



## Surgery for cystic tumors of pancreas: Report of high-volume, multicenter Indian experience over a decade



Vikram A. Chaudhari, DNB<sup>a</sup>, Rebala Pradeep, MCH<sup>b</sup>, H. Ramesh, MCH<sup>c</sup>,  
 Manish S. Bhandare, MCH<sup>a</sup>, Puneet Dhar, MCH<sup>d</sup>, Sujoy Pal, MCH<sup>e</sup>,  
 Senthilnathan Palaniswamy, DNB<sup>f</sup>, S. Jeswanth, MCH<sup>g</sup>,  
 Ramachandran Narayana Menon, MCH<sup>d</sup>, Anand Narayan Singh, MCH<sup>e</sup>,  
 Sandeep Sabnis, DNB<sup>f</sup>, G.V. Rao, MS, FRCS<sup>b</sup>,  
 Shailesh V. Shrikhande, MBBS, MS, MD, FRCS (HON)<sup>a,\*</sup>

<sup>a</sup> GI & HPB Service, Department of Surgical Oncology, Tata Memorial Hospital, Mumbai, Maharashtra, India

<sup>b</sup> Department of Surgical Gastroenterology, Asian institute of Gastroenterology, Hyderabad, India

<sup>c</sup> Department of Surgical Gastroenterology, VPS Lakeshore hospital, Kochi, India

<sup>d</sup> Department of Surgical Gastroenterology, Amrita Institute of Medical Sciences, Kochi, India

<sup>e</sup> Department of Surgical Gastroenterology, All India Institute of Medical Sciences, New Delhi, India

<sup>f</sup> Department of Surgical Gastroenterology, Gem Hospital & research Center, Coimbatore, India

<sup>g</sup> Department of Surgical Gastroenterology, Stanley Medical College, Chennai, India

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### ABSTRACT

**Background:** Pancreatic cystic neoplasms remain uncommon. Although data are accumulating on the incidence of pancreatic cystic neoplasms in the published literature, Indian data on these tumors are sparse. **Material and Methods:** We collated data from prospectively maintained databases of patients operated for cystic tumors of the pancreas from 2007 to 2016 at 7 academic centers across India to gain insights into clinical presentation and outcome of the operative treatment of these tumors. Data were compared with large series across the world to understand the regional differences in this pathology.

**Results:** Of the 423 patients, there were 98 (23.2%) serous cystic neoplasms, 128 (30.2%) mucinous neoplasms, 34(8%) intraductal papillary mucinous neoplasms, and 121 (28.6%) solid pseudopapillary epithelial neoplasms managed in these 7 academic centers. Malignancy (adenocarcinoma, malignant intraductal papillary mucinous neoplasms, and mucinous cystadenocarcinoma) was reported in 39 (9.2%) patients. Median age at presentation was 41 years, and the female-to-male ratio was 3.4:1. At presentation, 81% of patients were symptomatic. A total of 66.7% of lesions were located in body and tail region of the pancreas. Median tumor size was 6 cm. Operative resection with curative intent was performed in 405 of these 423 patients. Major morbidity occurred in 12%, and 30-day perioperative mortality was 0.9%. Laparoscopic resections were performed in 18% and spleen-preserving resections were performed in 3% of patients.

**Conclusion:** Female preponderance, young age, and a benign nature of most pancreatic cystic neoplasms were observed. Large size of tumors on presentation, fewer intraductal papillary mucinous neoplasm resections, and a much greater incidence of solid pseudopapillary epithelial neoplasms were distinctive of this study. Although the proportion of laparoscopic resections and splenic preservation was less compared with Western centers, the perioperative morbidity and mortality was on par with established standards.

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### Introduction

Pancreatic cystic neoplasms (PCNs) remain uncommon and occur less frequently than solid lesions. Cystic lesions are being detected with increasing frequency because of increased awareness and a recent surge in the use of cross-sectional imaging.<sup>1,2</sup> Many of these lesions are small, asymptomatic and benign. They can,

\* Reprint requests: Shailesh V. Shrikhande, MBBS, MS, MD, FRCS (HON), Division of Cancer Surgery, Consultant Surgeon, Division of Hepato-Pancreato-Biliary Surgical Oncology, Deputy Director, Tata Memorial Hospital, Ernest Borges Marg, Parel, Mumbai 400 012, India.

