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THE ROLE OF DIABETES AND WEIGHT LOSS AS PREDICTORS OF MALIGNANCY IN INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

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To my parents

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ABBREVIATIONS

AGA	American Gastroenterological Association
BD-IPMN	branch duct-IPMN
BMI	body mass index
CA19.9	serum carbohydrate antigen 19.9
CEA	carcinoembryonic antigen
cm	centimeter
CT	computed tomography
dl	deciliter
DM	diabetes mellitus
EUS	endoscopic ultrasound
ERCP	endoscopic retrograde cholangiopancreatography
FNA	fine-needle aspiration
HDG	high-grade dysplasia
IAP	International association of pancreatology
IC	confidence interval
IPMN	intraductal papillary mucinous neoplasm
LDG	low-grade dysplasia
MD-IPMN	main duct-IPMN
mg	milligram
mm	millimeter
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MPD	main pancreatic duct
MUC	mucin
PDAC	pancreatic ductal adenocarcinoma
OR	odds ratio

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1 INTRODUCTION

1.1. Intraductal papillary mucinous neoplasms

1.1.1. Definition

Intraductal papillary mucinous neoplasms (IPMNs) are mucin-producing cystic lesions of the pancreas that originate from the ductal epithelium of the main pancreatic duct or its branches, with a wide spectrum of differentiation and variable biological behavior (Tanaka et al. 2017, Matthaei et al. 2011). Following a classic “adenoma-carcinoma sequence”, these lesions may evolve from low-grade dysplasia to invasive carcinoma (Figure 1) (Tanaka et al. 2018, Matthaei et al. 2011). Based on the involvement of the pancreatic ductal system, IPMNs can be classified into three types: branch-duct-IPMN (BD- IPMN), main duct-IPMN (MD-IPMN), and mixed type (Figure 2). BD-IPMNs are defined as pancreatic cysts >5 mm developed from the epithelium of the distal branches communicating with a non-dilated main pancreatic duct (MPD) (<5 mm). By contrast, IPMNs with a segmental or diffuse dilation of the MPD ≥5 mm without other causes of obstruction are classified as MD-IPMN. Lesions meeting criteria for both MD- and BD-IPMN are currently classified as mixed-type IPMN (Tanaka et al. 2017). Different IPMN types present considerable differences in clinical presentation, histological pattern, and malignant potential.

1.1.2 History

The first cases of IPMN were described in Japan in 1982 by Ohashi et al. (Ohashi et al. 1982). Since then, these neoplasms have been reported with increasing

frequency and in 1996 the World Health Organization (WHO) defined for the first time the criteria to classify IPMN (Kloppel et al. 1996). In 2004, during the 11th Congress of the International Association of Pancreatology (IAP) in Sendai, Japan, a group of experts in the field drafted the first consensus guidelines for the management of IPMN (Tanaka et al. 2006). The “Sendai criteria”, as they became known, were validated and used for several years to establish the indication to surgery or surveillance in patients with IPMNs. In 2012, these guidelines were revised into the Fukuoka consensus guidelines, with the introduction of “worrisome features” and “high-risk stigmata” in the algorithm for the management of IPMNs (Tanaka et al. 2012). Afterward, other guidelines were published, as the guidelines proposed by the American Gastroenterological Association in 2015 (Vege et al. 2015) or by the European Study Group on Cystic Tumours of the Pancreas in 2018 (European Study Group on Cystic Tumours of the Pancreas 2018), as well as a revised version of the Fukuoka guidelines (Tanaka et al. 2017), however, with significant differences. Table 1 shows the high-risk features and indications for surgery according to these three guidelines. It is important to underline that the divergences between the guidelines highlight our still limited knowledge of the natural history of these neoplasms and the complexity of their management.

1.1.3 Epidemiology, risk factors, and clinical manifestation

The exact prevalence of IPMNs is unknown, as most of them are small and asymptomatic. As imaging steadily improves, discovering incidental pancreatic cysts during computed tomography (CT) or magnetic resonance imaging (MRI)

done for unrelated problems has become an event with increasing incidence. Several series have shown that the prevalence of incidentally discovered pancreatic cysts ranges between 2.4% and 19.6%, depending on the imaging modality (Zhang et al. 2002, Lee et al. 2010, Laffan et al 2008, De Jong et al. 2010, Zerboni et al. 2019), and it is strongly associated with age. Identifying an IPMN among all these pancreatic cystic lesions represents a complex task. In a recent study, the prevalence of pancreatic cysts consistent with IPMNs in an adult population was estimated at 6.6% (Laurent et al. 2017) and reaches the highest value during the sixth or seventh decades, and in males (Crippa et al. 2010, Tanaka et al. 2017). Smoking, obesity, chronic pancreatitis, and a family history of PDAC seem to predispose to the development of IPMN and its progression (Capurso et al. 2013, Capurso et al. 2020, Carr et al. 2017).

As already mentioned above, most IPMNs are asymptomatic and often incidentally discovered, therefore, an exact estimation of symptomatic cases is difficult to obtain. In follow-up series, more than 80% of patients do not have any symptoms (Pergolini et al. 2017, Petrone et al. 2018); by contrast, as expected, in surgical series the rate of symptomatic patients is higher, reaching even 50% (Del Chiaro et al. 2020). When present, the most frequent symptoms are abdominal pain in the upper abdominal quadrants, jaundice, weight loss, steatorrhea, and acute pancreatitis (Fernandez del Castillo et al. 2010). The presence of symptoms may reflect a more advanced disease and, therefore, some of them were included in the guidelines as relative or absolute indications to surgery (Tanaka et al. 2017).

1.1.4 Diagnosis

The diagnosis of IPMNs is based on high-resolution imaging and endoscopic modalities.

To decide the most appropriate management, the diagnostic work-up should pursue the following goals: (1) differentiating IPMNs from other pancreatic cystic lesions; (2) determining the type of IPMN, BD-, MD-IPMN or mixed-type, and (3) identifying the presence of worrisome features, needing further investigation, closer surveillance or surgical treatment. CT and MRI with magnetic resonance cholangiopancreatography (MRCP) are both effective and reliable methods (Seo et al. 2016). However, MRI/MRCP is considered the standard diagnostic imaging modality (Hecht et al. 2021). MRI/MRCP is more sensitive than CT for identifying the communication between cysts and MPD, evaluating the size and features of the MPD, and distinguishing nodules and thickened walls. Moreover, avoiding radiation exposure, MRI/MRCP represents the best imaging modality for the surveillance of IPMNs, before and after surgery. After MRI and CT, the second-level diagnostic modality is represented by the endoscopic ultrasound (EUS). Although EUS is an invasive and operator-dependent imaging technique, it is very useful to differentiate IPMNs from other pancreatic cysts and to detect and characterize thickened walls or mural nodules, with higher accuracy compared with CT/MRI (Lu et al. 2015, Tanaka et al. 2017). Moreover, EUS offers the possibility to perform fine-needle aspiration (FNA) and cyst fluid analysis. Here, fluid markers as carcinoembryonic antigen (CEA) and amylase can help to distinguish mucinous lesions from non-mucinous cysts, while cystic fluid cytology can be performed to detect atypical or malignant cells. Besides, in cyst fluid using next-generation sequencing, it is possible to identify DNA alterations, as KRAS

or GNAS mutations, improving the differential diagnosis. For all these reasons, EUS with FNA should be performed in case of worrisome imaging features on noninvasive imaging modalities (MRI or CT) to better differentiate neoplastic from non-neoplastic cystic lesions (Tanaka et al. 2017). Of note, FNA is considered a safe procedure and is unlikely to increase the frequency of peritoneal or needle-path seeding (Hecht et al. 2021).

