>
<tr>
<td>Chronic kidney failure</td>
<td>1 (2.8%)</td>
<td>1 (100%)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic liver failure</td>
<td>1 (2.8%)</td>
<td>0 (0%)</td>
<td>1 (100%)</td>
</tr>
<tr>
<td>Age &gt; 80 years and ASA score &lt; 3</td>
<td>7 (20%)</td>
<td>2 (28.6%)</td>
<td>5 (71.4%)</td>
</tr>
<tr>
<td>Patients’ refusal</td>
<td>9 (25.7%)</td>
<td>0</td>
<td>9 (100%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Some patients had more than one comorbidity.

Table 3
Features at diagnosis of the 8 patients who died due to IPMN during the follow-up.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>MD involvement</th>
<th>MD size</th>
<th>Mural nodules</th>
<th>BD size</th>
<th>Disease progression definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>80</td>
<td>Yes</td>
<td>15 mm</td>
<td>No</td>
<td>–</td>
<td>Metastasis appearance</td>
</tr>
<tr>
<td>Male</td>
<td>80</td>
<td>Yes</td>
<td>12 mm</td>
<td>Yes</td>
<td>18 mm</td>
<td>Metastasis appearance</td>
</tr>
<tr>
<td>Female</td>
<td>85</td>
<td>Yes (combined type)</td>
<td>11 mm</td>
<td>No</td>
<td>22 mm</td>
<td>Increase in size and vascular invasion</td>
</tr>
<tr>
<td>Male</td>
<td>82</td>
<td>Yes (combined type)</td>
<td>8 mm</td>
<td>No</td>
<td>22 mm</td>
<td>Metastasis appearance</td>
</tr>
<tr>
<td>Female</td>
<td>77</td>
<td>Yes (combined type)</td>
<td>12 mm</td>
<td>Yes</td>
<td>30 mm</td>
<td>Increase in size and vascular invasion</td>
</tr>
<tr>
<td>Male</td>
<td>82</td>
<td>No</td>
<td>–</td>
<td>No</td>
<td>80 mm</td>
<td>Metastasis appearance</td>
</tr>
<tr>
<td>Female</td>
<td>80</td>
<td>No</td>
<td>–</td>
<td>No</td>
<td>45 mm</td>
<td>Increase in size and vascular invasion</td>
</tr>
<tr>
<td>Female</td>
<td>77</td>
<td>No</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

MD, main duct; BD, branch duct; IPMN, intraductal papillary mucinous neoplasm.

In our cohort the only factors associated in a multivariate logistic regression analysis with a worse OS was age. This may suggest that in this specific subset of elderly patients with comorbidities and reduced life expectancy, IPMN is not the main factor affecting survival, as a third of them would die for other causes. Therefore, in such elderly patients DSS is a better end point, as a quote of patients would die from other causes.

Interestingly, the main pancreatic duct involvement resulted at the univariate analysis only as a significant risk factor both for OS and DSS and PFS. Therefore surgical resection should be strongly considered in all MD-IPMN. Only in patients with major co-morbidities resulting in a significant perioperative mortality risk surgery should be avoided. On the other hand, the number of BD lesions, their size, and the presence of mural nodules, were not associated with prognosis.

These findings confirm that BD-IPMNs, even if presenting with features suspect for malignancy, have a less aggressive clinical course than MD-IPMN, and that the size of the BD lesions per se does not represent a sufficient criterion for surgery, as now detailed in the 2012 consensus [4]. Indeed, in a series of BD-IPMNs resected according to Sendai criteria suggesting malignancy (i.e. size > 3 cm and nodules), the histological rate of malignancy was as low as 15% [9]. Recently, Genevay et al. showed that cytology added significant value to radiological examination for identifying malignancy especially in BD-IPMNs [17]. Based on these observations, EUS with fine needle aspiration (FNA) should be recommended for BD-IPMN with worrisome features or high-risk radiological stigmata for a better stratification of the malignancy risk.

The present study has a number of limitations. First, the number of enrolled patients is relatively low, and their follow-up brief. However, this is the first reported series of patients for which an outcome analysis possibly indicating the natural history of this specific population is provided, and the results may set the ground for further studies. Second, the retrospective nature of the study, although most patients received a similar follow-up protocol in the different centres, limits the significance of the data regarding tumour progression.

In this view, the present data provide a preliminary basis for the investigation of an area of IPMN management for which the current guidelines only offer marginal indications, and no previous data are available.

In conclusion, the present results suggest that in elderly subjects with IPMN, or in patients affected by relevant co-morbidities, a complete evaluation of the general medical status and life

Table 4
Risk factors for overall mortality in the 35 patients with intraductal papillary mucinous neoplasm with positive Sendai criteria for surgical resection.

<table>
<thead>
<tr>
<th>Age at diagnosis (years)</th>
<th>HR (95%CI)</th>
<th>P value</th>
<th>HR (95%CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Univariate</td>
<td>Multivariate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD involvement</td>
<td>3.29 (0.96–11.3)</td>
<td>0.053</td>
<td>2.3 (0.64–8.1)</td>
<td>0.009</td>
</tr>
<tr>
<td>Presence of comorbidities</td>
<td>2.04 (0.61–6.76)</td>
<td>0.23</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Diameter of BD lesion (mm)</td>
<td>0.96 (0.91–1.01)</td>
<td>0.13</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>MD dilatation (mm)</td>
<td>1.01 (0.9–1.14)</td>
<td>0.79</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Unifocal</td>
<td>0.94 (0.29–3.02)</td>
<td>0.92</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Presence of mural nodes</td>
<td>1.53 (0.44–5.3)</td>
<td>0.5</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Presence of symptoms</td>
<td>1.67 (0.53–5.24)</td>
<td>0.38</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Male sex</td>
<td>0.45 (0.14–1.45)</td>
<td>0.18</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>BMI</td>
<td>1.02 (0.77–1.35)</td>
<td>0.86</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

MD, main duct; BD, branch duct; BMI, body mass index.
expectancy are mandatory to make a therapeutic decision balanced between risk of IPMN-related malignancy and that of perioperative morbidity/mortality associated with pancreatectomy. In this subset of patients, a conservative approach could be reasonable and should be carefully discussed.

Conflict of interest statement
None declared.

References


