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The influence of some tumor characteristics on the long-term survival of proximal colorectal cancer patients

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Abstract

The article is devoted to the study of survival in colorectal cancer and the influence of some common clinical factors on the life expectancy. Colorectal cancer (CRC) is an urgent problem of today and modern oncology, as the incidence of CRC is constantly increasing. It is believed that the development of CRC in 50% of all cases is related to lifestyle and long-term exposure to carcinogens. Genetic factors play a decisive role in 5 to 20% of cases. It has been established that from 20 to 50% of patients with CRC already have distant metastases at the initial presentation. The understanding of the biology of colon cancer is based on the analysis of the degree of aggressiveness of its course, patient survival, the effect of performed operative and combined treatment methods on the course of the disease, and the presence of some other factors that are not yet completely understood by clinicians (the influence of hidden metastasis, circulating cancer cells, genetic causes, etc.). Proximal colon tumors are tumors that located in the cecum, ascending, and hepatic flexure of the colon, that is, in fact, tumors of the right half of the colon. The more proximally the tumor was located in the right half of the colon, the longer the patients lived. At a follow-up period of 24 months, the

duration of follow-up for patients with cecum, ascending colon, and hepatic angle tumors was 71.43%, 63.64%, and 72.73%, respectively. For the observation period of 32 months: 42.86%, 36.36%, 18.18%. For the observation period of 55 months: 14.29%, 9.09%, 0%, respectively. Thus, biology was the key factor, as the groups were equivalent in terms of stage, frequency of lymph node involvement, and degree of tumor differentiation. Therefore, from our point of view, the separation of right-sided RTK, r-RTK into a apparant nosoform has a clinically significant character: it is in the right half of the colon that the toxicoanemic form occurs more often; and less often (almost never) – obturation, much more characteristic of left-sided cancer, l-RTK. Typically, right-sided colon tumors have the following genomic context: MLH1 hypermethylation, BRAF mutation, and high-grade MSI, while left-sided colon tumors are p53 and KRAS mutant.

Key words: proximal colorectal cancer; surgical treatment; overall survival; Kaplan-Meier method; clinical and morphological characteristics of the tumor; genome.

Introduction. According to the American Society of Clinical Oncology (ASCO) and the European Society of Medical Oncology (ESMO), the term CRC includes colon and rectal cancer. CRC is a very common disease among oncology patients and is the 3rd most common malignancy in men and the 2nd most common in women. According to the literature, there are more than 3.5 million patients with colon cancer in the world, who were discovered in recent years, and up to 1 million new cases of cancer of this localization are diagnosed annually. The incidence rate of CRC is higher in industrialized, developed countries and is constantly increasing. The incidence of CRC in Ukraine is 41 per 100,000, in absolute numbers, it is almost 19,000 new cases every year, while the annual increase in the regions is 3-4%. According to the National Cancer Registry of Ukraine, CRC ranks third in the structure of mortality from malignant neoplasms. In Ukraine, the incidence has increased by more than 30% over the past 10 years.

CRC in the early stages is usually asymptomatic or mildly symptomatic, which is why the first manifestations of the disease are often symptoms of complications (signs of obstructive intestinal obstruction, bleeding or perforation due to tumor necrosis, tumor invasion into other organs, infectious-inflammatory paracancerous processes, etc.). Up to 70% or more of patients come to the hospital in the late stages of the disease. Despite the fact that the majority of patients with CRC are over 50 years old, there is information that the frequency of this disease in young patients is increasing. According to the literature (according to Regio B., Bussey H.J.R. "The pathology and prognosis of carcinoma of the

rectum in the young"), at a young age, CRC proceeds more adversely and aggressively, the percentage of involvement of lymph nodes in the pathological process and the percentage of complicated cases increases CRC (with tumor necrosis, perforation, etc.) The patient's age is a secondary prognostic factor [3]. According to the literature, women have a better prognosis than men [4].

