

Worldwide survey among polyposis registries of surgical management of severe duodenal adenomatosis in familial adenomatous polyposis

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Background: The lifetime risk of developing duodenal cancer in familial adenomatous polyposis (FAP) is about 5 per cent. When and to what extent surgical intervention should be undertaken to prevent death from invasive carcinoma is controversial. The aim of this study was to determine the effectiveness of various surgical treatments for cancer and severe duodenal adenomatosis.

Methods: A questionnaire was mailed to the members of the Leeds Castle Polyposis Group to obtain data on patients with FAP, treated for duodenal cancer or severe duodenal adenomatosis after 1990.

Results: Sixty-nine patients were included. The indication for surgery was invasive cancer in 13 patients, of whom six died from metastatic disease. Fifty-six patients were initially treated for severe duodenal adenomatosis, five (9 per cent) of whom died from metastatic disease ($P = 0.002$). In surviving patients, adenomas recurred after ampullectomy (six of eight, at mean follow-up of 11 months), after duodenotomy with polypectomy (17 of 21, at mean 29 months) and after pancreatoduodenectomy (six of 25, at mean 47 months). None of six patients who underwent a pancreas-sparing duodenectomy had recurrence of adenoma (mean follow-up 11 months).

Conclusion: Surgery for duodenal adenomatosis should take place before endoscopic biopsy reveals invasive cancer. Even after extensive surgical procedures, small bowel adenomas may occur, emphasizing the need for chemoprevention.

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Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant disorder caused by inactivating mutations of the *APC* (adenomatous polyposis coli) gene¹. Most patients with polyposis develop hundreds of colorectal adenomas during their second and third decades of life. Without surgical intervention patients almost inevitably develop colorectal carcinoma by the age of 40–50 years. For this reason prophylactic colectomy is recommended at a young age. Surveillance of families with FAP, generally

coordinated by polyposis registries, has led to a reduction in the incidence of colorectal cancer from 50 to 5 per cent^{2–4}.

Up to 90 per cent of patients with FAP also develop adenomas in the upper gastrointestinal tract, in particular in the duodenum^{5–7}. It is generally accepted that these adenomas also follow the adenoma–carcinoma sequence^{8–12}. Duodenal cancer is the main cause of cancer-related death in patients with FAP who have had prophylactic colectomy^{13,14}. The lifetime risk of

Table 1 Spigelman classification⁷

	1	2	3
No. of polyps	1–4	5–20	> 20
Polyp size (mm)	1–4	5–10	> 10
Histology	Tubular	Tubulovillous	Villous
Dysplasia	Mild	Moderate	Severe

Stage I, 1–4 points; stage II, 5–6 points; stage III, 7–8 points; stage IV, 9–12 points.

developing duodenal cancer is 3–4 per cent. This risk is 100–300 times higher than that in the general population, in which duodenal carcinoma is rare^{15–17}. Duodenal adenomatosis can be staged using the Spigelman classification⁷, which is used to score the number and histological features of adenomas (*Table 1*).

There are several endoscopic and surgical options available for treatment. Both endoscopic polypectomy and duodenotomy with surgical polypectomy provide temporary relief of the cancer threat, with low morbidity, but the recurrence rate is almost 100 per cent^{18–21}. Extensive surgical procedures such as (pylorus-preserving) pancreatoduodenectomy or pancreas-sparing duodenectomy may be curative but carry the potential of considerable morbidity and death^{22,23}. Whether adenomas recur after such procedures is unknown.

Most authors recommend surveillance of the upper gastrointestinal tract, although the value of surveillance is unknown. Before large-scale upper gastrointestinal tract surveillance of families with FAP is recommended, the World Health Organization criteria for epidemiological screening programmes should be satisfied²⁴. Thus, the disease must be an important health problem for the target group, the natural history must be known, there must be a recognizable latent stage, acceptable tests with high specificity and sensitivity must be available, surveillance and early treatment should improve life expectancy, costs should be acceptable and there should be an effective treatment. The aim of this study was to address the last of these criteria, namely to assess the effectiveness of various surgical treatments for duodenal adenomatosis and cancer.