E-mail address: [shailushrikhande@hotmail.com](mailto:shailushrikhande@hotmail.com) (S.V. Shrikhande).

however, be symptomatic and malignant or have malignant potential. Treatment strategies in the management of these lesions vary from observation and regular surveillance to conservative or radical resections depending on the type of lesion. Diagnosis on primary evaluation, therefore, is of immense importance. Each type of PCN has different clinicoradiologic characteristics, including age at presentation, sex predilection, location in the pancreas, and radiologic features that suggest a preoperative diagnosis.<sup>3,4</sup> Most PCNs are benign, many have malignant potential, and few are malignant. Resection is curative for most premalignant cysts in the pancreas. Even malignant varieties of cystic tumors have a relatively better prognosis than their solid counterparts.<sup>5</sup>

Pancreatic resection is associated with substantial morbidity. Surgical indications need to be clear and justifiable when treating benign or premalignant lesions in the pancreas. The risk of operative mortality must be less than the risk of the development of malignancy and eventual death associated with an observational approach. Assessment of the operative outcome, therefore, becomes extremely important in these tumors.<sup>6</sup>

India lacks a specific referral system for the management of complex and rare tumors. Although data are accumulating on the incidence of PCNs in the literature, data from India on these tumors is sparse, which prompted us to initiate this multi-institutional study to gain insights into the clinical presentation and the outcome of PCNs in India.<sup>7,8</sup>

## Methods

### Data collection

Tata Memorial Center (TMC) Mumbai, India acted as the principal center that coordinated with all seven participating centers for data collation. Permission by the respective institutional review board at each institute was obtained. A memorandum of understanding was signed between TMC and each participating center for sharing and publishing of the data and was submitted to review board at TMC. This study (TMC-IRB Project Number 1826) was approved with a consent waiver attributable to its retrospective, observational nature.

We obtained the prospectively maintained databases of operated patients of preoperatively diagnosed or suspected cystic lesions of the pancreas from January 2007 to December 2016 at 7 high-volume academic centers across India and collated them into a single database. The databases recorded demographic data, presenting symptoms, imaging and relevant perioperative variables, along with histopathologic data. The pathologic diagnosis followed World Health Organization (WHO) 2010 classification for exocrine and endocrine neoplasms of the pancreas.<sup>9</sup> The study protocol conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki.<sup>10</sup>

### Preoperative diagnostic evaluation and perioperative outcome record

Contrast enhanced computed tomography (CE-CT) was the most common diagnostic preoperative evaluation. Magnetic resonance imaging (MRI) or magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasonography (EUS) were performed selectively. A serum carbohydrate antigen 19-9 (CA 19-9) level  $\geq 37$  U/L and a carcinoembryonic antigen level  $\leq 5$  ng/mL were considered increased and abnormal. Cyst fluid analysis and serum tumor markers were also performed selectively. Postoperative complications were graded as per the Clavien-Dindo classification.<sup>11</sup> Pancreas-specific complications were diagnosed and classified according to the criteria of the International Study Group on Pancreatic Surgery.<sup>12–14</sup>

### Statistical analysis

Demographic, diagnostic, perioperative, and histopathologic variables were analyzed. Descriptive statistics, including median, frequency and percentage, for categorical variables was used to describe patient, tumor, and treatment characteristics. Statistical analysis was conducted using SPSS 21.0 (IBM, Armonk, NY, USA) for Windows. Differences between the patient groups were compared by  $\chi^2$  and ANOVA testing for continuous variables. Statistical significance was determined based on  $P$  value  $< .05$ .

## Results

### Demographic characteristics

Throughout the 10-year study period, all 7 participating centers combined performed 5,006 pancreatic resections for various indications, and 423(8.44%) of these were for PCNs (Table I). Of the 429 reported patients, 6 were excluded from the analysis because they were diagnosed histologically to be pancreatic pseudocysts. A total of 12 (2.8%) pancreatic ductal adenocarcinomas (adenoca), 16 (3.8%) neuroendocrine tumors (NETs), and 2 gastrointestinal stromal tumors (GISTs) masqueraded as pancreatic cysts. Benign cysts like simple cysts, lymphangiomas, and lymphoepithelial cysts were reported in 12 (2.8%) patients (Table II).

