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ORIGINAL ARTICLE – COLORECTAL CANCER

De Novo Secondary Adenocarcinoma in the Colon Used as Urinary Diversion Not in Contact with the Fecal Stream: Systematic Review and Meta-analysis

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ABSTRACT

Background. A systematic review with a meta-analysis was performed to determine the prevalence and risk factors for secondary de novo adenocarcinoma in the colon used as a urinary diversion not exposed to the fecal stream.

Methods. The systematic review of the literature identified 47 patients with secondary adenocarcinoma in a colonic urinary diversion not exposed to the fecal stream.

Results. The diagnosis of secondary adenocarcinoma was determined due to the presence major local symptoms and because the cancer in half of the patients was detected at an advanced stage. Diagnosis at an earlier stage was associated with long-term cancer-free survival.

Conclusions. The authors concluded that cystoscopy-colonoscopy screening as suggested by the American Gastroenterology Society for the general population should be applied to patients who have colon urinary diversion not exposed to the fecal stream. For patients with active high-grade inflammation, difficulty with self-catheterization, or symptoms, cystoscopy should be performed earlier. Resection of the tumor at an early stage offers better clinical outcomes with longer survival rates.

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Analysis of the factors correlated with the formation of secondary adenocarcinoma in the colon at a different environment away from the fecal stream offers the possibility of studying the problem from an alternative point of view.[1–5] Secondary tumors near or at the uretero-colonic anastomosis are a well-recognized complication after ureterosigmoidostomy.[6–9] The tumor risk for patients with ureterosigmoidostomy is reported to be 500-fold in 25- to 30-year-old patients and eightfold in 55- to 60-year-old patients compared with the general population. The cause for this increased prevalence of adenocarcinoma just near the uro-colic anastomosis has been attributed to the mixture of feces and urines.[8,10–12]

We performed a systematic review to analyze the reports of secondary adenocarcinomas arising in the colon used as a urinary conduit and not in contact with the fecal stream. We defined "secondary adenocarcinoma" as an adenocarcinoma arising de novo in the colon used as urinary diversion and not in contact with the fecal stream. Patients for whom it was doubtful that the adenocarcinoma was already present at the time of surgery were excluded from the study (diagnosis of the tumor within 12 months after surgery without normal preoperative colonoscopy). The primary outcomes of this systematic review were the prevalence of the problem and the potential risk factors. In our study, we included only adenocarcinomas arising from the colon or rectal wall. Patients with benign tumors or other forms of malignant tumors were not included in the analysis.

MATERIALS AND METHODS

The methods used for the study and the inclusion criteria were based on Preferred Reports Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.

A literature search was performed June 2019 by two investigators who conducted a review of papers reported in PubMed, EMBASE, MEDLINE, and the Cochrane Database. The strings "COLON URINARY CONDUIT," "ADENOCARCINOMA IN URINARY DIVERSIONS," and "URINARY DIVERSIONS" were used in combination with the Boolean operators "and" and "or." Editorials, letters to the editor, chapter in books, and abstracts in symposia were included in the search. There was no language or time restriction and a screened report. The registration number at the International Prospective Register of Systematic Review (PROSPERO) was CRD 42018089691.

Data Extraction

Data extraction was performed by two reviewers independently. A third reviewer was involved to solve any question in interpreting data. The primary outcome was possible risk factors for adenocarcinoma in the colon used as a continent or incontinent urinary conduit not in contact with the fecal stream. The secondary outcomes were prevalence of the complication, stage at the time of diagnosis, therapy, and clinical outcome.

Quality Assessment

Two independent reviewers determined the quality and risks for bias of analyzed studies by using the Newcastle–Ottawa scale.[13] This scale defines the quality of a paper, with a score ranging from 0 to 9. Papers with a score higher than 6 were considered of good quality.

Statistical Analysis

All primary outcomes were analyzed by the fixed-effects models. Student's *t* test and the Chi square test were used where appropriate.

