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Adenocarcinomas After Prophylactic Surgery For Familial Adenomatous Polyposis

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Abstract

The incidence of familial adenomatous polyposis (FAP) is one in 7,000 to 12,000 live births. Virtually, all surgically untreated patients with FAP inevitably develop colorectal-cancer in their lifetime because they carry the adenomatous polyposis coli gene. Thus prophylactic proctocolectomy is indicated. Surgical treatment of FAP is still controversial. There are however, four surgical options: ileorectal anastomosis, restorative proctocolectomy with ileal pouch-anal anastomosis, proctocolectomy with ileostomy, and proctocolectomy with continent-ileostomy. Conventional proctocolectomy options largely lie between colectomy with ileorectal anastomosis or ileal pouch-anal anastomosis. Detractors of ileal pouch-anal anastomosis prefer ileorectal anastomosis because of better functional results and quality of life. The functional outcome of total colectomy with ileorectal anastomosis is undoubtedly far superior to that of the ileoanal pouch; however, the risk for rectal cancer is increased by 30%. Even after mucosectomy, inadvertent small mucosal residual islands remain. These residual islands carry the potential for the development of subsequent malignancy. We reviewed the literature (1975–2012) on the incidence, nature, and possible etiology of subsequent ileal-pouch and anal transit zone adenocarcinoma after prophylactic surgery procedure for FAP. To date there are 24 studies reporting 92 pouch-related cancers; 15 case reports, 4 prospective and 5 retrospective studies. Twenty three of 92 cancers (25%) developed in the pouch mucosa and 69 (75%) in anal transit zone (ATZ). Current recommendation for pouch surveillance and treatment are presented. Data suggest lifetime surveillance of these patients.

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Keywords

Familial adenomatous polyposis; Restorative proctocolectomy; Ileal pouch-anal anastomosis; Ileorectal anastomosis; Adenocarcinomas

INTRODUCTION

Colorectal cancer remains a major problem in the treatment of patients with Familial adenomatous polyposis (FAP). Nearly one-fourth of these patients have colorectal cancer at initial operation, and one-fourth of patients will develop rectal cancer during surveillance follow-up. Many people with colorectal cancer experience no symptoms in the early stages of the disease. When symptoms appear, they will likely vary, depending on the cancer's size and location in the large intestine. Clinical manifestation of CRC may include: a change in bowel habits, including diarrhea or constipation or a change in the consistency of stool, rectal bleeding or blood in the stool, persistent abdominal discomfort, such as cramps, gas or pain, a feeling that the bowel doesn't empty completely, weakness or fatigue and unexplained weight loss.

FAP is an inherited autosomal dominant disease caused by mutations in the *adenomatous polyposis coli (APC)* gene located on chromosome 5q 21-q22. [1234] The incidence of FAP is one in 7,000 to 12,000 live births.[5,6] If FAP patients are not surgically treated virtually all will develop adenocarcinoma in their lifetime. [7,8,9,10] The disease is characterized by hundreds of colorectal adenomas leading to a 100% lifetime transformation of colorectal cancer (CRC) if the colon is not removed. [5,11] CRC has been incriminated as the main cause of death in FAP patients. [12,13,14] A prophylactic colectomy/total proctocolectomy (TPC) is therefore advocated for such patients to prevent CRC. [15] However, all somatic cells carry the *APC* gene, while FAP patient cells have a germline mutated *APC* gene. Thus even the ileal mucosa has the potential for malignant transformation. [16] Four surgical options are available for patients with FAP: [17–1920] colectomy with ileorectal anastomosis (IRA), restorative proctocolectomy (RPC) with ileal pouch-anal anastomosis (IPAA), proctocolectomy with ileostomy, and proctocolectomy with continent ileostomy (Kock). Surgical treatment via TPC with mucosectomy to the dentate line is observed to reduce the incidence of cancer in the anal transit zone (ATZ) [212223] and a restorative IPAA preserves trans-anal defecation, but inadvertent small mucosal residual islands may remain.[4,24] Hence a subsequent development of malignancy may be inevitable. [4] RPC is an alternative procedure to IRA.[25,26] The power of disease itself is the factor which determines the type of operation. While total colectomy with IRA provides superior functional results [because] it leaves the rectum intact, patients remain at a higher probability, compared to IPAA, of developing rectal cancer. [227] After IRA, 30% of FAP patients develop rectal cancer before the age of 60 years with an average mortality of about 25%.[28] This development relates to the time before the surgical interventions of the 1980s, when surgical options were much more limited. This review includes reports of carcinomas appearing not only in the residual rectal mucosa or anastomosis after IRA (10–31%) but also in the ileal pouch body mucosa after Kock or IPAA (8–62%).[2930313233344, 35–38]

