World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
wjg@wjgnet.com
doi:10.3748/wjg.v19.i40.6774

World J Gastroenterol 2013 October 28; 19(40): 6774-6783
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

REVIEW

Risk of ileal pouch neoplasms in patients with familial adenomatous polyposis

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Received: June 26, 2013 Revised: August 14, 2013
Accepted: August 17, 2013
Published online: October 28, 2013

Abstract

Restorative proctocolectomy is the most common surgical option for patients with familial adenomatous polyposis (FAP). However, adenomas may develop in the ileal pouch mucosa over time, and even carcinoma in the pouch has been reported. We therefore reviewed the prevalence, nature, and treatment of adenomas and carcinoma that develop after proctocolectomy in the ileal pouch mucosa in patients with FAP. In 25 reports that were reviewed, the incidence of adenomas in the ileal pouch varied from 6.7% to 73.9%. Several potential factors that favor the development of pouch polyposis have been investigated, but many remain controversial. Nevertheless, it seems certain that the age of the pouch is important. The risk appears to be 7% to 16% after 5 years, 35% to 42% after 10 years, and 75% after 15 years. On the other hand, only 21 cases of ileal pouch carcinoma have been recorded in the literature to date. The diagnosis of pouch carcinoma was made between 3 to 20 years (median, 10 years) after pouch construction. Although the risk of malignant transformation in ileal pouches is probably low, it is not negligible, and the long-term risk cannot presently be well quantified. Regular endoscopic surveillance, especially using chromoendoscopy, is recommended.

Key words: Familial adenomatous polyposis; Restorative proctocolectomy; Ileal pouch; Ileal pouch-anal anastomosis; Ileo-rectal anastomosis; Adenoma; Adenocarcinoma; Pouch polyp; Pouch neoplasm

Core tip: To eliminate the risk of colorectal cancer, the majority of patients with familial adenomatous polyposis (FAP) are treated with restorative proctocolectomy and an ileal pouch-anal anastomosis. However, as these patients are followed-up for longer intervals, it has gradually become recognized that adenomas and adenocarcinomas may develop in the ileal pouch. If the standard-of-care surgery for FAP patients does not eliminate all cancer risk, surgical and follow-up strategies may need to be altered. In this review, we summarize the data from the published English literature regarding the incidence of adenomas and carcinomas in the ileal pouch after proctocolectomy in FAP patients.

Tajika M, Niwa Y, Bhatia V, Tanaka T, Ishihara M, Yamao K. Risk of ileal pouch neoplasms in patients with familial adenomatous polyposis. *World J Gastroenterol* 2013; 19(40): 6774-6783 Available from: URL: http://www.wjgnet.com/1007-9327/full/v19/i40/6774.htm DOI: http://dx.doi.org/10.3748/wjg.v19.i40.6774

INTRODUCTION

Familial adenomatous polyposis (FAP) is an inherited, autosomal-dominant disease caused by a germline muta-

tion of the adenomatous polyposis coli gene (*APC*)[1]. The phenotype is characterized by the development of hundreds of colorectal adenomas, leading to a 100% lifetime risk of colorectal cancer[2]. For this reason, a prophylactic colectomy is recommended for patients with FAP to prevent the development of colorectal cancer. The main surgical strategy in patients with FAP is restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA)[3-6]. As originally described by Parks *et al*[7], IPAA included an anal mucosectomy to eliminate the risk of malignancy in the remaining anorectal mucosa. However, many surgeons now prefer to preserve the anal transition zone (ATZ) during the double-stapled IPAA technique because of its simplicity and better functional outcome[8-10]. The trade-off is a risk of neoplasia developing in the retained ATZ mucosa[8], with a 10%-15% incidence of adenoma[8,11-13]. Another widely accepted surgical procedure is colectomy with ileorectal anastomosis (IRA), performed when there are few polyps in the rectum. The major advantage of IRA is preservation of the rectal innervation, with subsequent better quality of life. However, continuing endoscopic surveillance for adenomas in the rectum is necessary, and there is a 13%-25% cumulative risk of rectal cancer after 15-25 years despite surveillance[14-16]. On the other hand, it has been thought that IPAA theoretically eliminates the risk of colorectal cancer and adenomas, and perhaps the need for further lower gastrointestinal surveillance. However, there are recent reports of adenomas or carcinomas developing not only in the residual rectal mucosa or anastomosis after IRA, but also in the ileal pouch mucosa after IPAA[17-39]. In addition, there are several reports of cancers arising from the ileal pouch mucosa, as opposed to the anastomotic site, in patients with FAP[31,36,37,40-47].

