EDITORIAL

EARLY COLORECTAL CANCER

DIAGNÓSTICO PRECOCE DO CÂNCER COLORRETAL

Large intestine cancer persists as one of the highest incidence in the western world. It is, in the USA, the second in frequency and the first one in death rate as far as malignant diseases are concerned. One person in ten will develop this disease in the USA, which corresponds to 150,000 new cases a year and to 15% of all cancer diagnoses[1-11].

The great majority of the colorectal malignant lesions are of epithelial origin, and their most common histologic type, the adenocarcinoma, is present in almost 97% of these cases, and the occurrence of synchronous cancer is also possible in 3% of them[1,2,5,6,9].

About 75% of the patients are between 45 and 75 years old, and the disease is slightly more frequent in women (this author's casuistry: 52.5% - women and 47.5% - men, independently of race)[9,13,14].

Large bowel cancer is more frequent in its distal segments, with a tendency to increase in the right colon, especially in the American population[1,2,4,6]. In this author's series its distribution was: 48% in the rectum, 28% in the sigmoid, 6% in the descending colon, 8% in the transverse and 10% in the ascending colon and cecum[9,13,14].

Diagnosis of colorectal cancer includes a complete and careful physical examination, rectal touch, anuscopy, rectosigmoidoscopy, colonoscopy and/or radiological examination of the large bowel (opaque enema), and, when possible, histopathologic study of the lesion through biopsies. Examination with fecal occult blood testing may be useful to investigate colorectal cancer in groups of risk (Plate 1).

Large intestine cancer must be investigated[7,9,15-18].

- in all patients showing symptoms or signs that can generate clinical suspicion,
- if there is a conditioning factor of risk of colorectal cancer or
- in the section of non-symptomatic individuals belonging to groups of risk of colorectal cancer.

Plate 1. Group of risk for colorectal cancer.

Basic risk	patients over 40
Average risk	patients with familiar history of cancer, adenomas or adenomatous polypoid syndromes.
High risk	patients with a prior history of adenomas and/or cancer and with chronic inflammatory disease.

