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ORIGINAL PAPER

Sensitivity of Symptomatology Versus Diagnostic Procedures and Concentration of CEA and CA19-9 in the Early Detection of Colorectal Cancer

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ABSTRACT

Introduction: Colorectal cancer is the major diagnostic and therapeutic problem. The number of patients in the world has increased recently. In our country it is detected late and patients visit doctor in the advanced stage of the disease with already developed metastases. **Material and methods:** A clinical study was conducted at the Clinic of gastroenterohepatologists, Clinical Center of Sarajevo University on 164 patients. Special attention was given to the symptoms, which are considered to be a macroscopically visible as bleeding, anemia pain, weight loss and disturbance of defecation. Smoking had no effect because a small number of observed patients smoked. Endoscopic examination revealed localization of the tumor in the colon and then underwent targeted biopsy, histological analysis by pathologist, and we determined the concentration of CEA and CA19-9 in the serum. **Results:** In order to get the most relevant results we used larger data set. The program used to prepare the data was Microsoft Excel 2013, and for the creation of decision trees is a used software RapidMiner version 5. Our research has shown that patients older than 55 years with significant stenosis, metastasis and diarrhea that lasted longer than 3.5 months and bleeding that lasted up to 10 months had cancer of the rectum. Bleeding that lasts longer than 10 months indicated that it was the case of cancer that was localized in the rectum in men and sigma in women. Patients older than 82.5 years and had diarrhea up to 3.5 months developed cancer in the sigma part of the colon. Analyzing pain as a symptom of an alarm, the study found that pain that lasts longer than a few days, is caused by rectal cancer, and occurs after the age of 70.5 years, and in patients younger than 63 years anemia as a alarm symptom, which lasted more than two months in men was caused by cancer of the rectum and in women cancer in other localizations within colon. In patients without stenosis developed bleeding as the most important symptom. We can say that after the age of 74 years cancer of the rectum and sigmoid is more common in men and in women dominate sigma and other locations in the colon. In patients under the 70 years of age with short time of bleeding, cancer predominates in rectum. In patients younger than 63 years can be concluded that weight loss is greater than 8 kg follows rectal cancer. In patients with bleeding that lasted one month or more as classifier occurring the age and gender. Patients younger than 74 years have rectal cancer, while older than 73 years have cancer at other sites. In women these locations are sigma and rectum. **Conclusion:** Based on this study we can conclude that regardless of the technical advances in medicine must pay special attention to the symptoms that doctors will refer to the localization of the tumor, stenosis of the intestine and possibly metastasis. **Key words:** Colorectal cancer, diagnostic procedures, concentration of CEA and CA19-9.

1. INTRODUCTION

Colorectal cancer is still one of the most common, human tumors in the population. Regardless of the technical advances in medicine, in our country diagnosis is late in the first contact with the doctor, patients have widespread disease with obvious penetration through all the layers of the wall, into the surrounding adipose tissue, lymph nodes, adjacent organs and distant metastases. According to gender there are more men 2:1, and the cancer is more common in area of the rectum in relation to the other sites. By exploring colon cancer in our study we noticed that

the bleeding is a common symptom that could last up to two years, and that patients did not report to the doctor. Mostly occurred in case of developed stenosis of the affected bowel malignancy, where the disorder of defecation dominate the clinical picture. Medical staging showed that patients come late to a doctor because they were numerous metastases and survival time was short. Our research has shown that the population which was affected, in many cases involves retired persons. Unfortunately in this population among retired people we have university-educated patients and we realized that regardless of the

level of education, patients conceal problem. Whether they learn to live with them, whether they are scared or they are ashamed to admit that they are sick it is a big question on which we don't have an answer yet. Is it the question shame or fear of the disease is still unclear, but when they come, with tumor penetrating into the surrounding tissue, or lymph nodes, with metastases evident in close or distant organs, then it is already too late and the prognosis is extremely poor for the patient. It is important to note that our clinic has complete endoscopic equipment for early diagnosis with experienced endoscopists, excellent pathology and appropriate laboratory for radiology diagnostics. Biochemical laboratory is always available and adequately meets our needs.

