Tumors of the major duodenal papilla

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A wide variety of tumors arise at the major duodenal papilla. The special significance of these lesions is that they represent a less serious prognosis for patients compared with that for other peripapillary neoplasms.1 However, cure depends on correct diagnosis at an early stage. Endoscopy is the most valuable of the available imaging methods because it provides not only direct visualization of the lesion but often a tissue diagnosis as well. Moreover, because the major duodenal papilla is encountered during routine upper endoscopy, albeit only partially seen in most cases, it is important to recognize and understand the characteristic endoscopic findings of papillary tumors. In addition, endoscopy now plays an important role in the treatment of these tumors.

BENIGN TUMORS

A wide array of benign tumors arise at the major papilla including the following pathologic types: adenoma, lipoma, fibroma, lymphangioma, leiomyoma, and hamartoma.2 Heretofore, benign papillary tumors were regarded as rare. However, with the growing use of endoscopy, especially the use of side-viewing instruments and ERCP, these lesions are being recognized more and more often. Of the various types of benign tumors, adenoma is clinically the most important because this lesion is premalignant.

Adenoma

Adenoma is the most common benign tumor of the major duodenal papilla.3 It is classified histopathologically as tubular, villous, or tubulovillous depending on microscopic architecture.4 Papillary adenomas are premalignant with the villous type having the highest potential for malignant transformation. The evidence for this derives almost entirely from the frequent detection of elements of benign adenoma within malignant tumors and the presence of foci of carcinoma within adenomas that are for the most part benign. An analogy is frequently drawn between papillary adenoma and carcinoma and the widely accepted adenoma-carcinoma sequence for colonic adenoma and carcinoma.5-8

Clinical findings

Symptoms of benign papillary adenoma include biliary colic and obstructive jaundice. Because of obstruction of the pancreatic duct, recurrent pancreatitis may also occur.2,9 Occult GI bleeding is relatively common,9 but overt bleeding and duodenal obstruction are rare. Abnormal liver function tests (an increase in serum alkaline phosphatase (ALP) or γ-glutamyl transpeptidase (GTP) on a screening profile of laboratory tests may be the only manifestation of a benign papillary tumor.10 Essentially, the symptoms and signs of benign papillary tumors are not much different from those associated with the malignant variety. The triad of intermittent painless jaundice, anemia, and a palpable, large gallbladder is relatively specific for papillary carcinoma; however, this triad occurs in less than 10% of patients with papillary carcinoma.

Diagnosis

Identification of early-stage papillary tumors requires appropriate levels of clinical suspicion and aggressiveness in pursuing the diagnosis. Prompt evaluation of patients with jaundice offers the opportunity for an early diagnosis. Conventional transabdominal US is often useful in the initial evaluation of patients who present with abdominal pain and/or jaundice; dilated intrahepatic and extrahepatic bile ducts are usually readily evident. However, a major limitation of US is the technically inadequate examination, which occurs in 15% to 20% of patients. The advantages include the ease and availability of the examination, lack of radiation exposure, and relatively low cost. CT can detect a peripapillary mass if it is at least 2 cm in size and also provides important information as to the level of biliary obstruction with respect to the pancreatic parenchyma; when a pancreatic mass is not evident, the obstruction is likely to be at the papilla. With biliary obstruction caused by papillary tumors, the dilated portion of the bile duct typically includes the pancreatic segment proximal to the papilla. Intravenous and oral contrast-enhanced spiral (helical) CT is currently the optimal imaging technique.
for evaluation of the peripapillary area. However, CT and US often do not provide an exact diagnosis, especially if the tumor is small.\textsuperscript{10,11} The role of magnetic resonance imaging, with or without gadolinium enhancement, in the evaluation of papillary lesions is currently under investigation.

Endoscopy, the main diagnostic procedure for papillary tumors, accurately localizes the lesion and provides biopsy confirmation. Magnetic resonance cholangiopancreatography (MRCP) has become competitive with diagnostic ERCP in a variety of pancreatobiliary diseases.\textsuperscript{11,12} The role of MRCP in patients with an obstruction at the level of the papilla, however, has not been studied adequately. Endoscopic examination has several obvious advantages over MRCP in these patients inasmuch as it allows direct visualization and tissue sampling.\textsuperscript{13} Because of the nonspecific nature of the symptoms caused by papillary tumors, the paucity of physical findings, and the possibility of other disorders that produce similar signs and symptoms, it is essential to adopt a systemic approach to the diagnosis of papillary tumors.

