Assessment of Duodenal Adenomas and Strategies for Curative Therapy

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Keywords

Duodenal adenoma · Endoscopy · Familial adenomatous polyposis · Surgery

Abstract

Background: The increasing incidence of duodenal neoplasm has underlined different methods of resection depending on the clinical presentation, endoscopic features and histopathology. In this comprehensive review, we systematically describe the current knowledge concerning the diagnosis and management of duodenal adenomas (DAs) and discuss data considering all possible therapeutic approaches. **Summary:** Among a variety of duodenal lesions, including neuroendocrine tumors and gastrointestinal stromal tumors, DAs present precancerous lesions of the duodenal papilla or non-ampullary region necessitating removal. DAs can occur sporadically (SDA) as rare lesions or relatively common in polyposis syndromes. The endoscopic resections of DA are associated with an increased degree of complexity due to distinctive anatomical properties of the duodenal wall, luminal diameter and the presence of ampulla with pancreatic and biliary drainage. The endoscopic techniques including cold snare polypectomy (CSP), endoscopic mucosal resection (EMR), and argon plasma coagulation ablation are suggested to be less invasive than surgical treatment, associated with shorter hospital stay and lower cost.

According to the current clinical practice, surgery has been accepted as standard therapeutic approach in familial adenomatous polyposis patients with severe polyposis or DA not amenable to endoscopic resection. **Key Messages:** The strategy for endoscopic resection of DAs depends on the lesion size, morphology, location, and histopathology findings. Small adenomas are most frequently diagnosed and removed by standard CSP techniques, while large laterally spreading lesions and ampullary adenoma are referred for EMR or endoscopic papillectomy respectively. Screening colonoscopy is indicated in patients with SDA. Additional studies for new endoscopic strategies and techniques for curative therapy of DAs are needed to refine future management decisions. Complete resection of DA is considered curative, but nevertheless, long-term endoscopic follow-up is still required to detect and treat any recurrent arising lesions.

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Introduction

The earliest mention of duodenal carcinoma in medical literature was done by Hamburger in 1746 [1]. Pery [2] described a villous tumor for the first time in 1893, while a year later Pic et al. [3] classified duodenal tumors as suprapapillary, peripapillary, and infrapapillary. The historical background on surgical proce-

Table 1. Surveillance data on duodenal adenoma malignancy in FAP patients

	Number of points			Spigelman stage	Risk of cancer* (15 year follow-up), %
	1	2	2	0	0.7*
No. of polyps	1–4	5–20	>20	1	
Polyp size, mm	1–4	5–10	>10	2	
Histology	Tubular	Tubulovillosus	Villous	3	
Dysplasia	Milde	Moderate	Severe	4	7–34.3**

Spigelman stage (points): 0 (0); 1 (1–4); 2 (5–6); 3 (7–8), 4 (9–12).
 * Bülow et al. [14].
 ** Serrano et al. [13].
 FAP, familial adenomatous polyposis.

dures of duodenal tumors extend from the late 19th and early 20th century including the first successful surgical resection of an ampullary mass by WS Halstad and pancreaticoduodenectomy performed by Whipple in 1935 [4, 5].

Duodenal adenomas (DAs) are the most frequently encountered polyps of the duodenum, at times associated with genetic syndromes and predominantly classified according to their location as non-ampullary or ampullary. In addition to these classic adenomas, Brunner's gland adenomas and villous adenomas are also described [6–9]. Due to their malignant potential, their endoscopic or surgical resection is mandatory. Nevertheless, anatomical features of the duodenum with thin, vascular walls, narrow luminal diameter and pancreatic and biliary drainage add to the increased complexity of endoscopic procedures [6, 7, 10].

Sporadic DAs (SDAs) are rare, with estimated prevalence of non-ampullary SDA being less than 0.5% and ampullary being between 0.04 and 0.12% [6, 10]. Most SDAs are flat or sessile solitary lesions with pearly villi surface and occur on the posterior or lateral walls of the descending duodenum [6, 11]. The low incidence of tumor appearance in the duodenum could be explained by an interplay of protective factors as secretory immunoglobulins, small intestinal hydroxylases and higher level of benzyl peroxidase, alkaline environment, rapid transit of liquid bowel contents, and lack of bacteria [6, 9].

