学　位　論　文

Characteristics and Clinical Outcomes of Duodenal Neoplasia in Japanese Patients With Familial Adenomatous Polyposis

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Characteristics and Clinical Outcomes of Duodenal Neoplasia in Japanese Patients With Familial Adenomatous Polyposis

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Background: After colorectal cancer and desmoid tumors, duodenal adenocarcinoma is the next leading cause of death in familial adenomatous polyposis (FAP) patients, but it has not been thoroughly investigated.

Patients and Methods: To investigate the clinical course of duodenal neoplasia, including adenoma and cancer, we investigated 77 Japanese FAP patients treated at the National Cancer Center Hospital, Tokyo, Japan. We evaluated the clinicopathologic features, Spigelman severity score, and management of duodenal neoplasms. Data were acquired from a prospectively enrolled database.

Results: Fifty-one (66%) of the 77 FAP patients had duodenal neoplasia during this observational period, and 47 of 51 patients had extra-ampulla duodenal neoplasia; 42 (58%) had duodenal neoplasms (extra-ampulla), 4 had duodenal adenomas with high-grade dysplasia (HGD), and 1 had invasive carcinoma. Among the 45 patients (extra-ampulla) with duodenal adenoma with HGD or low-grade dysplasia, 8 (18%) patients were treated using endoscopic resection (ER). During the short observation period, ER was performed only in HGD cases. None of the patients died from duodenal neoplasia. In total, during the surveillance period, duodenal HGD was detected in 5 (63%) of 8 patients graded as Spigelman stage IV; HGD was not detected in stage 0 (n = 33), I (n = 0), II (n = 12), or III (n = 20) patients.

Conclusions: Short-interval endoscopic surveillance and appropriate ER may help prevent duodenal invasive carcinoma. In addition, there was little development of invasive carcinoma during the follow-up. The Spigelman classification is beneficial for the risk assessment of duodenal neoplasia in Japanese FAP patients.

Key Words: familial adenomatous polyposis, adenocarcinoma, adenoma, management, duodenal neoplasia, high-grade dysplasia

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Familial adenomatous polyposis (FAP) is an autosomal dominant disease, characterized by multiple colorectal adenomatous polyps (polyposis), is caused by truncating mutations in the adenomatous polyposis coli (*APC*) gene,[1] and is responsible for ≤1% of all colorectal cancers (CRCs). Colorectal adenomatous polyposis normally appears in approximately 85% of FAP patients at 20 years of age; if these lesions are not treated, the prevalence rates of CRC of FAP at 40 years of age and over a lifetime are almost 50% and 100%, respectively. Because of the high penetration of CRC, prophylactic total colectomy is recommended as a standard treatment to reduce the mortality rate.[2] In many FAP patients, extracolonic neoplastic lesions are also present, especially gastric and duodenal neoplasms, desmoid, thyroid, and brain tumors, osteomas, and epidermoid cysts. CRC accounts for 61% to 69% of deaths in FAP patients; after CRC and desmoid tumors, the third most common cause of mortality is duodenal carcinoma (including ampullary carcinoma), accounting for approximately 3% of all deaths in these patients.[3–5]

The standardization of prophylactic total colectomy in FAP patients has led to decreased CRC-related mortality. However, the clinical progression and treatment of non-ampullary duodenal neoplasms, including adenomas and cancers, have been rarely investigated in FAP patients. In western countries, the Spigelman classification is used for the clinical staging of duodenal neoplasms. The Spigelman disease stage should be used to determine the esophagogastroduodenoscopy (EGD) surveillance interval and treatment. Although the growth of duodenal dysplasia is slow and highly nonsymptomatic,[6] periodic EGD surveillance and appropriate, timely treatment are necessary. The EGD surveillance interval is recommended to be every 4 to 5 years for stage 0 lesions, 2 to 5 years for stage I lesions, 2 to 3 years for stage II lesions, and 6 months to 2 years for stage III lesions.[7,8] For patients with stage IV lesions; advanced, atypical adenomas; or high-density polyposis, surgical assessment or EGD surveillance every 6 to 12 months is recommended. Given this context, the aim of our study was to investigate the clinical features of duodenal neoplasia in Japanese FAP patients at our institution.

PATIENTS AND METHODS

This study involved FAP patients diagnosed by both colonoscopy and EGD between 1997 and 2014 at the National Cancer Center Hospital, Tokyo, Japan. A medical diagnosis of FAP was dependent on clinical findings or genetic analysis.[2] Clinical findings were characterized by the presence of approximately 100 or more adenomas distributed throughout the colon and rectum or the presence of 100 or fewer multiple adenomas in addition to a family history of FAP.

