

# Endoscopic management of patients with familial adenomatous polyposis after prophylactic colectomy or restorative proctocolectomy - systematic review of the literature

Aleksandar Gavric<sup>1</sup>, Liseth Rivero Sanchez<sup>2,3,4</sup>, Angelo Brunori<sup>2,3,4</sup>, Raquel Bravo<sup>3,4,5</sup>, Francesc Balaguer<sup>2,3,4</sup>, Maria Pellisé<sup>2,3,4</sup>

<sup>1</sup> Department of Gastroenterology and Hepatology, University Medical Centre Ljubljana, Slovenia

<sup>2</sup> Department of Gastroenterology, Hospital Clinic de Barcelona, Barcelona, Spain

<sup>3</sup> Institut d'Investigacions Biomediques August Pi I Sunyer (IDIBAPS), Barcelona, Spain

<sup>4</sup> Center for Biomedical Research in the Hepatic and Digestive Diseases Network (CIBERehd), Barcelona, Spain

<sup>5</sup> Surgery Department, Hospital Clinic de Barcelona, Barcelona, Spain

Radiol Oncol 2024; 58(2): 153-169.

Received 6 March 2024

Accepted 16 April 2024

Correspondence to: Maria Pellisé, M.D., Ph.D., Department of Gastroenterology Hospital Clinic de Barcelona. Institut d'Investigacions Biomediques August Pi I Sunyer (IDIBAPS). Hospital Clinic of Barcelona. Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBERehd). Universitat de Barcelona, Barcelona, Spain. E-mail: mpellise@clinic.cat

Disclosure: Maria Pellisé: consultant fees from Olympus and Fujifilm, speaker fees from Norgine, Mayoli and Casen recordati. Francesc Balaguer: consultant fees from Olympus, Nouscom and Norgine, editorial fees from Elsevier, endoscopic equipment on loan of FujiFilm and Olympus, research grant from FujiFilm, ZiuZ and Casen recordati, consultancy for FujiFilm, Olympus, and speakers' fee from Olympus, Fujifilm, Norgine, IPSEN.

This is an open access article distributed under the terms of the CC-BY license (<https://creativecommons.org/licenses/by/4.0/>).

**Background.** Patients with familial adenomatous polyposis (FAP) develop early colorectal adenomas and if left untreated, progression to cancer is an inevitable event. Prophylactic surgery does not prevent further development of cancer in the rectal remnant, rectal cuff in patients with ileal pouch anal anastomosis (IPAA) and even on the ileal mucosa of the pouch body. The aim of this review is to assess long-term rates of cancer and adenoma development in patients with FAP after prophylactic surgery and to summarise current recommendations for endoscopic management and surveillance of these patients.

**Materials and methods.** A systematic literature search of studies from January 1946 through to June 2023 was conducted using the PRISMA checklist. The electronic database PubMed was searched.

**Results.** Fifty-four papers involving 5010 patients were reviewed. Cancer rate in the rectal remnant was 8.8–16.7% in the western population and 37% in the eastern population. The cumulative risk of cancer 30 years after surgery was 24%. Mortality due to cancer in the rectal remnant is 1.1–11.1% with a 5-year survival rate of 55%. The adenoma rate after primary IPAA was 9.4–85% with a cumulative risk of 85% 20 years after surgery and a cumulative risk of 12% for advanced adenomas 10 years after surgery. Cumulative risk for adenomas after ileorectal anastomosis (IRA) was 85% after 5 and 100% after 10 years. Adenomas developed more frequently after stapled (33.9–57%) compared to hand-sewn (0–33%) anastomosis. We identified reports of 45 cancers in patients after IPAA of which 30 were in the pouch body and 15 in the rectal cuff or at the anastomosis.

**Conclusions.** There was a significant incidence of cancer and adenomas in the rectal remnant and ileal pouch of FAP patients during the long-term follow-up. Regular endoscopic surveillance is recommended, not only in IRA patients, but also in pouch patients after proctocolectomy.

Key words: familial adenomatous polyposis; ileorectal anastomosis; ileal pouch-anal anastomosis

## Introduction

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited disease caused by pathogenic variants in the adenomatous polyposis coli (APC) gene<sup>1</sup> with reported incidence of one in 8,000 to 12,000 live births.<sup>2</sup> The main hallmark of the disease is the presence of multiple colorectal adenomas, leading to a 100% lifetime risk of developing cancer if the colon remains in situ.<sup>3</sup> To prevent the development of cancer, prophylactic colectomy or proctocolectomy is performed when the adenoma burden cannot be managed endoscopically or at the age of 18–25 years old. The following types of surgery are available<sup>4</sup>: total colectomy with ileorectal anastomosis (IRA) or ileosigmoid anastomosis (ISA); proctocolectomy with/without mucosectomy and stapled ileal pouch-anal anastomosis (IPAA) or hand-sewn IPAA; and total proctocolectomy with end ileostomy. Until restorative proctocolectomy with IPAA and pouch reconstruction was described in the 1970s, colectomy with IRA or end ileostomy was the only surgical prophylactic procedure available and was associated to a considerable high CRC incidence and mortality.<sup>5</sup> After this, proctocolectomy with pouch reconstruction (IPAA) was the technique of choice in patients with a high adenoma burden and was sought to eliminate the risk of CRC in FAP patients. However, since the first report of pouch cancer in 1994<sup>6</sup>, there has been a substantial increase in published literature reporting rates of adenoma and cancer development after primary IPAA. The development of adenomas along life in remnant rectal mucosa is a natural phenomenon

in this population. Long live periodical surveillance with rectoscopies is widely recommended in international guidelines as shown in Table 1.<sup>4,7-10</sup> As there are no randomised trials comparing endoscopic surveillance and management strategies for FAP patients with IRA and IPAA, we aimed to systematically evaluate adenoma and cancer development after prophylactic surgery, define potential risk factors and to summarise endoscopic practices from published series.

## Materials and methods

Our review is reported according to the PRISMA guidelines.<sup>11</sup>

### Search strategy

We searched PUBMED from inception to June 2023 to identify studies evaluating long-term adenoma and cancer development in patients with FAP after prophylactic surgery. Deduplication was performed using Zotero software.<sup>12</sup> Reference lists of included studies were hand-searched for additional relevant studies. The search was limited to studies, published in English. We used the following keywords: “FAP”, “IRA”, “IPAA”, “familial adenomatous polyposis” and “proctocolectomy”.

### Inclusion criteria

We included single-or multicentre retrospective cohort studies, prospective cohort studies and retrospective analyses of polyposis registries. Due to

**TABLE 1.** Summary of recommendations from the international guidelines

First author and publication date (ref.)	Endoscopic surveillance – patients with IRA	Indications for secondary proctectomy patients with IRA	Endoscopic surveillance – patients with IPAA
Vasen et al., 2008 <sup>7</sup>	Every 3 to 6 months	Multiple large adenomas (> 5 mm) Adenomas with dysplasia	Every 6 to 12 months
Balmaña et al., 2013, ESMO <sup>8</sup>	Every 12 months	No recommendations	Every 12 months
Stoffel et al., 2015, ASCO <sup>9</sup>	Every 6 to 12 months	No recommendations	Every 6 months to 5 years (Intervals should be determined on a case-by-case basis and may be even shorter than 1 year for some individuals)
Sygnal et al., 2015, ACG <sup>10</sup>	Every 12 months	No recommendations	Every 12 months
Herzig et al., 2017, ASCRS <sup>4</sup>	Every 12 months	No recommendations	Every 12 months
Van Leerdam ME et al., 2019, ESGE <sup>53</sup>	Every 12 to 24 months	No recommendations	Every 12 to 24 months
Yang J et al., 2020, ASGE <sup>54</sup>	6 months after surgery with 6 to 12 months further surveillance interval		12 months after surgery with 12 to 24 months further surveillance interval. 6 months if advance adenoma

ACG = American College of Gastroenterology; ASCO = American Society of Clinical Oncology; ASCRS = American Society of Colon and Rectal Surgeons; ASGE = American Society for Gastrointestinal Endoscopy; ESGE = European Society of Gastrointestinal Endoscopy; ESMO = European Society for Medical Oncology; IPAA = ileal pouch anal anastomosis; IRA = ileorectal anastomosis

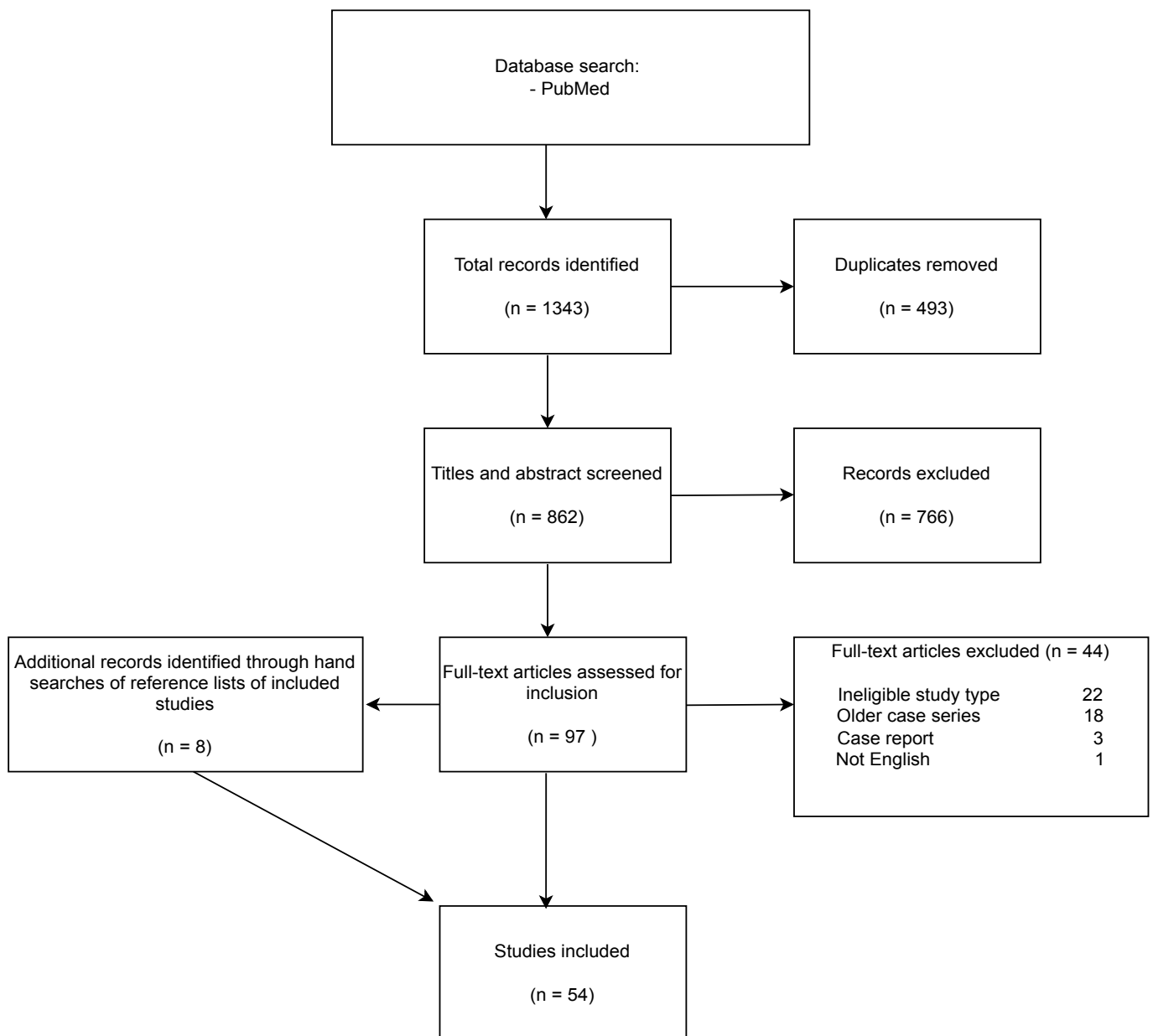


FIGURE 1. Flowchart of the systematic review according to the Preferred Reporting Items for Systematic Reviews (PRISMA) schema.

