Main- and Branch-Duct Intraductal Papillary Mucinous Neoplasms: Extent of Surgical Resection

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Summary

Background: Surgical treatment of intraductal papillary mucinous neoplasms (IPMN) requires a differentiated approach regarding indications and extent of resection. **Methods:** The review summarizes the current literature on indication, timing, and surgical procedures in IPMN. **Results:** The most important differentiation has to be made between main-duct and branch-duct IPMN as well as mixed-type lesions that biologically mimic main-duct types. In main-duct and mixed-type IPMN, the resection should be indicated by the time of the diagnosis – in accordance with the international consensus guidelines – and should follow oncological principles. Depending on IPMN localization, this implies partial pancreatoduodenectomy, distal pancreatectomy, or total pancreatectomy and includes the corresponding types of lymphadenectomy. Furthermore, branch-duct IPMN > 3 cm or bearing high-risk features (mural nodules in magnetic resonance imaging, computed tomography, or endoscopic ultrasound imaging; symptomatic lesions; elevated tumor markers) are similarly treated. As the risk for malignancy in smaller branch-duct IPMN is lower, the decision for surgical treatment is often individually made – despite the updated 2012 guidelines. In these lesions, limited surgical approaches, including enucleation and central pancreatectomy, are possible. **Conclusion:** Timely and radical resection of IPMN offers the unique opportunity to prevent pancreatic cancer, and even in malignant IPMN surgery can offer a curative approach with excellent long-term outcome in early stages. A structured imaging follow-up should be considered to recognize IPMN recurrence and metachronous pancreatic cancer as well as gastrointestinal neoplasias by endoscopic surveillance.

Introduction

Surgical decision making in the treatment of intraductal papillary mucinous neoplasms (IPMN) of the pancreas must be based on the type of IPMN diagnosed in the preoperative work-up. Due to the high risk of malignancy of 60–90% in main-duct and mixed-type IPMN (fig. 1), these two entities represent indications for surgical treatment by the time of their diagnosis [1, 2]. Surgical therapy must be in accordance with an oncological principle which implies a formal pancreatic resection and lymphadenectomy.

In contrast, indications for resection in branch-duct IPMN have to be more balanced and are currently under debate regarding criteria, timing, and extent of resection. As malignancy occurs in approximately 20–25% of branch-duct IPMN, they have to be regarded as precursors of pancreatic cancer as well and should thus not be underestimated [3–5].

Main-Duct and Mixed-Type IPMN

Depending on the localization of the lesions, the surgical standard procedures include partial, distal and total pancreatectomy [6, 7]. If the IPMN is limited to the pancreatic head, pylorus-preserving pancreatoduodenectomy is the routine approach. A classical pancreatoduodenectomy with stomach resection is rarely required and should be restricted to situations where the lesion extends towards the pylorus and gastric antrum or when distal stomach perfusion is compromised after the resection. Preservation of the pylorus offers the advantage of physiological food passage and is therefore regarded as superior regarding weight loss and quality of life in the long-term outcome, which may be especially important for patients resected for benign pancreatic lesions with a good prognosis. After completion of the resection, it is mandatory to perform an examination of the pancreatic resection margin by means of intraoperative frozen sections to ensure the absence of main-duct IPMN in this position [7, 8]. The operative strategy has to be adjusted afterwards, which implies that completion pancrea-

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Fig. 1. MRI in mixed-type IPMN: Dilated main duct in the head and body of the pancreas, multiple branch-duct lesions throughout the gland, total pancreatectomy performed, histopathologically two invasive carcinomas in the resected specimen (pT1m, N0).