RESULTS

Literature Search

The study identified 3350 papers published from June 1970 to June 2019. Of 165 papers fully evaluated, only 44 papers clearly reported patients with a colon conduit not in contact with the fecal stream for whom a diagnosis of adenocarcinoma was made. We excluded the reports for two patients whose adenocarcinoma or adenoma with high dysplasia may already have been present at the time of surgery because the diagnosis of the tumor was made within 4 months after surgery[14,15] and for one patient whose rectal cancer occurred after 9 years, with independent exposure first to urine alone and later to feces alone.[16]

The majority of the analyzed papers described single case reports. Three papers reported two patients, and one paper analyzed the 10-year data from several centers in Germany, reporting three patients. Overall, 47 patients were reported as having a secondary adenocarcinoma in the colon-rectum used as a urinary conduit away from the fecal stream. Tables 1, 2, 3 and 4 describe the characteristics of the included studies.

The quality of the papers was good (average, 7.5), with a detailed description of the clinical characteristics of all but five patients. The follow-up period after the diagnosis of de novo adenocarcinoma ranged from 3 to 84 months (average, 13 months).

Clinical Characteristics of the Patients

The study enrolled 27 males and 16 females. For 4 of the 47 patients enrolled in the study, the gender was not specified. The mean age at the time of the secondary adenocarcinoma diagnosis was 62.7 years (range, 29–82 years). The indication for the initial surgery was malignant disease in 27 patients and benign disease in 15 patients. In four cases, the secondary adenocarcinoma arose in patients who had simultaneous kidney transplantation with immunotherapy (1 patient had a colon conduit, 3 patients had a colocystoplasty). In one patient, the indication for the initial surgery was not identifiable. Except for the last five patients, the patients who initially had surgery for benign disease, as expected, were younger than the patients who had surgery for malignant disease (43.2 vs. 57.7 years; $p < 0.0001$).

All the patients underwent cystoscopy and diagnosis of the secondary adenocarcinoma because of major symptoms. The most common symptoms were bleeding and pain. At the time of the secondary adenocarcinoma diagnosis, the mean age of patients who had previous surgery for benign disease was 52.2 years, whereas it was 68.9 years for the patients who had initial surgery for malignant disease ($p < 0.001$). Two patients had a family history of colorectal cancer. The ages of the patients at the time of the secondary adenocarcinoma diagnosis were respectively 73 and 82 years, so it was difficult to determine the real meaning of the family history for these two patients.

A metachronous/synchronous cancer in the native colon was diagnosed in two patients. In another patient, a metachronous rectal polyp was removed (6.3%, 3/48). Histology showed a well-differentiated adenocarcinoma in 21 patients, a poorly differentiated adenocarcinoma in 6 patients, a mucinous poorly differentiated adenocarcinoma in 2 patients, and a signet cell carcinoma in 1 patient. Six

TABLE 1 Secondary adenocarcinoma in isolated recto-sigmoid bladder

Author (year)	Age/sex	Indication for cystectomy	Years from initial surgery	Graft	Stage at the time of diagnosis	Therapy	Available follow-up
Harzmann et al. (1986)[17]	?/M	Tuberculosis	28	Isolated recto-sigmoid bladder	Localized	Not stated	Not stated
Shabaan et al. (1992)[18]	61/M	Bladder cancer	11	Isolated recto-sigmoid bladder	Locally advanced	Not stated	Early death
Shokeir et al. (1995)[19]	50/M	Bladder cancer	11	Isolated recto-sigmoid bladder	Locally advanced	Supportive	Early death
Shokeir et al. (1995)[19]	47/M	Bladder cancer	18	Isolated recto-sigmoid bladder	Locally advanced	Supportive	Early death
Kotanagi et al. (2001)[20]	77/M	Bladder cancer	6	Isolated recto-sigmoid bladder	Locally advanced	Palliative resection	Death 18 months-diffuse metastases

TABLE 2 Secondary adenocarcinoma in the colon as a noncontinent urinary conduit

Author (year)	Age/sex	Indication for urinary conduit	Years from Initial Surgery	Graft	Stage at the time of diagnosis	Therapy	Available follow-up
Chiang et al. (1982)[21]	29/M	Congenital anomalies	23	Sigmoid colon	T2N0M0	Colon resection	Alive and well-12 months
Wilson & Morales (1982)[22]	66/F	Cancer vagina	3	Transverse colon	Metastatic disease	Colon resection	Early death-diffuse metastases
Marchetti et al. (1984)[23]	79/F	Cancer cervix	11	Sigmoid colon	Metastatic disease	Colon resection	Early death-diffuse metastases
Erb et al. (1999)[24]	69/F	Cancer vagina	10	Sigmoid colon	T3N0M0	Colon resection	Alive and well-1 month
Pelaez et al[a] (2002)[25]	39/M	Congenital anomalies, kidney transplant	21	Right colon	T2N0M0	Colon resection	Alive and well-1 month
Kälble et al. (2011)[26]	?/?	?	> 30	Right colon	?	?	?