the rarity of the events, we only considered case reports for inclusion when summarising reports on cancers after primary IPAA. Only the most recent series from the same institution or polyposis registry were included in the analysis, as some research groups regularly publish retrospective analyses of their cohorts or polyposis registries. Full-text screening and data extraction were performed by a single researcher (AG). Manuscripts of three case reports could not be obtained, data were summarised from the two review articles.<sup>13,14</sup>

## Results

### Studies identified

Of 97 full-text articles screened for eligibility (Figure 1), 46 met our inclusion criteria. A further 8 articles were identified by hand searching the reference lists of the included studies (6 case reports, 1 retrospective cohort, 1 polyposis registry analysis). We included 22 retrospective analyses, 14 case reports (carcinoma development after primary IPAA), 15 retrospective analyses of prospectively

maintained polyposis registries and 3 prospective cohort studies. Only 5 studies were multicentre and 1 was bi-centre. The studies were published between 1994 and 2023. The studies included between 1 and 925 patients. A total of 5010 patients were included in the review. Summary characteristics of the included studies are shown in Table 2.

### Total colectomy with ileorectal anastomosis

#### Adenomas

Five studies described the rate of adenoma development in the residual rectum (Supplementary Table 1). In 8 studies that analysed the frequency of secondary proctectomy due to endoscopically unmanageable polyposis, the rate of proctectomy ranged from 3.7% to 35%.<sup>15</sup> Five studies described adenoma evaluated in the neoterminal ileum (Table 3), with a high variance in reported rates from 0%<sup>16</sup> to 47.6% in patients followed-up for median of > 20 years<sup>17</sup> in one study including a paediatric cohort<sup>18</sup>, 2 patients required resection of the terminal ileum and construction of a new IRA, one due to low grade dysplasia (LGD) and one due to high grade dysplasia (HGD) adenoma.

#### Rectal cancer

The reported rate of cancer in the rectal remnant (Table 4) after primary IRA is 8.8%<sup>18</sup> to 16.7%<sup>19</sup> with a median follow-up from surgery<sup>19</sup> of 91.1 months (3–557 months). However, studies from Japan report higher rates of up to 37%<sup>20</sup>, but this is due to the inclusion of *in situ* carcinoma in the cancer definition. The same study had the longest median follow-up of 21.1 years (3–35). On the other hand, a small cohort of 21 patients from France reported zero cases of cancer during a median follow-up of 8.4 years. Jenner *et al.*<sup>21</sup> only included patients with a confirmed mutation. Five studies reported a cumulative incidence of rectal cancer ranging from 3%<sup>22</sup> to 17.2%<sup>19</sup> at 5 years, 7.7%<sup>23</sup> to 24.1%<sup>19</sup> at 10 years, 11%<sup>22</sup> to 23%<sup>23</sup> at 20 years, and 24%<sup>22</sup> at 30 years after the primary IRA. In one of the largest studies<sup>24</sup>, which analysed data from 4 national registries and 776 patients, the 10-year cumulative risk of residual rectal cancer was 4.4% (95% CI, 2.6–6.2) for patients who underwent surgery before 1990 and only 2.5% (0–5.5) after the 1990. Only one study reported the time from surgery to cancer diagnosis (median 102 months [1–26 years])<sup>23</sup>; other studies reported follow-up time from surgery, but did not clearly define when follow-up started nor the surveillance regime. Five studies reported mortality ranging from

1.6%<sup>23</sup> to 11.1%<sup>20</sup> in which 3 out of 27 patients died from cancer in the rectal remnant. Only one of two studies that examined long-term survival after diagnosis of residual rectal cancer reported a 5-year survival rate of 55%.<sup>22</sup> In a study from Japan, 5-year survival was 94%<sup>25</sup>, but the excellent survival was explained by the inclusion of carcinoma *in situ* despite the exact proportion of these was not given.

#### Risk factors for progressive phenotype of rectal remnant

Eleven studies reported nine risk factors predictive of the progressive rectal residual phenotype (Supplementary Table 2). Four studies analysed the genotype-phenotype relationship; The presence of a pathogenic variant between codons 1250–1464 was an independent risk factor for subsequent cancer development (HR 4.4 [1.3–15.0]<sup>23</sup> and for the secondary proctectomy<sup>26,27</sup> (HR 3.91 [1.45–10.51],  $P = 0.007$ ). In a small study of 25 patients, all patients ( $n = 3$ ) with carpeting rectal remnant polyposis had a pathogenic variant in codon 1309, but this was only descriptive data.<sup>28</sup> An aggressive colonic phenotype with at least 500 polyps at time for surgery was identified as a risk factor in three studies (Supplementary Table 2). Two studies<sup>15,25</sup> have identified > 20 rectal remnant polyps at the time of surgery or during the endoscopic surveillance<sup>26</sup> as an independent risk factor for secondary proctectomy (HR 30.99 [9.57–100.32]  $P < 0.001$ ), while in one study a cut-off of > 10 rectal adenomas<sup>28</sup> was associated with a more aggressive phenotype, as these patients developed a mean of 9.29 rectal residual adenomas per patient per year compared with 0.67 adenomas per patient per year if they had < 5 rectal polyps at the time of surgery. Other potential risk factors included patient age at diagnosis of rectal residual cancer, time since surgery, presence of congenital hypertrophy of the retinal pigment epithelium, and presence of colon cancer at the time of primary surgery. APC site mutation, preoperative colon phenotype, presence of duodenal adenomas and rectal remnant phenotype on surveillance were not identified as risk factors for progressive rectal remnant disease phenotype only in one study.<sup>20</sup>

### Proctocolectomy with ileal-pouch anal anastomosis

#### Adenomas

Seventeen studies (Table 5) reported on the development of adenomas after IPAA, of which eight studies differentiated between the pouch body

TABLE 2. Characteristics of included studies

First author and publication date (ref.)	No. of patients	Country	Setting	Study design	Surgery performed (period)	Study population
Aelvoet <i>et al.</i> , 2023 <sup>55</sup>	144 (111 IPAA, 33 ileostomy)	The Netherlands	Single	Cohort/Retrospective	/	IPAA, ileostomy
Tatsuta <i>et al.</i> , 2023 <sup>56</sup>	65 (22 IRA, 20 IPAA)	Japan	Single	Cohort/Retrospective	1976–2022	IRA, IPAA
Anele <i>et al.</i> , 2022 <sup>57</sup>	199 (199 IRA)	United Kingdom	Single	Cohort/Retrospective	1990–2017	IRA
Colletti <i>et al.</i> , 2022 <sup>58</sup>	715 (715 IRA)	Italy	Multicentre	Retrospective analysis of the Registry	1977–2021	IRA
Pasquer <i>et al.</i> , 2021 <sup>59</sup>	289 (197 IRA, 92 IPAA)	France	Multicentre	Retrospective analysis of the Registry	1965–2015	IRA, IPAA
Ardoino <i>et al.</i> , 2020 <sup>60</sup>	925 (585 IRA, 340 IPAA)	Italy	Multicenter	Retrospective analysis of the Registry	1947–2015	IRA, IPAA
Tajika <i>et al.</i> , 2019 <sup>16</sup>	47 (14 IRA, 25 IPAA, 8 ileostomy)	Japan	Single	Cohort/Retrospective	1965–2017	IRA, IPAA and ileostomy
Ganschow <i>et al.</i> , 2018 <sup>61</sup>	192	Germany	Singe	Cohort/Prospective and retrospective analysis of Polyposis Registry	Endoscopy data collected during 2010–2013	IPAA
Kariv <i>et al.</i> , 2017 <sup>62</sup>	45	Israel	Single	Cohort/Retrospective	1986–2013	IPAA
Patel <i>et al.</i> , 2016 <sup>42</sup>	21 (6 IRA, 5 IPAA, 10 intact colon)	Indianapolis, USA	Single	Cohort/Retrospective	Endoscopies performed between 2004–2016	IRA, IPAA and intact colon
Walsh <i>et al.</i> , 2016 <sup>63</sup>	1	Ireland	Single	Case report	1987	IPAA - cancer
Maehata <i>et al.</i> , 2015 <sup>20</sup>	27	Japan	Single	Cohort/Retrospective	1990–2004	IRA
Ganschow <i>et al.</i> , 2015 <sup>50</sup>	100; 50 hand-sewn and 50 stapled anastomoses	Germany	Single	Cohort/Prospective	?	Hand-sewn vs. stapled anastomosis
Goldstein <i>et al.</i> , 2015 <sup>43</sup>	59	Israel	Single	Cohort/Retrospective	1986–2013	IPAA
Zahid <i>et al.</i> , 2015 <sup>64</sup>	27	Australia	Single	Cohort/Retrospective	1984–2011	IPAA
Kennedy <i>et al.</i> , 2014 <sup>65</sup>	95; 85 hand-sewn and 1 stapled anastomosis	Rochester, Mayo Clinic, USA	Single	Cohort/Retrospective	1987–2011	IPAA
Koskenvuo <i>et al.</i> , 2013 <sup>22</sup>	140	Finland	Single	Cohort/Retrospective	1963–2012	IRA
Pommaret <i>et al.</i> , 2013 <sup>35</sup>	118	France	Single	Cohort/Retrospective	/	IPAA and IRA
Boostrom <i>et al.</i> , 2013 <sup>66</sup>	117	Rochester, Mayo Clinic, USA	Single	Cohort/Retrospective	1972–2007	IPAA
Ozdemir <i>et al.</i> , 2013 <sup>37</sup>	260; 86 hand-sewn and 175 stapled anastomoses	Cleveland, USA	Single	Analysis of polyposis registry	1983–2010	Hand-sewn vs. stapled anastomosis
Wasmuth <i>et al.</i> , 2013 <sup>67</sup>	61; 39 hand-sewn with mucosectomy and 22 without of which 15 were stapled and 7 hand-sewn anastomoses	Norway	Multicenter	Analysis of polyposis registry	1986–2008	IPAA (mucosectomy vs. no-mucosectomy)
Yan <i>et al.</i> , 2012 <sup>68</sup>	42 (33 IPAA; 6 IRA ?)	China	Single	Cohort/Retrospective	1988–2008	IPAA and IRA

