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REVIEW ARTICLE

A systematic review of primary ileostomy site malignancies

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Abstract

Background This paper aimed to elucidate the etiologies of all primary ileostomy site malignancies published in the literature.

Methods A review of the literature was conducted following PRISMA guidelines by querying PubMed, Global Health, and Web of Science for articles published before November 2020. Search criteria contained broad terminology for ileostomy site neoplasms without language, date, or publication limitations. A full-text review of the abstracts confirmed primary malignant pathologies and was evaluated for study inclusion.

Results Literature search discovered 858 publications, with 76 meeting eligibility criteria. The final sample contained 91 patients, with equal males and females. The mean age of patients with ileostomy site malignancy was 62.0 ± 12.2, with an average ileostomy age of 29.4 ± 12.4. The most common indications for ileostomy creation were inflammatory bowel disease (IBD) (73.6%) and familial adenomatous polyposis (FAP) (20.9%). There was a total of eight ileostomy malignant pathologies reported, with adenocarcinoma being the most common (76.9%), followed by squamous cell carcinoma (SCC) (11.0%). Adenocarcinoma was diagnosed at a younger age than SCC (59.7 vs. 72.3) and developed over a shorter time (28.8 vs. 37.0). Patients with FAP almost exclusively developed adenocarcinoma (94.4%) at a younger stoma age (25.8 vs. 31.4) than those with IBD who developed seven diverse pathologies. With a median follow-up of 0.75 years, four patients developed disease recurrence and received oncologic resection of their cancer less often than the 55 negative patients ($p = 0.04$).

Conclusion Ileostomy site malignancies are late-appearing complications that require curative surgery. Their presentation is associated with ileostomy duration and creation indication, such as FAP or IBD. We recommend screening at a stoma age ≥ 20 or patient age ≥ 50 for patients with FAP, while stoma age ≥ 25 or patient age ≥ 60 for IBD patients.

Keywords Ileostomy · Complication · Adenocarcinoma · Squamous cell carcinoma · Inflammatory bowel disease · Familial adenomatous polyposis

Ileostomy site neoplasm is a rare complication that can often present decades after stoma creation. [1]. In the latest review of 57 cases from 1969 to 2018, James et al. (2018) determined adenocarcinoma as the most common neoplastic finding at the ileostomy site initially created for ulcerative colitis or familial adenomatous polyposis (FAP) [1]. There have been a few reports of other malignancies, including squamous cell carcinoma (SCC), eccrine syringofibroadenoma, melanoma, lymphoma, verrucous carcinoma, extramammary Paget's disease, and neuroendocrine tumor [2–20]. Additionally, there have been reports of ileostomy site neoplastic changes in patients with Crohn's disease (inflammatory bowel disease (IBD)), Behcet's disease, Hirschsprung disease, rectal adenocarcinoma, and urothelial transitional cell carcinoma [10–13, 16, 21–27].

To date, there have been no prospective or retrospective controlled studies due to the rarity and late presentation of ileostomy site neoplasia. Additionally, case series and studies have not encompassed the variety of pathologies and symptoms of this phenomenon. Hence, there have been no screening recommendations. This case series aims to elucidate the etiologies and management course of all primary ileostomy site malignancies reported. A systematic review and meta-analysis of all recorded cases of ileostomy site neoplasms with malignant potential were performed.

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Materials and methods

A systematic review following the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) recommendations was conducted (Fig. 1) [28]. A literature search through the PubMed, Global Health, and Web of Science databases was performed until November 2020 without publication date and language or publication type limitations. Broad keywords and MeSH (medical subject headings) terms, when appropriate, alongside Boolean operators to develop a sensitive search strategy for any ileostomy site neoplasms in each of the three databases. Reviewing existing public literature does not risk a breach in patient confidentiality; therefore, this study was exempt from the institutional review board (IRB) approval. The search strategy included the following phrases: ileostomy site, ileostomy/complications, Ileostomy/adverse effects, adenocarcinoma, carcinoid, carcinoma, neoplasms, and tumor.

The citations were uploaded to the Qatar Computing Research Institute's (QCRI) systematic review software (Rayyan QCRI) [29]. Two blinded, independent reviewers screened the abstracts for any benign or malignant neoplasia