As is known, the life expectancy of patients with CRC is most closely related to the stage of the disease. According to ASCO (2017), in the United States of America, patients with CRC at stages I and II have a five-year survival rate of up to 90%, at stage III - up to 70%, and at IV - up to 13%. Important prognostic indicators in patients with cancer are recurrence-free and overall survival. Survival analysis (analysis of the occurrence of events) is a method by which, during a certain period of time, patterns of occurrence of a certain result in representatives of a certain sample are studied. At the same time, the researcher is interested in survival (measured in fractions of a unit or in percentages) and the time period before the occurrence of the event being studied.

There is a certain genetic and protein heterogeneity in colon tumors of different localization. In particular, this applies to the main genes included in the so-called "vogelgram", a set (the term was taken from the card terminology, "full house"), which constitute the carcinogenesis of colon cancer of molecular genetic breakdowns against the background of chromosomal and genomic instability that develops in CRC [7]. The term denoting the set of genes characteristic of colon cancer was described as "Vogelgram" by Fearon and Vogelstein in 1990 and became classic, along with the "Correa cascade" for gastric cancer or such persistent terminology as "triple negative" breast cancer, " Napoleon's cancer" or "Angelina Jolie's cancer". The fogelgram includes such widely known genes as p53, APC, BRAF, KRAS, hypermethylation of MLH1 and some others. Although, for the sake of fairness, not all of them are directly relevant for the carcinogenesis of CRC. It is also necessary to further clarify, some of these genes are more characteristic of cancer of the left half of the colon, and some - for the right.

Purpose. The purpose of this study is to analyze the correlation of the overall survival rates of patients with CRC depending on the age and sex characteristics of the body, the main macroscopic characteristics of the tumor (intestinal section, tumor volume, stage of the disease).

Materials and methods. The study was conducted on the basis of the Odesa Regional Clinical Antitumor Center of the OOR, it is single-center and retrospective. Forty-five patients (21 men and 24 women) with verified colon cancer who underwent surgery between

2017 and 2020 were included. The average age of the patients was 69.3 years. Patients were divided by age as follows: 1) up to 60 years (inclusive) – 14 patients; 2) after 60 years – 31 patients. According to the macroscopic characteristics of the tumor, the patients were divided as follows: 1) localization of the tumor (caecum - 9, ascending part of the colon - 19, hepatic flexure and proximal third of the colon - 17); 2) tumor volume (up to 50 cubic cm - 18, from 50 to 100 cubic cm - 15, from 100 cubic cm - 12); 3) stage of the disease (1 stage – 1, 2A stage – 22, 2B stage – 11, 3B stage – 11). The main criteria for inclusion in the study were: 1) localization of the tumor - cecum, ascending part of the colon, proximal third of the colon; 2) pathohistologically confirmed malignant neoplasm of the large intestine, ; 3) stage according to the international TNM classification (8th edition) – I, IIA, IIB, IIIB; 4) radical surgical treatment (total right-sided hemicolectomy with lymph node dissection); 5) availability of information on the life expectancy of each patient after surgery (data provided by the structural unit of the Odesa Regional Clinical Antitumor Center of the National Cancer Institute - the information and analytical department with the cancer registry). When analyzing the life expectancy of patients after radical surgical treatment of CRC, we came to the conclusion that the composition of the sample was changing, and the follow-up time for the members of the sample was different. As a result, data was collected containing incomplete information about certain representatives of the sample - censored data (these are data characterizing a process that, at the time of the last examination, does not end with the occurrence of the result being studied). For each patient, the time period from the start of observation (the day of surgery for CRC) to the occurrence of the final outcome (death of the patient) or the last contact with the patient (with some patients, contact was lost before the occurrence of the final result) was determined. This period was then divided into shorter periods (one-, two-, three-year survival and five-year survival). All members of the sample observed for more than a year were included in the group for assessing the probability of one-year survival; those observed for more than two years - to the group of two-year survival assessment, etc.

