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Adenocarcinoma of the Interposed Colon Graft for Esophageal Substitution-Point of View from a Tertiary Center in Esophageal Surgery and Review of Literature

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Rezumat

Adenocarcinomul de grefon colic ca substitut esofagian - punct de vedere al unui centru terțiar în chirurgie esofagiană și revizia literaturii de specialitate

Chirurgia rezecțională sau de by-pass pentru patologii benigne sau maligne esofagiene prezintă multiple provocări, motiv pentru care este adresată centrelor de excelență. O astfel de provocare este refacerea continuității tubului digestiv, colonul fiind o opțiune importantă pentru substituție esofagiană. Evaluarea la distanță a pacienților cu reconstrucție colică este în mod esențial legată de problemele digestiv-nutriționale. O situație de excepție, prin particularitate și evoluție o reprezintă apariția leziunilor pre-maligne (polipi) sau franc maligne ale grefonului colic. Scopul articolului a fost cel de a atrage atenția asupra riscului de apariție a unei astfel de complicații la distanță, neprevăzute, dificil de gestionat diagnostic și terapeutic. În același timp, datele reduse din literatură, de regulă prezentări de cazuri, lasă o serie de întrebări fără răspuns medicului curant, atât dpdv etiologic cât și al managementului de caz. De aceea ne-am dorit să facem o revizie a literaturii, să identificăm elemente comune cu ale altor autori, astfel încât să căutăm ipoteze de lucru și să identificăm mecanisme sau, cel puțin, să semnalăm o astfel de complicație posibilă.

Cuvinte cheie: cancer colonic, reconstructie esofagiana cu colon, polip colonic

Abstract

Resection or bypass surgery for benign or malignant esophageal conditions presents multiple challenges, which is why it is addressed to centers of

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excellence. One such challenge is the restoration of the continuity of the digestive tract, the colon being an important option for esophageal substitution. Lon-term follow up of patients with colon reconstruction is essentially related to digestive-nutritional problems. An exceptional situation, by its particularity and evolution, is the appearance of pre-malignant lesions (polyps) or frankly malignant lesions of the colon graft. The aim of the article was to draw attention to the risk of such a long-term complication, unforeseen, difficult to manage diagnostically and therapeutically. At the same time, the limited data in the literature, usually case reports, leave a series of unanswered questions for the attending physician, both in terms of etiology and case management. That is why we chose to review the literature, identify common elements with other authors, so as to seek working hypotheses and identify mechanisms or, at least, to signal such a possible complication.

Key words: colon cancer, esophageal reconstruction with colon, colon polyp

Introduction

Resection or bypass surgery for benign or malignant esophageal conditions presents multiple challenges, which is why it is addressed to centers of excellence. One such challenge is the restoration of the continuity of the digestive tract, with three possible esophageal substitution options: stomach, colon, and small bowel (1).

Against this background, arguments for using the whole stomach as gastric tube appear: easy preparation of the gastric conduit, a predictable and much more robust vascularization (well-represented submucosal vascular plexus, the lack of additional digestive anastomoses except for the gastroesophageal (hypopharyngeal) cervical one, significantly reduced operating time and a more than convenient complication rate (2). Resection of the lesser curvature of the stomach allows for the lengthening of the gastric graft and a safe cervical anastomosis (1,3,4). In cases with previous gastrectomy, caustic or peptic gastric stenosis, gastric tumors or failed esophageal-stomach reconstruction techniques, the colon becomes the visceral organ of choice for reconstruction. The surgical principles and anatomical bases for using the colon as a substitute for the esophagus were established as early as 1911 by Kelling and Vuillet (5). The colon is used only in approximately 20% of cases, the technique being a laborious one, dependent on a very poor colonic vascularization, with many variables and numerous digestive anastomoses, obviously with labor, considerable operating time and commensurate postoperative risks (6). Its use is useful in benign conditions, such as caustic or peptic strictures and malignant conditions, especially when the stomach cannot be used, as well as in children with congenital anomalies (7-10). The left colon is preferred as an esophageal substitute due to its optimal diameter and favorable vascularization, but the right colon or transverse colon can also be used (11).

Although the colon, especially the left, has long been considered the optimal organ for substitution, the stomach has been the most widely used in recent decades. The question naturally arises as to why so? The answer comes from the arguments for stomach reconstruction presented above – an "easier" technique, with sustainable perioperative risks and complications but which are compounded by a much more difficult long-term outcome. The use of a colic graft would seem essentially disadvantageous, but, apparently, the colic graft as an esophageal substitute reports much better long-term results regarding swallowing parameters, digestive transit and quality of life (12).

In other words, gastric grafting is convenient in the short term but loses to colic grafting in the long term in terms of functionality, metabolic balance, risk of complications, and quality of life.

Greene et al. examined 63 patients who underwent esophagectomy and colonic interposition for cancer (45 patients) or benign disease (18 patients). Over a 13-year follow-up period, food satisfaction was 9 out of 10. All patients enjoyed a good quality of life. In the early postoperative period, the most common complaints were early satiety (63%) and dumping syndrome (43%). These symptoms disappeared or decreased in intensity, partly because the patients modified their eating habits, eating more slowly and avoiding sweet dairy products. Episodes of regurgitation or aspiration of varying intensity were described in 17 patients. In general, all patients presented an optimal nutritional status (13).

Long-term follow-up of patients with colon

reconstruction is essentially related to digestive-nutritional problems and, as a consequence, to hydro-electrolytic and metabolic ones. Incidentally or sporadically, exceptional situations are presented such as ischemic colitis, fistula due to diverticulitis, cardio-pulmonary impact due to graft distension, etc. (14-17).

An exceptional situation, by particularity and evolution, is represented by pre-malignant lesions (polyps) or frankly malignant lesions of the colon graft. Reported at the time of surgery, the relatively rapid appearance (> 1 year) is most likely related to a deficiency or insufficient preoperative diagnosis of these lesions. When the time interval from reconstruction to the appearance of neoplasia is a considerable one, most often decades, other mechanisms intervene according to the etiopathogenic, a situation we have also faced.

Sf. Maria Clinical Hospital is a tertiary center specialized in the pathology of the esophagus, including postcaustic esophageal stenoses and its reconstruction with visceral material. Over a period of 25 years between January 1, 2000, and August 31, 2024, 263 esophageal reconstructions were performed for this indication, in various reconstructive variants, 249 cases of esophageal bypass and 13 cases in which esophagectomy were performed. A number of 67 cases benefited from conservative, dilator-type endoscopic treatment. In our group of patients, we identified three cases of colon cancer on the esophageal substitution graft, both at a great distance from the moment of reconstruction, over 30 years, detected at various tumor stages and with different therapeutic solutions-endoscopic ablation, surgical resection and transtumoral stenting.