Patients and methods

A questionnaire was sent to members of the Leeds Castle Polyposis Group (LCPG) to obtain data on patients who underwent surgical treatment for severe duodenal adenomatosis or cancer after 1990. Severe adenomatosis was classified as Spigelman stage IV or Spigelman stage III with severe dysplastic features noted during endoscopy (*Table 1*). Data were requested with

regard to whether surgery was indicated after a regular surveillance examination or whether the patient was already symptomatic. Other questions concerned the age at operation and type of surgery, as well as complications of, and long-term outcome after, surgery. Complications of surgery, such as wound infection, atelectasis and urinary tract infection, were scored as minor morbidity whereas complications such as anastomotic leakage and fistula formation, wound abscess, sepsis and pancreatitis represented major morbidity.

After surgery for duodenal adenomatosis or cancer, the remaining small bowel was classified as Spigelman stage 0. Recurrence of adenomas after surgery was defined as Spigelman stage greater than 0 during follow-up endoscopy. After major surgical procedures comprising total duodenectomy, such as (pylorus-preserving) pancreatoduodenectomy or pancreas-sparing duodenectomy, the appearance of new adenomas in the reconstructed small bowel was also defined as recurrence.

If the questionnaire was not completed fully, the member was contacted to obtain the missing information. If the information was not received, the patient was not included in the study. Patients were studied with respect to the risk of recurrence of small bowel adenomas. Observation time was measured from the date of surgery until recurrence of adenoma, death or the closing date of the study (October 2000). The number of patients with recurrence of adenoma and mean follow-up were calculated for patients who did not die from metastatic disease.

The cumulative risk of recurrent adenomatosis was compared between patients who underwent less extensive surgical procedures such as ampullectomy and duodenotomy with local excision of polyps, and patients who underwent extensive surgical procedures such as (pylorus-preserving) pancreatoduodenectomy and pancreas-sparing duodenectomy. The mortality rate from metastatic disease was compared between patients operated on for cancer and those operated on for severe duodenal adenomatosis. Data were analysed by Kaplan–Meier survival analysis and by χ^2 test using Statistical Package for the Social SciencesTM version 10.0 for Windows (SPSS, Chicago, Illinois, USA). $P < 0.050$ was considered to be significant.

Results

Participating registries and their contributions

The questionnaire was sent to the 71 members of the LCPG. A reply was received from 16 members (23 per cent). The contribution of one member (one patient) had to be excluded owing to insufficient patient information. The data from two members were not used as they comprised

information on patients who were treated endoscopically for severe adenomatosis. The data concerning 69 patients (30 men and 39 women) from the remaining 13 members in six countries were used. Seventy-two surgical procedures in these patients are described. Three patients have had two surgical procedures for duodenal adenomatosis.

Severe adenomatosis as indication for surgery

The indication for surgery was severe duodenal adenomatosis in 56 patients (59 procedures). Sixteen patients were staged Spigelman III and 36 patients Spigelman IV. In four patients, the Spigelman stage was not scored, but an adenoma with severe dysplasia was given as the indication for surgery. The duodenum was staged during a regular surveillance examination in 53 of these patients (90 per cent) while six patients (10 per cent) were symptomatic. For 11 of the 56 patients, the histology of the resected duodenum showed a higher degree of dysplasia than was identified in preoperative endoscopic biopsies. Therefore, the Spigelman score of these patients was higher after surgery than before. In ten patients with a preoperative diagnosis of severe adenomatosis, invasive carcinoma was diagnosed in the resected duodenum.

Invasive carcinoma as indication for surgery

Thirteen patients underwent surgery with a preoperative diagnosis of invasive cancer. The cancer was detected during regular surveillance examinations in five patients while eight patients were symptomatic.

Age at time of surgery

The mean age of all twenty-three patients treated for invasive cancer was 53 (range 40–70) years. The average age of the 46 patients (49 procedures) in whom severe adenomatosis was diagnosed in the resected part of the duodenum was 43 (range 24–65) years.

