

Risk of misdiagnosis and overtreatment in patients with main pancreatic duct dilatation and suspected combined/main-duct intraductal papillary mucinous neoplasms

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Background. Segmental/diffuse dilatation of the main pancreatic duct (MPD) is the typical feature of combined/main-duct intraductal papillary mucinous neoplasms (CMD-IPMNs). MPD dilation in IPMNs may be also expression of mucus hypersecretion/obstructive chronic pancreatitis (OCP). The aim of this study was to evaluate the presence and extension of MPD involvement by tumor/OCP and assess the risk of overtreatment.

Methods. Retrospective analysis of suspected CMD-IPMNs resected between January 2009 and October 2014 were included. Pathologic correlations among MPD dilatation, IPMN, and OCP was searched.

Results. Overall, 93 patients were resected for suspected CMD-IPMNs. At pathology, CMD-IPMNs were found in 69 patients (74%). Branch-duct IPMNs (BD-IPMNs) were found in 8 cases (9%), pancreatic ductal adenocarcinoma (PDAC) in absence of IPMN in 9 (10%), cystic neuroendocrine tumor (NET G2) in 1 (1%), serous cystadenoma in 2 (2%), and OCP alone/mucinous metaplasia in 4 patients (4%). Overall, 18 patients (19%) underwent an overtreatment because unnecessary (2 BD-IPMNs, 2 serous cystadenomas, and 4 OCPs only) or too extensive resections (9 CMD-IPMNs and 1 PDAC with associated OCP). In these, total pancreatectomy was the most common procedure (67%). Median size of MPD in IPMN-involved area was 12 mm compared with 7 mm when only OCP was found ($P < .05$).

Conclusion. There is a considerable risk of overtreatment in patients with a preoperative morphologic diagnosis of CMD-IPMNs. Partial pancreatectomy with margin examination should be performed instead of upfront total pancreatectomy. Radiologic observation can be considered in asymptomatic patients with “worrisome” MPD dilatation (5–9 mm) and lacking other high-risk stigmata. (Surgery 2016;159:1041-9.)

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Source of funding: None.

Accepted for publication November 4, 2015.

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0039-6060/\$ - see front matter

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<http://dx.doi.org/10.1016/j.surg.2015.11.003>

THE PRESENCE AND EXTENT of main pancreatic duct (MPD) involvement in intraductal papillary mucinous neoplasms (IPMNs) are crucial for the appropriate management of these patients.^{1,2} Our understanding of IPMN has evolved significantly in the last 2 decades, and it has become evident that IPMNs can originate from the MPD (MD-IPMNs), from its secondary branches (BD-IPMNs) or from both (combined IPMNs). This distinction is not only of morphologic significance because IPMNs involving the main duct, either MD-IPMNs or combined IPMNs, have a high rate of malignancy, whereas BD-IPMNs are more often benign.³⁻⁷ For these reasons, resection of all

combined/main-duct (CMD)-IPMNs is warranted.¹⁻⁶

Segmental or diffuse dilation of MPD, in the absence of other causes of duct obstruction, is the typical imaging feature of CMD-IPMNs. According to recent international consensus guidelines, a threshold for MPD dilation of >5 mm can be adopted for CMD-IPMNs, thereby increasing the sensitivity for radiologic diagnosis without losing specificity.¹ The extent of operative resection is planned based on MPD features, although frozen section margins are of paramount importance for deciding the resection line in partial pancreatectomies. However, in CMD-IPMNs, MPD can be dilated for reasons other than direct tumor involvement, including ductal hypertension caused by mucin hypersecretion/mucin plugs, and obstructive chronic pancreatitis (OCP). In this light, pancreatic resections planned for presumed CMD-IPMNs based on MPD dilation may result in possible overtreatment with exposure of patients to short- and long-term morbidity and possible mortality as a consequence of pancreatic surgery. Of note, some authors recently showed that diagnostic errors are fairly common in the preoperative assessment of pancreatic cystic neoplasms (PCNs).⁸⁻¹¹ Although most of these erroneous diagnoses involved serous cystadenomas and branch duct IPMNs, the rate of incorrect diagnosis was not negligible, even for CMD-IPMNs.⁸⁻¹¹

In this study, we compared the preoperative and postoperative pathologic diagnoses in a series of patients who underwent pancreatic resection for presumed CMD-IPMNs. We aimed to determine the presence and extension of MPD dilation owing to IPMN or to other causes, to evaluate the clinical relevance of diagnostic errors, and to identify new strategies to improve the diagnostic accuracy in these patients.