[a]Excluded from analysis (immunotherapy kidney transplant)

patients had an adenoma with high-grade dysplasia. For 11 patients, histologic details were not available.

Isolated Rectosigmoid Bladder (Table 1)

Five patients experienced de novo adenocarcinoma in the rectum after isolated rectosigmoid bladder (cystectomy with ureterosigmoidostomy and proximal diverting colostomy). Four patients had recurrent episodes of proctitis, with active inflammation. For all four patients, histology showed undifferentiated adenocarcinoma with local diffuse disease and poor clinical outcome. The fifth patient did not report episodes of proctitis. The tumor was well differentiated and localized in extension.

Incontinent Colon Conduit (Table 2)

Six patients had an adenocarcinoma arising in an incontinent colon conduit. Detailed information was available for five patients. Two of the patients had radiotherapy for their gynecology malignancy with recurrent episodes of active inflammation. The histology of one patient showed poorly differentiated adenocarcinoma. Both patients had diffuse metastatic disease at the time of the diagnosis and poor clinical outcome. Two patients showed no evidence of active high-grade inflammation, and their adenocarcinoma was well differentiated, with long term survival after resection. One patient had a kidney transplantation and immunosuppression.

Colocystoplasty (Table 3)

Adenocarcinoma in the colon, used as cystoplasty, was found in 16 patients. Two patients with recurrent infections and active inflammation had poorly differentiated mucinous adenocarcinoma.

Continent Colon Pouch (Indiana-Arizona Pouches) and Orthotopic Neobladder (Table 4)

In 20 patients, a new adenocarcinoma arising in the colon was used as a continent urinary pouch (Indiana pouch [$n = 18$], Arizona pouch [$n = 1$]) or orthotopic neobladder ($n = 1$). One of the patients had a poorly

TABLE 3 Secondary colon adenocarcinoma in colocystoplasty

Author (year)	Age/sex	Indication for colocystoplasty	Years from initial surgery	Graft	Stage at the time of diagnosis	Therapy	Available follow-up
Kirby and Lloyd Davies (1985)[27]	42/F	Cancer cervix	10	Cecum	T4N0M0	Colectomy–cystectomy	Alive and well-24 months
Steg et al. (1985)[28]	59/M	Tuberculosis	21	Cecum	T4N1M?	Colectomy–cystectomy	Early death-diffuse metastases
Harzmann et al. (1986)[17]	44/M	Tuberculosis	17	Cecum	Not specified	Colectomy–cystectomy	Not specified
Kadow et al. (1989)[29]	39/M	Aspecific cystitis	15	Cecum	Locally advanced	Colectomy–cystectomy	Not specified
Llarena-Ibarguren et al. (1989)[30]	56/F	Tuberculosis	19	Cecum	T4N1M?	Pelvic exnteratio	Not specified
Tellez-Martinez-Fornes (1983)[31]	66/M	Tuberculosis	14	Cecum	Metastatic disease	Supportive therapy	Early death-diffuse metastases
Docimo et al[a] (1999)[32]	43/M	Kidney transplant	20	Cecum	Locally advanced	Colectomy–cystectomy	Not specified
Yip et al[b] (1999)[33]	38/F	Tuberculosis	13	Cecum	Multiple adenomata colon and bladder-renal adenocarcinoma	Colectomy–cystectomy–nephrectomy	Alive and well-1 month
Bono Arino et al. (2001)[34]	49/M	Tuberculosis	27	Cecum	Signet cell carcinoma/ T4N1M0	Colectomy–cystectomy	Alive and well-12 months
Vallejo et al. (2008)[35]	59/M	Tuberculosis	29	Cecum	T2N0M0	Colectomy–cystectomy	Alive and well-6 months
Husmann and Rathbun[a] (2008)[36]	?	Kidney transplant	?	Cecum	?	?	?
Husmann and Rathbun[a] (2008)[36]	?	Kidney transplant	?	Cecum	?	?	?
Takezawa et al. (2011)[37]	60/F	Tuberculosis	38	Sigmoid	Locally advanced	Pelvic exenteratio	Alive and well-6 months
Rubino et al. (2011)[38]	39/M	Congenital anomalies	> 25	Cecum	Apparently large adenoma	Colectomy–cystectomy	Diffuse metastases-48 months
Ramamurthy & Susikar (2013)[39]	56/M	Tuberculosis	16	Cecum	T3N1M0	Pelvic exenteratio	Alive and well-6 months
Kimura et al. (2015)[40]	69/M	Tuberculosis	40	Right colon	T4N1M0	Colectomy–cystectomy	Alive and well-2 months

