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Cystic tumors of the pancreas. An update of the surgical experience in a single institution

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ABSTRACT

Background: the aim of the present study was to analyze the clinicopathological features of patients undergoing pancreatic surgical resections due to cystic neoplasms of the pancreas.

Material and methods: demographic data, form of presentation, radiologic images and location of the tumors within the pancreas were analyzed. Data was also collected on the type of surgery (open/laparoscopic), postoperative complications and their severity and oncologic outcomes.

Results: eighty-two pancreatic resections were performed. The mean age of patients was 57 years and 49 (59%) were female. Forty-one tumors (50%) were incidental and the most frequent symptoms in the group of symptomatic patients were abdominal

pain (63.4%) and weight loss (36.5%). Thirty-two tumors (39%) were located in the tail of the pancreas, 25 (30.5%) in the head and 20 (24.4%) in the body. Thirty-nine (47.5%) distal pancreatectomies, 16 central, ten duodenal pancreatectomies and one enucleation were performed; 40 (48.5%) were carried out laparoscopically. Mean hospital stay was ten days and eight patients (7%) experienced severe complications, one was a pancreatic fistula. Sixty-six tumors (80.5%) were recorded as non-invasive and 16 (19.5%) as invasive: seven intraductal mucinous papillary tumors, one cystic mucinous tumor, four solid pseudopapillary tumors and four cystic neuroendocrine tumors. There was a median follow-up of 64 months; disease-free survival at five and ten years was 97.4% in the patients with non-invasive tumors and 84.6% and 70.5% in the invasive tumors group ($p < 0.01$).

Conclusions: fifty percent of cystic neoplasms of the pancreas are incidental. Two phenotypes exist, invasive and non-invasive.

Key words: Cystic neoplasm pancreas. Incidentaloma. Laparoscopic pancreatectomy. Outcomes.

INTRODUCTION

Cystic neoplasms of the pancreas (CNP) make up a heterogeneous group of lesions which include benign tumors, potentially malignant tumors and malignant tumors (1-4). Given the now widespread use of more sensitive imaging techniques, the prevalence of such tumors has risen considerably over the last decade and they currently account for 30-40% of all pancreatic resections (5-8). Due to their indolent symptomatology, approximately 40-50% of these tumors are diagnosed incidentally, which has led to a certain controversy surrounding their diagnosis and treatment (9-12). Recently, several clinical guidelines and expert recommendations have been updated and decision algorithms have been proposed with the aim of guiding the therapeutic decision (2,13-15). Furthermore, patients with these tumors usually present when they are older than 65 years of age and the morbidity and mortality associated with pancreatic resections are 30-40% and 2-4%, respectively, in reference centers (16,17).

The main objective of this study was to describe tumor phenotype and presentation along with the outcome of the surgical treatment of CNP. The secondary objective was to analyze morbidity and mortality as compared with the normal standards of care in pancreatic surgery.

MATERIAL AND METHODS

The study was approved by the Ethics Committee of the center. A retrospective study of a prospectively collected database of all resected cystic neoplasms of the pancreas between 1995 and May 2018 was performed. The STROBE guidelines were followed in all cases (18).

Tumors were categorized using the pathologic classification of the World Health Organization (WHO) for serous cystic neoplasms (SCN), cystic mucinous neoplasms (CMN), intraductal papillary mucinous neoplasms (IPMN), solid pseudopapillary tumors (SPT), cystic neuroendocrine neoplasms (CPanNETs) and the European and American guidelines for cystic neoplasms of the pancreas (2,14,19-22). The degree of dysplasia and the categorization of IPMN were assessed using the classification of Tanaka and Adsay (13,23).

The following demographic data were extracted from the electronic records: age, sex, body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared), ASA classification (American Society of Anesthesiologists physical status) (24), previous history of pancreatitis, diabetes and the presenting complaint. Tumors were considered to be incidental when they were detected in two imaging studies and in the absence of digestive or neurohormonal symptoms, such as back ache or weight loss (9,10). Most patients underwent two imaging studies, either multidetector computed tomography (MDCT), magnetic resonance imaging (MRI) or endoscopic ultrasound (EUS), depending on the preferences of the responsible clinician. Two of the authors (JAC and AB) reviewed the radiologic images, especially in the case of IPMN. The size of the lesion, its relationship to the main duct and the degree of dilation of the Wirsung duct were recorded. In most cases, endoscopic ultrasound guided-fine needle aspiration (EUS-FNA) was performed for the identification of mucin and cytological analysis (25).