IPMNs can be also examined by endoscopic retrograde cholangiopancreatography (ERCP). The presence of mucin extrusion from a dilated duodenal papilla, known as “fish-mouth papilla”, is a pathognomonic sign of IPMN, in particular with intestinal-type (Aso et al. 2012). However, ERCP, as a more invasive and less accurate procedure, has been largely replaced by MRI/MRCP and EUS and, according to the IAP guidelines, is not recommended in the diagnostic work-up (Tanaka et al. 2017).

1.1.5 Pathology

IPMNs originate from stem cells of the epithelium of the pancreatic ducts which can differentiate into four histological subtypes: gastric, intestinal, pancreaticobiliary, and oncocytic (Figure 3) (Furukawa et al. 2005, Fernandez-del Castillo et al. 2010). Gastric and intestinal types are the most represented types. IPMNs of gastric subtype are more frequently BD-IPMNs and harbor usually low-grade dysplasia. By contrast, intestinal IPMNs involve more frequently the MPD and are more frequently lesions of high-grade (Koh et al. 2015). Pancreatobiliary IPMNs are less frequent, however, they represent the subtypes with the highest likelihood of progression to invasive cancer (Koh et al. 2015).

To classify the IPMN epithelial subtypes, the pathologists combine morphology with immunohistochemistry. Here, the immunohistochemistry is based on mucin staining: the intestinal subtype usually expresses Mucin-2 (MUC2), MUC5AC, and caudal type homeobox 2 (CDX2), but not MUC1 and MUC6; whereas, IPMNs of gastric type express MUC5AC and MUC6, but they are usually negative or only focally positive for MUC1 and/or MUC2 (Grützmann et al. 2010, Fernandez-del Castillo et al. 2010). In a recent study, the analysis of circulating plasma extracellular vesicles from patients with IPMN showed that the expression of MUC5AC is significantly higher in high-grade lesions and can predict the presence of invasive IPMN (Yang et al. 2021). These authors suggested the addition of MUC5AC as biomarker to imaging and high-risk stigmata to detect high-risk IPMNs requiring surgery.

Different epithelial subtypes progress differently to invasive carcinoma and present varying prognoses (Furukawa et al. 2011, Mino-Kenudson et al. 2011, Koh et al. 2015). When IPMNs become invasive, two different subtypes of carcinoma can be identified: tubular and colloid type. The tubular carcinoma usually arises from gastric and pancreatobiliary IPMNs and is morphologically and prognostically similar to PDAC. By contrast, the colloid type normally develops from intestinal IPMNs and is morphologically characterized by wide paucicellular pools of mucin with scant carcinoma cells; colloid carcinomas have usually a better prognosis than tubular type (Figure 3) (Fernandez-del Castillo et al. 2010, Koh et al. 2015, Mino-Kenudson et al. 2011).

In the progression from adenoma to invasive carcinoma, IPMNs develop several specific genetic alterations. Up to 90% IPMNs have been shown somatic mutations in KRAS and GNAS oncogenes. Here, GNAS mutations are more

prevalent in intestinal-type IPMNs and colloid carcinomas; whereas, KRAS mutations are more frequent in tubular invasive IPMNs. Both mutations are considered as early events for the development of IPMN. Other mutated genes have been detected as responsible for the malignant progression of IPMNs, such as TP53, CDKN2A/p16, SMAD4, and, less frequently, PIK3CA, BRAF, PTEN, and STK11 (Wu et al. 2011, Singhi et al. 2018, Tan et al. 2015). However, the exact underlying mechanisms of progression to PDAC are still unraveled and currently under investigation. Recently, Fisher et al. performed a comprehensive genomic analysis of neoplastic tissues obtained from multiple regions of 20 resected IPMNs to evaluate the diversity of somatic mutations involved in the tumorigenesis. They found that in IPMNs in early-stage, there is a high heterogeneity of mutations in driver genes across the entire lesion. Moreover, the whole-exome sequencing showed that IPMNs contained multiple independent clones, each with distinct mutations, suggesting a polyclonal origin. This heterogeneity in initiating driver genes decreases with the progression to high-grade dysplasia, suggesting a selection and expansion of a single clone after the acquisition of additional alterations (Fisher et al. 2019). However, these results are at odds with the traditional hypothesis of a monoclonal origin of pancreatic tumors. For instance, Makohon-Moore et al. argue that carcinomas develop from noninvasive precursor lesions derived from an ancestral cell that initiates and then clonally expands to form one or more lesions. In other words, distinct precursor lesions observed in an individual patient represent a single neoplasm that can spread, contiguously or discontiguously, along the ductal system accumulating genetic alterations over time (Makohon-Moore et al. 2018).

1.1.6 Malignant potential, therapy, and prognosis

As well-known, MPD involvement is associated with more aggressive biology and MD/mixed-IPMNs showed a significantly higher risk of developing invasive cancer when comparing to BD-IPMNs. In large surgical series, the rate of invasive cancer is more than 40% for MD/mixed-IPMNs, whereas it is estimated to be 16% for the BD-IPMNs (Tanaka et al. 2012, Marchegiani et al. 2015). However, since most data available in the current literature are based on retrospective surgical series and most BD-IPMNs are managed conservatively, it is important to highlight that the malignant potential of BD-IPMNs is probably overestimated. In observational series, the risk of progression to invasive cancer for BD-IPMN seems to be likely less than 5%, but it persists even after 10 years after the first diagnosis (Pergolini et al. 2017). Further investigations and reliable data from prospective observational series in the long term are needed for understanding the natural history of IPMNs and obtaining an accurate estimate of the risk of progression.

As the natural history is still unknown, the management of IPMNs continues to evolve. In the past, before the Sendai consensus, the treatment choice was based predominantly on institutional or individual experience and most patients with IPMNs underwent surgical resection. Thereafter, because many IPMNs, especially those asymptomatic and small, did not harbor any malignancy at pathology, an alternative conservative approach started to be proposed by clinicians. As a result, in 2006 the IAP consensus guidelines suggested that asymptomatic BD-IPMNs smaller than 30 mm without solid nodules could undergo surveillance (Tanaka et al. 2006). Since then, several guidelines were published and the indications for resection or surveillance have changed over

time. Although using different terms, all guidelines identify signs of malignancy that require immediate surgery (“high-risk stigmata” or “absolute indications for surgery”) or additional examinations before surgery or close surveillance (“worrisome features” or “relative indications for surgery”). As already written above, Table 1 shows the criteria for the management choice of the three most current and important international guidelines: AGA guidelines (Vege et al. 2015), IAP guidelines (Tanaka et al. 2017) and, those of the European Study Group on Cystic Tumours of the Pancreas (European Study Group on Cystic Tumours of the Pancreas 2018).

Despite multiple guidelines, the choice of the treatment and timing remains a great challenge for clinicians. On one hand, it is well-known that the prognosis of resected IPMNs with low-grade or high-grade dysplasia is excellent, as the five-year disease-specific survival can reach 100%, whereas the prognosis of invasive IPMNs is similar to PDAC (Hipp et al. 2019, Woo et al. 2008, Koh t al. 2014). On the other hand, pancreatic surgery is still burdened by high morbidity and mortality. In this setting, pancreatologists have constantly tried to balance between the risk of progression to invasive cancer and the risk of serious complications and mortality. In addition, also other factors have to be considered in the management choice, e.g., age, comorbidities, quality of life, risk of recurrence, risk of concomitant PDAC and, not least, the costs of surveillance. In more detail, several studies demonstrated that after partial resection, metachronous IPMNs can develop in the remaining pancreas in 1-20% of cases, and, accordingly, a lifetime continuous follow-up is required (Tanaka et al. 2017, Hirono et al. 2020). Besides, patients with IPMNs have an increased risk for developing a concomitant but distinct PDAC, with a rate between 2 to 9% (Tanaka

et al. 2017); this risk must be taken into account for the follow-up of both resected patients and those under surveillance (Tanaka et al. 2017). Accordingly, young patients under surveillance or after resection need periodic examinations for a long time, with considerable associated costs and stress (Marinelli et al. 2020, Huang et al. 2010).

