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Adenocarcinoma in the transposed colon: High grade active inflammation versus low grade chronic inflammation

Antonio V. Sterpetti*, Paolo Sapienza

University of Rome La Sapienza, Italy

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ABSTRACT

Despite strong hereditary components, most cases of colorectal cancer are sporadic. The possibility to manipulate in the clinical setting the many presumed risk factors is almost impossible, and long-term epidemiological studies are the only reliable form for comparisons. We performed a systematic review to analyze the reports of de-novo adenocarcinoma arising in the transposed colon, used for conduit after esophagectomy, after total gastrectomy, and for vaginal reconstruction. In all these situations, the colon is transposed in different physiological conditions from its natural environment. We excluded patients in whom the colon was transposed as urinary conduit because the well known carcinogenic effect of the contact with urine. Overall 45 patients were identified with a de-novo adenocarcinoma arising in the transposed colon (36 after esophagectomy; 1 after total gastrectomy; 8 as neovagina). The only common risk factor in these different anatomic position was the possibility of active or chronic inflammation. There was not a close correlation between time after implantation and occurrence of the carcinoma. The occurrence of the de novo carcinoma was related to ageing, supporting the hypothesis of a major role of inflammation in facilitating deregulation of the immune system, associated with ageing.

Despite strong hereditary components, most cases of colorectal cancer are sporadic. Epidemiological studies have shown a statistical correlation with cigarette smoking, alcohol abuse, red and processed meat high intake, obesity, reduced physical activity [1–3] Experimental and clinical research has been focused on several hypotheses: reduced colorectal transit time and consequent longer exposure of the mucosa to several proposed toxic agents; degradation products of substances at the basis of the daily diet; presence of specific bacteria in the colorectal flora. The possibility to manipulate in the clinical setting the many presumed risk factors is almost impossible, and long-term epidemiological studies are the only reliable form for comparisons [4].

The colon has been used to replace the esophagus and the stomach after esophagectomy and total gastrectomy. In vaginal reconstruction, for agenesis or after vaginectomy for cancer, the colon offers many advantages in comparison to other autologous tissues [5–7].

In all these situations, the colon is transposed in different physiological conditions from its natural environment. We performed a systematic review to analyze the reports of adenocarcinoma arising in the transposed colon. We excluded adenocarcinomata arising in the colon used as bladder substitute. The contact of the colonic mucosa with the urine has already been shown to be a significant risk factor for cancer occurrence. The primary outcome of this systematic review was to analyze the prevalence of the problem, and possible risk factors.

Material and methods

The methods used for the study and inclusion criteria were based on Preferred Reports Items for Systematic Reviews and Meta analyses (PRISMA) recommendations. A literature search was performed in June 2018 by two investigators who conducted a review of papers reported in PubMed, EMBASE, MEDLINE and Cochrane Database. The strings “COLON TRANSPLANT “, “ESOPHAGECTOMY”, “VAGINAL RECONSTRUCTION” “ADENOCARCINOMA IN TRANSPOSED COLON” were used in combination with the Boolean operators “and” “or”. Editorials, letters to the Editor, Chapter in Books, Abstracts in Symposia, were included in the search. There was no language or time restriction and screened report. The registration number at International prospective register of systematic review (PROSPERO) was CRD 42018089691.

* Corresponding author. Viale del Policlinico, 00167, Rome, Italy.
E-mail address: antonio.sterpetti@uniroma1.it (A.V. Sterpetti).

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Data Extraction: Data extraction was performed by two reviewers independently; a third reviewer was involved to solve any question in interpreting data. The third reviewer (ES) was never consulted. The primary outcome was to determine possible risk factors for adenocarcinoma in the transposed colon. 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 of bias of analyzed studies by using the Newcastle-Ottawa scale [8]. This scale defines the quality of a paper with a score ranging from 0 to 9. Papers with a score greater than 6 were considered of good quality.

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

Results

Literature Search: 6,650 papers published from June 1938 to December 2018, were identified. Two hundred five papers were fully evaluated, but only 45 papers clearly reported patients with a transposed colon autograft in which a de-novo adenocarcioma was diagnosed. We excluded the reports of patients in whom there was possibility that the carcinoma was already present at the time of transposition. The 45 included papers described single case reports of patients with a de-novo growth of an adenocarcinoma in the transposed colon; one patients had colon interposition after total gastrectomy for cancer, 36 patient had colon interposition after esophagectomy, 8 patients had reconstruction of the vagina with the colon Tables 1 and 2 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 the patients in all but 1 patient. The majority of the papers reported a short follow up (mean 8 months).