The decision to operate and the type of surgical procedure used was taken by a multi-disciplinary committee that included surgeons, gastroenterologists, radiologists and internists depending on the symptoms, the location of the lesion, distance from the Wirsung duct and cytology report. As from 2003, techniques that spare the pancreatic parenchyma were introduced and central and distal pancreatectomies were performed laparoscopically following techniques described elsewhere (26,27). In 2003, a program of fast-track surgery was implemented and no pancreatic drain was left in place following the current recommendations (28).

The type of surgery, operative time, use of blood products and hospital stay were recorded. Operative mortality was considered as any death occurring within the first 30 days of the postoperative period. Two authors (JAC and LH-P) classified the severity of postoperative complications using the Dindo-Clavien scale (29), which stratifies complications into five groups (0-5). All complications of category IIIb or greater were considered as severe. When more than one complication occurred, the more severe one was recorded. All patients who returned to inpatient status within the first 30 days of the postoperative period were classified as readmissions. The definition of pancreatic fistula, postoperative bleeding, delayed gastric emptying and postoperative new-onset diabetes was established following the criteria of the International Study Group on pancreatic Surgery and the classification of the American Diabetes Association, respectively (30-33).

Surgical specimens were analyzed following the norms of the American Society of Pathologists (34). The anatomical and pathologic reports and the hematoxylin and eosin slides of IPMN were reviewed to confirm the degree of dysplasia and the phenotype involved (23). With regard to mucinous tumors, lesions were classed as invasive if there was a high degree of dysplasia, carcinoma *in situ* or invasive carcinoma (15,20,23). Solid pseudopapillary tumors and neuroendocrine cystic tumors of stages IIA-IIIB (> 2 cm or N1), as defined by the European Neuroendocrine Tumor Society (ENETS), were also considered as invasive (35).

All patients were followed-up every 6-12 months during the first five years via imaging studies and subsequently in the patients' home or hospital. Locoregional recurrence was defined as the clinical and/or radiologic identification of a mass in the pancreatic

bed and distant relapse as evidence of liver, lung or peritoneal metastasis. Disease-free survival was defined as the time to tumor recurrence or death from any cause. Follow-up was updated in May 2018.

Statistical analysis

Continuous variables are reported as means and standard deviations (SD). Categorical variables are expressed as absolute numbers and percentages. Univariate analysis was performed using the Chi-square test or Fisher's exact test for categorical variables and the Student's t-test for continuous variables. A p-value of < 0.05 was considered as significant. Disease-free survival was estimated according to the Kaplan-Meier method and the log-rank test was used for the comparison of survival between the invasive and non-invasive phenotypes. All statistical analysis was performed using Stata version 12 (StataCorp LP, College Station, Tx).

RESULTS

Of a total of 387 pancreatic resections, 82 (21%) were cystic neoplasms of the pancreas. Table 1 shows the demographic and clinical characteristics of the series divided by incidental (n = 41; 50%) and non-incidental (n = 41; 50%) tumors. The average age of patients was 57 years (SD 15.7) and most (n = 49; 59%) were female. Among the non-incidental tumors, the most frequent symptoms were abdominal pain (n = 26; 63.4%), weight loss (n = 15; 36.5%), pancreatitis (n = 5; 12%), nausea and vomiting (n = 3; 7.3%), an abdominal mass (n = 2; 4.8%) and jaundice (n = 1; 2.4%).

The most frequently used technique was endoscopic ultrasound (EUS) (n = 60; 73.2%) and 54 fine-needle aspirations (FNA) were performed with an accuracy of 81% (n = 44) for the detection of a mucinous *vs* non-mucinous etiology, which was inconclusive in ten cases (18.5%). MDCT was performed in 57 patients (69.5%) and MRI in 24 (29.3%) (Figs. 1 and 2). The most frequent location of tumors was the tail of the pancreas (n = 32; 39%), followed by the head (n = 25; 30.5%) and a central location (n = 20; 24.4%). Thirty-nine distal pancreatectomies (47.5%) were performed, ten open and 29 laparoscopic. Eighteen (62%) were performed with a sparing of the spleen and splenic vessels, 19 (23%) cephalic duodenal pancreatectomies, 16 (19%) central

pancreatectomies (six open and ten laparoscopic), six (7.3%) total pancreatectomies (one laparoscopic) and two enucleations.