METHODS

A retrospective analysis identified patients with a preoperative clinical-radiologic diagnosis of CMD-IPMNs who underwent pancreatic resection between January 2009 and October 2014 in the Division of General Surgery of the Sacro Cuore-Don Calabria Hospital, Negrar and in the Department of Surgery of Ospedali Riuniti, Università Politecnica delle Marche, Ancona, Italy.

Demographic information, clinical history, diagnostic workup, type of surgery, postoperative course, and pathology were recorded. Perioperative mortality was defined as in-hospital or 60-day death.

The clinical-radiologic diagnosis of CMD-IPMNs was defined by the presence of segmental or diffuse dilation of MPD >5 mm without other causes of duct obstruction, possibly associated to ≥ 1 dilated cyst communicating with the MPD (combined IPMNs). Preoperative workup for suspected CMD-IPMNs included multidetector computed tomography with contrast medium and/or MRI with MR cholangiopancreatography (MRCP). Because the presence of CMD-IPMNs on multidetector computed tomography/MRCP represents an indication for surgical resection according to international consensus guidelines,¹ further testing including endoscopic ultrasound with fine-needle aspiration (EUS/FNA) or endoscopic retrograde cholangiopancreatography (ERCP) were not performed routinely. Peroral and/or intraoperative pancreatoscopy are not performed at either institution.

A review of preoperative imaging was not performed, and preoperative diagnosis was recorded at the time of initial diagnosis before surgical operation. We specifically avoided re-reviewing of radiologic images to describe our actual experience.

The type of resection was planned according to the site of the tumor, as indicated by preoperative imaging findings. Because of the significant risk of harboring malignancy, all CMD-IPMNs are treated with typical pancreatectomies with lymph node dissection. The extent of resection was determined based on preoperative workup, intraoperative findings, and the results of frozen section analysis of the resection margin. Pancreatic resection margin was referred as "positive" for the presence of either intermediate- or high-grade dysplasia and invasive carcinoma, and "negative" for either the presence of a normal ductal epithelium or low-grade dysplasia. If a "positive" margin was found at intraoperative examination, the resection was extended up to a total pancreatectomy. The presence of a dilated MPD lacking any epithelial lining (denudation) at the margin was an indication to extent the resection as well. In fact, some studies showed that denudation represents one of the factors associated with IPMN recurrence.¹² Also International Association of Pancreatology (IAP) guidelines highlighted that denudation may prove the presence of an adjacent tumor.¹ For these reasons, the presence of denudation at the resection margin is an indication for further resection.

However, the decision to perform a total pancreatectomy was individualized considering also patient's age and comorbidities. Preoperative

clinical-radiologic diagnosis was compared with the final pathologic diagnosis based on the 2010 World Health Organization classification system for the tumors of the pancreas.⁷ The method for routine systematic pathologic evaluation was based on the recommendation by the World Health Organization 2010 Classification of IPMNs and by Capella et al.^{7,13} The IPMNs were divided into noninvasive and invasive neoplasms. Noninvasive IPMNs were graded on the basis of the greatest degree of dysplasia into low-grade dysplasia, moderate dysplasia, and high-grade dysplasia or carcinoma in situ. In patients with pathologically confirmed IPMNs, we focused our attention to the presence in the specimen of OCP, to the extension of IPMN-involved areas and to the size of MPD in IPMN-involved area and in areas when only OCP was found. The assessment of duct diameter in relation to areas of IPMN and area with only OCP was acquired from the pathology reports. All pathologic examinations were performed or supervised by 2 senior pathologists (C.R., G.Z.).

Data are presented as median values and ranges. Categorical variables are presented as numbers and percentage and were compared using a Chi-square test and Fisher's exact test as appropriate. When comparing 2 groups, normally distributed continuous variables were analyzed using a 2-sample Student *t* test, and the Mann-Whitney *U* test was used for nonnormally distributed variables.

RESULTS

In the study period, 93 patients (60 males, 33 females; median age, 67 years; range, 31–80) with a preoperative clinical-radiologic diagnosis of CMD-IPMNs underwent surgical resection.

