

Symptoms of colorectal cancer contributes to its localization and advancement

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A- Conception and study design; **B** - Collection of data; **C** - Data analysis; **D** - Writing the paper; **E**- Review article; **F** - Approval of the final version of the article; **G** - Other (please specify)

ABSTRACT

Introduction: Colorectal cancer is one of the most common cancers occurring in Poland. Unfortunately, this cancer is most often diagnosed at the time of great advancement. This is caused by the appearance of specific symptoms only in the late stages of cancer. Also, such low detection of early stages of adenocarcinoma may be caused by disregarding of slight symptoms.

Purpose: To analyse symptoms in patients with colorectal cancer and correlate with chosen clinical-pathological parameters.

Materials and methods: The study group consisted of 46 patients diagnosed with colorectal cancer. Information on symptoms associated with cancer (subjective and objective) have been selected from patients' medical history. The presence of these symptoms was correlated with the age and sex of patients, tumor location, histological type of cancer, grade of histological malignancy (G), stage of tumor

(T stage), presence of lymph node metastases and distant metastases.

Results: It has been shown that the presence of pain complaints described by the patient are associated with the occurrence of cancer in the colon. The painfulness and pathological resistance diagnosed by the physician are more often associated with cancer located in the colon. In the case of tumors located in the rectum, faecal admixtures appear more frequently. It has also been shown that the presence of admixtures of blood and mucus in the stool is associated with more advanced local tumors, infiltrating pericorectal tissues (T3 + T4).

Conclusions: Familiarity with clinical symptoms of colorectal cancer could make patients more sensitive to more often screening for cancer. Analysis of these symptoms could indicate to the physician the location or stage of the cancer.

Keywords: Cancer localization, colorectal cancer, symptoms

DOI

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Received: 19.02.2019

Accepted: 27.03.2019

Progress in Health Sciences

Vol. 9(1) 2019 pp 76-82

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INTRODUCTION

Colorectal cancer (CRC) is a disease with constantly increasing frequency. In 2018 CRC was the third most common cancer in the world and the second cause of death due to cancer. In the same year, about 1.8 million people have been diagnosed with this disease and approximately 860 000 have died. A high percentage of cases is observed in the developing countries of Central and Eastern Europe, Asia and South America. In turn, in countries with very high development rates (Western Europe, North America, Australia) the number of new cases is stabilizing. Colorectal cancer is more common in people over age 50, and more often in men. This cancer has a poor prognosis, the average 5-year survival is about 65% in highly developed countries and less than 50% in less developed countries [1-5].

Group of the most important factors which are responsible for development of colorectal cancer include: age (> 50 years), male gender, family history, obesity, low physical activity and sedentary lifestyle, diabetes and a high amount of red meat in the diet. In addition, existing inflammatory bowel diseases may contribute to the development of cancer [6,7]. What is more, genetic predispositions play a significant role in development of CRC. Increased incidence of colorectal cancer is observed in patients with familial adenomatous polyposis (FAP) and hereditary non-polyposis colorectal cancer (HNPCC). They are responsible for about 5% of all CRC cases [8,9].

During the development of colorectal cancer, numerous mutations of genes accumulate: *APC*, *TP53*, *DCC*, *K-RAS*. However, there are differences that include gene defects and the mechanism for the accumulation of mutations. Therefore, there are two separate ways of developing colorectal cancer: one is the adenoma-cancer sequence and the other is associated with mutator gene disorders [10]. The gold standard in colorectal cancer diagnosis is colonoscopy and sigmoidoscopy. They are characterized by very high sensitivity. Recent reports indicate that screening studies conducted using these methods have reduced the morbidity and mortality rate by approximately 70% in the case of colonoscopy and 50% in the case of sigmoidoscopy. In addition, the following are used in the diagnosis: guaiac-based fecal occult blood test (gFOBT) and fecal immunochemical tests (FIT) for human haemoglobin in stool. However, they are characterized by lower sensitivity [1,11-14].