There were no operative deaths or readmissions in the first 30 days. Mean hospital stay was 10.5 days (SD 13.8) with no significant differences between the two groups (8.2 *vs* 12.8; p = 0.31). Eight patients experienced some kind of severe complication (Dindo-Clavien ≥ IIIb). There was one (1.3%) pancreatic fistula (excluding the six total pancreatectomies). However, 30 (36%) peripancreatic fluid collections were recorded, which did not require drainage except for one patient who underwent a percutaneous drainage in his home town (grade A "biochemical fistula"). There were five cases (6.5%) of intra-abdominal bleeding (two grade B and three grade C) and four cases (4.9%) of delayed gastric emptying which resolved spontaneously. Seven (9.7%) patients went on to develop postoperative diabetes, excluding the ten who were previously diabetic.

With regard to the histopathologic findings, it is noteworthy that mucinous tumors were the most frequent (p = 0.04) in the symptomatic tumor group, especially IPMN (n = 18; 43.9%). Serous cystadenoma was the most frequent (n = 15; 36.6%) in the incidental tumor group. Table 2 shows the distribution of tumors according to invasive or non-invasive phenotype. Most (n = 66; 80.5%) were non-invasive and 16 (19.5%) (p < 0.01) exhibited an invasive phenotype, seven of which (43.7%) corresponded to IPMN. The mean diameter of the invasive tumors was significantly greater than that of the non-invasive neoplasms (66.1 mm *vs* 28.6 mm; p < 0.01). Seventy-seven percent of incidental neoplasms were located in the body and tail of the pancreas *versus* only 48.7% in the non-incidental group (p = 0.02).

After a mean follow-up of 64 months (IQR 15-114), there was a recurrence of distant tumors in five patients, one distant and one locoregional, three from the symptomatic group and two from the incidental group. Disease-free survival at five and ten years was 97.4% in patients with non-invasive tumors and 84.6% and 70.5%, respectively, in the group with invasive tumors (p < 0.01) (Fig. 3).

DISCUSSION

Of the 82 pancreatic resections, pancreatic parenchyma sparing techniques were used in 55 (67%) patients (two enucleations, 16 central and 37 distal pancreatectomies), 39 (67%) of which were performed laparoscopically. This figure is higher than that reported in the literature given that laparoscopic resections are limited to centers with accredited experience and generally refer to distal pancreatectomies (36,37).

In addition to laparoscopic techniques, a program of fast-track surgery was implemented, which explains the hospital stay of ten days. Hospital mortality was 0% and there were no readmissions during the first 30 days after surgery. Eight (10%) severe complications (≥ IIIb Dindo-Clavien) were recorded. There was one (1.4%) pancreatic fistula, a figure lower than that normally reported, which may be related to the fact that drains were not being systematically left in the pancreatic cell (6,8,38). The definition of pancreatic fistula requires the presence of a pancreatic drain and the current trend is to avoid such drains (39). This criteria could explain the presence of fluid collections in 25 (33%) patients which were reabsorbed spontaneously and if they had been drained, would probably have been clinically irrelevant (grade A) "biochemical leaks" which are not considered as true fistulas (38). One fluid collection was drained in another center (grade A fistula) and the remaining were reabsorbed spontaneously.

The percentage of resections due to cystic tumors and the demographic pattern in our series are consistent with the data reported in more extensive surgical series (6,8,40). It is worth highlighting that 50% of the tumors were incidental, a figure which is slightly higher than that reported in other studies. However, most authors have reported an increase in the prevalence of such tumors (5,8-10,41). Most of the incidental tumors were found in the body and tail of the pancreas, unlike symptomatic tumors, which present more frequently in the head and would explain their silent presentation. Furthermore, the cystic mucinous neoplasms and IPMN were significantly more likely to be symptomatic, which is also in agreement with most other studies (6,8,9,42).

In our series, it is worth noting that 25% of patients had serous cystadenoma, which may seem an unusually high figure given the benign character of this lesion. In spite of this, most surgical series report a 20-30% rate of resections due to serous cystadenoma. The introduction of parenchyma-sparing surgical techniques

(enucleation, central and distal pancreatectomy), laparoscopic techniques and the fact that such lesions typically occur in the body and tail may explain this figure.