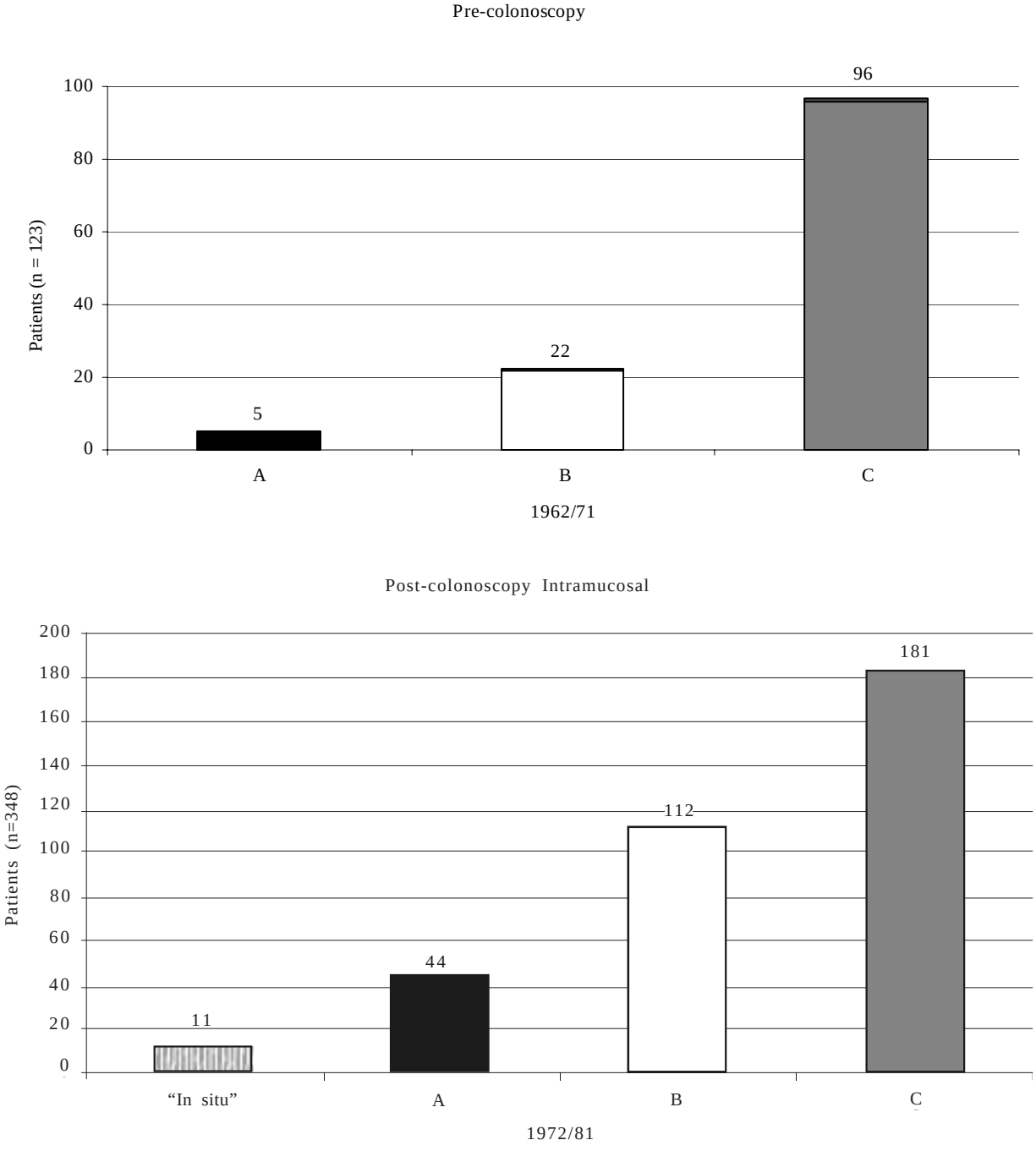

Figura 1. Comparison of pre-colonoscopy group (pre-c) with post-colonoscopy one (post-c) as to tumoral invasion by dukes' classification.

In the great majority of cases, the treatment of colorectal adenocarcinomas is still surgical, applying all the oncological precepts. In the last decades, developments in surgery and anesthesia have led to a significant decrease in the mortality related to this treatment[1-3,5,6,9].

Colonoscopy and Colorectal Cancer

Colonoscopy has an important role in early diagnosis of colorectal tumors, as it allows identification of pre-malignant lesions (adenomatous polyps), malignant polyps and early colorectal cancer. This diagnosis is possible even when handling lesions smaller than 1cm[9,14,19-21].

The importance of colonoscopy in this early diagnosis was pointed out in a retrospective study of this author's series, in which patients with colorectal cancer were evaluated considering the degree of tumor invasion, according to Duke's classification, and its localization in the large bowel[9,22-24].

Patients were divided in to two groups, according to the date of their diagnosis: one group was called pre-colonoscopy period (PRE-C), from 1962 to 1971, and the other called post-colonoscopy period (POST-C), from 1972 to 1981.

In the PRE-C group (123 patients), Duke's C cancer was diagnosed in 78%, Duke's B in 18% and Duke's A in only 4%. In the POST-C group, a fundamental difference occurred in the diagnosis, as less advanced stages were observed, resulting in a better prognosis for these patients. From the 348 individuals belonging to this group (Figure 1), only 52% were Duke's C, 32% were Duke's B and 12% were Duke's A[9,13,20,21].

In the POST-C group, adenocarcinoma was diagnosed in the initial stage, and the tumors were restricted to the colon mucosa in 11 patients (4%) with no invasion of the *muscularis mucosae*; these individuals presented, therefore, an intramucosal tumor, which is 100% curable. It is important to note that intramucosal carcinoma could only be diagnosed after the use of colonoscopy.

Regarding the location of the tumors in the large intestine, there was also a difference between the two groups, occurring an increase of the diagnosis in the right colon in the POST-C group.

Besides an early diagnosis, colonoscopy allows the collection of material from lesions for histopathologic examinations, in order to differentiate it histocytologically. It is also possible to diagnoses intestinal diseases concomitantly with the tumors.

Another contribution of colonoscopy is to provide the resection of some lesions, and it is, in this way, therapeutic. These resections could be performed for some pre-malignant lesions as adenomatous polyps as well as for malignant polyps and early cancer.