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We retrospectively investigated the clinicopathologic features, endoscopic findings, clinical outcomes, management, and Spigelman classification of the duodenal neoplasms.[9] A histopathologic examination was performed in accordance with the recommendations of the Vienna classification[10]; all specimens were reviewed by at least 2 pathologists with expertise in gastrointestinal pathology. We converted pathologic data from Japanese to western criteria; for example, a noninvasive carcinoma in Japanese criteria is referred to as an adenoma with high-grade dysplasia (HGD), and invasive cancer in Japanese criteria is referred to as a submucosal carcinoma.

We recommended annual EGD surveillance for FAP patients, in principle, and this procedure was routinely performed by 10 experienced endoscopists using forward-viewing endoscopes (Olympus Medical Systems, Tokyo, Japan). Usually, EGD was performed using white-light imaging, and chromoendoscopy was conducted using narrow-band imaging; side-viewing EGD was additionally used when it was difficult to observe the ampulla. In addition, we performed biopsies on neoplastic lesions >10 mm in size or on those that had morphologically changed since the last EGD. We treated all cases of biopsy-confirmed HGD or carcinoma, regardless of their size. Although some studies have described the treatment of all adenomas, regardless of size, we chose to only observe single lesions <10 mm in size; any lesion >10 mm was subjected to endoscopic resection (ER). In cases of multiple neoplasms, those <10 mm were observed, those 10 to 19 mm were considered for possible ER, and those ≥20 mm were definitely indicated for ER. Ampullary tumors <10 mm in size were observed without biopsy. ER of duodenal adenomas included polypectomy, endoscopic mucosal resection (EMR), or endoscopic submucosal dissection; however, endoscopic submucosal dissection in the duodenum carries a high risk of perforation, and comparatively small lesions are often discovered during surveillance. Therefore, EMR was (and is) the primary ER method at our institution.

RESULTS

Overall, 77 FAP patients (50 men and 27 women) with a mean age of 40 ± 14 years were examined during the study period. Regarding the colorectal adenomatous polyp (polyposis) phenotypes, 9 cases (12%) showed the profuse type, which is described as having a "dense, carpet-like" appearance, and 68 cases (88%) showed the classical type, involving adenomatous polyps that are not covered with normal mucosa. Most of the patients underwent surgical treatment of the colorectum, including 65 patients (84%) who had total colectomies and 3 patients who underwent other colectomy procedures (abdominoperineal resection, right hemicolectomy, or sigmoidectomy); only 9 patients were not treated surgically. The mean age of the patients at the time of surgery was 32 ± 10 (range, 18 to 61) years, following a median observational period of 8.5 (range, 0 to 17) years. We verified each patient's family history at his or her initial consultation and at the time of admission for the surgical treatment and/or ER. Fifty-six patients (73%) had a familial history of CRC or FAP; a definitive FAP familial history was confirmed in 41 (53%) of these patients (Table 1).

Duodenal neoplasia was observed in 51 (66%) of the 77 FAP patients; 27 (53%) had neoplasms detected at the baseline EGD, and 24 (47%) had neoplasms detected during surveillance EGD with 4 lesions localized only to the ampullary region. Each ampullary neoplasm of the 4 cases was adenomatous in the biopsy. Thus, in this study, we focused on nonampullary duodenal neoplasms. Specifically, we investigated 47 cases of duodenal lesions, excluding the 4 cases of neoplasms localized to the ampullary region only. We excluded these 4 cases because we focused on nonampullary duodenal neoplasms (Table 3).

TABLE 1. Characteristics of the 77 FAP Patients

Parameters	Value
Age at first EGD (mean ± SD) (y)	40 ± 14
Male/female (n)	50/27
FAP phenotype (profuse/classical) (n)	9/68
Colectomy (n)	
Total colectomy	65
Other	3
None	9
Age at the time of surgery (mean ± SD) (y)	32 ± 10
Family history of FAP (present/absent or unknown)	41/36
Duodenal neoplasm (present/absent)	51/26
Median observation period in years (range)	8.5 (0-17)

EGD indicates esophagogastroduodenoscopy; FAP, familial adenomatous polyposis.