In this complex context, several nomograms based on radiologic findings of IPMN have been proposed in the last years, to predict the risk of malignancy and help the decision process (Attiyeh et al. 2018, Lee et al. 2020, Wu et al. 2020).

1.2 Diabetes in IPMN: current knowledge

Since IPMNs may progress following a classic “adenoma-carcinoma sequence”, understanding the mechanisms behind this process and determining predictors of progression to invasive cancer is crucial for early diagnosis and prevention of pancreatic cancer. Accordingly, many studies sought to identify clinical, morphological, and molecular factors that may help in clinical practice. In this context, however, little attention has been paid till today to diabetes mellitus (DM) and other metabolic disorders in IPMN (Pergolini et al. 2021). In the current literature, DM has been mostly investigated as a long-term complication after surgery, depending on the extension of resection (Falconi et al. 2008, Leal et al. 2015). By contrast, little is known about the exact prevalence of preoperative DM among patients with IPMN and its potential role in the progression to HGD and invasive carcinoma (Leal et al. 2015, Mimura et al. 2010, Gausman et al. 2018, Duconseil et al. 2018, Morales-Oyarvide et al. 2017, Del Chiaro et al. 2020, Pergolini et al. 2021). As a result, the AGA and IAP guidelines cited above do not

mention at all diabetes mellitus and other metabolic factors in the choice of management (Vege et al. 2015, Tanaka et al. 2017). Only in 2018, the European guidelines for the management of IPMN have proposed new-onset diabetes as a relative indication for surgery, however with a low level of evidence (European Study Group on Cystic Tumours of the Pancreas et al. 2018).

In pancreatology, DM has been more extensively studied in PDAC. Approximately 50% of the patients with sporadic pancreatic cancer have diabetes, and in nearly 50% of these patients, DM is diagnosed at or shortly before cancer diagnosis (Pannala et al. 2009). In PDAC, DM seems to play a double role. On one hand, several studies showed that a clinical history of DM represents a risk factor for PDAC and diabetic patients have a 2-fold higher risk of developing pancreatic cancer (Pannala et al. 2009, Magruder et al. 2011). In those patients with new-onset diabetes, this risk is even 6-fold higher than the normal population. On the other hand, DM can be considered as a manifestation or consequence of pancreatic cancer, or, in other words, a paraneoplastic phenomenon. As proof of that, several studies demonstrated that pancreatic cancer-associated diabetes may improve after tumor resection, despite the removal of a considerable amount of gland parenchyma (Pannala et al. 2009, Pannala et al. 2008). Besides, some studies showed that DM induced by PDAC is paradoxically associated with weight loss (Hart et al. 2011). Here, since these metabolic changes precede the onset of other cancer-specific symptoms by several months, weight loss cannot be attributed to cachexia, which oft accompanies PDAC, but rather to a paraneoplastic phenomenon due to the interactions between pancreatic cancer and adipose tissue (Sah et al. 2013). In this context, DM, especially new-onset DM, not only identifies a high-risk group

for pancreatic cancer but may also be a marker of early, asymptomatic cancer (Pannala et al. 2009) and an attractive screening target for early diagnosis of pancreatic cancer (Sah et al. 2013).

Although IPMNs are considered a different entity rather than PDAC with important biological and molecular differences, these results offer interesting insights for further investigations also in IPMNs.

1.3 Aim of the study

Based on the experience with PDAC described above, we have questioned if any association between DM and weight loss also occurs in IPMN with HGD that may help for earlier diagnosis and prevention of invasive pancreatic cancer. Therefore, with this study, we sought to determine the prevalence of DM in a cohort of IPMNs resected in our department and to evaluate the association of preexisting DM with other clinical-morphological features and with the progression to HGD and invasive cancer, with special regard to the relationship of DM with weight loss.

2 MATERIALS AND METHODS

2.1 Study population

Patients who consecutively underwent pancreatic resection for histologically confirmed IPMN at the Department of Surgery of the Klinikum Rechts der Isar, Technical University of Munich, Germany, between July 2007 and December 2018, were included and retrospectively reviewed. The following demographic and clinicopathologic features of the included patients were recorded: sex, age at initial diagnosis and surgery, past medical history, medications, symptoms at the time of diagnosis, serum tumor markers [carcinoembryonic antigen (CEA, normal value <5 ng/ml) and serum carbohydrate antigen 19-9 (CA19.9, normal value 0-37 U/ml)], cyst morphology and localization, MPD size and features, indication for surgery, date, and type of surgery, postoperative complications, and final pathological findings. We excluded from the analysis patients with IPMN associated with pancreatic or duodenal neuroendocrine tumors at pathology, as well as, patients with distinct concomitant PDAC. The study was approved by the Ethics Committee of the Technical University of Munich (approval nr. 118/19s).

2.2 Definition and assessment of preoperative DM

Patients were considered as diabetic when a history of DM and/or intake of oral antihyperglycemic drugs or insulin were reported in the medical reports at the preoperative consultation. Patients were defined as diabetic also when, according to the current American Diabetes Association guidelines, the fasting plasma glucose was ≥126 mg/dl at the preoperative workup (Diagnosing diabetes and learning about prediabetes. American Diabetes Association.

[updated 2016 November 21, cited 2017 May 1] Available from: http://www.diabetes.org/diabetes-basics/diagnosis). To avoid bias, patients with diabetes type I were excluded from the study.

New-onset DM was defined as DM diagnosed within 2 years prior to the initial diagnosis of IPMN or at the time of the preoperative laboratory tests. Worsening DM at the time of IPMN diagnosis was also registered. When DM was referred as pre-existing for a long time (> 2 years) before IPMN diagnosis, it was classified as long-standing.

2.3 Clinical-morphological features of IPMNs

Patients were considered symptomatic in presence of the following symptoms: jaundice, pancreatic abdominal pain, acute pancreatitis, worsening or new-onset DM, unjustified weight loss, or steatorrhea. Weight loss was defined as a significant unexplained weight reduction (≥5%) occurring within the last 12 months before the preoperative visit. During the preoperative workup, patients underwent CT, MRI/MRCP, and/or EUS or ERCP. EUS with or without FNA was performed at the discretion of the clinician; when performed, data on cytology and CEA values in cyst fluid were recorded. Data on the following morphological features at the time of diagnosis and during follow-up were collected: localization, cyst size, communication of the cyst with the MPD, MPD diameter, presence of septations, wall thickening, and solid component with or without enhancement. For patients who underwent multiple radiological examinations during the surveillance before surgery, we collected the largest size and the worse features developed by the cyst and the MPD. A clinical or radiological diagnosis of chronic pancreatitis in the past medical history was also recorded, when present. IPMNs

were preoperatively classified as mixed-/MD-IPMNs in presence of MPD dilation ≥5 mm with/without associated cystic lesions in side branches. By contrast, BD-IPMNs were defined as cysts >5 mm in communication with the MPD in absence of MPD dilation.

All patients were retrospectively reviewed for worrisome features and high-risk stigmata according to the revised IAP Guidelines (Tanaka et al. 2017) (Table 1).

2.4 Surgical indications and pathology

Surgery was proposed in presence of signs of malignancy and in accordance with the patients´ decision. All surgical indications were also preoperatively discussed by a multidisciplinary team. Surgery was always performed after patients´ informed consent. The extension of the surgical resection was determined based on the dimension and the site of the tumor, the intraoperative findings, and the results of the frozen section analysis of the resection margin.