SURGERY

The aim of surgical treatment of FAP is to intervene in the polyp-cancer sequence by removing the polyps before the transformation to malignancy occurs.[21,39,40] To date, there are no standardized guidelines as to when TPC or IRA or IPAA should be offered to patients, and there is no consensus about which surgical procedure is the better first-line treatment.[1841] The difficulty of course is that the power of disease itself is the factor which

determines the type of operation. Thus in a polyposis population correctly selected for RPC the alternative is TPC, since in both cases at the point of decision colectomy with IRA is no longer a surgical option. However, there are factors to be considered in the surgical decision process. The advantages and disadvantages, indications, contraindications, and timing for surgery are depicted in Table 1.

COLECTOMY WITH ILEORECTAL ANASTOMOSIS

An IRA can be defined as removal of the entire colon, leaving 15 cm of rectum for optimal bowel function.[4,42,43] Triaging the fate of the rectum according to the number, size, and histology of rectal polyps is effective in minimizing the need for future proctectomy. If there are fewer than 20 adenomas, none larger than 1 cm and none dysplastic, the rectum may be retained. [42] The IRA preserves excellent bowel function, is simple, and can be done with major benefits to the lifestyle of patients. [43]

RESTORATIVE PROCTOCOLECTOMY WITH ILEAL-POUCH ANAL ANSATOMOSIS

RPC with IPAA requires removal of the entire colon and rectum down to the pelvic floor achieving significant prevention of both colon and rectal cancer but needs construction of an ileal pouch. An anastomosis between an ileal pouch and the upper anus is performed. There are three options that affect the conduct of the operation: the type of pouch, the type of anastomosis, and construction of a diverting loop ileostomy.

TYPE OF POUCH

There are different pouch conformations (J-, S-, W-, and H- shaped). [17] The most common and easiest pouch to make is the J-shaped pouch. [44] Limbs are 15 to 20 cm long but the main factor determining length is the position of the apex of the superior mesenteric artery. [17]

TYPE OF ANASTOMOSIS

The simpler type of anastomosis is a double-stapled end of pouch to anus anastomosis. [45] The rectum is stapled distally at the level of the pelvic floor, a purse string suture is inserted into the open end of the pouch and used to tie in the anvil of the stapler, and the anastomosis is completed by transanal insertion of the stapler cartridge; uniting the cartridge with the anvil and firing the stapler. Residual anal transition zone is often less than 1.0 cm, as the stapler removes 0.5 to 1.0 cm. Alternatively, the ATZ is mucosectomized and the pouch pulled into the anus and anastomosed by hand transanally to the dentate line. The stripping and hand-sewn anastomosis takes longer and in some studies is associated with more complications and poorer function than the stapled anastomosis, [46] but its putative advantage is removal of all anal transitional and rectal epithelium with more complete prevention of anal transitional neoplasia. [18]

DIVERSION OF LOOP ILEOSTOMY

Patients with FAP are at low risk for an anastomotic leak or fistula because they are generally healthy, are not taking immunosuppressive medications, and have normal bowel except for the adenomas. Although an ileostomy creates the need for another surgery for closure and has its own risks of postoperative complications, an undiverted pouch is at a higher risk of anastomotic leak. [47] Therefore, in most patients a “safety first” approach is better and the postoperative course is smoother. To our knowledge, to date, there are no published data available on the relationship between establishments or not of a diverting loop ileostomy and the incidence of cancer development of the pouch or ATZ.

