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## Extent of surgical resections for intraductal papillary mucinous neoplasms

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### Abstract

Intraductal papillary mucinous neoplasms (IPMNs) can involve the main pancreatic duct (MD-IPMNs) or its secondary branches (BD-IPMNs) in a segmental or multifocal/diffuse fashion. Growing evidence indicates that BD-IPMNs are less likely to harbour cancer and in selected cases these lesions can be managed non operatively. For surgery, clarification is required on: (1) when to resect an IPMN; (2) which type of resection should be performed; and (3) how much pancreas should be resected. In recent years parenchyma-sparing resections as well as laparoscopic procedures have been performed more frequently by pancreatic surgeons in order to decrease the rate of postoperative pancreatic insufficiency and to minimize the surgical impact of these operations. However, oncological radicality is of paramount importance, and extended resections up to total pancreatectomy may be necessary in the setting of IPMNs. In this article the type and extension of surgical resections in patients with MD-IPMNs and BD-IPMNs are analyzed, evaluating perioperative and long-term outcomes. The role of standard and parenchyma-sparing resections is discussed as well as different strategies in the case of multifocal neoplasms.

### INTRODUCTION

The diagnosis of intraductal papillary mucinous neoplasms of the pancreas (IPMNs) has increased markedly in the last decade thanks to the widespread use of high-resolution imaging<sup>[1,2]</sup>. Nowadays they represent one of the most common indications for pancreatic resection at high-volume centers. IPMNs can be classified into main-duct (MD-IPMNs), including combined-IPMNs, and branch-duct type (BD-IPMNs), depending on the type of involvement of the ductal system of the pancreas<sup>[2]</sup>. It is well known that IPMNs encompass a spectrum of lesions from adenoma to invasive carcinoma, being considered as precancerous lesions, and that these neoplasms often involve the entire pancreas in a diffuse or multifocal fashion<sup>[2-5]</sup>. In this light, some authors have hypothesized that IPMNs represent a "field defect" that may involve the whole gland, clinically or subclinically<sup>[6]</sup>. From a surgical standpoint, there are three questions of importance to be

answered: (1) when to resect an IPMN; (2) which type of resection should be performed; and (3) how much pancreas should be resected. Surgical resection allows eradication of IPMNs, and should be tailored to the tumor topography in order to perform as complete a resection as possible, weighting the risk of tumor recurrence with the morbidity associated with extended resections as well as with the risk of postoperative pancreatic insufficiency. However, preoperative imaging is not completely reliable for evaluating the degree of tumor extension along the pancreas, and the intraoperative examination of the transection margin is of crucial importance to determine whether or not extend the resection up to total pancreatectomy<sup>[2,6-9]</sup>.

Aim of this paper is to analyze the type and extension of surgical resections in patients with MD-IPMNs and BD-IPMNs, evaluating perioperative and long-term outcomes, and the role of standard and parenchyma-sparing resections.

## MANAGEMENT OF MAIN-DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

### **Indications for surgery**

In patients with MD-IPMNs, the presence of a main pancreatic duct > 10 mm in size, mural nodules, and symptoms (new onset or worsening diabetes, steatorrhea, jaundice, and weight loss) are all significant predictors of malignancy<sup>[2-4,10,11]</sup>. However, Sugiyama *et al*<sup>[12]</sup> have reported malignancy in the absence of mural nodules and dilated main duct, while Salvia *et al*<sup>[4]</sup> showed that 29% of patients with malignant MD-IPMNs are asymptomatic. In this setting, reliance on clinical and radiological parameters can not safely exclude malignancy. Moreover, the frequency of malignancy (*in-situ* and invasive carcinoma) in MD-IPMNs is high, ranging between 60% and 92% with a mean of 70%<sup>[2-4,10,11]</sup>, and different series showed MD-IPMNs with noninvasive tumors may progress to malignancy<sup>[4,10]</sup>. For all these reasons, the current recommendation is that all MD-IPMNs, including the combined type, should be resected<sup>[2]</sup>.