At final pathology, IPMNs consisting in cystic lesions >5 mm without the involvement of the MPD were defined as BD-IPMN; by contrast, in presence of MPD involvement with/without associated cystic lesions IPMNs were classified as mixed-/main-duct IPMN (Tanaka et al. 2017). According to the 2015 Baltimore Consensus, IPMNs were classified as: (1) IPMNs with low-grade dysplasia (LGD-IPMN), (2) IPMNs with high-grade dysplasia (HGD-IPMN), and (3) invasive ductal carcinoma arising from IPMN (invasive-IPMN) (Basturk et al. 2015). In detail, invasive-IPMNs were defined as invasive carcinoma originating within the area with the known pancreatic cyst and extending contiguously to the IPMN. Patients with pancreatic cancer arising separately from the IPMN were defined as concomitant or distinct pancreatic ductal carcinoma and were excluded from our

study. In addition, patients with associated neuroendocrine tumors were also not considered.

2.5 Statistical analysis

This study was designed according to the REMARK and STROBE guidelines (Altman et al. 2012, von Elm et al. 2014). The main endpoints of our studies were determining the prevalence of preoperative DM and evaluating the association of DM with other clinical-morphological features and with the progression to HGD and invasive cancer. Statistical analyses were performed using SPSS software (SPSS, Chicago, IL, USA).

Categorical variables are reported as frequencies and percentages, and continuous variables as median and range. Depending on the number of observations, comparisons of categorical variables were performed using the Chi-square or Fisher exact tests. Unadjusted- and multivariable-adjusted binomial logistic regressions were conducted to calculate the odds ratio (OR) and 95% confidence interval (CI). Continuous variables were compared by Mann–Whitney U-test or Kruskal-Wallis test. All hypothesis tests were two-sided and statistical significance was set at $p<.05$.

3 RESULTS

3.1 Study population

Between July 2007 and December 2018, 148 patients underwent pancreatic resection for IPMN at the Department of Surgery at Klinikum rechts der Isar; of these, 134 met the selection criteria and were included in the analysis. Tables 2 and 3 show clinical and morphological characteristics of the included patients, while Tables 4 and 5 report surgical and pathological data.

Thirty-eight patients (28%) underwent primary surveillance before surgery for more than 6 months. Overall, the median follow-up before surgery was 2 months (range 0-123). New worrisome features or high-risk stigmata or a worsening of them were detected during follow-up in 25 patients. Overall, 51% of patients underwent resection because of high-risk stigmata. Only 6 patients (4.5%) were resected in absence of worrisome features or high-risk stigmata at diagnosis or during follow-up. Here, in 2 cases the indication to surgery was given because of increasing cysts, even though under 3 cm; in one patient the cytology was suspicious for a solid pseudopapillary tumor, and in another patient the cystic lesion was preoperatively suspicious for mucinous cystic neoplasm. For the remaining 2 patients, the indication to surgery was unknown. Pancreaticoduodenectomy was the most frequent procedure (44%), while 35 patients (26%) underwent total pancreatectomy (Table 4). For 32 of these 35 patients, a total pancreatectomy was justified by the presence of multifocal disease or an IPMN diffuse to the entire gland with massive dilation of the MPD; for the remaining 3 patients without multifocal or diffuse IPMN a total pancreatectomy was performed after positive frozen section margin.

At the final pathology, 58 patients (43%) had an invasive pancreatic cancer arising from IPMN, while other 16 patients (12%) HGD (Table 5). 31 patients (25%) presented BD-IPMN, while 94 IPMNs (75%) were defined as MD-IPMN. In the remaining 9 patients, the type of IPMN was undetermined or unknown (Table 5).

3.2 Diabetes mellitus and clinical-morphological features

The global prevalence of preoperative DM was 37% (50/134). Of them, 20 patients (15%) had a new-onset or worsening DM: 10 patients presented positive laboratory tests during the preoperative workup (within 1 month before surgery), while in the other 10 cases new or worsening DM had been determinant for the diagnosis of IPMN.

Tables 2 and 3 show the comparison of the clinical-morphological features between diabetic and non-diabetic patients. Diabetic patients were more frequently male and older in comparison with non-diabetic patients. No differences were registered regarding comorbidities between the two groups. Surprisingly, body mass index (BMI) was not associated with DM (median BMI, diabetic: 25.3 vs non-diabetic: 24.5, p=0.115) and did not correlate with progression to malignancy. By contrast, patients with DM had more frequently weight loss at the time of diagnosis as reason for medical consultation and diagnosis of IPMN (diabetic: 37% vs non-diabetic: 16%, p=0.009). Among the 10 patients where new-onset or worsening DM led to the diagnosis of the IPMN, 7 presented weight loss at diagnosis, but none of them had jaundice. Pre-existing DM, as well as new-onset DM, was not associated with jaundice. Moreover, a clinical or radiological preoperative diagnosis of acute and chronic pancreatitis

did not correlate with DM. Interestingly, diabetic patients showed significantly higher median CA19.9 in comparison with non-diabetic patients (diabetic: 35 mg/dl vs non-diabetic:13.5 mg/dl, p=0.042). Moreover, CA19.9 was significantly higher in patients with HGD/invasive cancer (LGD: 12 mg/dl vs HGD/invasive cancer: 39.5 mg/dl, p=0.023).

Regarding the morphological features of IPMN, diabetic patients harbored more frequently a multifocal IPMN (diabetic: 58% vs non-diabetic: 33%, p=0.005) with diffuse localization in the pancreatic gland (diabetic: 42% vs non-diabetic: 21%, p=0.001). Although no differences in median cyst size were found between diabetic and non-diabetic patients (diabetic: 32 mm vs non-diabetic: 30 mm, p=0.064), 63% of patients with a cyst ≥4 cm had DM (p=0.003). Moreover, patients with a diabetic status showed a significantly larger MPD diameter (diabetic: 8 mm vs non-diabetic: 6 mm, p= 0.006).

3.3 Diabetes mellitus and worrisome features/high-risk stigmata

Analyzing the association between DM and worrisome features/high-risk stigmata according to the revised Fukuoka IAP guidelines, we found that diabetic patients had more frequently high-risk stigmata in comparison with non-diabetic patients (diabetic: 74% vs non-diabetic: 38%, p <0.001). In detail, DM was significantly associated with the presence of a nodule or solid component and a MPD ≥10 mm.

3.4 Diabetes mellitus and surgical outcomes

Diabetic patients underwent total pancreatectomy more frequently than non-diabetic patients (diabetic: 42% vs non-diabetic: 17%, p=0.002); we presumed

that this might be due to the fact that diabetics harboring more frequently multifocal and, as we describe later, malignant IPMNs. Similarly, vascular resections were performed more often in patients with DM (diabetic: 30% vs non-diabetic: 12%, p=0.009). Despite this, during the postoperative course, DM was not associated with a higher rate of complications and mortality.

3.5 Diabetes mellitus and type of IPMN, epithelial subtypes, and grade of dysplasia

At the final pathology, 40% of patients harboring a MD-IPMN were diabetic vs 19% of patients with BD-IPMN (p=0.033). Here, diabetic patients showed a significantly higher risk of MPD involvement (OR 2.827, 95% IC 1.059-7.546; p=0.038). In our cohort, DM did not correlate with specific epithelial subtypes. In 23 patients the epithelial type was unknown or undetermined. Overall, gastric and intestinal subtypes were recognized more frequently, but without differences between diabetic and non-diabetic patients.

Regarding the association between DM and the grade of differentiation, we found that 50% of patients with invasive IPMN were diabetic, vs 38% and 25% of those with HGD and LGD respectively (p=0.018). DM was associated with a significantly higher risk of HGD/invasive cancer in the unadjusted analysis (OR 2.692, 95% IC 1.283-5.651; p=0.009) and after adjusting for worrisome features (OR 2.380, 95% IC 1.021-5.550, p=0.045). By contrast, this association was no longer present after adjusting for high-risk stigmata (OR 1.546, 95% IC 0.605-3.948, p=0.363) (Table 6).

