Endoscopic management of tumors of the major duodenal papilla: refined techniques to improve outcome and avoid complications

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Background: Adenomas of the major duodenal papilla have malignant potential and are traditionally treated by pancreaticoduodenectomy. This is a report of our experience with endoscopic management and a description of techniques for decreasing complications and enhancing efficacy.

Methods: Forty-one patients were referred for endoscopic management of papillary tumors. If there was no duct invasion and the appearance suggested a benign lesion, biductal sphincterotomy with pancreatic duct stent placement was performed. If the lesion could be elevated by injection of an epinephrine solution, piecemeal resection was performed. The base of the lesion was thermally ablated as needed. Resection/ablation together with stent removal was performed 1 month later.

Results: Nine patients (22%) had lesions other than papillary adenoma or cancer. Malignant appearance, ductal stricturing, or extension into the ducts was found in 16 of 41 patients (39%) in whom biopsy specimens alone were obtained. Three patients with adenomas (7%) did not undergo endoscopic resection (because of extremely large lesions and/or comorbid illnesses). Thirteen patients with adenomas (32%) had endoscopic resection; 12 (92%) were lesion-free after 32 ERCPs (mean 2.7). Endoscopic management was unsuccessful in 1 patient (8%). Pancreatitis developed in 1 patient.

Conclusions: Endoscopically treatable papillary neoplasms can be identified on the basis of endoscopic, radiographic, and biopsy features. Preresection sphincterotomy, stent placement, elevation by epinephrine injection, and piecemeal resection may reduce complications and permit more aggressive treatment. (Gastrointest Endosc 2001;54:202-8.)

Neoplasms of the major duodenal papilla are rare but are being recognized more frequently.1-3 Malignant transformation of benign lesions into carcinoma has been documented,4,5 and papillary adenomas are thought to mimic the colonic adenoma-to-carcinoma sequence.6 Historically, these neoplasms were managed by pancreaticoduodenectomy, or more recently, by local surgical excision.7-9 However, even wide local excision, with its attendant morbidity and modality, is a relatively extreme measure when the goal of intervention is essentially preventative. It is indisputable that a cancer operation is needed for papillary cancer, but less invasive alternatives are increasingly being sought for definitive management of benign papillary adenomas. There are several reports of endoscopic assessment and treatment of benign papillary neoplasms, especially endoscopic resection.10-12 This is a report of our experience with endoscopic evaluation and selective removal of adenomatous tumors of the major duodenal papilla, emphasizing the approach and techniques developed to decrease complications.

PATIENTS AND METHODS

Data were retrospectively reviewed on 41 patients (18 women, 23 men; mean age 68 years, range 24-90 years) referred for possible endoscopic resection of papillary neoplasms from January 1991 to January 2000. Gardner's syndrome and familial adenomatous polyposis (FAP) had been diagnosed, respectively, in 3 and 5 patients. Most patients had presented with varying combinations of jaundice, abdominal pain, fever, and pruritus. Ten had presented with pancreatitis. Three patients with FAP or Gardner's syndrome were asymptomatic at presentation, the lesions being discovered during surveillance endoscopy. Written informed consent was obtained from each patient or by proxy before each ERCP.
Endoscopic resection

Endoscopy was performed with standard duodeno-
scopes (JF-140, TJF-140; Olympus America, Inc., Melville,
N.Y.). The following criteria were considered to indicate
resectability: (1) a soft tumor that was not indurated or
ulcerated, (2) ability to elevate tumor by saline solution/
epinephrine injection, (3) absence of stricturing and
extension into pancreatic or biliary ducts, and (4) size no
greater than half the circumference of the duodenum,
about 4 cm in maximal diameter. For lesions larger than
this, the low likelihood of success and increased risk of
perforation, even with piecemeal resection, were consid-
ered as precluding endoscopic management.

Lesions were selected for resection in the following
fashion. Features indicative of malignancy were sought
first: bleeding, friability, puckering, induration, ulceration,
and/or erythema (Fig. 1). A pancreatogram and cholan-
giogram were then obtained to determine whether there
was ductal invasion or stricturing. If the lesion appeared
to be benign (well marginated, soft, pale) and invasion or
ductal stricture were not evident, wire-guided biliary and
pancreatic sphincterotomies were performed.13 Within
the limits of safety, the sphincterotomies were carried
onto normal duodenal tissue, thereby isolating the lesion
and ensuring adequate drainage. If the sphincterotomies
were of sufficient length, stents that might be placed
would be nearer the margin of the neoplasm. This facil-
tated subsequent piecemeal resection.