Clinical Characteristics of the Patients: Tables 1 and 2 show the clinical characteristics of the 45 patients. We were not able to identify any significant risk factor. Only two out of the 36 patients, in whom details were reported, abused of alcohol and cigarette smoking. Age ranged from 33 to 83 years (mean 63.9+-7 years) and a synchronous adenocarcinoma in the native colon was evident in 3 patients (6.7%). There was no evidence of familiarity for colorectal cancer or for inflammatory bowel disease.

Colon Transplant after Esophagectomy: In 36 patients a diagnosis of de novo carcinoma in the transposed colon was made. Age at the diagnosis ranged from 40 to 83 years (65.6 +- 5). There were 22 males and 13 females (one report did not specify the gender of the patient). The histology was reported in 31 patients, and in all cases the adenocarcinoma was defined as moderately or highly differentiated. All patients had an elongated colon, with the possibility of delay empting and reflux in the colon of acid gastric content. In two patients a diagnosis of synchronous adenocarcinoma in the native, in-situ, colon was made (2/36: 5.5.%). Two patients abused of tobacco smoking and alcohol. All patients had a regular, standard diet (presumably small and more frequent meals). No patient was reported as eating red meat. Details about their life style were available for 27 patients, who had a regular life style. None of the patients was obese. Time interval between the initial surgery and the diagnosis ranged from 1 to 55 years (mean 22.1+-10 years) (Table 3). The clinical characteristics of these 36 patients were not different from those of patients among the general population with a diagnosis of colorectal cancer.

Colon Transplant for Vaginal Reconstruction. Age at the diagnosis ranged from 33 to 73 years (mean 54.1+-8 years). Histology showed a highly secreting mucinous adenocarcinoma in all patients. Around the tumor there were evident signs of inflammation. Details of colonoscopy were reported in 6 patients: one had a synchronous mucinous adenocarcinoma, but in the other patients the colon did not show any abnormality and no signs of inflammation. Herpes virus was absent in all patients with vaginal reconstruction who developed adenocarcinoma. Among the 8 patients who had vaginal reconstruction, 4 patients (50%) did not have any sexual intercourse. Adenocarcinoma developed at a mean of 28.5 year from neo-vagina reconstruction (range 3–53 years). The clinical characteristics of these 8 patients were not different from those of patients among the general population with a diagnosis of mucinous colorectal cancer.

Colon Transplant after Total Gastrectomy. One patient (Female, 68 years old) developed adenocarcinoma in the left colon transposed to re-establish intestinal continuity 9 years after total gastrectomy for cancer [9]. Histology showed a moderately differentiate adenocarcinoma, which was resected. Colonoscopy did not show abnormalities in the native colon rectum.

Prevalence of de-novo adenocarcinoma in the transposed colon . The real prevalence of the problem is not identifiable from the literature data. The 45 patients were reported as “case reports”. We reviewed the clinical outcomes of 23 reports which analyzed the long term clinical outcome of patients who had colon transposition for vaginal reconstruction [6,7,10] and after esophagectomy [11–20]. Overall 2900 patients were included in the review. (1000 patients had a follow up longer than 5 years and 450 a follow up longer than 10 years). None of the reviews of patients who vaginal reconstruction with the colon reported the occurrence of adenocarcinoma in the transposed colon. Two papers [12,13] reported a patient with occurrence of adenocarcinoma in a colon interposed after esophagectomy, with an incidence respectively of 1/271 (0.5%) and 1/308 (0.3%). One epidemiological study [19], which analyzed the 380 patients operated on for esophagectomy and colon interposition in England in the last 10 years, noted that 5 of the interviewed thoracic surgeons touched on the possibility of polyps in the transposed colon.

Preoperative Symptoms and Late Diagnosis: In 43 out of the 45 patients the diagnosis was made because of evident symptoms: dysphagia for patients who had colon transplant after esophagectomy and neo vagina bleeding for those who had colon neovagina reconstruction. At the time of diagnosis, the adenocarcinoma was at an advanced stage: 24 patients required resection; in 13 patients the disease had already metastasized, they only had radio-chemitoherapy with a very short life expectancy. Six patients had endoscopic removal of the tumor, but only two were asymptomatic. In two patients details about therapy were not available.