DAs are relatively common in up to 90% of patients with familial adenomatous polyposis (FAP) and estimated in 17–25% patients with MUTYH-associated polyposis (MAP) [6, 12]. The distribution of DAs in FAP, mostly found in D2, distal or adjacent to the papilla or in the duodenal cap, could be due to mucosal exposure to bile

flow growth-promoting factors [13, 14]. The risk of duodenal adenomatosis in FAP for developing carcinoma is stratified according to the Spigelman 5 grade classification system based on the number and size of the lesions, histologic features, and severity of dysplasia (Table 1) [15]. Furthermore, patients with determined MAP have an estimated lifetime duodenal cancer risk of up to 4%. Analogous to FAP, factors promoting adenoma progression in MAP are increasing adenoma size and villous histological type [12, 16].

The management challenges of DAs include the risk of procedural complications due to anatomical configuration of duodenal walls and demanding endoscopic identification as a result of similarly displaying normal villiform mucosa. This review article discusses the principles of endoscopic detection and diagnosis of DAs, effective and safe methods of resection, procedural complications, and specific follow-up recommendations.

Results

DAs are mostly asymptomatic, detected incidentally during gastroscopy for other gastrointestinal indications [6, 17]. Early detection of DAs has been upgraded by newly introduced high-definition endoscopes, digital chromoendoscopy like narrow band imaging (NBI), and conventional dye-based chromoendoscopy [18–21]. An unimpaired examination of duodenum is achievable using a side-viewing duodenoscope and transparent distal cap attached to the gastroscope [8, 20].

The emerging evidence for the prediction of advanced histology relies upon a variety of factors including the size of DA larger than 1 cm, the extent of involved duodenal

circumference, and the relation to the ampulla of Vater [19, 22–27]. Features of submucosa invasion including a depressed component within the lesion (Paris 0–IIc), type 5 Kudo pit pattern, surface ulceration, and non-lifting sign after submucosal injection emphasize the therapeutic management of DA [22–25].

Although ampullary DAs are investigated using a side-viewing duodenoscope, biopsies for histopathological confirmation are recommended [6, 27, 28]. Additionally, brush cytology, polymerase chain reaction analysis of DNA for K-ras gene mutations, immunohistochemical staining (p53 tumor suppressor gene; other panels composed of CK7, CK20, CDX2, MUC1, and MUC2), microRNA expression, and flow cytometry for assessment of aneuploidy have been suggested for clinical practice but still remain investigational [8]. So far, no definitive guideline has been established regarding the surveillance consensus or lesion size of ampullary adenomas for exclusive surgical removal.

The imaging role of endoscopic retrograde cholangiopancreatography (ERCP), endoscopic ultrasound (EUS), and intraductal ultrasound can provide the assessment of intraductal extension (IDE) of the adenoma [8]. In addition, magnetic resonance cholangiopancreatography is also used to exclude IDE and pancreas divisum [29, 30]. EUS is needed for local tumor staging, mostly reserved for lesion larger than 2 cm and those endoscopically suspicious for cancer with overall accuracy up to 90% [30–33]. ERCP should be performed to evaluate IDE to locate the pancreatic/biliary orifice during the placement of stents following papillectomy [34].

Endoscopic papillectomy is usually achieved by snare endoscopy and electrocautery [8]. Endoscopic treatment for ampullary adenoma with IDE can encompass balloon dilatation of the ductal orifice/trawls with a balloon catheter or placement of fully covered self-expanding metal stent into the distal common bile duct after papillectomy to facilitate exposing the adenomatous tissue and assisting in subsequent resection [35, 36].

The endoscopic approach to non-ampullary lesions by conventional polypectomy techniques include cold snare polypectomy (CSP) for small lesions (<10 mm) and piecemeal endoscopic mucosal resection (EMR) for larger lesions [37, 39]. Endoscopic submucosal dissection (ESD) is considered contraindicated in the duodenum due to high risk of delayed perforation estimated up to 30% [40, 41].