The aim of the article was to draw attention to the risk of such a remote, unforeseen complication, difficult to manage diagnostically and therapeutically. At the same time, the limited data in the literature, usually case reports, leave a number of unanswered questions for the treating physician, both in terms of etiology and case management. That is why we wanted to make a review of the literature, to identify common elements with those of other authors, so as to seek working hypotheses and to identify mechanisms or, at least, to signal such a possible complication. This paper examines and reviews current hypotheses regarding the pathogenesis, risk factors, and surveillance strategies associated with this rare complication. Perspectives on diagnostic, endoscopic intervention and surgical management from a high-volume tertiary center are discussed to guide future research and clinical practice.

The article is based on the analysis of data considered relevant from studies and articles published in the last 25 years identified in Embase (Excerpta Medica Database), PubMed Central (PMC), Cochrane Library, MEDLINE Complete (EBSCO) corresponding to the period January 1, 2000, and August 31, 2024.

Inclusion Criteria

Inclusion Criteria: only literature in English such as book chapters, studies, study updates, case presentations, original articles or reviews related to adenocarcinoma on interposed colon.

Screening of Studies

The search strategy was based on keywords and phrases used in search engines, namely the following terms or combinations of the following terms were used: "polyp", "interposition", "colon", "adenocarcinoma interposed colon", "cancer colonic graft", "tumor in the interposed colon". Following the search, 41 book chapters, articles and studies on the issue were identified.

Exclusion Criteria

We excluded unpublished data from abstracts contained in volumes from various congresses or conferences as well as papers that were not in English.

We associated with them a series of articles from the initial reference list for additional information considered relevant to the problem. Two authors (A.C. and D.P.) independently selected articles deemed relevant, preferring articles from high-ranking journals written in English. The decision to select an item was made by mutual agreement. Differences were discussed and if consensus could not be reached between the two reviewers, we requested the consultation and recommendation of a third reviewer (F.A.).

Colon Graft Cancer

Patients who have undergone esophagectomy with esophageal substitution with colon interposition present a complex anatomic postoperative status. The occurrence of colon cancer (a highly aggressive neoplasia) on the colon graft creates an extremely complex oncological circumstance. Adenocarcinoma inserted on the colon graft is a rare complication, but the challenges it poses warrant special attention from the medical community. The first case of colonic adenocarcinoma on the graft was described by Goldsmith et al. in 1968 (18,19). Tranchart et al. in a review of the literature reported only 1 patient

with this complication out of 271 (0.4%) who underwent esophagectomy and colon interposition for caustic lesions (20). The true incidence is, however, difficult to establish due to the small number of cases reported in the literature. Most authors approach the subject in the form of case reports. Tranchart et al. estimate an incidence of about 0.5% (20). However, given that most cases have a follow-up period of less than 10 years, the literature suggests that the incidence is higher, possibly approximately similar to that of colorectal cancer in the general population, adjusted for age and sex (21). As an esophageal substitute, the colon is exposed to a non-physiological environment, with chemical and physical parameters different from those for which the colon is "set". Assuming that the incidence of neoplasia on such a graft is not much different from that reported in the general population, we can assume that, in addition to the obvious overexpression of some procancer factors, other elements appear that counterbalance this equation in the new status of the interposed colon segment.

The question naturally arises: what are the mechanisms that initiate oncological degeneration in the new digestive condition of the colonic graft? What changes in favor or against etiological mechanisms? Let us not forget the new "physiology" of a colonic graft: 1) attenuation of the intraluminal microbiome, to which the colonic mucosa is ontogenetically accustomed, 2) modification of the intraluminal pH and shift towards an acidic level secondary to the quasi-permanent reflux into the graft of proximal digestive juices (gastric but also tryptic, bilio-duodeno-pancreatic), 3) modification of the physical parameters of the intraluminal content (from fecal, quasi-solid, constant temperature, to a completely heterogeneous physical character, specific to the food bolus), 4) important modification from a qualitative point of view of the intraluminal substances that come into contact with the colonic mucosa (from those specific to fecal content, some proven carcinogenic, to a completely different range of substances present in the food bolus), 5) significant modification of the time of action of intraluminal products on the colonic epithelium (from a slow, "quasi-permanent" transit of colonic content, to intermittent transit and fast, gravitational, with long periods of lumen "free" of content).

Risk of Malignancy

Colorectal cancer has a high incidence. It is the third most common cancer diagnosed in men and the second most common cancer diagnosed in women worldwide (22). There are more than one to two million new cases diagnosed each year, with over 600,000 deaths from this cause (23). Colorectal cancer accounts for 9% of all cancers (24). It is the third most common malignancy and the fourth leading cause of cancer death worldwide (25). The incidence in men is 9.4% and 10.1% in women worldwide (26). There is a significant geographical difference, with the incidence being higher in the Western world. The incidence ranges from more than 40% per 100,000 in the USA, Australia, New Zealand and Western Europe to less than 5% per 100,000 in Africa and Asia (27). Several etio-pathogenic hypotheses have been proposed for colorectal cancer. The most common are age, inflammatory bowel disease, adenomatous polyps, a strong family history, familial adenomatous polyposis, hereditary non-polyposis colon cancer, diets high in animal fat, smoking, and alcohol consumption (24). It is documented that genetic mutations, polyps, adenomas, and the constant action of anaerobic bacteria such as Clostridium on the intestinal mucosa play a major role in the pathogenesis of colorectal cancer (28). Although an important genetic component in the occurrence of colorectal cancer is documented, most cases are sporadic. Epi-demiological studies have shown a statistical correlation with smoking, alcohol abuse, high consumption of red meat, processed meat, obesity, and low physical activity (29).

Clinical and experimental studies in general focus on several hypotheses: the slowed digestive transit at this level and consequently the prolonged exposure time of the mucosa to certain intraluminal toxic agents; the harmful action of degradation products in the usual diet; the presence of specific bacteria in the intraluminal flora. The introduction of all suspected risk factors as variables in clinical studies is almost impossible. Long-term studies are the only viable source of pertinent conclusions in this direction (30).

From this point of view, the new location of the transposed colon prevents the action of toxins derived from the degradation of ingested substances, such as red meat, which have been correlated with the formation and progression of cancer. Obesity, alcohol or tobacco abuse have been sporadically reported in these patients (31).

Regarding the risk of malignancy of the interposed colon, a Japanese working group suggests that colonic changes occur secondary to exposure to chemical substances and altered flora (32). In these studies, the time to the appearance of neoplasia on

the graft varies between 1 and 40 years (33). However, the very low prevalence of this complication does not seem to be consistent with the multitude of risk factors. Moreover, the left colon, most frequently used in esophageal substitution, has the highest incidence of colon cancer and, probably, the rare occurrence of adenocarcinoma in the interposed colon may also be spontaneous, by genetic determination (34). At the same time, certain elements, unanimously accepted as risk factors for colon cancer, are nevertheless majorly modified by the transposition of the colonic segment for esophageal substitution. This observation motivates a detailed evaluation, even if a quantification of the new parameters of the functioning of the colonic graft is difficult to do due to the limited number of cases available. Many conclusions can only be drawn "observationally" by comparing obvious differences between the status of the interposed colonic graft and that of the "native" colon, and others can only be speculated upon, as working hypotheses.

