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Intraductal Papillary Mucinous Tumors of the Pancreas. Surgical Treatment: At What Point Should We Stop?

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Summary

The intraoperative management of the margins of intraductal papillary mucinous tumors (IPMNs) undergoing pancreatic resection is crucial. The surgeon must discontinue the resection whenever the pancreatic margin is negative and, of course, when a total pancreatectomy is indicated.
Nevertheless, a wide gray area exists. The real surgical problems are represented by i) IPMNs involving only a segment of the pancreatic gland, thus necessitating intraoperative histological examination of the resection and the decision as to "when to stop the resection"; ii) the intraoperative management of those margins which are neither clearly negative nor clearly positive; iii) the actual indications either for surgery or for follow-up in those patients affected by peripheral IPMNs.
In the literature, negative resection margins have a range of between 49 to 81% with a pancreatic recurrence rate of from 0 to 25% in follow-ups ranging from 6 months to 11 years after the first operation.
In general, in this disease which mainly involves the head and uncinate process of the gland, decisions are a "balance" between the patient and the disease. In fact, on the one hand, there is the usual elderly patient with possible comorbidities, symptoms and the presence of diabetes; on the other hand, the disease, which usually involves the head and the uncinate process of the gland, tends to grow along the duct and be potentially malignant if carcinoma is not already present.

Described for the first time in 1982 as a mucin producing neoplasm with dilatation of the main duct and protruding papilla (the Ohashi triad) [1], intraductal papillary mucinous neoplasms of the pancreas (IPMNs) have had a remarkable "epidemiological explosion" in recent years [2, 3, 4, 5, 6].
The disease originates from the epithelium of the pancreatic ducts and can evolve through different biological stages ranging from mild dysplasia to invasive carcinoma; the different stages could be simultaneously present within the same lesion [7]. Currently, most of the Authors agree that evolution towards the carcinoma stage is slow, but probably inexorable [8, 9, 10].
In consideration of the improvement in radiological imaging, IPMNs are diagnosed with increasing frequency and at earlier stages. It is remarkable that nowadays pancreatic main duct dilatation of less than 1 cm and small cysts can be clearly identified by MRCP instead of invasive diagnostic tools such as ERCP [11].
If we trust in the potential malignancy of IPMNs, the therapy of all the "ectasiae" involving the main pancreatic duct should be surgical resection.
Thus, the correct answer to the question "IPMNs, at what point should we stop in the operating theatre?" is only "*if*" a normal

epithelium is shown at intraoperative frozen section examination of the resection margin. The presence of any positive resection margin must push the surgeon to proceed with pancreatic resection in order to achieve a negative margin up to total pancreatectomy when necessary. Actually, the first studies reported in the literature consider surgery as the only treatment for IPMNs [3, 12, 13].

At the end of the 90's, IPMNs were divided into two different groups: those with involvement of the main pancreatic duct and those with involvement of the side branch of the ductal system [14, 15, 16].

In 1999, some authors [15, 16] showed for the first time that "branch-duct" IPMNs may have a less aggressive biological behavior as compared to the main duct type thus suggesting limited resection or, at least, conservative surgical treatment.

Between 1999 and 2001 several studies identified some radiological findings as criteria in discriminating between benign and malignant forms; in particular parameters related to malignancy were well-characterized [17, 18, 19, 20].

Not only radiological findings, but also clinical, demographic and laboratory parameters should be considered to understand whenever a "wait and see" follow-up is the best option for these patients.

A recent paper analyzed the databases from Harvard University and the University of Verona [6] in order to describe the clinical characteristics and outcomes of a large number of patients affected by IPMNs involving the main pancreatic duct. A total of 140 patients were considered and the results of the study showed interesting findings never before described in a large series. First of all, patients with malignant tumors were found to be almost seven years older than those with adenomas or borderline tumors. This observation supports the evidence that the neoplasm arises as benign and subsequently becomes malignant, thus making it possible to evaluate the median time required for this progression.