tectomy should be performed in most patients unless there is already proven adenocarcinoma in the resected specimen. In this situation, an individual decision has to be made as prognosis is not dependent on the remaining IPMN tissue and the pancreatic remnant may be preserved. An oncological lymphadenectomy should always accompany resections of main-duct IPMN. This comprises the lymph nodes of the hepatoduodenal ligament as well as the lymph nodes along the right side of the celiac axis and the superior mesenteric artery. Reconstruction is performed by pancreaticojejunostomy or pancreaticogastrostomy, hepaticojejunostomy, and duodeno- or gastrojejunostomy. In the case of main-duct IPMN of the pancreatic body or tail, distal pancreatectomy is the standard resection [6–9]. This operation is again performed following oncological principles, including lymphadenectomy along the left side of the celiac axis, the superior mesenteric artery, and the hepatoduodenal ligament as well as splenectomy. Division of the pancreas above the portal vein/superior mesenteric vein axis can be done by stapling devices or scalpel followed by suture closure of the remnant [10]. Coverage of the resection margin by patches (e.g. jejunum/teres hepatis ligament, artificial patches) or a pancreaticojejunostomy to avoid postoperative pancreatic fistula is optional. None of the mentioned methods has yet been proven to actually decrease the incidence of this complication, which is observed in roughly one third of all patients [11].

Total pancreatectomy in main-duct IPMN is performed either as a primary en bloc resection if IPMN extension is preoperatively assessed throughout the entire gland or as a sequential procedure in situations where intraoperative frozen sections show IPMN progression after partial pancreatectomy, as mentioned before. As this procedure is also carried out oncologically, a combination of the lymphadenectomy fields of partial pancreaticoduodenectomy and distal pancreatectomy is required, and, in general, the spleen is removed.

Branch-Duct IPMN

Surgical management of branch-duct IPMN is more differentiated and the subject of ongoing international controversies with regard to indication, correct timing, and extent of surgical interventions. Based on the 2006 consensus guidelines that were updated in 2012 [1], the so-called 'Sendai' criteria have been established to describe the risk of malignancy in these lesions. The guidelines recommend the resection of branch-duct IPMN of more than 3 cm in diameter in general. Smaller branch-duct IPMN should only be resected in the presence of 'high-risk' stigmata including mural nodules, positive cytology, symptoms, or a synchronously dilated main duct. However, there is growing evidence that these guidelines are not sufficient enough in order to recognize all premalignant lesions in time. In different larger surgical series examining resected IPMN, the incidence of malignant branch-duct IPMN (including in situ and invasive carcinoma) was approximately 25% among all IPMN below 3 cm without any reliable cut-off in diameter [3, 12–14] (table 1). Although these are certainly selected collectives of patients, the findings of malignant potential in a relevant proportion of the patients underlines that a clear stratification and decision for conservative or surgical treatment is very difficult up to the present. Neither the existence of mural nodules as a guideline predictor of malignancy nor the existence of clinical symptoms did correlate with malignancy [14]. These findings underline that size alone as well as currently established markers of potential malignancy are no reliable predictors and that even small branch-duct IPMN have a relevant risk of malignancy. Individual decisions for resection based on an evaluation of all morphological and clinical factors (including imaging, tumor markers, symptoms, progression, and prior patient history) seem to offer the best approach at the moment. The standard surgical approach for all suspected malignant branch-duct IPMN is an oncological resection with lymphadenectomy, which is comparable to the approach in main-duct IPMN. Depending on the location of the lesion, either partial pancreaticoduodenectomy or distal pancreatectomy is the adequate procedure. As surgery for branch-duct IPMN should aim at a prevention of malignancy and can be regarded as a prophylactic procedure in many patients, other less extensive operative approaches, i.e. enucleations or central pancreatectomies, are possible as well [15–20]. Enucleation for small branch-duct IPMN is a limited type of local resection with the aim of preserving all healthy pancreatic tissue. These approaches can be performed if the benign character of the excised lesion is confirmed by intraoperative frozen section and when the location and morphology of the cystic lesion are suitable for this procedure. In order to evaluate this adequately, an accurate localization of the IPMN is essential. Besides preoperative imaging, the most important tool for tumor location is the experience of the surgeon performing the exploration [15–17]. Mobilization of the pancreas offers a careful digital examination of the suspected lesion. In addition, intraoperative ultrasound examination is a very useful tool. By means of intraoperative ultrasound, an identification of the cystic lesion is feasible; however, a possible relation to the pancreatic duct can only be