First author and publication date (ref.)	No. of patients	Country	Setting	Study design	Surgery performed (period)	Study population
Makni <i>et al.</i> , 2012 <sup>69</sup>	1	Tunisia	Single	Case report	1996	IPAA - cancer
Tonelli <i>et al.</i> , 2012 <sup>51</sup>	69	Italy	Single	Cohort/ Prospective data collection	1984–2008	IPAA
von Roon <i>et al.</i> , 2011 <sup>70</sup>	140; 44 hand-sewn and 76 stapled anastomoses	UK	Single	Retrospective analysis of St. Mark's Hospital Polyposis Registry	1978–2007	Hand-sewn vs. stapled anastomosis
Banasiewicz <i>et al.</i> , 2011 <sup>32</sup>	165	Poland	Bicenter	Bicenter/ Retrospective analysis	1985–2009 operated, Clinical data from endoscopy FUP between 2004–2009	IPAA
Booij <i>et al.</i> , 2010 <sup>18</sup>	43 (34 IRA)	The Netherlands	Single	Cohort/ Retrospective	1977–2005	IRA and IPAA
Sinha <i>et al.</i> , 2010 <sup>26</sup>	427	UK	Single	Retrospective analysis of St. Mark's Hospital Polyposis Registry	1990–2008	IRA
Ault <i>et al.</i> , 2009 <sup>71</sup>	2	Los Angeles, USA	Single	Case series	1990, 1993	IPAA - cancer
Nieuwenhuis <i>et al.</i> , 2009 <sup>27</sup>	475	Denmark, Finland, Sweden, Netherlands	Multicenter	Analysis of polyposis registry	/	IRA
Yamaguchi <i>et al.</i> , 2009 <sup>25</sup>	59	Japan	Single	Cohort/ Retrospective	1962–2007	IRA
Friederich <i>et al.</i> , 2008 <sup>31</sup>	212; 71 hand-sewn with mucosectomy and 115 stapled anastomoses	The Netherlands	Single	Analysis of National Polyposis Registry	1985–2005	IPAA
Campos <i>et al.</i> , 2008 <sup>19</sup>	36	Brasil	Single	Cohort/ Retrospective	1977–2006	IRA and IPAA
Bullow <i>et al.</i> , 2008 <sup>24</sup>	776; 576 operated in pre-pouch period and 200 in pouch period starting in 1990	Denmark, Finland, Sweden, Netherlands	Multicenter	Analysis of polyposis registry	1950–2006	IRA
Gleeson <i>et al.</i> , 2008 <sup>30</sup>	16	Rochester, Mayo Clinic, USA	Single	Cohort/ Retrospective analysis	1964–2003 (Analysis of endoscopies between 1992–2006)	IPAA and IRA
Lee <i>et al.</i> , 2008 <sup>72</sup>	1	Korea	Single	Case report	1998	IPAA - cancer
Linehan <i>et al.</i> , 2007 <sup>73</sup>	1	Ireland	Single	Case report	1997	IPAA - cancer
Valanzano <i>et al.</i> , 2007 <sup>28</sup>	25	Italy	Single	Cohort/ Prospective	1986–2004	IRA
Moussata <i>et al.</i> , 2007 <sup>17</sup>	21	France	Single	Cohort/ Retrospective	/	IPAA and IRA
Ulas <i>et al.</i> , 2006 <sup>74</sup>	1	Turkey	Single	Case report	1993	IPAA - cancer
Campos <i>et al.</i> , 2005 <sup>19</sup>	1	Brazil	Single	Case report	/	IPAA - cancer
Groves <i>et al.</i> , 2005 <sup>34</sup>	60	UK	Single	Retrospective analysis of St. Mark's Hospital Polyposis Registry	/	IPAA
Vroueraets <i>et al.</i> , 2004 <sup>75</sup>	2	The Netherlands	Single	Case report	1990, 1991	IPAA – cancer
Ooi <i>et al.</i> , 2003 <sup>36</sup>	2	Cleveland, USA	Single	Case report	/	IPAA – cancer

First author and publication date (ref.)	No. of patients	Country	Setting	Study design	Surgery performed (period)	Study population
Church <i>et al.</i> , 2003 <sup>38</sup>	197; 62 operated in pre-pouch period and 135 in pouch period starting in 1983	Cleveland, USA	Single	Analysis of polyposis registry	1950–1999	IRA
Cherki <i>et al.</i> , 2003 <sup>76</sup>	1	France	Single	Case report	/	IPAA - cancer
Thompson-Fawcett <i>et al.</i> , 2001 <sup>77</sup>	33	Canada	Single	Cohort/Prospective	/	IPAA
Church <i>et al.</i> , 2001 <sup>15</sup>	213 (165 IRA)	Cleveland, USA	Single	Analysis of polyposis registry	/	IRA and IPAA
Brown <i>et al.</i> , 2001 <sup>78</sup>	1	Singapore	Single	Case report	/	IPAA - cancer
Bertario <i>et al.</i> , 2000 <sup>23</sup>	371	Italy	Multicenter	Retrospective analysis of Hereditary tumor registry	1955–1997	IRA
Vuilleumier <i>et al.</i> , 2000 <sup>79</sup>	1	UK	Single	Case report	1990	IPAA - cancer
Jenner <i>et al.</i> , 1998 <sup>21</sup>	55	Australia	Single	Analysis of polyposis registry	?–1994	IRA
Bassuini <i>et al.</i> , 1996 <sup>80</sup>	1	UK	Single	Case report	1991	IPAA - cancer
Hoehner <i>et al.</i> , 1994 <sup>6</sup>	1	Iowa, USA	Single	Case report	/	IPAA - cancer

FUP = follow up; IPAA = ileal pouch anal anastomosis; IRA = ileorectal anastomosis

and the anastomosis, one study only reported the anastomotic adenoma rate, while in the remaining seven studies the authors did not precisely define the anatomical location of the adenomas. The median age of patients at the time of surgery ranged from 15.4 to 34.6 years, with a median follow-up from surgery of 5.4 years to a median of 21.6 years. The reported rate of adenoma in the pouch body ranged from 9.4%<sup>29</sup> to 76.9%.<sup>30</sup> The proportion of HGD histology among adenomas at the polyp level ranged from 5.9%<sup>17</sup> to 53.2%.<sup>31</sup> In one study, the proportion of advanced adenomas on a per-patient basis was 11.2%.<sup>31</sup> The cumulative risk of adenoma development after primary IPAA was 12% and 58% at 5 and 20 years after the surgery respectively.<sup>16</sup> According to the analysis from Poland<sup>32</sup>, 50% of all patients would develop LGD 15 years after the surgery, while HGD is estimated to be present in half of the patients 17.5 years after the surgery. Six studies analysed the rate of adenoma development in the neo terminal ileum, the proportion of patients with histologically confirmed adenoma varied from 4.2%<sup>33</sup> to 23.1%<sup>30</sup> with at a median follow-up from surgery of 6.5<sup>34</sup> to 23.1 years.<sup>16</sup> The cumulative risk of developing an adenoma in the neo terminal ileum was 4.4% at 20 years and increased to 36% at 30 years after the surgery as reported in the same study. The presence of pouch body ad-

enomas was the only independent risk factor for the neo terminal ileum adenomas (OR, 2.16,  $P = 0.007$ ).<sup>35</sup>

### Cancer

Since the first case report of cancer arising in the ileal pouch of a FAP patient in 1994<sup>6</sup>, we have identified 45 (Table 6) cancers that have developed in FAP patients after primary IPAA. Of these, 30 were located in the pouch body and 15 in the anastomosis/rectal cuff. The time from surgery to cancer diagnosis was reported for 22 patients and ranged from 2.3<sup>36</sup> to 33 years.<sup>37</sup> The information about the interval since last follow-up was reported for only 15 patients. The shortest interval between normal endoscopic surveillance and cancer diagnosis was 9 months.<sup>16</sup> Of the studies that reported the final outcome, 13 (28.9%) patients were alive at the last follow-up (range 8 months to 6 years) after surgical therapy and 9 patients died of disseminated cancer (1 month to 4 years after diagnosis), most despite an initial R0 resection.

### Hand-sewn vs. stapled IPAA

Six studies (Supplementary Table 3) compared the rates of adenoma development at the anastomosis between hand-sewn and stapled techniques. The incidence of adenoma was lower for hand-sewn



**TABLE 3.** Rate of adenoma development in the neoterminal ileum in patients after ileorectal anastomosis (IRA) and ileal pouch anal anastomosis (IPAA)

First author and publication date (ref.)	Adenomas in the neoterminal ileum – after primary IPAA; n (%)	Cumulative risk for development of neoterminal adenomas	Years since surgery	Risk factor for adenomas in neoterminal ileum	Rate of adenomas in the neoterminal ileum – after primary IRA; n (%)	Years since surgery
Tajika <i>et al.</i> , 2019 <sup>16</sup>	4/24 (16.7)	4.4% at 20 years and 36% at 30 years after primary surgery	23.1 ± 5.8		0/14 (0.0)	
Boostrom <i>et al.</i> , 2013 <sup>66</sup>	4/33 polyps (12.0)					
Pommaret <i>et al.</i> , 2013 <sup>35</sup>	9/118 (6.5)			Presence of pouch adenomas (OR, 2.16, <i>P</i> = 0.007)		
Booij <i>et al.</i> , 2010 <sup>18</sup>					5/34 (14.7) 2 patients had resection of neo-terminal ileum, one due to LGD and other due to HGD adenoma.	
Gleeson <i>et al.</i> , 2008 <sup>30</sup>	3/13 (23.1)		Median 6.5 (0–15)		4/16 (25.0)	Median 12 (1–29)
Moussata <i>et al.</i> , 2007 <sup>17</sup>			Mean 17.6 ± 7.8 (6–35) Mean from colectomy to diagnosis: 16.4 ± 8.5 (5–30)		10/21 (47.6) of which 2 were advanced adenomas.	
Groves <i>et al.</i> , 2005 <sup>34</sup>	2/20 (10.0)		6 (1–14)		1/47 (2.0%)	12 (0–39)
Thompson-Fawcett <i>et al.</i> , 2001 <sup>77</sup>	1/24 (4.2)		Median 7 (1–19)			

HGD = high grade dysplasia; LGD = low grade dysplasia

anastomosis, ranging from 0 to 33%, and for stapled anastomosis, ranging from 33.9 to 57%. The 10-year cumulative risk of adenoma development is 20–22.6% for hand-sewn anastomosis and 51.1–64% for stapled anastomosis.

### Risk factors for adenoma development after primary IPAA

Nine studies analysed risk factors for adenoma development (Supplementary Table 4). None of the seven studies found a genotype-phenotype association. There was no association between colon adenoma burden at the time of surgery and subsequent development of pouch adenomas in three out of four studies. In the only positive study, none of the patients with < 200 colon polyps developed pouch adenomas, whereas almost half of the patients with > 1000 colon polyps later developed later pouch adenomas. Three studies have identified age of the pouch as a risk factor, while three others found no association between time since surgery and the rate of pouch adenomas. An association

between the Spigelman score and the development of pouch adenomas was not confirmed. One study identified the presence of gastric adenomas as an independent risk factor for the development of pouch adenomas.

