

ORIGINAL ARTICLE

Pancreaticoduodenectomy for advanced duodenal and ampullary adenomatosis in familial adenomatous polyposis

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Abstract

Background: Patients with familial adenomatous polyposis (FAP) develop duodenal and ampullary polyps that may progress to malignancy via the adenoma–carcinoma sequence.

Objective: The aim of this study was to review a large series of FAP patients undergoing pancreaticoduodenectomy for advanced duodenal and ampullary polyposis.

Methods: A retrospective case notes review of all FAP patients undergoing pancreaticoduodenectomy for advanced duodenal and ampullary adenomatosis was performed.

Results: Between October 1993 and January 2010, 38 FAP patients underwent pancreaticoduodenectomy for advanced duodenal and ampullary polyps. Complications occurred in 29 patients and perioperative mortality in two. Postoperative histology revealed five patients to have preoperatively undetected cancer ($R = 0.518$, $P < 0.001$).

Conclusions: Pancreaticoduodenectomy in FAP is associated with significant morbidity, but low mortality. All patients under consideration for operative intervention require careful preoperative counselling and optimization.

Keywords

familial adenomatous polyposis, adenomatosis, pancreaticoduodenectomy

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Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant, generalized disorder of tissue growth regulation secondary to mutations of the adenomatous polyposis coli (*APC*) gene on chromosome 5.^{1,2} The defining phenotypic feature is the development of multiple colorectal adenomas in the early adolescent period, which usually undergo malignant change by the third or fourth decades of life. However, mortality caused by colorectal

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cancer in FAP has significantly decreased following the widespread introduction of prophylactic colectomy, and duodenal cancer and desmoid disease are now the most significant causes of death in patients with FAP.³

Familial adenomatous polyposis patients develop multiple adenomatous polyps in the small as well as the large bowel and these can similarly become symptomatic or undergo malignant change.^{4–7} Small bowel polyps occur almost exclusively within the duodenum and ampulla, although they also occur on ileostomies and within ileoanal pouches.⁸ The cumulative incidence of duodenal polyps in FAP increases with age to reach 65% at 38 years and 90–95% by 70 years.^{9,10}

Duodenal adenomas can undergo dysplastic change, most often in the second and third parts of the duodenum,¹¹ where prolonged contact with bile acids may lead to mutational changes in the

Table 1 Spigelman scoring for duodenal and periampullary polyps in familial adenomatous polyposis¹⁵

Polyps, <i>n</i>	1–4	5–20	>20
Polyps, size	1–4 mm	5–10 mm	>10 mm
Histology	Tubular adenoma	Tubulovillous adenoma	Villous adenoma
Dysplasia	Mild	Moderate	Severe
Points	1	2	3

surrounding mucosa.^{12–14} However, only approximately 5% of all duodenal polyps will undergo malignant change,¹⁰ via the adenoma–carcinoma sequence,^{4–7} and the cumulative incidence of duodenal cancer in FAP is 4.5% at 57 years.⁹

The Spigelman scoring system takes into account the polyp number, size, histology and degree of dysplasia¹⁵ (Table 1) and is applicable to duodenal and periampullary regions.¹⁶ Higher scores indicate greater risk for neoplastic transformation: the risk for developing duodenal cancer over 10 years is 2% in Spigelman stages II and III, and 36% in stage IV.¹⁷ However, the identification of patients at risk for developing neoplastic disease remains problematic because, although the cumulative incidence of Spigelman stage IV is 52% at the age of 70 years,⁹ the rate of progression between stages is highly variable and the disease can take 4–11 years to progress from one stage to another.¹⁸

Ampullary adenomatosis has been shown to correlate strongly with the degree of duodenal polyp burden and is estimated to occur in approximately 28% of FAP patients.¹⁶ Further, the risk for malignant transformation may be higher in patients with a larger periampullary than duodenal polyp burden and the cumulative risk for developing stage IV disease and adenocarcinoma in the periampullary region by 60 years of age has been estimated as 20% and 10%, respectively.¹⁹

Early identification of malignant duodenal and ampullary invasion may be insufficient to decrease mortality and many centres therefore offer operative intervention following the diagnosis of benign but advanced disease (Spigelman stage III or IV).¹⁷ St Mark's Hospital in London introduced endoscopic surveillance for duodenal and ampullary polyps in 1988 (Table 2); outcomes of the practice of utilizing pancreaticoduodenectomy for the management of advanced duodenal and ampullary adenomatosis are analysed and presented here.