The aim of this review is to describe the prevalence, nature, and treatment of adenomas and carcinoma developing in the ileal pouch mucosa after proctocolectomy in patients with FAP.

INCIDENCE OF ILEAL POUCH ADENOMAS

The basic premise underlying the popularity of IPAA in patients with FAP is that it results in a significantly lower risk of rectal cancer than IRA. Although this is likely to be true, the risk of pouch polyposis and pouch cancer has not been recognized so far. After the advent of pouch surgery, several reports of adenomatous polyps in the pouches of FAP patients have appeared in the literature. In 1982, Beart *et al*[17] first described a FAP patient with continent ileostomy, in whom a large sessile tubulovillous adenoma and multiple smaller adenomatous polyps developed. Since then, there have been at least 25 reports of ileal pouch adenomas developing in these patients (Table 1). We reviewed only those studies that clearly described adenomas appearing within the ileal pouch mucosa. These included 8 case reports, 7 retrospective studies, and 10 prospective studies. The incidence of adenomas in the ileal pouch varied from 6.7% to 73.9%. This variation in the prevalence of ileal pouch adenomatosis could be due to differences in the way endoscopy was performed in the various studies. Adequacy of bowel preparation, type of instrument employed, use of chromoendoscopy, and other miscellaneous factors influence the detection rates of pouch polyps. Good bowel preparation and a flexible video colonoscope are essential in identifying pouch polyps because most ileal adenomas are flat or sessile, measuring only 1 mm to 3 mm in diameter, and having a morphology different from large bowel adenomas[36]. Therefore, a careful examination of the entire pouch, anal canal, and pouch-anal anastomosis should be performed. Although Polese *et al*[25] reported the prevalence of ileal pouch adenomas as 6.7%, these investigators used a rigid sigmoidoscope with enema preparation, without chromoendoscopy. These technical factors may explain the low prevalence of ileal pouch adenomas in the study by Polese *et al*.

The only meaningful estimates of adenoma incidence have come from prospective studies, with all 10 prospective studies showing that the incidence of pouch adenomas increases with the follow-up duration[4,21,22,24,28,29,31,32,35,36]. The risk appears to be 7% to 16% after 5 years, 35% to 42% after 10 years, and 75% after 15 years. The great majority of pouch polyps described in the literature are small, tubular adenomas with mild atypia. The incidence of adenoma with advanced pathology (size > 1 cm, villous pattern, or moderate-to-severe dysplasia) is less. According to Banasiewicz *et al*[35], the estimated frequency of low-grade dysplasia 4 years after IPAA surgery is 4%, and increases to 50% after 15 years. The same percentage of patients, but with high-grade dysplasia, develop high-grade dysplasia 2.5 years later, that is to say, 17.5 years after IPAA, and with neoplasia 18.5 years after the above procedure. The full impact of pouch polyposis will not be fully understood until most pouch patients reach a follow-up duration of 20 to 40 years[48].