2. MATERIAL AND METHODS

The study was a prospective-retrospective and conducted at the Clinic of Gastroenterohepatology, Clinical Center of Sarajevo University. The research covered the period since 2010 until 2013. We followed patients who were hospitalized at the Clinic due to the staging or due to hematochezia, as well as irregular defecation.

In all cases by colonoscopy was visualized tumor infiltration and localized the tumor site. All patients underwent targeted biopsy and histopathological findings confirmed the macroscopic, clinical diagnosis. Histopathological analysis of biopsy samples that are placed in formalin, cut and stained, was done at the Institute of Pathology, Clinical Center of Sarajevo University. All patients underwent CT of the abdomen and pelvic MRI depending on the cancer localization. In all patients, we determined the serum levels of CEA, CA 19-9 and AFP.

During endoscopy, we verified and noted eventual stenosis, caused by malignant infiltration and recorded its localization. From the majority of the patients during anamnesis taking we get information about smoking and alcohol consumption. In anamnesis we get the data on the occurrence and duration of pain, the stool, the form of the stool, the number of defecations, bleeding, duration of bleeding, weight loss and false calls for defecation. In all patients who had anemia, was noted the period of the phenomena, or the duration of the anemia.

The patients have been divided by gender, by age, according to the localization of the tumor, according to the presence of stenosis and the site of stenosis, the values of tumor markers CEA, CA 19-9, AFP, according to the spreading of the disease in the surrounding organs and distant metastases, enlarged lymph nodes, surrounding adipose tissue. We also divided the patients according to the characteristics of defecation and the number of stools, possible diarrhea or constipation, bleeding (hematochezia), anemia and loss of body weight.

3. RESEARCH GOALS

Driven with a difficult and neglected disease and

patients who come with metastases in the first contact with a gastroenterologist, we decided to set up the following goals of the research:

The goal of our study was that with a good history and physical examination of the patient at the first contact record symptoms and the length of their duration.

By analysis of the symptoms, their occurrence and duration to try to prove that on the basis of them can be confirmed the clinical suspicion of malignancy and the possible presence of metastases.

Make correlation of symptoms with diagnostic tools at our disposal such as: abdominal CT, MRI of the rectum, CEA, CA 19-9, colonoscopy, targeted biopsy, histological analysis of biopsy samples.

4. RESULTS AND DISCUSSION

The study included 164 patients who were treated at the Clinic for Gastroenterohepatology during period 2011-2013, suffering from colon cancer. These were the patients who for the first time contacted the counseling center of the Clinic with complaints of various duration. Mostly already had developed metastases and complications in terms of stenosis as well as the penetration of the tumor into the lymph nodes and surrounding organs. (Figure 2,3).

In order that process statistically the obtained results we have used the following methods and used are the following statistical tools.

The tool used to prepare the data was Microsoft Excel 2013, while for creating a decision tree we used RapidMiner software versions 5. RapidMiner is a flexible Java environment for knowledge discovery in databases, machine learning and text data mining. It is a modern system for data mining, which is characterized by high quality user interface.

Tool, RapidMiner 5 on the basis of the algorithm "ID3" generated a decision tree based on prepared data that are presented in Chapter X. In order to get results as relevant as possible we used the larger data set, and consequently, the tool generated a decision tree that has a significantly more nodes as shown in Figure 1.

Analysis of the decision tree revealed the following:

Present stenosis and older than 55 years

For patients in which are identified **metastasis** is true that if the **diarrhea** lasts for more than 3.5 months, most likely the cancer will be localized in the rectum as well as in patients in which, regardless of sex, **bleeding** lasted up to 10 months.

For those in whom **bleeding** lasted for more than 10 months, an important classifier is **gender**, as in men more frequent is the localization in the **rectum**, and in women in **sigma**.

If the diarrhea **lasted for up to 3.5 months**, then the patients, who have more than 82.5 years, had the cancer which is usually localized in the **sigmoid colon**.