Table 1. Reported rates of malignancy in various series of branch-duct IPMN in retrospective surgical series

Study	n	Malignancy rate (carcinoma in situ or invasive cancer)			
		<1 cm	1–2 cm	2–3 cm	total <3 cm
Schmidt et al., 2007 [12]	103	3/18	8/53 (16%)	5/29 (17%)	16/82 (20%)
Jang et al., 2008 [13]	138	1/31 (3%)	7/42 (17%)	6/25 (24%)	14/89 (16%)
Walsh et al., 2008 [33]	56	–	–	–	12/56 (21%)
Fritz et al., 2012 [3]	123	3/12 (25%)	11/40 (28%)	3/17 (18%)	17/69 (25%)
Wong et al., 2013 [34]	105	4/7 (57%)	5/19 (26%)	31/44 (70%)	40/70 (57%)
Sahora et al., 2013 [35]	217	0/4 (0%)	6/46 (13%)	15/75 (20%)	21/125 (17%)

clarified intraoperatively if there is any doubt about it [15]. During enucleation itself, careful attention needs to be paid to the connection of the branch-duct IPMN to the pancreatic duct. This should be identified and closed by clip or suture ligation to avoid high-volume enzyme leakage. A tumor size of 3 cm in diameter can be regarded as the limit for a safely performed enucleation. Tumors measuring more than 3 cm in size show malignant histological changes significantly more often, making a local surgical approach impossible. Besides, tissue trauma and wound surface following an enucleation reach a critical size for the development of fistulas or other complications, including bleeding or postoperative pancreatitis. The resected IPMN should always be examined by intraoperative frozen section to confirm its benign nature. In the case of unexpected malignancy, a more extended oncological resection must be chosen. Drain placement at the end of the operation is recommended as fistula rates of approximately 30% are currently reported; however, most of them are clinically irrelevant [15–17]. Another limited and parenchyma-sparing resection approach for localized and benign IPMN is central pancreatectomy if the finding is located in the body of the pancreas. A segment between the level of the superior mesenteric vein/portal vein axis and the remaining tail of the gland can be resected under preservation of all healthy tissue [19, 20]. Pancreatic transection towards the pancreatic head can be carried out either with a stapler or by scalpel with a consequent suture closure, similar to the procedure during distal pancreatectomy. Towards the pancreatic tail, the transection is performed sharply to avoid tissue damage on the cut margin. After completing the resection, the distal stump of the pancreas is further mobilized from the splenic vein and artery, with ligation of small tributaries, over 2 cm lateral to the cut end. Reconstruction is accomplished with a retrocolic Roux-en-Y loop of the jejunum. The already closed pancreatic head remnant can finally be covered with the same jejunal loop by sutures between the seromuscular layer of the jejunum and the capsule of the pancreas. Reconstruction is completed by an infracolic Roux-en-Y enteroenterostomy [20]. Alternatively, a double anastomosis technique with two pancreaticojejunostomies is possible; however, it prolongs the operation time and does not necessarily offer any benefit compared to merely closing the cut margin towards the pancreatic head. To date, fistula rates of approximately 40% are reported for central pancreatectomy. Comparable to enucleation, most of these fistulas are uncomplicated, do not lead to consecutive complications, and can be treated conservatively [19, 20].

