

Peculiarities of diagnosis and treatment in the polyp-cancer sequence

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Rezumat

Particularități de diagnostic și tratament în secvența polip-cancer

Problemă de sănătate publică cu implicații sociale majore, cancerul colo-rectal a focalizat în ultimele decade resurse economice majore și centre specializate orientate în direcția obținerii unui diagnostic precoce, pornind de la mijloace de screening eficiente. Este de domeniul evidenței că rezultatele terapeutice și costurile sociale sunt în primul rând dependente de precocitatea diagnosticului. Lucrarea își propune să aducă în atenție o serie de direcții de acțiune, care pot deschide o nouă perspectivă în abordarea la nivel genetic și molecular a acestor leziuni. Dintre acestea, este subliniată valoarea screeningului molecular bazat pe detecția genei APC situată pe brațul scurt al cromozomului 5, metodă care permite selecționarea subiecților ce vor fi supuși ulterior screeningului endoscopic. Se realizează astfel optimizarea costurilor alături de complianță crescută a subiecților la o astfel de metodă.

Cuvinte cheie: polip, cancer colorectal

Abstract

Colorectal cancer, a public health problem with major social

implications, has attracted major economic resources and specialized centers focused in the direction of obtaining an early diagnosis from effective screening means in the last decades. It is obvious that the therapeutic results and the social costs are primarily dependent on the precocity of diagnosis. The present paper aims to bring to attention a number of orientations, which may open a new perspective in approaching the genetic and molecular level of these lesions. Out of these, the value of the molecular screening based on the detection of the APC gene located on the short arm of chromosome 5, a method that allows the selection of the subjects to be subjected to further endoscopic screening is underlined. The optimization of the costs as well as the increased compliance of the subjects to such a method is thus accomplished.

Key words: polyp, colorectal cancer

Introduction

The equation of the polyp-cancer relationship begins from the statistical findings that most colorectal cancers are preceded by polyps, but most polyps do not progress to colorectal cancer (12,13).

From this paradigm, the bibliographic research as well as the clinic one has proposed possible answers to many questions located at different levels of the genetic, cytological, histological and clinical investigation.

On one hand, as practitioners in general surgery, we face a high frequency of neoplasias located on this digestive segment and on the other hand, the colonoscopic exploring, nowadays

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a routine, describes a frequency of colorectal polyps and a lesion simultaneity which raises questions about the nature of these lesion associations.

This paper aims to answer to the following questions:

- Is there a lesion polyp-cancer colorectal continuity?
- What is the value of “signal” lesion of the colorectal adenomata?
- Is there a common genetic substratum of the two injuries?
- What are the promoters of the “leap” from adenoma to adenocarcinoma?
- Are there specific markers for each of the stage lesion?
- What is the best way of screening of these injuries?
- What objective criteria underlie the option therapeutic-endoscopic surgery versus open surgery?

With these objectives, the study starts from the reality of the high frequency of neoplasia with colorectal localization, respectively the fourth place of all the neoplasias and first place of the malignancies of the digestive localizations.

These objectives are part of the efforts to connect the management of the colorectal cancer to the preventive health necessity, in the promoting of the sanogenic factors and the optimal management of the health resources.

Thus we are trying to draw some conclusions or directions of actions in terms of optimal methods of screening, treatment options appropriate to each type of lesion, the ultimate goal being to reduce mortality following the colorectal cancer.

Material and Method

The clinical trial carried out in the General and Emergency Surgery Clinic III in SUUB (The University Emergency Hospital) in the period 2003-2010 had a retrospective character, including a total of 709 cases, patients with polypoid colorectal tumors in various stages of evolution.

Out of this number, 62 patients were classified as adenomatous polyps, having at most moderate dysplasia but with pedicle and basis of implantation with normal histological epithelium, the remaining 647 cases being colorectal neoplasms.

Of the 647 cases of colorectal neoplasm, an important aspect to remember is that in 139 patients, the colorectal neo-

plasm was accompanied by unique polyps or even by polyposis located in the proximity or at distance from the tumor.

The idea of starting our study started from the fact that the epidemiological research shows a surprising incidence of the colorectal polyps in Europe and North America of about 30% of people aged over 50 years, the rate increasing by 10% per every decade age (2,3).