Materials and methods

Endoscopic surveillance

Since the initiation of a surveillance programme in 1988, all FAP patients undergoing follow-up at the Polyposis Registry (St Mark's Hospital, London) are subject to endoscopic surveillance for duodenal and ampullary polyps. Surveillance commences at the age of 25 years (no small bowel polyps requiring treatment at younger ages have been observed) via a side-viewing duodenoscope to optimize views of the ampullary and periampullary region. Duodenal polyp size is measured by comparison with

Table 2 Current follow-up and management protocol of familial adenomatous polyposis patients with duodenal and ampullary polyposis, according to Spigelman stage

Spigelman stage	Points	Action
0–I	0–4	Repeat endoscopy at 5 years
II	5–6	Repeat endoscopy at 3 years
III	7–8	Repeat endoscopy at 6 months Consider endoscopic therapy or chemoprevention
IV	9–12	Repeat endoscopy at 6 months Computed tomography and endoscopic ultrasound staging Consider surgery or endoscopic therapy + chemoprevention
Cancer	N/A	Surgery

This protocol was developed by the Polyposis Registry at St Mark's Hospital, in combination with the Department of Hepatopancreaticobiliary Surgery at University College London Hospital
N/A, not applicable

open biopsy forceps and the number of polyps defined as the number of discrete areas of mucosal abnormality. Multiple biopsies are taken for assessment of histology and dysplasia, and completion of Spigelman staging.

Patients are followed according to their Spigelman stage (Table 2) and referred for consideration of surgery when they are diagnosed with Spigelman stage IV disease or with suspected or histologically proven malignancy. Patients with diffuse duodenal or ampullary adenomatosis (>20 polyps; score of 3 for polyp number on Spigelman staging) are also considered for surgery at Spigelman stage III.

Surgical management

All FAP patients in the Polyposis Registry with advanced duodenal or ampullary adenomatosis are referred to a single centre (University College London Hospital [UCLH]) for consideration of pancreaticoduodenectomy (unless a patient has a particular preference for referral elsewhere). All patients undergo preoperative staging via computed tomography (CT) and endoscopic ultrasound (EUS), and further examinations and assessments (including cardiopulmonary exercise [CPEX] testing) are arranged as necessary. All patients undergo pancreaticoduodenectomy with reconstruction via pancreaticogastrostomy (PG) formed by the burial of the pancreatic remnant in the posterior wall of the

stomach utilizing two layers of 3–0 polydioxanone sutures (PDS) (Ethicon, Inc., Somerville, NJ, USA), and the insertion of a common bile duct (CBD) stent.

Postoperative complications

Anastomotic leaks were diagnosed via CT or contrast study and postoperative haemorrhage via CT angiogram or clinically. Clinical diagnosis was also used to identify both pancreatic exocrine insufficiency (based on a clinical diagnosis of steatorrhoea, supplemented by faecal elastase tests where necessary) and delayed gastric emptying (based upon symptoms of nausea, vomiting and decreased oral intake, some of which may be attributable to bile reflux); however, such gastrointestinal (GI) diagnoses can be difficult to assess in FAP patients who have undergone prior colectomy.

Patient identification

Familial adenomatous polyposis patients undergoing pancreaticoduodenectomy for advanced duodenal and ampullary adenomatosis were retrospectively identified from surgical databases at UCLH, data held at the Polyposis Registry and via contact with general practitioners and alternative operating centres. Following patient identification, a review of computerized and written hospital notes, pathology results and operative notes was undertaken and all data entered into a relational database using Microsoft Office Access 2007 (Microsoft, Redmond, WA, USA).