**Endoscopic findings**

There are no extensive endoscopic descriptions of benign tumors of the major papilla, but there is no reason to believe that any one of these has unique endoscopic features. At endoscopy, the papilla is generally enlarged in the case of adenoma. The enlargement may be symmetrical with preservation of the normal configuration of the papilla. The overlying mucosa frequently has a discolored granular appearance but without ulcer or ulcer.\textsuperscript{14,15} Moreover, the evenness of granularity of the mucosa also helps to distinguish benign adenoma from cancer (Fig. 1). Also, vital dye staining, as with methylene blue or indigocarmine, creates contrast between the granular and normal mucosa, and may therefore be of assistance in distinguishing adenoma from cancer. The surface of the papillary adenoma may be smooth and it is soft in consistency, which may allow relatively easy cannulation of papillary orifice. A cauliflower-like, lobulated sessile polypoid mass without ulcer or erosion is the characteristic endoscopic appearance of a villous adenoma of the papilla.\textsuperscript{16}

Adenoma of the major papilla may harbor carcinoma.\textsuperscript{17} Indeed, up to 50\% of villous adenomas arising at the papilla contain foci of adenocarcinoma at the time of diagnosis.\textsuperscript{7} The presence of malignancy is likely when there is surface nodularity, increased friability, and spontaneous bleeding during endoscopic examination\textsuperscript{14,18} (Fig. 2). Most studies to date have not demonstrated a clear correlation between size and malignant change.\textsuperscript{19,20} Malignant transformation is frequently focal. Therefore, it is impossible to be certain that a lesion is benign by examination of standard forceps biopsy specimens alone; these represent only a small portion of the superficial mucosa and are not representative of the overall histology of the lesion. The use of a brush to obtain cytologic specimens may also be helpful; however, interpretation still has the difficulty of distinguishing severe dysplasia from invasive carcinoma. More invasive methods of procuring tissue specimens will sometimes be required such as obtaining biopsy specimens after endoscopic sphincterotomy, using a large forceps, or performing a snare excision of a portion of the tumor.\textsuperscript{15,21-23}
Although endoscopy is the most sensitive and specific method for the diagnosis of papillary tumors, endoscopic diagnosis has several important caveats.\textsuperscript{14} First, the major papilla is seen only in part with a forward-viewing endoscope so that complete evaluation almost always requires the use of a side-viewing duodenoscope. At endoscopy, a side-viewing instrument is essential for proper visualization and access to the papilla; one half of adenomas that are grossly evident are missed when the examination is conducted with an end-viewing instrument alone.\textsuperscript{24} Second, the endoscopic appearance of papillary tumors varies from minor enlargement and/or deformity of the papilla, to a polypoid lesion that is not obviously malignant, to an ulcerated tumor mass that is certainly cancerous. In clinical practice, papillary tumors are missed in a certain percentage of cases, even in patients who undergo examination with a side-viewing duodenoscope.\textsuperscript{25} Third, standard endoscopic biopsy specimens from the surface of papillary tumors, and even specimens obtained by using special techniques, may not reveal malignancy.\textsuperscript{22,26,27} This problem with endoscopic biopsy specimens is so significant that negative findings can never be considered unequivocal proof that cancer is not present.