Demographics, clinical presentation, and preoperative diagnosis. Demographic, preoperative, and surgical details are outlined in Table I. Overall, 41 patients (44%) were asymptomatic. All patients underwent cross-sectional high-resolution imaging. MRI/MRCP was performed in 89 patients (96%) and multidetector computed tomography in 45 (48%). Twenty patients (22%) had an EUS/FNA and 13 (14%) underwent ERCP. ERCP was performed as a diagnostic procedure in 4 patients, and in the remaining 9 it was required to achieve a preoperative biliary drainage in jaundiced patients. Results of FNA are also shown in Table I. In 27 patients (29%), a diffuse involvement of the entire gland by IPMN was found at imaging, whereas CMD-IPMN occurred in the pancreatic head in 40 patients (43%) and in the body/tail in 26 (28%;

Table I. Demographics and clinical-radiologic characteristics, operative procedures, postoperative complications, and mortality of the 93 resected patients with preoperative diagnosis of combined/main-duct intraductal papillary mucinous neoplasms (CMD-IPMNs)

Characteristic	n (%)
Median age, y (range)	67 (31–80)
Gender	
Male	60 (65)
Female	33 (35)
Median CA 19.9, U/L (range)	16.5 (0.8–1,043)
Symptoms at the diagnosis	
Yes	52 (56)
No	41 (44)
Pre-operative radiologic workup	
MRI/MRCP	89 (96)
Multidetector computed tomography	45 (48)
ERCP	13 (14)
EUS-FNA	20 (22)
Undetermined cytology	5 (25)
Malignant cells	5 (25)
Atypical cells	1 (5)
Benign cells	4 (20)
Mucinous cells	5 (25)
Preoperative CMD-IPMN location	
Head	40 (43)
Body-tail	26 (28)
Entire pancreas	27 (29)
Operative procedures	
Total pancreatectomy	31 (33)
Pancreaticoduodenectomy	37 (40)
Distal pancreatectomy	25 (27)
Postoperative complications	37 (40)
Pancreatic fistula	16 (26)*
Biliary fistula	4 (6)†
Delayed gastric emptying	6 (6)
Intraabdominal abscess	24 (26)
Bleeding	11 (12)
Reoperation	4 (4)
Mortality	4 (4)

*The rate of pancreatic fistula was calculated considering 62 patients who underwent partial pancreatectomy.

†The rate of biliary fistula was calculated considering 68 patients who underwent pancreaticoduodenectomy or total pancreatectomy.

CA 19.9, Carbohydrate antigen 19.9; CMD-IPMN, combined/main-duct intraductal papillary mucinous neoplasms; ERCP, endoscopic retrograde cholangiopancreatography; EUS-FNA, endoscopic ultrasound with fine-needle aspiration; MDTC, contrast-medium computed tomography; MRCP, MRI with cholangiopancreatography.

Fig 1). Among these 93 patients, a malignant CMD-IPMN was suspected after preoperative workup in 22 cases (24%) because of the presence of solid components, atypical/malignant cytology, or jaundice. Table II summarizes the criteria for resection in the 93 patients.