The aim of this study was to present characteristic clinical symptoms in patients with colorectal cancer, associated with local tumor spread and analysis of the relationship between symptoms and selected clinicopathological parameters, such as: age and sex of patient, location, histopathological type of cancer, grade of malignancy, local

infiltration (T stage), metastasis to lymph nodes as well as distant metastases.

MATERIALS AND METHODS

Study group

The study involved 46 patients treated surgically due to colorectal cancer in the 2nd Clinical Department of General and Gastroenterological Surgery at the University Hospital in Białystok, in the years 2005–2010. The study group consisted of 28 men and 18 women. Mean age of study group was 68.8, 10 patients were ≤60, and 36 >60 years old. Symptoms associated with cancer have been selected from the patient's medical history. The subjective symptoms, described by the patient included: pain complaints, characteristic and localization of pain and the characteristic of bowel movements and stool. In addition, objective symptoms founded in a physical examination carried out by a doctor (pain and pathological resistance) have been described. Pain complaints symptoms have been described as absent or present. The pain characteristic was divided into dull and acute as well as continuous and intermittent. The pain localization were found in the epigastric, umbilical or/and hypogastric region. The stool description includes its consistency (watery, mushy or formed), the color (yellow, light brown, brown, dark brown and black), the frequency of defecation (<1/day, 1/day, 2/day, ≥3/day), the presence of admixtures and their type (blood, mucus and mixed). Painfulness and pathological resistance were classified as absent or present. In accordance with the GCPs (Guidelines for Good Clinical Practice), this research was approved by the Bioethical Commission of the Medical University of Białystok (R-I-002/83/202).

Histopathological examination

Each tumor was cut along a line that was parallel to the longest tumor axis. In this way 4 to 8 slices contained the cancer and also adjacent macroscopically unchanged tissues of 1-1.5cm in size was taken for histopathological assessment. Tissues were fixed in 10% buffered formalin within 24 to 48 hours.

The specimens were embedded in paraffin at a temperature of 56°C. Paraffin blocks were cut into 4µm thick sections.

The obtained sections were stained with hematoxylin-eosin (H+E staining).

In the H+E stained sections the parameters as histological type (Hp), grade of histological malignancy (G), clinical-anatomical advancement (pTN) have been evaluated.

Statistical analysis

For statistic evaluation STATISTICA 13.3 software (Statsoft, Cracow, Poland) was used.

Correlations between colorectal cancer symptoms (pain complaints, pain character, pain localization, stool consistency, colour of stool, frequency of defecation, presence admixtures, type of admixture, painfulness and pathological resistance) and chosen clinicopathological parameters (age and sex of patients, tumor location, histological type of cancer, grade of histological malignancy (G), stage of tumor (T stage), presence of lymph node metastases and distant metastases) were tested with the use of Pearson’s correlation test. A *p* value of <0.05 was considered statistically significant. Missing data were removed in pairs.

RESULTS

Clinical symptoms

The pain complaints reported by patients occurred in 65.21% of patients with colorectal cancer.

Most often the pain was dull and intermittent. Mainly pain was localized in the hypogastric region (58.33% of patients), less frequently in the epigastric region (20.84% of patients) and umbilical region (16.66% of the patients).

The most common consistency of stool was formed type (62.22%), less frequent was mushy (33.33%) and watery (4.45%). The predominant colour of the stool was brown (57.77% of patients) and dark brown (24.44% of patients).

Admixtures in the stool were observed in 48.88% of patients, and the most common of them was blood. Painfulness reported by a physician on physical examination were present in 55.55% of patients and pathological resistance described in only 13.63% of the patients with colorectal cancer (Table 1).