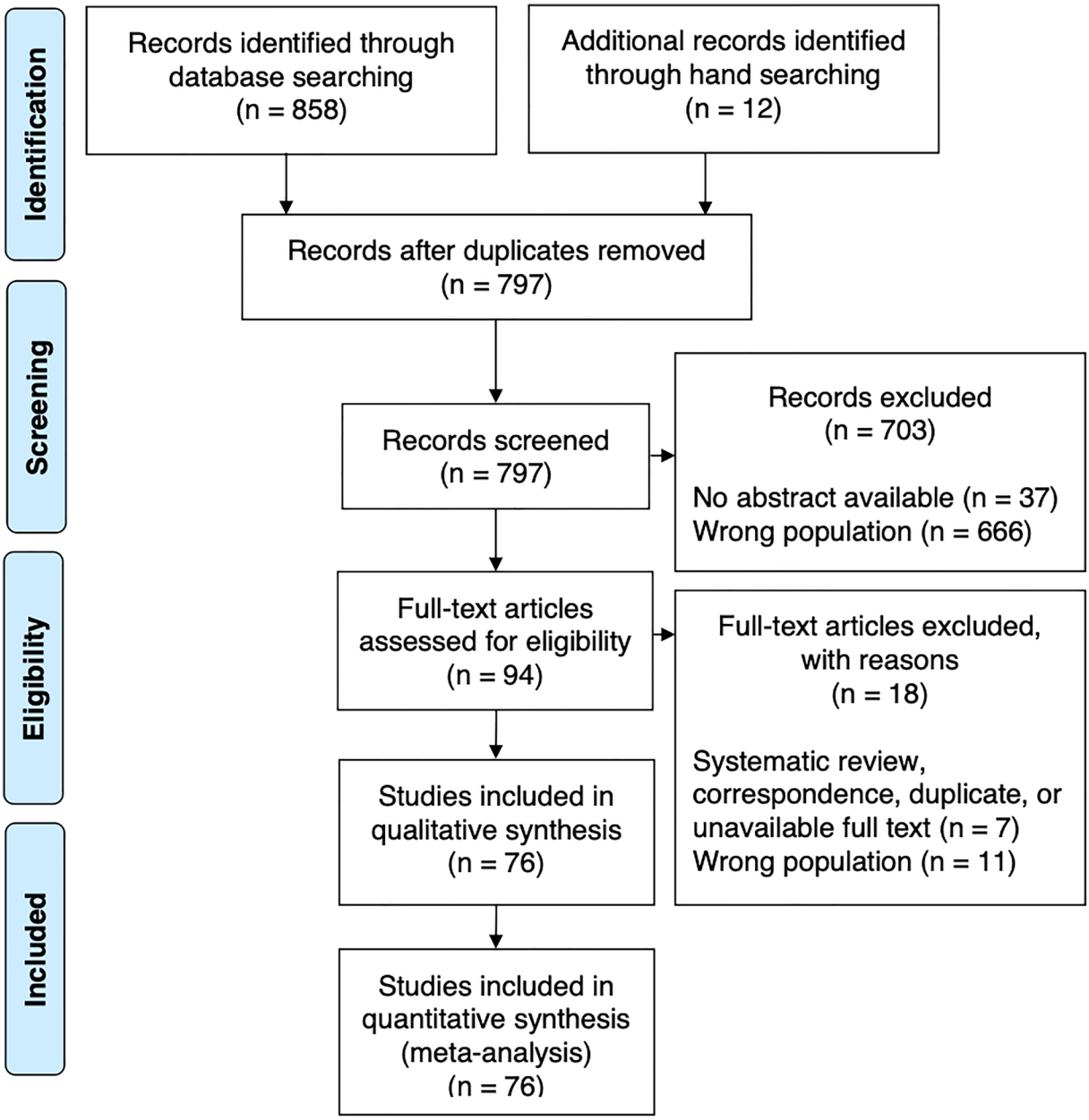

Fig. 1 Flowchart of the literature search and article selection

description in the citation's abstract or title. After completing their reviews, the two authors resolved conflicts through consensus agreement or a third arbitrator in Rayyan QCRI.

After collecting full-text articles of the positively screened abstracts, four independent reviewers excluded all review articles, commentary, or letters that refrained from any cases of primary ileostomy site malignant or premalignant lesions. All of the selected manuscripts met the quality requirements of publication within a peer-reviewed journal that qualified for PubMed (PMC or MEDLINE), Global Health (Public Health and Tropical Diseases (PHTM), Bureau of Hygiene and Tropical Diseases (BHTD), or health and disease information from the Commonwealth Agricultural Bureaux (CAB) abstracts) or Web of Science indexing requirements [30–33].

Variables including citation, patient number, age of ileostomy creation, age of ileostomy site cancer diagnosis, age of stoma, sex, race, indication for ileostomy creation, presenting symptoms, ileostomy neoplasm description, initial biopsy result, pathology after excision, the time between biopsy and excision, lymph node status, metastasis found at presentation, management of ileostomy neoplasm, follow-up duration, metastasis or recurrence status, and mortality status were extracted. Additionally, the reviewers developed variable definition guidelines a priori to aggregate free-text data from different authors, countries, and time periods. The investigators also refined the variable definitions before data analysis to simplify known synonyms.

Surgical management was categorized into local, nononcologic, oncologic, and no surgery. We defined local surgery as any resection of the mass or stoma site that does not penetrate the parietal peritoneum. Oncologic, or curative or primary surgery, described patients who had resection of the ileostomy, small bowel, and negative lymph nodes. We reserved the term "nononcologic resection" for any ileostomy and small bowel resection descriptions without mentioning the mesentery and mesenteric lymph node dissection.

The four reviewers checked each manuscript's eligibility and data extraction variables twice before inclusion in the qualitative and quantitative analyses. Additionally, a manual search of the qualified articles' reference lists was performed, and relevant articles not captured using the search engine were included after validation by two investigators.

The results were analyzed through the statistical software R version 4.0.2 [34]. Shapiro–Wilk normality test differentiated normal and non-normal distributions for analysis. Non-normal distributions were presented as median [interquartile range], and normal distributions were presented as mean (standard deviation). The Student's t-test, one-way analysis of variance, Mann–Whitney U Test, or Kruskal–Wallis one-way analysis of variance calculated the continuous variables; *chi*-squared test and Fisher's exact test evaluated categorical data.

Results

The literature search of ileostomy site cancers resulted in 858 articles. After removing duplicates, enacting screening and eligibility requirements, the systematic review yielded 64 articles [2, 3, 5–13, 15–20, 24–26, 35–78]. A manual review of these articles' references produced 12 additional studies [4, 14, 27, 79–87] (Fig. 1). The systematic review contained 91 patients. Table 1 summarizes the demographics of patients with ileostomy site cancers. In the study cohort, subjects developed malignancies on average 29.4 ± 12.4 years after their stoma creation. There was an equal ratio of male to female patients. While 82.4% of the studies withheld race demographics, authors often reported Caucasian subjects. Inflammatory bowel disease (67%) and FAP (19%) were the most common indicators for stomal creation. Examining postoperative variables, Table 2 reveals the pathology results and management course of patients with ileostomy site malignancies. Adenocarcinoma (76.9%) and squamous cell carcinoma (11%) were the most common ileostomy site cancers among a diverse group of other malignancies (12.1%) constituting eccrine syringofibroadenoma, extramammary Paget's disease, lymphoma, melanoma, neuroendocrine tumor, and verrucous carcinoma.

Table 3 compares patients with the two most common ileostomy site cancers: adenocarcinoma and SCC. Adenocarcinoma was diagnosed in patients who were on average 13 years younger than those with SCC. Additionally, a quarter of subjects with adenocarcinoma had a history of FAP, while those with SCC had none. IBD comprised most ileostomy site creation indications (73.6%). While providers waited a median time of 1 year from biopsy to resection (missing values = 83.5%, Table 2), most of the initial biopsies corresponded with the final diagnoses. As shown in Table 3, 56% of patients with adenocarcinoma on initial biopsy had an agreeing diagnosis on surgical excision, while 23.2% omitted the initial biopsy altogether. Additionally, 90% of patients with SCC had paired biopsy and surgical results, with 10% proceeding directly to surgery.

Compared to patients with IBD, FAP patients developed ileostomy site malignancies at a younger age and had a shorter stomal duration (Table 4). When examining all pathologies, patients with FAP almost exclusively developed adenocarcinoma, while patients with IBD developed seven of the eight pathologies illustrated in the literature. When we simplified pathology to the two most common cancers, patients with FAP developed adenocarcinoma more often than IBD patients and never developed SCC.