[a]Excluded from analysis (immunotherapy kidney transplant)

[b]Benign at histology, but multiple local metastases

differentiated cancer. The remaining patients had well or moderately differentiated cancer. In two patients, the cancer developed on a polyp previously removed endoscopically. In three patients, the specimen showed an adenoma near the adenocarcinoma. Four patients had a polyp with high-grade dysplasia.

TABLE 4 Secondary adenocarcinoma in the colon as continent urinary conduit (Indiana -Florida pouche, orthotopic neo-bladder)

Author (year)	Age/sex	Indication for initial surgery	Years from initial surgery	Site secondary adenocarcinoma	Stage at diagnosis	Therapy	Available follow-up
Albertini et al. (1998)[41]	82/M	Bladder cancer	7	Right colon-cecum	T2N0M0	Segmental resection	Alive and well- 6 months
Gazzaniga et al. (2000)[42]	73/M	Bladder cancer	2	Right colon-cecum	T2N0M0 (2 cancers)	Segmental resection	Alive and well-6 months
Lisle et al. (2000)[43]	76/M	Bladder cancer	6	Right colon-cecum	T3N0M0	Colon resection	Alive and well-9 months
L'Esperance et al. (2001)[44]	72/F	Bladder cancer	5.5	Right colon-cecum	T3N1M1	Colon resection–nephrectomy–resection 1 liver metastasis	Alive and well-1 month
Uesugi et al. (2002)[45]	71/M	Bladder cancer	9.5	Right colon-cecum	T3N0M0	Colon resection–nephrectomy	Alive and well-5 months
Komai et al. (2005)[46]	63/F	Bladder cancer	6	Right colon	T4N1M?	Colon resection–nephrectomy	Death 17 months after diffuse metastases
Ho et al. (2007)[47]	66/F	Cancer cervix	17	Right colon	Not reported	Not reported	Not reported
Ryochi et al. (2007)[48]	76/F	Rectal cancer	15	Right colon	Cancerous polyp	Endoscopic Resection	Alive and well- 15 months
Raman et al. (2007)[49]	66/M	Bladder cancer	7	Right colon-cecum	Adenoma with high-grade dysplasia	Endoscopic resection	Alive and well-36 months
Ikeda et al. (2010)[50]	76/F	Bladder cancer	11	Right colon	Metastatic disease	Supportive therapy	Death at 4 months- diffuse metastatic disease
Kälble et al. (2011)[26]	Not reported	Bladder cancer	10-20	Right colon-cecum	Not reported	Not reported	Not reported
Kälble et al. (2011)[26]	Not reported	Bladder cancer	<10	Right colon-cecum	Not reported	Not reported	Not reported
Jian et al. (2012)[51]	73/F	Bladder cancer	10.5	Right colon-cecum	T1N0M0	Colon resection	Alive and well-36 months
Jian et al. (2012)[51]	77/F	Bladder cancer	9	Right colon	T2N0M0	Colon resection	Death 3 months (sepsis from bowel fistula)
Moyer et al. (2012)[52]	69/F	Bladder cancer	21	Right colon-cecum	T1N0M0	Colon resection	Alive and well- 24 months
Saba et al. (2013)[53]	80/M	Bladder cancer	6	Right colon	Diffuse metastases	Supportive therapy	Deaths at 7 months-diffuse metastatic disease.
Manka et al. (2015)[54]	42/F	Congenital anomaly	24	Right colon	Adenoma with high-grade dysplasia	Local resection	Alive and well- 6 months
Morganstern et al. (2015)[55]	73/M	Bladder cancer	9	Right colon	Adenoma with high-grade dysplasia	Local resection	Not specified
Bell et al. (2018)[56]	80/F	Bladder cancer	8	Right colon	T4N0M0	Colon resection	Alive and well- 4 months
Murray et al. (2018)[57]	66/M	Bladder cancer	12	Right colon	T3N0M0	Endoscopic resection	Alive and well- 96 months