Surgical treatment is recommended in cases of DA larger than 2 cm and in cases with the presence of severe dysplasia, suspicious carcinomatous infiltration, or when there is

recurrence after complete endoscopic resection [37, 38]. According to the recent management studies from 2017, ampullary DAs should be primarily treated with endoscopic papillectomy, except in cases with suspected areas of invasive malignancy, IDE larger than 1 cm or patient's preference [6]. Previous surgical methods including pancreaticoduodenectomy or surgical ampullectomy by longitudinal duodenotomy were more expensive and associated with higher risk of morbidity and mortality [42, 43].

Discussion/Conclusion

DAs are reported in higher incidence than in the previous decade due to the increasing prevalence of gastroscopy. The incidence of SDA differ in range between 1.5 and 4.6% according to the large retrospective study conducted by Höchter et al. [44] and prospective studies of Jepsen et al. [45] and Jung et al. [10].

The potential progression of DA to carcinoma is in a sequence similar to colonic adenomas [11, 46]. The evolution from DA with low-grade dysplasia to adenocarcinoma can last up to 20 years [46, 47]. Meanwhile, larger lesions than 2 cm and with a high degree of dysplasia can indicate more invasive disease. Ampullary DAs have higher risk of developing cancer compared to sporadic non-ampullary lesions [48]. Additionally, there is established association between the presence of a DA and colorectal neoplasia; thus, screening colonoscopy is also recommended for these patients [49].

FAP patients with Spigelman stage IV have the highest risk for malignancy, with a reported study of 218 patients over a 30-year follow-up period and estimated risk for developing duodenal adenocarcinoma of 2.1% at 15 years [13]. The reported data on risk progression to cancer in MAP patients is less inclusive. Recently, Walton et al. [16] conducted a study on MAP patients with duodenal polyposis found in 34% of cases. Analogous to FAP, the increasing size of DA and villous change led to the progression to carcinoma. Nevertheless, restricted data are available on DAs in a minority of patients with multiple colorectal adenomas without germline argon plasma coagulation (APC) or MUTH mutation, underlying the need for appropriate upper gastrointestinal screening [50]. Endoscopic surveillance guidelines and recommendations for duodenal polyposis in FAP and MAP are similar. Gastroscopy screening with forward-viewing gastroscope and side-viewing duodenoscope should be initiated at the time of onset of colonic polyps or age between 25 and 30 years. Upper endoscopy should be repeated every

6 months to 4 years depending on the Spigelman level [12].

Recently, chemoprevention has been introduced as a strategy to control premalignant lesions using pharmaceutical drugs, natural agents, or dietary supplements [14]. Current studies in FAP patients are evaluating the efficacy of this approach at delaying polyp progression and preventing the recurrence of adenoma after colectomy. Similarly, data on the use of the non-steroidal anti-inflammatory drugs, cyclooxygenase non-selective inhibitor sulindac and of the selective cyclooxygenase-2 inhibitors celecoxib and rofecoxib may be beneficial to polyposis regression in the future [14]. Nevertheless, potential cardiovascular and renal side effects, in addition to the risk of gastrointestinal bleeding, must be taken into account.

According to the study by Kiesslich et al. [21], conventional dye-based chromoendoscopy with indigo carmine detected significantly more duodenal lesions than standard white light endoscopy. However, dye-based chromoendoscopy is time consuming and undependable in differentiating DAs from non-adenomas [27]. A small pilot study highlighted magnification endoscopy with NBI in differentiating adenomatous from non-adenomatous ampullary lesions based upon villi aspect as follows: type I oval-shaped indicated inflammatory or hyperplastic changes, while type 2 pinecone-shaped and type III irregular non-structured predicted adenoma and adenocarcinoma [18]. Yet, Lopez-Ceron et al. [19] study reported examination with NBI with no increased detection of DA compared with high definition WLE. Although NBI appears to be a practical diagnostic modality, further data are needed. Still, the optimal imaging approach for the detection of DA and diagnosis remains to be determined.