Table 1 Demographics of patients with ileostomy site malignancies

Variables	Overall ($n=91$)	Missing (%)
Age at ileostomy creation, years[a]	32.0 [25.0, 40.0]	4.4
Age at ileostomy neoplasm diagnosis, years	62.0 (12.2)	0.0
Age of stoma, years	29.4 (12.4)	4.4
Sex		0.0
Female	43 (47.3)	
Male	48 (52.7)	
Race		82.4
Black	1 (6.2)	
Indian	1 (6.2)	
White	14 (87.5)	
Indication for ileostomy creation		0.0
Familial adenomatous polyposis	19 (20.9)	
Inflammatory bowel disease	67 (73.6)	
Crohn's disease	5 (5.5)	
Ulcerative colitis	62 (68.1)	
Other	5 (5.5)	
Behcet's disease	1 (1.1)	
Hirschsprung disease with colectomy	1 (1.1)	
Rectal adenocarcinoma	2 (2.2)	
Urothelial transitional cell carcinoma	1 (1.1)	

Variables presented as following: normal distribution = mean (standard deviation); non-normal distribution = median [interquartile range]; categorical = *n* (%)

[a]Non-normal distribution with a Shapiro–Wilk normality test *p*-value ≤ 0.05

Overall, the meta-analysis demonstrated that malignancies developed on average 29.4 years after ileostomy creation. Figure 2 presents a histogram of ileostomy age at malignancy diagnosis. Patients with FAP developed malignancies six years sooner than those with IBD (Table 3). Additionally, when we separate pathology in the histogram, the FAP facet reveals zero SCC cases.

The meta-analysis also revealed the most common presenting symptoms as a growing mass (55, 60.4%), bleeding from the ileostomy site (35, 38.5%), irritation (20, 22.0%), and ileostomy appliance difficulty (20, 22.0%). Patients with adenocarcinoma and SCC had no clinically significant difference in presenting symptoms.

The systematic review results mentioned in Table 2 reported a 6% recurrence rate with a median follow-up of 0.75 years. There was 35.2% of missing data. A subgroup analysis of the four patients with recurrent disease versus the 55 without disease progression illustrated no demographic differences. Only one of the four patients with recurrent disease received an oncologic resection, while the remaining three had a nononcologic resection, resection requiring reoperation, or no surgery at all. In comparison to the group without recurrence, these subjects more often received local (5.6%), nononcologic resection (53.7%), or oncologic (37.0%) resections ($p=0.04$). Only one patient in this negative group required a second surgical debulking, and one patient did not require surgery. After investigating the one case without surgery or progressive disease, the author disclosed that the patient received palliative care radiotherapy; however, the patient was lost to follow-up [7]. Additionally, this subgroup analysis revealed equivalent adjuvant chemotherapy and radiotherapy rates, as well as mortality statistics ($p>0.05$, data not presented).

Discussion

This systematic review found 76 unique citations that documented eight ileostomy site malignancies. Tables 1 and 2 demonstrate that adenocarcinoma and SCC are the two most common ileostomy site malignancies; however, differential diagnoses should include lymphomas, melanomas, neuroendocrine tumors, eccrine syringofibroadenomas, extramammary Paget's disease, and verrucous carcinoma. The results also showed an association with the malignancies and the pathologies that resulted in ostomy creation. Tables 3 and 4 demonstrate that patients with FAP most likely developed adenocarcinoma at a younger age than patients with IBD. Besides IBD and FAP, patients with Behcet's disease, Hirschsprung's disease, rectal adenocarcinomas, and urothelial transitional cell carcinomas are also at risk of developing ostomy site malignancies. The most common presenting

Table 2 Pathology and management of patients with ileostomy site malignancies

Variables	Overall ($n=91$)	Missing (%)
Pathology result		0.0
Adenocarcinoma	70 (76.9)	
Squamous Cell Carcinoma	10 (11.0)	
Other	11 (12.1)	
Eccrine syringofibroadenoma	2 (2.2)	
Extramammary Paget Disease	1 (1.1)	
Lymphoma	3 (3.3)	
Melanoma	3 (3.3)	
Neuroendocrine Tumor	1 (1.1)	
Verrucous Carcinoma	1 (1.1)	
Largest dimension of neoplasm, cm[a]	4.00 [3.0, 5.3]	60.4
Resection type		6.6
Nononcologic resection	46 (54.1)	
Resection resulting in reoperation	2 (2.4)	
Local resection	3 (3.5)	
No surgery	2 (2.4)	
Oncologic	32 (37.6)	
Lymph node positive	9 (19.1)	48.4
Metastatic disease	8 (13.1)	33.0
Adjuvant therapies		
Fulguration	2 (2.4)	6.6
Chemotherapy	2 (2.4)	6.6
Radiation	3 (3.5)	6.6
Follow-up period, years [a]	0.75 [0.00, 2.00]	0.0
Recurrence/metastasis	4 (6.8)	35.2
Mortality	13 (14.3)	0.0

Variables presented as following: normal distribution = mean (standard deviation); non-normal distribution = median [interquartile range]; categorical = n (%)

[a]Non-normal distribution with a Shapiro–Wilk normality test p-value ≤ 0.05

symptoms in these case reports were a growing mass, bleeding, irritation, and difficulty with stoma appliance. However, neither tumor pathology nor past medical history presented differently. Overall, ileostomy site malignancies developed on average 29.4 years after stoma creation for all pathologies. In the FAP subgroup, the 11 diagnosed ileostomy cancers were diagnosed 25.8 years after ileostomy creation, which was much earlier than the stoma cancers diagnosed in IBD patients at 31.4 years duration.

While researchers have not discovered the exact pathophysiology of ileostomy cancers, a few prior studies have suggested potential mechanisms. The most popular hypothesis offers that chronic irritation at the mucocutaneous junction instigates epithelial oncogenesis [40, 54, 75]. Similarly, investigators have also proposed that ileostomy "backwash" contributes to the colonic metaplasia seen in adenocarcinoma [75, 88, 89]. However, without backwash documentation or measurements, these limitations make this hypothesis difficult to test. Table 4 demonstrated that 94.7% of FAP subjects developed adenocarcinoma, potentially suggesting a genetic influence. Previous genetic studies of FAP patients showed a general susceptibility to bowel adenomas through K-ras, β-catenin, and p53 mutations, which may impact the presentation of ileostomy adenocarcinoma [44]. However, more formal controlled studies are required to determine this association which is out of the scope of this meta-analysis.

Despite all efforts to design a robust search methodology, a study on case reports has its limitations. To minimize the subjectivity from free-text data extraction, at least two authors independently reviewed data from a manuscript before inclusion in the analysis. The reviewers cross-referenced the data extracted against any published systematic reviews to clarify variable definitions and ensure accurate representation. As terminology varied by physician, time-period, and country, an attempt was made to aggregate free-text descriptions through strict guidelines determined a priori and refined before data analysis. For example, not all articles contained full descriptions of surgical management, and the term "nononcologic resection" referred to manuscripts that failed to meet the requirements for an oncologic or primary surgery as described in the methods.