Because pancreatic sphincterotomy had been per-
fomed, a pancreatic duct (PD) stent was then placed to
protect the PD orifice. Although the specific type of PD
stent is probably inconsequential, a 5F, 5-cm, double-
barbed, Geenen stent (Wilson-Cook Medical, Winston-
Salem, N.C.) was used. The flaps were not removed from
the stents because it was intended that the stents remain
in place until the second endoscopy (on average 36 days
later). At the second procedure, further thermocoagulation
was performed as needed with the stent still in place. A bili-
ary stent was occasionally placed if the sphincterotomy
did not move the biliary orifice sufficiently away from the
neoplasm to ensure adequate drainage after resection. If
further resection or ablation was needed at subsequent
ERCPs, a PD stent might again be placed, but in general
this was not necessary.

The neoplasm was then elevated with large-volume sub-
mucosal injections of 1:20,000 saline solution/epinephrine
solution by using a sclerotherapy needle, until all parts
were separated from the muscularis propria. The number
of injections and total volume of solution injected (3 to 10 mL)
varied with the size of the lesion. Electrosurgical snare
resection was then performed with a standard polypecto-
my snare and standard generator settings (30 W pure
coaulation current; Valleylab 2, Valley Laboratories,
Boulder, Colo.) (Fig. 2). The neoplastic tissue was snared
piecemeal, placing the snare loop against the stent and
resecting large pieces until resection was complete. With
larger polyps, an effort was made to remove at least 95%
of the lesion at the first ERCP. After resection, the area
was irrigated with saline solution, and any ongoing bleed-
ing or oozing of blood was stopped by additional injections
of epinephrine. At the discretion of the endoscopist, the
base of the resected lesion was ablated with an argon plas-
ma beam (Erbe America, Inc, Marietta, Ga.) with a 7F
catheter with a flow rate of 1.2 L/min and power of 60 W.
A 7F multipolar electrocautery probe set at 25 to 35 W
was occasionally used for this purpose.

Surveillance

Resection of any residual neoplastic tissue and ther-
mocoagulation of the base of the lesion were performed as
needed 1 month later. Thereafter, surveillance endoscopy
was performed at 3-month intervals until no residual neo-
plastic tissue could be detected endoscopically or by biop-
sy. Afterward the surveillance interval was lengthened to
1 year. At each surveillance endoscopy a cholangiogram
and a pancreatogram were obtained to determine whether
recurrence in distal ducts was present.

Complications

Complications were assessed according to consensus
criteria.14 After the initial endoscopy with biductal sphinc-
terotomy and electrosurgical snare resection, patients
were observed overnight in hospital. At subsequent proce-
dures, that is, after initial biductal sphincterotomy, the
risk of complications was thought to be lower and the pro-
cedures were performed on an outpatient basis.

RESULTS

The management of 41 consecutive patients
referred for endoscopic treatment is summarized in
Figure 3. Nine were found on initial ERCP to have a
nonpolyloid lesion (e.g., mucin-secreting tumors,
hypertrophic papillae, lymphangioma, cancer of the
head of the pancreas involving the papilla) and were
excluded. Of the remaining 32 patients, 15 had
endoscopic, cholangiographic, or pancreatographic features of carcinoma and did not undergo endoscopic resection. Endoscopic forceps biopsies or needle aspiration (HBAN-22, Wilson-Cook Medical, Inc., Winston-Salem, N.C.) confirmed the diagnosis of cancer in 12 of 15 patients (80%). One patient with negative findings from biopsies and a large neoplasm was thought to have cancer based on the appearance of a distal common bile duct stricture. He was referred for pancreaticoduodenectomy and was found to have a 5-mm T1N0M0 adenocarcinoma arising in a large (35 mm) tubulovillous adenoma. The remaining 2 patients with findings suggestive of carcinoma had comorbid conditions that precluded surgery. Therefore, cancer was confirmed in 13 of 15 patients (87%). Of these 15 patients, 6 were referred for pancreaticoduodenectomy, 5 underwent chemoradiation, and 4 were followed conservatively after oncologists and surgeons declined to offer therapy. Among the patients who underwent surgery, a postoperative wound infection developed in 1; there were no surgery-related deaths.

Seventeen patients had benign adenomas of the papilla, 13 of whom were selected for endoscopic treatment (Table 1). The adenomas were eradicated
in 12 patients (92%). This required 32 ERCP procedures (mean 2.7 per patient, range 1-5). The patient in whom endoscopic management was unsuccessful had FAP and had already undergone proctocolectomy. She underwent a total of 9 ERCPs with resection and coagulation of an extremely aggressive residual neoplasm in an effort to avoid pancreatoduodenectomy. However, migration of the tubulovillous adenoma into the bile and pancreatic ducts necessitated pancreatoduodenectomy, which was performed without complication.