DIAGNOSIS

Pouch cancer is typically diagnosed on surveillance pouchoscopy and/or incidentally detected on diagnostic pouchoscopy. Metastasis to lymph nodes or distant organs at the time of cancer diagnosis is not uncommon. Pouch mucosa should be deemed as having malignant potential once polyps 1–3 mm in size with high-grade dysplasia in one of them is detected and practicing physicians should remain vigilant. Because most pouch-related adenocarcinoma is located at the ATZ, digital examination of the area may suggest areas harboring cancer and a full examination under anesthesia in the operating room is warranted.

TREATMENT

When rectal or pouch cancer is diagnosed the role of IPAA is uncertain because of concerns that may compromise oncologic therapy and oncologic therapy may compromise IPAA function. Most patients in this review had their pouch removed (pouchectomized) with permanent re-stoma. Adjuvant chemotherapy or radiotherapy or both was not commonly practiced and when it was prescribed complications such as enteritis and or pouch failure requiring dose reduction or interruption was commonly observed.

Patients with IRA need proctoscopy in 6 months to a year to monitor the rectum. [48] When polyps start to grow, small (< 5 mm) lesions can be ignored whereas large (>5 mm) are snared. [48] Chemoprophylaxis with Sulindac or Celebrex may minimize adenoma growth but will not necessarily prevent cancer. [49] They can be used for patients with significant polyp burden but who are not ready or suitable for proctectomy. Further, patients who have had IPAA need close lifelong endoscopic surveillance as well. [1350] The incidence is time-dependent from surgery.[29] Mucosectomy does not guarantee complete excision of rectal epithelium and cancer still occurs in these patients. [2,5,51] This is not surprising, considering the additional combination of fecal stasis, [52] a germline *APC* mutation, and rapid epithelial turnover. [53,54,55,56]

Some patients (IPAA and IRA) are treated endoscopically within the ileal mucosa using argon plasma coagulation.[57,58] There is evidence that indicators for proctectomy after IRA include an increasing instability of the rectal mucosa as evidenced by increasing polyp size or number. [6] Severe dysplasia is also an indication, as is cancer. In most cases, proctectomy and IPAA can be done although occasionally an IPAA is not possible because of inadequate bowel length or mesenteric desmoids tumors.

NATURAL HISTORY OF ADENOCARCINOMA AFTER SURGERY FOR FAP

When fecal stasis occurs such as in the pouch, the incidence of neoplasia in ileal pouch mucosa may increase. [2,59] It appears that the causative sequence starts with a chronic inflammatory process leading to a colonic-type epithelial metaplasia.[30,60,61] It is thought that cytological atypia and architectural abnormalities may ensue in a process of dysplasia that eventually may lead to carcinoma.

Until the age of 50 years, the cumulative risk of rectal carcinoma after FAP-IRA has been shown to be 10%, increasing sharply to 30% by the age of 60 years.[19,28] This indicates that surveillance of the retained rectum in older patients must either be improved or they should undergo a complete proctectomy (with or without ileo-anal pouch) in early middle age. The five year survival rate of patients with FAP developing rectal cancer after RPC is reported to be 71%.[62] Penna *et al.* reported seven cases of rectal carcinoma in a series of 29 cases (24%) with IRA for FAP. [63] Three carcinomas were diagnosed prior to surgery, but four at the time of surgery. [63] Moreover; Heiskanen and Jarvinen observed nine cases of rectal carcinoma (9%) that developed among 100 patients with FAP treated with IRA, although surveillance

was performed. [64] This means that even close surveillance, though highly recommended, cannot guarantee the prevention of rectal carcinoma. It is also not clearly known whether there is a metaplasia-dysplasia-carcinoma sequence following pouch surgery, or if there is simply increased risk of sporadic cancer in the ileal pouch of certain susceptible individuals. Further studies are needed for clarity.