Prevalence of a New Adenocarcinoma

It is not easy to determine the real prevalence of adenocarcinomas in colon conduits not exposed to the fecal stream. We were able to collect 47 patients from the literature, and almost all the patients were published as "case reports." In the majority of the reported series using the colon as a conduit away from the fecal stream, no mention was made of a secondary colon adenocarcinoma.

Kälble et al.[26] reviewed the prevalence of benign and malignant tumors in 17,758 patients who had surgery at 44 urology centers in Germany from 1970 to 2007. In their study, they confirmed the increased prevalence of adenocarcinomas at the level of uretero-sigmoistomy (22-fold), in which the colon was exposed simultaneously to urine and feces. In 2940 patients who had the colon exposed to urine but not to the fecal stream, they found only three patients with adenocarcinoma (3/2940, 0.001%) and five patients who had benign tumors (3 patients) or other forms of malignant tumor (1 patient with carcinoid, 1 patient with squamous cell carcinoma). They concluded that the prevalence of adenocarcinoma in colon exposed to urine but not to the fecal stream may be similar to that of colorectal cancer in the general population, adjusted for age and sex. However, they found an increased prevalence of de novo adenocarcinoma in patients with ileo-cystoplasty and orthotopic colonic neo-bladder, and recommended regular endoscopic surveillance from at least the fifth year after surgery. Similar conclusions were reached by Husmann and Rathbun.[36]

Risk Factors: Ageing

A limited number of patients in our review did not allow any meaningful multiple regression analysis. The interval between the initial surgery and the diagnosis of secondary colon adenocarcinoma was much longer for patients who had colocystoplasty than for patients with other forms of urinary conduits ($p < 0.001$). For patients who had surgery for benign disease, the interval was significantly longer than for patients who had surgery for malignant disease ($p < 0.001$). The majority of patients with colocystoplasty had surgery for benign disease, so was it difficult to determine the influence of each factor. The interval between the initial surgery and the adenocarcinoma diagnosis varied significantly. The mean age of the patients at the time secondary adenocarcinoma diagnosis was more homogeneous than the time of exposure to urine and varied independently by the type of reconstruction (Table 5). The diagnosis of secondary adenocarcinoma was made at a younger age for patients who had surgery for benign disease, despite a longer exposure to urine, than for those who had surgery for malignant disease.

Active High-Grade Inflammation Versus Chronic Low-Grade Inflammation

Eight patients (3 who originally had surgery for benign disease and 5 who had surgery for malignant disease) showed clinical signs of active inflammation. The diagnosis of secondary adenocarcinoma was made at an earlier age (mean, 55 years) and after a shorter time of urine exposure than for patients without clinical signs of high-grade inflammation ($p < 0.001$). Histology showed poorly

TABLE 5 Time from initial surgery to diagnosis of secondary adenocarcinoma in the colon exposed to urine, away from the fecal stream (43 patients)[a]

Indication for surgery	Isolated rectal bladder		Colon conduit		Colocystoplasty		Colonic pouch	
	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant
Time from initial surgery (years)								
1–10		1		2		1		12
11–15		2		1	3			4
16–20		1			3			2
21–30	1		1		3		1	1
> 30			1(?)		3			
Mean interval (years)	14.8 ± 4		11.7 ± 6		21.8 ± 7		10.4 ± 3	
Mean age at initial surgery (years)	42.0 ± 4		49.1 ± 5		30.2 ± 7		59.9 ± 5	
Mean age at diagnosis of secondary adenocarcinoma (years)	56.6 ± 5		60.8 ± 5		52.0 ± 6		71.3 ± 8	

[a]In 5 patients, complete details were not reported

differentiated adenocarcinoma in all the patients, and all had diffuse disease as well as a poor clinical outcome.