Results. In our study, overall survival was estimated using the Kaplan-Meier method. The Kaplan-Meier method estimates the cumulative survival function at the time of occurrence of each case of the final outcome. All criteria were met, which made it possible to determine overall survival in this study using the Kaplan-Meier method: 1) the moment of the start of observation was clearly formulated - the day of surgical intervention in a patient for CRC; 2) the end result was clearly defined (progression of the disease or death of the patient); 3) for censored cases, the date of the last contact was known or the period of time from the

beginning of the observation to the contact, when the observer had not yet registered the final result under study; 4) the methods of assessing survival and determining the final result were the same for objects included in the study at earlier or later times; 5) conditions affecting survival (for example, treatment methods) did not change over time; 6) the number of objects in the analyzed sample was more than thirty. Using the Kaplan-Meier method, the overall survival rates of patients with CRC in the sample were analyzed depending on gender (Table 1) and age (Table 2) characteristics of the organism, the main macroscopic characteristics of the tumor (intestinal section (Table 3), volume tumor volume (Table 4), disease stage (Table 5).

Table 1. Kaplan-Meier analysis of overall survival in patients with CRC depending on gender

Life expectancy in women	Overall survival in women	Life expectancy in men	Overall survival in men
1 month	92,86%	-	-
-	-	3 months	91,67%
-	-	8 months	83,33%
21 months	85,71%	-	-
22 months	78,57%	-	-
23 months	71,43%	23 months	75,00%
24 months	64,29%	24 months	66,67%
25 months	57,14%	-	-
26 months	50,00%	26 months	58,33%
27 months	42,86%	27 months	50,00%
30 months	35,71%	30 months	41,67%
31 months	28,57%	31 months	33,33%
32 months	21,43%	-	-
53 months	14,29%	53 months	25,00%
-	-	54 months	16,67%
55 months	7,14%	55 months	8,33%
56 months	0	56 months	0

It is clear that the gender of the patients could not directly affect the aggressiveness of the course of CRC, at least we do not find this in the literature. A few years ago, there were reports in the literature indicating the influence of estrogen levels on the occurrence and course of this disease in patients. And the levels of estradiol, estrone and estriol are traditionally higher in women (estradiol circulates in the blood of men). However, the academic mainstream denies such influence. Therefore, gender could influence survival only indirectly. No one survived the conventional 60 months (5 years) in our study, despite the fact that all patients underwent D2-lymph nodes dissection, which does not represent a particular

technical difficulty in operations for CRC and was performed as a standard in 100% of cases. Women lived a little longer, but we did not explain this in any special way. As we have already indicated in the abstract, there are so-called "other" factors, which in our conditions have not yet been possible to track (genetic factors will be discussed in future works). Median survival for women was 26 months, for men - 27 months. However, 2-year survival was 64.29% in women and 58.33% in men, respectively. Taking into account the method of calculations (some mathematical features of the tools used), at this stage it was possible to track only these indicators.

Table 2. Analysis of overall survival by the Kaplan-Meier method in patients with CRC depending on age

Life expectancy i	Overall survival less than 60 years old pts	Life expectancy	Overall survival pts older than 60 years old
3 months	87,50%	3 months	93,75%
-	-	8 months	87,50%
-	-	21 months	81,25%
-	-	22 months	75,00%
23 months	75,00%	23 months	68,75%
-	-	24 months	62,50%
-	-	25 months	56,25%
-	-	26 months	50,00%
27 months	62,50%	27 months	43,75%
30 months	50,00%	30 months	37,50%
31 months	37,50%	31 months	31,25%
32 months	25,00%	32 months	25,00%
53 months	12,50%	53 months	18,75%
-	-	54 months	12,50%
55 months	0%	55 months	6,25%
-	-	56 months	0%