Controversies exist about the danger of developing carcinoma in the remaining rectum after colectomy and IRA. The degree of probability varies from series to series, from 0% at the Cleveland Clinic [2] to 32% at Mayo Clinic. [25] The discrepancies are not clear, but it appears that the chance of developing carcinoma increases with time.[9,65] Although carcinoma is rare before the age of 20 in patients with FAP, a study from Mayo Clinic reported three cases, two of which were in the rectum and undetected preoperatively.[15]

Although a number of groups have provided surveillance options for diagnosis and treatment of the ileal pouch cancer lesions, no standardized treatment guidelines have gained acceptance in general medical practice. Saurin et al. [66] illustrated the methods of surveillance and possible therapeutic indications in patients with FAP following colectomy. [67,68] Despite there being no validated data in the literature; on the basis of experience, follow-ups should happen six months and one to two years after surgery.[66]

LITERATURE REVIEW

A systematic literature search using Medline, PubMed, and Google Scholar from 1975 through 2012 was systematically reviewed. Secondary and hand searches of reference lists, other studies cross-indexed by authors, reviews, commentaries, books and meeting abstracts were also performed. The search terms included: FAP, colectomy, total proctocolectomy, ileorectal anastomosis, Kock pouch, continent ileostomy, restorative proctocolectomy, ileal pouch-anal anastomosis and mucosectomy - consisting of case reports, prospective and retrospective studies reporting postoperative pouch related adenocarcinoma adverse events of patients' undergone prophylactic surgery for FAP. Studies were included only if the cancers were clearly within ileal pouch mucosa and/ or ATZ. The search excluded non-English language and non-human studies as well as five editorials.

POSTOPERATIVE SURVEILLANCE

Patients were followed up for an average period of 5.8 (1.5 to 46.4) years. Fewer than 20% in China to 37.1% to 54.5% [9] in the UK of FAP patients have had a regular postoperative follow-up visits. [69] The failure of surveillance is seen differently based on geographical, economical and cultural stigma. [969] The mean duration of pouch endoscopic follow-up was 6.2±4.1 years. Although, the median age and median follow-up duration of IRA patients (13.5 years) was longer than that of the IPAA patients (10.3 years), there was no statistically significant difference. Complication rates of IPAA and IRA were deemed to be indifferent.[70,71] The functional outcome of the IRA is observed superior to that of the IPAA; however the function of an IPAA after an IRA is similar to that of a de novo pouch. [72,73,74]

ADENOCARCINOMA OF ILEAL POUCH AND ANAL TRANSIT ZONE

To date there are 24 articles reporting cancers in connection with pouch surgery for FAP; 15 case reports, 4 prospective and 5 retrospective studies, Table 2. Currently there are 92 FAP-pouch-related cancers reported, 23 of 92 (25%) cases arising in the ileal pouch mucosa and 69 (75%) developed in the ATZ. [75,76] Multivariate analysis of the risk of cancer formation in the anorectal segment was associated with stapled ileoanal anastomosis (IAA) and age at RPC older than 40 years and was independent predictors of cancer formation, Table 2. There

is a reported correlation between risk of cancer incidence and age at pouch surgery and the type of anastomosis (stapled *vs.* handsewn), $p < 0.001$, Table 3.

The mean age of patients at FAP diagnosis was 30.6 years and the median age at the time of pouch surgery was 41 years. More cancers developed in those between 50 and 60 years of age. However, because of a few younger patients, the mean age of development of pouch anal cancer was 48.3 years.