Digestive Transit Through the Graft

Exposure of the colonic mucosa to carcinogenic intraluminal substances is an almost unanimously accepted risk factor for the occurrence of colon cancer. The slower transit for the left colon compared to the right is also incriminated for the higher incidence of adenocarcinoma for this topography. The passage through the colonic graft is achieved by completely different mechanisms. Although most frequently positioned anisoperistaltically, unfavorable to the progression of the content (left colonic graft), the passage is largely achieved gravitationally. The vast majority of studies conducted regarding the functioning and motor behavior of the colonic graft mounted iso- or anisoperistaltic, regardless of the evaluation methods used (radionuclides, manometric, pH-metric), advocate for a deficient propulsive activity compared to the esophageal one (35-39). The longer the graft, the more pronounced the retention phenomena are, while a limited segment has an evacuation similar to that of the esophagus. In the initial phase, of several months, the food passage through the aniso-peristaltic loop is eminently passive, being dependent on gravity, the graft appearing to be devoid of contractile waves (40).

An experimental study of the motility pattern of the isolated colic graft in the dog notes the presence of a contractile activity in the graft, regardless of the change in digestive direction (41). It seems that the key elements of a contraction (amplitude, frequency) undergo unsystematic, non-specific, individual changes. At the same time, the electrical activity has a different behavior for different sites but harvested from the same isolated segment. Last but not least, despite an anisoperistaltic montage, a reversal may occur regarding the direction of the motor activity, most likely at a distance from the operator's gesture. The study cannot specify, however, whether this conversion phenomenon definitely occurs and, if so, how long it will take for it to be established.

Moreover, long-term studies often find a disturbing motor diversity, but one thing is certain: there is peristaltic activity in the graft (42). Regarding the anisoperistaltic assembly, the grafted loop has the ontogenetic and physiological tendency for antidigestive propulsion, by preserving the motility pattern. In other words, the graft does not behave inertly, like a tube. However, the contractile waves have a flawed character in terms of duration, amplitude and motility indices. The consequence is prolonged esophageal clearance, with the accumulation of food content that will produce distension of the colonic wall and the appearance of a state of motor activity by direct stimulation. The inefficiency of enteral contractions opposite to the gravitational direction seems to initiate the mechanism of adaptation and modification of the intestinal pacemaker. The longer the period of time elapsed since the operative moment, the more the peristaltic mechanism seems to be restored to the new digestive conditions (43). Even in these favorable adaptive conditions, gravity will play the key role in the passage of the bolus from the hypopharyngeal to the gastric segment.

Graft stasis is therefore a reality, described especially in cases with redundancy that causes graft stasis of varying degrees. This phenomenon in principle does not attract attention from the perspective of an oncological risk factor, since dysphagia with subsequent nutritional disorders and alteration of the quality of life are positioned in the foreground from the point of view of managing these patients. Reflux in the colic graft is described in over 50% of cases, the incidence being similar for both the right and left colon. Moreover, surgical correction is required in one in ten cases (44).

Intraluminal Carcinogens

The direct action of some intraluminal carcinogens on the colonic mucosa is documented in

the literature. Processed meat, defined as meat products that have been salted, smoked, fermented, or otherwise processed to improve taste or preserve them, and red meat were added in 2015 to the list of foods that contribute to an increased incidence of colon cancer by the International Agency for Research on Cancer (45). The European Prospective Investigation into Cancer and Nutrition documented that daily meat consumers have a 20% higher risk of developing colon cancer compared to those who consume meat occasionally or not at all (46). Furthermore, the Norwegian Women and Cancer study concluded that consuming more than 60 grams of processed meat per day doubles the risk of colon cancer compared to consuming less than 15 grams per day (47). In contrast, white meat consumption is not associated with colon cancer incidence (48).

The carcinogenic effect of red and processed meat is related to growth-stimulating products such as heme and arginine, which in the specific environment of the colon cause chronic inflammation (49). The most studied mechanism involves the colonic conversion of heme into a cytotoxic factor that alters the colonic epithelium, inducing an epithelial hyperproliferative reaction (50). At the same time, processed meat is frequently supplemented with nitrites to improve preservation. Nitrosamines synthesized from nitrites under the action of the colonic flora are particularly carcinogenic for the mucosal epithelium (51). Arginine, as a precursor of polyamines, is considered to have carcinogenic potential (52). Polyamines (putrescein, spermidine and spermine) are involved in a number of cellular processes including proliferation, thus establishing the link between red meat consumption and colon cancer (53). The peroxidation of lipids in the colon with the production of O6-Carboxymethyl guanine, which has a toxic and mutagenic effect on the colonic epithelium, also contributes to the increase in the incidence of colon cancer. Regardless of the amount of red or processed meat consumed, the colon transposed to the thoracic level as an esophageal substitute does not meet the conditions to be exposed to the secondary carcinogenic products of this diet, due to the rapid, gravitational transit, which, on the one hand, does not allow the obtaining of the products incriminated above, nor prolonged exposure to them.

Bile Reflux in the Colonic Graft

The absence of the natural action of the lower sphincter causes a significant reflux of gastric contents and acid into the interposed colon. All of this represents a conceptual basis for metaplasia and the development of cancer. Gastric reflux into the graft exposes the colonic mucosa to bile acid aggression. Such aggression is known to be an etiological factor for cancers of the pharynx, esophagus, stomach, and small intestine (54).

The documentation of an increased risk of digestive tract cancer after cholecystectomy, with the specification that this risk is all the greater the closer the respective digestive segment is to the bile duct (the place of discharge into the duodenum), and starting from the premise that this increase in cancer incidence is related to the increased flow of bile acids, is the basis for the speculation of an increased risk of cancer in the colonic graft, in the context of bile reflux into the graft (27). On the one hand, products resulting from the colonic microflora under the stimulation of bile acids increase the risk of colorectal cancer. On the other hand, the products resulting from the degradation of bile acids, especially lithocholic acid and deoxycholic acid, have a molecular structure similar to polycyclic aromatic hydrocarbons, which are known to be carcinogenic (55).

Bile acids are produced by the liver from cholesterol. The primary bile acids, cholic acid and chenodeoxycholic acid, are conjugated with either taurine or glycine and then secreted by the liver for storage in the gallbladder. The gallbladder releases bile acids stored in the duodenum to facilitate the digestion of saturated fats (56,57). Most bile acids are actively reabsorbed in the small intestine, especially in the distal ileum, and transported back to the liver, where they are subsequently stored in the gallbladder again, thus achieving a continuous circulation between the liver and the intestine (58). Bile acids can be recycled 4-12 times per day in the enterohepatic circulation between hepatocytes in the liver and enterocytes in the intestine. Approximately 10% of bile acids reach the systemic circulation (59).