In the current sense, the polyp term defines a well circumscribed lesion in the colon lumen or that protrudes into the lumen of the colon or rectum, having as histological substratum - the proliferation of the mucosal epithelium. (Table 1)

Our study refers to the first category of polyps, the neoplastic polyps, respectively, the rest being of minimal importance in frequency and etiopathogenetic involvement in the relation with the colorectal neoplasm.

On the other hand, the study of the gastrointestinal polyposis syndromes in general and of the colorectal ones especially has constituted the starting point of the research for the genetic substratum of the colorectal carcinogenesis.

From this point of view the familial adenomatous polyposis (FAP) is the entity most researched, being a dominant autosomal hereditary condition caused by a hereditary inactivating mutation of the APC gene located on the long arm of chromosome 5, a change seen also in the sporadic colorectal cancer (5,8,10).

The genetic abnormalities associated with the colorectal cancer development permit its classification in:

- hereditary colorectal cancer with inherited genetic anomalies that interest the susceptibility genes (12,17).
- sporadic or non-heritable colorectal cancer, where the genetic abnormalities are acquired during life, under the action of the environmental factors, heredity having a minor role (17).

The accumulation of a abundance of data on genetic and cellular level changes led to the development of some possible models of colorectal carcinogenesis, including the Vogelstein model which is nowadays the most accepted (16,17). (Fig. 1)

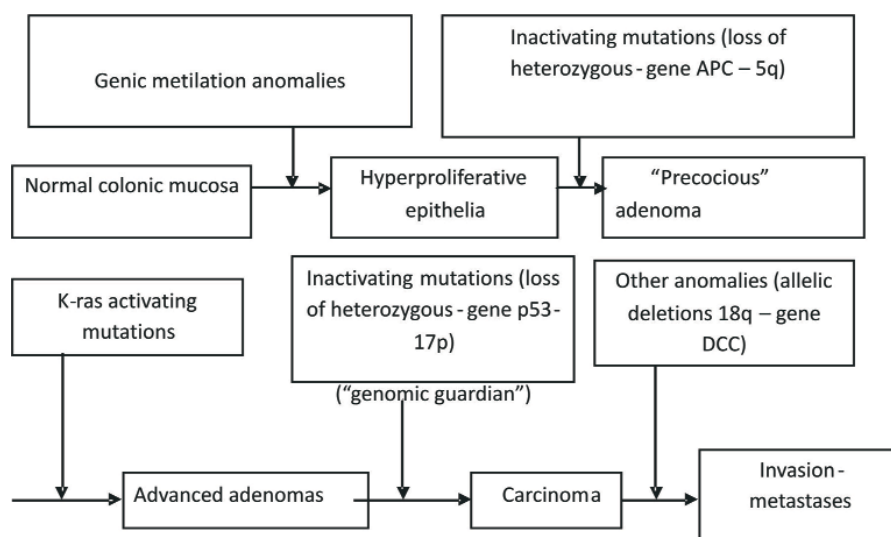
The “key genes” of this model are the K-RAS Proto-oncogene located on the short arm of chromosome 12 mutation, found in half of the colorectal cancers and two tumor suppressor genes:

- APC moved in 50% of the sporadic adenomata and

Table 1.

Neoplastic polips	Non neoplastic polips	Non epithelial polipoid mass (submucosal)
Tubular adenoma	Mucosal polips	Cystic pneumatosis
Vilous adenoma	Hiperplastic polip	Lipoma/Liposarcoma
Tubulo-vilous adenoma	Inflammatory polip(pseudopolip)	Leiomyoma/Leiomyosarcoma
Malign transformed adenoma	Juvenil hamartoma	Fibroma/Fibrosarcoma
Carcinoma	Peutz-Jegher's syndrome's hamartoma	Hemangioma/Hemangiosarcoma
		Schwanoma and other neurogenic tumors
		Carcinoid
		Metastatic tumors
		Deep cystic colitis

Figure 1.



75% of the sporadic colorectal cancers;

- p 53 considered the protective gene of the colorectal cancer.

DCC encodes a transmembrane protein with a role in the cell adhesion.

In the current state of knowledge, there are some reliable data on the correlation of the clinical data (progress, prognosis), with quantifiable genetic data, correlation demonstrated also by Vogelstein in his model of carcinogenesis. He described the pathogenesis of the colon cancer as if it follows a predictable sequence of events, from adenoma to carcinoma with histological changes developed simultaneously with the appearance of genetic mutations over time. The colorectal cancer frequently has chromosomal instability, indicating this as the most common genetic cause of carcinogenesis.