Extension of Secondary Adenocarcinoma

In all the patients, the diagnosis of adenocarcinoma was based on the presence of major local symptoms. In eight patients, the adenocarcinoma was diagnosed at a metastatic stage, with early death. Six patients had advanced local disease, which required extended resection of pelvic organs. In 26 patients, the secondary adenocarcinoma was more localized. For 13 of these patients, diagnosis was at an early stage, with 7 undergoing local surgical resection and 6 undergoing endoscopic resection, all with a favorable outcome. The remaining 13 patients underwent colon resection and cystectomy. One of these patients had removal of a large colon adenoma, but he died 48 months later from diffuse metastases of adenocarcinoma. For seven patients, details about the type of surgery and follow-up evaluation were not available.

Site of Secondary Adenocarcinoma

Table 6 shows the site at which the secondary adenocarcinoma developed. For eight patients, the site of the secondary adenocarcinoma was not specified. In 12 of the 39 patients for whom the site was specified, the secondary cancer occurred near the anastomosis of the colonic wall with the ureter or the bladder (12%). In 22 patients, the secondary adenocarcinoma developed in the colon distant from the anastomosis. In patients with a continent colonic pouch, the secondary adenocarcinoma was located more often distant from the ureteric or bladder suture and associated with evident clinical signs of infection. The secondary adenocarcinoma developed more often near the suture with the ureters and the bladder in patients with colocystoplasty and incontinent conduit and was less frequently associated with clinical signs of infection ($p < 0.001$).

DISCUSSION

The prevalence of adenocarcinoma in the colon exposed simultaneously to urine and feces is reported to be 40- to 550-fold compared with the prevalence of sporadic cancer in the general population, adjusted for age and sex.[10] Stewart[7] found increased excretion of nitrosamines in patients after uretero-sigmoidostomy, suggesting a basic oncogenic role for the nitrosamines formed from the contact of urine and feces. Crissey et al.[11] prevented cancer from occurring at the uro-colonic anastomosis in animals, diverting the fecal stream by a proximal end colostomy.

TABLE 6 Site of secondary adenocarcinoma in the colon used as urinary diversion away from the fecal stream

Type of diversion (*n* patients)	Site of secondary adenocarcinoma					Clinical signs of infection	
	Near ureter anastomosis	Colo-baldder anastomosis	Exclusively colorectal mucosa	Mainly in the colonic mucosa invading the bladder	Other or not specified	Yes	No
Isolated rectal bladder (5)	3	–	2	–	–	4/5	1/5
Incontinent colon conduit (6)	2	–	2	–	1 Stoma	2/6	4/6
					1 As specified		
Colocystoplasty (16)	–	5	5	3	3 As specified	5/16	11/16
Continent urinary conduit (pouches) (19)	2	–	13		4 As specified	15/19	4/19
Neobladder (1)	–	–	–	–	1 Anastomosis bowel-urethra	1/1	0/1

They found no significant nitrosamine excretion in rats that experienced the development of adenocarcinoma connecting the bladder to the sigmoid colon, a result confirmed in humans.[8–12]

The finding of increased concentrations of growth factors and inflammatory cytokines at the level of the urocolic anastomosis supports the hypothesis that the ultimate factor leading to cancer formation in case of uretero-sigmoistomy may be a severe local inflammatory reaction.[11,12] The causative factor for the inflammation itself is difficult to define. In our study, the clinical characteristics of secondary adenocarcinoma in the colon-rectum exposed to urine but isolated from the fecal stream were similar to those of sporadic colorectal cancer occurring in the general population, with the colon exposed only to the fecal stream.

Only two patients were reported to be heavy smokers, and only two patients were alcoholic. No patient was reported to be obese. Only two of the patients had a family history of colon cancer. In the population we analyzed, the many presumed risk factors for sporadic colon cancer in the general population were not present. The colon, isolated from the fecal stream, is not exposed to recognized risk factors for adenocarcinoma occurrence. The daily diet such as red meat and sugars involves no contact with degradation products of substances and no specific bacteria proliferating in the colon in its original position. In this study, the adenocarcinoma arose more often in the middle of the colon, away from the ureteral anastomosis. In patients who had uretero-sigmoidostomy, the secondary adenocarcinoma arose always at the level of the ureteral anastomosis.