Another limitation of this study was the percentage of missing data. Separating negative and missing values was a daunting task. Generally, the reviewers confirmed a negative finding through the text, figures, or tables and represented overlooked data as "Not Available (NA)." The reviewers checked these data points against published tables for validity when available. As a result, certain variables contained a high percentage of missing data, as reported in Tables 1 and 2. The prevalence of missing data also limited statistical analyses. At the end of data extraction, none of the eligible articles encompassed all the variables of interest and contained at least one NA value impeding our ability to perform a multivariate analysis.

The nature of reviewing case reports also limits access to the patient's complete history and physical, muddying our ability to control for confounding variables. As mentioned earlier, we proposed an association with stoma creation reason and final pathology. Similarly, in the case of ileostomy site lymphoma, the three authors proposed a possible extrapolated mechanism from regular small bowel lymphomas [5, 13, 17]. Each patient had a medical history, such as coeliac disease or autoimmune deficiency syndrome, that may have contributed to the ileostomy site malignancy [5, 13, 17]. Our study's limitation also reveals the necessity to consider other comorbidities when examining potential ileostomy site neoplasia.

Despite the limitations, this study emphasizes the importance of screening ileostomy site malignancies for

Table 3 Comparison of demographics and management of patients with adenocarcinoma and squamous cell carcinoma (SCC) of the ileostomy site

Variables	Adenocarcinoma ($n=70$)	SCC ($n=10$)	Other ($n=11$)	p-value
Age at ileostomy creation, years[a]	30.5 [24.3, 37.0]	33.0 [25.0, 45.0]	41.0 [29.0, 51.5]	0.10
Age at ileostomy neoplasm diagnosis, years	59.7 (11.4)	72.30 (5.7)	67.5 (15.0)	< 0.05*
Age of stoma, years	28.8 (11.3)	37.00 (14.4)	26.2 (15.1)	0.10
Indication for ileostomy creation[b]				0.05*
Familial adenomatous polyposis	18 (25.7)	0 (0.0)	1 (9.1)	
Inflammatory bowel disease	50 (71.4)	8 (80.0)	9 (81.8)	
Other	2 (2.9)	2 (20.0)	1 (9.1)	
Largest dimension of neoplasm, cm[a]	4.00 [3.0, 5.0]	4.0 [3.0, 10.0]	6.5 [2.8, 11.3]	0.79
Initial biopsy results[b]				< 0.05*
Adenocarcinoma	39 (56.5)	0 (0.0)	0 (0.0)	
Adenoma	5 (7.2)	0 (0.0)	0 (0.0)	
Atypia	1 (1.4)	0 (0.0)	0 (0.0)	
Chronic inflammation	2 (2.9)	0 (0.0)	0 (0.0)	
Dysplasia	1 (1.4)	0 (0.0)	0 (0.0)	
Eccrine syringofibroadenoma	0 (0.0)	0 (0.0)	1 (9.1)	
Inflammation	0 (0.0)	0 (0.0)	1 (9.1)	
Melanoma	0 (0.0)	0 (0.0)	1 (9.1)	
Metaplasia	2 (2.9)	0 (0.0)	0 (0.0)	
Neoplasia	0 (0.0)	0 (0.0)	1 (9.1)	
No biopsy performed	16 (23.2)	1 (10.0)	7 (63.6)	
Polyp	2 (2.9)	0 (0.0)	0 (0.0)	
Squamous cell carcinoma	0 (0.0)	9 (90.0)	0 (0.0)	
Ulcerative colitis	1 (1.4)	0 (0.0)	0 (0.0)	
Time between biopsy and resection, years[a]	0.5 [0.0, 3.0]	NA [NA, NA]	2.0 [2.0, 2.0]	0.71

Variables presented as following: normal distribution = mean (standard deviation); non-normal distribution = median [interquartile range]; categorical = n (%); *NA* not available. Univariate analysis performed with *t*-test or *chi*-squared test as appropriate unless otherwise specified

*Statistical significance p-value ≤ 0.05

[a]Kruskal–Wallis Rank Sum Test

[b]Fisher's exact test

asymptomatic patients. For FAP and IBD patients, this meta-analysis suggests a combined ileostomy age and patient's age as a potential tool for stoma site cancer screening. In patients with a history of FAP, a threshold stoma age ≥ 20 encompassed 87.5% of patients with 68.4% aged ≥ 50. Combining these two criteria resulted in capturing 78.9% of patients. Similarly, in IBD patients, stoma age ≥ 25 comprised 69.7%, with 70.1% aged ≥ 60. When combined, 80.6% of IBD patients were captured.

Conclusion

This systematic review aimed to elucidate all reported primary ileostomy site malignancies. Eight diverse pathologies were found, with adenocarcinoma and SCC as the most common ones. Analysis of the patients' medical history revealed an association between stoma creation and type of ileostomy site cancer. The collected literature demonstrated FAP and IBD as the most common indicators for stoma creation. Patients with a history of FAP almost exclusively developed adenocarcinoma on average 25.8 years after the index surgery. Patients with IBD developed more diverse pathologies much later after stoma creation. The most common symptoms of ileostomy site malignancies were growing mass, bleeding, irritation, and difficulty with the stomal appliance. However, neither tumor pathology nor past medical history influenced presentation significantly. Treatment analysis revealed that biopsies correlated with final pathology results and can help determine treatment options. Additionally, first-line curative surgery with lymph node dissection may reduce disease recurrence or metastasis.

Ileostomy site masses can cause obstruction, difficulty with stomal appliances, and reduced patient quality of life. We believe that screening in this select group may lessen complications and potentially lead to a stoma reversal.

Table 4 Comparing patients' demographics and managements with an ileostomy creation indication of familial adenomatous polyposis (FAP) or inflammatory bowel disease (IBD)