Clinical Background of FAP Patients With Duodenal Neoplasia

The patients included 35 men and 12 women; the mean patient age at the time of the first EGD was 38 ± 13 years. EGDs were performed a median of 12 times (range, 1 to 40); 2 patients were examined only once. EGDs were generally performed at 6- to 12-month intervals [biannually for 11 patients, annually for 33 patients, and less frequently (≥18 mo apart) for 1 patient], but the examination interval did not exceed 24 months for any patient. The median observation period was 10.0 (range, 0 to 17) years, and the mean age at the time of a duodenal neoplasm diagnosis was 40 ± 14 years; the mean age at the time of duodenal HGD (HGD) or invasive cancer diagnosis was 43 ± 14 years (Table 2).

TABLE 2. Clinical Background of FAP Patients With Duodenal Lesions (47 Cases)

Parameters	Value
Age at the first EGD (mean ± SD) (y)	38 ± 13
Male/female (n)	35/12
FAP phenotype (profuse/classical) (n)	6/41
Median number of EGDs (range)	12 (1-40)
Endoscopy interval (n) (mo)	
6	11
12	33
≥18	1
Median observational period (range) (y)	10.0 (0-17)
Age at the time of diagnosis (mean ± SD) (y)	
For duodenal lesions	40 ± 14
For duodenal carcinoma or HGD	43 ± 14

EGD indicates esophagogastroduodenoscopy; FAP, familial adenomatous polyposis; HGD, high-grade dysplasia.

TABLE 3. Endoscopic Findings in Familial Adenomatous Polyposis Patients With Extra-ampullary Duodenal Lesions (47 Cases)

Parameters	Value
Histologic type (dysplastic lesion/cancer) (n)	46/1*
Single/multiple lesions (n)	7/40
Tumor size [median (range)] (mm)	8 (2-30)
Main lesion macroscopic type (n)†	
Protruded (0-I, 0-IIa)	33
Depressed (0-IIc)	12
Mixed (0-IIa + IIc)	2
Location of lesion (n)	
Bulb	1
Second portion	40
Bulb and second portion	6
Ampullary tumors (present/absent) (n)	17/30

*One case of simultaneous onset of cancer and adenoma.
†According to the Paris classification.[11]

Endoscopic Findings of Duodenal Neoplasms in FAP Patients

Thirty-nine patients were diagnosed with adenoma during their first examination, with 1 patient experiencing simultaneous onset of invasive cancer and adenoma. The lesions of 7 patients were detected during follow-up examinations. Seven patients (15%) developed single lesions, and 40 (85%) developed multiple lesions. The median size of the largest tumor was 8 mm (range, 2 to 30 mm), and these tumors were classified according to the Paris classification[11] as type 0 to I [1 case (2%)], type 0 to IIa [32 (68%)], type 0 to IIc [12 (26%)], or type 0 to IIa + IIc [2 (4%)]. The lesions were located only in the duodenal bulb (1 case, 2%) or second portion of the duodenum, including the ampulla (40 cases, 85%). In 6 patients (13%), multiple lesions were observed throughout the duodenum; the coexistence of tiny ampullary tumors was observed in 17 cases (36%). No relationship was found between the incidence of duodenal carcinoma and the surveillance interval (Table 3).

Duodenal Neoplasm Treatment Outcomes

In this investigation, EMR was performed on 7 patients with low-grade dysplasia and 2 patients with HGD. In 1 patient, with both invasive carcinoma and multiple adenomas, pyloric-ring-preserving pancreaticoduodenectomy was performed. EMR was performed on 16 lesions in 9 patients. Fourteen lesions were treated with en bloc resection; 2 lesions required multiple resections. One patient had postoperative bleeding that occurred 2 days after EMR.

Treatment Progression and Long-term Endoscopic Surveillance Follow-up

Among the 46 adenoma patients, except 1 invasive cancer case, 9 lesions were initially treated by EMR because of their size (mean, 14 ± 8 mm; range, 5 to 30 mm), macroscopic type, or patient request; the remaining 37 received follow-up observations (Fig. 1). Two of the 9 EMR-treated patients were found to have metachronous HGD in the second portion of the duodenum after 2 and 3 years, respectively, from the baseline EGD (a different location than for the first EMR) and underwent a subsequent EMR; however, 1 of the 2 patients with HGD died because of rectal cancer and its liver metastasis. For the remaining 7 patients, recurrence of duodenal neoplasms requiring treatment was not observed. In the 37 patients undergoing follow-up observations, 3 were found to have HGD after 1, 8, and 9 years, respectively, from the baseline EGD. These 3 patients were diagnosed with Spigelman classification stage IV lesions during the first EGD; 1 underwent EMR, and the other 2 opted for continued observation for personal reasons (pregnancy or religious conviction) (Fig. 1, Table 4).