The remaining 4 of the 17 patients with adenomas did not undergo endoscopic resection (Table 1). Three had extremely large lesions, as defined above, which in our opinion would have made endoscopic resection hazardous and unlikely to be successful. These 3 patients were also rejected for surgery because of comorbid conditions. Therefore, biliary or pancreatic duct sphincterotomy and/or partial removal were carried out to relieve obstruction. The fourth patient had extension of a benign adenoma into the bile and pancreatic ducts necessitated pancreatoduodenectomy, which was performed without complication.

Among the 13 patients with adenomas who underwent endoscopic resection, 41 ERCPs were performed. In all patients a stent was placed in the main PD except for 1 patient with a recurrent neoplasm after surgical resection and a gaping PD orifice, and 1 patient (of 2) with pancreas divisum. A biliary stent was required in only 3 patients. One complication occurred in the 13 patients (8%) over a total of 41 procedures. This patient had pancreas divisum and it was not possible to insert a stent into the ventral PD. Mild pancreatitis developed and 2 additional days of hospitalization were required. He had FAP, and adenomatous polyps had been removed from both the major and minor papillae. Although a stent was placed in the minor papilla, the lack of a stent in the ventral duct presumably contributed to the development of pancreatitis.

One hundred eight ERCPs were performed in the 41 patients in the series for a range of purposes including diagnosis, palliation of malignant biliary obstruction, and resection. In 1 patient with severe cholangitis and a liver abscess, extension of a benign adenoma into both the biliary and pancreatic ducts was noted at the initial ERCP. Biliary sphincterotomy was performed preoperatively for drainage. This resulted in moderately severe postsphincterotomy bleeding (transfusion of 7 units packed red cells). He subsequently underwent elective pancreatoduodenectomy and staged liver resection without complication.

Including the single episode of pancreatitis after endoscopic resection noted above, complications occurred in 2 of 41 patients (4.9%) or 2 of 108 ERCPs (1.9%). There were no other episodes of post-ERCP bleeding, perforation, or cholangitis. No patient required surgery for a complication, and there were no procedure-related deaths.

Among the 12 patients in whom adenomas were eradicated, there have been no recurrences over a mean follow-up of 19 months (range 2-66). Based on surveillance biopsy specimens obtained after eradication of the adenomas, there have been no recurrences at the time of the latest follow-up.
culation, no patient has been found to have underlying cancer, and none has had a cancer develop during the follow-up period. No strictures of the biliary or PD orifices were noted. Minor changes in the main PD side branches were occasionally noted and attributed to PD stent placement.

**DISCUSSION**

As endoscopic technology improves and emphasis shifts toward less invasive treatments, endoscopic management of benign ampullary neoplasms has become more popular. However, complication rates as high as 20%\(^1\) and some deaths\(^10\) have tempered enthusiasm for this approach. In the series of Ponchon et al.,\(^10\) 1 of 16 electrosurgical snare resections was complicated by arterial bleeding, and 3 of 47 sphincterotomies were also complicated by hemorrhage. In addition, 2 episodes of pancreatitis occurred among their 52 patients. Of greatest concern were infectious complications: there were 4 episodes of cholangitis and 1 of septic pancreatitis. Two patients died of septic shock, and surgery or percutaneous drainage was needed in the other 3. In the series of Binmoeller et al.\(^11\) of 25 carefully selected patients with adenomas alone, there were 2 episodes of postpapillectomy bleeding and 3 of pancreatitis, for an overall complication rate of 20%. No patient required operative management of a complication, and there were no procedure-related deaths.

The overall complication rate in the present series was lower than that of other published series. This may be attributable to methodological aspects that differ from those published previously.

First, biductal sphincterotomy with PD stent placement is carried out before resection. In our experience, placing a PD stent after resection can be extremely difficult because the orifice is hidden in the coagulum in the base of the neoplasm. Furthermore, preresection stent placement may protect the PD orifice during subsequent electrosurgical excision and thermal ablation of the base. Indeed, the 1 patient who had pancreatitis develop in our series had pancreas divisum, and a ventral duct stent could not be placed. If further electrosurgical snare resection or ablation is needed at the second ERCP, it can be done with the original stent still in place, thereby protecting the PD.

Second, the sphincterotomies are extended onto normal duodenal tissue to assist with drainage after polyectomy. A biliary stent can be placed if there is a question of inadequate bile duct decompression or delayed drainage of contrast. There were no episodes of post-ERCP cholangitis or septic pancreatitis in our series.

Third, injection of a dilute solution of epinephrine (1:20,000) is used routinely to separate the neoplasm from the muscularis propria before resection. This may prevent unnecessary resections because inability to elevate the lesion is predictive of invasion, and it may also decrease the risk of bleeding. The only patient in our series who had significant bleeding (after sphincterotomy alone) did not have epinephrine injection because invasion of the ducts precluded resection. Injection of saline solution alone might be equally effective for both elevating the neoplasm and preventing bleeding, but this has never been studied in prospective, randomized fashion.