In a review by Kälble et al.,[10] secondary adenocarcinomas in the colon were more common in cases of ileocystoplasty and cecal pouches than in cases of incontinent colon conduits. These authors hypothesized that in the first two types of reconstruction, the urine remains in contact with the intestinal wall for a longer period, and that the not-flowing urine can represent the humus for bacterial overgrowth and infection. Histologic studies of the colon in contact with the urine have shown inflammatory changes, less or more severe.[58]

In our review, the occurrence of secondary adenocarcinoma in incontinent colon conduits was rare. We could not make any proper statistical comparison without having a specific numerator. However, we found that in continent colonic pouches, the secondary adenocarcinoma arose more often distant from the ureteric anastomosis and was associated with clinical signs of infection. In incontinent colon conduits and in colocystoplasty, the secondary adenocarcinoma occurred more often near the anastomosis with the ureter or the bladder, and clinical signs of infection were uncommon. It is possible that the mechanisms leading to secondary cancer development differ according to the type of reconstruction. The final common etiologic pathway is inflammation, related to infection or to a biochemical condition.

Thus, the only probable common causal factor associated both with the formation of secondary adenocarcinoma in urinary colon diversions isolated from the fecal stream and with sporadic colon cancer in the general population is inflammation, related or not to infection. Inflammation is a physiologic defense response to contrast pathogens. When the stimuli for inflammation persist or the reparative action is out of control, a condition of chronic inflammation can be facilitated.[59–62]

Several studies have focused attention on the time of colonic wall exposure to the offending agent. Our analysis found significant variability between the time of exposure to urine and the diagnosis of secondary adenocarcinoma. Despite this evidence, the mean age of the patients was similar to that of patients with sporadic cancer in the general population.

We found a close correlation between ageing per se and the diagnosis of the secondary adenocarcinoma. This correlation was more evident than the correlation between the time of the colonic wall exposure to urine and the time of the cancer diagnosis. The patients who underwent surgery originally for benign disease experienced development of a secondary adenocarcinoma after a longer exposure to the urine compared with the patients who initially had surgery for malignant disease. The patients who initially had surgery for malignant disease, as expected, were older, but the longer exposure to urine in patients who initially had surgery for benign disease significantly reduced the difference in age at the time of diagnosis. The longer time of exposure to urine before the diagnosis of secondary adenocarcinoma in patients who initially had surgery for benign disease can be interpreted as a greater resistance of the colonic wall in younger patients, without predisposition to cancer occurrence. Alternatively, we could hypothesize that the inflammatory stimuli require an advanced age before they can become effective. The local inflammatory response associated with tumor cell growth might become a systemic condition and stimulate hematopoiesis in the bone marrow, accentuating the proliferation of the cells involved in the immune response, able to stimulate local tumor cell growth and diffusion.[63,64]

Chronic inflammation might determine a double action, both local and systemic. We found a dose-dependent effect of inflammation. In patients with active high-grade inflammation, the secondary adenocarcinoma occurred at an earlier age, with a worse clinical outcome.[65]

The hypothesis that anti-inflammatory drugs such as aspirin might have a local and systemic action in preventing cancer formation and progression is attractive.[66–68]

CONCLUSIONS

Secondary adenocarcinoma occurs in colonic urine diversions not exposed to the fecal stream, with characteristics similar to those of sporadic colorectal cancer in the general population. The two different anatomic and physiologic positions to which the colorectal wall is exposed have in common only the possibility of inflammatory stimuli, which could represent the cause for cancer occurrence and progression. High-grade active inflammation is associated with an earlier occurrence of adenocarcinomas and a worse clinical outcome.

Even if practical guidelines are difficult to draw due to the small number of patients analyzed, it is wise to assert that cystoscopy-colonoscopy screening, as suggested by the American Gastroenterology Society for the general population, should be applied to these patients. Resection of the tumor at an early stage offers better clinical outcomes with longer survival. Candidates for this type of surgery, if older than 35 years, should have a preoperative colonoscopy to exclude the presence of colorectal polyps or adenocarcinomas.

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