Variables	FAP ($n=19$)	IBD ($n=67$)	Other ($n=5$)	p-value
Age at ileostomy creation, years[a]	29.0 [24.8, 37.0]	31.5 [25.0, 38.8]	43.0 [35.0, 53.0]	0.20
Age at ileostomy neoplasm diagnosis, years	56.0 (12.3)	64.1 (11.1)	57.0 (18.5)	0.02*
Age of stoma, years	25.8 (7.7)	31.4 (12.4)	14.5 (13.9)	< 0.05*
Sex				0.45
Female	9 (47.4)	33 (49.3)	1 (20.0)	
Male	10 (52.6)	34 (50.7)	4 (80.0)	
Race				< 0.05*
Black	1 (16.7)	0 (0.0)	0 (0.0)	
Indian	0 (0.0)	0 (0.0)	1 (100.0)	
White	5 (83.3)	9 (100.0)	0 (0.0)	
Largest dimension of neoplasm, cm[a]	4.5 [3.0, 9.0]	4.0 [3.0, 5.0]	3.4 [2.7, 8.2]	0.63
Resection type[b]				0.35
Nononcologic resection	7 (41.2)	36 (57.1)	3 (60.0)	
Resection resulting in reoperation	0 (0.0)	2 (3.2)	0 (0.0)	
Local	1 (5.9)	2 (3.2)	0 (0.0)	
No surgery	0 (0.0)	1 (1.6)	1 (20.0)	
Oncologic	9 (52.9)	22 (34.9)	1 (20.0)	
Pathology Result				0.05*
Adenocarcinoma	18 (94.7)	50 (74.6)	2 (40.0)	
Squamous Cell Carcinoma	0 (0.0)	8 (11.9)	2 (40.0)	
Other	1 (5.3)	9 (13.4)	1 (20.0)	
Eccrine syringofibroadenoma	1 (5.3)	1 (1.5)	0 (0.0)	
Extramammary Paget disease	0 (0.0)	1 (1.5)	0 (0.0)	
Lymphoma	0 (0.0)	3 (4.5)	0 (0.0)	
Melanoma	0 (0.0)	3 (4.5)	0 (0.0)	
Neuroendocrine tumor	0 (0.0)	1 (1.5)	0 (0.0)	
Verrucous carcinoma	0 (0.0)	0 (0.0)	1 (20.0)	
Lymph node positive[b]	0 (0.0)	9 (25.7)	0 (0.0)	0.14
Metastatic disease[b]	0 (0.0)	7 (15.2)	1 (25.0)	0.22

Variables presented as following: normal distribution = mean (standard deviation); non-normal distribution = median [interquartile range]; categorical = n (%). Univariate analysis performed with t-test or chi-squared test as appropriate unless otherwise specified

*Statistical significance p-value ≤ 0.05

[a]Kruskal–Wallis Rank Sum Test

[b]Fisher's exact test

Future analysis of ileostomy site malignancy incidence with comorbidity history can generate variables of interest and their thresholds for screening guidelines. As a result of our meta-analysis, we discovered that a stoma age ≥ 20 and a patient age ≥ 50 captured 78.9% of the FAP patients. Similarly, cutoffs of stoma age ≥ 25 and patients age ≥ 60 accounted for 80.6% of the IBD subjects. We recommend stoma duration and patient age as potential guidelines to screen asymptomatic ileostomy patients with a FAP or IBD history.

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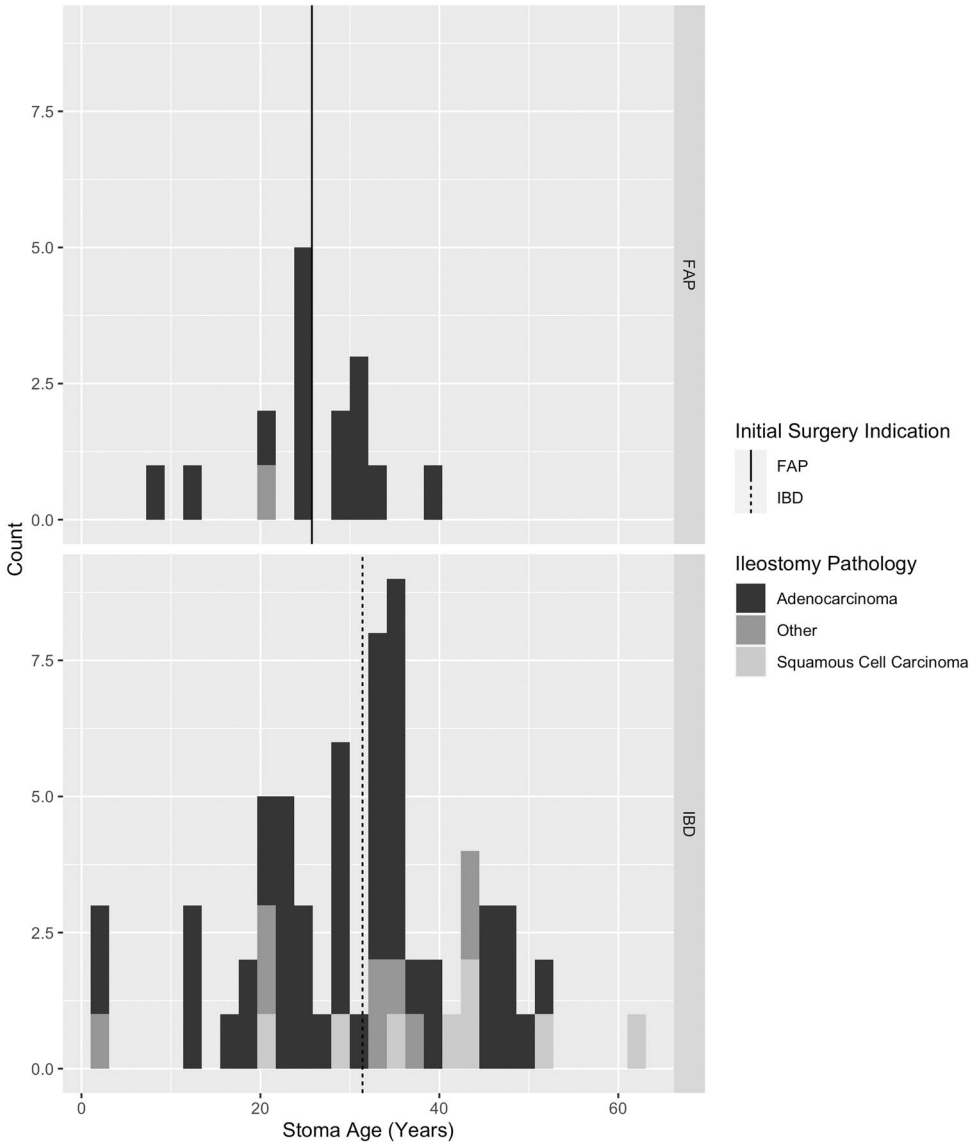

Fig. 2 Histogram of ileostomy site malignancy diagnosis by stoma age. Mean stoma age in patients with familial adenomatous polyposis (FAP) before ileostomy site cancer diagnosis = 25.8 years. Mean stoma age in patients with Inflammatory bowel disease (IBD) before ileostomy site cancer diagnosis = 31.4 years

Declarations

Disclosures Anthony Onde Morada, Sri Harshavardhan Senapathi, Amir Bashiri, Seungwoo Chai, and Burt Cagir do not have any financial conflicts of interest to disclose.