Statistical analysis

Differences among proportions of categorical variables (i.e. postoperative morbidity and mortality) were compared using Fisher's exact test. Pearson's correlation coefficient model was used to indicate the strength and direction of the relationship between preoperative endoscopic biopsy histology and surgical resection histology. Outcome measures of survival and all-cause mortality rates were analysed using the Kaplan–Meier log-rank test. Two-tailed *P*-values of <0.05 were considered to indicate statistical significance. Statistical analysis was carried out using spss Version 17.0 (SPSS, Inc., Chicago, IL, USA).

Results

Demographics

Between October 1993 and January 2010, 46 patients were referred from the Polyposis Registry at St Mark's Hospital for consideration of surgical intervention. Of these, 41 patients were referred to a single centre (UCLH) and five were referred to alternate UK centres and have been excluded from analysis. Of the 41 patients, one underwent polypectomy and cholecystectomy and two were found to be inoperable at laparotomy; of the latter two patients, one had widespread, intra-abdominal, malignant disease and one had extensive intra-abdominal desmoid disease.

Thus, 38 FAP patients underwent pancreaticoduodenectomy for advanced duodenal and ampullary polyps at a single centre, representing approximately 5.0% of all patients undergoing primary colonic surgery for FAP at St Mark's Hospital. The study

cohort included 17 male and 21 female FAP patients with a median age of 49 years (range: 32–67 years).

Preoperative staging

Four of the 38 patients were referred with Spigelman stage III disease; all four underwent pancreaticoduodenectomy for diffuse polyps involving the duodenal or ampullary regions. Of the remaining patients, 27 had Spigelman stage IV disease and four had a preoperative diagnosis of malignancy on endoscopic surveillance (one duodenal, three ampullary). In three patients, the preoperative Spigelman stage was not given.

Surgical management

All 38 patients were operated upon at a single centre, undergoing pancreaticoduodenectomy by one of two consultant surgeons. The number of patients undergoing pancreaticoduodenectomy increased over time: 14 of the 38 patients underwent resection during 1993–2001 and 24 underwent resection during 2002–2010 (*P* = 0.003, one-sample *t*-test). The median length of stay was 38 days (interquartile range [IQR]: 15–51 days) and the median follow-up was 42 months (IQR: 13–99 months).

Postoperative histology

Postoperative histology revealed five patients to have preoperatively undetected cancer (four duodenal, one ampullary). Two further patients were also stage-upgraded on surgical histology (from Spigelman stage III to IV), whereas four patients were downgraded (from Spigelman stage IV to III). Therefore, postoperative histology revealed nine cancers in total, of which five were duodenal and four were ampullary. Correlation between preoperative endoscopic and postoperative surgical staging (Fig. 1) revealed a Pearson's kappa correlation coefficient of 0.518 (*P* < 0.001).

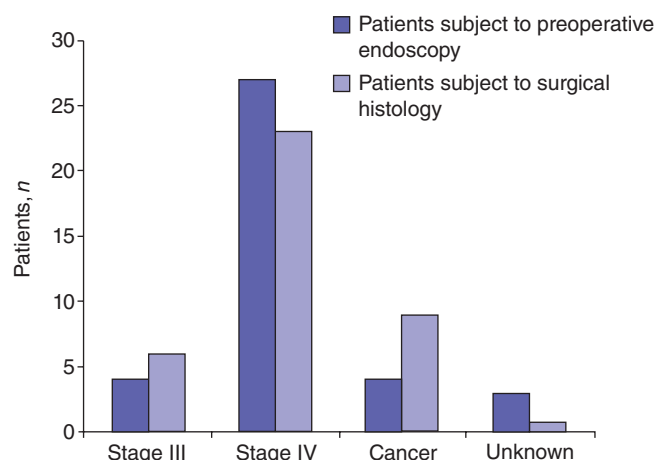


Figure 1 Analysis of preoperative and operative staging showed five patients to have preoperatively undetected cancer (four duodenal and one ampullary; Pearson's kappa correlation coefficient: 0.518 [*P* < 0.001])