Conventional TPC is indicated and the surgical options largely lie between IRA or RPC[17,77–83,84,85] for patients with FAP. RPC with IPAA offers the best available prophylaxis and is considered the criterion surgical procedure. [77] However, subsequent malignancies originating from residual mucosa may develop in the pouch and the IAA. Therefore, ileoanal pouch (IAP) mucosa and the anorectal mucosa below the IAA are potential areas for undergoing malignant transformation. [81] The cause of true pouch cancer seems to be different from the cancer arising from residual rectal or anal transitional epithelium, and the risks associated with these true pouches are controversial.[16] It has been suggested that TPC may not be a “cancer free” alternative to IRA. [86] Incidence of cancer in the ATZ in mucosectomized, handsewn IPAA, and stapled IPAA in patients with FAP have been reported in a study by von Roon et al. [9] They surveyed 140 patients out of 260 who were followed-up endoscopically for a median of 10.3 years after RPC. Fifty-two patients (37%) developed neoplastic transformation in the anorectal segment, with a cumulative risk at 10 years of 22.6% after mucosectomy with manual anastomosis and 51.1% after stapled IAA ($p < 0.001$).

CAUSES OF DEATH

Although the effects of prophylactic colectomy on prognosis and survival are encouraging, the cancer problem is not finished even after curative surgery for FAP. [1387] The attendance rate for surveillance colonoscopy is of utmost importance. [72888990] CRC is the main cause of death in this population, but it is progressively less common within families under surveillance, occurring almost exclusively in individuals exhibiting new mutations and with no family history of the syndrome. [9192] In the Finnish polyposis Registry experience, rectal stump cancer was the second cause of death. In a group of 236 FAP, primary CRC occurred in 18.2% and rectal cancer after IRA was the cause in 4.6%, comprising nearly one fifth of all FAP- related causes. [87] Arvantis et al [91] had reported that cancer caused 8.3% of all deaths after prophylactic colectomy. Yan et al [69] had similar observations mostly due to liver metastasis and advanced rectal cancer. This risk was addressed in long-term follow-up studies, suggesting that a more frequent indication of RPC instead of IRA may improve life expectancy by reducing rectal stump cancer rates. [87,93] Data from the St. Marks Hospital had previously shown a three-fold relative risk of death after IRA. [94]

CONCLUSION

Surgical treatment of FAP is still controversial and the choice between IPAA and IRA procedures is still a matter of debate. IPAA remains the alternative to IRA for the prophylactic treatment of FAP. The incidence of cancers in the anal canal (10%–31%) and ileal pouch (8%–62%) is apparent. Where there are polyps encroaching on the pectinel line, a mucosectomy should be indicated, but it is also noteworthy that this does not necessarily eliminate evolution risks. Most importantly, regardless of the anastomotic technique used, careful regular endoscopic surveillance of all patients surgically treated for FAP and having retained functionally acceptable pouches is critical.

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Table 1

Indications, contraindications, advantages and disadvantages summarized of surgical options for patients with FAP

Option	Indications	Contraindications	Advantages	Disadvantages
IRA	• < 20 rectal adenomas • < 1000 colonic adenomas [67,49,57,58]	• Severe dysplasia in the rectum • Cancer anywhere in large bowel • Large (>3cm) rectal adenomas	• Avoiding pelvic dissection[31] • Simple surgery • Lower complications • Good functional results • No stoma [58]	• Retained rectum may need to be removed later • Possibility of rectal cancer if patient is not compliant with follow-up
RPC with IPAA • Stapled or • Mucosectomy	• > 20 rectal adenomas, >1000 colonic adenomas[57] • Severe dysplasia in the rectum • Cancer anywhere in large bowel • Large (>3cm) rectal adenomas • ATZ clear of adenomas	• Incompetent sphincters • Rectal cancer invading sphincters • Pouch won't reach anus	• Avoid permanent stoma • Good function in most patients [23]	• Higher complication rate • May provoke desmoids • Decreased ability to conceive in women. [80,99] • Retained anal and lower rectal mucosa may develop neoplasia (28%) [26]
TPC & IL	• > 20 rectal adenomas, >1000 colonic adenomas [57] • Severe dysplasia in the rectum • Cancer anywhere in large bowel • Large (>3cm) rectal adenomas • ATZ clear of adenomas	• Incompetent sphincters • Rectal cancer invading sphincters • Pouch won't reach anus	• Avoids permanent stoma • Reasonable function in most patients. No residual anal mucosa (although neoplasia can still occur) [23,26]	• Higher complication rate • May provoke desmoids • Decreased ability to conceive in women.[80,99] • Retained anal and lower rectal mucosa may develop neoplasia (28%) • Frequent seepage • Night time incontinence.[23] • Anal neoplasia in 14%.[26]
TPC with CIL (Kock)	• > 20 rectal adenomas, >1000 colonic adenomas[37] • Severe dysplasia in the rectum • Cancer anywhere in large bowel • Large (>3cm) rectal adenomas • ATZ clear of adenomas • Incompetent sphincters	• Competent sphincters • No rectal cancer • Pouch reaches anus	• Lower complication rate • Lower chance of reoperation • No anal incontinence	• Permanent stoma