References

1. James SD, Hawkins AT, Moma AE (2018) Adenocarcinoma at the ileostomy site after a proctocolectomy for ulcerative colitis and/or familial adenomatous polyposis: an overview. Ostomy Wound Manag 64:30–40. https://doi.org/10.25270/owm.2018.6.3040
2. Bani Hani M, Butler B, Leberer D, Attuwaybi B (2020) Primary squamous cell carcinoma at ileostomy site. Two case reports and review of literature. Clin Case Rep 8:1437–1439. https://doi.org/10.1002/ccr3.2931
3. Carne PWG, Farmer KCR (2001) Squamous-cell carcinoma developing in an ileostomy stoma: report of a case. Dis Colon Rectum 44:594. https://doi.org/10.1007/BF02234336
4. Chan CC, Roy A, Stanley PRW, Mathew B (2012) A rare case of primary malignant melanoma in an ileostomy. J Plast Reconstr Aesthetic Surg 65:e354–e356. https://doi.org/10.1016/j.bjps.2012.09.009
5. Chang A, Davis B, Snyder J et al (2014) Considerations for diagnosis and management of ileostomy-related malignancy: a report of two cases. Ostomy Wound Manag 60:38–43
6. Clarke LE, Ioffreda M, Abt AB (2003) Eccrine syringofibroadenoma arising in peristomal skin: a report of two cases. Int J Surg Pathol 11:61–63. https://doi.org/10.1177/106689690301100116
7. Ejtehadi F, Nizamoglu M, Sivakumar R (2013) Squamous cell carcinoma at an ileostomy site: fifty-four years following colectomy for ulcerative colitis: a case report and literature review. Int J Surg Case Rep 4:678–680. https://doi.org/10.1016/j.ijscr.2013.04.036
8. Wu JS, Sebek BA, Fazio VW (2000) Parastomal squamous cell carcinoma in an ileostomy 44 years after proctocolectomy. J Am

Coll Surg 191:107. https://doi.org/10.1016/S1072-7515(00)00301-X
9. Gilbert RWD, Harvey HM, Nessim C (2019) Malignant melanoma arising from an end ileostomy. BMJ Case Rep. https://doi.org/10.1136/bcr-2019-230265
10. Gupta AD, Bandari J, Ross AE et al (2011) Management of primary squamous cell carcinoma at the mucocutaneous junction of an ileal conduit. Urology 78:1229–1231
11. Hirano Y, Miyazu T, Sugimoto K (2020) A rare lesion at the ileostomy site of a patient with intestinal Behçet's disease. Gastroenterology 159:e14–e15. https://doi.org/10.1053/j.gastro.2019.12.037
12. Joybari AY, Azadeh P, Honar BN (2018) Cutaneous verrucous carcinoma superimposed on chronically inflamed ileostomy site skin: a case report. Iran J Pathol 13:285–288. https://doi.org/10.30699/ijp.13.2.285
13. Levecq H, Hautefeuille M, Hoang C et al (1990) Primary stomal lymphoma. An unusual complication of ileostomy in a patient with transfusion-related acquired immune deficiency syndrome. Cancer 65:1028–1032
14. Liu X, Melton GB, Xie H, Dietz DW (2012) Extramammary paget disease in peristomal skin: report of a unique case. J Gastrointest Surg 16:1967–1971. https://doi.org/10.1007/s11605-012-1900-z
15. Mattoch IW, Pham N, Robbins JB et al (2008) Reactive eccrine syringofibroadenoma arising in peristomal skin: an unusual presentation of a rare lesion. J Am Acad Dermatol 58:691–696. https://doi.org/10.1016/j.jaad.2007.08.032
16. O'Connell PR, Dozois RR, Irons GB, Scheithauer BW (1987) Squamous cell carcinoma occurring in a skin-grafted ileostomy stoma: report of a case. Dis Colon Rectum 30:475–478. https://doi.org/10.1007/BF02556501
17. Pranesh N (2002) Lymphoma in an ileostomy. Postgrad Med J 78:368–369
18. Ramanujam P, Venkatesh KS (2002) An unusual case of squamous cell carcinoma arising at the stomal site: case report and review of the literature. J Gastrointest Surg 6:630–631. https://doi.org/10.1016/S1091-255X(01)00007-5
19. Warrier SK, Suhardja TS, Kumar B, Hastie I (2011) Stomal melanoma - Myth or reality? Int J Colorectal Dis 26:391–392. https://doi.org/10.1007/s00384-010-1004-8
20. Yu L, Braun A, Hansen NJ et al (2020) Primary neuroendocrine tumor of the ileostomy stoma on 68Ga-DOTATATE PET/CT. Clin Nucl Med 45:463–464. https://doi.org/10.1097/RLU.0000000000003040
21. Campana LG, Scarpa M, Sommariva A et al (2013) Minimally invasive treatment of peristomal metastases from gastric cancer at an ileostomy site by electrochemotherapy. Radiol Oncol 47:370–375. https://doi.org/10.2478/raon-2013-0051
22. Prouty M, Patrawala S, Vogt A et al (2016) Benign colonic metaplasia at a previous stoma site in a patient without adenomatous polyposis. J Cutan Pathol 43:276–279
23. Raghu P, Tran TA, Rady P et al (2012) Ileostomy-associated chronic papillomatous dermatitis showing nevus sebaceous-like hyperplasia, HPV 16 infection, and lymphedema: a case report and literature review of ostomy-associated reactive epidermal hyperplasias. Am J Dermatopathol 34:E97–E102. https://doi.org/10.1097/DAD.0b013e3182562526
24. Bakhshi GD, Shenoy SS, Jadhav KV et al (2013) Adenocarcinoma of an ileostomy in a case of Hirschprung's disease with retroviral disease. Clin Pract 3:27. https://doi.org/10.4081/cp.2013.e27
25. Basar N, Ali A, Khan NA, Memon AS (2013) Metastasis to ileostomy of mucinous adenocarcinoma of rectum. J Pak Med Assoc 63:1302–1304
26. Metzger PP, Slappy ALJ, Chua HK, Menke DM (2008) Adenocarcinoma developing at an ileostomy: report of a case and review of the literature. Dis Colon Rectum 51:604–609. https://doi.org/10.1007/s10350-007-9188-x
27. Sherlock DJ, Suarez V, Gray JG (1990) Stomal adenocarcinoma in Crohn's disease. Gut 31:1329–1332. https://doi.org/10.1136/gut.31.11.1329
28. Moher D, Liberati A, Tetzlaff J et al (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6:e1000097. https://doi.org/10.1371/journal.pmed.1000097
29. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A (2016) Rayyan-a web and mobile app for systematic reviews. Syst Rev 5:210. https://doi.org/10.1186/s13643-016-0384-4
30. US National Library of Medicine (2021) How to Include a Journal in MEDLINE. In: Natl. Libr. Med. https://www.nlm.nih.gov/medline/medline_how_to_include.html. Accessed 4 May 2021
31. US National Library of Medicine (2021) How to include a journal in PMC. In: Natl. Institutes Heal. https://www.ncbi.nlm.nih.gov/pmc/pub/addjournal/. Accessed 4 May 2021
32. Clarivate (2021) Web of Science Journal Evaluation Process and Selection Criteria. In: Web Sci. https://clarivate.com/webofsciencegroup/journal-evaluation-process-and-selection-criteria/. Accessed 4 May 2021
33. Wolters Kuwer Health (2021) CAB Global Health Database Guide. In: Ovid. http://ospguides.ovid.com/OSPguides/caghdb.htm. Accessed 4 May 2021
34. 3.5.1. RDCT (2018) A language and environment for statistical computing. R Found. Stat. Comput. 2:https://www.R-project.org
35. Ferrandez Rivera M, Baltar Boileve J, Cameselle Teijeiro JM et al (1990) Adenocarcinoma at an ileostomy site following colectomy for ulcerative colitis. J Chir (Paris 1980) 127:412–415
36. Adamic B, Holfinger S, Sharma N et al (2016) Adenocarcinoma at an ileostomy site. Am J Gastroenterol 111:S1034. https://doi.org/10.14309/00000434-201610001-02167
37. Yousaf A, Beatty C, Zinn Z et al (2020) Ileostomy adenocarcinoma in Crohn's disease. Int J Colorectal Dis 35:963–966. https://doi.org/10.1007/s00384-020-03554-6
38. Azem J, López-Cano M, Ponseti JM et al (2005) Ileostomy-site adenocarcinoma after proctocolectomy for ulcerative colitis [2]. Int J Colorectal Dis 20:549–550
39. Ewlng HP, Manolas SG (1989) Primary adenocarcinoma arising at an ileostomy site: an unusual cause of bowel obstruction. Aust N Z J Surg 59:898–899. https://doi.org/10.1111/j.1445-2197.1989.tb07037.x
40. Roberts PL, Veidenheimer MC, Cassidy S, Silverman ML (1989) Adenocarcinoma arising in an ileostomy: report of two cases and review of the literature. Arch Surg 124:497–499. https://doi.org/10.1001/archsurg.1989.01410040107025
41. Stryker SJ (1983) Primary stomal adenocarcinoma: an unusual complication of ileostomy. Dis Colon Rectum 26:47–49. https://doi.org/10.1007/BF02554680
42. Lopez JF, Granger P, Dupre A (1991) Degenerescence maligne sur ileostomie pour polypose recto-colique. J Chir (Paris) 128:201–203
43. Bedetti CD, DeRisio VJ (1986) Primary adenocarcinoma arising at an ileostomy site: an unusual complication after colectomy for ulcerative colitis. Dis Colon Rectum 29:572–575. https://doi.org/10.1007/BF02554258
44. Mimura T, Kuramoto S, Yamasaki K, Kaminishi M (1999) Familial adenomatous polyposis: a case report and histologic mucin study. J Clin Gastroenterol 28:372–376. https://doi.org/10.1097/00004836-199906000-00021
45. Cox CL, Butts DR, Roberts MP et al (1997) Development of invasive adenocarcinoma in a long-standing kock continent ileostomy:

report of a case. Dis Colon Rectum 40:500–503. https://doi.org/10.1007/BF02258400
46. Iizuka T, Sawada T, Hayakawa K et al (2002) Successful local excision of ileostomy adenocarcinoma after colectomy for familial adenomatous polyposis: report of a case. Surg Today 32:638–641. https://doi.org/10.1007/s005950200116
47. MacLean Mags ME, McMillan S, Chong D et al (2006) Ileostomy carcinomas: a review: the latent risk after colectomy for ulcerative colitis and familial adenomatous polyposis. Color Dis 8:725–726. https://doi.org/10.1111/j.1463-1318.2006.01101.x
48. Gadacz TR, McFadden DW, Gabrielson EW et al (1990) Adenocarcinoma of the ileostomy: the latent risk of cancer after colectomy for ulcerative colitis and familial polyposis. Surgery 107:698–703
49. Quah HM, Samad A, Maw A (2005) Ileostomy carcinomas a review: the latent risk after colectomy for ulcerative colitis and familial adenomatous polyposis. Color Dis 7:538–544. https://doi.org/10.1111/j.1463-1318.2005.00807.x
50. Carter D, Choi H, Otterson M, Telford GL (1988) Primary adenocarcinoma of the ileostomy after colectomy for ulcerative colitis. Dig Dis Sci 33:509–512. https://doi.org/10.1007/BF01536039
51. Baciewicz F, Sparberg M, Lawrence JB, Poticha SM (1983) Adenocarcinoma of an ileostomy site with skin invasion: a case report. Gastroenterology 84:168–170
52. Suarez V, Alexander-Williams J, O'Connor HJ et al (1988) Carcinoma developing in ileostomies after 25 or more years. Gastroenterology 95:205–208. https://doi.org/10.1016/0016-5085(88)90313-7
53. Forbes R, Riviello R, Herline AJ et al (2008) W1692 primary ileostomy adenocarcinoma: rare condition after proctocolectomy. Gastroenterology 134:908. https://doi.org/10.1016/s0016-5085(08)64265-1
54. Attanoos R, Billings PJ, Hughes LE, Williams GT (1995) Ileostomy polyps, adenomas, and adenocarcinomas. Gut 37:840–844
55. Talanow R, Shrikanthan S, Neumann DR (2010) An interesting view: volume-rendered PET of an adenocarcinoma at the ileostomy site. Clin Nucl Med 35:550–551. https://doi.org/10.1097/RLU.0b013e3181e05dd3
56. Smart PJ, Sastry S, Wells S (1988) Primary mucinous adenocarcinoma developing in an ileostomy stoma. Gut 29:1607–1612. https://doi.org/10.1136/gut.29.11.1607
57. Carey PD, Suvarna SK, Baloch KG et al (1993) Primary adenocarcinoma in an ileostomy: a late complication of surgery for ulcerative colitis. Surgery 113:712–715. https://doi.org/10.5555/uri:pii:003960609390365K
58. Johnson JA, Talton DS, Poole GV (1993) Adenocarcinoma of a Brooke ileostomy for adenomatous polyposis coli. Am J Gastroenterol 88:1122–1124
59. Sigler L, Jedd FL (1969) Adenocarcinoma of the ileostomy occurring after colectomy for ulcerative colitis: report of a case. Dis Colon Rectum 12:45–48. https://doi.org/10.1007/BF02617197
60. Coen LD, Lambert WG, Gray PB (1988) Adenocarcinoma at the ileo-cutaneous junction following subtotal colectomy for ulcerative colitis. Case report. Acta Chir Scand 154:685–686
61. Procaccino L (2015) Adenocarcinoma arising at ileostomy sites: two cases and a review of the literature. World J Gastrointest Surg 7:94. https://doi.org/10.4240/wjgs.v7.i6.94
62. Matsushima K (2009) Two different types of polypoid lesion at ileostomy site. Surgery 145:337–338. https://doi.org/10.1016/j.surg.2007.08.021
63. Achneck HE, Wong IY, Kim PJ et al (2005) Ileostomy adenocarcinomas in the setting of ulcerative colitis. J Clin Gastroenterol 39:396–400. https://doi.org/10.1097/01.mcg.0000159216.39795.4a
64. Al-Niaimi F, Lyon CC (2010) Primary adenocarcinoma in peristomal skin: a case study. Ostomy Wound Manag 56:45–47
65. Huntington JT, Stanich PP, Harzman AE (2017) Adenocarcinoma arising from an end ileostomy in a patient with familial adenomatous polyposis. Clin Gastroenterol Hepatol 15:A27–A28. https://doi.org/10.1016/j.cgh.2016.11.022
66. Annam V, Panduranga C, Kodandaswamy C, Suresh DR (2008) Primary mucinous adenocarcinoma in an ileostomy with adjacent skin invasion: a late complication of surgery for ulcerative colitis. J Gastrointest Cancer 39:138–140. https://doi.org/10.1007/s12029-009-9066-y
67. Cuesta MA, Donner R (1976) Adenocarcinoma arising at an ileostomy site Report of a case. Cancer 37:949–952. https://doi.org/10.1002/1097-0142(197602)37:2%3c949::AID-CNCR2820370251%3e3.0.CO;2-D
68. Liu K, Prasad MA, Lo A et al (2016) Primary adenocarcinoma of an ileostomy in crohn's disease. ACG Case Rep J 3:e112. https://doi.org/10.14309/crj.2016.85
69. Jiménez Rodríguez RM, Perea del Pozo E, Díaz Pavón JM, De la Portilla F (2017) Mucinous adenocarcinoma arising in an end ileostomy: a video vignette. Color Dis 19:787. https://doi.org/10.1111/codi.13803
70. Roth JA, Logio T (1982) Carcinoma arising in an lleostomy stoma. An unusual complication of adenomatous polyposis coli. Cancer 49:2180–2184. https://doi.org/10.1002/1097-0142(19820515)49:10%3c2180::AID-CNCR2820491033%3e3.0.CO;2-3
71. Pellissier PE, David A, Coppere H et al (1990) Adenocarcinome primitif sur ileostomie apres proctocolectomie totale pour rectocolite ulcero-hemorragique. Gastroenterol Clin Biol 14:672–674
72. Agabiti E, Loganathan A, Rimmer M et al (2005) Cancer of ileostomy: a late complication of colectomy for ulcerative colitis. Acta Chir Belg 105:99–101. https://doi.org/10.1080/00015458.2005.11679676
73. Vasilevsky C-A, Gordon PH (1986) Adenocarcinoma arising at the ileocutaneous junction occurring after proctocolectomy for ulcerative colitis. Br J Surg 73:378–378. https://doi.org/10.1002/bjs.1800730521
74. Hata K, Watanabe T, Kawamura YJ et al (2003) K-ras mutation and loss of heterozygosity at 17p with β-catenin accumulation in intramucosal carcinoma of the ileostomy in familial adenomatous polyposis: a case report. Dig Dis Sci 48:2310–2314. https://doi.org/10.1023/B:DDAS.0000007868.52339.22
75. Reissman P, Avroutis O, Cohen DY, Shiloni E (1997) Ileostomy-site colonic metaplasia with adenocarcinoma after proctocolectomy for ulcerative colitis. Am J Gastroenterol 92:1932–1933
76. Gilson TP, Sollenberger LL (1992) Adenocarcinoma of an ileostomy in a patient with familial adenomatous polyposis: report of a case. Dis Colon Rectum 35:261–265. https://doi.org/10.1007/BF02051020
77. Lux N, Wedell J, Busch M, Vancalker H (1993) Adenocarcinoma of an ileostomy site following total prostatectomy in familial polyposis: case-report and literature-review. Chirurg 64:416–418
78. Shenoy S, Cassim R (2009) Ileostomy adenocarcinoma associated with familial adenomatous polyposis (FAP): new problem in old disease. Int J Colorectal Dis 24:1475–1476. https://doi.org/10.1007/s00384-009-0739-6
79. Primrose JN, Quirke P, Johnston D (1988) Carcinoma of the ileostomy in a patient with familial adenomatous polyposis. Br J Surg 75:384–384. https://doi.org/10.1002/bjs.1800750430
80. Johnson WR, McDermott FT, Pihl E, Hughes ESR (1980) Adenocarcinoma of an ileostomy in a patient with ulcerative colitis. Dis Colon Rectum 23:351–352. https://doi.org/10.1007/BF02586844
81. Johnson CD, White H (1988) Colonic metaplasia with colonic-type polyps on an ileostomy stoma in polyposis coli: report of a case. Dis Colon Rectum 31:405–407. https://doi.org/10.1007/BF02564900