### **Type of surgical resection**

The surgical management of main-duct IPMNs represents a unique challenge to the surgeon, because the preoperative localization of a main-duct IPMN may be difficult. High-resolution imaging (CT, MRCP) may show a dilated main pancreatic duct with or without cysts, intraductal masses or nodules. Dilation can involve a segment or the entire main pancreatic duct. This may be related to the neoplasm since MD-IPMNs can spread along the entire duct, but it might also occur both proximal and distal to the tumor because of overproduction of mucus and/or associated chronic pancreatitis. In consideration of tumor site and extension, a typical resection with lymph node dissection should represent the treatment of choice<sup>[2]</sup>.

Nowadays pancreaticoduodenectomy (PD) and left pancreatectomy with splenectomy (LP) can be performed safely, and are associated with low mortality and acceptable morbidity in high-volume centers<sup>[13-15]</sup>. These procedures result in the removal of normal pancreatic tissue, leading to long-term exocrine/endocrine impairment. In the absence of chronic pancreatitis the incidence of postoperative diabetes ranges from 10% to 24 % after PD and from 8% to 60% after LP<sup>[16-22]</sup>. PD result in exocrine insufficiency in 30%-60% of patients, while LP is associated with exocrine insufficiency in up to 40% of cases, depending on the extent of resection<sup>[17-20,23,24]</sup>.

Surgical strategy can be changed based on intraoperative findings (i.e. transection margin, see below), and extension of surgical resection up to total pancreatectomy may be required<sup>[2,4,7,8]</sup>. When a significant dilatation of the main pancreatic duct is present along the entire gland, a total pancreatectomy (TP) should be considered as the first surgical choice, especially if predictors of malignancy are evident at preoperative imaging (i.e. mural nodules). In the case of diffuse dilatation of the duct but with a diameter < 1 cm and with no mural nodules, the surgeon can initially perform a partial pancreatectomy, evaluate the surgical margin and, if necessary further extend the resection up to a TP, in the same procedure.

The decision to perform TP should be made following consideration the surgical risk and long-term complications associated with the procedure, and needs to be carefully balanced with factors such as patient age, presence of co-morbidities and of preoperative diabetes. In the past, TP led to obligate diabetes mellitus with frequent hypoglycaemic episodes<sup>[25-27]</sup> as well as the development of severe malabsorption due to exocrine insufficiency<sup>[25-29]</sup>. Moreover the procedure was associated with significant mortality and morbidity. However in the last two decades the management of patients undergoing TP has improved. Insulin-dependent diabetes and malabsorption are better controlled with new drugs and, in recent series, mortality and morbidity after TP are 5% and 30%-40% respectively, with acceptable quality of life<sup>[28-31]</sup>. At the University of Verona, total pancreatectomy was performed in 65 patients with no mortality and morbidity of 38.5%; planned-elective total pancreatectomy was performed in 14 (21.5%) patients with IPMNs, while other nine (14%) underwent total pancreatectomy after an initial partial pancreatectomy for a positive resection margin.

Parenchyma-sparing resections, such as middle pancreatectomy (MP), offer the advantage of sparing pancreatic parenchyma and preserving exocrine and endocrine function. On the other hand MP is associated with a high rate of complications, particularly pancreatic fistula. Roggin *et al*<sup>[6]</sup> in a review of 207 patients from 16 series who underwent MP reported an overall morbidity rate of 33% and a fistula rate of 22%. In the combined experience of the University of Verona and of the Massachusetts General Hospital with a series of 100 MPs, overall morbidity was 58% with no mortality or reoperation and the rate of clinically significant pancreatic fistula was 17%. In relation to