## Discussion

Using a systematic approach, we identified a wide range of reported adenoma and cancer rates in the rectal remnant, pouch body, at IPAA and in the neoterminal ileum. The wide range in adenoma rates is probably partly due to the wide range of included studies in terms of year of publication. The equipment and quality of optical diagnosis has improved considerably in recent years, allowing better detection of adenomas and more precise examination of the pouch and rectal remnants. In addition, the risk stratification of patients at the time of surgery has also improved, allowing patients with a more aggressive phenotype to un-



**TABLE 4.** Patient characteristics and rate of rectal remnant cancer rate in patients after ileorectal anastomosis (IRA)

First author and publication date	Proportion of men; n / (%)	APC mutation Underwent n / (%); Positive in; n/(%)	Follow-up (years/ months) since surgery	Years since surgery to cancer diagnosis	Age at surgery	Age at cancer diagnosis	Rectal remnant cancer rate; n/ (%)	Cumulative risk for rectal cancer	Rectal cancer mortality
Colletti et al., 2022 <sup>58</sup>	57.4%	93.6% /	/	Median of 13 years	/	/	47 / 715 (6.57)	/	14/47 (29.8%) at median follow up of 13 years.
Pasquer et al., 2021 <sup>59</sup>	95 (48.2)	/	/	/	/	/	12 / (6.1); 1 was metastatic, 2 were resected endoscopically, 10 surgically	/	/
Maehata et al., 2015 <sup>20</sup>	16 (59.3)	21 (77.8) 14 (66.7)	21.1 (3–35)	/	Median 27 years (9–66)	/	10/27 (37.0); 6/10 cancers were TisNOM0	8% at 10 years; 19% at 20 years; 57% at 30 years	3/27 (11.1)
Koskenvuo et al., 2013 <sup>22</sup>	59 (42.1)	/	Median 15 years (0–44)	/	Mean 36 years (18–71)	Cumulative risk 2% at 40 years age; 7% at 50; 13% at 60 years age and 16 % at 70 years age.	18/140 (13%)	3% at 5 years; 4% at 10 years; 11% at 20 years; 24% at 30 years after IRA	10/140 (7%); 5-year survival 55%. Cumulative risk for death due to rectal cancer after IRA: 2% at 5 years, 3% at 10 years and 9% at 30 years.
Booij et al., 2010 <sup>8</sup>	19 (44.2)	/	/	/	Median 16 (7–25)	/	3/34 (8.8)	/	2/34 (5.8)
Sinha et al., 2010 <sup>26</sup>	232 (54.3)	/ 311/427 (72.8)	Median 15 years (7–25)	/	Median 21 years (11–47)	/	48/427 (11.2%)	/	/
Yamaguchi et al., 2009 <sup>25</sup>	35 (59.3)	/	Median 8.9 years	/	Median 30 years (13–65)	/	17/59 (30%)	/	5-year survival 94%; 10-year survival 94%.
Nieuwenhuis et al., 2009 <sup>27</sup>	/	/	/	/	/	/	/	3.7% for group 1; 9.3% for group 2; 8.3% for group 3. <sup>28</sup>	/
Campos et al., 2008 <sup>19</sup>	/	/	91.1 (3–557)	/	Mean 45.8 years	Mean 50.6 years	6/36 (16.7)	17.2% at 5 years; 24.1% at 10 years; 43.1% after 15 years	/
Gleeson et al., 2008 <sup>30</sup>	/	/	FUP initiated median 12 (1–29) years after surgery	/	/	40 and 59 years.	2/16 (12.5)	/	/
Bullow et al., 2008 <sup>24</sup>	401 (51.7)	/	Median 7 years (0–13). Patients were operated between 1950–2006	/	Median 27 (7–75)	/	60/776 (7.7%) (56/576: 10% and 4/200: 2%)	10-year cumulative risk 4.4% [95% CI 2.6–6.2] in pre-pouch era; 10-year cumulative risk 2.5% [95% CI 0–5.5] in pouch era;	/
Moussata et al., 2007 <sup>17</sup> They only watched ileal mucosas above the IRA	10 (47.6)	21/21 (100.0) 14/21 (66.7)	Mean 8.4 years ± 5 since colectomy	/	/	/	0/21 (0.0)	/	/
Church et al., 2003 <sup>38</sup>	92 / (46.7)	/	Pre-pouch era: 212 months (IQR 148 months); Pouch era: 60 months (IQR 80 months)	/	Median age 23 years (IQR 15.5 years pre-pouch and 17 years pouch)	/	8 (12.9%) in the pre-pouch era and 0 in pouch era.	/	/
Bertario et al., 2000 <sup>23</sup>	206/371 (55.5)	297/371 (80.1) 200/297 (67.3)	Median 81 months	Median 102 months (1–26 years)	Mean 32 years	/	27/371 (7.3)	10 years – 7.7% 15 years – 13.1 % 20 years – 23.0%	6/371 (1.6)
Jenner et al., 1998 <sup>21</sup>	25/55 (45.0)	55/ (100.0)	Median 10 (1–31)	/	Mean age 30 (13–62)	Median 41	7/55 (12.7)	/	/

Colonic phenotype divided in 3 groups: (Group 1 - <100 polyps and mutation in codons 1–157, 312–412 and 1596–2843; Group 2 Hundred of polyps and mutation in codons 158–311, 413–1249 and 1465–1595; Group 3 Thousand of polyps and mutation in codon 125

APC = adenomatous polyposis coli; FUP = follow up

dergo primary restorative proctocolectomy while primary IRA can still be offered to patients with an attenuated phenotype or low rectal disease burden. Indeed, in the largest study of four European national polyposis registries, the cumulative risk

of cancer in the rectal remnant (CRR) was 10% in patients operated in the ‘pre-pouch’ period and only 2% in those who were operated in the ‘pouch period.’<sup>24</sup> Similar findings have been reported from the USA<sup>38</sup> where 8 patients operated before

TABLE 5. Patient characteristics and rate of adenomas in patients after primary ileal pouch anal anastomosis (IPAA)

First author and publication date	Sex (man); n (%)	APC mutation Underwent; n (%); Positive in; n (%)	Distinguish between pouch body and rectal cuff	Follow-up (months/years)	Time from surgery to first adenomas (years)	Age at surgery (years)	Rate of adenomas (≥ 1 polyp)	Size of adenomas, mm	Histology of adenomas; n (%)	Number of Adenomas
Aelvoet AS et al., 2023 <sup>55</sup>	81 (56)	101 (91) 96 (86)	Yes	Median 152 (77–240)	15% at 5 years; 48% at 10 years; 85% at 20 years.	Median 24 (18–32)		Median 5 (3–15)	Tubular adenomas 31 (28%), Tubulovillous 26 (23%), Villous 5 (5%)	Prepouch ileum 4(2–13), Pouch body 20 (5–50), rectal cuff 6 (3–10)
Tajika et al., 2019 <sup>26</sup>	16 (47.1)	/	Yes	Median 21.6 (3.7–8.8)	32 (35.9) of patients showed progression of pouch adenomas during FUP	Median 34.6 (17–52)	24/34 (70.6)	2–40 mm	6 advanced adenomas (25.0)	1–300
Ganschow et al., 2018 <sup>61</sup>	100 (52.1)	133 (69.3) ? / 133	No	Median 12.8 (9–17) for patients with pouch adenomas and (2.5–12.2) for patients without pouch adenomas;	32 (35.9) of patients showed progression of pouch adenomas during FUP	27.5 years (10.2–58.5)	90/192 (46.9) at a median of 8.5 years (0.9–25.1) after IPAA. 5 years after IPAA 84.9% patients free of adenoma; 15 years after 40.4% and 20 years after 21.9% patients were free of adenomas.	53/192 (58.9) ≤ 4 mm; 24/192 (26.7) 5–10 mm; 13/192 (14.4) ≥ 10 mm	Tubular adenomas in 69/192 (76.7); tubulovillous adenomas in 16/192 (17.8); villous in 5/192 (5.6)	46/192 (51.1) had < 4; 14/192 (15.6) 5–10; 30/192 (33.3) > 10 adenomas
Goldstein et al., 2015 <sup>63</sup>	24 (41.0)		Yes	Mean 11.6 years ±14.6 years	Median adenoma free time interval since surgery; Cuff 10.8 years Pouch 16.9 years	Mean 30.8 years ±10.8 years	35/59 (59.0); - 20 isolated in cuff - 4 isolated in pouch body - 11 in pouch and body	/	All LGD	/
Zahid et al., 2015 <sup>19</sup>	14 (51.8)		No	Mean 9.2 years	Median: 72 months (18–249)	Median 31 years (14–65)	12/27 (44.0)	/	Only 1 polyp HGD (< 99%)	/
Kennedy et al., 2014 <sup>64</sup>	43 (45.0)		Watched only anastomosis	Mean 7.6 (0–24)		Mean 15.4 (4–20)	9/95 (9.4)			
Pommaret et al., 2013 <sup>36</sup>		110 / 139 92 / 110 (Cohort included IRA, ileostomy and IPAA patients but did not distinguish between).		/	Median 15 years	25 years (9–61 years)	57/118 (48.3)	> 10 mm:12	94% LGD; 6% HGD	1–4: 22 5–20: 18 > 20: 17
Boostrom et al., 2013 <sup>66</sup>	52 (44.5)		Yes	125 months (25–423 months)	12.4 years (15–405 months)	26 years (4–60 years)	30/117 (25.6)	5.9 mm (2 mm to 20 mm)	22 LGD, 8 tubulovillous	/
Wasmuth et al., 2013 <sup>67</sup>	34 (55.7)	/	Yes (body and anastomosis)		Cumulative rate of adenomas at 28 years 17% for mucosectomy group and 75% at 15 years in a group without mucosectomy (P < 0.0001)	20 (10–49)	Anastomosis: 4/39 (10.0) vs. 14/22 (64.0) (P < 0.0001) Pouch body: 8/39 vs. 6/22 (P 0.57)			
Tonelli et al., 2012 <sup>61</sup>	/	45 (65%)	No	Median 133 months (12–288 months)	Mean 7 years (1–15 years)	33 years (17–63 years)	25 (36.0)	Mean 3 mm (1–40)	Adenomas, dysplasia not specified	Mean 8 (1–47)
Yan et al., 2012 <sup>68</sup>	30 (71.5)	/	Yes	Median 7.2 (2.2–20)		29 (16–65)	At the anastomosis 6/33 (18.2)	/	/	/
Banasiewicz et al., 2011 <sup>33</sup>	79 (47.9)	/	/	Endoscopies performed 2–19 years since surgery.	Mean 14 months to LGD; Mean 16 months to HGD. Estimated frequency LGD 15 years later 50% and for HGD 17.5 years later 50%.		21/165 (12.7)		LGD - 21/32 (65.6); HGD - 11/32 (34.4)	
Gleeson et al., 2008 <sup>61</sup>	/	/	Yes	/	FUP began median 6.5 (0–15) after surgery	/	13/13 (100); 10/13 pouch body; 2/13 anastomosis; 3/13 ileum above anastomosis	< 5 mm	/	5–30