The age of the patients played a significant role in influencing the survival of patients, as can be seen in Table 2. Even without complex statistical calculations, we can see that in the early periods of observation, from 3 to 31 months of life, younger patients who were younger than 60 years lived longer . The "young" group reached a median survival of 30 months, the older group - 26 months of follow-up. Then, after 32 months of follow-up, where the statistics of the groups equalized and reached ¼ of the surviving patients, the opposite trend was observed: patients from the "elderly" (we remind you that according to the WHO, old age starts at 60 years old) group lived longer. 12.5% of young patients and 18.75% of elderly

patients passed the 53-month mark. As already mentioned, no one overcame the 5-year mark, and at 55 months of observation, all patients of the younger group died; among the elderly, 6.25% remained alive and underwent dispensary observation. What could such statistical indicators indicate? It would be possible to establish a conditional threshold in the observations of patients operated on for CRC at the KNP "ORKPC" OOR" and note that the remote postoperative period was divided into "early remote" and "late remote" observation periods by the biological properties of tumors and the metabolism of the patients themselves . The border at 32 months was a "watershed", when the younger group lived longer due to greater physical reserves of the body (which is obvious and does not require proof or explanation). And after 32 months, some other factors came into effect, such as greater aggressiveness of tumor biology, metabolic "youth" of tumor tissue in young patients under the age of 60 (according to WHO, this age is called average, 45-59 years). Thus, without asserting anything, we can think about the probability of using more aggressive methods of perioperative medical therapy, introduction of targeted therapy, immunotherapy (and for this, more intensive genetic and immunohistochemical examination) in this group of patients, etc. In addition, it is necessary to take into account the changes made by the American Association of Oncologists to the screening methods in the general asymptomatic population group, starting in 2020. Namely, the start of endoscopic screening (conducting the first screening video colonoscopy in life) in an asymptomatic patient without negative heredity should not start at the age of 50, as was recommended earlier, but 5 years earlier - at the age of 45. Thus, as it follows from table #2, our experience correlates with the experience of our foreign colleagues and justifies the concept of earlier detection of "young" colon cancers. Prevention is much better than cure. What we can see from the application of the concept of long-term postoperative observation of patients.

The more proximally the tumor was located in the right half of the colon, the longer the patients lived. For example, at a follow-up period of 24 months, the follow-up rates for patients with tumors of the cecum, ascending colon, and hepatic angle were 71.43%, 63.64%, and 72.73%, respectively. For the observation period of 32 months: 42.86%, 36.36%, 18.18%. For the observation period of 55 months: 14.29%, 9.09%, 0%, respectively. Thus, biology ruled here as well, as the groups were equivalent in terms of stage, frequency of lymph node involvement, and degree of differentiation.

Table 3. Analysis of overall survival according to the Kaplan-Meier method in patients with CRC depending on the large intestinal department

Life expectancy	Overall survival (cecum)	Life expectancy	Overall survival (ascending colon)	Life expectancy	Hepatic flexure and transverse colon
-	-	1 month	90,91%	1 month	90,91%
8 months	85,71%	-	-	-	-
-	-	21 months	81,82%	-	-
-	-	22 months	72,73%	-	-
-	-	-	-	23 months	81,82%
24 months	71,43%	24 months	63,64%	24 months	72,73%
-	-	-	-	25 months	63,64%
-	-	26 months	54,55%	26 months	54,55%
-	-	-	-	27 months	45,45%
-	-	30 months	45,45%	30 months	36,36%
31 months	57,14%	-	-	31 months	27,27%
32 months	42,86%	32 months	36,36%	32 months	18,18%
53 months	28,57%	53 months	27,27%	-	-
-	-	54 months	18,18%	54 months	9,09%
55 months	14,29%	55 months	9,09%	55 months	0%
56 months	0%	56 months	0	-	-

The genetics of the colon is briefly described by the following constants: a) from left to right, clockwise, among colon epitheliocytes, the degree of KRAS mutation decreases; b) increases the so-called wild type RAS; c) BRAF V600E mutant (replacement of glutamic acid valine in the 600 locus of the 7th chromosome) first increases, then decreases. Thus, the change in patient survival that we found in a rather large sample of patients could be related to recently discovered features of the genomic landscape of epitheliocytes of the mucous colon. Or for some other, still unknown reasons, which is unlikely, given the same trends revealed before us and by other authors [5,6]. Thus, in our opinion, further research and tracking of changes in the biology and genomics of the colon mucosa in cancer could shed light on the patterns we discovered.