**Table 1** Mortality, morbidity and long-term functional outcomes after different pancreatic resections

Procedure	Mortality (%)	Morbidity (%)	Exocrine insufficiency (%)	Endocrine insufficiency (%)
Pancreaticoduodenectomy	< 3	30-40	30-60	10-24
Left pancreatectomy	< 1	20-30	0-40	10-60
Total pancreatectomy	< 5	30-40	100	100
Middle pancreatectomy	< 1	40-60	< 5	< 4
Enucleation	< 1	40-60	< 2	< 2

long-term functional results, MP is an effective procedure to preserve pancreatic function. In our experience, after a median follow-up of 54 mo, the incidence of endocrine and exocrine insufficiency after MP was 4% and 5%, respectively<sup>[32]</sup> and similar results were reported by others<sup>[16,33,34]</sup>. In another study we evaluated the development of pancreatic insufficiency in 162 patients with benign tumors who underwent standard and parenchyma-sparing resections<sup>[35]</sup>. The probability of developing both endocrine and exocrine insufficiency was higher for PD and DP than for MP and enucleation (58%, 29% and 3% at 5 years).

However, from an oncological standpoint, the role of MP in treating MD-IPMNs is debatable<sup>[2]</sup>. In our experience, of six patients with MD-IPMN who underwent MP, four had positive resection margins at final histological examination and two of them recurred<sup>[32]</sup>. Blanc and colleagues reported more favorable results in patients with noninvasive IPMN<sup>[36]</sup>. It is notable that in MP there are two resection margins, and both must carefully evaluated intraoperatively. In case of positive resection margin(s) MP should be converted into standard pancreatic resection. However, considering the high rate of malignancy in MD-IPMNs, standard pancreatectomies should be the preferred treatment in this setting. Table 1 shows the rate of morbidity, mortality and pancreatic insufficiency according to different pancreatic resections.

In recent years, laparoscopic pancreatic resection techniques have been developed<sup>[37-41]</sup>. Early reports suggest that laparoscopic pancreatic surgery can be accomplished with acceptable morbidity and mortality for the resection of small benign and low-grade malignant lesions in the body and tail of the pancreas<sup>[37-41]</sup>. Laparoscopic distal pancreatectomy is associated with a similar morbidity to open LP, but with shorter length of hospital stay and faster recovery. Interestingly Baker *et al.*<sup>[42]</sup> showed in a prospective study that laparoscopic LP failed to provide a lymphadenectomy comparable to open LP. Therefore further studies are needed to evaluate the role of laparoscopic resection for malignant IPMNs, and at the moment an “open” approach should be attempted.

### Role of the transection margin

Intraoperative examination of the transection margin is of paramount importance in the management of MD-IPMNs<sup>[2,11]</sup>. Surgical margins in IPMN can be classified as negative (normal epithelium or mucinous hyperplasia without dysplasia in the main duct) or positive for adenoma, borderline neoplasm, or carcinoma. The IAP guidelines for the management of IPMNs suggest that when ad-

enoma or low-grade PanIN lesions are found intraoperatively in a resection margin, no further resection is needed, but that the presence of borderline neoplasm, high-grade dysplasia or invasive carcinoma requires an extension of the surgical resection to a negative margin, up to a total pancreatectomy<sup>[2]</sup>. Finally, the presence of denudation, namely de-epithelialized ducts at the pancreatic margin, is not uncommon. In our experience denudation should be considered as a positive resection margin since local recurrence can occur<sup>[9,43]</sup>. Recently Partelli *et al.*<sup>[44]</sup> showed in a cohort of 104 patients with invasive IPMNs, that the presence of denudation was associated with worse prognosis at univariate analysis. In this series, 12 patients (11.5%) showed denudation at final histological examination and 5 of 12 had a recurrence in the pancreatic stump, 4 in the liver and only 3 were free of disease during follow-up. The detection of denudation on frozen section examination should lead the surgeon to extend the resection<sup>[44]</sup>.

In our experience with 140 patients affected by MD-IPMNs who underwent surgical resection, the surgical margins were negative in 72% of patients who had a partial pancreatectomy and in all cases the definitive examination of the transection margins confirmed the intraoperative diagnosis. The results of the intraoperative frozen section analysis modified the surgical plan in 29 patients (21%), leading to an extension of the resection or to total pancreatectomy<sup>[4]</sup>. Couvelard *et al.*<sup>[43]</sup> studied frozen sectioning (FS) in a group of 127 patients who underwent partial pancreatectomy for IPMNs with a total of 188 FS. Definitive examinations corroborated FS in 176 of 188 cases (94%) and overall, 54 of 188 (29%) FS comprised at least IPMN adenoma on the transection margin leading to 46 further resections in 38 patients (30%). Conflicting results between FS and definitive examination resulted in inadequate extent of the resection in only four patients (3%)<sup>[43]</sup>.