**Familial adenomatous polyposis**

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease characterized by the development of innumerable adenomas in the large intestine.\textsuperscript{28} FAP and the Gardner variant of this syndrome involve the upper GI tract much more frequently than previously recognized. The major papilla is a common site of extracolonic adenoma.\textsuperscript{29} A recent study found an accumulative lifetime incidence for duodenal polyps of 97%.\textsuperscript{30} Duodenal adenomas in patients with FAP tend to be multiple and are predominantly found in the second portion of the duodenum, especially the peripapillary region (Fig. 3).\textsuperscript{31,32} Peripapillary adenomas, defined as adenomatous lesions arising on or within 2 cm of the major papilla, occur almost invariably in patients with FAP.\textsuperscript{33,34} Peripapillary adenomas, defined as adenomatous lesions arising on or within 2 cm of the major papilla, occur almost invariably in patients with FAP.\textsuperscript{33,34} Recently published data\textsuperscript{35} clearly demonstrate progression of FAP-associated peripapillary adenomas in terms of size, number, and histologic features. The peripapillary region is second only to the colorectum as a site of malignancy in patients with FAP. Compared with the general population, the relative risk of cancer arising in the major papilla is 123.\textsuperscript{36} After colectomy, peripapillary carcinoma is the most common malignancy, occurring in 4.5% to 8.5% of patients.\textsuperscript{37-39} One result of prophylactic colectomy is that peripapillary carcinoma is now the leading cause of death in FAP.\textsuperscript{40-43} Because peripapillary adenomas are premalignant, histologic surveillance and removal of these lesions therefore appear to be justified.\textsuperscript{44,45}

**Treatment**

Although there is uniform agreement that papillary adenomas should be resected, opinions differ as to the optimal method of excision. Regardless of the type of procedure, however, complete removal is mandatory.\textsuperscript{2,46,47} Papillary adenomas can be excised surgically or endoscopically. The surgical options include transduodenal local excision and radical pancreateoduodenectomy.\textsuperscript{2,14} Snare papillectomy (or “ampullectomy”) and thermal ablation by laser, argon plasma coagulation, monopolar or bipolar electrosurgery comprise the endoscopic methods.\textsuperscript{4,47,48} Traditionally, the conventional and main method of treatment has been surgery.\textsuperscript{49} Although available data are not extensive, local surgical excision is assumed to have a lower operative morbidity and mortality but with a high risk of recurrence. Pancreateoduodenectomy has a high risk of complications but a small probability of recurrence.\textsuperscript{49-52} Endoscopic therapy can be performed successfully with the patient under conscious sedation alone, even on an outpatient basis. The trend in the management of papillary adenomas has been toward increasing use of endoscopic therapy, especially snare papillectomy. This can be attributed to a general increase in the use of endoscopic mucosal resection in the GI tract, with improvements in techniques as experience has accumulated.\textsuperscript{37} Endoscopic snare papillectomy is a clinically effective alternative when performed by an experienced endoscopist.\textsuperscript{44,48} Furthermore, evidence is accumulating to indicate that endoscopic resection, abla-

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**Figure 3.** Duodenoscopic view of multiple duodenal adenomas in patient with familial adenomatous polyposis. Polyp in 12 o’clock position arises from the major papilla.
tion, or both are the treatments of choice for papillary adenomas. However, optimal timing of surveillance and the best methods of ablation have not been established.\(^4\)

The unresolved issue in the management of peripapillary adenomas in patients with FAP is whether these patients can be managed predominantly by endoscopy and whether surgery can be avoided. The outcome for patients managed by surgical excision has been disappointing.\(^5\) There is a high rate of recurrence and progression of the disease, which are points that favor interventional endoscopic approaches. There is accumulating evidence that endoscopic resection, ablation, or both, when performed by experienced endoscopists, are safe and effective treatments for peripapillary adenomas in patients with FAP.\(^4\)\(^-\)\(^5\) However, a randomized controlled study comparing endoscopic and surgical therapies is needed.

Patients with FAP should undergo surveillance duodenoscopy on a regular basis. Even when the papilla appears normal on gross examination, biopsy specimens should be obtained because of the high frequency of adenomatous change.\(^5\) However, the clinical significance of microscopic adenomatous change has not been established.

**Endoscopic snare papillectomy.** When clinical and endoscopic findings, endoscopic forceps biopsies, and EUS findings suggest a benign papillary adenoma that is confined to the mucosal layer, there is an increasing trend toward endoscopic snare papillectomy as a first treatment rather than surgical therapy. Again, the effectiveness and safety of papillectomy relates directly to the experience of the endoscopist. If histopathologic assessment of the resection specimen reveals complete removal, therapy is complete and the patient should undergo regular endoscope surveillance including biopsies to rule out recurrence. If histopathologic assessment indicates that the excision was incomplete, snare papillectomy is repeated. When this is not feasible, a thermal ablation technique can be used. If the resection specimen contains superficial (in situ) carcinoma but the margin is uninvolved by cancer, resection is thought to be complete. In this case, the current acceptable practice is to closely observe the patient rather than to resort to imme-