First author and publication date	Sex (man); n (%)	APC mutation Underwent; n (%); Positive in; n (%)	Distinguish between pouch body and rectal cuff	Follow-up (months/years)	Time from surgery to first adenomas (years)	Age at surgery (years)	Rate of adenomas ( $\geq 1$ polyp)	Size of adenomas, mm	Histology of adenomas; n (%)	Number of Adenomas
Friederich <i>et al.</i> , 2008 <sup>32</sup>	119 (56.0)	/	/	Mean 7.9 (0.4–20.3 years)	Cumulative risk of 16% at 5-years and 42.4% at 10 years for adenoma development. Cumulative risk of 12.8% at 10 years for advanced adenoma development.	Mean 30.0 years (10–62.6 years)	47/212 (35%)	/	/	/
Campos <i>et al.</i> , 2008 <sup>17</sup>	/	/	No	50.8 (5–228)			3/26 (11.5)			
Moussata <i>et al.</i> , 2007 <sup>25</sup>	12 (57.1)	23/23 (100.0) 22/23 (95.7)	Yes (only polyps in the ileal mucosa of the pouch body are described)	Mean 5.4 $\pm$ 2.6 (1–11)	Mean 4.7 $\pm$ 3.3 years (1–14)		17/23 (74.0)	Mean size 5.2 mm $\pm$ 3.4 mm; 3 polyps were > 10 mm.	LGD 16/17 (94.1); HGD 1/17 (5.9)	/
Groves <i>et al.</i> , 2005 <sup>35</sup>	35 (58.3)	/	Between pouch and above anastomosis ileum	6 years (1–17 years)	/	32.5 years (13–66 years)	34/60 (57%) of which 5 were > 10 mm / 11 were advance adenomas	Mean size 5 mm (1–40 mm)	/	Median number 4
Thompson-Fawcett <i>et al.</i> , 2001 <sup>77</sup>	/	20/33 (60.6) 18/20 (90.0)	Only pouch body	/	/	/	20/33 (60.0) adenomas	1–3 mm	/	Median 10 (1–100) Also lymphoid hyperplasia included

APC = adenomatous polyposis coli; FUP = follow up; HGD = high grade dysplasia; IRA = ileorectal anastomosis; LGD = low grade dysplasia

1983 (12.9%) were diagnosed with CRR compared to none of those operated after 1983 when pouch surgery was introduced at the Cleveland Clinic. Recently published data from two Japanese studies reporting an overall CRR rate of 30%<sup>25</sup> – 37%<sup>20</sup> must be interpreted with caution as carcinoma *in situ* was also included in the definition of cancer in their cohorts. The risk of metachronous cancer after IRA has been recognised early and these patients have been advised to undergo regular surveillance of the rectal remnant. Traditionally, surveillance was recommended every 3 to 12 months. This recommendation has been maintained ever since and can be also found in the recently published international guidelines (Table 1). The French national guidelines published in 2005<sup>39</sup> are the only ones to include the genotype information, as they recommend more frequent surveillance if the pathogenic variant is located between codons 1250–1500. However, they were published in 2005.

The main obstacle to refining recommendations for endoscopic surveillance is the lack of high-quality, prospective data. Unfortunately, we have not found a single randomised trial that has compared different surveillance strategies or aimed to identify factors that would allow risk stratifi-

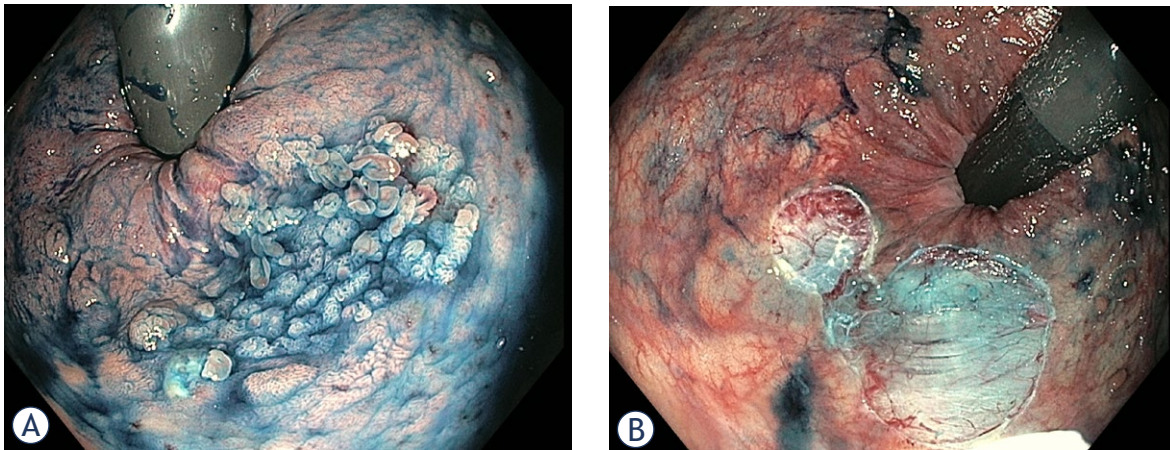
cation. Members of the International Society for Gastrointestinal Hereditary Tumors (InSiGHT)<sup>40</sup> proposed a staging system<sup>41</sup> and stage-specific interventions for patients with intact colon and those with IRA, but unfortunately no effort has been made to validate this staging system. Data on endoscopic treatment modalities are even more descriptive. In fact, in five international recommendations (Table 1), only Vasen *et al.*<sup>7</sup> recommended endoscopic removal of all polyps with dysplasia or those larger than 5 mm. Endoscopic management of these patients has therefore been influenced by expert groups. Unfortunately, preferred methods of endoscopic management were rarely described in the reviewed studies. Maehata *et al.*<sup>20</sup> recommend removal of all polyps larger than 8 mm. A descriptive study with a small sample size (n = 6)<sup>42</sup> showed that large-scale cold snare polypectomy can effectively reduce the polyp burden in the rectal remnant even in cases of very high polyp numbers. The mean number of polyps removed was 78.5 (30–155). During the follow-up (mean 10.7 months), none of the patients developed rectal cancer and there were no complications related to polypectomy. This is in contrast to another study from the USA<sup>30</sup>, which advocates the use of ablative therapy with argon plasma coagulation. A similar

TABLE 6. Cancer rate after primary ileal pouch anal anastomosis (IPAA)

First author and publication date (ref.)	No of patients	Age at cancer diagnosis (years)	Time to cancer (years)	Interval since last surveillance endoscopy and findings	Endoscopic findings at diagnosis	Location	Staging of cancer and status
Aelvoet et al., 2023 <sup>55</sup>	3/111 (2.7%)	/	/	/	/	/	Pouch excision
Pasquer et al., 2021 <sup>58</sup>	1/92 (1.1)	30	/	1 month	/	Pouch body	Endoscopic resection
Ganschow et al., 2018 <sup>61</sup>	1	/	27	/	/	Pouch body	Resection and reconstruction of a new pouch - alive
Walsh et al., 2016 <sup>63</sup>	1	54	/	Regular annual surveillance	New endoscopy due to anemia and rectal blood loss	Anastomosis	T3N2Mx, resection and ileostomy, alive during last FUP.
Wasmuth et al., 2013 <sup>67</sup>	1	/	11	/	/	Rectal cuff	Resection and ileostomy - alive
Boostrom et al., 2013 <sup>66</sup>	1	/	23.7	/	/	Pouch body	Transanal resection - alive
Ozdemir et al., 2013 <sup>38</sup>	4	/	Mucosectomy group; median 11.3 years (8.3-22) Without mucosectomy; 8 years	Regular annual surveillance	/	All ATZ	3 underwent APR - alive 1 transanal resection - died 4 years later dissemination
Makni et al., 2012 <sup>69</sup>	1	26	10	8 months	Polyps, LGD?	Pouch body?	Pouch excision - died 12 months later dissemination
Tonelli et al., 2012 <sup>51</sup>	2	29 58	10	12 months, normal 6 months, normal	? Ila + Ilc polyp	Pouch body Pouch body	Excision with ileostomy, T3N0M0, died 6 months later dissemination / Excision with ileostomy, T2N0M0, alive after 56 month FUP
voon Roon et al., 2011 <sup>70</sup>	1	/	13	/	/	Pouch body	Excision of a pouch - died 2 years of disseminated disease
Banasiewicz et al., 2011 <sup>33</sup>	5	/	/	/	/	Pouch body	/
Ault et al., 2009 <sup>71</sup>	2	61 50	11 10	6, normal /	Pain and blood per rectum, 3 cm mass/ Sacral pain, bleeding ulcer	Pouch body / Pouch body	T2N1Mx, died of AMI prior treatment / Metastatic disease, chemotherapy
Tajika et al., 2009 <sup>83</sup>	2	55 68	8.6 20	9 months, normal No FUP	30x25 mm cancer / Polyposis and 25 x 25 mm polyp	Pouch body/ Kock's pouch body	T4N2M0 - died 1 year later T3N2M? - died (MDS)
Lee et al., 2008 <sup>71</sup>	1	/	7	/	Ulcerating tumor	Pouch body	T4N1M0, APR ileostomy. Developed metastases 2 years later.
Friederich et al., 2008 <sup>32</sup>	4	35 37 32 36	14 10.2 16.4 6.2	4.4 years, normal 2.1 years, normal No control (symptoms) 0.6 years, Tubulovillous HGD	/	All pouch body	Dukes C Dukes B Dukes B Dukes B
Linehan et al., 2007 <sup>72</sup>	1	40	10	/	Pelvic pain, discharge	Pouch body (patient had ileostomy but pouch was left in situ)	Excision. At last FUP patient was well.
Ulas et al., 2006 <sup>74</sup>	1	/	9	/	/	Anastomosis	Dukes B, APR, metachronous cancer after 1 year
Campos et al., 2005 <sup>19</sup>	1	/	12	No FUP	Presented with rectal bleeding Presented after 1 year with rectal bleeding /	Pouch body	T2N0Mx, APR and ileostomy, patient well at 6 years FUP.
Vroueraets et al., 2004 <sup>25</sup>	2	48 36	9 10	5 years normal, then 2 and 1 years (both multiple LGD adenomas refused surgery) / Regular FUP every 2 years	Normal. Routine biopsies at subsequent FUP revealed adenoca.	Anastomosis Anastomosis	T2N0M0, APR, alive 1 year later / T4N0M0, APR, alive 8 months later
Cherki et al., 2003 <sup>76</sup>	1	35	3.5	1.5 years	/	Pouch body	T3N1M1, resection with ileostomy, died 1 month later T3N0M0, APR, ileostomy, died 2.5 years later dissemination / T2N0M0, transanal excision with ileostomy (refused APR), died 4 years later, dissemination
Ooi et al., 2003 <sup>36</sup>	2	36 /	2 years 3 months 8 years	/ /	Symptoms of anal bleeding/ /	Anastomosis Anastomosis	/
Brown et al., 2001 <sup>78</sup>	1	44	7 years 4 months	Under FUP every 6 months	/	Anastomosis	Resection with ileostomy - died 12 months later dissemination
Vuilleumier et al., 2000 <sup>79</sup>	1	38	7	No FUP	/	Anastomosis	T4NOM? - alive
Palkar et al., 1997 <sup>15</sup>	1	39	4.7	3 months	?	Pouch body	/
Kim et al., 1997 <sup>15</sup>	1	/	/	/	/	Pouch body?	/
Bassuini et al., 1996 <sup>80</sup>	1	31	3	No FUP	/	Pouch body	/
Von Herbay et al., 1996 <sup>4</sup>	1	33	8	/	/	Anastomosis	T1N0M0
Hoehner et al., 1994 <sup>7</sup>	1	34	20	/	/	Anastomosis	/

\*The data from these cases has been drawn from reviews by Tajika<sup>14</sup> and Smith<sup>13</sup> as full-text of the papers were not accessible.