RISK FACTORS FOR DEVELOPMENT OF ADENOMAS IN THE ILEAL POUCH

Phenotype

At present it does not seem possible to predict who is at risk for developing polyps in the pouch. Some studies show that there is no apparent high-risk phenotype for the development of ileal polyps[22,24,30,33]. However, other studies describe risk factors that favor the development of pouch polyposis. Parc *et al*[49] observed that patients with pouch polyps are younger, and have a longer follow-up period since IPAA, than patients without pouch polyps. A more aggressive disease requiring earlier surgery could explain these features. However, Groves *et al*[28] analyzed the risk factors by using logistic regression, and found that age was a more significant predictor of pouch adenomas than the follow-up period, sex, or type of primary or secondary procedures. Groves *et al*[28] reported that, in their experience, all patients older than 60 years

Table 1 Summary of 25 reports of ileal pouch adenomas in familial adenomatous polyposis

Ref.	Study	Year	Operation	*n*	Type of pouch	Findings	% of adenoma	Time to neoplasia
Beart *et al*[17]	Case	1982	Kock	1	Kock pouch	Tubulovillous Adenomas		6 yr
Wolfstein *et al*[18]	Case	1982	IAA	2	Soave	Adenomas in 2 pts		3 and 7 yr
Shepherd *et al*[19]	Retro	1987	IPAA	12	N	Tubular Adenoma in 2 pts	16.7	
Stryker *et al*[20]	Case	1987	Brooke ileostomy	1	Kock pouch	Tubular Adenomas		12 yr
Nugent *et al*[16]	Retro	1993	IPAA	38	N	Tubular Adenoma in 5 pts	13.2	4 yr (1-7)
Bertoni[21]	Pros	1995	IAA	3	N	Tubular Adenoma in 2 pts	66.7	53.7-75.4 mo
Wu *et al*[22]	Pros	1998	IPAA	26	S/J-pouch 9/16, 1 N	Tubular Adenoma in 11 pts	42.3	1-14 yr
Valle *et al*[23]	Case	2001	IPAA	5	N	Adenomas	20	5 yr
Thompson-Fawcett *et al*[24]	Pros	2001	Kock 5, IPAA 28	33	N	Adenoma in 14 pts (with microadenoma 20 pts)	42.4 (60.6)	7 yr (1-19)
Parc *et al*[4]	Pros	2001	IPAA	85	J-pouch	30 pts (28 grossly visible, 2 microadenoma)	35.3	Cumulative risk of 7%, 35%, and 75% at 5, 10, and 15 yr
Polese *et al*[25]	Retro	2002	IPAA	46	S/W/J-pouch 2/1/43, Kock 4	Adenoma in 2 of 30 pts	6.7	risk of Adenoma after 8 yr; 20%, (9-11 yr)
Beveridge *et al*[26]	Case	2004	IPAA	2	J-pouch 1, Kock 1	2 large VA, VA		4-10 yr
Vrouenraets *et al*[27]	Case	2004	IPAA	1	J-pouch	Adenomas with focal severe dysplastic change		6 yr
Groves *et al*[28]	Pros	2005	Kock 4, IPAA 56	60	W/J-pouch 13/43, Kock 4	Mild dysplasia 23, more advanced 11	56.7	6 yr (1-17)
Nilubol *et al*[29]	Pros	2007	IPAA	10	N	Tubular Adenoma in 1of 9 pts	11.1	11.3 yr
Moussata *et al*[30]	Retro	2008	IPAA	23	N	Low-grade 16, high-grade 1	73.9	4.76 yr (1-14)
Friederich *et al*[31]	Pros	2008	IPAA	212	N	Adenoma 74 pts, AAP 25 pts	46.7	Cumulative risk of 16% and 42.2% at 5 and 10 yr
Schulz *et al*[32]	Pros	2008	IPAA	35	N	Low-grade 8	22.8	mean of 5 yr
Tajika *et al*[33]	Retro	2009	Kock 8, IPAA 16	24	J-pouch	16 pts, (advanced 1, carcinoma 2)	66.7	Cumulative risk of 13%, 43%, and 72% at 5, 10, and 20 yr
Kang *et al*[34]	Case	2010	Kock	2	Kock pouch	2 (the largest one is 15mm in size)		
Banasiewicz *et al*[35]	Pros	2011	IPAA	165	J-pouch	Low-grade 13, high-grade 8, neoplasia 5	15.8	Cumulative risk of 50%, Low-grade at 15 yr, high-grade at 17.5 yr, neoplasia 18.5 yr
Tonelli *et al*[36]	Pros	2012	IPAA	69	S/J-pouch 25/29, SIMM 15	Adenoma 25 pts, carcinoma 2 pts	39.1	Cumulative risk of 28.5% at 5 yr
Makni *et al*[37]	Case	2012	IPAA	1	J-pouch	Adenoma and carcinoma		10 yr
Wasmuth *et al*[38]	Retro	2013	IPAA	61	N	14 pts	23	Estimated cumulative rate of first Adenoma diagnosed was 38%
Pommaret[39]	Retro	2013	IPAA	118	J-pouch	57 pts (12 advanced Adenomas)	48.3	15 yr