WHO-defined PCN pathologies serous cystic neoplasms [SCNs], mucinous neoplasms [MCNs], solid pseudopapillary epithelial neoplasms [SPENs], and intraductal papillary mucinous neoplasms [IPMNs]) were finally reported in 381 of 423 (90.07%) patients. We observed 98 (23.2%) SCNs, 128 (30.2%) MCNs, 34(8%) IPMNs, and 121 (28.6%) SPENs. Malignancy (adenocarcinoma, malignant IPMN, mucinous cystadenocarcinoma) was reported in 39 (9.2%) patients (Table II). Median age at presentation was 41 years (range 9–83 years). Patients with benign diagnoses presented a decade earlier than those with malignant

**Table I**  
Participating centers and reported pancreatic and PCN resections during the study period (2007–2016)

Institute	Pancreatic resections	PCN resections (%)
Asian Institute of Gastroenterology, Hyderabad	1,262	103 (8.1)
VPS Lakeshore Hospital, Kochi	719	98 (13.6)
Tata Memorial Hospital, Mumbai	1,050	74 (7.0)
Amrita Institute of Medical Sciences, Kochi	424	67 (15.8)
All India Institute of Medical Sciences, New Delhi	603	42 (6.9)
Gem Hospital & Research Center, Coimbatore	463	21 (4.5)
Stanley Medical College, Chennai	485	18 (3.7)
Total	5,006	423 (8.4)

**Table II**  
Histologic classification

Pathology	Number of patients (%)
SPEN	121 (28.6)
MCN	113 (26.7)
Mucinous cystadenocarcinoma	15 (3.5)
SCN	98 (23.2)
IPMN	22 (5.2)
Malignant IPMN	12 (2.8)
Neuroendocrine tumor (NET)	16 (3.8)
Ductal adenocarcinoma	12 (2.8)
Simple cyst	7 (1.7)
Lymphoepithelial cyst	2 (0.5)
Lymphangioma	3 (0.7)
Gastrointestinal stromal tumor	2 (0.5)
Total	423 (100)

PCNs (age 40.18 years versus 51.28 years). Age of presentation varied according to the type of lesion ( $P = .01$ ; Fig 1). SPEN was the most common diagnosis in young female patients (median age 25 years). Overall, PCNs were more common in females, with a male-to-female ratio of 1:3.4. SPEN had the greatest female predilection with a male-to-female ratio of 1:11, followed by MCN, with the ratio of 1:5. Each subtype of PCN had variable characteristic age and sex predilection (Table III). Median tumor size (maximum tumor diameter) was 6 cm. Patients with lymphatic cysts and IPMN had relatively smaller lesions, with a median tumor size of 4–5 cm. All other PCNs were large, with a median size more than 7 cm. Maximum tumor diameter, however, did not show statistically significant variation according to histology of the tumor ( $P = .14$ ; Fig 2).

#### Location of the lesion

Two-thirds (66.9%) of the lesions were located in the body and tail region of the pancreas (Table III). IPMN was the only pathology located more commonly in the head region. About 90% of MCNs were located in the body/tail region of the pancreas. SPENs showed similar distribution across the pancreas. Large tumors diffusely involving the whole pancreas or with a completely atrophic pancreatic remnant were reported in 6 patients.

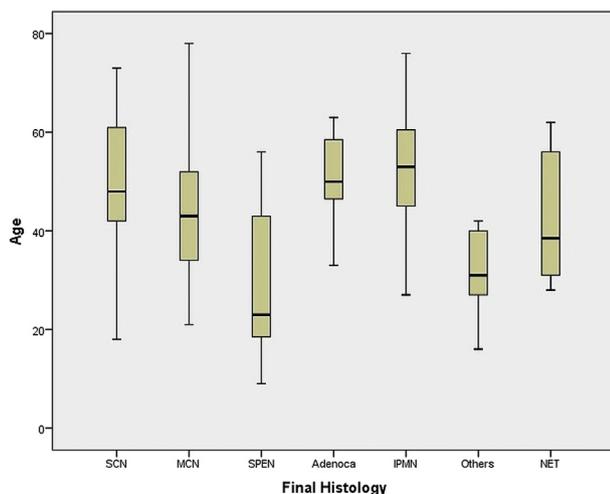


Fig 1. Age and final histology.