Approximately 5% of bile acids are not reabsorbed in the small intestine and reach the colon (60). In the colon, bile acids are metabolized by intestinal microorganisms by deconjugation and dehydroxylation to form hydrophobic secondary bile acids (deoxycholic acid and lithocholic acid). Deoxycholic acid can be reabsorbed from the colon, transported to the liver, and reenter the bile acid cycle. Lithocholic acid is less readily reabsorbed from the colon, and is mostly excreted in the feces. Overall, the enterohepatic bile acid cycle comprises

approximately 30% of deoxycholic acid and 5% of lithocholic acid. Repeated exposure of the gastrointestinal tract to high physiological levels of secondary bile acids is an important risk factor for gastrointestinal cancer (61).

Bile acids can alter the cell membrane by acting directly on its lipid component and thus making it vulnerable to the action of oxygen radicals, which cause an alteration of cellular DNA (62). It is documented that deoxycholic acid can modify the DNA of colonic epithelial cells to induce apoptosis (63). On the other hand, certain deficiencies of the proteins responsible for DNA repair, such as PMS2, ERCC1 and XPF, determine the access of another DNA repair pathway. Such cells are genetically unstable and can acquire mutations in the direction of resistance to apoptosis, an aspect characteristic of neoplastic cells (61). Colonic epithelial cell cultures exposed to high concentrations of deoxycholic acid have developed a natural selection in the direction of resistance to apoptosis (64). Analysis of the molecular changes of these apoptosis-resistant cells revealed particular gene changes in response to persistent exposure to bile acid, and some of these could be related to the progression to colon cancer (65). One such example is the overexpression of the antiapoptotic protein B-cell lymphoma 2 (BCL-2). In humans, the colonic mucosa in the vicinity of adenocarcinomas is associated with increased expression of the antiapoptotic protein B-cell lymphoma 2, which defines a zone of major carcinogenic potential (66). Thus, elevated levels of bile acids and secondary bile acids lead to resistance to apoptosis, genomic instability and, together with the hydrophobicity of bile acids, increase the risk of malignancy (67). They modify colonic polyps derived from glandular epithelium, which ultimately lead to cancer (68). In addition, in patients with colorectal cancer, there is an escalation of the activity of dehydrogenase, bacterial beta-glucuronidase, alpha decarboxylase and cholesterol (69). 7-Alpha decarboxylase converts bile acids to deoxycholic acid, which is a potential carcinogen (70).

Nagathihalli et al. document that bile acids induce carcinogenesis by stimulating "mitogenic receptor tyrosine kinase signaling pathways" and propose a mechanism involving "ectodomain shedding of the epidermal growth factor receptor ligands amphiregulin" (28).

Sessile adenomas, considered premalignant, degenerate neoplastically following complex mechanisms that include mutations in the BRAF oncogene, microsatellite instability, mutations in "the CpG island methylator phenotype" (71). These mechanisms are accele-rated by bile acid degradation products (72).

The bile reflux into the graft, although frequently quantitatively important, thus contains, at least theoretically, only this small percentage of secondary bile acids, originating only from the enterohepatic circuit. The degradation of primary bile acids into secondary ones cannot be achieved inside the graft lumen due to the absence of the conditions specific to the native colon for the development of this bile degradation (modified microflora). In these circumstances, it can be speculated that reflux into the graft, if it is involved in the development of cancer, has other carcinogenic mechanisms than those closely related to the action of secondary bile acids.

According to a systematic review of the literature, the development of mucosal changes occurs with an average of 8.5 years after the initial operation (73). Schraps et al. reports a case of malignancy of the colic graft at 57 years postoperatively (colic graft for esophageal atresia operated at the age of 6 months) (17). Significant reflux of gastric contents (acid/alkaline) into the interposed colon is incriminated in the mechanism of chronic inflammation (74).

Altering the Colonic Flora

Increased bile acids in the colon then alter the colonic microbiome. In general, the human gut microbiota is dominated by three primary phyla: *Firmicutes* (30-50%), *Bacteroidetes* (20-40%), and *Actinobacteria* (1-10%) (75). The amount of bile acids in the colon can substantially alter the composition of the microbiome. *Firmicutes* are a type of bacteria ("phylum of bacteria"), most of which have a Gram-positive cell wall structure. *Bacteroidetes* are mostly Gram-negative. Gram-positive bacteria are more sensitive to bile acids than Gram-negative bacteria (76). Bile acids each have a certain level of bactericidal activity, with deoxycholic acid, the most active, being approximately 10 times more bactericidal than cholic acid (77). Thus, high levels of bile acids in the colon, especially deoxycholic acid, modify the colonic microbiota, causing dysbiosis.

The link between dysbiosis and carcinogenesis is documented in the literature. An eloquent example in this direction is the study carried out by Tjalsma et al., starting from the fact that the concentration of bacteria in the colon is 10^{12} cells per mL, while in the small intestine the

concentration is 10^2 cells per mL (78). The high concentration of bacteria in the colon is assumed to be responsible for the 10-fold higher incidence of colon cancer compared to small intestinal neoplasia. The etiopathogenic mechanism would be the production of compounds that alter cellular DNA by bacterial populations colonizing the colon in the context of dysbiosis. This would result in DNA modifications with subsequent mutations in the mucosa. An example in this direction could be *Enterococcus faecalis*. It produces extracellular superoxide which, when converted to hydrogen peroxide, can cause DNA damage in colonic epithelial cells. Another example is that certain populations of *Escherichia coli* accumulate polyketide synthetase islands that encode a genotoxin, called colibactin, which induces single-strand DNA breaks (61).

Epithelial proliferation and massive colonization with *Escherichia coli* are strongly correlated with the incidence of colon cancer. Sun and Kato propose *Streptococcus bovis* as an example as a germ selected under dysbiosis conditions, with carcinogenic potential (79). It is a gram-positive bacterium that can cause systemic infections in humans. It has a particular capacity to grow on media conta-ining up to 40% bile, so it can colonize the colon with a high content of secondary bile acids. Up to 60% of patients with systemic infections or endocarditis with *Streptococcus bovis* are diagnosed with adenomas or colon cancers. Other bacteria, such as *Bacteroides fragilis*, *Fusobacterium nucleatum*, and *Salmonella enterica*, may also be associated, to varying degrees, with the occurrence of colorectal cancer. Zuccato et al., in a study investigating the increased incidence of colorectal cancer after cholecystectomy, have attributed significant importance to the alteration of the intra-luminal flora secondary to the constant and increased concentration of bile acids in the colon (80). In this regard, the *Phylum Bacteroidetes* species play an essential role in the occurrence of cancer (81,82). At the same time, exposure to acid reflux reduces the possibility of bacterial overgrowth in the colon. A study regarding the type of reflux in the post-esophagectomy colic graft revealed that alkaline reflux is recorded 5 times more frequently than acid reflux (83).