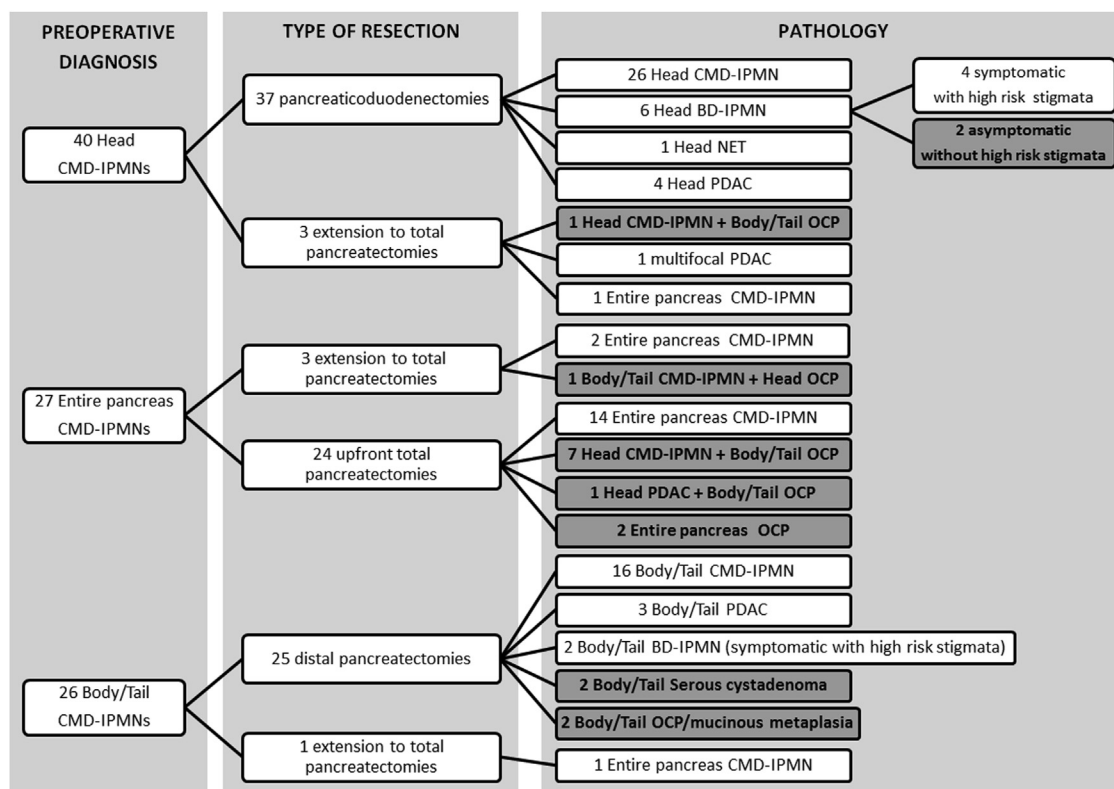


Fig 1. Course of 93 patients with suspected combined/main-duct intraductal papillary mucinous neoplasms (CMD-IPMNs) from the preoperative diagnosis to pathology. Cases of overtreatment are highlighted. *BD-IPMN*, Branch-duct intraductal papillary mucinous neoplasm; *NET*, G2 neuroendocrine tumor grading 2; *OCP*, obstructive chronic pancreatitis; *PDAC*, pancreatic ductal adenocarcinoma.

Surgical treatment, frozen section analysis, and postoperative course. We performed 37 pancreaticoduodenectomies (PD; 40%), 31 total pancreatectomies (33%) and 25 distal pancreatectomies (27%; Table I). Among 31 total pancreatectomies, 7 patients initially underwent a partial pancreatectomy that was extended subsequently to total pancreatectomy because of positive resection margins. In all patients who underwent partial pancreatectomy, 69 patients (74%) frozen section analysis of the resection margins was carried out. Positive resection margins were found intraoperatively in 17 patients (25%), including 7 patients with invasive carcinoma (41%), 5 (29%) with high grade dysplasia, 3 (18%) with intermediate dysplasia, and 2 (12%) with epithelial denudation. These 17 patients underwent an extension of resection. Six patients—3 with resection margins positive for invasive carcinoma, 2 for high-grade dysplasia, and 1 for intermediate dysplasia—underwent total pancreatectomy immediately. In the remaining 11 patients, an extension of surgical resection was performed, up to total pancreatectomy in 1 case (positive for high-grade dysplasia).

Therefore, 58 of 69 patients (84%) had a single frozen section analysis, 10 (15%) had 2, and only 1 patient (1%) underwent 2 extensions of surgical resection with 3 frozen section analysis, for an overall number of 81 intraoperative examinations of transection margins. Definitive examination corroborated frozen section in 79 cases (98%). In the remaining 2 cases, the diagnosis changed from negative to positive (1 for high-grade dysplasia and 1 for intermediate-grade dysplasia), but none underwent reoperation.

Overall, major postoperative complications occurred in 37 patients (40%), including clinically relevant pancreatic fistula (26%), biliary fistula (6%), delayed gastric emptying (6%), intraabdominal abscess (26%), and bleeding (12%). Four patients required reoperation (4%) because of bleeding in 3 patients and intraabdominal abscess in 1. The 60-day postoperative mortality rate was 4% (1 patient for cardiac arrhythmia, 2 for sepsis and multiorgan failure, and 1 for postoperative bleeding complicated by acute myocardial infarction).

Table II. Indications for surgery of the 93 patients with a preoperative suspected combined/main duct intraductal papillary mucinous neoplasm (CMD-IPMN)

<i>Preoperative suspected diagnosis</i>	<i>N (%)</i>
MD-IPMN (MPD dilation >5 mm)	23 (25)
Median MPD diameter (mm)	9 (5–30)
MPD diameter ≥1 cm	12 (52)
Presence of nodule	4 (17)
Symptoms at the diagnosis	10 (43)
Jaundice	1 (4)
Abdominal pain	5 (22)
Acute pancreatitis	3 (13)
Weight loss	2 (9)
Diabetes	4 (17)
C-IPMN (MPD dilation > 5 mm and cyst > 5 mm)	70 (75)
Median MPD diameter (mm)	7.5 (5–30)
MPD diameter ≥ 1 cm	27 (39)
Presence of nodule	11 (16)
Symptoms at the diagnosis	42 (60)
Jaundice	7 (10)
Abdominal pain	18 (26)
Acute pancreatitis	13 (19)
Weight loss	5 (7)
Diabetes	7 (10)

C-IPMN, Combined intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; MD-IPMN, main-duct intraductal papillary mucinous neoplasm.