FUP = follow up; HGD = high grade dysplasia; LGD = low grade dysplasia



**FIGURE 2.** Surveillance endoscopy in a 48-year old patient with FAP after colectomy with IRA revealed 18 mm LST-G (A). After submucosal injection with gelofusine, indigo carmine and adrenaline, piecemeal endoscopic mucosal resection (pEMR) (B) was performed.

practice was supported by a study published in France in 2007.<sup>17</sup> National French guidelines published in 2005 recommend ablation with APC for small polyps (a few millimetres) and mucosectomy for larger polyps.<sup>39</sup>

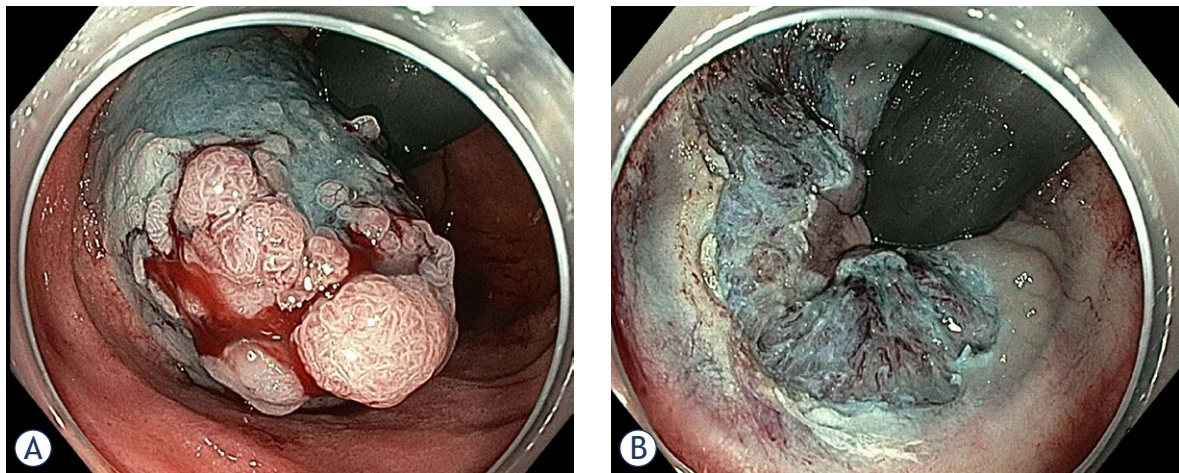
Improvements in endoscopic resection techniques have also been applied to the treatment of large lesions in the rectal remnant. Recently two reports, both from Japan<sup>43,44</sup>, have been published of successful endoscopic submucosal dissection (ESD) of 75 mm Is + IIa adenoma and residual adenoma at the IRA. In our endoscopy unit (Hospital Clinic, Barcelona) we also perform advanced endoscopic resection techniques. Figure 2 (A and B) shows a recent endoscopic mucosal resection (EMR) of an 18mm laterally spreading tumour granular type (LST-G) in the rectal remnant of a patient with FAP.

There is little data on the use of advanced imaging techniques. The study from St. Mark's hospital in London<sup>45</sup> showed no benefit of dye-based chromoendoscopy to detect additional adenomas in the rectal remnant. The European Society of Gastrointestinal Endoscopy (ESGE) guidelines<sup>46</sup> published in 2014 did not recommend the use of advanced endoscopic imaging in patients with FAP, but did not specifically differentiate between the patients with intact colon and those after surgery. On the other hand, the French Society of Endoscopy<sup>39</sup> recommended the use of dye-based chromoendoscopy with indigo carmine. We believe that use of dye-based chromoendoscopy in these patients does not increase the detection of clinically relevant lesions and it is not routinely performed in our unit. Considering the data on a

cumulative risk of 57% for CRR 30 years after surgery<sup>20</sup> and the fact that adenoma development in the rectal remnant is an inevitable event<sup>16</sup>, regular endoscopic surveillance is mandatory. Our recommendations are in line with other guidelines and our patients are recommended annual endoscopic surveillance, despite alarming data from an early study published in 2001<sup>5</sup> from four European registries in which 75% of patients with CRR had a negative rectoscopy within 12 months and 35% within 6 months prior to diagnosis of CRR. There was no information on the endoscopy equipment used for surveillance. We believe that the high rates of negative rectoscopies prior to cancer diagnosis may – to some extent – be influenced by the quality of endoscopy, which has been limited by the technical aspects of the equipment used in the past. This problem needs to be addressed again in the light of developments in endoscopic equipment.

When restorative proctocolectomy with IPAA was first described in 1978<sup>47</sup>, it was believed that this operation would eliminate the risk of colorectal cancer in patients with FAP. However, a few years later, as the first pouches began to age, case reports of cancers arising in the pouch began to appear in the literature.<sup>6</sup> Since then, reports have become more frequent and we have identified 45 cases of cancer after primary IPAA, of which 26 arose in the ileal mucosa of the pouch body and 15 at the anastomosis. Furthermore, we now know that cancer can develop even after mucosectomy down to the dentate line<sup>48</sup>, because even after removal of all visible rectal mucosa, some microscopic rectal columnar epithelium remains at the ATZ.<sup>49</sup> In the study from the Heidelberg Polyposis





**FIGURE 3.** Surveillance endoscopy in a 49-year old patient with FAP after proctocolectomy with IPAA revealed 25 mm LST-G mixed type lesion in the rectal cuff. Lesion was spreading from the anastomosis to the dentate line. Patient had undergone surgery five years earlier and did not show up for endoscopy follow-up since then (A). Lesion was removed with pEMR (B).

Registry with 100 patients<sup>50</sup>, rectal residual mucosa (defined as visible mucosa or detected by histology from blinded biopsies) was found in 42 (84%) cases after stapled and in 21 (42%) cases after hand-sewn anastomosis.

Researchers from Japan<sup>16</sup> found a 70% incidence of adenomas in the pouch body with one of the longest follow-up periods reported to date (> 20 years). Similarly, in a study from France, 74% of patients had at least one adenoma in the pouch, but with a mean follow-up of only 5.4 years. In contrast, one study found that isolated rectal cuff adenomas were more common than isolated pouch adenomas (49.1% *vs.* 6.8%), while 18.7% of patients had both pouch and rectal cuff adenomas. Cumulative 5-year, 10-year and 20-year risks for pouch adenomas were 32%, 52% and 68% in the Japanese study<sup>16</sup>, a slightly lower 5-year cumulative risk but a similarly high 10-year risk was observed in a Dutch study<sup>31</sup>; 16% and 42%, but the authors of this paper did not specifically define the exact location of the adenomas. The authors also reported a 10-year cumulative risk of developing precancerous adenomas of 12.8%.

On the other hand, the adenoma rates – at least in the stapled group – seem to be higher in the studies that only looked at the anastomosis and compared hand-sewn with stapled: 0–33% *vs.* 33.9–57%. In view of these figures, it is essential that patients with primary IPAA also undergo regular endoscopic surveillance. Particular attention should be paid to the rectal cuff and anastomosis, and the pouch should be examined in both forward and retroflexed position.

International guidelines most commonly recommend annual endoscopy examination, whereas ASCO guidelines<sup>9</sup> advocate ‘case-by-case’ interval allocation. In 11 of only 12 studies that described a surveillance protocol, an interval of 12 months was recommended except in Brazil where endoscopy of the pouch was recommended every 2 years.

Interestingly, in the Netherlands pouch endoscopy was recommended every 1 to 3 years in the late 1990s but in 2001 the protocol was changed to annual endoscopic surveillance regardless of the anastomotic technique (hand-sewn or stapled).

One of the main concerns is the short interval (< 1 year) between the last normal endoscopy and the cancer diagnosis and the aggressive course of the disease despite an initial R0 resection (Supplementary Table 4). It is not entirely clear whether the adenoma-carcinoma sequence is faster in the ileal mucosa compared with the colon and rectum, or whether “negative” endoscopies prior to cancer diagnosis could be explained by the poor quality of pouch endoscopy. Chromoendoscopy improves the detection of diminutive adenomas<sup>31</sup> and lymphoid hyperplastic nodules<sup>45</sup>, but its use is discouraged<sup>33,35</sup> for the same reasons as in the examination of rectal remnants – increased detection of clinically irrelevant polyps. Endoscopy should be performed with a gastroscope or paediatric colonoscope, as stricture can occur at the anastomosis, especially after hand suturing.

There are no official recommendations for endoscopic management of FAP patients after IPAA. We have found considerable heterogeneity in local practice. Italian authors recommend resection of

all adenomas > 3 mm.<sup>51</sup> On the contrary, ablation with argon plasma coagulation is the preferred resection technique in a French study.<sup>17</sup> Ablative techniques were also supported by the study from the Mayo Clinic.<sup>30</sup> In a small descriptive cohort of only 5 patients<sup>42</sup>, large-scale cold snare polypectomy with a mean of 110.6 (30–342) resected polyps demonstrated the efficacy of cold snare in controlling large polyp burden (> 30 polyps) with no reported polypectomy related complication. In our unit we do not use nor encourage use of argon plasma coagulation. We recommend resection of all polyps > 3 mm. Advanced resection techniques, when performed in the tertiary centres, may be a viable alternative prior to surgical resection. A case report of successful *en bloc* ESD of a 15 mm ‘non-lifting’ HGD adenoma in the ileal pouch has recently been published.<sup>52</sup> Figure 3 (A and B) shows an EMR of 25 mm LST in a patient with FAP after IPAA. The polyp was located in the rectal cuff and extended from the anastomosis to the dentate line. The procedure was performed at our Endoscopy Unit. It should be emphasised that the wall of the ileum is very thin and special care must be taken when resecting larger lesions.

Although there is no randomised trial comparing different endoscopic surveillance intervals, it is unlikely that prospective data will be available in the future. The main reason is ethical issue, as these patients are at increased risk of colorectal cancer. However, with the introduction of high quality colonoscopy and improvements in endoscopy technique, a ‘negative’ endoscopy before cancer diagnosis should become highly unlikely if not impossible.

## Acknowledgement

Funded by Instituto de Salud Carlos III (PI19/01050) and Beca de la Marató de TV3 2020 (Beca la Marató—201932-30). Co-funded by European Regional Development Fund/European Social Fund; “A way to make Europe”/“Investing in your future”. CIBERehd is funded by the Instituto de Salud Carlos III.