Eighty percent of patients with new-onset/worsening DM harbored HGD or invasive cancer, vs 63% and 46% of patients with long-standing DM and without

DM respectively. When compared to patients without DM, those with new-onset/worsening DM had a significantly higher risk of HGD/invasive cancer in the unadjusted analysis (OR 4.615, 95% IC 1.423-14.698; p=0.011); this risk was even higher after adjusting for worrisome features (OR 8.165, 95% IC 1.967-33.886, p=0.004) (Table 7). By contrast, patients with long-standing DM did not show an increased risk of HGD/invasive cancer in comparison with patients without DM (OR 1.993, 95% IC 0.845-4.698, p=0.115) and with new-onset/worsening-DM (OR 0.432, 95% IC 0.115-1.622, p=0.214).

3.6 Diabetes mellitus and weight loss

Analyzing the relationship between DM and weight loss, we found that 58% (18/31) of patients with weight loss at the time of diagnosis had a DM status vs 32% (31/97) of those with stable weight (p=0.009). Moreover, patients with weight loss showed more frequently new-onset or worsening DM at diagnosis in comparison with patients without weight loss [26% (8/31) vs 11% (11/97)], p=0.026). Of note, in our series weight loss was not associated with HGD and/or invasive carcinoma.

Similar to the results reported for PDAC (Hart et al. 2011) mentioned above, diabetic patients had an increased risk of presenting weight loss at the time of IPMN diagnosis (OR 2.948, 95% IC 1.284-6.769, p=0.011). This association was still present even when the analysis was conducted considering only IPMN with LGD and HGD, and excluding patients with invasive carcinoma, where the association between DM and weight loss was expected as in PDAC. Here, 50% (8/16) of patients with weight loss at diagnosis were diabetic vs 21% (12/66) of patients with constant weight (p=0.024). By contrast, restricting the analysis to

patients with LGD and excluding IPMNs with HGD, DM and weight loss were no longer associated [42% (5/12) vs 21% (9/44), p=0.133]. In other words, the association between DM and weight loss in IPMNs was found only in presence of HGD or invasive cancer, but not with benign lesions.

4 DISCUSSION

IPMNs, as precancerous lesions that progress following the classic sequence adenoma-carcinoma, represent certainly a challenge for clinicians, who have to balance between risks and benefits in the choice of the most appropriate management, but also a great opportunity for understanding the mechanisms behind cancerization. Here, identifying predictors of progression of IPMNs to invasive cancer may offer the possibility to achieve early diagnosis and prevent pancreatic cancer. Pursuing this goal, with our study we sought to investigate the role of DM and other metabolic disorders, like weight loss, as predictors of malignancy in IPMN.

In our retrospective cohort, the global prevalence of DM at the time of IPMN diagnosis was 37%, which is higher compared to the general population of the United States, where the prevalence of DM in individuals aged 65 years and older reaches 20.8% (Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017). Our results are in line with the prevalence of DM reported in previous studies (15-43%) (Chang et al. 2015, Sturm et al. 2012, Del Chiaro et al. 2020, Mimura et al. 2010, Morales-Oyarvide et al. 2017, Khoury et al. 2018, Okabayashi et al. 2013). As a possible explanation of this high prevalence, a case-control study demonstrated that a previous history of DM is a risk factor for the development of IPMN, in particular for the development of MD/mixed-type IPMNs (Capurso et al. 2013). This has been confirmed in our series, where DM was significantly associated with the involvement of the MPD, and diabetic patients had a significantly higher risk of MPD involvement (OR 2.827, 95% IC 1.059-7.546; p=0.038). Focusing on the

other morphological features of IPMN, we found that patients with DM had more frequently an IPMN with multifocal localization in the pancreatic gland and with cyst bigger than 4 cm, suggesting the need for more extensive resections. Not surprisingly, diabetic patients underwent total pancreatectomy more frequently than non-diabetic patients (diabetic: 42% vs non-diabetic: 17%, p=0.002).

Our analysis showed that patients with a previous history of DM revealed not only a more extensive but also a more aggressive disease. Preoperatively, diabetic patients showed significantly higher median CA19.9 in comparison with non-diabetic patients and, higher CA19.9 was significantly associated with HGD/invasive cancer. Moreover, we found that patients with DM showed more frequently high-risk stigmata in comparison with non-diabetic patients (diabetic: 74% vs non-diabetic: 38%, p <0.001), in particular, the presence of a nodule or solid component and a MPD ≥10 mm. From the comparison between DM and grade of dysplasia, in our cohort patients with invasive-IPMN were diabetic in 50% of cases, similarly to the prevalence reported in patients with PDAC (Pannala et al. 2008). This percentage was significantly reduced at 38% in IPMNs with HGD and 25% in those with LGD (P=0.018). In this light, diabetic patients showed a 2.7-fold higher risk (OR 2.692, 95% IC 1.283-5.651; p=0.009) of harboring a malignant IPMN (HGD/invasive cancer) in comparison with non-diabetic patients.

These results are consistent with those of other studies that have investigated predictors of malignant progression in IPMN (Mimura et al. 2010, Morales-Oyarvide et al. 2017, Del Chiaro et al. 2020, Jang at al. 2016). However, it is important to highlight that, in the present literature, only a few papers specifically focus on the role of DM in IPMN (Morales-Oyarvide et al. 2017, Leal et al. 2015,

Capurso et al. 2013) and, therefore, our knowledge on this topic is still limited (Pergolini et al. 2021). Further investigations in larger series are needed to consolidate these results and understand the possible mechanisms behind the association between diabetes and malignancy in IPMN.

As explained above, the role of DM has been much better investigated in PDAC, and, although IPMN represents a different entity than PDAC, we may learn from this experience. In PDAC, several authors agree that probably between DM and PDAC there is a bidirectional association. Here, DM has been described as a risk factor for the development of PDAC, but also as a status induced by pancreatic cancer (Sah et al. 2013, Magruder et al. 2011). Moreover, PDAC-induced diabetes, which by definition is a new-onset DM, is paradoxically associated with weight loss and both occur several months earlier than other cancer-specific symptoms (Sah et al. 2013, Hart et al. 2011). In particular, a weight reduction seems to occur from 3 years before the diagnosis of cancer, but, despite this reduction, in these patients the glycemic control worsens over time. By contrast, as well-known, patients with type 2 diabetes are frequently overweight and the glycemia improves through weight loss (Hart et al. 2011, Pannala et al. 2009). Overall, these results suggest that, as in PDAC (Pannala et al. 2009), new-onset diabetes not only may define a high-risk group for pancreatic cancer but also may represent an early marker of cancer; accordingly, it can be considered an attractive screening target for early diagnosis of pancreatic cancer and deserve further investigations.

In the current literature, the association between weight loss and DM in IPMN has not been investigated yet. In our study, we found that BMI was not associated with DM, and patients with weight loss at diagnosis were more frequently diabetic

than patients with stable weight (58% vs 32%, p=0.009), and, in particular, had more frequently a new-onset or worsening DM. Moreover, this association between DM and weight loss persists, when we restrict the analysis to HGD- and LGD-IPMNs, excluding patients with invasive cancer, but it is no longer present among patients with only LGD-IPMNs (diabetic: 42% vs non-diabetic: 21%, p=0.151). In other words, as expected from the “PDAC-experience”, the association between DM and weight loss was present in case of invasive-IPMN and absent in benign lesions (LGD-IPMNs), but, more interestingly, occurred and became recognizable already in presence of HGD.