Option	Indications	Contraindications	Advantages	Disadvantages
	• Rectal cancer invading sphincters • Pouch won't reach anus			

Abbreviation: IRA = Ileorectal anastomosis, RPC = Restorative proctocolectomy, IPAA = Ileal pouch-anal anastomosis, TPC & IL = Proctocolectomy and Ileostomy, TPC with CIL = Proctocolectomy with continent ileostomy (Kock), ATZ = anal transit zone

Table 2

Summary of published data of the incidence of adenocarcinomas after prophylactic surgery for FAP. This table underscores the fact that mucosectomy does not necessarily prevent the development of adenomas in the ATZ

Author	Nature of Study	Age at FAP Diagnosis, Year	Operation Technique	Interval, Surgery to Cancer, Years	Age at Cancer Diagnosis, years	Number of Patients	Location	Histology
Nugent, 1992 (28)	Retrospective series	Mean 26 (median 26)	IRA	Mean 13.6 (range 1–43)	Median 48 (range 28–67)	22	Rectal stump	Adenocarcinoma Dukes Classification A=9, B=4, C=8. A/C=1
Hoehner, 1994 (95)	Case report	34	IPAA/Handsewn	20	54	1	IAA	T4N0M0
Bassuini, 1996 (35)	Case report	28	IPAA/Handsewn	3	31	1	Ileal pouch	T3N0M0
von Herbay, 1996 (96)	Case report	14	IPAA/MUC	8	33	1	Pouch-anal canal	T1N0M0
Palkar, 1997 (36)	Case report	39	IPAA	4.7	44	1	Ileal pouch	T4N0M0
Vuilleumier, 2000 (97)	Case report	31	IPAA/Stapled	7	38	1	IAA	T4N0M0
Brown, 2001 (109)	Case report	37	IPAA /MUC	7.4	44	1	Anastomotic ring	T4N0M0
Cherki, 2003 (37)	Case report	31	IPAA/Handsewn	3.5	34.5	1	Pouch body	T3N1M0
Ooi, 2003 (98)	Retrospective series	33 & 33	IPAA/DS	3 and 8	36 and 41	2	ATZ and ATZ	T1N0M0 and T1N0M0
Vrouenraets, 2004 (99)	Case report	28 & 38	IPAA/DS	8 and 10	36 and 48	2	Anal site and Anal site	T2N0M0 and T4N0M0
Campos, 2005 (106)	Case report	30	IPAA/MUC/Handsewn	12	40	1	Anal margin	Mucinous T2N0Mx
Ulas, 2006 (38)	Case report	36	IRA & IPAA/MUC	19 and 28	55 and 64	1 & 1	Rectal stump and at anastomosis	Metachronous cancer
Linehan, 2008 (4)	Case report	30	IPAA /DS	6	40	1	Pouch mucosa and Muscle wall	Adenocarcinoma Dukes A Adjuvant chemotherapy. Doing well.
Tajika, 2009 (8)	Case report	46	IPAA	8.6	55	1	Ileal pouch, 5 cm above anastomosis	T4N2M0
Tajika, 2009 (16)	Case report	39	KP	29	68	1	Mid pouch	T3N0M0
Lee, 2009 (100)	Case report	49	IPAA	6	56	1	Above anal verge	T2N0M0 Adenocarcinomas
de Campos, 2010 (101)	Prospective study	Average 35.1 (14–82)	IRA			12	Ileal pouch (#2) &/or Rectal stump (#10) Pouch body	5 Adenocarcinomas, 13 Low-grade dysplasia, 8 High-grade dysplasia.
				LGD 0.3–1.3				
			13 IRA/Stapled					