Carcinogenesis

It is a process of multiple stages, in which the cumulative genetic damage is continuously expressed in phenotypes of progressive malignancy. According to the genetic and molecular biology point of view, cancer is the result of this process of multiple stages, controlled by genetic alterations, giving origin to a cell clone with proliferating advantages over the others[9,12,25-29].

The biological cycle includes cellular proliferation, development, differentiation, migration and death. This cycle is controlled by means of permanent activation of the suppressive genes of the tumor and by the constant inactivity of the oncogenes.

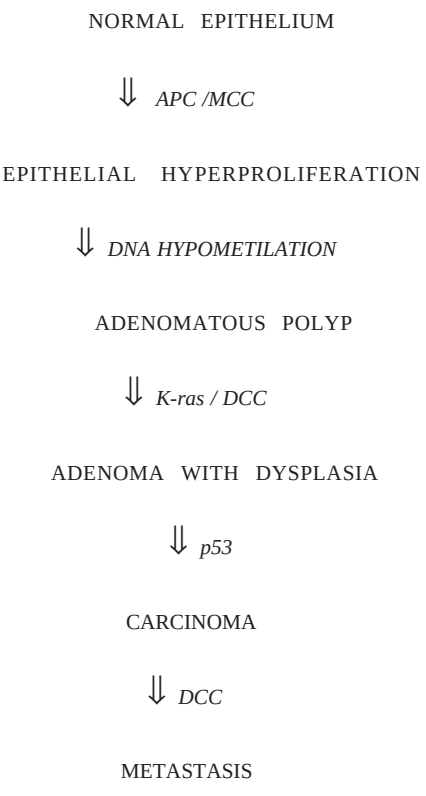

Figure 2. Carcinogenesis of the "adenoma-carcinoma sequence".

The tumor suppressive genes act as stabilizers of the genome, and controllers of cellular proliferation, apoptosis or cellular suicide[9].

The oncogenes have the capacity to cause alterations in the various stages of the cellular cycle. The genetic alterations can occur by means of mutations, which modify the controlling process of the fundamental cellular cycle (Figure 2)[26,27].

Most of these genetic alterations are acquired as somatic mutations, through environmental factors, especially dietary; they are responsible for sporadic cases of malignant neoplasias, with no familiar history, and are called sporadic colorectal cancer. They correspond approximately to 85% to 90% of colorectal carcinomas[9,25-27].

The dietary factors which predispose to carcinogenesis in the large bowel are: excess of animal fat, meat and calories; lack of fiber ingestion; and probably alcohol and tobacco. As factors of chemoprotection we have: diets rich in fibers, vitamin D, calcium, methionine and aspirin[26,27].

When genetic mutations occur in the germ lineage of the cellular cycle, they are responsible for the hereditary cancer, called familiar colorectal cancer[27].

The large bowel familiar cancer may be associated or not with the colic polyposis. When it is associated with the polyposis, the hereditary colorectal cancer occurs because of the malignant degeneration of the neoplasic polyps, in the so-called polypoid adenomatous syndromes. They correspond to less than 1% of the cases. These polypoid syndromes are related to dominant autosomal

genes and include familiar adenomatous polyposis (FAP) and the syndromes of Gardner, Turcot and Muir-Torre[13].

Familiar cancer with no polyposis, however, may be connected with up to 10% to 15% of the large bowel tumors. It is called hereditary non-polypoid colorectal cancer (HNPCC), and it is associated with codifying genes of the DNA cellular repair (genes: hMSH2, hMLH1, hPMS1 and hPMS2). It corresponds to Lynch I syndrome when the tumors are restricted to the colon, and to Lynch II when the colorectal cancer is associated with extracolic tumors[27].

Colorectal carcinogenesis is considered as a phenotypical mutation of multiple ways, according to the principal schools of pathology. From these multiple ways, two are known. One is the dependent polyp tumor, in which, previous to the carcinoma, the mucosa presents an adenomatous lesion (adenomatous polyp) that can undergo genetic mutations, causing malignancy. This is considered the most frequent way for colorectal cancer, denominated "adenoma-carcinoma sequence". According to western authors, 56% to 90% of the patients may have this type of cancer[9,15,30-32]. The other is the "de novo" cancer, which is originated directly from the colorectal mucosa, without previous adenomatous lesion. It seems to be related to carcinoma of younger patients (under 40 years old)[21,22].