Discussion

Colon interposition after esophagectomy compares favorably to gastric pull-up as regard quality of life and alimentary satisfaction; however, it is a more difficult operation to be performed in dedicated centers. Adenocarcinoma arising in the colon conduit is considered a rare complication. The real prevalence of this complication is difficult to define. Tranchart et al. [13] reported a prevalence of about 0.5%; however, considering that many of the patients had a follow-up shorter than 10 years, we can hypothesize a higher prevalence, approaching that of sporadic colorectal cancer in the general population, adjusted for age and sex. As esophageal substitute, the colon is exposed to an “un physiological” environment with different chemical and physical properties. Transit time is significantly longer for the reduced peristalsis in the interposed colon. The absence of the natural action of the lower sphincter, determines a significant reflux of gastric acid content in the interposed colon; these factors represent a conceptual basis for chronic

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Table 1
Cancer in the transposed colon after esophagectomy.

Case report	*Age/Sex*	*Indication for esophagectomy/Years fromsurgery*	*Graft*	*Therapy*	*Diagnosis*	*AvailableFollow up*
Goldsmith et al., 1968 [21]	**51/F**	Squamous Carcinoma/2	Right colon	SegmentalResection	Squamouscell carcinoma	Alive and well 17 months
Licata et al., 1978 [22]	51/M	Corrosive/11	Right colon	Supportivetherapy	Metastatic Adenocarcinoma	Early death
Haerr et al., 1987 [23]	72/M	Squamous Carcinoma/9	Right colon	Supportivetherapy Chemotherapy	Locallyadvanced T4	Died7 months
Houghton et al., 1989 [24]	64/M	Corrosive/20	Right colon	Colon Resestion and Gastric pull-up	Localized Adenocarcinoma	1 month Alive and well
Thiele et al.,1992 [25]	55/M	Adenocarcinoma/12	Left Colon	SegmentalResection	T3N2M0	1 month Alive and well
Lee et al., 1994 [26]	75/F	Squamous Carcinoma/20	Unkonown	Colon Resection and jejunal interposition	Localized Adenocarcinoma	1 month Alive and well
Altorjay et al., 1995 [27]	72/M	Corrosive/6	Left colon	SegmentalResection	Adenocarcinoma	9 years Alive and well
Jeyasingham et al1999 [12]	?/?	Corrosive/?	Left colon	?	Adenocarcinoma	?
Kasaktin et al1999 [28]	59/M	Corrosive/8	Right Colon	SegmentalResection	Adenocarcinoma	18 months Alive and well
Goyal et al2000 [29]	78/M	Adenocarcinoma/7	Left Colon	SegmentalResesction	Locallyadvanced T3N0M0	Died 13 months.
Mukai et al2001 [30]	?/M	Squamous carcinoma/6	Left colon	EndoscopicResection	Localizedcancer	12 monthsAlive and well
Liau et al2004 [31]	79/M	Squamous Carcinoma/30	Unknown	Chemotherapy	Metastatic adenocarcinoma	Died 4 months
Martìn et al., 2005 [32]	65/F	Corrosive/40	Right colon	SegmetalResection	Dukes B Adenocarcinoma	1 monthAlive and well
Hsieh et al., 2005 * [33]	57/M	Corrosive/39	Right colon	SegmentalResesction	LocalizedAdenocarcinoma	1 month Alive and well
Hwang et al., 2007* [34]	60/F	Corrosive/40	Notspecified	EndoscpicResection	Intramucosal Adenocarcinoma	1 month Alive and well
Roos et al. 2007 [35]	72/M	Adenocarcinoma/7	Right colon	SegmentalResesction	LocalizedCancer	1 monthAlive and well
Kia et al., 2010 [36]	76/M	Adenocarcinoma/15	Unknown	EndoscopicResection	Localized adenocarcinoma	1 month Alive and well
Sikorszki et al., 2010 [37]	75/M	Corrsoive/44	Right colon	SegmentalResesction	Adenocarcinoma	Notspecified
Bando et al2010 [38]	80/M	Squamous carcinoma/14	Unknown	EndoscopicResection	Localized adenocarcinoma	1 monthAlive and well
Shersher et al., 2011 [39]	60/M	Corrosive/40	Notspecified	Colon resection and esophagogastroplasty	T1 N0 Adenocarcinoma	3 months Alive and well
Spitali et al., 2012 [40]	66/M	Adenocarcinoma/2	Right colon	SegmentalResection	Localized adenocarcinoma	24 monthsAlive and well
Suzumura et al., 2012 [41]	72/M	Squamous carcinoma/1	Right colon	SegmentalResection	Localized adenocarcinoma	36 monthsAlive and well
Kim et al., 2012 [42]	70/F	Corrosive/47	Right Colon	Chemotherapy	Metastatic Adenocarcinoma	Died 6 months
Wang et al., 2012 [43]	41/F	Corrosive/15	Unknown	Chemotherapy	Metastatic Adenocarcinoma	Died 4 mopnths
Aryal et al., 2013 [44]	60/M	Corrosive/30	Right Colon	Supportive	Metastatic Adenocarcinoma	Early Death
Grunner et al., 2013 [45]	59/F	Corrosive/55	Transverse colon	SegmentalResection	Localized adenocarcinoma	Alive and well 6 months
Sallum et al., 2014 [46]	53/F	Atresia/42	Unknown	Colon resection and gastric pull-up	Locally Invasive Adenocarcinoma	Died after 9 months for surgery-related complications.
Tranchart et al., 2014 [13]	66/M	Corrosive/19	Right Colon	Chemotherapy	Metastatic Adenocarcinoma	Died3months
Ng et al. 2014 [47]	60/M	Corrosive/19	Unknown	Supportive Metastaticlungcancer	Severe dysplasia	Earlydeath
Cheng et al., 2015 [48]	40/F	Corrosive/15	Right Colon	Supportive	Metastatic Adenocarcinoma	Died4months
Yamamoto et al., 2015 [49]	83/M	Carcinoma/?	Left Colon	SegmentalResection	T2N1M0	24 months. Alive. Lymph node recurrence
Kroner et al. 2015 [50]	67/M	Carcinoma/10	Left Colon	Supportive Endoscopicstenting	Metastaticadenocarcinaoma	Unknown
Taslimi et al., 2017 [51]	84/F	Unknown/34	Unknown	Supportive	Carcinoma Colo-tracheal fistula	Earlydeath
De Moura et al., 2018 [52]	63/F	Corrosive/8	Unknown	Supportive	Metastatic Adenocarcinoma	Died 2 months
Barbosa et al., 2018 [53]	70/F	Corrosive/19	Left Colon	Supportive	Poor General Conditions	Died 6 months
Iascone et al., 2019 [54]	67/F	Corrosive/37	Left Colon	EndoscopicResection	Localizeddisease	60 months. Alive and well