## References

- Kinzler KW, Nilbert MC, Su LK, Vogelstein B, Bryan TM, Levy DB, et al. Identification of FAP locus genes from chromosome 5q21. *Science* 1991; **253**: 661-5. doi: 10.1126/science.1651562
- Church J. Familial adenomatous polyposis. *Surg Oncol Clin N Am* 2009; **18**: 585-98. doi: 10.1016/j.soc.2009.07.002
- de Campos FGCM, Perez RO, Imperiale AR, Seid VE, Nahas SC, Cecconello I. Evaluating causes of death in familial adenomatous polyposis. *J Gastrointest Surg* 2010; **14**: 1943-9. doi: 10.1007/s11605-010-1288-6
- Herzig D, Hardiman K, Weiser M, You N, Paquette I, Feingold DL, et al. The American Society of Colon and Rectal Surgeons Clinical Practice Guidelines for the management of inherited polyposis syndromes. *Dis Colon Rectum* 2017; **60**: 881-94. doi: 10.1097/DCR.0000000000000912
- Vasen HF, van Duijvendijk P, Buskens E, Bülow C, Björk J, Järvinen HJ, et al. Decision analysis in the surgical treatment of patients with familial adenomatous polyposis: A Dutch-Scandinavian collaborative study including 659 patients. *Gut* 2001; **49**: 231-5. doi: 10.1136/gut.49.2.231
- Hoehner JC, Metcalf AM. Development of invasive adenocarcinoma following colectomy with ileoanal anastomosis for familial polyposis coli report of a case. *Dis Colon Rectum* 1994; **37**: 824-8. doi: 10.1007/BF02050149
- Vasen HFA, Mösllein G, Alonso A, Aretz S, Bernstein I, Bertario L, et al. Guidelines for the clinical management of familial adenomatous polyposis (FAP). *Gut* 2008; **57**: 704-13. doi: 10.1136/gut.2007.136127
- Balmaña J, Balaguer F, Cervantes A, Arnold D, ESMO Guidelines Working Group. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. *Ann Oncol* 2013; **24**(Suppl 6): vi73-80. doi: 10.1093/annonc/mdt209
- Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MWY, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. *J Clin Oncol* 2015; **33**: 209-17. doi: 10.1200/JCO.2014.581322
- Singal S, Brand RE, Church JM, Giardiello FM, Hampel HL, Burt RW. ACG Clinical Guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol* 2015; **110**: 223. doi: 10.1038/ajg.2014.435
- Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, et al. The PRISMA Statement for Reporting Systematic Reviews and Meta-Analyses of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009; **339**: b2700. doi: 10.1136/bmj.b2700
- Zotero. About. [internet]. [cited 2029 Jul 03]. Available at: <https://www.zotero.org/about/>
- Smith JC, Schäffer MW, Ballard BR, Smoot DT, Herline AJ, Adunyah SE, et al. Adenocarcinomas after prophylactic surgery for familial adenomatous polyposis. *J Cancer Ther* 2013; **4**: 260-70. doi: 10.4236/jct.2013.41033
- 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**: 6774-83. doi: 10.3748/wjg.v19i406774
- Church J, Burke C, McGannon E, Patean O, Clark B. Predicting polyposis severity by proctoscopy: how reliable is it? *Dis Colon Rectum* 2001; **44**: 1249-54. doi: 10.1007/BF02234779
- Tajika M, Tanaka T, Ishihara M, Hirayama Y, Oonishi S, Mizuno N, et al. Long-term outcomes of metachronous neoplasms in the ileal pouch and rectum after surgical treatment in patients with familial adenomatous polyposis. *Endosc Int Open* 2019; **7**: E691-8. doi: 10.1055/a-0849-9465
- Moussata D, Nancey S, Lapalus MG, Prost B, Chavaillon A, Bernard G, et al. Frequency and severity of ileal adenomas in familial adenomatous polyposis after colectomy. *Endoscopy* 2008; **40**: 120-5. doi: 10.1055/s-2007-995363
- Booij KAC, Mathus-Vliegen EMH, Taminiau JAJM, Ten Kate FJW, Slors JFM, Tabbers MM, et al. Evaluation of 28 years of surgical treatment of children and young adults with familial adenomatous polyposis. *J Pediatr Surg* 2010; **45**: 525-32. doi: 10.1016/j.jpedsurg.2009.06.017
- Campos FG, Imperiale AR, Seid VE, Perez RO, da Silva e Sousa AH, Kiss DR, et al. Rectal and pouch recurrences after surgical treatment for familial adenomatous polyposis. *J Gastrointest Surg* 2009; **13**: 129-36. doi: 10.1007/s11605-008-0606-8
- Maehata Y, Esaki M, Nakamura S, Hirahashi M, Ueki T, Iida M, et al. Risk of cancer in the rectal remnant after ileorectal anastomosis in patients with familial adenomatous polyposis: single center experience. *Dig Endosc* 2015; **27**: 471-8. doi: 10.1111/den12414
- Jenner DC, Levitt S. Rectal cancer following colectomy and ileorectal anastomosis for familial adenomatous polyposis. *Aust N Z J Surg* 1998; **68**: 136-8. doi: 10.1111/j.1445-2197.1998.tb04724.x



- 22 Koskenvuo L, Renkonen-Sinisalo L, Järvinen HJ, Lepistö A. Risk of cancer and secondary proctectomy after colectomy and ileorectal anastomosis in familial adenomatous polyposis. *Int J Colorectal Dis* 2014; **29**: 225-30. doi: 10.1007/s00384-013-1796-4
- 23 Bertario L, Russo A, Radice P, Varesco L, Eboli M, Spinelli P, et al. Genotype and phenotype factors as determinants for rectal stump cancer in patients with familial adenomatous polyposis. Hereditary Colorectal Tumors Registry. *Ann Surg* 2000; **231**: 538-43. doi: 10.1097/0000658-200004000-00013
- 24 Bülow S, Bülow C, Vasen H, Järvinen H, Björk J, Christensen IJ. Colectomy and ileorectal anastomosis is still an option for selected patients with familial adenomatous polyposis. *Dis Colon Rectum* 2008; **51**: 1318-23. doi: 10.1007/s10350-008-9307-3
- 25 Yamaguchi T, Yamamoto S, Fujita S, Akasu T, Moriya Y. Long-term outcome of metachronous rectal cancer following ileorectal anastomosis for familial adenomatous polyposis. *J Gastrointest Surg* 2010; **14**: 500-5. doi: 10.1007/s11605-009-1105-2
- 26 Sinha A, Tekkis PP, Rashid S, Phillips RKS, Clark SK. Risk factors for secondary proctectomy in patients with familial adenomatous polyposis. *Br J Surg* 2010; **97**: 1710-5. doi: 10.1002/bjs7202
- 27 Nieuwenhuis MH, Bülow S, Björk J, Järvinen HJ, Bülow C, Bisgaard ML, et al. Genotype predicting phenotype in familial adenomatous polyposis: A practical application to the choice of surgery. *Dis Colon Rectum* 2009; **52**: 1259-63. doi: 10.1007/DCR0b013e3181a0d33b
- 28 Valanzano R, Ficari F, Curia MC, Aceto G, Veschi S, Cama A, et al. Balance between endoscopic and genetic information in the choice of ileorectal anastomosis for familial adenomatous polyposis. *J Surg Oncol* 2007; **95**: 28-33. doi: 10.1002/jso20672
- 29 Kennedy RD, Zarroug AE, Moir CR, Mao SA, El-Youssef IM, Potter DD. Ileal pouch anal anastomosis in pediatric familial adenomatous polyposis: a 24-year review of operative technique and patient outcomes. *J Pediatr Surg* 2014; **49**: 1409-12. doi: 10.1016/j.jpedsurg.2014.03.003
- 30 Gleeson FC, Papachristou GI, Riegert-Johnson DL, Boller AM, Gostout CJ. Progression to advanced neoplasia is infrequent in post colectomy familial adenomatous polyposis patients under endoscopic surveillance. *Fam Cancer* 2009; **8**: 33-8. doi: 10.1007/s10689-008-9203-y
- 31 Friederich P, de Jong AE, Mathus-Vliegen LM, Dekker E, Krieken HH, Dees J, et al. Risk of developing adenomas and carcinomas in the ileal pouch in patients with familial adenomatous polyposis. *Clin Gastroenterol Hepatol* 2008; **6**: 1237-42. doi: 10.1016/j.cgh.2008.06.011
- 32 Banasiewicz T, Marciniak R, Kaczmarek E, Krokowicz P, Paszkowski J, Lozynska-Nelke A, et al. The prognosis of clinical course and the analysis of the frequency of the inflammation and dysplasia in the intestinal J-Pouch at the patients after restorative proctocolectomy due to FAP. *Int J Colorectal Dis* 2011; **26**: 1197-203. doi: 10.1007/s00384-011-1241-5
- 33 Thompson-Fawcett MW, Marcus VA, Redston M, Cohen Z, Mcleod RS. Adenomatous polyps develop commonly in the ileal pouch of patients with familial adenomatous polyposis. *Dis Colon Rectum* 2001; **44**: 347-53. doi: 10.1007/BF02234731
- 34 Groves CJ, Beveridge IG, Swain DJ, Saunders BP, Talbot IC, Nicholls RJ, et al. Prevalence and morphology of pouch and ileal adenomas in familial adenomatous polyposis. *Dis Colon Rectum* 2005; **48**: 816-23. doi: 10.1007/s10350-004-0835-1
- 35 Pommaret E, Vienne A, Lefevre JH, Sogni P, Florent C, Desaint B, et al. Prevalence and risk factors for adenomas in the ileal pouch and the afferent loop after restorative proctocolectomy for patients with familial adenomatous polyposis. *Surg Endosc* 2013; **27**: 3816-22. doi: 10.1007/s00464-013-2980-x
- 36 Ooi BS, Remzi FH, Gramlich T, Church JM, Preen M, Fazio VW. Anal transitional zone cancer after restorative proctocolectomy and ileoanal anastomosis in familial adenomatous polyposis: report of two cases. *Dis Colon Rectum* 2003; **46**: 1418-23. doi: 10.1097/01DCR000008905720288C9
- 37 Ozdemir Y, Kalady MF, Aytac E, Kiran RP, Erem HH, Church JM, et al. Anal transitional zone neoplasia in patients with familial adenomatous polyposis after restorative proctocolectomy and IPAA: incidence, management, and oncologic and functional outcomes. *Dis Colon Rectum* 2013; **56**: 808-14. doi: 10.1097/DCR0b013e31829005db
- 38 Church J, Burke C, McGannon E, Pastean O, Clark B. Risk of rectal cancer in patients after colectomy and ileorectal anastomosis for familial adenomatous polyposis: a function of available surgical options. *Dis Colon Rectum* 2003; **46**: 1175-81. doi: 10.1097/01DCR00000843621248848
- 39 Saurin JC, Napoleon B, Gay G, Ponchon T, Arpurt JP, Boustiere C, et al. Endoscopic management of patients with familial adenomatous polyposis (FAP) following a colectomy. *Endoscopy* 2005; **37**: 499-501. doi: 10.1055/s-2005-861295
- 40 International Society for Gastrointestinal Hereditary Tumours, InSiGHT. [cited 2019 Mar 28]. Available at: <https://www.insight-group.org/>
- 41 Lynch PM, Morris JS, Wen S, Advani SM, Ross W, Chang GJ, et al. A proposed staging system and stage-specific interventions for familial adenomatous polyposis. *Gastrointest Endosc* 2016; **84**: 115-25e4. doi: 10.1016/j.gie.2015.12.029
- 42 Patel NJ, Ponugoti PL, Rex DK. Cold snare polypectomy effectively reduces polyp burden in familial adenomatous polyposis. *Endosc Int Open* 2016; **4**: E472-4. doi: 10.1055/s-0042-104114
- 43 Sansone S, Nakajima T, Saito Y. Endoscopic submucosal dissection of a large neoplastic lesion at the ileorectal anastomosis in a familial adenomatous polyposis patient. *Dig Endosc* 2017; **29**: 390-1. doi: 10.1111/den12834
- 44 Ishii N, Akiyama H, Suzuki K, Fujita Y. Endoscopic submucosal dissection for the complete resection of the rectal remnant mucosa in a patient with familial adenomatous polyposis. *ACG Case Rep J* 2016; **3**: 172-4. doi: 10.14309/crj201640
- 45 Groves CJ, Beveridge IG, Swain DJ, Saunders BP, Talbot IC, Nicholls RJ, et al. Prevalence and morphology of pouch and ileal adenomas in familial adenomatous polyposis. *Dis Colon Rectum* 2005; **48**: 816-23. [internet]. doi: 10.1007/s10350-004-0835-1. [cited 2019 Jan 24]. Available at: <https://pubmed.ncbi.nlm.nih.gov/15747076/>
- 46 Kamiński MF, Hassan C, Bisschops R, Pohl J, Pellisé M, Dekker E, et al. Advanced imaging for detection and differentiation of colorectal neoplasia: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2014; **46**: 435-49. doi: 10.1055/s-0034-1365348
- 47 Parks AG, Nicholls RJ. Proctocolectomy without ileostomy for ulcerative colitis. *Br Med J* 1978; **2**: 85-8. [internet]. doi: 10.1136/bmj.2.6130.85. [cited 2019 Jan 24]. Available at: <https://pubmed.ncbi.nlm.nih.gov/667572/>
- 48 Remzi FH, Church JM, Bast J, Lavery IC, Strong SA, Hull TL, et al. Mucosectomy vs stapled ileal pouch-anal anastomosis in patients with familial adenomatous polyposis: Functional outcome and neoplasia control. *Dis Colon Rectum* 2001; **44**: 1590-6. doi: 10.1007/BF02234377
- 49 Kartheuser A, Stangherlin P, Brandt D, Remue C, Sempoux C. Restorative proctocolectomy and ileal pouch-anal anastomosis for familial adenomatous polyposis revisited. *Fam Cancer* 2006; **5**: 241-60. Discussion 261-2. doi: 10.1007/s10689-005-5672-4
- 50 Ganschow P, Treiber I, Hinz U, Leowardi C, Büchler MW, Kadmon M. Residual mucosa after stapled vs handsewn ileal J-pouch-anal anastomosis in patients with familial adenomatous polyposis coli (FAP) – a critical issue. *Langenbecks Arch Surg* 2015; **400**: 213-9. doi: 10.1007/s00423-014-1263-x
- 51 Tonelli F, Ficari F, Bargellini T, Valanzano R. Ileal pouch adenomas and carcinomas after restorative proctocolectomy for familial adenomatous polyposis. *Dis Colon Rectum* 2012; **55**: 322-9. doi: 10.1097/DCR0b013e318241e6f2
- 52 Sugimoto T, Yoichi T, Suzuki K, Kawai T, Yashima Y, Sato S, et al. Endoscopic submucosal dissection to treat ileal high-grade dysplasia after ileoanal anastomosis for familial adenomatous polyposis: report of a case. *Clin J Gastroenterol* 2014; **7**: 481-3. doi: 10.1007/s12328-014-0533-z
- 53 van Leerdam ME, Roos VH, van Hooft JE, Dekker E, Jover R, Kaminski MF, et al. Endoscopic management of polyposis syndromes: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2019; **51**: 877-95. doi: 10.1055/a-0965-0605
- 54 Yang J, Gurudu SR, Koptiuch C, Agrawal D, Buxbaum JL, Abbas Fehmi SM, et al. American Society for Gastrointestinal Endoscopy Guideline on the role of endoscopy in familial adenomatous polyposis syndromes. *Gastrointest Endosc* 2020; **91**: 963-82e2. doi: 10.1016/j.gie.2020.01.028
- 55 Aelvoet AS, Roos VH, Bastiaansen BAJ, Hompes R, Bemelman WA, Aalfs CM, et al. Development of ileal adenomas after ileal pouch-anal anastomosis versus end ileostomy in patients with familial adenomatous polyposis. *Gastrointest Endosc* 2023; **97**: 69-77e1. doi: 10.1016/j.gie.2022.08.031