Pathology. Table III shows the final pathologic data. The presence of CMD-IPMNs was confirmed in 69 of 93 (74%) patients. In the remaining 24 patients (26%), BD-IPMNs were found in 8 cases (9%), pancreatic ductal adenocarcinoma (PDAC) in the absence of IPMN in 9 (10%), cystic neuroendocrine tumor (NET G2) in 1 (1%), serous cystadenoma (SCA) in 2 (2%), and OCP alone/mucinous metaplasia in 4 patients (4.5%; Fig 1). In 81% of patients, OCP was recognized histologically in the specimens, either in the tissue around the IPMN, or concomitant with IPMN but in a different area of the specimen.

Comparison between preoperative clinical-radiologic diagnosis and final pathologic diagnosis. Considering 69 pathologically confirmed CMD-IPMNs, a diffuse involvement of entire pancreas was recognized in 18 cases (26%), whereas head and body/tail were involved in 34 (49%) and 17 (25%) patients, respectively (Table II). Of these 69 patients (Fig 2), 26 underwent pancreaticoduodenectomy (38%)—16 distal pancreatectomy (23%) and 27 total pancreatectomy (39%)—21 (78%) as an upfront procedure and 6 (22%) after a partial

Table III. Pathologic data

<i>Pathology</i>	<i>n (%)</i>
Final histologic diagnosis	93 (100)
CMD-IPMN	69 (74)
Low-grade dysplasia	7 (10)
Intermediate-grade dysplasia	21 (31)
High-grade dysplasia	14 (20)
Invasive carcinoma	27 (39)
BD-IPMN	8 (9)
Low-grade dysplasia	2 (25)
Intermediate-grade dysplasia	6 (75)
High-grade dysplasia	/
Invasive carcinoma	/
PDAC	9 (10)
NET	1 (1)
SCA	2 (2)
OCP/mucinous metaplasia	4 (4)
Histologic subtype of IPMN	
CMD-IPMN	69 (74)
Gastric	15 (22)
Intestinal	20 (29)
Mixed (gastric/intestinal)	12 (17)
Pancreatobiliary	6 (9)
Colloid	12 (17)
Tubular	4 (6)
BD-IPMN	8 (9)
Gastric	6 (75)
Intestinal	2 (25)
Concomitant OCP in the surgical specimen	
Yes	75 (81)
No	18 (19)
CMD-IPMN location	69 (74)
Entire pancreas	18 (26)
Head	34 (49)
Body/tail	17 (25)

BD-IPMN, Branch-duct intraductal papillary mucinous neoplasm; CMD-IPMN, combined/main-duct intraductal papillary mucinous neoplasm; NET, G2 neuroendocrine tumor grading 2; OCP, obstructive chronic pancreatitis; PDAC, pancreatic ductal adenocarcinoma; SCA, serous cystadenoma.

resection. In all 42 patients (61%) who underwent a partial resection, a segmental IPMN localization was observed at pathology. In 21 patients who underwent upfront total pancreatectomy, a diffuse MPD involvement by IPMN was recognized only in 14 cases (67%). In the remaining 7 cases (33%), CMD-IPMN was located only in the head of the pancreas, being OCP present in the remaining portion.

Considering 6 patients who underwent an extension of resection up to total pancreatectomy, a diffuse MPD involvement by CMD-IPMN was found in 4 cases (67%). In the remaining 2 patients (33%), IPMN was present only in a portion of the pancreas.