Regarding clinical findings, a recent onset or worsening of diabetes, steatorrhea and, mainly, jaundice were significantly associated with malignancy. On the contrary, patients with benign IPMNs had a higher frequency of abdominal pain and a longer duration of the symptoms.

Further considerations lead us to carefully consider the surgical option in IPMNs. Most patients are elderly with a mean age of 65-70 years at diagnosis and they can be affected by co-morbidity increasing the surgical risk. The lesion mainly affects the head of the pancreas and the uncinate process (60%) but the entire gland may be involved. Therefore, in agreement with this finding, pancreaticoduodenectomy is the most common surgical procedure followed by total pancreatectomy [5, 6, 21, 22, 23].

Moreover, as regards the concept of transformation from benign neoplasm to invasive carcinoma, studies involving a large cohort of patients showed a "progression time" ranging from 5 to 7 years [5, 6].

Even if there is still a lack of data regarding non-surgical follow-up, this "wait and see" policy may be suggested in asymptomatic patients with branch IPMNs and absence of any malignancy criteria together with high operative risk.

Therefore, patients affected by peripheral IPMNs without any malignant parameters should be candidates for a strict clinical-radiological "wait and see" follow-up.

In such instances, surgery is not indicated.

In the remaining patients, surgical resection is still the treatment of choice.

Among those undergoing surgery, some patients present a dilatation of the entire ductal system of the gland with an involvement of the main pancreatic duct and side branches. Total pancreatectomy has to be considered the main surgical option.

IPMNs involving only a segment of the pancreatic gland represent the real challenge for the surgeon. In these cases, an intraoperative histological examination of the resection margin is mandatory [2] in order to answer the question "when to stop?".

Because the extent of ductal involvement may be difficult to determinate prior to surgery, many authors have stressed the importance of

obtaining a tumor-free surgical margin by intraoperative frozen section pathological examination [10, 12, 22, 24].

In a previous report from our institution, we evaluated the resection margins in 49 patients who had undergone a partial pancreatectomy for IPMNs between 1988 and 1998. Forty-seven percent of the 49 patients had negative resection margins at pathological examination while 18%, 22% and 2% had mild, moderate and high-grade dysplasia, respectively.

Five patients (10%) presenting with invasive IPMN had a de-epithelialized resection margin.

In 4 of these patients there was local recurrence of the tumor, and a fifth patient, who underwent pylorus-preserving pancreaticoduodenectomy, has had too short a follow-up to be properly assessed. The presence of de-epithelialization should therefore be regarded as a "positive resection margin" [2].

In our recent paper, reporting the Harvard-Verona combined experience, the rate of negative margins in the surgical specimen was 58.5% [6].

The results of the intraoperative frozen section analysis altered the surgical plan by extending resection or leading to total pancreatectomy in 29 patients.

Considering the long-term follow up of these patients, recurrence in the remaining pancreas occurred in 8 patients (7%). Only one of these patients did not have invasive cancer in the initial pathology. He underwent a Whipple procedure for an adenoma and had a pancreatic margin that was negative. Five years later, he developed a recurrence and underwent a complete pancreatectomy for a carcinoma in situ in the distal pancreas.

The other 7 recurrences occurred in patients who had presented invasive cancer. Two patients presented recurrence within 6 months and they also had liver metastases. Five presented recurrence in the remnant between 28 and 67 months. Three of them underwent further resection but subsequently developed metastases and died; 2 are currently disease-free after the re-resection.

None of the transection margins of these patients showed invasive cancer: 2 borderline, 2 de-epithelialized and one was negative.