In our study, we have avoided the terms “potentially malignant” and “low risk” and “high risk”. The tumors were classified as invasive and non-invasive according to the histopathologic criteria of the most recent classifications for each cell line, epithelial or neuroendocrine (2,15,20-22,43). These criteria are well established in mucinous tumors, solid pseudo-papillary tumors and less clear in cystic neuroendocrine tumors, probably because they are less frequent (44,45). We classified cystic neuroendocrine tumors using the same criteria used for solid neuroendocrine tumors and have considered stages IIa-IIIb (T2N0-1M0) as invasive. Recent studies have confirmed that both phenotypes share a similar biologic behavior (44,46).

In our cohort, 20% (n = 16) of patients had the invasive phenotype, of which 50% were mucinous (seven IPMN and one CMN). These findings are in accordance with data from the successive clinical guidelines and expert recommendations. In our series, 66 (80.5%) patients had non-invasive tumors with an excellent disease-free survival at five and ten years (97.4%), which is similar to that found in most studies (6-8,42). In contrast, 16 (20%) patients had the invasive phenotype, five of which experienced a relapse of their disease (three IPMN and two cPanNETS); two were incidental with a ten-year disease-free survival rate of 70%. These findings raise the basic questions with regard to the treatment of cystic tumors, especially incidentalomas (5,9,10): is a population at a low risk of malignancy being over-treated and are patients being exposed to an unnecessary risk? Are techniques which spare the pancreatic parenchyma justified in this disease? Are radiologic tests overused in the follow-up of these patients with the consequent extra cost and radiation exposure risk? This dilemma explains why it is so difficult to apply the recommendations from the clinical and expert guidelines and why, in many cases, therapeutic decisions will continue to be made on the basis of the good clinical judgement and surgical experience of each particular center. Recent studies have reported discrepancies in the pre- and post-operative treatment of one of every three patients (47). Cytologic and molecular analyses of the content of the cyst and identification of signs of radiologic risk seem to be crucial for decision making (1,3,41).

Study limitations

We are aware of the limitations of our study, the retrospective design and the fact it was a surgical series of 82 patients carried out during a period of time in which both surgical techniques and the recommendations in clinical guidelines had undergone considerable changes. To avoid possible bias in the classification of tumors as invasive or non-invasive, we followed the criteria of more extensive series and current pathologic classifications, both for epithelial and neuroendocrine tumors. In spite of the limited number of cases, our series does include different CNP phenotypes. Our results on long-term survival confirm the different behavior in both types of tumor (invasive and non-invasive), as have most other studies. In spite of the consensus guidelines and good prognosis, the diagnosis and treatment of cystic neoplasms of the pancreas remains controversial due to their heterogeneity. As a result, we recommend that they are treated in centers with experience in the disease and pancreatic surgery. Laparoscopic resections and pancreatic parenchyma-sparing techniques are good options in those cases in which surgery is indicated.

In conclusion, cystic tumors of the pancreas represent a heterogeneous group of lesions which include benign lesions and also potentially malignant and malignant lesions. Given that approximately 40-50% present incidentally, they represent a diagnostic and therapeutic challenge. To avoid both “over-” and “under-treatment”, current updated clinical guidelines should be used to individualize treatment. Both parenchyma-sparing and laparoscopic techniques are good alternatives due to their lower morbidity.

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Table 1. Characteristics of patients who underwent a surgical resection for pancreatic cystic neoplasms

Baseline characteristics	*All patients (n = 82)*	*Incidental (n = 41)*	*Non incidental (n = 41)*	*p*
Age (mean, SD) years	57 (15.7)	58.7 (15.2)	55.8 (16.2)	0.48
Gender				0.12
Female, n (%)	49 (59.8)	28 (68.3)	21 (51.2)	
Mean body mass index, kg/m^2 (SD)	24.8 (4.4)	25.6 (5.1)	23.9 (3.2)	0.09
Diabetes, n (%)	10 (12.2)	4 (9.8)	6 (14.6)	0.5
ASA				0.22
I	4 (5.3)	1 (2.6)	3 (7.9)	
II	41 (54)	23 (60.5)	18 (47.4)	
III	29 (38.2)	14 (36.8)	15 (39.5)	
IV	2 (2.6)	-	2 (5.3)	
Location of tumor, n (%)				0.02
Head	25 (30.5)	8 (19.5)	17 (41.5)	
Body	20 (24.4)	14 (34.1)	6 (14.6)	
Tail	32 (39)	18 (43.9)	14 (34.1)	
Diffuse	5 (6.1)	1 (2.4)	4 (9.8)	
Type of surgery, n (%)				0.29
Whipple procedure	19 (23.1)	7 (17.1)	12 (29.3)	
Central pancreatectomy (open/lap)	6/10 (19.5)	8 (19.5)	8 (19.5)	
Distal pancreatectomy (open/lap)	10/29 (47.5)	24 58.5)	15 (36.5)	
LVPDP	18 (62)	-	-	
LRDPS	11 (38)	-	-	
Total pancreatectomy (open/lap)	5/1 (7.3)	1 (2.4)	5 (12.2)	
Enucleation	2 (2.4)	1 (2.4)	1 (2.4)	