#### Tumor markers

A serum CA 19-9 level was performed in 62.1% patients (Table III). The baseline serum CA 19-9 value was increased in 59 (22.4%) of these patients. Increases in Ca 19-9 levels ( $> 37$  IU/mL) predicted the possibility of malignancy with a sensitivity of 66%.

#### Clinical presentation

Although abdominal pain (63.6%) was the most common primary complaint, 19.1% lesions were detected incidentally. Incidental detection was proportionate among all PCNs. Jaundice (6.9%) and a mass detected in the abdomen (4.7%) were uncommon presentations. A total of 69 (16.3%) patients had multiple presenting symptoms or signs. Loss of appetite and weight were the most common associated secondary complaint in 28 patients (6.2%). A total of 2 patients with large SCNs and portal hypertension secondary to involvement of the splenic vein and the splenoportal vein confluence presented with upper gastrointestinal bleeding.

#### Radiologic and preoperative diagnosis

CE-CT remained the preferred primary investigations in 412 patients (97.4%). EUS was performed in 70 patients (16.5%) to obtain supportive information and definitive diagnosis. Despite the known advantages of MRI in PCNs, MRI was performed in only 26 (6.4%) patients and was the primary investigation in only 10 patients. A total of 12 patients underwent all 3 diagnostic investigations (ie, CE-CT, MRI, and EUS). EUS-guided fine-needle aspiration cytology and fluid analysis was not standardized and was not reported uniformly. Preoperative diagnosis was established in 56% of patients.

#### Operative details and perioperative complications

Of the 423 patients explored for surgical intervention, 18 patients were reported to be inoperable owing to either local extent precluding safe or complete resection (nonresectable) or intraoperatively detected metastatic spread of disease (Table IV). Preoperative diagnosis, possibility of malignancy, and the location of tumor determined the type of operation performed. Distal pancreatectomy (DPS) was the most common operation performed in 225 (53.2%) patients. Pancreatoduodenectomy (PD) was performed in 104 (24.6%) patients. A total of 76 (18%) resections were performed laparoscopically, 74 patients underwent laparoscopic distal pancreatic resections, and only 2 laparoscopic PDs were performed. The conversion rate was 0.65%. A total of 14 portal vein resections and 15 multi-visceral resections were performed. Spleen-preserving DPs were performed in 13 (3%) patients. Median (central) pancreatectomy was the only pancreas-sparing procedure reported in 36 (8.5%) patients.

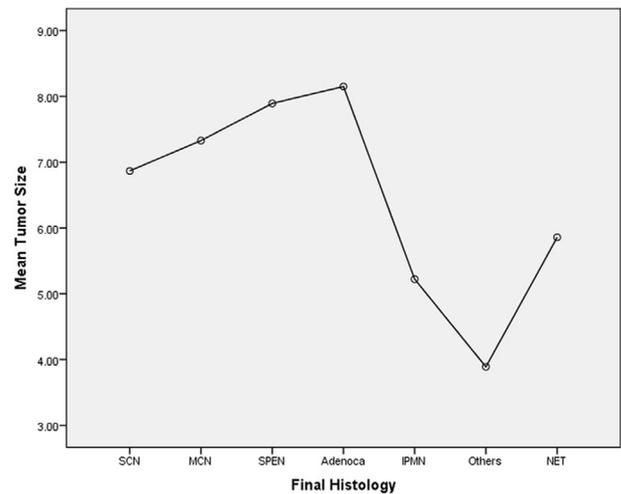
The median hospital stay was 12 days. Hospital stays after a DPS and PD were 11 and 15 days, respectively. Hospital stay varied with the type of resection performed ( $P = .001$ ). Postoperative complications are detailed in Table IV. Overall morbidity was 28.9%, with a major morbidity rate of 12% (Clavien Dindo IIIa and above). Perioperative mortality (30 days) was 0.9%. Mortality was related to pancreas-specific complications ([POPF C] and acute postoperative portal vein thrombosis) in 2 patients. A total of 2 patients died of medical (cardiac) cause in the postoperative period.