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**Figure 4.** Endoscopic views of snare papillectomy. **A,** Submucosal injection of saline solution. **B,** Polypoid appearance after saline solution injection. **C,** Papilla grasped by snare. **D,** Appearance after papillectomy.
diat surgery. However, if the resection specimen contains invasive carcinoma, surgery is required, the operation of choice being pancreatoduodenectomy. A decision for definitive surgery must be based on excision and histopathologic assessment of the entire tumor.\textsuperscript{14,15,44}  

\textbf{Indications.} The indications for endoscopic snare papillectomy of papillary adenomas as suggested by Binmoeller et al.\textsuperscript{54} are as follows: (1) size less than 4 cm; (2) no evidence for malignancy based on endoscopic appearance (regular margin, no ulceration, soft consistency); (3) benign histologic findings (minimum 6 forceps biopsies); and (4) absence of intraductal involvement as demonstrated by ERCP. However, these criteria are currently seen as flexible; for example, tumors larger than 4 cm have been completely resected piecemeal fashion during sequential procedures. When there are small adenomatous tissue remnants, even after multiple sessions of snare papillectomy, thermal ablation can be used to obliterate remaining adenoma.\textsuperscript{4,44,54}  

Adenomas thought to contain only superficial or early-stage carcinoma have also been removed by endoscopic snare papillectomy, ablation, or both.\textsuperscript{55-58} Endoscopic snare papillectomy remains contraindicated if the tumor extends into the biliary or pancreatic duct; however, ERCP is not always possible because of difficulty in cannulating the papillary orifice blocked by tumor. EUS is therefore being used increasingly in an attempt to evaluate and visualize intraductal extension of the tumor as well as depth of invasion.\textsuperscript{47,59-63}  

\textbf{Technique.} Papillectomy is performed by snare resection by using blended electrosurgical current. Compared with other sites in the GI tract, endoscopic snare papillectomy seems hazardous because of the thinness of the duodenal wall. However, the mucosa is, in fact, easily lifted and separated from the underlying muscle layer by injection of saline solution into the submucosa (Fig. 4). Lesions that cannot be resected en bloc can usually be resected piecemeal.\textsuperscript{55}  

\textbf{Outcomes.} The series of Zadorova et al.\textsuperscript{48} included 16 patients with confirmed adenoma of the major duodenal papilla. Postendoscopic snare papillectomy complications included bleeding in 2 patients and acute pancreatitis in another 2 patients. All complications resolved with conservative management and there were no procedure-related deaths. Duodenoscopy was performed at 6 and 12 months after papillectomy and yearly thereafter. The tumor recurred in 3 patients (19%, benign adenoma in all cases). Two patients were treated again endoscopically, and 1 patient with extension of tumor into the distal common bile duct underwent surgery. In the series of Binmoeller et al.,\textsuperscript{54} 23 patients underwent complete endoscopic excision of benign papillary adenomas; 6 (26%) had recurrences at a median follow-up of 37 months. Biopsy specimens revealed these recurrences to be benign adenomas in all cases. Recurrences were evident within 1 year of papillectomy in all but 1 patient.  

The complications of endoscopic snare papillectomy are bleeding, perforation, bile duct stricture, and pancreatitis. Among these, the main concern has been the potential risk for pancreatitis. To prevent pancreatitis, Fukushima et al.,\textsuperscript{57} in a preliminary report of their experience with 75 cases, advocate placement of a pancreatic stent in all patients after snare papillectomy. However, another group of investigators, in a fully reported series, advocated the use of pancreatic stents only when the pancreatic duct fails to drain after papillectomy.\textsuperscript{44,54} Our practice is similar; insertion of a pancreatic duct stent is reserved for cases in which the pancreatic orifice is difficult to identify upon conclusion of the resection procedure. By using this approach, no episodes of pancreatitis were encountered in the 8 patients in whom papillectomy was performed (Kim MH, unpublished data). A prospective, randomized, controlled study comparing the efficacy of pancreatic stent placement in patients undergoing papillectomy is needed. As with the pancreatic duct, the scarring associated with papillectomy may evoke stricturing of the bile duct and a stent should also be inserted in the bile duct when the orifice cannot be identified. In our experience, papillary stenosis combined with choledocholithiasis occurred in a patient at 3 months after endoscopic papillectomy (Kim MH, unpublished observation).  