Length hospitalization (mean, SD) days	10 (13.8)	8.2 (7.1)	12.8 (17.9)	0.312
Complication grade* (D-C)				0.434
I	67 (81.7)	35 (85.4)	32 (78)	
II	4 (4.9)	3 (7.3)	1 (2.4)	
IIIa	3 (3.7)	1 (2.4)	1 (4.9)	
IIIb	6 (7.3)	1 (2.4)	5(12.2)	
IVa	1 (1.2)	1 (2.4)	-	
IVb	1 (1.2)	-	1 (2.4)	
Histopathology diagnosis				0.04
Mucinous cystic neoplasm	19 (23.2)	7 (19.5)	11 (26.8)	
Serous cystadenoma	20 (24.4)	15 (36.6)	5 (12.2)	
Solid pseudopapillary neoplasm	4 (4.9)	3 (7.3)	1 (2.4)	
Cystic neuroendocrine neoplasm	8 (9.8)	5 (12.2)	3 (7.3)	
IPMN	27 (32.9)	9 (22)	18 (43.9)	
Other	4 (4.9)	1 (2.4)	3 (7.3)	
Invasive phenotype, n (%)				0.58
Non-invasive	66 (80)	34 (82.9)	32 (78)	
Invasive	16 (19.5)	7 (17.1)	9 (22)	
Recurrence, n (%)				0.98
Locoregional	1 (1.2)	1 (2.4)	-	
Distant	5 (6.1)	2 (4.9)	3 (7.3)	
Clinical follow-up after surgery				0.42
Deceased due to pancreas cancer	2 (2.4)	0	2 (4.8)	
Deceased due to unrelated causes	3 (3.7)	1 (2.4)	2 (4.8)	
New-onset diabetes, n (%)[†]	7 (9.7)	1 (2.7)	6 (17.1)	0.05

ASA: American Society of Anesthesiologists physical status (24) classification; IPMN: intraductal papillary mucinous neoplasm; D-C: Dindo-Clavien grade (30); LVPDP:

laparoscopic vessels-preservation distal pancreatectomy; LRDPS: laparoscopic radical distal pancreatosplenectomy. *Pancreatic fistula rate was calculated considering the 76 patients who underwent a partial pancreatectomy. †New-onset diabetes was calculated considering the patients who were not diabetic pre-surgery.

Table 2. Pathological characteristics and outcome in resected pancreatic cystic neoplasms

Baseline characteristics	*Non-invasive* *n = 66 (80.5%)*	*Invasive* *n = 16 (19.5%)*	*p*
Histopathology diagnosis, n (%)			< 0.01
Serous cystadenoma	20 (30.3)	-	
Mucinous cystic neoplasm	18 (27.3)	1 (6.3)	
Solid pseudopapillary tumor	-	4 (25)	
Cystic neuroendocrine neoplasm*	4 (6.1)	4 (25)[†]	
IPMN	20 (30.3)	7 (43.7)	
Other[‡]	4 (6.1)		
Mean size of lesion by pathology, mm (SD)	28.6 (32.2)	66.1 (66.3)	< 0.01
Location of tumor, n (%)			0.35
Head	19 (28.8)	5 (37.5)	
Body	18 (27.3)	2 (12.5)	
Tail	26 (39.4)	6 (37.5)	
Diffuse	3 (4.5)	2 (12.5)	
Recurrence, n (%)			
Locoregional	1 (1.5)	-	
Distant	1 (1.5)	4 (25)	< 0.01
Clinical follow-up after surgery			0.06
Deceased due to pancreas cancer	1 (1.5)	1 (6.3)	
Deceased due to unrelated causes	1 (1.5)	2 (12.5)	

IPMN: intraductal papillary mucinous neoplasm; SD: standard deviation. *Cystic neuroendocrine neoplasm non-invasive, T1 N0 M0 (stage I). [†]Invasive T2 N0-1 M0 (stage IIa-IIIb) according to European Neuroendocrine Tumor Society (ENETS) (37). [‡] One choristoma, one mucinous non-neoplastic cyst, two retention cysts.