#### Discussion

Multi-institutional collaboration is an effective way to study uncommon lesions of the pancreas. Multi-institutional experience

**Table III**  
Tumor Characteristics as per pathology

Histology	No. of Patients	Age		Sex		Sex Ratio		Location		Tumor Size(cm)		CA 19-9 Levels	
		Median (Range)	Male	Female	Male	Female	Head	Body	Mean	SD	(No. of Patients)	Performed	Median
SCN	98	48 (18-83)	24	74	1:3	33	63 (2)	6.9	4.5	59	11	16	
MCN	128	41.50(17-80)	21	107	1:5.1	13	112(3)	8.4	3.5	85	28	29	
SPEN	121	25 (9-59)	10	111	1:11.1	52	68(1)	7.9	3.9	71	6	13	
Adenoca	12	50 (20-69)	8	4	2:1	4	8	8	3.5	7	4	74	
IPMN	34	57 (27-76)	26	8	3.25:1	23	11	5.2	4.0	23	10	33	
Others (Simple/Lymphatic)	14	36.5 (16-58)	5	9	1:1.8	6	8	3.8	1.8	10	0	12,90	
NET	16	42 (28-77)	5	11	1:2.2	3	13	5.8	3.5	8	0	12,60	
<b>Total</b>	<b>423</b>	<b>41 (9-83)</b>	<b>95</b>	<b>328</b>	<b>1:3.45</b>	<b>134</b>	<b>283(6)</b>	<b>7.4</b>	<b>-</b>	<b>263</b>	<b>59</b>	<b>21</b>	



**Fig 2.** Tumor size (cm) and final histology.

of the management PCNs has been reported by groups around the world, but large studies reporting resections are few.<sup>15–17</sup> Indian data have been limited to case reports and relatively small, single-institution series.<sup>18,19</sup> This study reports the first national coordination among high-volume Indian academic centers documenting presentation and outcome of operated patients of PCNs.

The accurate preoperative diagnosis of the various types of PCN remains challenging. Cross-sectional imaging methods often may not reliably provide an accurate preoperative diagnosis.<sup>20</sup> Diagnostic errors are known to be common in preoperative assessment, although the errors are clinically relevant in less than 10% of patients.<sup>21,22</sup> Preoperative diagnosis was specified in 56% of patients, and EUS was performed only in 16.5% of patients in the current study. Symptomatic and clinicoradiologically suspected premalignant PCNs are usually considered clear operative candidates. In the current study, we observed less than conventional utilization of EUS in diagnostic evaluation of PCNs. It is plausible that, because of financial limitations, additional investigations are often avoided once the operative indication is more or less defined aided by a single, baseline, cross-sectional imaging at many of the centers. CE-CT remained the most commonly performed cross-sectional imaging for diagnosis, staging, and preoperative planning. CE-CT and MRI are reported to have similar efficacy in diagnosis of PCNs.<sup>23</sup> In the current study, however, only 6.4% patients underwent MRI, for the most part in conjunction with CE-CT. This most likely is not only an indicator of surgeons' comfort and familiarity with CE-CT over MRI, but also the fact that this is a series of operated patients, and MRI and EUS are most likely used more when patients are being planned for observation or surveillance only and more efforts are made to obtain definitive diagnosis. Moreover, the availability of MRI and EUS is a potential limitation of their use.

PCNs are common in females and this was observed across all histologies except for IPMN and ductal adenocarcinoma. Female sex preference of SPENs and MCNs was starkly evident. Ductal adenocarcinoma patients did not show predilection for any sex. IPMNs are also known to have either a small or no male predilection.<sup>24</sup> In contrast, our study found a definite male preponderance with a ratio of 3.25:1 for IPMNs. Nearly 90% of MCNs were located in the body and tail region of pancreas, similar to that reported in literature.<sup>17</sup> SCNs are usually benign, indolent lesions with no malignant potential. Small, asymptomatic lesions are observed, and operative resection is only offered in selected cases for large, symptomatic, or growing lesions. Despite few indications, it is pertinent to note that as many as 61% of SCNs in a study from Europe underwent

operative resection because of size, symptoms, or diagnostic uncertainty.<sup>15</sup> SCNs formed 22.5% of PCNs in this series. Most of these lesions were large (>7cm) and 80 (82%) patients reported clinically relevant symptoms. This is in contrast to the report of European cystic tumors of pancreas study group, in which 61% patients were asymptomatic and the same number of patients underwent surgery for diagnostic uncertainty.<sup>15</sup>