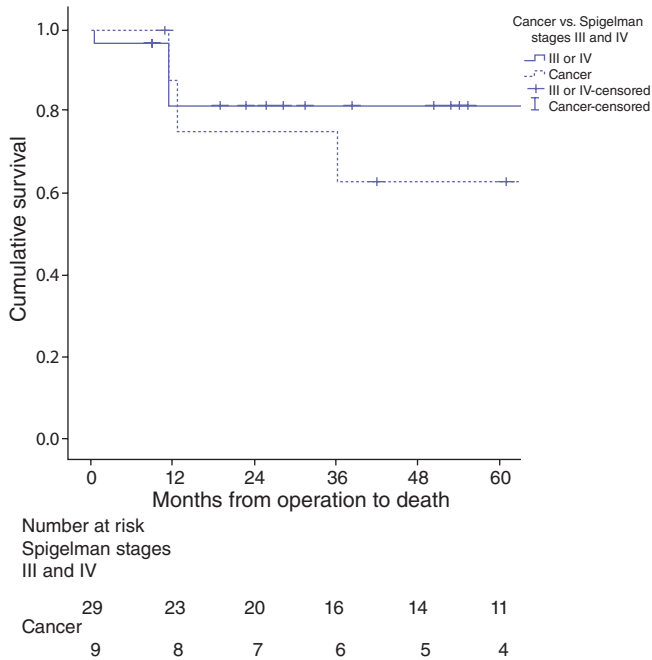


Figure 2 Longterm follow-up of 38 familial adenomatous polyposis patients undergoing resection for advanced duodenal and ampullary adenomatosis illustrates a shorter, overall 5-year survival in patients with postoperative histology demonstrating frank malignancy compared with those with Spigelman stage III or IV disease (62.5% vs. 81.6%; $P = 0.325$)

All-cause and cancer-related five-year survival (Fig. 2) was lower in patients with postoperative histology illustrating frank malignancy ($n = 9$) than in patients with Spigelman stage III or IV disease ($n = 29$) (62.5% vs. 81.6% [$P = 0.325$], 62.5% vs. 88.5% [$P = 0.116$], respectively), although these differences did not reach statistical significance.

Outcome

Two patients died while in hospital, both from multi-organ failure after re-operation for intra-abdominal haemorrhage resulting from a pseudoaneurysm which developed following a diagnosed anastomotic leak. Another six patients died following discharge, four from metastatic disease (one at 11 months, one at 13 months and two at 3 years after surgery), one from a glioblastoma (at 10 months after surgery) and one from unknown reasons (Fig. 3).

Postoperative complications were diagnosed in 29 patients (Fig. 4). The most common complication was anastomotic leak, which occurred in 16 patients, who were treated via radiological drain insertion, although one required laparotomy for biliary peritonitis and three developed enterocutaneous fistulae. Significant postoperative haemorrhage occurred in seven patients (five with confirmed anastomotic leaks), necessitating three re-laparotomies for the cessation of haemorrhage (two patients died) and two angiographic embolizations of a gastroduodenal artery and a

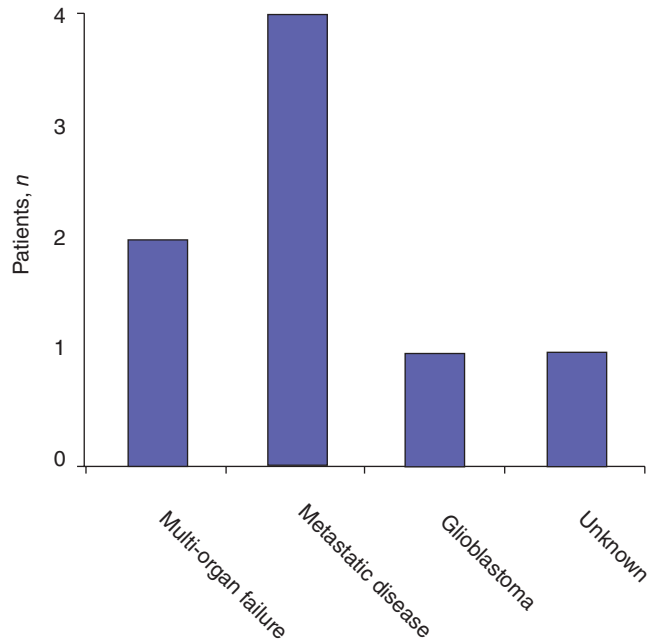


Figure 3 All-cause mortality in 38 familial adenomatous polyposis patients undergoing resection for advanced duodenal and ampullary adenomatosis