For other patients is true that, if the **pain lasted more than a few days**, then they are older than 70.5

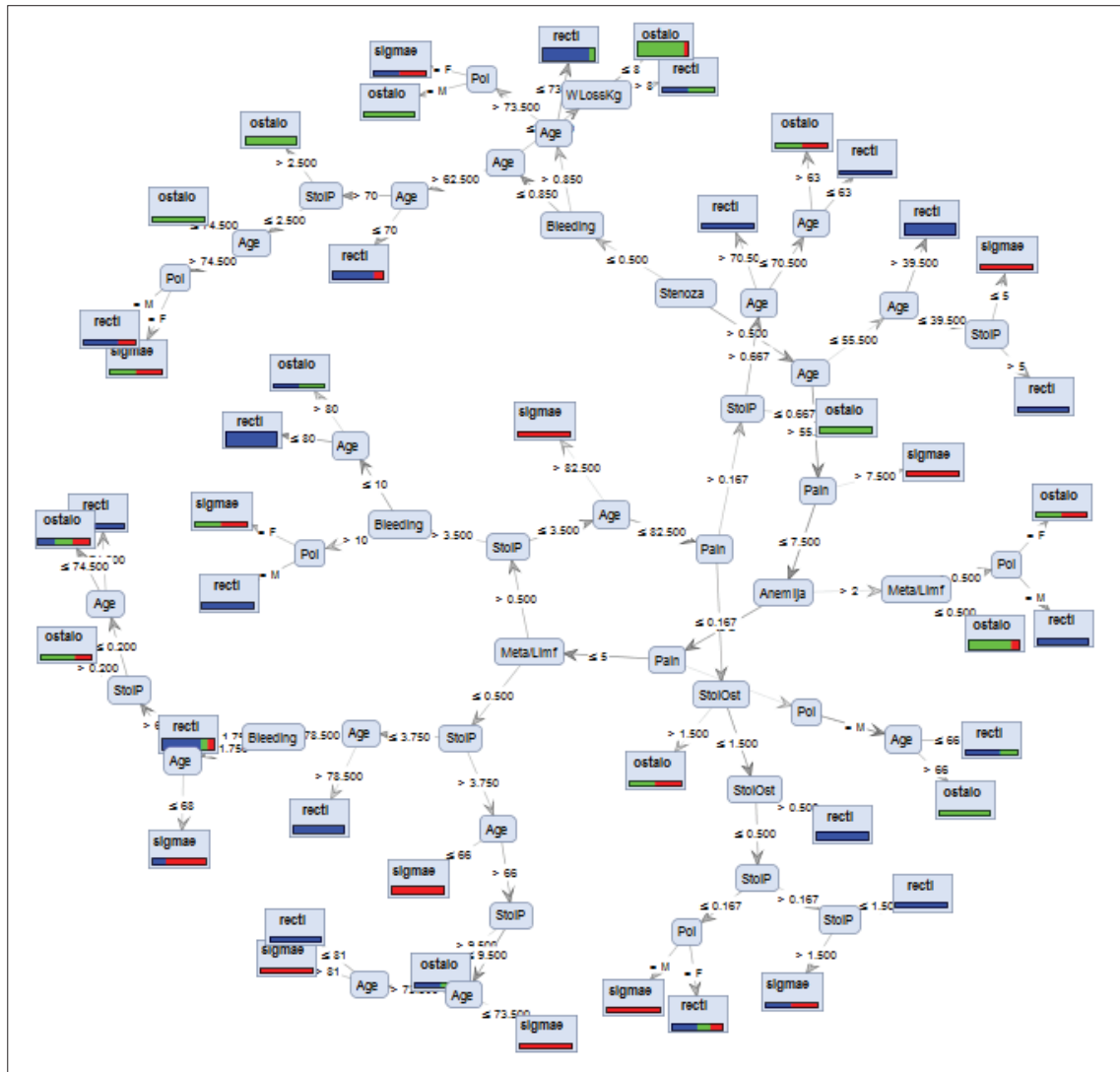


Figure 1. Algorithm in detecting of colorectal cancer in our research

years and had **rectal cancer** as well as **younger than 63 years**.

For those who have **other defecation problems, with duration of more than half a month**, it is very likely that the **cancer is localized in the rectum**.