Therefore, from our point of view, the separation of right-sided RTK, pRTK into a separate nosoform has a clinically significant character: it is in the right half of the colon that the toxic anemic form occurs more often and less often (almost never) – obturation, much more characteristic of left-sided cancer, lRTK. All this, in combination with different blood circulation (the right sections – from the basin of the superior mesenteric artery, the left – from the basin of the lower mesenteric artery), lays the foundation for a new understanding of

these two localizations as biologically different forms. Which behave completely differently and have different carcinogenesis, different course, including being treated differently. For the treatment of "right-sided cancers", surgeons perform a right-sided hemicolectomy, for "left-sided" - a left-sided hemicolectomy. There are even a number of authors who consider resection of the sigmoid colon not fully justified from the point of view of oncological radicalism [8]. In addition, the genomic and proteomic machinery of these types of cancer requires clarification: BRAF V600E mt, KRAS G12D mt, KRAS G13D mt, KRAS G12 mt and others. Typically, right-sided colon tumors have the following genomic context: MLH1 hypermethylation, BRAF mutation, and high-grade MSI, while left-sided colon tumors are p53 and KRAS mutant.

Table 4. Kaplan-Meier analysis of overall survival in patients with CRC depending on tumor volume

Life expectancy	Overall survival (less than 50cm^3)	Life expectancy	Overall survival (50-100cm^3)	Life expectancy	Overall survival (more than 100cm^3)
1 month	90,00%	-	-	1 month	87,50%
-	-	-	-	8 months	75,00%
-	-	21 months	87,50%	-	-
-	-	22 months	75,00%	-	-
23 months	80,00%	-	-	23 months	62,50%
-	-	24 months	62,50%	24 months	50,00%
-	-	25 months	50,00%	-	-
-	-	26 months	37,50%	-	-
27 months	70,00%	-	-	27 months	37,50%
30 months	60,00%	-	-	-	-
31 months	50,00%	-	-	-	-
32 months	40,00%	-	-	-	-
53 months	30,00%	-	-	53 months	25,00%
54 months	20,00%	54 months	25,00%	-	-
55 months	10,00%	55 months	12,50%	55 months	12,50%
56 months	0%	56 months	0%	56 months	0%

As indicated in the table, the volume of tumor tissue practically did not affect survival. Significant fluctuations in the volume of the tumor or, one might say, the tumor mass (assuming that the density of the tumor masses was approximately the same in all patients) did not affect the life expectancy at RTK. All patients were divided into groups: volume of removed tumor up to 50 cm3, 50-100 cm3 and more than 100 cm3, ie. fluctuations were x2-3 times, i.e., almost three times the volume of tumors of the third group could exceed the

volumes of tumor lesions in the first. The homogeneity of the group, which included patients with stages 2A, 2B, and 3, is confirmed by the homogeneous survival of RTK patients in these groups, as indicated in Table 5.

Table 5. Analysis of overall survival according to the Kaplan-Meier method in patients with CRC depending on the stage of the disease

Life expectancy	Overall survival (stage IIA)	Life expectancy	Overall survival (stage IIB)	Life expectancy	Overall survival (stage III)
3 months	92,86%	3 months	85,71%	3 months	88,89%
-	-	-	-	8 months	77,78%
21 months	85,71%	-	-	-	-
22 months	78,57%	-	-	-	-
23 months	71,43%	23 months	71,43%	-	-
24 months	64,29%	24 months	57,14%	24 months	66,67%
25 months	57,14%	-	-	-	-
26 months	50,00%	-	-	-	-
27 months	42,86%	-	-	27 months	55,56%
30 months	35,71%	-	-	-	-
31 months	28,57%	-	-	-	-
32 months	21,43%	-	-	32 months	44,44%
53 months	14,29%	53 months	42,86%	53 months	33,33%
-	-	54 months	28,57%	54 months	22,22%
55 мес.	7,14%	55 мес.	14,29%	55 мес.	11,11%
56 мес.	0%	56 мес.	0	56 мес.	0