We reviewed the literature to compare the outcomes of our study with large studies of operated patients of PCNs published in last 10 years (Table V). The Chinese experience was the largest report of operated patients on PCNs (available only as an abstract in English literature). This study showed greater proportions of SPEN resections (31.7%) among operated PCNs, similar to our study.<sup>25</sup> At 2 high-volume centers in the United States (Massachusetts General Hospital, Boston, and Memorial Sloan Kettering Cancer Center, New York City), most patients presented after 60 years of age, with tumor size less than 3 cm at presentation, and SPENs contributed only 2%–3% of all patients.<sup>6,21</sup> Indian patients presented early in the fifth decade (mean 42 years) of life. Despite early age at presentation, tumor size on diagnosis was much larger in Indian patients (6 cm). Final histology revealed SPEN in 27.7% patients in the current study. The proportion of SPEN patients in Indian and Chinese centers is greater compared with the US centers and many other Western series.<sup>26–28</sup> In the current study, a greater proportion of SPEN and MCN patients and a lesser incidence of IPMN resulted in lesser median age of presentation and a greater female preponderance compared with the Western series.

The incidence of malignancy among operated PCNs at Indian centers was less than 10%. In the current study, IPMNs contributed 8% (34) of all operated patients, 12 of which were malignant, which also contrasts with Western experience where approximately 25% of the resected PCNs and 50% of the incidentally detected pancreatic cysts are IPMNs.<sup>21,27,29,30</sup> It would be difficult to comment on causality of genetic or ethnic difference from this study; however, it may be possible that regional, genetic, or ethnic factors play a role resulting in the substantial differences in incidence of various PCNs across these continents.<sup>31</sup> Our overall morbidity rate was 28.9%, with a major morbidity rate of 12%. Perioperative mortality (30 day) was 0.9%. These figures compare well with the US centers discussed earlier in this report (Table V).<sup>6</sup>

PCNs are a good indication for laparoscopic surgery and spleen-preserving DP because many of these lesions are benign.<sup>32,33</sup> In our study, 76 (18.5%) resections were performed laparoscopically. However, spleen-preserving DP was performed only in 13 (3%) patients. Lack of definitive preoperative diagnosis in as many as 44% patients and the large size of the tumors most likely contributed to infrequent splenic preservation in this series.

In the absence of centralization and regulatory mechanisms, referral pattern is variable in India. Many small tumors are operated at peripheral centers and major centers most likely get a greater proportion of large, complex, and symptomatic tumors. This reality leads to a natural triage, wherein small tumors are less represented than their actual incidence in large data sets such as ours.

Illiteracy, poverty, a life philosophy of tolerance (where the first point of contact with a physician is attributable to pain or a symptom not responding to traditional measures), and suboptimal penetration of secondary and tertiary care coupled with a lack of state- or individual-sponsored health insurance schemes often result in late presentation and subsequent delay in diagnosis and treatment.<sup>34</sup>

The current study was designed as a multicenter study of all operated patients with PCNs. Complementary data of patients under observation was not available or evaluated. We believe the results of this study should also serve as a starting point for a prospective study evaluating the natural history of PCNs that are not operated and kept under observation.