Study: Type of study; Retro: Retrospective series; Pros: Prospective series; *n*: Number of patients in the study; IPAA: Ileal pouch-anal anastomosis; Kock: Kock continent ileostomy; N: Not described; AV: Anal verge; pts: Patients.

will develop polyps in the pouch. Tonelli *et al*[36] reported that an age of more than 50 years was associated with pouch adenomas, but not sex or elapsed time since restorative proctocolectomy.

Several studies found that the severity of duodenal polyposis was related to the presence of pouch adenomatous polyps. In a multivariate analysis of 118 FAP patients who had undergone surgery, Pommaret *et al*[39] discovered that the presence of advanced duodenal adenomas was an independent risk factor for the development of pouch adenomas, in addition to follow-up duration. Tonelli *et al*[36] found that patients affected by pouch adenomas had high polyp counts (> 1000) at colectomy, as well as duodenal adenomas.

Several potential factors that favor the development of pouch polyposis have been investigated; a number of them remain controversial, although it seems certain that the age of the pouch is important.

Pathogenesis

The mucosa of the ileal pouch may be subjected to not only the tumorigenic consequences of *APC* gene mutations[50], but also to luminal factors due to fecal stasis, which may also exert an important effect. Fecal stasis, such as occurs in a reconstructed pouch, may promote neoplastic changes in the ileal mucosa. Several authors have implicated colonic metaplasia of the ileal mucosa as a precursor for the development of ileal adenomas[19,51,52], and even carcinomas in the surgically constructed pouches of patients with FAP[53-55]. Colonic metaplasia was frequently recognized even in earlier descriptions of the changes observed in the ileal pouch mucosa. Some authors have considered colonic metaplasia as an adaptive response of the ileal pouch to its role as a neo-

rectum[18,19,56,57]. Further investigations have shown that colonic transformation is only partial. Small-bowel brush border disaccharidase activity is preserved, as is the ability to absorb vitamin B12, D-xylose, phenylalanine, and bile acids[52,58-60]. The mucosal changes described as colonic metaplasia are likely a response to chronic inflammation caused by changes in the luminal contents due to stasis. In FAP, these changes may, at least in theory, favor the development of adenomas in a region of the gut where they are not usually observed. There is an increase in the concentration of luminal short chain fatty acids to levels that are seen in the colon[61], an increase in anaerobic bacterial counts with a more colonic type flora[62,63], and increased deconjugation and dehydroxylation of bile acids by the anaerobic bacteria[64]. In particular, deoxycholic acid and lithocholic acid, which are known carcinogens, have concentrations several times higher in an ileal pouch than in an end ileostomy[65]. On the other hand, reduction of glutathione S-transferase (GST) detoxification activity in the pouch compared with the afferent ileal loop after IPAA may promote tumorigenesis[64].

APC gene mutations

FAP develops due to a dominant autosomal mutation of the *APC* gene in more than 80% of patients[65]. Recently, it has been discovered that a biallelic mutation of the *MUTYH* gene might exist in 5% of patients with colorectal polyposis and 20% of FAP patients, with no *APC* mutation found[66]. Many researchers have investigated *APC* gene mutations in pouch patients with FAP, although none has demonstrated obvious genotype-phenotype correlations that would predict the development of pouch adenomas[28,30,36,49]. Hence, the available evidence suggests that systematic surveillance of all patients who undergo IPAA is necessary. Targeted surveillance of a defined subgroup of patients is currently not feasible.