During the long-term follow-up investigation, 6 of the 77 FAP patients died (median observation period, 8.5 y). During the investigation of 47 patients with duodenal neoplasia (median observational period, 10 y; range, 0 to 17 y), the survival rate was 96% (45 patients); 1 death resulted from invasive rectal carcinoma with liver metastasis, and 1 death was related to the treatment and occurred during chemotherapy for small intestinal carcinoma. None of the deaths resulted from duodenal neoplasm, and localized recurrence was not observed in the 9 EMR-treated patients.

Investigation of the Spigelman Classification

In this study, we had only 41 cases for which histologic findings were obtained by biopsy or resection of the duodenal neoplasm during the observational period. Other patients who had not undergone a biopsy received a minimum dysplasia and histology score of 1 point. Of the patients with dysplasia, the distribution of Spigelman stages at the initial diagnosis was stage 0 (33 cases), stage I (0 cases), stage II (12 cases), stage III (20 cases), and stage IV (8 cases). Seven of 33 cases diagnosed as stage 0 at the initial EGD showed worsened (stage II) Spigelman scores during the follow-up period. In stage I to III cases, cancer was not detected during the EGD surveillance period; however, HGD was confirmed in 4 of the 8 stage IV patients.

DISCUSSION

In 2 studies, duodenal neoplasms were present in 30% to 90% of FAP patients,[6,7] with the occurrence of dysplasia increasing after the age of 40 years[6]; the lifetime penetrance of duodenal neoplasms approaches 100%.[7,8] In our study of 77 FAP patients, 51 (66%) were confirmed to have duodenal neoplasms, consistent with the reported rate. The incidence of upper gastrointestinal carcinoma in FAP patients is reported to be 4.5%,[8] and the relative risk of duodenal carcinoma, compared with the general population, has been reported to be 330.8.[12] In this study, 5 cases of duodenal HGD were detected within a median observational period of 8.5 years. The median period between HGD detection and the first EGD was 8.5 (range, 0 to 11.9) years.

Previously published studies have suggested that the number of duodenal neoplasms tends to increase during the average 3- to 6-year follow-up period,[13–15] and our investigation revealed 4 cases of HGD during a similar follow-up period. HGD occurred in 4 cases at 1, 8, 8, and 12 years after the initial diagnosis. However, none of the patients died because of duodenal neoplasia during the follow-up, indicating that periodic examination and appropriate treatment might prevent duodenal HGD from becoming invasive cancer. Moreover, although 2 patients opted not to undergo treatment after being diagnosed with duodenal HGD, the lesions did not worsen, and both patients survived over a 1927-day (5.3-year) or 1467-day (4.0-year)