Chari *et al*. [25], in a series of 73 patients with non-invasive IPMNs, performed partial pancreatectomy in 60 cases and total pancreatectomy in the remaining 13. Considering patients who underwent partial pancreatectomy, a negative or hyperplastic resection margin was achieved in 58 cases while mild or moderate dysplasia was found in 2; recurrence was observed in 5 of 60 patients (8%) and, in all cases, the surgical margin was negative after the initial resection. Two recurrences were benign and 3 were malignant (carcinoma in situ in one case and invasive carcinoma in the remaining two). Patients with benign recurrences presented IPMN adenoma both at the first and at the second surgical resection. Patients with carcinoma in situ and invasive carcinoma had, after initial surgery, a borderline tumor and carcinoma in situ, respectively.

Sohn *et al*. [5] showed a recurrence of disease in 9 of 136 (7%) patients with resected non-invasive (n=84) or invasive (n=52) IPMNs. Seven patients had an invasive IPMN after the second surgery: 5 of them had carcinoma in situ after initial surgery, with negative resection margins in 3 cases, while the remaining two had invasive carcinoma. One patient operated on for an IPMN with moderate dysplasia and a borderline resection margin had a recurrence one year later and the pathological examination showed the same histological findings. The last patient, who had an initial carcinoma in situ with a negative resection margin, presented a recurrence of the same neoplasm 11 years later.

On the one hand, the presence of malignant growth at the pancreatic resection margin requires an extension of the surgical resection up to a total pancreatectomy [10, 23, 26]; on the other hand, in the case of microscopic benign dysplastic lesions at the pancreatic margin, the optimal surgical strategy remains controversial.

Traverso *et al*. [22] and Sugiyama and Atomi

[23] reported completion of total pancreatectomy in 24% and 29% of their patients, respectively. A significantly different strategy was carried out by the Erasme University Hospital group [3, 27]. These authors reported the presence of benign dysplasia at the surgical margin in 57% of their patients but none of those underwent subsequent total pancreatectomy; it is remarkable that only one patient experienced a recurrence in the remnant gland 66 months after distal pancreatectomy.

Since IPMNs are usually diffuse or multicentric within the pancreatic gland, the surgeon should ask himself if surgical margin examination is the only factor to be considered in determining the extent of the resection.

For this reason, Gigot *et al*. [28] suggested intraoperative endoscopic staged biopsies of the main pancreatic duct as complementary tools.

Finally, in patients with IPMNs undergoing pylorus-preserving pancreaticoduodenectomy, pancreo-gastric anastomosis may be more indicated than pancreatico-jejunostomy. Actually, this reconstructive technique allows direct access to the pancreatic stump by endoscopy during follow-up.

Chari *et al*. [25] showed that, in patients with invasive IPMNs associated with a negative resection margin, 50% of the recurrences were identified by CT scan before clinical symptoms developed. However, surveillance CT scan is not necessary after total pancreatectomy for noninvasive tumors, because this operative approach seems to be curative.

At the moment, it is unclear whether there is a role for resection of isolated or distant metastases in selected patients with asymptomatic recurrence.

Recurrence after resection of non-invasive IPMN may occurred because there is residual dysplastic tissue at the surgical margins, due to the fact that there is multifocal disease in the remnant pancreas or because metachronous lesions develop in the remnant pancreas as a result of a neoplastic tendency of the entire gland.

In conclusion, the question “at what point should we stop the surgical treatment?” is really difficult. The surgeon has to consider the possibility of a “wait and see” follow-up for the patient. When he decides on a surgical approach, he has to be aware and inform the patient about the high possibility of being forced to extend the resection up to a total pancreatectomy.

In the operating theatre, the aim of reaching a negative resection margin is, in general a “balance” between the disease and the patient. In fact, on the one hand, there is the usual elderly patient with possible comorbidities, symptoms and the presence of diabetes; on the other hand, the disease which usually involves the head and the uncinate process of the gland, tends to grow along the duct and be potentially malignant if carcinoma is not already present.

Keywords Surgical Procedures, Operative; Neoplasms, Cystic, Mucinous, and Serous; Pancreaticoduodenectomy; Pancreatectomy

Abbreviations IPMN: intraductal papillary mucinous tumor

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