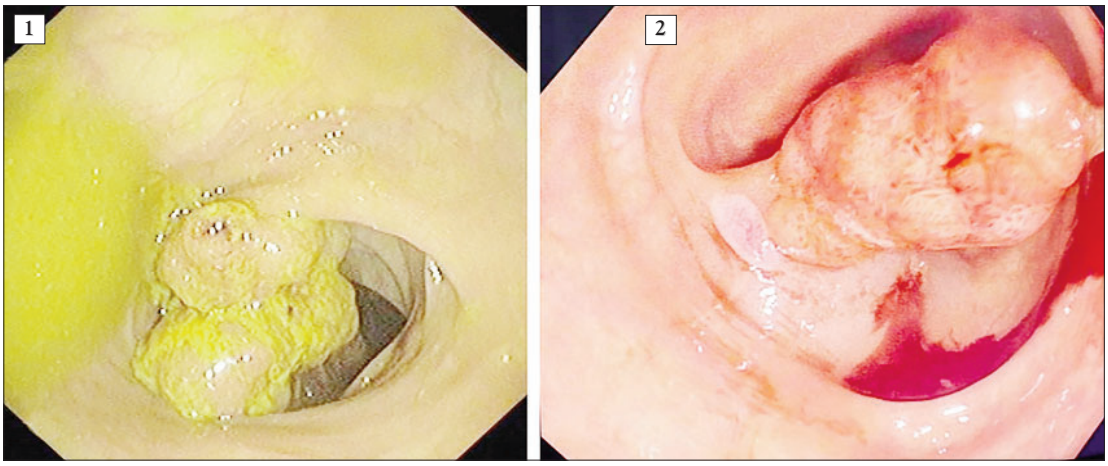
Exposure to bile acids over a long period of time, along with mutations and epigenetic changes that occur over the years, causes the appearance of a clone from a mutated stem cell that can lead to the development of colon cancer.

Diagnosis

Colon cancer is one of the most common types of cancer worldwide in both women and men (84). Therefore, in addition to routine colon cancer screening, which is performed from the age of 50 years, colonoscopy is routinely performed before colonic interposition to exclude pathologies, primarily colon cancer or polyps (85-86). In addition to preoperative screening, the possibility of colon cancer as a late complication of colonic interposition requires a separate endoscopic graft monitoring program. This could, to a certain extent, overlap with the known colon cancer screening. In this regard, a repeat colonoscopy is currently recommended after 10 years if there are no pathological findings (85). On the other hand, Heresbach et al. documented an error rate in identifying colonic neoplasia of 23.4% for colonoscopy (87). For this reason, the literature suggests an endoscopic examination of the graft one year postoperatively for the early detection and treatment of a possible neoplasia at this level. According to a systematic review, the risk of such a pathology is relatively small, but increases with the length of time since the initial operation (73). Thus, the time interval at which endoscopic examinations are performed could be adjusted according to individual risk factors, with more frequent follow-ups after 5 years. Any patient who has undergone esophagectomy or esophageal by-pass with colonic sub-stitute and develops late semiotic changes such as dysphagia, reflux symptoms, respiratory infections, unjustified weight loss, should be investigated including in the direction of neoplastic degeneration (11). Paraclinical investigations (in principle specific to colonic investigations) however need to be adapted (in terms of performance technique and interpretation of results) according to the new status of the colon segment.

Upper Digestive Endoscopy

Upper digestive endoscopy can only be performed under sedation, after prior preparation (colon graft aspiration), especially in conditions of redundancy that will make systematic and rigorous evaluation of the colonic mucosa difficult (*Figs. 1*, *2*). The type of neck anastomosis (*side-side* or *end-to-side*) may make it difficult to employ the transanastomotic endoscope, and may require general anesthesia with IOT in the operating room, in order to assess the graft. Evident anastomotic stenoses need to be evaluated by repeated biopsies (11).



Figures 1, 2. Standard endoscopic image appearance – tumor in the colonic graft
(collection of the Center of Excellency in Esophageal Surgery, Clinical Hospital "Sf. Maria" Bucharest)

Upper Digestive Endoscopy with Narrow Band Imaging

Upper digestive endoscopy with narrow band imaging (NBI) allows visualization of the microvascularization of colonic polyps, which can make the differential diagnosis between a benign adenomatous polyp and a malignant polyp (*Fig. 3*) (89).

Barium swallow requires experience in interpretation, colonic graft bending causing stasis of the substance and limiting the provision of morphological information. Radiological exploration brings important elements regarding the functionality of the colonic graft with the identification of retentive areas of the duct or reflux in the graft *(Figs. 4, 5)*. It is recommended to precede endoscopic exploration, providing important information on the morphology of the neck anastomosis and the graft, with direct consequences on the preparation for endoscopy (preparation of the graft by aspiration,

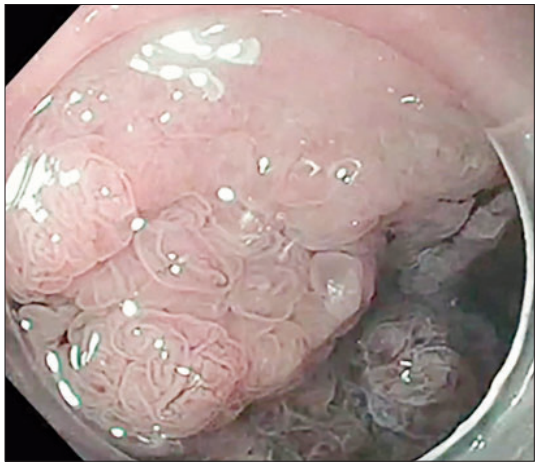


Figure 3. Endoscopic evaluation using NBI (narrow band imaging) of colonic polyps - appearance of adenomatous polyps with neoplastic degeneration confirmed by HP exam
(collection of the Center of Excellency in Esophageal Surgery, Clinical Hospital "Sf. Maria" Bucharest)

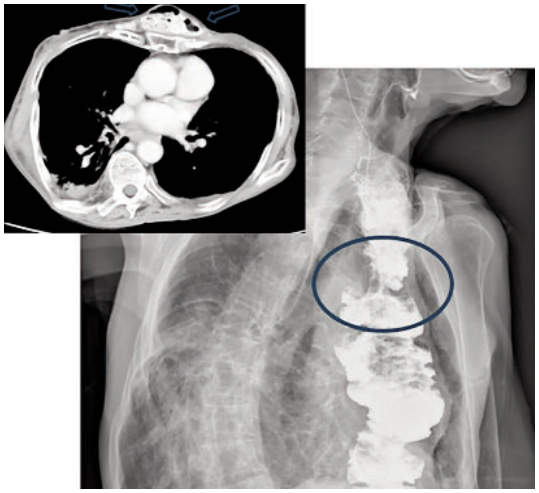


Figure 4. Barium swallow. Time of passage of the barium substance through the graft, highlighting an area of stenosis with a neoplasia-like appearance. In the inset, CT image, cross-section confirming the presence of a tumor formation with invasion of the entire parietal wall
(collection of the Center of Excellency in Esophageal Surgery, Clinical Hospital "Sf. Maria" Bucharest)