Table 1. Characteristic of clinical symptoms in colorectal cancer patients

Symptoms		No. of cases
Pain complaints	Absent	16 (34.78%)
	Present	30 (65.22%)
Pain characteristic	Dull	22 (75.86%)
	Acute	7 (24.14%)
	Continuous	7 (26.92%)
	Intermittent	19 (73.08%)
Pain localization	Epigastric	5 (20.84%)
	Umbilical	4 (16.66%)
	Hypogastric	14 (58.34%)
	All localizations	1 (4.16%)
Stool consistency	Watery	2 (4.45%)
	Mushy	15 (33.33%)
	Formed	28 (62.22%)
Colour of stool	Yellow	2 (4.44%)
	Light Brown	5 (11.11%)
	Brown	26 (57.77%)
	Dark brown	11 (24.44%)
	Black	1 (2.22%)
Frequency of defecation	<1/day	8 (17.77%)
	1/day	23 (51.12%)
	2/day	1 (2.23%)
	≥3/day	13 (28.88%)
Admixtures	Absent	23 (51.12%)
	Present	22 (48.88%)
Type of admixture	Absent	23 (51.12%)
	Blood	14 (31.11%)
	Mucus	2 (4.44%)
	Blood+mucus	6 (13.33%)
Painfulness	Absent	20 (44.45%)
	Present	25 (55.55%)
Pathological resistance	Absent	38 (86.36%)
	Present	6 (13.63%)

Correlations between clinical symptoms and clinicopathological parameters.

There were no statistically significant correlations between clinical symptoms and age and sex of patients, histological type, grade of histological malignancy (G), lymph node and distant metastases. Data not shown.

However, statistically significant correlations between symptoms and tumor localiza-

tion have been observed. Admixtures in the stool were more frequent in tumors located in the rectum ($p=0.024$), while pain, painfulness and pathological resistance were more frequently observed in tumors located in the colon ($p=0.014$, $p=0.026$ and $p=0.04$ respectively) (Table 2). Correlations with other symptoms were not statistically significant.

Table 2. Correlation between clinical symptoms and tumor localization

Symptoms		Localization of tumor		p
		Colon	Rectum	
Pain complaints	Absent	6 (22.22%)	9 (60.00%)	0.014
	Present	21 (77.78%)	6 (40.00%)	
Admixtures	Absent	17 (62.96%)	4 (26.67%)	0.024
	Present	10 (37.04%)	11 (73.33%)	
Painfulness	Absent	8 (30.77%)	10 (66.67%)	0.026
	Present	18 (69.23%)	5 (33.33%)	
Pathological resistance	Absent	19 (76.00%)	15 (100.00%)	0.040
	Present	6 (24.00%)	0 (0.00%)	

Statistical analysis revealed relationship between clinical symptoms and T stage. Admixtures in the stool were more common in patients with less advanced tumors (T1+T2) compared to more advanced tumors (T3+T4) ($p=0.032$). In patients with less advanced tumors more often occurred a mucus or mixed (blood and mucus) admixture in the

stool. On the other hand, patients with more advanced cancer had rather blood admixture ($p<0.001$) (Table 3). It has not been shown statistically significant relationship with other clinical symptoms.

Table 3. Correlation between clinical symptoms and tumor advancement

Symptoms		T stage		p
		T1 + T2	T3 + T4	
Admixtures	Absent	0 (0.00%)	13 (100.00%)	0.032
	Present	5 (38.46%)	8 (61.54%)	
Type of admixture	Absent	0 (0.00%)	13 (100.00%)	<0.001
	Blood	1 (12.50%)	7 (87.50%)	
	Mucus	2 (100.00%)	0 (0.00%)	
	Blood+mucus	2 (66.67%)	1 (33.33%)	

DISCUSSION

Studies on the characteristic symptoms of colorectal cancer are still being described in the literature. This is to sensitize medical staff about the symptoms reported by patients. The purpose of these efforts is also to educate physicians about the importance of accurate physical and subjective examinations in patients reporting symptoms described in the literature. In addition, the aim of these studies is to make patients aware of not underestimating even discrete and less vexing symptoms, as this increases the probability of detecting the cancer on the early stages of its

development [15]. Some studies suggest that symptoms lasting for 3 months or longer, indicate a high probability of diagnosing colorectal cancer at an advanced stage [16-18]. Other studies show no relationship between the duration of symptoms and advancement of the disease at the time of diagnosis [19-21]. The most common symptoms occurring in patients with colorectal cancer and described in the literature are: rectal bleeding, abdominal pain and palpable tumor [22-24]. Our research also indicates frequent pain (present in 65.21% of patients). In our study, we have also observed admixture of blood in the stool in about 50% of patients, which is similar with the reports of other authors.