This is primarily confirmed by the long history of oncology science and practice, leading to the existence of such expressions as "small tumors give large metastases" and the most frequent detection of tumors of gigantic sizes, generally devoid of both distant and regional metastases. It is precisely such observations that call for an intellectual insight into the deeper mechanisms driving the biology of such tumors. Whether it's genetics or something else is still completely unknown. Publications are already appearing, which indicate that the expression of a certain protein due to the mutation of such a gene causes earlier metastasis. For example, in the case of CDH-1 mutated gastric cancer, the production of the protein E-cadherin, which is the "intercellular cement", is inhibited. Which clinically leads to the fact that genetically stable gastric cancer (according to the TTGA classification) metastasizes hematogenously early, causing the worst prognosis in the diffuse form of gastric cancer compared to the intestinal form.

The unfavorable prognosis in CRC is due to late detection of the disease, rapid progression (most often in young patients), frequent recurrence and metastasis of tumors. The

analysis of the relationship between the overall survival of patients and their age and gender characteristics made it possible to establish that overall survival (calculated by the Kaplan-Meier method) in this study was higher in men (2-year overall survival in women was 64.29%, and 66.67% in men, 7.14% in women and 8.33% in men, in contrast to the data given in the literature. Overall survival was higher in the group of patients after 60 years. The analysis of overall survival depending on the intestinal section allowed us to establish that the best results were obtained in the group of patients with tumor localization in the cecum (survival after 55 months was 14.29%), in contrast to the group of patients with tumor localization in the ascending colon (after 55 months survival was 9.09%) and the group of patients with a tumor in the hepatic flexure and lumbar colon (after 55 months survival was 0%), despite the fact that 2-year survival was the highest in the group with tumor localization in the hepatic flexure and lumbar colon (72.73%). Tumor volume had no effect on overall survival. Depending on the stage of the disease, the highest survival rates after 55 months were obtained in the group of patients with stage 2B (14.29%) compared to stage 3B (11.11%) and stage 2A (7.14%). But the highest 2-year survival rate was obtained in the group of patients with stage 2A (64.29%) in comparison with stage 3B (66.67%) and stage 2B (57.14%). It is important to further analyze the impact of pathohistological, genetic and immunohistochemical (proteomic) characteristics of tumors in RTK on life expectancy and overall survival of patients. Interestingly, in regions of the world with a low incidence of colorectal cancer, the low incidence and mortality rates may reflect a low prevalence of colon cancer risk factors and low life expectancy and survival. The existence of cancer of the right half of the colon, pRTK or the so-called "proximal" CRC, represents a certain far-reaching interest from the point of view of both fundamental, research oncology, and from the point of view of practical applications of this fact: the existence of some other original tumor biology. Which correlates in this case with different anatomy, different physiology, different genetics, oncology and therapy. This can have important practical implications both in clinical oncology (targeted therapy, immuno-oncology, etc.) and oncology surgery. The following, more detailed studies can, in our opinion, shed light on these data.

Conclusions

The more proximally the tumor was located in the right half of the colon, the longer the patients lived. At a follow-up period of 24 months, the duration of follow-up for patients with cecum, ascending colon, and hepatic angle tumors was 71.43%, 63.64%, and 72.73%, respectively. For the observation period of 32 months: 42.86%, 36.36%, 18.18%. For the observation period of 55 months: 14.29%, 9.09%, 0%, respectively. Thus, biology was the

key factor, as the groups were equivalent in terms of stage, lymph node involvement, and degree of differentiation.

Conflicts of interest: authors have no conflict of interest to declare.

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