Type of pouch and anastomosis

There are different pouch configurations. Parks *et al*[7] originally devised a triple-limb S-shaped pouch. This pouch was relatively complicated to construct, and suffered from kinking of the efferent limb if it was left too long[67]. Alternative designs have included the high-capacity W-pouch, the H-pouch and the J-pouch. The majority of surgeons now favor the J-pouch due to ease of construction, economical use of the terminal ileum, and reliable emptying[68]. Functional results are equal to those of other reservoir designs[69-71]. The pouch is formed from the terminal 40 cm of ileum, using several applications of a linear-cutting stapler to join the anti-mesenteric borders of two 20-cm ileal limbs.

Several authors have shown that there is no apparent relationship between the development of pouch polyps and the type of ileal pouch construction[36] or the suture used (hand-sewn or stapled)[25,28,36]. However, other authors have reported that patients with a stapled IPAA are at a significantly increased risk of developing adenomas at the anastomotic site: 1.5% to 20.9% *vs* 27% to 66% for hand-sewn and stapled anastomoses, respectively[9,11,22,36,72,73]. These data suggest that a hand-sewn IPAA may be a preferable strategy for decreasing the occurrence of adenomas at the anastomotic ileo-anal site. Recently, Wasmuth *et al*[38] evaluated the differences between adenoma formation at the anastomotic site and in the ileal pouch after IPAA, with or without mucosectomy. These investigators found that an occurrence of adenomas at the anastomotic site was significantly reduced after mucosectomy. However, there was no difference in the occurrence of ileal pouch adenomas between patients who underwent mucosectomy and those who retained a rectal mucosal remnant (8/39 *vs* 6/22; $P = 0.57$)[38].

Pouchitis

In patients with ulcerative colitis, concern about the risk of neoplasia in ileal pouches was raised after observing a combination of histologic changes in the ileal mucosa of the pouch, including villous atrophy, inflammation and metaplasia[74-76]. These transformations in the ileal pouches are likely caused by the chronic inflammatory state. The inflammatory process in pouchitis may lead to dysplasia[47] and loss of heterozygosity, consistent with precancerous lesions of the colon[77]. Thus, a dysplasia-to-neoplasia progression can occur in ileal pouches and can lead to cancer of the pouch. The cumulative risk of pouchitis is up to 50% in patients with ulcerative colitis[78-81], with most patients experiencing at least one episode of pouchitis during the first ten years after surgical pouch construction. In contrast, the pouchitis rate is below 25% in patients with FAP[4-6,29,33,35]. Banasiewicz *et al*[35] analyzed the frequency and progression of dysplasia and inflammation in the intestinal pouch of FAP patients after restorative proctocolectomy. Although these authors diagnosed pouchitis in 20.6% of patients after restorative proctocolectomy, no relationship was found between pouchitis and pouch dysplasia in FAP patients.

THE PREVALENCE OF ADENOMAS IN THE PRE-POUCH ILEUM

Although it is currently recognized that adenomas may develop in the ileal pouch, the risk of adenomas occurring in the afferent ileal loop above the pouch is unclear. The incidence of adenomas above the IPAA pouch was rarely recognized previously, and it seemed to be low, with reported figures ranging from 4% to 16%[22,28,33,82]. The majority of pre-pouch ileal adenomas have measured 4 mm or smaller. Pommaret *et al*[39] reported that only nine (6.5%) of 118 patients had afferent ileal loop adenomas after an IPAA. The only independent predictive factor for the occurrence of afferent ileal loop adenoma was found to be the presence of pouch adenomas (OR: 2.16; 95%CI: 0.17-26.98; $P = 0.007$). Pommaret *et al*[39] concluded that because afferent ileum loop adenomas are rare and have an unclear pathologic significance, there is no justification for their systematic search, particularly among patients without any duodenal or pouch adeno-