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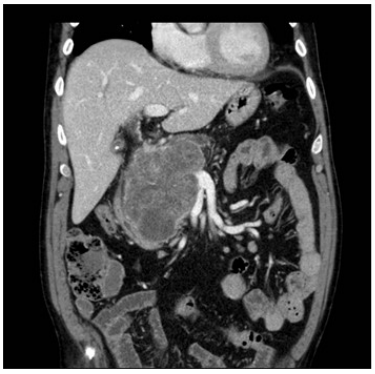
1.a)



1.b)

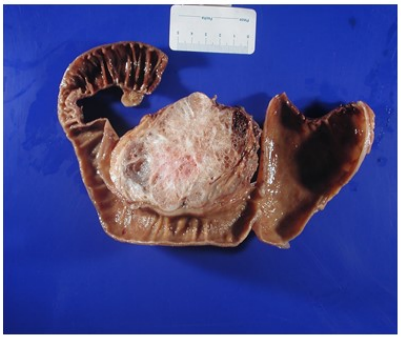


Fig. 1. A. CT showing a large cystic mass in the head of the pancreas with a "honeycomb" pattern typical of serous cystadenoma. B. Gross appearance of serous cystadenoma, composed of innumerable small cysts ("microcystic") creating a sponge-like or honeycomb appearance. A stellate scar is commonly present.

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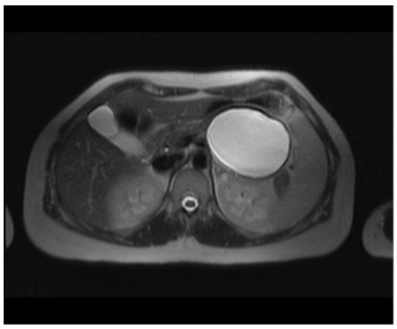
2.a)



2.b)

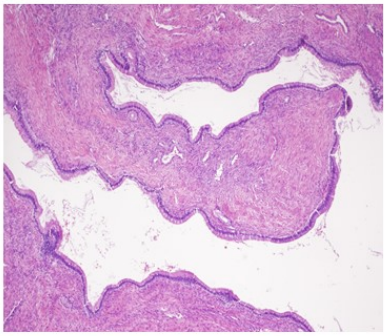


Fig. 2. A. MR imaging showing a large mucinous cystadenoma in the tail of the pancreas with a homogeneous high T2 signal intensity. B. Mucinous cystic neoplasm. Tall columnar mucinous epithelium displaying low-grade dysplasia with ovarian type stroma (hematoxylin and eosin).

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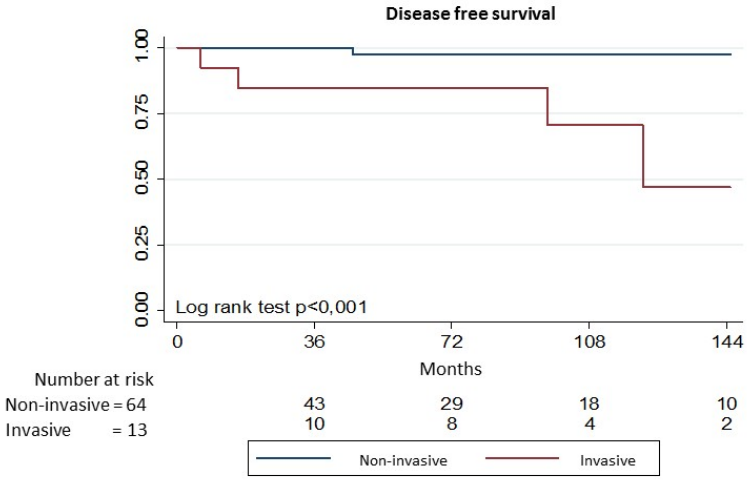

Fig. 3. Kaplan-Meier disease-free survival curves for non-invasive and invasive cystic pancreatic neoplasms.