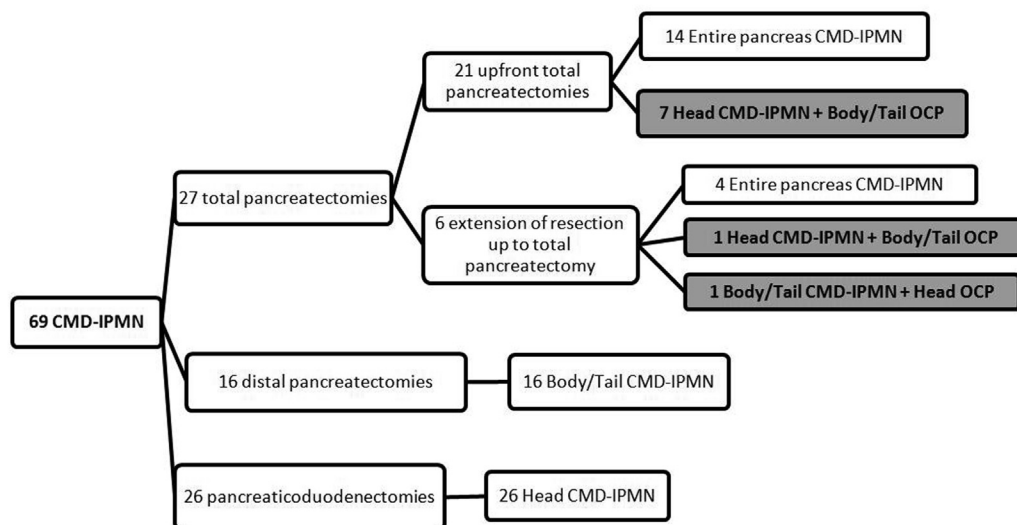


Fig 2. The flow chart of 69 pathologically confirmed combined/main-duct intraductal papillary mucinous neoplasms (CMD-IPMNs). Operative procedures and final pathology with localization of CMD-IPMN in the surgical specimen. Cases of too extensive resection are highlighted. OCP, Obstructive chronic pancreatitis.

The median size of MPD in IPMN-involved areas was 12 mm, compared with 7 mm in areas where only OCP was found ($P < .05$). Considering 69 patients with a confirmed diagnosis of CMD-IPMN at pathology, we have found a “worrisome” MPD dilation of 5–7 mm and of 5–9 mm in 26 (38%) and in 35 patients (51%), respectively. [Supplementary Figure 1](#) shows an example of total pancreatectomy performed for a suspected CMD-IPMN with dilation of the entire MPD at preoperative imaging but with evidence of IPMN only in the distal pancreas. Twenty-four patients (26%) had a pathologic diagnosis other than CMD-IPMN, but surgery was still indicated in 6 of 8 patients with BD-IPMNs because they were symptomatic and/or with high-risk stigmata, and in patients with NET G2 ($n = 1$) and PDAC ($n = 9$). In the PDAC group, 1 patient underwent total pancreatectomy after initial PD because of positive resection margin for high-grade dysplasia but at final pathology no tumor was found in the distal pancreas. In these 9 patients, preoperative imaging showed the typical features of CMD-IPMN, with a high suspicion of malignant because of the presence of a solid component. The carbohydrate antigen 19-9 value did not differ between patients with malignant IPMN and/or PDAC and those with benign lesions (median carbohydrate antigen 19-9, 43 vs 12; $P = .83$).

Therefore, considering the entire cohort of 93 patients, overtreatment was observed in 18 cases (19%), because of unnecessary resection (2 BD-IPMNs, 2 serous cystadenomas, and 4 OCPs only)

or too extensive resections (9 CMD-IPMNs and 1 PDAC; [Fig 1](#)). Of these 18 patients, 12 had no symptoms or mild symptoms such as vague abdominal pain. Three patients with OCP had mild symptoms and 1 was asymptomatic. Conservative or endoscopic management could be considered in these cases. Preoperative workup did not differ between patients who underwent overtreatment and the remaining ones, although only 2 of 18 patients (11%) underwent EUS compared with 18 of 75 (24%; $P = .194$). Total pancreatectomy was the most common procedure (67%) performed in these 18 patients ([Fig 1](#)). Five of these 12 patients had severe postoperative complications including biliary fistula followed by sepsis and multiorgan failure in 1 case, postoperative bleeding ($n = 2$), myocardial infarction in 1 case, and intraabdominal abscess in another. Two of these patients required reoperation and overall 2 patients died of postoperative complications. No patient died of insulin-related coma in the long-term follow-up.