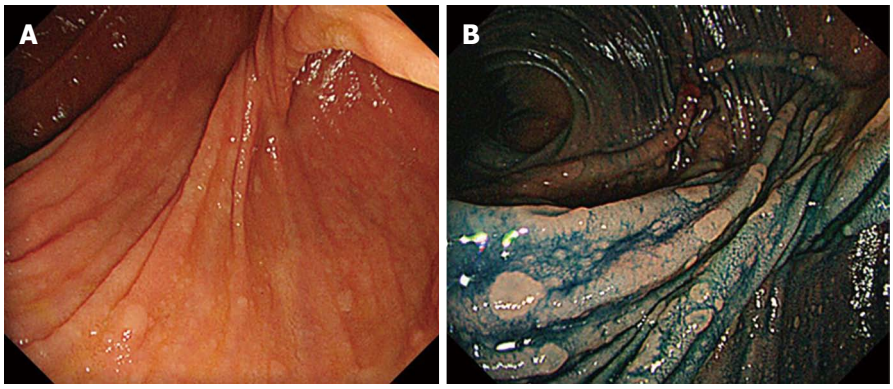

Figure 1 Endoscopic view of ileal pouch adenomas in patients with familial adenomatous polyposis. A: Multiple white flat lesions are observed in the ileal pouch mucosa; B: Multiple sessile polyps are revealed by indigo carmine. The data available from reference [33].

mas. In cases of extensive pouch polyposis with a significant cancer risk, this viewpoint could allow clinicians to consider resection of the adenomatous pouch, with construction of a new one using the afferent ileum.

SURVEILLANCE OF THE ILEAL POUCH

Saurin *et al*[83] described methods of surveillance and therapeutic indications in FAP patients following colectomy. Although there are no validated data in the literature, on the basis of expert opinion, endoscopic surveillance is performed at 6 mo, 1 year, and then every 2 years after surgery. In the presence of polyps with high-grade dysplasia, and/or polyps > 1 cm size, and/or presence of large polyp number (> 30), surveillance should be repeated every 6 mo[83]. Many authors have performed pouch endoscopy every 6-12 mo after surgery[30,33,35,36,38,84]. Optimum bowel preparation and the use of indigo carmine surface staining are necessary[31-33,35]. The main utility of chromoendoscopy is to highlight the small lymphoid lesions that are characteristic of the terminal ileum in FAP patients, and to distinguish flat polyps (Figure 1). In the experience of the Dutch Registry[31], indigo carmine chromoendoscopy significantly increases the detection rates of adenomas < 5 mm in size. Investigators with the Dutch Registry found that 75.7% of FAP patients harbored adenomas in the pouch at a median follow-up duration of 8 years after IPAA[31]. Because some patients have a stricture at the anal anastomosis, a pediatric colonoscope or gastroscope may sometimes be required[35].

TREATMENT OF ADENOMAS IN THE ILEAL POUCH

According to Saurin *et al*[83], no systematic endoscopic treatment of adenomas of the ileal pouch or afferent loop can be recommended. For large adenomas (> 1 cm), or in patients with high-grade dysplasia, endoscopic resection must be considered; however, a skilled team is needed because of the thin ileal mucosa[83]. Our current strategy in patients with IPAA is regular follow-up starting at 1 year after surgery, and then every year thereafter[33]. If adenomas are observed in the pouch, we recommend endoscopic resection or argon plasma coagulation where feasible, and then follow-up every 6 mo. Other reports[30,35,36,84] also describe polypectomy of large polyps, and ablation by fulguration or electrocoagulation for small lesions. In patients having extensive pouch polyposis with no possibility of endoscopic treatment, together with invasive cancer, pouch excision and terminal ileostomy has to be considered[40,83].