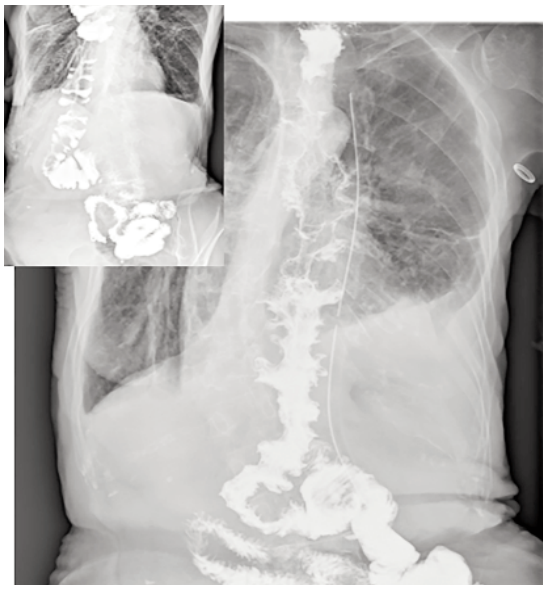


Figure 5. Barium swallow with evaluation of graft transit at 5 days postoperatively and, in the cartridge, at 3 months postoperatively
(collection of the Center of Excellency in Esophageal Surgery, Clinical Hospital "Sf. Maria" Bucharest)

type of anesthesia, assessment of the difficulty of endoscopic exploration), as well as on the optimal interpretation of endoscopic images.

Computer Tomography

Computer Tomography (CT) provides important information about anatomical relationships with adjacent organs, with the identification of invasions of adjacent structures but also of possible metastases. The path of ascending the colonic graft at the neck (pre/retrosternal, posterior mediastinum) involves specific difficulties for each technique of ascent in terms of the interpretation of imaging reports and possible invasion of surrounding organs. Image interpretation requires meticulousness and is recommended to be performed in a multidisciplinary team (imagist, gastroenterologist and esophageal surgeon).

PET-Scan

PET-scan is essential in the oncological context, not only in the evaluation of the graft tumor but also in order to document possible metastases. Appropriate TNM staging is the basis for developing an optimal treatment protocol.

Endoscopic Ultrasound

Endoscopic ultrasound may be useful in assessing parietal stratigraphic invasion (89). Superior results are obtained using high-frequency endoscopic ultrasound probes. Once the tumor is identified in the colonic graft, the diagnostic tactic overlaps with the colon neoplasia evaluation protocol, with the classification in TNM staging, which will be the basis for the development of the treatment protocol.

The evaluation from the perspective of TNM staging will be formally done according to colon cancer. However, certain particularities closely related to the new status of the colonic segment need to be mentioned. The parietal stratigraphic evaluation of tumor invasion can be performed by MRI but in practice, endoscopy is the exploration that brings clearer elements from this perspective. Lymphatic dissemination must be viewed in the context of the anatomical changes secondary to graft preparation, which involves the interruption of vascular pedicles, obviously simultaneously with the interruption of lymphatic efferents. The impact on the lymphatic extension of the graft neoplasia is difficult to quantify. The evidence of distant metastases has the same oncological significance as in the case of the native colon, unequivocally classifying the neoplasia in stage IV.

Treatment

Prophylactic Treatment

Although some studies document that changes in the mucosa of the interposed colon are rare, being more frequently described in the non-ascended (native) colon, a good preoperative colon evaluation is necessary to identify intrinsic or predisposing factors for alteration of the colonic mucosa (90,91).

Patients considered for colonic interposition as an esophageal substitute require preoperative colonoscopy. The presence of extensive diverticulosis with inflammatory fibrosis, extensive polyposis, or malignancy are obvious contraindications. The presence of several colonic polyps does not exclude the use of the colon for this purpose, but their endoscopic resection is mandatory (92). Cerfolio et al. (93) systematically evaluated all patients by barium enema and colonoscopy preoperatively. There were no colonic changes in any patient. Thomas et al. (94) performed preoperative colonoscopy only in patients over 45 years of age. In 2 cases, adenomatous polyps were identified and endoscopically resected.

Even if the initial strategy involves the use of the stomach for esophageal substitution, preoperative colonoscopy would prove useful if it is found that mobilization of the stomach is technically impossible during surgery, the colon being in such a situation the reserve option.

In patients with a colonic graft, endoscopic

evaluation of the graft has been suggested to be performed 2 years postoperatively (95). Monitoring requires repeating endoscopy every 2-3 years to identify the appearance of polyps or neoplastic lesions. In the event of identification of a lesion, the graft is similar to that in the case of the native colon. Patients at high risk of developing colorectal cancer, such as those with a family history of colorectal cancer or colonic polyps, should have alternative options for esophageal reconstruction and a different postoperative monitoring protocol.

Curative Treatment

The treatment of adenocarcinoma of the colonic graft, up to a point, does not differ from the treatment of colon cancer *in situ*. Chemotherapy, radiotherapy, surgical resection retain their efficiency and indications, adapted to the staging but also to the new topography.

If the patient is in a precarious biological status and still in the recovery period after the previous intervention (esophagectomy with esophageal reconstruction with colon), palliative procedures are worth considering to improve dysphagia in an effort to improve their nutritional status. Endoscopic stenting, insertion of a feeding tube (jejunostomy or gastrostomy) bring certain benefits from this perspective. In such situations, the problem of a major deficiency in the pretherapeutic evaluation of the colon is obviously raised. Endoscopic stenting of the colonic graft is indicated in the presence of metastases, or when the patient status does not allow it, until the patient is stabilized "bridge to surgery" (*Fig. 6*)(96).

The technique of colonic stent placement involves the insertion of a TTS (through the scope) 0.035 inch guidewire under endoscopic and fluoroscopic guidance, caudal to the colonic tumor, followed by the insertion and expansion of the stent on the guidewire, under radiological and endoscopic guidance. Uncovered or partially covered self-expanding metallic colonic stents (SEMS) are placed, due to the low risk of migration. An important time in the placement of a self-expanding colonic stent is represented by the calculation of the length and diameter of the stent. The inappropriate choice of the colonic stent can lead to complications: perforation or hemorrhage at the proximal or distal end of the stent, colonic fistula or stent migration. The length of the colonic stent is calculated as follows: the length of the tumor formation, to which is added 2 cm of length for the cranial end and 2 cm for the caudal end (97).