Interestingly, in our series, we also found that the association between DM and HGD/invasive IPMN was present also after adjusting for worrisome features (OR 2.380, 95% IC 1.021-5.550, p=0.045), suggesting that DM may be considered a valuable predictor, as well as the other worrisome features of the IAP guidelines. By contrast, this association did not persist after adjusting for the high-risk stigmata (OR 1.546, 95% IC 0.605-3.948, p=0.363). In this context, Morales et al. demonstrated that in patients with MPD <10 mm, DM was associated with a significantly higher risk of HGD, but not of invasive cancer (Morales-Oyarvide et al. 2017). In another study, DM, male sex, and recent weight loss were associated with a higher risk of developing HGD and invasive cancer in patients with low-risk IPMN (asymptomatic IPMNs without worrisome features) (Gausman et al. 2018). On the same line, Duconseil et al. found that 67% of male patients with Fukuoka-negative BD-IPMNs and recent DM (diagnosed within 1 year) harbored a malignant IPMN (Duconseil et al. 2018). Overall, these results suggest that DM, especially when associated with weight loss and in low-risk IPMNs, may be a helpful tool to early predict IPMN progression. Accordingly, we support the

importance of further investigations for understanding the pathogenesis behind these disorders and for including diabetes as a worrisome feature in the future guidelines for the management of IPMN. The stratification of patients with IPMNs is crucial, considering the excellent prognosis of those resected at the right time. In this context, new-onset DM should receive special attention. New-onset DM was recently introduced in the European guidelines as a relative indication for surgery (European Study Group on Cystic Tumours of the Pancreas et al. 2018), however, its role in IPMN is still unknown and controversial. In our series, patients with new-onset or worsening DM had a significantly higher risk of harboring HGD/invasive cancer in comparison with non-diabetic patients, even after adjusting for worrisome features. By contrast, another study showed that recent-onset DM (diagnosed within 12 months) did not correlate with an increased risk of IPMN (Capurso et al. 2013) and progression to HGD/invasive cancer (Del Chiaro et al. 2020). In this context, it is also important to underline that the current literature does not provide a clear definition of new-onset/recent DM, as the onset-timing of new-onset DM is often not defined or greatly vary from 1 to 5 years before the diagnosis of IPMN (Del Chiaro et al. 2020, Capurso et al. 2013, Duconseil et al. 2018, Morales-Oyarvide et al. 2017). Certainly, new-onset DM deserves a consensus on its definition, as well as further investigations to better define its role in IPMN.

This study has several limitations. At first, the retrospective nature of the study and the limited sample size increases the risk of selection and data collection bias and limits the possibility of robust conclusions. Secondarily, the indications for surgery changed during the study period and most of the included patients

underwent surgery because of signs of malignancy, selecting cases with more aggressive or advanced IPMNs. Despite this, all patients were selected and surgically treated in the same institution, a referral center for pancreatic surgery, and, by an established multidisciplinary team, guaranteeing collegial decisions.

5 CONCLUSIONS

In conclusion, the prevalence of DM in patients with IPMN is high, and DM is associated with a more aggressive disease requiring surgery. Accordingly, we advise surgeons to pay more attention to DM in IPMN and to be aware of that in the choice of treatment. Further investigations focusing on the role of DM and weight loss in larger series of patients are necessary to consolidate our results and to include DM in the future guidelines for the management of IPMN.

6 FIGURE

Figure 1. Macroscopic and microscopic features of IPMNs according to the degree of cytoarchitectural atypia. (Figure from Singhi et al., Gastroenterology 2019, May;156(7):2024-2040. doi:10.1053/j.gastro.2019.01.259. Licence at the following link: https://creativecommons.org/licenses/by-nc-nd/4.0/)

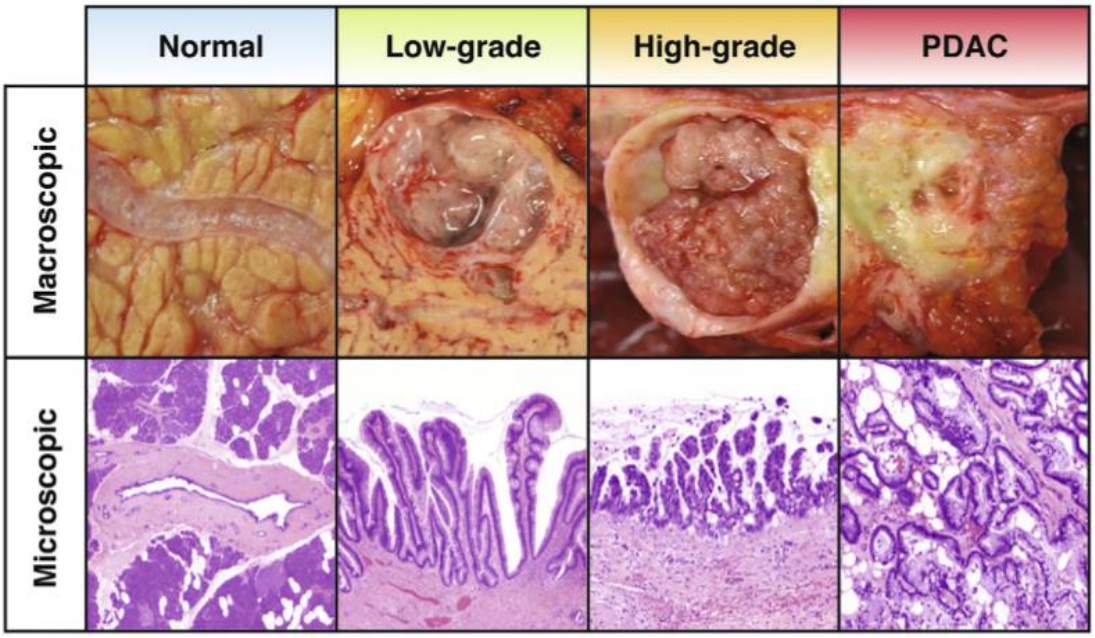


Figure 2. MRCP images showing the three morphological types of IPMN.

A. Main duct type with a mural nodule (arrow). B. Branch duct type. C. Mixed type. (Figure from Tanaka et al., Pancreatology. Sep-Oct 2017;17(5):738-753. doi: 10.1016/j.pan.2017.07.007. License provided by Elsevier and Copyright Clearance Center. Licence Number: 5081970090971)