Types of surgery, morbidity and mortality

All surgical procedures were performed between 1990 and 2000. Types of surgery included duodenotomy with local excision of polyps ($n = 22$), ampullectomy ($n = 8$) and extensive surgical procedures such as pancreas-sparing duodenectomy ($n = 6$), pylorus-preserving pancreatoduodenectomy ($n = 12$) and classical Whipple pancreatoduodenectomy ($n = 23$). Three patients underwent a duodenotomy with local excision of polyps twice. Minor morbidity was associated with 13 per cent of all procedures, but major morbidity occurred only after extensive surgical procedures (Table 2). One 70-year-old patient died after a Whipple procedure from leakage of the pancreatojejunostomy resulting in multiorgan failure.

Outcome after surgery

Eleven of 23 patients operated on for cancer died from metastatic disease, five of 56 patients (one screen-detected) in the severe adenomatosis group, and six of 13 patients (three screen-detected) in the group treated for invasive carcinoma ($P = 0.002$). The mean survival of patients with metastatic disease was 19 (range 1–59) months. Of the 46 patients treated for severe adenomatosis, one died from metastatic ovarian carcinoma.

The long-term outcome after duodenal surgery is shown in Table 2. Recurrence of adenoma was observed in six of eight patients after ampullectomy (mean follow-up 11 months), and in 17 of 21 patients who underwent duodenotomy with polypectomy (mean follow-up 29 months). The adenomas were detected during follow-up endoscopy. Adenoma recurrence was also observed in six of 25 patients who were treated with a (pylorus-preserving) pancreatoduodenectomy (mean follow-up 47 months). These adenomas were detected at the anastomosis, and both in the afferent and efferent loops during follow-up endoscopy. No adenomas were detected in patients who underwent a pancreas-sparing duodenectomy (mean follow-up 11 months). The cumulative risk of recurrent adenomatosis for patients who underwent ampullectomy

Table 2 Outcome after surgery

	<i>n</i>	Minor morbidity	Major morbidity	Death from metastatic disease	Recurrence	Follow-up (months)*
Ampullectomy	8	1	–	–	6 of 8	11 (4–13)
Duodenotomy with polypectomy	22	1	–	1	17 of 21	29 (5–103)
Pancreas-sparing duodenectomy	6	1	3	0	0 of 6	11 (2–15)
Pylorus-preserving pancreatoduodenectomy	12	1	4	3	3 of 9	45 (7–93)
Classical Whipple	23	5	12	7†	3 of 16	47 (7–96)
Explorative laparotomy	1			1		

*Values are mean (range). †One patient died from postoperative complications.

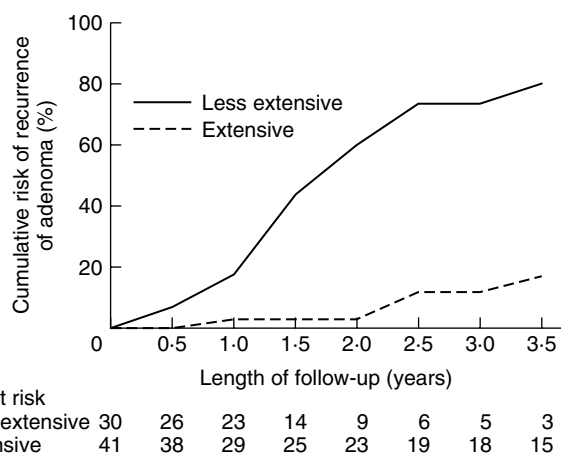


Fig. 1 Cumulative risk of recurrence of adenoma in patients who underwent (pylorus-sparing) pancreatoduodenectomy or pancreas-sparing duodenectomy (extensive resection) with those who underwent ampullectomy or duodenotomy with polypectomy (less extensive resection)

or duodenotomy with polypectomy was significantly higher than that for patients who underwent (pylorus-preserving) pancreatoduodenectomy or pancreas-sparing duodenectomy ($P < 0.001$, log rank test) (Fig. 1).

The mean interval between the first and second surgical procedures of the three patients who had two operations was 8 (range 7.8–8.2) years. The mean interval to recurrence of adenoma in these three patients was 2 years.