DISCUSSION

International consensus guidelines recommend surgical resection in all surgically fit patients with CMD-IPMNs.¹ The preoperative localization of CMD-IPMN is of crucial importance for the appropriate planning of surgical resection, and it is based on the extension and size of MPD dilation. However, pancreatic tumors other than CMD-IPMNs and OCP can affect the presence of MPD dilation.¹ It is well-known that the preoperative diagnostic accuracy in the

setting of PCNs is quite low, ranging from 47 to 78%, although improved results are reported for CMD-IPMNs.^{8,11,14,15}

In this study, we analyzed retrospectively data from patients who underwent pancreatic resection for a presumed CMD-IPMNs. We found that the rate of correct diagnosis for CMD-IPMNs was 74%. These results are in keeping with Salvia et al¹⁵ and Barron et al,⁹ who reported a diagnostic accuracy for CMD-IPMNs of 80.7 and 74.9%, respectively. In contrast, Correa-Gallego et al⁸ have shown an accuracy as high as 94% for 16 patients with CMD-IPMNs, but of only 68% for all 125 patients with pancreatic cystic lesions included in their experience. In our experience, 10% of errors in preoperative diagnosis were PDAC with retrograde MPD dilatation. These data are in line with other large series of qualified centers. Del Chiaro et al¹¹ reported a 9.5% rate of misdiagnosis between IPMN and PDAC in patients resected with a preoperative diagnosis of IPMN. Salvia et al¹⁵ showed an incidence of ductal adenocarcinoma of 4.8% (23/497) in a cohort of population resected for presumed PCNs, but it increased to 22% in those 103 with an incorrect preoperative diagnosis. Small PDAC may, therefore, present with a cystic phenotype because of pancreatic duct obstruction and differential diagnosis with CMD-IPMNs cannot be obvious. Unfortunately, in the 9 patients with PDAC, EUS with FNA was not performed. The restricted use of EUS/FNA is a limit of our study. As suggested by IAP guidelines, EUS with FNA can be used for detecting mural nodules and invasion, and it can be of help in identifying PDAC as well.¹ However, despite the misdiagnosis, it must be underlined that these 9 patients with a final diagnosis of PDAC deserved a surgical resection. In fact, another important issue that should be considered is the clinical relevance of the diagnostic error. In this setting, Del Chiaro et al¹¹ found a rate of incorrect preoperative diagnosis of 39.1% in a cohort of 141 PCNs that underwent resection but with a rate of clinically relevant errors of only 8.5%. On the contrary, our study showed a rate of overtreatment of 19% owing to too extensive surgical resections or to erroneous preoperative diagnosis. In these patients, a different therapeutic management should have been performed. Specifically, in 9 CMD-IPMNs and 1 PDAC, we performed total pancreatectomy, but final pathology showed the presence of tumor only in a segment of the specimen, with OCP in the remaining pancreas. Then, another 8 patients—2 with asymptomatic BD-IPMNs without high-risk stigmata, 2 with serous cystadenomas,

and 4 with OCP alone/mucinous metaplasia—were misguided to an aggressive management; in these cases, pancreatic resection could have avoided. IPMN are commonly associated with OCP,¹⁶ and an OCP was histologically recognized in >80% of specimens in our study. How these 2 entities occur coincidentally remains unclear. It is likely that OCP may be the result of partial ductal obstruction by mucin plugs in patients with IPMNs. Then, the concomitant presence of pancreatic cystic lesions, duct dilation, and calcification should raise the suspicion of an IPMN, especially when patients do not present typical clinical and demographics characteristics of those with chronic pancreatitis (ie, male sex, age <50 years, history of smoking and/or alcohol intake).^{16,17} Two possible areas of errors can be identified, namely, the preoperative workup and the intraoperative decision making. The overall diagnostic accuracy for CMD-IPMNs is reported between 75 and 94%.^{8,9,15} Consensus guidelines recommend CT and MRI with MRCP as the preferred diagnostic modalities for the workup of pancreatic cystic lesions including IPMNs.^{1,18} When “high-risk stigmata” (ie, MPD >10 mm, enhancing solid components, jaundice) are identified, surgery is mandatory. Whereas, when IPMNs with “worrisome features” (ie, MPD 5–9 mm, non-enhancing solid components, abrupt change of MPD caliber, branch duct size >30 mm) are found, further workup with EUS/FNA is required. However, several authors showed that preoperative imaging procedures are poorly reliable to predict the extent of CMD-IPMN.^{8,11,19} In this light, Barron et al⁹ recently suggest that cross-sectional imaging studies and EUS should not be the only methods used for the classification of IPMN type and the choice of surgical management. In this work, we performed a limited number of EUS (22%) and this represents a limitation of the study, because an increased number of EUS may have lessened the rate of overtreatments. In fact, when a radiologic diagnosis of CMD-IPMNs was done after CT and/or MRI/MRCP, surgical treatment was planned immediately, especially in patients with symptoms or high-risk stigmata, without further workup. EUS was performed in only 11% of patients with unnecessary surgery compared with 24% of the remaining ones; therefore, one could argue that EUS could improve the diagnostic yield particularly in the overtreatment group and it could be used more frequently, especially to evaluate suspected multifocal disease and to better analyze “worrisome features.” However, EUS with FNA did not improve the diagnostic accuracy in PCNs in several recent studies, and its role and