Although there have been some reports suggesting the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in suppressing the development of ileal pouch adenomas[32,48,85], this has not been systematically studied[34].

THE PREVALENCE OF ADENOCARCINOMAS IN THE ILEAL POUCH

The progression from a dysplastic lesion in the ileal pouch to invasive carcinoma appears to be rare, occurring in no more than 1% of patients with ileal pouches[31]. However, in the past few years, several cases of carcinoma have been observed after IPAA, although the majority of them occurred at the level of the anal canal[8,9,13,27,38,86-91]. Patients with either hand-sewn or stapled IPAA are at risk for developing a carcinoma in any residual rectal mucosa that harbors dysplasia or is prone to dysplasia. To date, only 21 cases of ileal pouch carcinoma have been recorded in the literature (Table 2). No relationship has been found between the occurrence of pouch carcinoma and the shape (J or S) of the pouch, or the type (hand-sewn or stapled) of IPAA[36]. These pouch cancers have clearly appeared in the ileal pouch, and not in the ATZ. The time elapsed between pouch construction and diagnosis of pouch carcinoma has been between 3 and 20 years (median, 10 years).

It is noteworthy that in at least seven patients, the development of advanced cancer was detected within a very short interval-within 1 year since last pouch endoscopy[25,36]. Furthermore, in four of the patients, ileal polyps

Table 2 Summary of 21 cases of ileal pouch cancer in familial adenomatous polyposis

Ref.	Year	Sex	Operation	Type of pouch	Staging of initial surgery	Age of pouch (yr)	Shape	Size (mm)	Staging of pouch cancer	No. of pouch polyps	Time to cancer (yr)	Outcome	Interval since last endoscopy (yr)
Bassuini *et al*[40]	1996	M	IPAA	/handsewn	No cancer	28	Large polypoid	N	T3,N+	N	3	N	No follow-up
Palkar *et al*[41]	1997	F	IPAA	J-pouch handsewn	No cancer	39	Large polypoid	40 × 35	T4N0	Exist	4.7	Alive	0.3
Kim *et al*[42]	1997	N	N	N	N	N	N	N	N	N	N	N	N
Cherki *et al*[43]	2003	F	IPAA	J-pouch handsewn	TisN0M0	35	N	N	T3N1M1	N	3.5	Died	0.5
Linehan *et al*[44]	2007	M	IPAA	/double stapled	Dukes A	30	N	N	T3N0	N	9	Alive	No follow-up
Friederich *et al*[31]	2008	M	IPAA	/handsewn	No cancer	21.3	N	N	Dukes C	0	14	N	4.4
		M	IPAA	/stapled	No cancer	26.7	N	N	Dukes B	0	10	N	2.1
		M	IPAA	/handsewn	No cancer	16	N	N	Dukes B	N	16	N	No follow-up
		F	IPAA	/stapled	No cancer	29.6	N	N	Dukes B	exist	6	N	0.6
Tajika *et al*[45]	2009	F	IPAA	J-pouch/ handsewn	TisN0M0	46	Type 2	30 × 25	T4N2M0	0	8.6	Died 3Y	0.75
		M	Kock	Kock/ handsewn	No cancer	48	Type 1	40 × 35	T3N0M0	10 <	20	Died by U	No follow-up
Ault *et al*[46]	2009	M	IPAA	S-pouch/ handsewn	Four cancer	61	ND	20-30	T2N1	N	11	Died by U	6
		F	IPAA	ND	No cancer	40	Type 1	N	N	N	13	meta	No follow-up
Lee *et al*[47]	2009	F	IPAA	J-pouch/	T2N0	56	Type 2	30 × 25	T3N2	0	7	meta 2Y	4
Banasiewicz *et al*[35]	2011	N	IPAA	J-pouch/	N	N	N	N	N	N	N	N	N
		N	IPAA	J-pouch/	N	N	N	N	N	N	N	N	N
		N	IPAA	J-pouch/	N	N	N	N	N	N	N	N	N
		N	IPAA	J-pouch/	N	N	N	N	N	N	N	N	N
Tonelli *et al*[36]	2012	M	IPAA	S-pouch/ handsewn	No cancer	26	Type 2	20 <	T3N0M0	ND	3	Died 6 mo	1
		F	IPAA	S-pouch/ handsewn	TisN0M0	47	IIa + IIc	N	T2N0M0	0	11	Alive at 56 mo	0.5
Makni *et al*[37]	2012	F	IPAA	J-pouch/	No cancer	26	N	20	N	Many	10	Died 1Y+	0.66