**Table IV**  
Operative Details, and Perioperative Complications

Operative Details	Total Number of Patients (%)	Median Hospital Stay (Days)
DPS	225(53.2%)	11
PD	104(24.6%)	15
<b>Median Pancreatectomy</b>	36(8.5%)	13.5
<b>Total Pancreatectomy</b>	7(1.7%)	18
<b>Enucleation/Local Excision</b>	20 (4.7%)	11
<b>Inoperable +/- Palliative procedure</b>	18(4.3%)	10
<b>Spleen preserving DP</b>	13(3.1%)	9
<b>PD/ DPS with Portal Vein Resection</b>	14(3.3%)	14
<b>Multi Visceral Resection</b>	15(3.5%)	15.5
<b>Total</b>	423	12
<b>Approach</b>	Number of Patients (%)	
<b>Open</b>	347(82%)	
<b>Laparoscopic</b>	71(16.8%)	
<b>Laparoscopic converted to open</b>	5(0.65%)	
<b>Blood Loss (ml)</b>		
<b>Median</b>	200	
<b>Mean</b>	511	
<b>Range</b>	(20- 23000ml)	
<b>Standard Deviation</b>	1492	
<b>Hospital Stay (Days)</b>		
<b>Median</b>	12	
<b>Mean</b>	14.1	
<b>Range</b>	(2-72 days)	
<b>Standard Deviation</b>	8.0	
<b>Perioperative Complications</b>	No. of patients (%)	
<b>POPF A /Biochemical Leak</b>	84 (19.9%)	
<b>Morbidity</b>	122 (28.9 %)	
<b>Major Complications (Clavien- Dindo IIIA and above)</b>	50 (12%)	
POPF C –	05 (1.2%)	
POPF B	31 (7.3%)	
PPH C –	01 (0.2%)	
Intra- abdominal collection requiring percutaneous intervention	9 (2%)	
<b>30-day perioperative mortality</b>	4 (0.9%)	
Pancreas related	2 (0.45%)	
Cardiac	2 (0.45%)	

DP – Distal Pancreatectomy

PD – Pancreatoduodenectomy

POPF – Post operative Pancreatic Fistula

PPH – Post Pancreatectomy Hemorrhage

In conclusion, this is the first and largest multi-institutional report from India for resection of PCNs. Female preponderance, young age, and the benign nature of most PCNs were observed. Large size of tumors on presentation, fewer IPMN resections, and a considerably greater incidence of SPEN were distinctive of this study. Although the proportion of laparoscopic resections and splenic preservation was less compared with many Western centers, the perioperative morbidity and mortality was on par with established standards. The results of this study should also serve as a starting point for a prospective study evaluating the natural history of PCNs that are not operated and kept under observation.

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### Conflict of interest/Disclosure

Authors declare no conflict of interest.

**Table V**  
Comparison of large series of operated patients of cystic neoplasms of pancreas in published in current decade (> 400 patients)

Salient Comparison Variable/Parameter	USA MGH 2012	USA MSKCC 2012	China 2018 (Abstract only)	Current Study India 2018
<b>Participation</b>	Single Institution	Single Institution	16 Institutions	7 Institutions
<b>Number of patients</b>	851	422 operated (>1400 patients reported)	2251	423
<b>Study Period (Y)</b>	33(1978 to 2011)	15(1995–2010)	10 (2006– 2016)	10(2007 –2016)
<b>Male to Female ratio</b>	1:2	1:2.3	1:2.4	1:3.4
<b>Age at Presentation (Y)</b>	60	63	47.5	41
<b>Symptomatic</b>	345(40.5%)	213 (51%)	-	342(81%)
<b>Size on Presentation (mean, cm)</b>	1.6– 3.2	3	-	7.4
<b>Location</b>	(727 reported)	-	-	-
<b>Head</b>	348 (40.9%)	182 (42%)	-	134 (33%)
<b>Body and Tail</b>	379 (44.5%)	240 (58%)	-	283 (66.9%)
<b>Histology</b>				
<b>IPMN</b>	326 (38.4%)	114 (27%)	495 (22%)	34 (8%)
<b>SCN</b>	137 (16.1%)	98 (23%)	678 (30%)	98 (23.2%)
<b>MCN</b>	199 (23.4%)	45 (11%)	365 (16.2%)	128 (30.2%)
<b>Adenocarcinoma</b>	-	60 (14%)	-	12(2.8%)
<b>SPEN</b>	29 (3.4%)	8 (2%)	713 (31.67%)	121 (28.6%)
<b>NET</b>	63 (7.3%)	27 (7%)	-	16 (3.8%)
<b>Incidence of Malignancy</b>	108 (12.69%)	94 (23%)	0.6–32.1% (as per pathology)	39 (9.2%)
<b>Perioperative Mortality</b>	0.5%	0.7%	-	0.9%
<b>Morbidity</b>	38%	35%	-	28.9%

MGH - Massachusetts General Hospital

MSKCC - Memorial Sloan Kettering Cancer Center

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