\textbf{Endoscopic thermal ablation.} Laser photoablation of adenomas of the papilla was reported in 8 patients by Lambert et al.\textsuperscript{4} Tumors were successfully ablated in 7 patients; recurrence was observed in 1 patient. Although thermal ablation methods with laser, argon plasma coagulation, and electrosurgical monopolar or bipolar current appear to be effective, they all have the risk of undertreatment of lesions that may harbor carcinoma. Thermal ablation methods have the further disadvantage that complete histopathologic evaluation of the entire lesion is impossible. Moreover, photoablation with the NY:YAG laser may produce deep tissue injury with resulting duodenal stenosis. At present, thermal ablation is used mostly as a complementary technique when snare papillectomy is unsuccessful or incomplete.  

\textbf{Surveillance.} When a papillary adenoma has been treated endoscopically, whether by resection or thermal ablation, close follow-up is mandatory, including duodenoscopy and biopsies, because of the
possibility of recurrence. Surveillance duodenoscopy is usually performed at 1, 6, and 12 months after removal of an adenoma and yearly thereafter. If a recurrence is suspected, multiple biopsy specimens are obtained and ERCP is repeated. Indications for surgery during follow-up are histologic documentation of carcinoma and suspected intraductal extension of the tumor.

MALIGNANT TUMORS

The primary malignant tumors of the major duodenal papilla are carcinoma, lymphoma, and neuroendocrine tumor. Metastatic tumors include malignant melanoma, hypernephroma, and lymphoma. Adenocarcinoma is the most common malignant tumor.

Carcinoma

Malignant neoplasms of the distal common bile duct, head of pancreas, major duodenal papilla, and duodenum are known collectively as peripapillary cancers. The clinical presentations of the several types of neoplasm are in most cases similar. However, compared with other peripapillary cancers, carcinoma of the major duodenal papilla has a high rate of resectability and a better prognosis. The 5-year survival rate after resection is substantially better than that for the other peripapillary neoplasms. This may, in part, be due to the earlier development of symptoms and presentation related to anatomic location, but also in part to the fact that adenocarcinoma of the papilla tends histologically to be more differentiated. Primary papillary cancer can eventually involve the pancreas, bile duct, and adjacent duodenum as the disease progresses. Unfortunately, carcinoma of the major duodenal papilla is grouped with other peripapillary tumors in many surgical series, making interpretation of results difficult.

It is sometimes difficult to distinguish between a papillary cancer and the other peripapillary malignancies by endoscopic findings alone. Invasion of the duodenum by pancreatic cancer is rarely confined to the major duodenal papilla; there is usually involvement of the surrounding duodenal mucosa as well. However, the ulcerative type of papillary cancer in particular can be difficult to distinguish from duodenal invasion by pancreatic cancer. In a majority of the latter cases, narrowing of the duodenal lumen or extrinsic compression of the duodenal wall will be evident. In addition, an asymmetric mass in the papillary region with an erosive or ulcerative change in the surrounding duodenal mucosa is another finding of duodenal invasion by pancreatic cancer. Primary duodenal cancer usually produces severe luminal narrowing of the second portion of the duodenum. The most narrowed segment is usually ulcerated and hemorrhagic, and frequently the endoscope cannot be passed beyond the involved area. Even with the most careful and astute duodenoscopic assessment, it may not be possible to determine whether a malignant tumor arises from the papilla, pancreas, or duodenum, and additional imaging modalities such as US, CT, or ERCP may be needed.

Clinical findings. Most patients with cancer of the major duodenal papilla present with jaundice, the most common symptom. However, many patients have constitutional symptoms such as malaise and/or anorexia for several weeks or months before the appearance of jaundice. It is relatively common that jaundice is intermittent because these tumors undergo necrosis and sloughing. Some patients are not icteric and complain only of itching during the early stages of the disease. Abdominal pain without jaundice and anemia in the absence of overt GI bleeding is common. In advanced cases, there may be weight loss. Patients with papillary cancer may present with cholangitis, although this is uncommon. In some instances, the clinical picture is that of pancreatitis. Laboratory tests may reveal an increase in serum ALP, GGT, amylase, and/or lipase. The patient with early-stage papillary cancer may be asymptomatic with dilatation of bile duct, pancreatic duct, or both seen on imaging studies; this may be the only clue to early detection. Gallstones are found in 40% to 50% of the cases. Bile stasis, assumed to be present with malignant obstruction, may also contribute to gallstone formation. The presence of bile duct calculi has frequently resulted in errors in diagnosis inasmuch as the clinical manifestations of papillary carcinoma and choleodocholithiasis are similar.