M: Male; F: Female; IPAA: Ileal pouch-anal anastomosis; Kock: Kock continent ileostomy; N: Not described; AV: Anal verge; U: Unrelated disease; Time to cancer: Interval between cancer diagnosis and pouch construction.

were not found during endoscopic follow-up until the development of pouch carcinoma. It seems that neoplasia that appears in the ileal pouch may not always follow the classic adenoma-carcinoma sequence. We strongly recommend a strict surveillance program for FAP patients, including annual flexible colonoscopy, irrespective of the phenotype and genotype.

IRA *VS* IPAA

In a review of 12 studies containing 1002 patients with FAP (53.4% IPAA, 46.6% IRA), Aziz *et al*[92] showed that bowel frequency, nocturnal defecation, and incontinence rates were significantly less in IRA patients, although fecal urgency was less among IPAA patients. There was no significant difference between IPAA and IRA in terms of sexual dysfunction, dietary restrictions, or postoperative complications. In their review, Aziz *et al*[92] could not identify any malignancies in IPAA patients, and rectal cancer was a diagnosis only in the IRA patients (5.5%). At the present time, IPAA anastomosis is recommended by a majority of surgical teams as the preferred option for FAP patients[4-6,10,92,93]. Although cancer formation after IPAA in patients with FAP may be rare, it is of concern that several of the recently reported patients had an advanced stage at diagnosis, with poor outcome.

Recent reports of a high frequency of adenomas after IPAA, together with favorable functional outcomes in patients who underwent IRA, may lead to reconsideration of the latter surgical option for some FAP patients, especially when quality of life and fertility criteria are taken into account[30]. In clinical practice, the results of preoperative evaluation of the rectal stump using indigo carmine chromoendoscopy are a major deciding factor. A limited number (< 10-20) of rectal polyps without any cancer would lead to preservation of the rectal stump in a majority of patients[94,95]. However, with the availability of better endoscopic instruments and resection techniques, and the possibility of enhanced post-operative surveillance, > 20 rectal polyps and/or non-invasive cancers can now also be managed endoscopically. So, there is a possibility that the criteria for IRA will expand in the near future. Of course, based on clinical and genetic data, a stepwise surgical strategy with a primary IRA followed at a later age by a secondary proctectomy and IPAA could be proposed[5].

An ongoing multicenter study in Japan is being conducted by Ishikawa *et al*[96] under the title "Intervention trial for colorectal cancer prevention by endoscopic polypectomy in patients with familial adenomatous pol-

yposis" (UMIN000009365). The aim of this study is to evaluate the usefulness and safety of thorough endoscopic polypectomy in FAP patients who have (or had) ≥ 100 colonic adenomas and who refuse surgery, as well as post-operative patients who have (or had) ≥ 100 colonic adenomas and who have ≥ 10 cm of remnant colon.

CONCLUSION

The development of adenomas with high-grade dysplasia and carcinoma in the ileal pouch is an important issue because the choice between IPAA and IRA is based mainly on the expected low risk of cancer development after the former surgery. Although the risk of malignant transformation in ileal pouches is probably low, it is not negligible, and the long-term risk cannot presently be well quantified. IPAA will not prevent cancer development in the terminal remnant intestine, and patients who undergo IPAA require regular follow-up similar to patients who receive IRA. A detailed analysis of the phenotypes and mutations in the *APC* gene of patients with FAP may allow tailoring of the surgical options in the future.

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ISSN 1007-9327