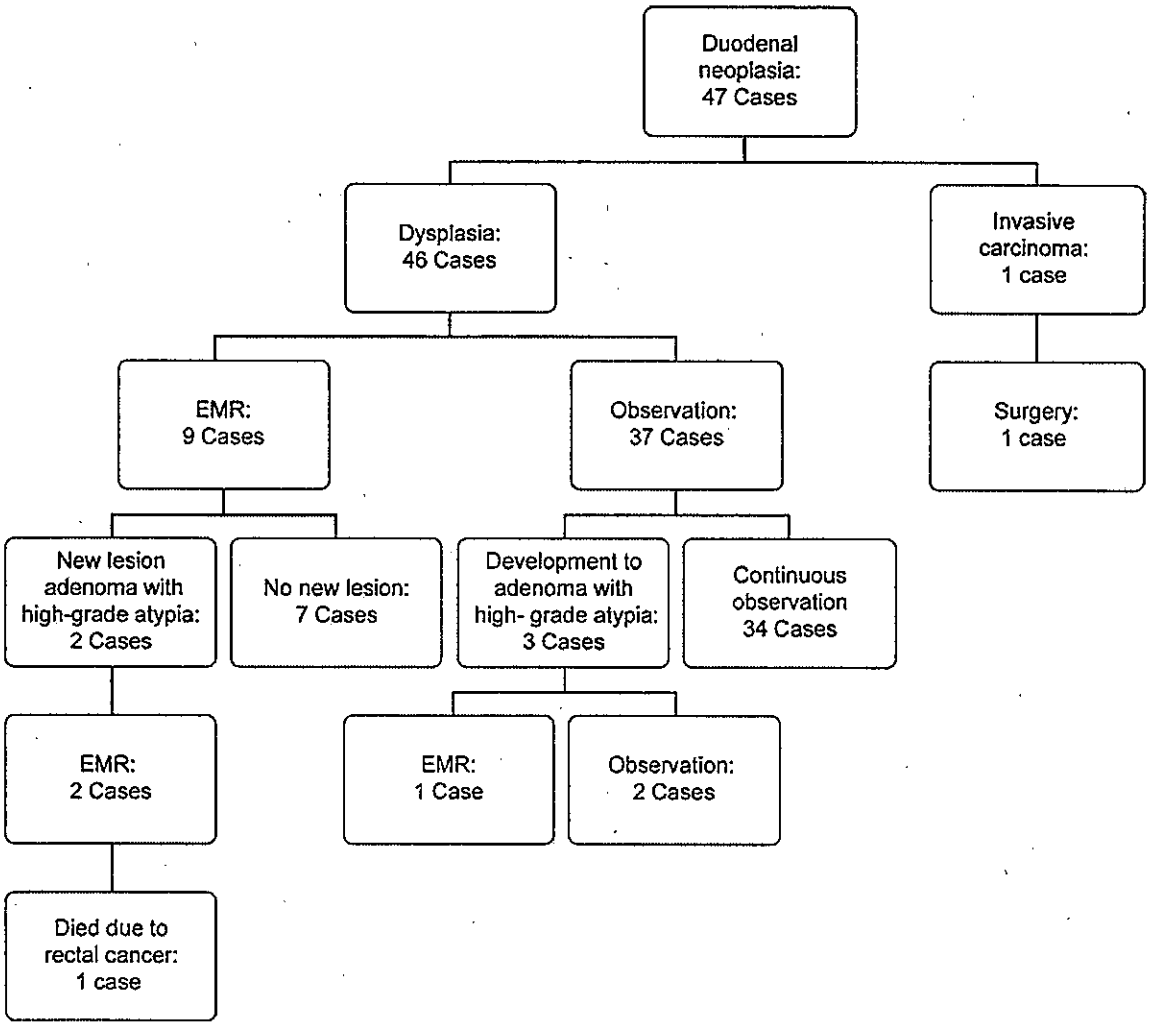

FIGURE 1. Treatment and follow-up of the 41 patients with duodenal neoplasia.[1] Two patients declined treatment because of pregnancy or religious conviction. EMR indicates endoscopic mucosal resection.

postdiagnosis observation period. Thus, the current results suggest the necessity of short-term EGD surveillance intervals and treatment. However, a comparative investigation of endoscopic treatment versus surgical treatment for duodenal neoplastic lesions in FAP patients has not been conducted, and the timing of disease-appropriate treatment remains undetermined.

The growth of duodenal adenomas is slow,[6] although periodic EGD surveillance and treatment are necessary.

TABLE 4. Investigation of Patients With Duodenal Lesions (n=47)

Parameters	Value
Localized relapse (EMR, 9 cases)	0
Survival [n (%)]	45 (96)
Cause of death [n (%)]	
Rectal cancer	1 (2)
Treatment-related death*	1 (2)
Median observation period (range) (y)	10 (0-17)

*Cerebral infarction during chemotherapy for small-intestine carcinoma.
EMR indicates endoscopic mucosal resection.

According to the Spigelman classification of duodenal neoplasia,[9] small, stage I/II polyps are usually treated by ER. If there are a large number of polyps, ER or duodenectomy alone is insufficient.[8] Moreover, several complications are associated with complete ER of stage II/III disease, leading to a 50% to 100% relapse rate.[16] Stage IV lesions have a 7% to 36% chance of becoming cancerous[8,17]; therefore, pancreaticoduodenectomy or pancreas-preserving duodenectomy is indicated. Groves et al[17] investigated 114 FAP patients and confirmed duodenal carcinoma in 6 patients; 4 of the 6 carcinoma patients were diagnosed with stage IV disease at their first examination. In addition, the frequencies of duodenal carcinoma onset at Spigelman stages II, III, and IV have been reported to be 2.3%, 2.4%, and 36.4%, respectively.[17] In our investigation, we found that of 8 patients diagnosed with stage IV disease, 4 (50%) subsequently developed HGD. Although the number of patients was small, these results suggest the usefulness of the Spigelman classification.