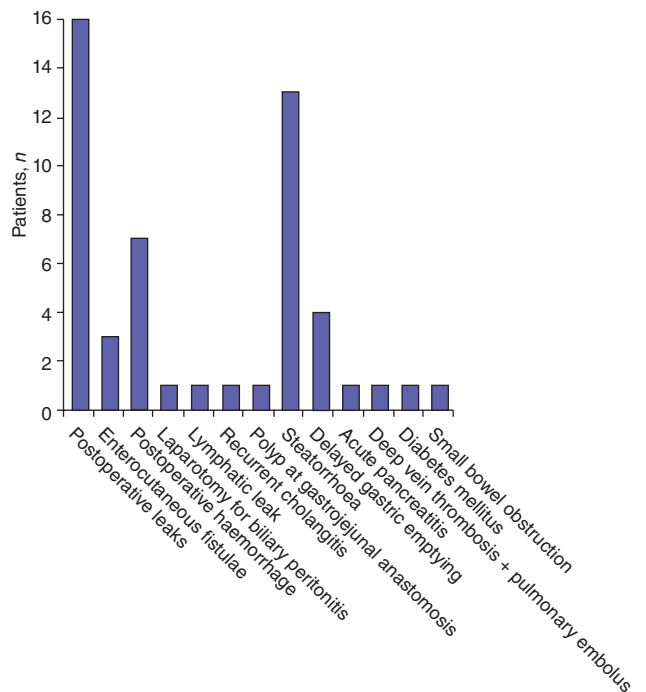


Figure 4 Postoperative complications in 38 familial adenomatous polyposis patients undergoing pancreaticoduodenectomy for advanced duodenal and ampullary adenomatosis

jejunal vessel. Exocrine pancreatic insufficiency occurred in 13 patients and delayed gastric emptying in four.

Patients were subsequently grouped according to their highest-grade complication on the revised Clavien–Dindo classification²⁰ (Table 3, Fig. 5), which revealed that 19 patients had a complication of grade III or above. However, there was no significant difference in complication rate between patients with Spigelman stage III/IV ($n = 23$) and patients with malignancy ($n = 6$) ($P = 0.830$).

Table 3 Clavien–Dindo classification of surgical complications (adapted from Dindo *et al.* 2004²⁰)

Grade	Definition
Grade I	Any deviation from the normal postoperative course, without the need for medication (excluding anti-emetics, laxatives, analgesics, anti-pyrexials, diuretics, electrolytes) or intervention (excluding physiotherapy)
Grade II	Pharmacological treatment including blood transfusion and parenteral nutrition (excluding medications allowed for Grade I)
Grade III	Surgical, endoscopic or radiological intervention
Grade IIIa	Intervention not under general anaesthesia
Grade IIIb	Intervention under general anaesthesia
Grade IV	Life-threatening complication requiring high dependency unit/intensive therapy unit management
Grade IVa	Single-organ dysfunction
Grade IVb	Multi-organ dysfunction
Grade V	Patient death
Suffix 'd'	Complication present at the time of discharge