clinical effectiveness in CMD-IPMNs remains unclear.^{11,14,15}

For these reasons, some authors have stressed the importance of frozen sectioning of the pancreatic resection margin during pancreatectomy for CMD-IPMNs, showing that frozen sectioning was better than preoperative morphologic assessment to accurately adapt the extent of pancreatectomy.^{5,19} In our series, in accordance with previous literature,^{6,10,18-21} definitive pathologic examination of resection margins confirmed frozen section analysis in 98%. These results underline that frozen section analysis would allow determining the resection line, and it is of paramount importance to choose the optimal surgical strategy. Of note, in our experience upfront total pancreatectomy was the most common procedure performed in case of overtreatment. Overall, 24 patients underwent upfront total pancreatectomy because of a “strong” preoperative suspect of a CMD-IPMN involving the entire pancreatic gland (ie, a diffuse MPD dilation). The decision was always individualized for each patient, considering age, comorbidities, and presence of preoperative diabetes. Ten of 24 upfront total pancreatectomies were considered as an overtreatment because of too extensive or unnecessary surgery. Therefore, in the setting of diffuse dilation without clear high-risk stigmata, more careful evaluation is warranted, because some of these patients may not have an IPMN involving the entire pancreas, but rather chronic pancreatitis.¹ In such patients, partial pancreatectomy should be planned instead of upfront total pancreatectomy, and operative resection should be eventually extended based on frozen sectioning results. On the contrary, when MPD dilation is diffuse with high-risk stigmata (ie, MPD >10 mm and/or multiple mural nodules) an upfront total pancreatectomy could be considered.

On pathology, we found a not surprising, significant difference in the median size of MPD between areas with and without CMD-IPMN (12 vs 7 mm; $P < .05$). In keeping with our results, Barron et al⁹ demonstrated that the diameter of MPD in CMD-IPMN is significantly greater than in BD-IPMN with dilated MPD. They also suggested that the dilation of MPD in cases of MPD-involved IPMN is likely greater than that resulting from chronic pancreatitis.⁹ These results support the IAP recommendations that MPD dilation of 5–9 mm should be considered as a “worrisome feature,” suggesting further workup and possibly no immediate resection but strict follow-up.¹ A further help in planning the extent of resection may be provided by pancreatoscopy, especially in

the setting of worrisome features. Pancreatoscopy can be performed both preoperatively and intraoperatively. Peroral pancreatoscopy and its associated investigations (ie, intraductal ultrasonography), can give additional data to support radiologic findings and may improve differential diagnosis between malignant and benign IPMNs.²²⁻²⁵ It allows tissue sampling under direct vision and irrigation cytology, for a determination of the presence and extent of MPD involvement.²⁵⁻²⁸ Yelamali et al suggested that intraoperative pancreatoscopy with narrow band imaging, through the cut end of the duct at the surgical margin during a partial resection, seems to be more accurate than preoperative pancreatoscopy and it does not carry the risk of pancreatitis associated with peroral pancreatoscopy.^{23,29} In this study, pancreatoscopy was not performed at all, and this represents another limitation of the study because pancreatoscopy could improve the diagnostic yield, thereby decreasing the rate of possible overtreatment.

In conclusion, there is a considerable risk of misdiagnosis and possible overtreatment in patients with preoperative diagnosis of CMD-IPMNs. To improve their diagnostic accuracy, EUS with FNA should be used more frequently, especially to evaluate suspected multifocal disease and to find “worrisome features” and new diagnostic strategies should be considered, including advanced endoscopic techniques such as pancreatoscopy. Partial pancreatectomy with frozen section analysis of pancreatic margin should be performed instead of upfront total pancreatectomy. Radiologic observation can be considered in asymptomatic patients with “worrisome” MPD dilatation (5–9 mm) and lacking other high-risk stigmata as suggested by IAP guidelines.¹

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.surg.2015.11.003>.

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