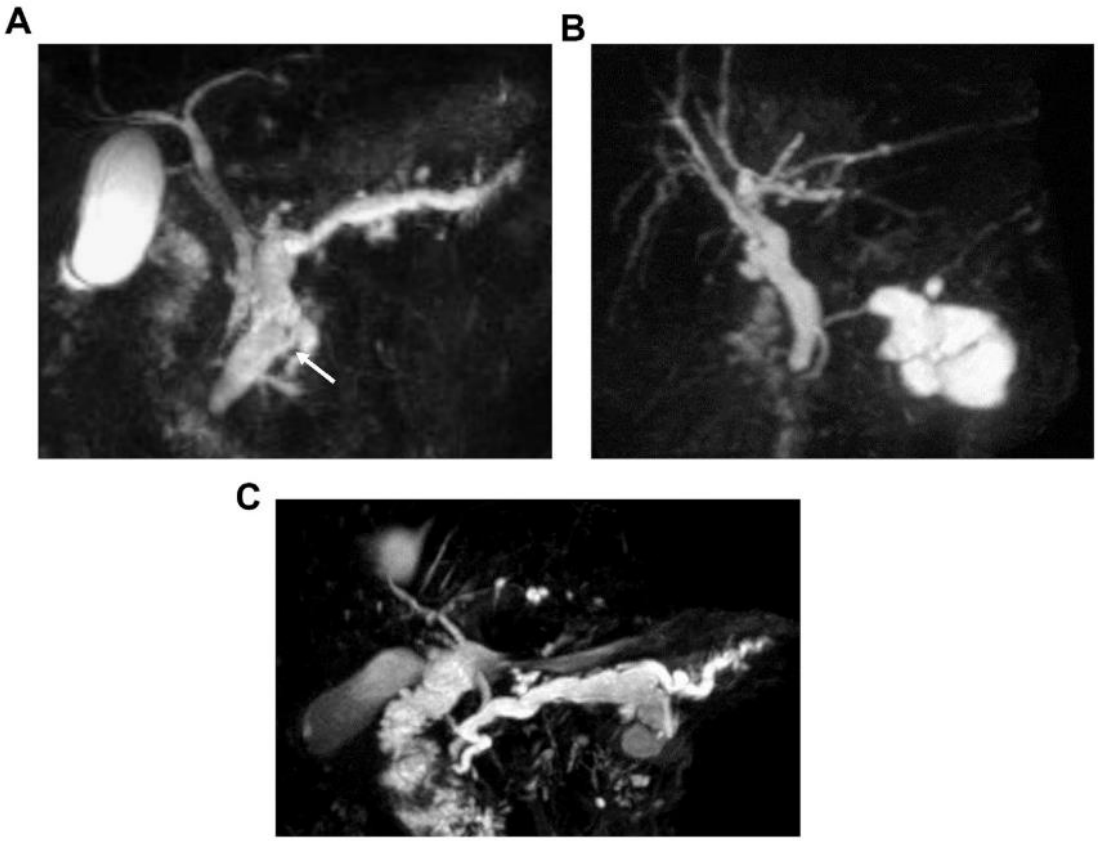
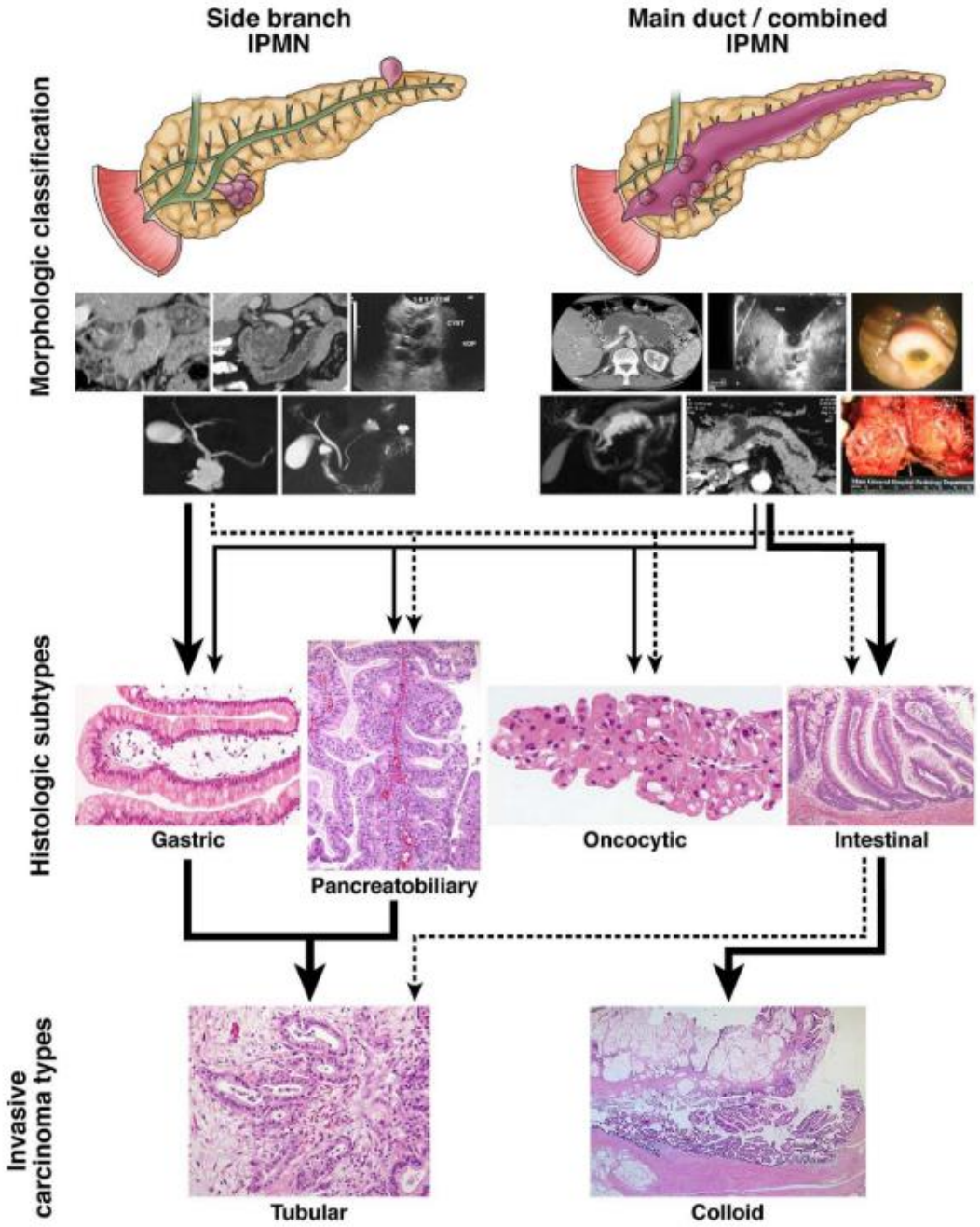


Figure 3. IPMN histological subtypes and progression to invasive cancer. (Figure from Fernandez-del Castillo et al. Gastroenterology. 2010 Sep;139(3):708-13, 713.e1-2. doi: 10.1053/j.gastro.2010.07.025. 2010 License provided by Elsevier and Copyright Clearance Center. License Number: 5081970531893).



7 TABLES

Table 1. High-risk features and indications for surgery according to three current guidelines for the management of IPMN: AGA, IAP, and European guidelines.

AGA guidelines 2015 (Vege et al. 2015)	**High-risk features:** - Cyst size ≥3cm - Presence of solid component - Dilated MPD - HGD or cancer on cytology
IAP guidelines 2017 (Tanaka et al. 2017)	**High-risk stigmata:** - Jaundice - Enhancing mural nodule ≥5mm - MPD ≥10 mm - HGD or cancer on cytology **Worrisome features:** - Cyst size ≥3cm - Acute pancreatitis (due to IPMN) - Enhancing mural nodule<5mm - Thickened and enhancing cyst wall - MPD dilation 5–9 mm - Abrupt change of MPD caliber with distal pancreatic atrophy - Presence of lymphadenopathy - Elevated serum CA 19–9 - Cyst growth rate >5 mm/2 years
European guidelines 2018 (European Study Group on Cystic Tumours of the Pancreas et al. 2018)	**Absolute indications for surgery:** - Jaundice - Enhancing mural nodule ≥5mm - MPD ≥10 mm - HGD or cancer on cytology - Solid mass **Relative indications for surgery:** - Cyst size ≥4cm - Enhancing mural nodule <5mm - MPD dilation 5–9.9 mm - Serum CA 19.9 ≥37 U/ml - Cyst growth rate >5 mm/years - Acute pancreatitis (due to IPMN) - New onset of diabetes

Table 2. Clinical features of the entire cohort and comparison between diabetic and non-diabetic patients.