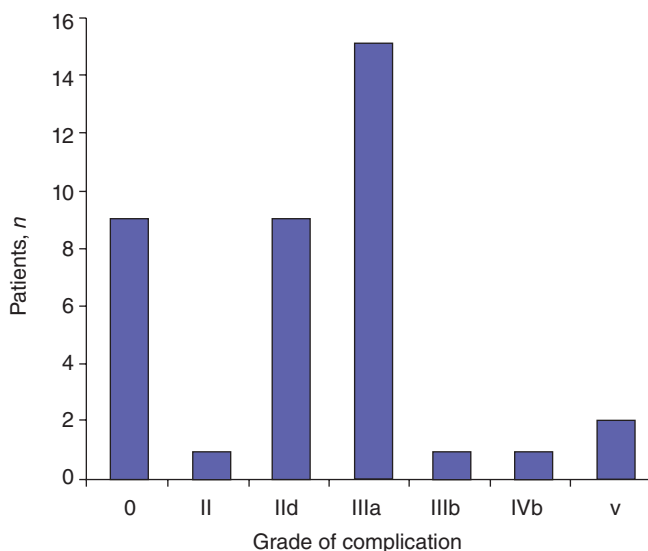


Figure 5 Analysis of highest-grade complication per patient, as defined by Clavien–Dindo grade, in 38 familial adenomatous polyposis patients undergoing resection for advanced duodenal and ampullary adenomatosis

Discussion

This report represents the largest published series of pancreaticoduodenectomies for advanced duodenal and ampullary adenomatosis in FAP. The results suggest that pancreaticoduodenectomy for advanced duodenal and ampullary polyps in FAP is associated with significant perioperative morbidity. However, a mortality rate of 5% is comparable to figures derived from series investigating outcomes of pancreaticoduodenectomy for non-FAP malignant lesions over the same time period, which demonstrate mortality rates of 3–25%.^{21–29}

The use of pancreaticoduodenectomy in this FAP cohort is associated with higher morbidity rates than those found in most pancreaticoduodenectomy series for non-FAP lesions (approximately 34–57%^{21,22,29}), probably because surgical intervention is significantly more technically demanding in FAP patients. All the patients in this study had previously undergone colonic resection and therefore had significant intra-abdominal adhesions and desmoplastic change, rendering mobilization technically more difficult. Further, the non-diseased, normal-texture pancreas, non-dilated ducts and increased tendency towards postoperative ileus or small bowel obstruction³⁰ in FAP patients may challenge anastomotic integrity and contribute to a greater tendency for anastomotic leak.

Pancreaticogastrostomy reconstruction was originally chosen over pancreaticojejunostomy (PJ) for the FAP patients in this series because PG has been associated with a decreased incidence of postoperative leak, particularly in patients with normal pancreatic texture,^{31–33} which possibly occurs in PJ patients secondary to jejunal limb oedema, obstruction and distension, which may lead to anastomotic tension. The close proximity of the stomach and pancreatic remnant, in combination with the easy placement of nasogastric tubes for decompression, may decrease anastomotic tension in PG patients.³⁴ Further, lack of enterokinase in the gastric remnant in PG patients may prevent pancreatic autodigestion³⁵ and the stomach's excellent blood supply facilitates the formation of a sound anastomosis.³⁴

Despite this, a significant incidence of anastomotic leak was discovered in this series and, in addition, some recent randomized studies and meta-analyses have demonstrated no benefit of one method of reconstruction over another.^{36,37} Further, PG formation has also been associated with pancreatic enzyme inactivation secondary to the reflux of gastric juices,^{38–40} which may help to explain the high incidence of pancreatic insufficiency seen in this FAP cohort.

The number of patients undergoing pancreaticoduodenectomy increased over the time course of the series, probably in response to improvements in the management of colonic disease which enable more patients to survive to an age at which duodenal disease becomes significant. These include the generalized introduction of upper GI surveillance and the identification of more patients with advanced, benign disease, as well as

enhanced disease awareness, which results in increased referrals to the Polyposis Registry and similar centres.

Endoscopic ultrasound was not available during the first decade of this series (1993–2003) and thus was not utilized in all patients. There remains a paucity of published data regarding the use of EUS in the assessment of upper GI polyps in FAP, partly because the small numbers of cases make it impossible to perform a randomized controlled trial for the direct comparison of CT with CT and EUS. Experiences to date indicate that duodenoscopy and EUS (performed with one oblique viewing electronic echoendoscope) are complementary to CT and provide useful information about polyp size, number and heterogeneity, depth of invasion (if present), nodal status and evidence of biliary and pancreatic obstruction, and EUS is now performed routinely as part of disease staging. In particular, EUS may be useful for the identification of positive nodal status and/or early pancreatic/biliary obstruction, thus expediting the decision to refer for surgery rather than to continue endoscopic surveillance. However, further data on the utility of EUS in this context are required.