Intramucosal carcinoma

Carcinoma is considered as intramucosal or *in situ* when degenerative alterations invade the basal mucosa or the mucosa lamina itself and are restricted to it. In these circumstances it is considered non-invasive, for its small potential of metastasizing. The five-year survival percentage for the patients examined in this stage is of approximately 100%[1,9,15,22,23,30,33-36].

The concept of intramucosal carcinoma being a non-invasive cancer is related to lymphatic drainage of the colic wall: the lymphatic vessels of the colic mucosa are limited to the region immediately below the muscular layer of the mucosa (*muscularis mucosae*)[34-37].

Invasive carcinoma

The transition from intramucosal carcinoma to invasive carcinoma occurs when the malignant cells reach the muscular layer of the mucosa (*muscularis mucosae*). In this stage there is a potential of metastasizing between 5% and 10%[9,22,23,30,34-41].

"De novo" cancer

"De novo" cancer is defined as a carcinoma originated directly from the colorectal mucosa. The malignant transformation happens in the normal intestinal epithelium itself, with no previous adenomatous lesion[9,12,20,22,23,25,42].

It is probably a sporadic type of tumor with no relation to hereditary factors, and it is developed from somatic genetic mutations originated in the mitotic zones of the colonic crypts. These mutations

are related to the p53 gene in 64% of the cases, whereas the adenomatous polyp dysplasia depends on the oncogene k-ras activation, according to Japanese authors[28,29,42].

Its natural history is still little known, but it is related to regional tumoral inductors, which would influence its predominance, including its localization, preferably in the right colon[22,23].

Its diagnosis is fundamentally endoscopic, and total colonoscopy should always be performed, considering that the tumor can occur in any segment of the large bowel.

Most of the lesions are small, measuring less than 1.5cm. Under colonoscopic examination their color is similar to normal mucosa, sometimes with slight hyperemia[9]. As they are difficult to observe during colonoscopy, chromoscopy is used to make clear their localization and limits. It is perfomed using indigo carmine at 0.5% or methylene blue at 0.3%, instilled in the intestinal lumen.

Videocolonoscopy with image magnifier may contribute to this diagnosis, especially in relation to the classification of the pits patterns existing in colic mucosa lesions.

Between 1995 and 1996, Brazilian casuistry included 19 "de novo" cancers in 16,445 total colonoscopies, with an average of 1.1 for each 1,000 examinations, which is in accordance with international publications[9,22].

Early colorectal cancer

Early colorectal cancer defines the carcinoma that invades as far as the submucosa, independently of the presence of metastasis[9,22,23,42]. Patients with this type of cancer have a five-year survival rate of nearly 90%. Fibercolonoscopy and, more recently, videocolonoscopy are the best methods for this diagnosis.

The success of the treatment of colorectal cancer depends on its early diagnosis, when the lesion is in the stage in which the carcinoma is still localized in the mucosa, or is invading, at most, the submucosa of the large bowel wall. Early colorectal cancer is classified by Kudo (Table 1)[22].

Table 1. Early colorectal cancer by kudos' classification.

Protuded type (I)	Ip	=	pedunculated
	Isp	=	subpedunculated
	Is	=	sessile
Superficial type (II)	Iia	=	flat elevated
	IIa+Iic	=	flat elevated with depression
	Iib	=	flat
	Iic	=	slightly depressed

After being diagnosed and delimited, infiltration can be performed through the colonoscope, from the surrounding mucosa to the early carcinoma, aiming to evaluate the degree of parietal fixing and, therefore, the presence or absence of submucosa layer invasion. If the lesion is restricted to the colon mucosa, its elevation will occur, making its endoscopic resection possible by doing the mucosectomy[22,31,33,38-41].

However, if there is submucosa layer invasion, the lesion will not be elevated and colonoscopic therapeutics is contraindicated. In this case, only biopsies should be taken and its limit should be made clear (tattoo) with China ink at 1%, through infiltration of the submucosa surrounding the lesion, in order to make its localization and surgical resection easier[9,22,31,33,38-41].

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Recebido para publicação em 25 de novembro e aceito em 28 de novembro de 2002.