Diagnosis. There is a wide range in the endoscopic appearance of papillary carcinoma so that endoscopic assessment alone is not entirely reliable for diagnosis; non-neoplastic disorders of the papilla may also have endoscopic findings that mimic carcinoma. Thus, endoscopic biopsy specimens are always required for diagnosis. Papillary cancer can be divided into 3 types according to gross morphology: polypoid, ulcerative (Fig. 5), and mixed (both polypoid and ulcerated). The polypoid type is subdivided into exposed (exophytic) and nonexposed (intramural) types according to whether the overlying mucosa is cancerous. Lymph node metastases are least common with the intramural type (24%) and most common with the ulcerating type (69%).

Enlargement of the papilla with an uneven granular or nodular appearance of the overlying mucosa
associated with an erosion or an ulcer is a typical endoscopic finding in papillary carcinoma.\textsuperscript{14,56} In the ulcerative type, the ulcer typically has a nodular base and irregular margins. Forceps biopsy specimens from the edge of the ulcer usually provide a diagnosis of malignancy. Examination with a conventional forward-viewing endoscopic examination may be sufficient to detect the exophytic or ulcerative types of papillary carcinoma.

The nonexposed (intramural) type of papillary carcinoma is one of the most difficult types to diagnose with an endoscope because it is covered with normal duodenal mucosa. Intramural tumors usually do not alter the architecture of the papilla, but a prominent infundibulum is often present and indicates a tumorous intramural lesion.\textsuperscript{56} Because conventional endoscopic biopsies alone cannot obtain cancer cells from a nonexposed-type papillary carcinoma, it is necessary that biopsy specimens be obtained after endoscopic sphincterotomy (Fig. 6A and B).\textsuperscript{56,71} Endoscopic sphincterotomy may be helpful in the detection of intramural papillary tumor, especially in cases of common bile duct dilatation in the absence of gallstones or in cases of unexplained pancreatic duct dilatation.

Procurement of endoscopic biopsy specimens after endoscopic sphincterotomy, however, presents certain problems.\textsuperscript{23} Bleeding is frequent; coagulated and/or necrotic tissue fragments present in the specimens may make interpretation difficult. The electrocautery current used in performing the sphincterotomy may induce microscopic changes that may be misinterpreted.\textsuperscript{23} When these problems arise, specimens should be obtained again, but after a lapse of at least 10 days during which swelling and inflammation will subside.\textsuperscript{56}

The duodenoscopic findings of an enlarged, bulging papilla with normal overlying mucosa can be seen with an impacted stone, nonexposed intramural tumor, or choledochocele. These diagnoses will be established, respectively, by endoscopic sphincterotomy and stone extraction, biopsies of the tumor, and characteristic cholangiographic findings.\textsuperscript{72,73}

**Treatment.** Pancreaticoduodenectomy (Whipple operation) and pylorus-preserving pancreatoduodenectomy (PPPD) remain the operations of choice in the treatment of malignant papillary tumors.\textsuperscript{18} The conventional Whipple operation includes resection of the gastric antrum. As a result, postgastrectomy syndromes, such as dumping, may occur and can lead to malnutrition. PPPD narrows the extent of resection and avoids these problems. Thus, PPPD is replacing the Whipple operation as the standard operation for papillary carcinoma.
In a minority of patients with no evidence of unresectability based on preoperative staging, surgical exploration nevertheless reveals unanticipated metastatic tumor beyond the area to be resected or vascular involvement that precludes curative resection. In these situations operative palliation is appropriate, including biliary decompression by creation of a biliary-enteric anastomosis. For patients found to have unresectable disease, surgical intervention for palliation is generally not indicated. Placement of a plastic or metallic expandable biliary stent through the papillary region is the standard approach for palliation of patients with jaundice. With respect to survival, the results of endoscopic and surgical palliation do not differ substantially. Patients for whom operative risk is high may be treated by endoscopic snare papillotomy if EUS reveals the lesion to be confined to the mucosal layer.