But if problems persist for less than half a month, then re-emerge as a classifier in form of diarrhea and gender. If the **diarrhea lasted up to 1.5 months**, according to the classification the **cancer is in rectum**, and among **men in this case with a brief diarrhea, prevalent localization is sigma**.

If **anemia lasted for more than two months**, then **in case of identified metastasis, cancer localization divided into the rectum for men, and other localizations for female patients**, whereas in patients with no evidence of metastasis prevalent localization is at other places.

For shorter anemia and pain lasting longer than five months, there are only male patients, and older than 66 years have preference of cancer in other parts of the colon.

In patients who are older than 55 years and where the pain lasted longer than 7.5 months, the localization is sigma.

For patients who have **stenosis** but are younger than 55 years is true that, if they are younger than 40 years, and diarrhea lasted more than five months, cancer is localized in the rectum, as well as in patients who are older than 39 years. Younger patients with diarrhea with duration of less than five months have the localization of the tumor in the region of sigma.

Patients who had stenosis showed the following:

In these patients, the most important classifier is the duration of bleeding. If there was no bleeding or it lasted less than one month, patients older than 70 years and with diarrhea which lasted longer than 2.5 months have localization in other parts of the colon, as well as patients with diarrhea with duration of less than 2.5 months and younger than 75 years. For those older than 74 years as a classifier occurs gender, in manner that among women dominate sigma and other parts of the colon, and in men rectum and sigma.

Patients younger than 70 years, with a short period of bleeding or without bleeding, in these cases dominate rectal cancer, regardless of other classifiers.

For patients who are younger than 63 years, an indicator of weight loss may be associated with location

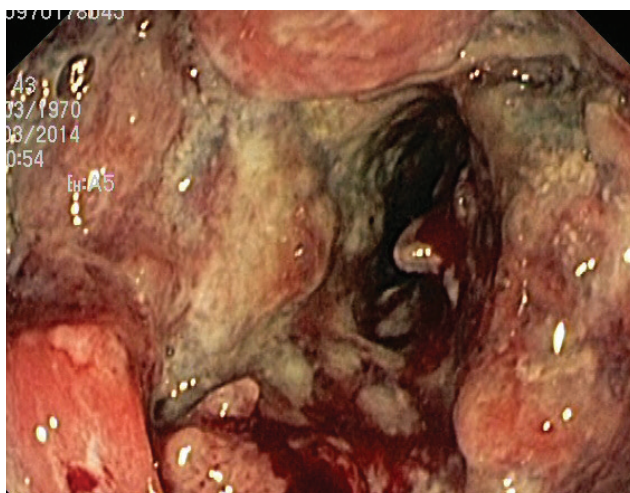


Figure 2. Colonoscopic cancer examination



Figure 3. Colonoscopic cancer examination

of cancer, in a way that, if the weight loss is less than or equal to 8 kg prevalent localization are other parts of the colon, while if the weight loss is greater than 8 kg prevalent localization is rectal cancer.

In a patient in whom the bleeding lasted a month or more, as a classifier occur age and sex. Patients younger than 74 years have cancer localization predominantly in the rectum with little tumor changes in other parts of the colon, whereas in patients older than 73 years, in men cancer have a preference for other parts of the colon, and women in the area of sigma and rectum.

During this study, we wanted to compare our results with the results of other researchers, but in the available databases we did not find similarly designed study.

Noriko Nishigo and associates in 2012 published the research on the presence of stenosis and bleeding and malignant processes in the colonic diverticulosis. They found several cases of stenosis in the elderly over 70 years of age. In one female patient they had found a circular stenosis with developed cancer in the area of colonic diverticulosis (1).

Furikawa H. and associates published their work 2013, submucous invasive colorectal cancer with multiple changes in the liver and lymphoid infiltration (2).

Basar N. with colleagues published metastatic lung cancer with colon cancer.

Our research shows that the most frequent metastases are in nearby lymph nodes, liver, rarely in the lungs. We also found metastatic changes in the spleen and prostate, as well as neighboring organs such as the urinary bladder, liver and uterus (3). We found liver metastases in 63 patients and in the lungs in 9 cases. Lymph nodes invasion had 51 patients. Infiltration through all the layers of the wall into the adipose tissue had 42 patients. Fascia was affected in 18 patients with adenocarcinoma of the rectum. Meta changes we found in the spleen in 2 patients, uterus in 3 patients, urinary bladder in 3 patients, the prostate in one and the peritoneum was affected in 5 patients.