82. Mohandas S, Lake S (2010) Primary adenocarcinoma of ileostomy: case report with review of the literature. Case Rep Med. https://doi.org/10.1155/2010/921328
83. Hammad A, Tayyem R, Milewski PJ, Gunasekaran S (2011) Primary adenocarcinoma in the ileostomy of a woman with familial adenomatous polyposis: a case report and literature review. J Med Case Rep 5:2–5. https://doi.org/10.1186/1752-1947-5-556
84. Ross DS, Bussing R, Dietrich J (1987) Carcinoma arising in an ileostomy. IMJ Ill Med J 172:163–166
85. Starke J, Rodriguez-Bigas M, Marshall W et al (1993) Primary adenocarcinoma arising in an ileostomy. Surgery 114:125–128
86. Abela J, Szczepanski M, LaFerla G (2004) Ileostomy adenocarcinoma: a case report. Malta Med J 16:42–43
87. Longo WE, Stephan RN, True LD et al (1986) Recurrent ileal mucinous adenocarcinoma in an ileostomy. J Clin Gastroenterol 8:192–194. https://doi.org/10.1097/00004836-198604000-00020
88. Berman JJ, Ullah A (1989) Colonic metaplasia of ileostomies. Biological significance for ulcerative colitis patients following total colectomy. Am J Surg Pathol 13:955–960. https://doi.org/10.1097/00000478-198911000-00006
89. Schlippert W, Mitros F, Schulze K (1979) Multiple adenocarcinomas and premalignant changes in "backwash" ileitis. Am J Med 66:879–882. https://doi.org/10.1016/0002-9343(79)91146-X