- 56 Tatsuta K, Sakata M, Iwaizumi M, Sugiyama K, Kojima T, Akai T, et al. Long-term prognostic impact of metachronous rectal cancer in patients with familial adenomatous polyposis: a single-center retrospective study. *Cancer Diagn Progn* 2023; **3**: 221-9. doi: 1021873/cdp10205
- 57 Anelli CC, Xiang J, Martin I, Hawkins M, Man R, Clark SK, et al. Regular endoscopic surveillance and polypectomy is effective in managing rectal adenoma progression following colectomy and ileorectal anastomosis in patients with familial adenomatous polyposis. *Colorectal Dis* 2022; **24**: 277-83. doi: 101111/codi15981
- 58 Colletti G, Ciniselli CM, Signoroni S, Cocco IMF, Magarotto A, Ricci MT, et al. Prevalence and management of cancer of the rectal stump after total colectomy and rectal sparing in patients with familial polyposis: Results from a registry-based study. *Cancers* 2022; **14**: 298. doi: 103390/cancers14020298
- 59 Pasquer A, Benech N, Pioche M, Breton A, Rivory J, Vinet O, et al. Prophylactic colectomy and rectal preservation in FAP: systematic endoscopic follow-up and adenoma destruction changes natural history of polyposis. *Endosc Int Open* 2021; **9**: E1014-E22. doi: 101055/a-1467-6257
- 60 Ardoino I, Signoroni S, Malvicini E, Ricci MT, Biganzoli EM, Bertario L, et al. Long-term survival between total colectomy versus proctocolectomy in patients with FAP: A registry-based, observational cohort study. *Tumori* 2020; **106**: 139-48. doi: 101177/0300891619868019
- 61 Ganschow P, Trauth S, Hinz U, Schaible A, Büchler MW, Kadmon M. Risk factors associated with pouch adenomas in patients with familial adenomatous polyposis. *Dis Colon Rectum* 2018; **61**: 1096-101. doi: 101097/DCR0000000000001157
- 62 Kariv R, Rosner G, Fliss-Isakov N, Gluck N, Goldstein A, Tulchinsky H, et al. Genotype-phenotype associations of APC mutations with pouch adenoma in patients with familial adenomatous polyposis. *J Clin Gastroenterol* 2019; **53**: e54-60. doi: 101097/MCG0000000000000950
- 63 Goldstein AL, Kariv R, Klausner JM, Tulchinsky H. Patterns of adenoma recurrence in familial adenomatous polyposis patients after ileal pouch-anal anastomosis. *Dig Surg* 2015; **32**: 421-5. doi: 101159/000439143
- 64 Zahid A, Kumar S, Koorey D, Young CJ. Pouch adenomas in familial adenomatous polyposis after restorative proctocolectomy. *Int J Surg* 2015; **13**: 133-6. doi: 101016/j.jjsu201411048
- 65 Kennedy RD, Potter DD, Moir CR, El-Youssef M. The natural history of familial adenomatous polyposis syndrome: a 24 year review of a single center experience in screening, diagnosis, and outcomes. *J Pediatr Surg* 2014; **49**: 82-6. doi: 10.1016/j.jpedsurg.2013.09.033
- 66 Boostrom SY, Mathis KL, Pendlimari R, Cima RR, Larson DW, Dozois EJ. Risk of neoplastic change in ileal pouches in familial adenomatous polyposis. *J Gastrointest Surg* 2013; **17**: 1804-8. doi: 101007/s11605-013-2319-x
- 67 Wasmuth HH, Tranø G, Myrvold HE, Aabakken L, Bakka A. Adenoma formation and malignancy after restorative proctocolectomy with or without mucosectomy in patients with familial adenomatous polyposis. *Dis Colon Rectum* 2013; **56**: 288-94. doi: 101097/DCR0b013e31827c970f
- 68 Yan Z, Liao G, Pei H. Surgical treatment of familial adenomatous polyposis: experience from a single institution in china. *Asia Pac J Clin Oncol* 2012; **8**: e23-8. doi: 101111/j1743-7563201101488x
- 69 Makni A, Chebbi F, Rebai W, Ayadi S, Fekih M, Jouini M, et al. Adenocarcinoma arising in the "J" pouch after total proctocolectomy for familial polyposis coli. *Tunis Med* 2012; **90**: 80-1.
- 70 von Roon AC, Will OCC, Man RF, Neale KF, Phillips RKS, Nicholls RJ, et al. Mucosectomy with handsewn anastomosis reduces the risk of adenoma formation in the norectal segment after restorative proctocolectomy for familial adenomatous polyposis. *Ann Surg* 2011; **253**: 314-7. doi: 101097/SLA0b013e318f3f498
- 71 Ault GT, Nunoo-Mensah JW, Johnson L, Vukasin P, Kaiser A, Beart RW. Adenocarcinoma arising in the middle of ileoanal pouches: report of five cases. *Dis Colon Rectum* 2009; **52**: 538-41. doi: 101007/DCR0b013e318199effe
- 72 Lee SH, Ahn BK, Chang HK, Baek SU. Adenocarcinoma in ileal pouch after proctocolectomy for familial adenomatous polyposis: report of a case. *J Korean Med Sci* 2009; **24**: 985-8. doi: 103346/jkms2009245985
- 73 Linehan G, Cahill RA, Kalimuthu SN, O'Connell F, Redmond HP, Kirwan WO. Adenocarcinoma arising in the ileoanal pouch after restorative proctocolectomy for familial adenomatous polyposis. *Int J Colorectal Dis* 2008; **23**: 329-30. doi: 101007/s00384-007-0400-1
- 74 Ulaş M, Neşşar G, Bostanoğlu A, Aydoğ G, Kayaalp C, Ozoğul Y, et al. Development of two cancers in the same patient after ileorectal and ileal pouch anal anastomosis for familial adenomatous polyposis. *Med Princ Pract* 2006; **15**: 83-6. doi: 101159/000089393
- 75 Vrouenraets BC, Van Duijvendijk P, Bemelman WA, Offerhaus GJA, Slors JFM. Adenocarcinoma in the anal canal after ileal pouch-anal anastomosis for familial adenomatous polyposis using a double-stapled technique: report of two cases. *Dis Colon Rectum* 2004; **47**: 530-4. doi: 101007/s10350-003-0073-y
- 76 Cherki S, Glehen O, Moutardier V, François Y, Gilly FN, Vignal J. Pouch adenocarcinoma after restorative proctocolectomy for familial adenomatous polyposis. *Colorectal Dis* 2003; **5**: 592-4. doi: 10.1046/j.1463-1318.2003.00486.x
- 77 Thompson-Fawcett MW, Warren BF, Mortensen NJ. A new look at the anal transitional zone with reference to restorative proctocolectomy and the columnar cuff. *Br J Surg* 1998; **85**: 1517-21. doi: 101046/j1365-2168199800875x
- 78 Brown SR, Donati D, Seow-Choen F. Rectal cancer after mucosectomy for ileoanal pouch in familial adenomatous polyposis: report of a case. *Dis Colon Rectum* 2001; **44**: 1714-5. doi: 10.1007/BF02234397
- 79 Vuilleumier H, Halkic N, Ksontini R, Gillet M. Columnar cuff cancer after restorative proctocolectomy for familial adenomatous polyposis. *Gut* 2000; **47**: 732-4. doi: 101136/gut475732
- 80 Bassuini MM, Billings PJ. Carcinoma in an ileoanal pouch after restorative proctocolectomy for familial adenomatous polyposis. *Br J Surg* 1996; **83**: 506. doi: 10.1002/bjs.1800830422