Iwata T. and associates presented the patient in hemorrhagic shock that has bleeding from the cancer in the ascending part of the colon. The symptom was hematochezia to which the patient was not paying attention. Cancer invaded the small intestine and the large blood vessels of the abdomen. The values of CEA and CA19-9 were negative, or they were in the reference range (4).

In our research, we had a large number of retired persons and it turned out that a large number of these patients had a different duration of bleeding. It remains an open question why patients do not came in due time with the macroscopically visible bleeding and anemia of long duration. We must conclude that patients are not adequately treated by the family medicine doctor or at the counseling with hematologist was not ask for the reason of anemia. Our research has shown that 75 patients had fresh blood in the feces. Anemia was present in 13 patients, and from that number, 8 patients had anemia for one year or longer (2 years).

Kruschewski M. et al. have investigated over 1000 colon cancers. More than 64% were rectal cancers and only the rest at the other parts of the colon. In correlation with the results of our research we have found that the rectal cancer was present in 45% of patients, 44 men and 28 women (5).

Edna TH. and associates investigated the prevalence of anemia in colon cancer, and her goal was to link the prevalence of anemia with tumor localization. Anemia was found in 74.7% of patients with carcinoma of the cecum and the ascending colon. Anemia had also 57.1% of patients with colon transverse cancer, 40.0% with carcinoma of the sigma and 30.5% of patients with rectal cancer. The conclusion was that the increasing number of patients with cancer localized at the proximal part of the colon had anemia (6).

Our study showed that anemia was present in 4 cases of 11 with adenocarcinoma of the ascending colon. Cecum cancer was found in 6 patients.

Cancer of the rectostigmoid part was recorded in 13 patients, 9 men and 4 women. Anemia was recorded

in one case. Cancer in the region of sigma had 37 patients, and equal number of men and women, while in 3 patients also anemia was present. Cancer of the descendent colon was recorded in 13 patients, one patient at lineal flexure, colon transverse in 5 patients, one had anemia, hepatic flexure in 5 patients, 3 patients had anemia. Cancer of the rectum had 72 patients, of that number, only two had anemia.

When it comes to stenosis, we found it in 121 patients, from which in 98 patients with rectal cancer, rectostigmoid transition and sigma.

We noticed that high CEA and CA19-9 values were present in patients with advanced colon cancer and already present metastases. Unlike Nahatoni A. et al. who described an elevated concentration of antigen CA19-9 in patients with sigmoid cancer without metastases (7).

Decision trees are very powerful and popular modeling techniques for classification and prediction problems. They are actually a classification algorithm in the form of tree structure in which the two types of nodes are connected with branches (8).

To build decision tree most often is used CART algorithm, which based on available data on input and output variables creates a binary tree branching records in each node by a specific function for each input variable. Evaluation function used to fracture the Gini index (IG) (8), is defined by the formula:

$$I_g(t) = 1 - \sum_{i=1}^m p_i^2$$

where "t" is the current node, "pi" is the probability of class and node "t", and "m" is the number of classes in the model. CART algorithm takes into account all the possible ramifications to find the best ramifications for the accuracy of the model. Top branching is determined for each attribute in each node, and the winner is chosen by the Gini index (9). The algorithm presented in Figure 1 works successfully with continuous and categorical variables (10).

5. CONCLUSION

Our research has shown that most of the stenosis was located in the left hemicolon and in its distal part. These are the patients of older age with diarrhea lasting longer than 3.5 months and bleeding that lasted longer than 10 months. These are the patients who at the first arrival to the hospital already had developed metastases. Patients who have had weight loss greater than 8 kg usually had cancer of the rectum. In patients with a longer time period of macroscopically evident bleeding, we recorded cancer of

the rectum in men, and in sigma part in women. At the end we can say that the symptom is important in the diagnosis and localization of tumors but it still remains a mystery why so many patients so late reported to a doctor.

CONFLICT OF INTEREST: NONE DECLARED

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