Perioperative Outcome

Depending on the performed resective procedure, perioperative morbidity is mainly determined by the occurrence of postoperative fistulas. In large series of resected IPMN in which all types of operations were performed, overall morbidity rates of approximately 35–50% and mortality rates of 0–1% are reported [21, 22]. Following partial pancreatoduodenectomy, the rate of postoperative fistulas is about 5–10%, while a higher rate of 17–30% is reported following distal pancreatectomy [10, 11, 22]. When the parenchyma-sparing approaches of enucleation and central pancreatectomy are regarded, postoperative fistulas occur in 20–40% of the patients [15–17]. As mentioned above, the majority of these fistulas is clinically harmless and can be treated by maintenance of an intraoperatively or interventionally placed drainage without further morbidity. Other complications such as postpancreatectomy hemorrhage or infected fluid collections are less frequently observed and can mainly be treated by interventional radiological therapy. The overall reoperation rate in the reported series ranges between 5 and 8%.

Long-Term Outcome and Prognosis

In IPMN patients undergoing enucleations or central pancreatectomies, no resection-related impairment of endocrine or exocrine pancreatic function has to be expected during long-term follow-up, and enzyme replacement or antidiabetic therapy is rarely necessary unless pancreatic function has already been compromised preoperatively. Furthermore, both procedures offer an excellent quality of life [15–20].

Following partial pancreatoduodenectomy or distal pancreatectomy, the incidence of exocrine or endocrine insufficiency is considerably higher; however, it has to be taken into account that in most of the IPMN patients the remaining pancreatic tissue is healthy and functionally intact, which implies a good capacity to completely replace the function of the resected tissue. This results in long-term exocrine insufficiency rates with the need for enzyme and vitamin replacement of approximately 20% after partial pancreatoduodenectomy and about 10% after distal resections. Regarding endocrine function, a new-onset postoperative diabetes mellitus has to be expected in 10% of all patients after partial duodenopancreatectomy and in up to 20% after distal pancreatectomy [10, 23, 24]. In the case of total pancreatectomy due to extensive

main-duct IPMN, insulin and enzyme replacement is mandatory, with a consecutive impairment of the patients' quality of life [25–27]. Larger follow-up series, however, show that adequate patient education and compliance as well as continuous medical care lead to a very good outcome with only little impairment of daily and professional activity as well as quality of life. Furthermore, there is no operation-associated reduction in life expectancy after total pancreatectomy for benign pathologies such as IPMN [25–27]. The disease-specific prognosis after resection of benign IPMN is excellent. In main-duct as well as branch-duct IPMN, the 10-year survival rates are 95% [28].

A very important aspect in the management of IPMN patients is the lifelong postoperative follow-up with annual imaging control of the pancreatic remnant. This is preferably performed by magnetic resonance imaging (MRI) or can alternatively be done by endosonographic ultrasound in experienced hands. In addition, regular endoscopic controls focused on colorectal adenomas and Barrett dysplasia of the esophagus are recommended as both pathologies are increasingly observed in IPMN patients [29, 30].

In the case of suspected IPMN recurrence, surgical re-resection should be attempted according to the recommendations given above. Depending on the extent of the prior resection, this implies the performance of a remnant pancreatectomy in a considerable number of patients.

Oncological prognosis in case of invasive and malignant IPMN is generally more favorable than in sporadic pancreatic adenocarcinoma. A large study by Wasif et al. [31] comparing 729 patients with IPMN-associated carcinoma with 8,082 patients with sporadic pancreatic cancer showed an overall survival of 34 versus 18 months, respectively. The most important explanation for this significant difference is the fact that a large number of IPMN-associated cancers are resected in Tis- and T1-stages which leads to 5- and 10-year survival rates of 70 and 60%, respectively. Another study including 132 patients with IPMN-associated cancers and 1,128 patients with non-IPMN cancers demonstrated that this survival benefit is dramatically reduced as soon as IPMN-associated cancers exceed T1 stages or lymph node metastases are found [32]. In this situation even adjuvant chemotherapy fails to improve the prognosis of IPMN-cancer patients in comparison to other pancreatic cancer collectives [23]. Both of these publications underline the great importance of early resection in these patient cohorts as well as the need for a consequent and structured lifelong follow-up.

Disclosure Statement

The authors declare no conflict of interests.

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