It is recommended to perform colonic graft endoscopy screening, due to the risk of developing tumors or colonic polyps. Colonic polyps discovered during the preoperative examination require endoscopic resection followed by histopathological examination (98).

Endoscopic resection of adenomatous or malignant polyps developed on the colonic graft, requires advances endoscopic skills, due to the difficult anatomical features (*Fig. 7*). Polypectomy is indicated for polyps developed on colonic grafts if their histopathological result is adenomatous polyps, malignant polyps without invasion into the submucosa (99).

When adenocarcinoma does not completely involve the colonic wall, endoscopic resection may be a viable alternative. Endoscopic resection is recommended for early cancers limited to the mucosa, without the presence of malignant lymph nodes on imaging investigations for tumor staging. In the case of adenomatous polyps, endoscopic resection can be of the in-bloc, piecemeal or submucosal endoscopic resection type (100).

For malignant polyps, two endoscopic resection techniques are recommended: the endoscopic submucosal resection (ESD) technique, dedicated to

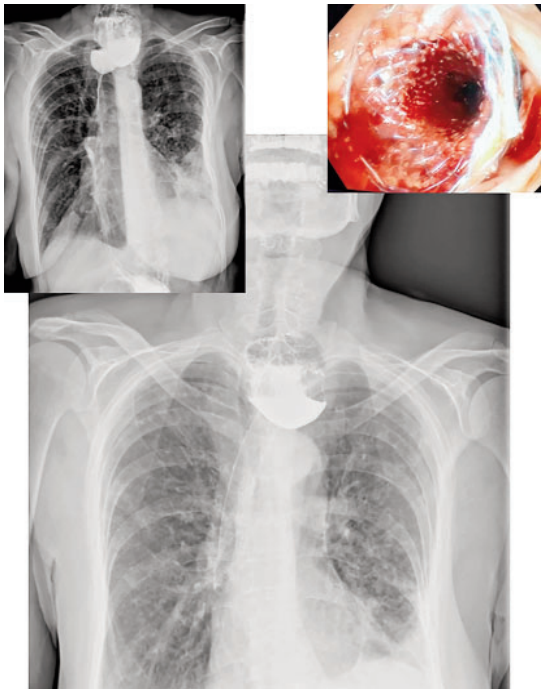


Figure 6. Upper digestive contrast study, with stent placed transtumorally through a colonic graft with unresectable adenocarcinoma. In the inset, the diagnostic radiology image showing a pseudo-obstructive tumor
(collection of the Center of Excellency in Esophageal Surgery, Clinical Hospital "Sf. Maria" Bucharest)

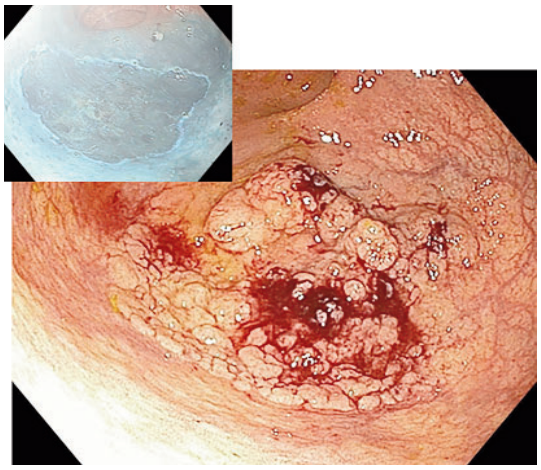


Figure 7. Endoscopic examination of a colonic graft with image of LST type colonic polyp (lateral spreading tumors) before endoscopic submucosal resection (ESD) and after ESD (in cartridge)
(collection of the Center of Excellency in Esophageal Surgery, Clinical Hospital "Sf. Maria" Bucharest)

flat, sessile polyps or those with lateral extension, malignant but limited to the colonic mucosa. The second technique is indicated for pedunculated, malignant colonic polyps, which implies the resection of the polyps as close to the base of the pedicle as possible, followed by endoscopic hemostasis techniques (clip mounting, endoloops) and recovery for histopathological examination (101).

Colon polyps that cannot be technically resected endoscopically, as well as neoplasms developed from the colonic prefundus, require biopsy confirmation for histopathological diagnosis and are subsequently directed to a possible surgical technique (102).

The indications for surgical resection are considered as radical treatment, in the case of cancer of the colonic graft, in the absence of secondary findings. The technique is feasible and brings favorable results from an oncological point of view. Hwang and colleagues present the first case of endoscopic resection of an adenoma with dysplastic changes in the colonic graft (103). The patient also had an adenoma in the remaining colon. Resection becomes technically more difficult when the tumor has already infiltrated the submucosa and impossible when it has invaded the muscularis mucosa (104).

Polypectomy is necessary for polyps or biopsy for lesions that cannot be resected endoscopically. In the absence of metastatic findings, surgical resection should be considered as a radical treatment.

Surgical resection of the involved colonic segment is a possible solution, allowing simultaneous correction of any redundancy of the interposed colon, if present. From a technical point of view, segmental resection needs to be performed "intervascularly", with preservation of the paracolic vascular arch. Although it is assumed that there are neo-formation vessels that, theoretically, could compensate for the graft vascularization in the context of the interruption of the paracolic arch, this aspect is difficult to document and quantify, with the risk of compromising the graft post-operatively, with serious consequences (*Fig. 8*). Cuneiform resection of a small anti-mesostenic cancer lesion can be a viable artifice. Also, excision of the entire graft, in the context of a neoplasia at this level, is justified. In this situation, restoring the continuity of the digestive tract (using another segment of the digestive tube) will be abandoned for a later time, after balancing the patient's biological condition and oncological status.

Making an esophagostomy and installing a feeding tube (gastrostomy or jejunostomy) at the end of the resection time will be sufficient at this point in the patient's management. Obviously, the time of excision (regardless of the extent) is directly related, in terms of difficulty, to the path of ascension of the colonic duct to the cervical level. The presternal route offers an easy approach to the graft. In contrast, the retrosternal or posterior mediastinal route, majorly changes the surgical tactics and technique, with an exponential increase in the extent of the intervention. When there are no documented metastases, surgical excision is the optimal course of action (33). If the graft is completely resected, endoscopic monitoring of the colon in situ is performed according to the guidelines for colorectal cancer surveillance. In the case of a segmental resection of the graft, the

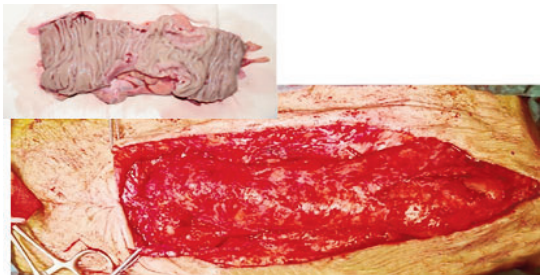


Figure 8. Intraoperative appearance of the presternal graft with colonic tumor, highlighted on the resection specimen, confirmed by HP exam
(collection of the Center of Excellency in Esophageal Surgery, Clinical Hospital "Sf. Maria" Bucharest)

remaining graft requires annual endoscopic monitoring, together with the colon *in situ* (33).