Because FAP is associated with a characteristic polyposis phenotype, the disease may be diagnosed clinically; hence, confirmatory genetic analysis is rarely performed. Because genetic testing for the *APC* mutation is not

currently covered under the Japanese national health insurance program, it is only performed in research settings. However, genetic testing needs to be conducted in the future to evaluate genotype-phenotype correlations for duodenal neoplasms.

A major limitation of this study is its retrospective nature. Other drawbacks include disparities in the surveillance duration and some selection bias because some FAP patients do not undergo surveillance EGD. In addition, the lack of biopsies of tiny lesions, particularly those < 10 mm in size, prevented pathologic assessments of those lesions. Finally, the observation period was not sufficiently long to analyze the natural history of duodenal adenomatosis in FAP.

In conclusion, we did not observe any deaths related to duodenal neoplasia in our study, indicating that periodic EGD surveillance and appropriate treatment, based on EGD findings, may prevent duodenal neoplasia from becoming a poor prognostic factor in FAP patients. This retrospective study demonstrated the prevalence of duodenal neoplasms and their approximate clinical course in Japanese FAP patients; the prognosis for duodenal neoplasm patients was comparatively good. In addition, our results suggest that the Spigelman disease severity classification is useful during follow-up observations of duodenal adenomas. Even when neoplasms do not exist in the ampullary region, surveillance for the development of neoplasms in other portions of the duodenum is required according to the Spigelman classification. However, further surveillance and prospective studies are required.

REFERENCES

1. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med.* 2003;348:919–932.
2. Burt RW, Barthel JS, Dunn KB, et al. NCCN clinical practice guidelines in oncology. Colorectal cancer screening. *J Natl Compr Canc Netw.* 2010;8:8–61.
3. Iwama T, Tamura K, Morita T, et al. A clinical overview of familial adenomatous polyposis derived from the database of the Polyposis Registry of Japan. *Int J Clin Oncol.* 2004;9:308–316.
4. Galle TS, Juel K, Bulow S. Causes of death in familial adenomatous polyposis. *Scand J Gastroenterol.* 1999;34:808–812.
5. de Campos FGCM, Perez RO, Imperiale AR, et al. Evaluating causes of death in familial adenomatous polyposis. *J Gastrointest Surg.* 2010;14:1943–1949.
6. Moozar KL, Madlensky L, Berk T, et al. Slow progression of periampullary neoplasia in familial adenomatous polyposis. *J Gastrointest Surg.* 2002;6:831–837. discussion 837.
7. Brosens LAA, Keller JJ, Offerhaus GJ. Prevention and management of duodenal polyps in familial adenomatous polyposis. *Gut.* 2005;54:1034–1043.
8. Bulow S, Bjork J, Christensen IJ. Duodenal adenomatosis in familial adenomatous polyposis. *Gut.* 2004;53:381–386.
9. Spigelman A, Williams CB, Talbot IC, et al. Upper gastrointestinal cancer in patients with familial adenomatous polyposis. *Lancet.* 1989;30:783–785.
10. Schlemper RJ, Riddell RH, Kato Y. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut.* 2000;47:251–255.
11. Participants in the Paris Workshop. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc.* 2003;58(6 Suppl):S3–43.
12. Offerhaus GJ, Giardiello FM, Krush AJ, et al. The risk of upper gastrointestinal cancer in familial adenomatous polyposis. *Gastroenterology.* 1992;102:1980–1982.
13. Nugent KP, Spigelman AD, Williams CB, et al. Surveillance of duodenal polyps in familial adenomatous polyposis: progress report. *J R Soc Med.* 1994;87:704–706.
14. Sawada T, Muto T. Familial adenomatous polyposis: should patients undergo surveillance of the upper gastrointestinal tract? *Endoscopy.* 1995;27:6–11.
15. Bülow S, Alm T, Fausa O, et al. Duodenal adenomatosis in familial adenomatous polyposis. DAF Project Group. *Int J Colorectal Dis.* 1995;10:43–46.
16. Iida M, Yao T, Itoh H, et al. Natural history of duodenal lesions in Japanese patients with familial adenomatosis coli (Gardner's syndrome). *Gastroenterology.* 1989;96:1301–1306.
17. Groves CJ, Saunders BP, Spigelman AD. Duodenal cancer in patients with familial adenomatous polyposis (FAP): results of a 10 year prospective study. *Gut.* 2002;50:636–641.