Author	Nature of Study	Age at FAP Diagnosis, Year	Operation Technique	Interval, Surgery to Cancer, Years	Age at Cancer Diagnosis, years	Number of Patients	Location	Histology
Banasiewicz, 2011 (105)	Retrospective study	22.49±12	13 IPAA/MUC	HGD 0.21 –1.42 Neoplasia 1.54	10 to 20	26	ATZ	1 Adenocarcinima, 19 Low-grade dysplasia, 10 High-grade dysplasia.
Booij, 2010 (107)	Retrospective study	26	IRA (#34) & IPAA (#9)	9, 10, 11 and 12	35, 36, 37 &38	4	Rectal stamp	Pouch excisions. Two died of metastasis
von Roon, 2011 (9)	Retrospective series		IPAA /MUC/ Handsewn	13	Mean 32 (14–62)	1	Pouch body	Adenocarcinoma Died of metastasis
Tonelli, 2012 (102)	Prospective study	19 & 42	IPAA/MUC (in 66) IPAA/DS (in 3)	IRA (16), IPAA 3 & 11	29 & 58	2	Pouch body	pT3,N0 & pT2N0
Makni, 2012 (103)	Case report	16	IPAA/MUC	10	26	1	Pouch body	Adenocarcinoma
Vitellaro, 2012 (104)	Prospective study	17, 17, 13, 13 & 18	IPAA	5, 0.4, 6.8, 2.6 & 1.1	22, 17.4,19.8, 15,6 & 19.1	5	ATZ	5 Dysplasia & 1 Desmoid tumor
Yan, 2012 (69)	Prospective study	Median 29 (range 16–65)	IPAA	15, 10, 5 & 6	48, 65,	4	Pouch mucosa	Adenocarcinomas T3N2M0

Abbreviations: IPAA, Ileo-pouch anal anastomosis; KP, Kock pouch; PP, Pouch polyposis; VA, Villous adenoma; IRA, Ileal rectal anastomosis; DS, Double stapled; FAP, Familai adenomatous polyposis; ATZ, Anal transtional zone; RPC, Restorative proctocolectomy; MUC, Mucosectomy; LGD, Low-grade dysplasia; HGD, High-grade dysplasia

Table 3

Incidence of (adenomas and) cancer in the ATZ in mucosectomized, handsewn IPAA and stapled IPAA in patients with FAP.

Author	Follow-up-yrs	Number of patients followed-up in the study	Number of patients developed neoplastic transformation	IPAA with mucosectomy that developed neoplastic transformation	IRA Stapled that developed neoplastic transformation	*P-value*
von Roon et al, 2011 [9]	10.3 (median)	140	52 (37%)	22.6%%	51.1%	*0.001*
Friedrech et al. 2008 [107]	6.8 (range 0.4–20.3)	212	74 (35%)	29%	64%	*0.0004*
von Roon et al. 2007 [23]	5 (range 0.1–24.75)	91	24 (26%)	11 (19%)	13 (38)%	*0.047*
Remzi et al. 2001 [21]	5.8 vs. 3.6	119	44 (58%)	9 of 42 (21%) in the pouch and 6 of 42 had it in mucosectomized ATZ	21 of 76 (28%) in ATZ and 8 (11%) had adenomas in the pouch body mucosa	
Van Duijvendijk et al, 1999 [22]	Median 5.5, range1–1.7)	97	48	13	35	*0.01*