Endoscopic imaging alone is not sufficient for accurately distinguishing adenomatous pathology. Use of histopathology, magnetic resonance cholangiopancreatography, EUS and computed tomography (CT) is recommended. Nevertheless, EUS is superior to CT and magnetic resonance imaging for local tumor staging in cases of suspected cancer [6, 30, 31]. Yet, magnetic resonance imaging is more precise for nodal staging and CT is more sensitive for detecting metastases. Additionally, compared with surgical pathology, the sensitivity and specificity of EUS and ERCP are the complementary for IDE [51].

Historically, surgical options including laparoscopic-assisted endoluminal surgery, laparoscopic polyp excision, duodenectomy and pancreaticoduodenectomy have been acknowledged as the standard treatment for duode-

nal neoplasms. Despite highly effective surgical procedures, life-threatening complications associated with perioperative morbidity requiring intensive care management, mortality, and long-term effect on patients' quality of life have been reported [6, 17]. Endoscopic resection as a less invasive approach has been introduced as an effective alternative.

EMR is suggested as an effective treatment approach for DAs larger than 1 cm in size [6, 22–25]. The EMR technique includes the separation of the mucosa and submucosa from the layer of muscularis propria by the injection of a dye-based solution, subsequently to piecemeal snare resection [22–25]. In a prospective study by Klein et al. [24], SDA ≥ 1 cm treated with EMR were completely resected in 96% of cases and procedural bleeding occurred in 43% with a recurrence rate of 14% on the first surveillance endoscopy, following repeated endoscopic resection. After 36 months of follow-up, more than 90% were free from adenomas. Bartel et al. [7] reviewed post-EMR patients and pancreas-preserving partial duodenectomy for sporadic non-ampullary duodenal neoplasm. While en bloc resection with negative margins was performed in all surgical resections, it was achieved in 53% of EMR specimens. Predictably, EMR compared to surgery had less hemorrhage and shorter procedure time and hospital stay. Neoplasia recurrence was not associated with polyp size and positive resection margin [7]. Overall, EMR is indicated for DAs ≤ 20 mm in size and less than 33% of the duodenal circumference. Nevertheless, long-term surveillance after EMR due to high recurrence rate is needed.

Data on CSP in treating DA has reveal the efficiency of this method even in patients with significant polyposis [6, 37]. Although APC was often used as an ablative method in FAP, CSP is shown to be a more effective approach. According to recent evidence, APC has shown to be ineffective in the treatment of detected residual adenomas. For resecting polyps larger than 1 cm in size, the process of electrocautery is frequently followed. Nevertheless, the “hot-snare” polypectomy technique is linked with a risk of delayed bleeding, serositis, or perforation due to thermal injury to the intestinal wall. The evidence for effective piecemeal CSP outcomes is derived from the resection of colonic adenomas, while recent studies showed a technically favorable risk profile for the resection of DAs [6, 11]. The use of other resection methods for DA including band-assisted mucosectomy, cap-assisted suction, and cut technique is limited due to insufficient prospective data.

Fig. 1. Management of ampullary DAs. EUS, endoscopic ultrasound; ERCP, endoscopic retrograde cholangiopancreatography.

Fig. 2. Management of non-ampullary DAs. EUS, endoscopic ultrasound.

Differentiating DAs from other types of duodenal polyps is essential for an optimal therapeutic approach. The management algorithm of ampullary and non-ampullary DA is shown in Figures 1 and 2. Procedural complications for advance endoscopic resection in the duodenum reach up to 25% for non-ampullary adenoma and approximately 35% for ampullary lesions. The most frequent adverse events are bleeding, perforation, and pancreatitis. Compared with surgical procedures, ER has lower morbidity and mortality rate. An individualized approach is needed in coordination with the experience of an endoscopist in terms of the size of the polyp, availability of investigative tools, and the patient's comorbidities.

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Authors Contribution

A.P.-M.: wrote and designed the review article. S.D.: wrote the article and performed the review of the literature. M.S.L.: analyzed current novelty data. M.K. and T.M.: provided guidance in this research.

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