The histogenesis and cytogenesis studies of the polyps are of a particular importance for the understanding of the significance of this type of benign proliferation and facilitate the understanding of the polyp-cancer relationship. Some studies have shown that the initial cell abnormalities occur in the cells at the surface level of the colorectal mucosa, identifying at this level, apparently normal, foci with early neoplastic changes: cells with reduced capacity of producing mucus, hyperchromatic nuclei, decreased nucleotide-cytoplasmic ratio; cellular changes are concomitant with an increase in the number of cells. More recent studies have deepened the ratio between the multiplicity of the lining cells and the cell loss by desquamation, the process of cell replacement at the level of the colon mucosa being one of the fastest in the body.

Results

The studied group analysis shows that in the overwhelming majority of cases, respectively in 72%, the diagnosed colorectal cancer was the only injury, lesion category for which the therapeutic attitude is standardized and applied according to

the current protocols.

The other two categories have attracted the most interesting observations and have imposed the most nuanced attitudes, both at the diagnosis time and in the follow up. The discussion is about 9% single or multiple adenomatous polyps and about 19% where there was polyp-cancer lesion simultaneity.

In the cases of the colorectal polyps with no malignancy, the main therapeutic option was the unique or serial endoscopic resection in over 50% of cases. The simple endoscopic surveillance at set intervals was considered sufficient in 13% of cases, given the minimum risk evolution.

We recorded a total of seven cases in which the endoscopic resection was not possible, fact which certifies the limitations of this procedure. The failures were related to the morphological characteristics of the polyps (size, absence of pedicle), to certain technical incidents or to the occurrence of bleeding or perforation complications.

It should be noted that in 21% cases the open resection of the polyps (polypectomy or colotomy) was resorted to, either because of the histological nature or because of the failures of the endoscopic attempts.

The therapeutic attitude towards these polyps at the moment of diagnosis practically addresses to those ones that are remote, the ones located near the neoplasia being removed at the same time with the surgical resection piece.

From the group of 27 cases who had concomitant colorectal cancer polyps at distance, undergoing polyp resection in one way or another, for colonoscopic checkup in one year time, 15 cases returned.

The appearance of two new lesions in the same colic segment, in which the initial polypectomy was performed, was noted.

The colonoscopic evaluation of this group three years after the initial interventions, provides extremely interesting data further emphasizing the existence of some strong correlations in the metaplasia-dysplasia-neoplasia sequence, fact which imposes a strict surveillance of these patients.

The appearance of three cases of metacron colorectal cancer, a clearly distinct lesion from the locally relapse was noted and imposed a proper surgery sanction.

Furthermore a polyp known to have an accelerated growth compared to the initial appearance imposed the endoscopic resection at the given time.

In terms of the genetic study, out of the total number of studied cases of colorectal cancer, in 103 cases - 16% an immunohistochemistry (IHC) examination was also performed, which showed activating mutations of interest for proto-oncogenes (RAS oncogene mutations), mutations leading to the loss of the heterozygosity of the tumor suppressor genes (mutations of the anti-oncogenes interesting the APC and p-53 genes). These tests draw the attention on the cellular mechanisms disorders at the molecular level in the colorectal cancer and in particular on the adenoma-adenocarcinoma sequence (polyp - cancer).

Discussions

The problems posed by the discovery of a colon polypoid are complex and require the clarification of at least some aspects:

1. Their histological nature?
2. The lesion uniqueness, multiplicity?
3. The malignant-benign association (patent cancer associated at the same time with polyp)?
4. The polyp-cancer sequence, the time required, the predisposing factors of this development, the optimal tracking intervals, and the endoscopic surveillance?
5. The therapeutic attitude?

The mere discovery of a protrusive colorectal formation is not enough; it is just the beginning of a process of development in order to define a correct and complete diagnosis.

The lesion association colorectal cancer - colorectal polyps, offers the most arguments in favor of the existence of a common genetic substratum of a continuity relationship between the adenomatous lesion and the patent neoplastic one.

The accumulated genetic, cell biology and IHC data in the polyp cancer-colorectal cancer relationship, allow now the deciphering of the mechanisms by which the alteration of the cell cycle is induced.

Under normal conditions, the proliferative zone of the glandular tubules, located basal proliferates and then migrates to the surface of the mucosa. The differentiation, maturation and subsequent desquamation occur simultaneously.