	Entire cohort n=134	Non-diabetic patients		Diabetic patients		P value
	N (%)	N	%	N	%	
Men	67 (50)	36	43%	31	62%	**0.032**
Age at diagnosis, median (range), years	68 (34-86)	66.0 (34-85)		70.5 (35-86)		**0.002**
Age at surgery, median (range), years	69 (35-86)	67.5 (36-85)		71 (35-86)		**0.009**
BMI, median (range)	24.6 (16.4-41.0) of 133 pts	24,5 (18-41)		25,3 (16-41)		0.115
Comorbidities						
Prostate hypertrophy	7 (5)	2	2%	5	10%	0.055
Hypertension	72 (54)	40	48%	32	64%	0.066
Hypercholestolemia	25 (19)	12	14%	13	26%	0.092
Cardiovascular disease	18 (13)	11	13%	7	14%	0.882
Hepatopathy	13 (10)	7	8%	6	12%	0.488
Dysthyroidism	39 (29)	28	33%	11	22%	0.162
Autoimmune disease	6 (5)	3	4%	3	6%	0.511
History of transplantation	3 (2)	3	2%	0	0%	0.177
Previous cancers	28 (21)	18	21%	10	20%	0.844
Chronic pancreatitis	29 (22)	18	21%	11	22%	0.938
Clinical Presentation						
Symptoms at diagnosis						
No	45 (35)	30	38%	15	30%	0.355
Yes	84 (65)	49	62%	35	70%	
Abdominal pain						
No	80 (62)	45	57%	35	70%	0.137
Yes	49 (38)	34	43%	15	30%	
Jaundice						
No	111 (85)	71	89%	40	80%	0.169
Yes	19 (15)	9	11%	10	20%	
Weight loss						
No	97 (76)	66	84%	31	63%	**0.009**
Yes	31 (24)	13	16%	18	37%	
History of acute pancreatitis						
No	102 (80)	60	76%	42	86%	0.182
Yes	26 (20)	19	24%	7	14%	
Steatorrhea						
No	118 (91)	75	94%	43	89%	0.237
Yes	11 (9)	5	6%	6	11%	
Nausea						
No	116 (91)	71	90%	45	92%	0.711
Yes	12 (9)	8	10%	4	8%	
Pre-operative CA19.9, median (range), ng/ml	22.5 (0-8667) of 82 pts	13.5 (0-2370)		35 (1-8667)		**0.042**
Pre-operative CEA, median (range), ng/ml	2..3 (0.5-621.0) of 66 pts	2.3 (0.5-10.2)		2.4 (0.8-621)		0.146

Table 3. Morphological features of the entire cohort and comparison between diabetic and non-diabetic patients.

	Entire cohort n=134	Non-diabetic patients		Diabetic patients		P value
	N (%)	N	%	N	%	
Morphological features						
Multifocal localization	57 (43)	28	33%	29	58%	**0.005**
Localization						**0.001**
Head	59 (44)	35	42%	24	48%	
Body/tail	36 (27)	31	37%	5	10%	
Diffuse	39 (29)	18	21%	21	42%	
Cyst size max, median (range), mm	30 (0-100) of 120 pts	30 (0-100)		32 (11-80)		0.064
Main duct size max, median (range), mm	7 (2-30) of 130 pts	6 (2-30)		8 (2-22)		**0.006**
MPD 5-9 mm						
No	76 (57)	44	52%	32	65%	0.146
Yes	57 (43)	40	48%	17	35%	
History of acute pancreatitis						
No	102 (80)	60	76%	42	86%	0.182
Yes	26 (20)	19	24%	7	14%	
Abrupt change of caliber						
No	120 (90)	75	89%	45	92%	0.663
Yes	13 (10)	9	11%	4	8%	
Cyst size ≥3 cm						
No	65 (49)	43	51%	22	45%	0.484
Yes	68 (51)	41	49%	27	55%	
Wall Thickening						
No	120 (91)	80	96%	40	82%	**0.004**
Yes	12 (9)	3	4%	9	18%	
Nodule/solid component						
No	72 (54)	53	64%	19	39%	**0.005**
Yes	60 (46)	30	36%	30	61%	
Lymphadenopathy						
No	106 (80)	69	83%	37	75%	0.287
Yes	26 (20)	14	17%	12	25%	
Obstructive jaundice						
No	111 (85)	71	89%	40	80%	0.169
Yes	19 (15)	9	11%	10	20%	
Enhanced solid component						
No	96 (72)	69	82%	27	55%	**0.001**
Yes	37 (28)	15	18%	22	45%	
MPD ≥10 mm						
No	93 (70)	67	80%	26	53%	**0.001**
Yes	40 (30)	17	20%	23	47%	
Positive cytology						
No	126 (95)	79	94%	47	96%	0.641
Yes	7 (5)	5	6%	2	4%	

Table 4. Surgical outcomes of the entire cohort and comparison between diabetic and non-diabetic patients.

	Entire cohort n=134	Non-diabetic patients		Diabetic patients		P value
	N (%)	N	%	N	%	
Surgery						
Type of resection						**0.002**
Duodenopancreatectomy	59 (44)	37	44%	22	44%	
Distal pancreatectomy	33 (25)	28	33%	5	10%	
Total pancreatectomy	35 (26)	14	17%	21	42%	
Enucleation	3 (2)	2	2%	1	2%	
Middle pancreatectomy	2 (1.5)	2	2%	0	0%	
other	2 (1.5)	1	1%	1	2%	
Vascular resection	25 (19)	10	12%	15	30%	**0.009**
Complications	77 (58)	49	58%	28	56%	0.792
Pancreatic fistula	18 (13)	15	18%	3	6%	0.052
Biliary fistula	4 (3)	3	4%	1	2%	0.605
Enteric fistula	3 (2)	2	2%	1	2%	0.885
Abdominal fluid collection	18 (13)	15	18%	3	6%	0.052
Bleeding	3 (2)	2	2%	1	2%	0.885
Delayed gastric emptying	16 (12)	8	10%	8	16%	0.264
Ileus	7 (5)	4	5%	3	6%	0.755
Wound infection	14 (10)	10	12%	4	8%	0.475
Systemic complications	42 (31)	25	30%	17	34%	0.609
Readmission	8 (7)	5	7%	3	8%	0.765

Table 5. Pathology of the entire cohort and comparison between diabetic and non-diabetic patients.

	Entire cohort n=134	Non-diabetic patients		Diabetic patients		P value
	N (%)	N	%	N	%	
Pathology						
Type of IPMN						**0.033**
MD-IPMN	94 (75)	56	69%	38	86%	
BD-IPMN	31 (25)	25	31%	6	14%	
Grade of dysplasia						**0.018**
Low-grade dysplasia (LGD)	60 (45)	45	54%	15	30%	
High-grade dysplasia (HGD)	16 (12)	10	12%	6	12%	
Invasive cancer from IPMN	58 (43)	29	35%	29	58%	
Malignant IPMN (HGD/invasive)						**0.008**
No	60 (45)	45	54%	15	30%	
Yes	74 (55)	39	46%	35	70%	
Pathological cyst size, median (range), mm	30 (4-90) of 118 pts	29 (4-70)		35 (7-90)		0.120
Pathological duct size, median (range), mm	10 (2-40) of 56 pts	9.5 (2-40)		10 (2-24)		0.554
Epithelial type						
intestinal	42 (38)	27	38%	15	38%	0.138
gastric	54 (49)	38	53%	16	41%	
pancreatobiliary	13 (12)	5	7%	8	21%	
oncocytic	2 (2)	2	3%	0	0%	
Presence of chronic pancreatitis						0.100
No	47 (36)	34	42%	13	27%	
Yes	83 (64)	48	58%	35	73%	

Table 6. Odds ratios for high-grade dysplasia and invasive carcinoma by diabetes mellitus compared to non-diabetic patients.

	Number of Patients	OR (95% IC)	P value
Diabetes			
Yes	50	1.00 (reference)	
No	84		
Unadjusted		2.692 (1.283-5.651)	0.009
Adjusted for worrisome features		2.380 (1.021-5.550)	0.045
Adjusted for high-risk stigmata		1.546 (0.605-3.948)	0.363

Table 7. Odds ratios for high-grade dysplasia and invasive carcinoma by new-onset/worsening diabetes compared to non-diabetic patients.

	Number of Patients	OR (95% IC)	P value
New-onset/worsening Diabetes			
Yes	20	1.00 (reference)	
No	84		
Unadjusted		4.615 (1.423-14.698)	0.011
Adjusted for worrisome features		8.165,1.967-33.886)	0.004
Adjusted for high-risk stigmata		3.853 (0.886-16.747)	0.072

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