Fourth, routine preresection placement of a PD stent necessitates piecemeal polyectomy. Although this may make complete removal of the papillary lesion more difficult at the initial ERCP, piecemeal resection may decrease the chance of a perforation by lowering the risk of accidental inclusion of deeper tissues in the snared specimen. Additional procedures to effect complete removal of the lesion are justified by the low complication rate.

Postpolyectomy strictures of the main pancreatic or biliary ductal orifices were not encountered in our series despite aggressive snare excision and thermal ablation, sometimes repeatedly, with an argon plasma beam. The generous length of the biliary sphincterotomy, carried onto normal duodenal mucosa where possible, undoubtedly contributed to the lack of stricturing. Likewise, routine PD sphincterotomy and stent placement maintained patency of the PD orifice during thermal ablation.

Recurrence of tumors after endoscopic therapy has also been problematic. In the series of Ponchon et al.,\(^10\) 11 patients underwent endoscopic therapy with curative intent with only 1 recurrence. However, 6 of 25 adenomas (24%) recurred in the series of Binmoeller et al.\(^11\) Endoscopic management failed in 1 of these cases and the patient ultimately required surgery. The total number of ERCPs was not reported.

With our technique of piecemeal resection, some residual polyp is often left behind after the initial ERCP, and the short-term “recurrence” rate is expected to be high. Only 3 of 13 adenomas resected endoscopically were completely removed after 1 ERCP (Table 1). However, our technique is really a staged resection. PD stent placement facilitates the liberal use of thermal ablation, which may have contributed to the low recurrence/failure rate. There were no recurrences in our series, and no patient was found to have cancer develop over a mean follow-up period of 19 months. This demonstrates that complete removal of these neoplasms is possible despite resection in a staged fashion.

It has been proposed that reliance on endoscopic features alone is insufficient for discrimination of
benign and malignant neoplasms. However, these investigators used endoscopic appearance and forceps biopsies to establish the “endoscopic” diagnosis. Although they used ancillary imaging techniques, they make no mention of the fluoroscopic evaluation of the biliary or pancreatic ducts. In the setting of a papillary mass, distal pancreatic or common bile duct strictures are predictive of invasive cancer. Thus, the accurate diagnosis of malignancy will be compromised if ductal architecture is ignored. Furthermore, these investigators did not use submucosal saline solution injection as a test of invasiveness.

That no cancers were found in resection specimens, or developed in any of our endoscopically treated patients during follow-up, suggests that the negative predictive value (the ability to exclude cancer) is high for our technique. Moreover no patient referred for surgery for a suspected malignant lesion was found to have a benign lesion by histopathologic evaluation of a resection specimen, indicating that the positive predictive value for malignancy is high as well. Indeed, cancer was confirmed by endoscopic biopsy or surgery in 13 of 15 patients (87%) in whom cancer was suspected, with the remaining 2 patients unable to undergo surgery to confirm the suspected diagnosis. Further studies are needed with additional patients to confirm that endoscopic appearance, ductal architecture, and ability to elevate the lesion by submucosal injection are reliable indicators of malignancy.

EUS has been used to augment ERCP and conventional imaging techniques in the staging of carcinoma of the major duodenal papilla. EUS appears to be most useful for determination of tumor size and extent, vascular involvement, and regional lymph node involvement. Intraductal US shows promise in the evaluation of depth of penetration of papillary cancers. However, EUS cannot reliably distinguish benign from malignant lesions, and estimates of invasion are substantially influenced by peripapillary inflammation when endoscopic manipulations such sphincterotomy have been performed prior to EUS.

EUS was not routinely used in the evaluation of our patients. Our greatest concern was the distinction between benign and malignant neoplasms, for which the performance of EUS is poor. In 2 of 4 patients who underwent EUS, the tumor was overstaged. Our suspicion is that local invasion can be more accurately predicted by careful evaluation of the radiographic appearance of the distal bile and pancreatic ducts, and by the behavior of the lesion in response to saline solution injection. It may be that EUS, although a useful adjunct, is not strictly necessary. Further research is needed to determine the exact role of EUS in this controversial area.

Twelve of the 13 patients with adenomas selected to undergo endoscopic treatment ultimately had complete resection of their lesions, an endoscopic success rate of 92%. This compares favorably with that of other series. It is unclear whether there are certain factors that predispose some patients to persistence of adenomas, whereas eradication is successful in others. Further research is needed in this area.

Our data support the conclusion that adenomas of the major duodenal papilla can be reliably distinguished from malignant lesions and can be successfully treated endoscopically with a low complication rate if certain procedural precautions are observed. These include the routine use of biductal sphincterotomy, PD stent placement before resection, elevation of the lesion by epinephrine injection, and piecemeal resection. Larger studies with long-term follow-up are needed to further validate these points.

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REFERENCES


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