The impairments of any of the stages of this journey lead to the accumulation of glandular epithelium and its protrusion at the surface of the mucosa.

For the complete lesion orientation several parameters have been taken into discussion, each having a certain weight in determining the therapeutic attitude.

Taking into account the location, the predominance is observed at the rectum and descending colon level, especially the sigmoid one in relation to the locations at the ceco-ascending and transverse colon level, with heavy weight of

unique polyps compared to multiple ones. Data from the literature support that these locations are the most common and most at risk of malignancy.

For the macroscopic characterization of significant importance are the sizes and the presence or the absence of the pedicle.

It is known that the malignancy risk increases proportionally with the size of the polyp, while the absence or the presence of the pedicle, although it is not a risk criterion with absolute value, is but an indicative feature.

The definite evaluation criterion for these lesions was the histological one that had to answer to two questions:

1. the type of adenoma: villous, tubular, tubulo-villous;
2. the degree of epithelial dysplasia: mild, moderate, severe.

The histological study of these polyps showed a higher weight of the villous component and of the degree of dysplasia, as the polyp gets closer to cancer itself, element with high significance for the major risk of malignancy of these tumors.

Although consistent with the literature data, the degree of dysplasia increases with the share of villous component; in our study we had five cases of severe dysplasia right at the level of some tubular pedunculated polyps, which again supports the mandatory need to histologically define these lesions.

The conception that the adenomatous polyp represents a lesion with certainly malignant potential has raised great controversies and incited numerous epidemiological, clinical, biological, anatomopathological studies.

They turned to finding the causes that can generate both types of lesions, as well as the sequence of cellular events that demonstrate the filiation between the benign adenomatous lesion and the colorectal adenocarcinoma.

The arguments in favor of this relationship are many and widely accepted.

The classic data of pathology regarding adenomata have clearly showed the more common association of polyp - colorectal cancer concurrently with the increase of the villous component of the polyp.

Each of these diagnosed parameters has its share in the establishing of an appropriate therapeutic conduct so that the therapeutic indications are different depending on the anatomopathological shape, the number of polyps, malignant transformation and the degree of malignancy. The current therapeutic attitude is dominated by the endoscopic polypectomy indications with histopathology examination, in various technical options.

If for the pedunculated benign polyp, the endoscopic polypectomy is widely recognized as sufficient, for the voluminous, sessile and especially villous polyps, for which the oncologic security limits can not be met accurately, the surgical techniques themselves come into question, respectively the segmentation colic resections with variable extensions. The histological detecting of the patent malignancies foci requires the changing of the treatment attitudes and the situating of the patient in the appropriate protocol for the colorectal cancer, the therapeutic approach of the colorectal cancer being differentiated with respect to the anatomical location of the tumor and its extension.

Despite the technological advances made in the recent years on the endoscopic resection techniques, the surgical approach on open path remains a major option in certain cases.

Beyond the failures and limitations of the endoscopic method, the open surgery should be considered especially in the case of clear or just suspected neoplasia.

Some controversial issues on the recto-colon polyps without signs of malignancy are to be discussed.

The total colectomy and the attempt to preserve the rectum are of clear indication; it should keep in mind that on one hand that part of the polyps from the remaining rectum may be kept under observation and possibly endoscopically approached and eventually that after colectomy, sometimes the rectal polyps regress. This regression suggests that there is a colon factor that stimulates the development of the rectal polyps and that disappears after total colectomy.

The regression of polyps can be temporary, which requires indefinite supervision of those patients given the frequency of rectal cancer occurrence following total colectomy, no matter if after the colectomy the polyp regression occurred or not.

The detailed knowledge of each of these stages may open new therapeutic horizons by discovering ways to control one or more levels of the changed cell cycle.

Conclusions

As a corollary of this study, we must specify the following:

1. In terms of the screening modality, it is necessary to develop rigorous protocols allowing clearer framing of the patients in the risk groups.
2. The interventional endoscopy should be associated to the surgical procedures in case of resectional failure.
3. The determination of the APC, DCC, p53 molecular markers in properly equipped laboratories is essential for a correct appreciation of the pathological process.
4. The genetic testing should become accessible to all patients.
5. The IHC tests should be performed in all patients with colorectal cancer:
 - a) to define as proper as possible the form of cancer in order to establish a targeted and personalized cancer therapy;
 - b) to assess the area where the neoplasia appears;
 - c) to determine the risk of neoplasia recurrence on such area.

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