Discussions

According to the literature, cancers reported in the interposed colon had clinical and histological features similar to those of sporadic adenocarcinomas described in the general population. Other clinical features similar between adenocarcinoma of the colonic graft and sporadic carcinoma in the general population included the age of the patients and the synchronous occurrence of cancer in the native colon in 5.6% of the patients (21).

The time elapsed between colon transposition and diagnosis of adenocarcinoma varied significantly. However, the age at diagnosis was similar to that reported in the general population. The mean age and histological features of the tumors in 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.

These data suggest the hypothesis of an age-related genetic predisposition. This genetic predisposition seems to be correlated with the presence of local inflammation. Most risk factors identified in patients with sporadic colon cancer, as well as in the case of de novo carcinoma arising in the transposed colon, have a common cause represented by chronic or acute inflammation that alters the colonic mucosa (105,106). Aging is undoubtedly one of the most powerful determinants of cancer development. However, what determines the occurrence of neoplasia with aging, beyond the obvious prolonged exposure to traditional risk factors, the proportion of which is modified in the case of colonic transposition, is unclear (107,108). In patients with familial colorectal cancer, such as Lynch syndrome, the MSI/MMR genetic mutation is present in more than 90% of patients. In patients with sporadic colorectal cancer, a genetic mutation is evident in less than 6% of patients, and several different genetic mutations have been documented, some with high penetrance and others with low penetrance. Thus, there is no common genetic mutation in sporadic colorectal cancer (105,109). On the other hand, patients with sporadic colorectal cancer present many similar clinical features, which lead to the hypothesis of the existence of a common etiological background.

Dysregulation of the immune system with advancing age is a known phenomenon (110,111). The link between the performance of the immune system and the progression of colorectal cancer, the close correlation of sporadic colorectal cancer with aging, and the alteration of the immune response with aging determine a conceptual cause-effect relationship between potential factors that could influence the aging-dependent alteration of the immune system and the occurrence of sporadic colorectal cancer. Inflammation in genetically predisposed patients may trigger somatic changes in hematopoietic cell lines leading to cancer. Thus, inflammation may have a dual action, local and systemic. The hypothesis that triggers linked to long-term inflammation could lead to a disorder of the hematopoietic system may explain the occurrence of other types of cancer in the elderly. Inflammation may be responsible for aging itself and for the consequences of aging (112,113). Moreover, cases have been reported in which cancer appeared synchronously in the transected colon and in the native colon, with similar histological features despite the differences between the two anatomical topographies. These synchronous cancers could be related to a genetically determined local cause; we cannot exclude the possibility of a general genetically determined disorder of the immune system (21).

Bando et al. reviewed 10 cases from the literature, including both adenomas and adenocarcinomas (114). Significant changes occur in the interposed colon, mainly secondary to exposure to chemicals and to an intraluminal flora very different from its normal environment (88,114). However, the influence that these changes exert on the colonic mucosa is unclear. Lindahl et al. reported on 12 patients followed for 12-26 years after colonic inter-position as an esophageal substitute (115). Interestingly, the colonic mucosa showed gastric metaplasia, colonic dysplasia, and aneuploid cell population, thus indicating premalignant potential. Isolauri et al. on the other hand, reported the histological findings of the colonic graft mucosa after a follow-up of 5 months to 15 years in 36 patients and concluded that the changes in the colonic mucosa were unexpectedly minor (116).

The new status of the colon segment interposed as an esophageal substitute offers conditions that are completely different from those of the colon *in situ* and at first glance completely inappropriate for this structure. However, the incidence of colon cancer on the graft is not higher than that in the general population, although the multitude of

oncological risk factors identified, at least from a theoretical point of view, could bring different results. The explanation is difficult to offer, on the one hand due to the multitude of variables in this direction, on the other hand, due to the small number of cases available for studies. Although certain newly created conditions for the graft seem to be favorable to the occurrence of neoplasia (biliary reflux, secondary dysbacteriosis), others seem to counterbalance (acid reflux - although strongly pro-inflammatory, effective antibacterial). At the same time, starting from the premise that the incidence of colon cancer is improved by optimal monitoring of preneoplastic lesions (colonoscopy) and their prompt treatment (colonoscopic resection of early lesions), we can speculate that due to the particular monitoring program of these cases, the occurrence of an adenocarcinoma on the colonic graft is exceptional. An additional argument for a periodic remote evaluation of these cases is the finding that in the case of patients with esophageal cancer there is a high risk of colonic lesions such as adeno-matous polyps and even cancer (117,118).

Regardless of the proposed monitoring protocols, which sometimes differ significantly and are far from being standardized, one thing is certain. These patients, due to their complexity, are subject to much more careful monitoring by medical teams, which may lead to the prevention of cancer or, at least, its identification at an early stage. Periodic assessments, both of general health and metabolic balance, must be supplemented with data on the functionality of the colic "assembly", of possible complications at this site. Therefore, performing a barium swallow at 6-month intervals, possibly annually, followed by an endoscopy with multiple biopsies from the graft and stomach appear mandatory.

The most obvious element is the colonoscopy (but also other investigations) performed preoperatively in the context of colon evaluation before being chosen as an esophageal substitute. In addition, the multitude of specific postoperative morbidities (dysphagia, reflux, food impactions) offers the opportunity, through the required explorations, for early identification and sanctioning of lesions with the potential for malignant degeneration.

Conclusions

In the literature, whenever the subject of the colon transposed to the thorax is addressed, the term "new environment" of the graft is almost formally overlapped with the term "hostile environment". However, the data provided by the studies do not unequivocally justify this qualification, taken over and accepted by most authors. The low incidence of cancer on the colonic graft, the superior long-term functionality of this type of esophageal substitute (compared to the gastric or enteral graft) should, if not to disprove it, at least make us reluctant to consider that the new hypostasis of the colonic segment, although indeed completely different from the "native" environment, is not so unfavorable for fulfilling the function of an esophageal substitute.

Author's Contributions

Conceptualization: A. C., D. P., F. A.; Investigation: A. C., F. A., A-C. M., C. G. R., A. R., D-V. S., D. P.; Writing-original draft preparation: A. C, , F. A., C. G. R., A. R., A-C. M., A. R., D-V. S, D. P.. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Ethical Statement

This study was conducted in accordance with the Declaration of Helsinki. and approved by the Saint Mary Hospital Ethics Committee (approval form no. 312 /4 november 2024).

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