While there are reports in the literature about the relationship between pain and the age of patients, the above studies did not show a statistically significant relationship between them. However, Banaszkiwicz et al. [22], concluded that rectal bleeding, anemia and significant weight loss are statistically more frequent in older people, whereas symptoms as a rectal bleeding and anemia occur less often in people before the age of 50. Additionally every third person lost weight. Also, Astin et al. [25] have shown that rectal bleeding has prognostic value in people over 50 years old.

We also analyzed the association of symptoms of colorectal cancer with the gender of patients. According to our results, clinical symptoms did not depend on this parameter. Banaszkiwicz et al. [22] also examined the relationship of symptoms in patients with colorectal cancer with gender, however, their results also did not confirm this relationship. In turn, Hailton et al. [26] showed that rectal bleeding occurs more frequently in men over 80 years, whereas this symptom has a low predictive value in women and younger people.

We also examined the association of colorectal cancer symptoms with its localization. The results indicate that the pain reported by patients, pain occurring during physical examination and the presence of pathological resistance are more often associated with the cancer location in colon, but not in rectal. In the case of tumors located in the rectum, admixtures (blood, mucus or mixed) appear more frequently in the stool. Synnestvedt et al. [27] observed that the presence of blood in the stool and changes in stool consistency are specific for cancers located in the rectum as well as in the left side of the colon. Similar results were obtained by Saidi et al. [28]. In their studies, they noticed that the incidence of rectal bleeding depends on the location of the tumor. In patients with rectal tumors, bleeding was noted four times more often (79% of patients) compared to patients with right colon cancer (21%) and two times more often than in patients with left colon cancer (44%). Banaszkiwicz et al. [22] showed that pain in patients with colorectal cancer was more common in right-sided lesion. The same authors [22] also described that constipation was more common in patients with rectal and left colon tumors, and diarrhea most frequently occurred in patients with rectal cancer. In addition, other studies showed that right-sided colorectal cancer is more often associated with the occurrence of anemia [29, 30].

We also analyzed clinical symptoms in correlation with the histological type and the degree of histological differentiation of colorectal cancer. Statistical analysis did not show any correlations. There are also no literature reports in which the above parameters were analyzed.

In addition, in our study we analyzed the relationship between the depth of primary tumor

infiltration (T) with the clinical symptoms of colorectal cancer. The results showed that the presence of admixtures and the presence of blood is associated with more advanced tumors (T3 + T4). Also, Banaszkiwicz et al [22] in their studies showed a significant relationship between the stage of the cancer and symptoms as abdominal pain, bloating, diarrhea, weight loss and obstruction. They found that abdominal pain was more frequent in patients with advanced colorectal cancer. They also showed that weight loss and diarrhea was associated with advancement of cancer. However, Nowaczyk et al. [31] did not show statistically significant relationships between abdominal pain or blood in the stool and the stage of cancer, but showed that loss of appetite is more common in patients with a more advanced cancers. Different results were obtained by Stapley et al. [32]. Their research proved that rectal bleeding indicates a less advanced cancer. In addition, Kiran et al. [33] showed that the length of symptoms is not related to cancer advancement. We also examined the association of clinical symptoms of colorectal cancer with metastases to local lymph nodes as well as distant metastases. However, the results of the analysis did not show a statistically significant relationship. There are also no literature data describing these correlations. This may indicate the existence of a relationship between clinical symptoms and local advancement of tumor but not with distant metastases. Therefore, more important are screening tests that enable the detection of cancer at an early stage than analysis of colorectal cancer symptoms.

CONCLUSIONS

It is necessary to constantly develop knowledge about the processes occurring during carcinogenesis. The literature presents many possible symptoms that accompany the development of colorectal cancer. Some of them may be associated with specific features of these disease like localization and tumor advancement. It is important to have a knowledge about colorectal cancer symptoms, because their identification can start further diagnostics.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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