Prevention and Management of Periampullary Tumors in Familial Adenomatous Polyposis

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Abstract

Familial adenomatosis polyposis (FAP) is one of two well described forms of hereditary colorectal cancer. The primary cause of death from this syndrome is colorectal cancer which develops usually by the fifth decade of life. The overall survival of FAP was significantly improved by screening by genetic testing and endoscopy with prophylactic surgery. Almost all patients with FAP develop duodenal polyposis most of which occurs in periampullary. The second leading cause of death in FAP is duodenal adenocarcinoma. Between 5% and 10% of FAP patients die from duodenal cancer, usually periampullary in origin. Therefore, I will discuss the clinicopathological features, management and prevention of duodenal neoplasma in patients with FAP.

Keywords

Familial Adenomatous Polyposis (FAP), Duodenal Adenocarcinoma, Spigelman Classification, Pancreas-Preserving Total Duodenectomy (PPTD)

Subject Areas: Gastroenterology & Hepatology

1. Introduction

Familial adenomatosis polyposis (FAP) is an autosomal dominant inherited polyposis syndrome caused by a germline mutation in the adenomatous polyposis coli (APC) gene on chromosome 5q21 [1]. The disease is characterized by the early onset of hundreds to thousands of adenomas throughout the colon. Colorectal polyposis develops by age 15 years in 50% and age 35 years in 95% of patients. The lifetime risk of colorectal carcinoma is virtually 100% if patients are not treated by colectomy [2].

Early prophylactic colorectal surgery has changed the prognosis of patients with FAP, and now desmoid tumors and periampullary duodenal cancers are the most common causes of death in these patients, rather than
After the colorectal, the duodenum is the second most affected site of polyp development in FAP [4]. Duodenal adenoma can be found in 30% - 70% of FAP patients [5] and the lifetime risk of these lesions approaches 100% [6]. Duodenal/periampullary adenocarcinoma is the main cause of death in FAP after colorectal cancer. These patients have a 100 - 330 fold higher risk of duodenal cancer compared with the general population [7]. Duodenal cancer is rare in the population, with an incidence of 0.01% - 0.04%. Estimates of the cumulative risk of developing duodenal cancer in FAP range from 4% at age 70 years to 10% at age 60 years [8].

This review will discuss the clinicopathological features, management and prevention of duodenal neoplasia in patients with FAP.

1.1. The Problem

Patients with FAP develop adenoma throughout the gastrointestinal tract. Polyps can be found throughout the duodenum, but the second and third proportion and the periampullary region are the most commonly affected sites. This pattern probably reflects exposure of duodenal mucosa to bile acids, suggesting a role for these compounds in duodenal carcinogenesis [9]. Most polyps in the duodenum are adenomas, on the contrary polyps in the stomach are usually benign nonadenomatous fundic gland lesions.

The risk of duodenal cancer in FAP is increased more than 100 times that of the general population. For example, of 222 FAP patients who had a total colectomy and ileorectal anastomosis at St Mark’s hospital from 1948 to 1999, duodenal cancer accounted for 11 death in their group [10].

In 1989, Spigelman et al published an endoscopic and histological classification system for evaluation of the severity of duodenal adenomatosis [11]; the Spigelman classification has become the gold standard in duodenal adenomatosis. The classification describes five (0 - IV) stages. Patients are accumulated for number, size, histology and severity of dysplasia of polyps (Table 1) [12]. Stage I is mild disease whereas stage III - IV is sever duodenal polyposis. About 70% - 80% of FAP patients have stage II or III, and 20% - 30% have stage 1 or stage IV [11].

In colonic polyposis, specific mutations in the APC gene can allow clinicians to predict the severity of disease, for example patients with mutations in codon 1309 are likely to have dense colonic polyposis and early development of colorectal cancer [13] whereas patients with mutations at the extreme ends of the gene are likely to have a milder form of disease [14]. Mutations downstream from codon 1051 seem to be associated with severe periampullary lesions.

1.2. Screening

Once the diagnosis of FAP is made, patients should undergo regular upper gastrointestinal endoscopy to detect duodenal disease. In general, duodenal cancers appear to develop about 10 years after the development of colorectal cancers, so it seems reasonable not to start screening until the patients reach the age of 25.

Recommendations concerning the age of initiation of upper tract surveillance are not uniform. The NCCN (National Comprehensive Cancer Net Work) recommended a baseline upper gastrointestinal endoscopic examination at 25 - 30 years of age [15]. In general, recommendations include stage 0, I every 5 years; stage II every 3 years; stage III every 12 months with consideration for surgery; and stage IV strongly consider surgery (Table 2).

| Table 1. Spigelman Classification for duodenal polyposis in familial adenomatous polyposis. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Points                         | 0               | 1               | 2               | 3               |
| Polyp number                   | 0               | 1 - 4           | 5 - 20          | >20             |
| Polyp size (mm)                | N/A             | 1 - 4           | 5 - 10          | >10             |
| Histology                      | normal          | tubular         | tubulovillous   | villous         |
| Dysplasia                      | none            | mild            | moderate        | severe          |

0 points = Stage 0; 1 - 4 points = Stage I; 5 - 6 points = Stage II; 7 - 8 points = Stage III; 9 - 12 points = Stage IV.
Table 2. Recommendations for management of duodenal polyposis in familial adenomatous polyposis in relation to Spigelman classification.