inflammation [63,64]. At the same time, exposure to acid reflux reduces the possibility of bacteria overgrowth in the colon. The new location of the transposed colon, prevents the action of toxins, derived from degradation of ingested substances, like red meat, which have been correlated to cancer formation and progression. None of the reported patients were obese, and only few abused of alcohol and tobacco. The clinical conditions of the patients, and the new position of the colon, did not allow the action of several factors, generally considered as major risk for cancer occurrence. The cancers arising in the interposed colon had clinical and histological characteristics similar to those of sporadic adenocarcinomata occurring in the general population. Other similar clinical characteristics between the adenocarcinoma arising in the colon conduit and the sporadic carcinoma in the general population included the age of the patients and the synchronous occurrence of a cancer in the native colon in 5.6% of the patients. Despite

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Table 2
Cancer in the transposed colon as neovagina.

Author	Age	Indication to Colon Neovagina/Years from Surgery	Graft	Therapy	Available Follow-up
LavandHomme (1938) [55]	33	Agenesy/20	Sigmoid	Radiation	Not specified
Andryjowicz et al. (1985) [56]	43	Malignancy/4	Cecum	Resection	Not specified
Ursic-VrscaJ et al. (1994) [57]	58	Malignancy/22	Sigmoid	Resection	30 months Alive and well
Hiroi et al. (2001) [58]	53	Agenesy/25	Sigmoid	Resection	18 months Alive and well
Van der Velden et*(2005)m [59]	45	Malignancy/17	Sigmoid	Resection	16 months Alive Liver mets
Kita et al. (2015) [60]	67	Agenesy/40	Sigmoid	Resection	6 moths Alive and well
Bogliolo et al. (2015) [61]	61	Agenesy/48	Sigmoid	Resection	12 months. Alive and well
Yamada et al. (2018) [62]	73	Agenesy/53	Sigmoid	Resection	2 months. Alive and well

*Synchronous cancer in the native colon.