Discussion

Patients with severe duodenal adenomatosis that is left untreated may have a considerable risk of developing a duodenal carcinoma^{25,26}. However, duodenal adenomas probably carry a lower risk of malignant change than colonic adenomas. Several studies have demonstrated a prevalence of duodenal adenomas in patients with FAP of up to 90 per cent, and the lifetime risk of duodenal cancer has been estimated at 3–4 per cent in these patients¹⁷. However, without prophylactic surgery almost all patients with FAP develop a colorectal carcinoma. Considering a prevalence of stage IV duodenal adenomatosis of 10–15 per cent and a lifetime risk of invasive duodenal carcinoma in the entire group of patients with FAP of about 3–4 per cent, the lifetime risk of a duodenal carcinoma in this subset of patients may be 30–40 per cent^{27–29}.

Invasive duodenal carcinoma in FAP has a poor prognosis, even if these carcinomas are detected during surveillance. In this study, almost half of the patients with duodenal carcinoma died from metastatic disease.

Therefore, surgical treatment of duodenal adenomatosis should ideally take place before endoscopic biopsy reveals invasive cancer. Unfortunately this is complicated by the fact that endoscopic biopsy is often not representative of the entire lesion. Ten of 36 patients with Spigelman IV disease were found to have invasive cancer. Endoscopic ultrasonography may provide additional information, for example in patients with Spigelman IV disease, to determine if malignant invasion has occurred^{30,31}.

When endoscopic treatment is no longer deemed possible, the decision on surgical intervention for severe duodenal adenomatosis becomes pertinent. Endoscopic coagulation may be impossible owing to the presence of a large number of polyps or because of the sessile nature of the polyps. Repeated coagulation may cause scarring that may result in stricture. Recurrent adenomatosis is often seen. Argon plasma coagulation may prove to be more efficient in destruction of smaller polyps and carries a small risk of perforation due to the superficial mucosal destruction^{25,32}.

The timing and technique of surgical intervention remain unclear. Age may be important in a patient with severe adenomatosis. In the present study, the mean age of patients at the time of surgery for invasive carcinoma (53 years) was 10 years higher than that of patients treated for severe adenomatosis (43 years). This suggests that major surgery, such as (pylorus-preserving) pancreatoduodenectomy, may be postponed until the fifth decade of life.

The least extensive surgical options are ampullectomy and duodenotomy with local excision of polyps. Ampullectomy and duodenotomy with surgical polypectomy are associated with an adenoma recurrence rate of almost 100 per cent, as demonstrated in this study and previous reports. The temporary relief of the cancer threat and the relatively minor complications associated with these procedures may be important considerations in the choice of initial treatment of severe adenomatosis, particularly in young patients^{18–21}. The present study has shown that, even after extensive surgical procedures such as (pylorus-preserving) pancreatoduodenectomy, small bowel adenomas may recur. In addition, almost half of these extensive surgical procedures were accompanied by major morbidity. However, in most patients, such as those with carpet-like polyposis, extensive surgery offers the only chance of cure or a prolonged disease-free interval. Adenomas did not recur after pancreas-sparing duodenotomy, but caution in the interpretation of the results after this procedure is warranted, owing to the relatively short follow-up time. Three patients in this study have undergone two duodenotomies with local excision of adenomas for severe

adenomatosis. The mean interval to recurrence of adenomas for these patients was 2 years, while the mean interval between the first and second surgical procedure was 8 years. This interval may indicate the timespan between Spigelman stage 0 and recurrence of adenomas with severe dysplastic features.

Optimum surgical management of duodenal adenomatosis is a difficult balance between outcome after surgery and the risk of invasive carcinoma. As operative and endoscopic measures fail in controlling duodenal adenomatosis in the long term, interest is now focused on drug therapies. With respect to this, the recent finding that inhibition of the cyclo-oxygenase 2 pathway using celecoxib has an effect on duodenal tissue in patients with FAP is promising³³. Continued careful evaluation of patients with FAP and duodenal adenomatosis, ideally in a prospective manner, may provide further insights into the management of the disease.

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