<table>
<thead>
<tr>
<th>Spigelman stage</th>
<th>Recommended protocol</th>
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<tr>
<td></td>
<td>Endoscopic frequency</td>
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<tr>
<td>Stage 0</td>
<td>5 years</td>
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<td>Stage II</td>
<td>3 years</td>
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<tr>
<td>Stage III</td>
<td>12 months</td>
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<td>Stage IV</td>
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2. Treatment

2.1. Medical Treatment

Cyclooxygenase-2 (COX2) is known to be an important mediator of colorectal neoplasia progression but expression of COX2 has not been extensively studied in duodenal or upper gastrointestinal adenomas. Shirvani et al. [16] found COX2 expression in normal duodenum and esophagus and significantly higher levels in esophageal dysplastic tissues. They showed that COX2 expression in Barrett’s esophagus increased in response to pulses of acid or bile salts.

Non-steroidal anti-inflammatory drugs (NSAIDs) regress colorectal adenoma in FAP patients. The value of these agents for duodenal polyposis regression is unclear.

Phillips et al. [17] investigated the effect of specific COX2 inhibitor celecoxib on duodenal polyp number and total polyp area. They found a 14% decrease in polyp number after six months of celecoxib 800 mg/day (n = 32) compared with placebo (n = 17). Winde et al. [18] compared effects of sulindac suppositories (n = 28) with placebo (n = 10) on rectal and upper gastrointestinal adenoma in patients that underwent colectomy. They found complete or partial reversion of rectal polyps but no effects on duodenal and papillary adenomas.

Drug therapy of duodenal adenomas would be appropriate treatment. But most published papers find no significant effect of NSAIDs or COX2 inhibitors on duodenal adenoma regression. Duodenal mucosa is exposed to different environment factors than that in the colon. Low pH and bile acids may affect control of growth and malignant potential of duodenal tumors [19].

2.2. Endoscopic Treatment

Endoscopic treatment options for duodenal lesions include snare excision, thermal ablation, argon plasma coagulation, and photodynamic therapy (PDT). Most reports of endoscopic therapy use snare excision. However, duodenal adenomas are often flat non-polypoid structures and, therefore, difficult to remove using conventional snare excision. Endoscopic treatment is usually insufficient to guarantee a polyp-free duodenum and fraught with complications. Recurrence rates of adenomatous tissue in duodenum of FAP patients treated endoscopically range from 50% to 100% [20] [21] and the treatment is associated with a high complication rate (perforation, haemorrhage, pancreatitis) (17%). The value of endoscopic treatment of patients with stage II and III is to delay major intervention (e.g., Whipple’s operation).

3. Surgical Treatment

Complete duodenectomy is the only definitive means of preventing duodenal cancer. For patients who have dysplasia, adenocarcinoma, or diffuse disease for which endoscopic therapy is impractical, surgical intervention is warranted.

Pancreaticoduodenectomy (PD) is established and well described for malignant pancreatic and duodenal disease and also has traditionally been the surgical procedure of choice for diffuse polyposis [22]. In an effort to reduce the extent of resection in focal peripancreatic disease, several surgeons employed local resection or ampullectomy [23]. Local duodenal polyp resection has been well described in FAP, but is also associated with a high recurrence rate and significant morbidity [24]. Pancreas-Preserving Total Duodenectomy (PPTD) consists of resection of the entire duodenum with preservation of the head of the pancreas. Chung et al. [25] described...
PPTD in 1995 for four patients with FAP and one patient with duodenal trauma. It is indicated in neoplastic or preneoplastic lesions that diffusely affect the duodenal mucosa, but with no potential for extension to the regional lymph nodes, and it should not be performed in patients with confirmed cancer. The most frequent indication of PPTD is familial adenomatous polyposis of the duodenum (Spigelman IV or III with severe dysplasia). PPTD is a challenging procedure requiring refined surgical technique and very through and detailed knowledge of the peripancreatic anatomy. PPTD has many advantages compared to conventional PD. PPTD removes the duodenal mucosa in its entirety while preserving a more normal upper gut function. Moreover, PPTD decreases the number of reconstructive anastomosis from three to two, prevents the risk of anastomosis for Familial Adenomatous Polyposis.

4. Conclusion
Duodenal polyposis and adenocarcinoma have emerged as major problems in patients with FAP. Although most patients eventually develop duodenal polyps, the polyps have lower potential for malignant change compared with colonic polyps. Duodenal adenomas seem less responsive to chemoprevention with NSAIDs than colonic counterparts. The main treatment for duodenal polyposis is frequent surveillance and targeted endoscopic treatment, adjusted by severity of duodenal lesions. But in patients with severe disease, duodenectomy may be necessary.

References


**Abbreviations**

Familial adenomatous polyposis (FAP), Adenomatous polyposis coli (APC), National Comprehensive Cancer Net Work (NCCN), Cyclooxygenase-2 (COX2), Non-steroidal anti-inflammatory drugs (NSAIDs), Photodyanotic therapy (PDT), Panreaticoduodenectomy (PD), Pancreas-Preserving Total Duodenectomy (PPTD).