## MANAGEMENT OF BRANCH-DUCT INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS

### Indications for surgery

BD-IPMNs are associated with malignancy in about 25% of cases, and parameters associated with the presence of a malignancy are the presence of symptoms, bigger lesions (> 3 cm) and of mural nodules<sup>[2,3,6]</sup>. When these criteria are present, surgical resection is indicated not only to alleviate symptoms but also because of the higher likelihood of malignancy. On the other hand, current guidelines rec-

commend a non-operative management for asymptomatic patients with BD-IPMNs less than 3 cm in size and without nodules<sup>[2]</sup>.

### Surgical treatment

Most BD-IPMNs require standard pancreatic resections. However MP can be an appropriate procedure for BD-IPMN < 3 cm in size in the neck of the pancreas and without malignancy features<sup>[32]</sup>. The intraoperative frozen section of the resection margins is less important for BD-IPMNs, except in the case of a malignant tumor or when there is concern about possible incomplete resection because of the proximity of the cyst to the margin or involvement of the main pancreatic duct<sup>[2]</sup>. At final histopathological examination it is important to rule out an extension of the IPMN from the BDs to the main pancreatic duct, because “combined” IPMNs show the same biological behavior as MD-IPMNs. Laparoscopic LP and spleen-preserving procedures should also be considered in patients with noninvasive BD-IPMNs.

### Management of multifocal branch-duct intraductal papillary mucinous neoplasms

Multiple BD IPMNs along the gland (multifocal disease) can be demonstrated in a significant number of patients<sup>[2,45]</sup>. They constitute a challenge, since extended resection up to total pancreatectomy can be necessary to treat this disease<sup>[5,46]</sup>.

In our experience with 145 resected BD-IPMNs, 25.5% of the patients had multifocal BD-IPMNs with no differences between benign (25%) and malignant (28%) neoplasms<sup>[5]</sup>. Schmidt *et al*<sup>[11]</sup> reported multifocal BD-IPMNs in 41% of their patients and that unifocal BD-IPMNs were invasive in 18% whereas multifocal lesions were invasive in only 7%. The appropriate management of these patients is still under debate and there are no specific guidelines. At the moment we suggest surgical resection only for symptomatic patients or for those with radiological findings associated with malignancy. For multifocal diseases that skip the body of the gland - including BD-IPMNs - we have recently proposed a parenchyma-sparing operation consisting of a middle-preserving pancreatectomy (MPP)<sup>[47]</sup>. With this procedure a total pancreatectomy can be avoided, and exocrine and endocrine pancreatic functions preserved in younger patients.

## ROLE OF LYMPHADENECTOMY

A standard lymphadenectomy should be performed during resections for IPMNs, especially if malignancy is suspected. The rate of lymph-node metastases in patients affected by malignant IPMN ranges from 16% to 46%<sup>[2,11]</sup>. Sohn *et al*<sup>[10]</sup> and D'Angelica *et al*<sup>[48]</sup> showed that lymph-node status was predictive of survival in a univariate model. Recently we have evaluated the combined experience of the University of Verona and of the Massachusetts General Hospital with 104 IPMN patients with invasive carcinoma (88 MD-IPMNs and 16 BD-IPMNs) who underwent surgical resection<sup>[44]</sup>. Forty-two percent of these patients had

lymph node metastases with a median number of 15 resected/evaluated nodes. Patients with lymph node metastases had a shorter 5-year disease-specific survival (28.9% vs 80.3%,  $P < 0.05$ ). Interestingly we found that lymph node ratio (LNR) was a significant predictor of survival in invasive IPMNs, with 5-year survival significantly decreasing as the LNR increased. The potential benefit of a more extensive lymphadenectomy remains speculative and should be probably explored in a prospective trial.

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