Neuroendocrine tumors

Primary neuroendocrine tumors of the major duodenal papilla are extremely rare. As with neuroendocrine tumors in the respiratory tract and other segments of the GI tract, those arising at the papilla have a histologic spectrum of progressively increasing malignancy from low-grade carcinoid to high-grade small cell undifferentiated carcinomas. There is no uniformity in the nomenclature used to describe these neoplasms when they arise in the papilla or in the remainder of the GI tract. Chejfec et al. recommended use of the term “neuroendocrine tumor” to encompass all GI epithelial neoplasms with neuroendocrine features with qualification according to hormonal staining characteristics. All intermediate and small cell neoplasms that exhibit malignant behavior are designated neuroendocrine carcinoma; if such behavior is not evident, the term “benign neuroendocrine tumors” or “carcinoid” is used. The differentiation between benign papillary carcinoid and neuroendocrine carcinoma, either small cell or non-small cell type, is based on histologic and cytologic differences. Differences in immunohistochemical staining may be of assistance. It is important to recognize the range of differentiation of neuroendocrine tumors.

The symptoms caused by neuroendocrine tumors arising in the papilla are similar to those caused by other tumors in this location and include melena, recurrent acute pancreatitis, and abdominal pain. Fluctuating jaundice, anemia, or episodic fever and chills are relatively common. There is a strong association between carcinoid tumors of the major duodenal papilla and neurofibromatosis (von Recklinghausen’s disease).

Endoscopic descriptions of neuroendocrine tumors are extremely sparse. These tumors have no distinguishing features, and the few available endoscopic descriptions mention only a round or oval tumor mass, sometimes with ulceration (Fig. 7A and B). Endoscopically, they often resemble tumors arising in the submucosa. Carcinoid tumor is the most common primary papillary neuroendocrine tumor. In contrast to carcinoid tumors arising in the jejunum and ileum, the clinical and laboratory findings of the carcinoid syndrome are absent in patients with papillary carcinoids.

The natural history of papillary carcinoid is not well established. These tumors often present at an early stage because of their location; obstructive symptoms arise when the tumor is relatively small.
It has therefore been postulated that the prognosis is generally good, and one review of 71 published cases found only 4 deaths caused by papillary carcinoid. However, despite reports emphasizing the slow growth and benign nature of this tumor, more aggressive behavior is possible. Of 8 patients followed at one institution, 3 died within 2 years of diagnosis. All 3 had extensive metastatic disease that was not responsive to aggressive chemotherapy.

The standard treatment for peripapillary carcinoid tumor is surgery. There have been several reports of endoscopic treatment of small carcinoid tumors arising from duodenum. Tumors smaller than 2 cm in diameter that do not invade the muscular layer of the gut are likely to be benign, as demonstrated by 5-year follow-up in a series of 99 patients. The important criteria for endoscopic resection of papillary carcinoid tumors are size, depth of invasion, and histopathologic type of the tumor. Endoscopic resection may be appropriate in selected patients.

Other malignant tumors

Histopathologically, malignant tumors of the major duodenal papilla are almost exclusively adenocarcinoma. Rarely, lymphoma (Fig. 8) may involve the papilla, and tumors with mucinous and squamous elements have been found. Carcinomas metastatic to the major papilla include malignant melanoma, hypernephroma, or lymphoma.

Hyperplasia of Brunner’s glands or adenofibromatosis of the major duodenal papilla may mimic malignant tumors clinically, radiologically, and endoscopically. These pseudotumors should be included in the differential diagnosis of papillary tumors. A definite diagnosis of pseudotumor is usually made by surgical resection; surgical resection also appears to provide the best management option for symptomatic cases of pseudotumors.

SUMMARY

The early discovery of papillary tumors is based on a high index of suspicion together with meticulous endoscopic examination of the papilla. Endoscopists should therefore be familiar with the characteristic endoscopic findings for tumors that arise at the papilla. A habit of close observation of the major duodenal papilla during routine upper endoscopy is highly recommended. Detection of subtle mucosal changes and guided biopsies are crucial for the detection of early-stage cancer and correct differentiation of the various papillary lesions.

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