Table 3
Time-interval between initial surgery of colon transposition and the diagnosis of a de novo carcinoma.

Time interval	NEOVAGINA [8]	POST- ESOPHAGECTOMY(35)	POST-GASTRECTOMY(1)
1–10 years	1	9	1
11–20 years	2	12	
21–30 years	2	4	
More than 30 years	3	10	

significant environmental differences, in 2 patients, the adenocarcinoma occurred simultaneously in the native and transposed colon, with similar histologic characteristics.

In the 8 patients, in whom the adenocarcinoma arose in the colon transposed for vaginal reconstruction, there was evidence of active inflammation. Histologically, the adenocarcinoma was mucinous adenocarcinoma, surrounded by acute inflammation. The risk factors for sporadic colonic cancer in the general population, or for intrathoracic transposed colon after esophagectomy (passage of food, reduced transit time, gastric reflux) were not present. The only probable risk factor was related to bacterial overgrowth, infection and consequent active inflammation. In these 8 patients the clinical and histological characteristics were similar to those of patients with colon cancer and inflammatory bowel disease, including an earlier diagnosis in comparisons to sporadic cancers.

The time elapsed between the transposition of the colon and the diagnosis of adenocarcinoma varied significantly. However, the age at the diagnosis was similar to that of the general population, adjusted for age and sex: the mean age and histological characteristics of patients with cancer arising in the transposed colon after esophagectomy, with probable chronic inflammation, were similar to those of patients with sporadic colon cancer in the general population; whereas, the mean age and histological characteristics of the 8 patients with cancer arising in the context of severe, active inflammation in the transposed colon for vaginal reconstruction, were similar to those of patients with inflammatory bowel disease and colon cancer.

These data suggest the hypothesis of an age-related genetic predisposition. This genetic predisposition seems to be correlated to the presence of local inflammation. The several risk factors identified in patients with sporadic colon cancer, as well as in de novo carcinoma arising in the transposed colon, have a common final action represented by chronic or acute inflammation and possible damage to the colonic mucosa [65–68].

Ageing is undeniably one of the most powerful determinants of the development of cancer. However, what drives development of cancer with ageing, beyond the obvious prolonged exposure to traditional risk factors, is unclear [69,70].

In patients with familial colorectal cancer, like Lynch syndrome, the genetic mutation MSI/MMR is present in more than 90% of the patients. In patients with sporadic colorectal cancer a genetic mutation is evident in less than 6% of the patients, and several different genetic mutations have been identified, some with high penetrance, other with low penetrance. Thus, there is not a common genetic finding in sporadic colorectal cancer [65,66] On the other hand, patients with sporadic colorectal cancer present many similar clinical characteristics, which bring to hypothesize a possible common causal background.

Deregulation of the immune system with ageing is a well know phenomenon [71,72].

The basic influence of immunity in colorectal cancer progression, the close correlation of sporadic colorectal cancer with ageing, and the derangement of the immune response with ageing [72] determine a conceptual cause-effect relationship between potential factors which could influence the ageing-dependent deregulation of the immune system and sporadic colorectal cancer occurrence. Inflammation in genetically predisposed patients may promote somatic changes in hematopoietic cell lines promoting cancer occurrence [71]. Thus, inflammation might determine a double action, local and systemic. The hypothesis that the stimuli related to a long term inflammation might determine a general derangement in the hematopoietic system, can explain the occurrence of other types of cancer in the elderly. Inflammation may be a driver for ageing per se and for ageing consequences [73,74]. Interesting enough, in 3 patients, the cancer occurred synchronously in the transposed colon and in the native colon, with similar histological characteristics despite the differences in the two anatomic positions. These synchronous cancers could be related to a local genetic-determined cause; we cannot exclude the possibility of a general genetic-determined derangement of the immune system.

Several other considerations should be advanced. In all patients there was a tardive diagnosis which brought to poor clinical outcomes. Early diagnosis was erratic and followed by good results. Even if practical guidelines are difficult to be drawn on the basis of the few number of patients analyzed, it is wise to assert that colonoscopy screening as suggested by the American Gastroenterology Society should be applied to these patients, starting at the age of 35–40 years.

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Conflicts of interest to disclose

None.

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