Despite the high morbidity rates associated with the use of pancreaticoduodenectomy in this study, it remains the most definitive treatment for advanced duodenal and ampullary adenomatosis in FAP. Pharmacological and endoscopic therapies can be helpful in delaying or preventing the need for surgery, but, once advanced or diffuse adenomatosis is present, surgical strategies are frequently required. Non-steroidal anti-inflammatory drugs, in particular, have been shown to be of some benefit. The use of celecoxib resulted in a significant (14–31%) reduction in duodenal involved areas,⁴¹ although its effect upon cancer prevention remains unknown. The use of sulindac led to non-significant duodenal polyp regression in one study⁴² and had no effect upon periampullary polyps in another.⁴³ However, treatment with ranitidine⁴⁴ and calciferol has been shown to have no effect.⁴⁵ Endoscopic therapy with argon plasma coagulation and Nd-YAG laser has been attempted, with varying results.⁴⁶

Endoscopic mucosal resection may represent a less invasive method than surgery for managing some stage III and IV patients, possibly in combination with drug therapies. However, open polypectomy via duodenotomy for the removal of large polyps has proved largely unsuccessful because not only does this procedure incorporate the risks of laparotomy and the triggering of desmoid disease, but any benefit is short-lived as polyps recur after 6–36 months^{18,47,48} and progression to further Spigelman stages occurs after 53 months.⁴⁷ Similarly, advanced ampullary lesions can be locally removed by endoscopic⁴⁹ or open ampullectomy. However, endoscopic ampullectomy carries a risk of incomplete resection margins, repeat procedures and complications (20%).⁵⁰ To date, surgical ampullectomy has been shown to carry a low risk of both morbidity and recurrence in patients without invasive disease^{51,52} or with invasive lesions measuring <2 cm.⁵³

Pylorus-preserving pancreaticoduodenectomy, although considered a less aggressive procedure than definitive pancreaticoduodenectomy, still carries significant complication and mortality rates (40% and 4.5%, respectively)⁵⁴ and the inherent nature of the procedure means that *de novo* lesions are capable of arising in residual small bowel.⁵⁵ Pancreas-sparing duodenectomy was developed as a similarly less aggressive procedure for the treatment of duodenal disease because it leaves the entire pancreas *in situ* and decreases the number of anastomoses required. However, it has been shown to have short-term morbidity (62% vs. 57%; $P > 0.05$) and mortality (4% vs. 3%; $P > 0.05$) rates comparable to those of standard pancreaticoduodenectomy for ampullary adenocarcinoma.²⁹ Further, operative techniques that spare the pancreas leave areas of ampullary mucosa that may still undergo malignant change⁵⁶ and may also result in increased anastomotic tension secondary to delayed gastric emptying, as well as adversely affecting the function of the patient's ileoanal pouch.⁸

Wide disease variability exists among FAP patients and only 36% of patients with stage IV disease will develop cancer.^{9,57,58} Therefore, given the high postoperative morbidity and mortality rates, some have previously advocated a watch-and-wait policy in patients with advanced but benign disease. However, once malignant duodenal or ampullary disease is established, prognosis is poor.^{3,59} Further, a discrepancy between endoscopic biopsy and surgical resection histology has been noted in this study and others^{54,60,61} and some patients may therefore have preoperatively undetected malignancy, further mandating the use of definitive resection in advanced but benign disease.

For patients in whom complete resection is possible, the long-term prognosis can be good. However, although distal small bowel polyps are less likely to develop⁶² and less likely to undergo dysplastic and malignant change than duodenal polyps,⁶³ further malignant lesions may still be diagnosed in residual small bowel if FAP patients are followed for sufficient periods of time.⁶⁴

Currently, the selection of FAP patients requiring surgical intervention for high risk of duodenal and ampullary malignant transformation remains challenging; improved methods of identifying patients at risk are required. Thus, FAP patients with advanced duodenal and ampullary adenomatosis require careful counselling and preoperative optimization as surgical intervention still carries significant rates of morbidity and mortality.

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Conflicts of interest

None declared.

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