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ORIGINAL ARTICLE

Features of the cell cycle in patients with colorectal cancer

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ABSTRACT

Purpose of the study. The objective of this study was to evaluate cell cycle indices in tumor cells and conditionally intact intestinal tissue (resection line) in male and female patients with colorectal cancer (CRC).
Patients and methods. Cell cycle phases were analyzed in 36 male and 36 female patients with CRC involving the rectum, and with right-sided or left-sided tumor localization. The mean age was 66 years. The degree of tumor differentiation in all cases corresponded to G2. None of the patients had received neoadjuvant treatment before surgery. In 10 % of tumor homogenates and resection line samples, cell cycle phases were determined using an ADAMII LS fluorescent cell analyzer (Korea). For cell cycle analysis, propidium iodide (PI), specially prepared for the ADAMII LS, was used. This reagent mixture contained PI and RNaseA, and cells were stained directly without an additional fixation step. The instrument's high sensitivity enabled precise discrimination of cells in the G0/G1 phase (resting cells [G0] and early G1), S phase, and G2/M phase. Statistical analysis was performed using Statistica 10.0 software.
Results. The proportions of viable and dead cells in the samples were generally comparable. In men, viable cells ranged from 56.6 % to 73.6 %, and dead cells from 26.4 % to 43.4 %. In women, viable cells ranged from 60.8 % to 77.3 %, and dead cells from 22.7 % to 39.2 %. In men, tumor samples from left-sided CRC contained predominantly S and G2 phase cells, whereas in right-sided CRC and rectal tumors, the majority of cells were in the G1 phase. In women with left-sided CRC, tumor samples showed the highest proportion of cells in the G1 phase, while samples from right-sided CRC and rectal tumors contained predominantly S phase cells.
Conclusion. The identified cell cycle characteristics and tumor cell death patterns in CRC patients, depending on sex and tumor localization, reflect the proliferative status of the tissue. These findings may provide a basis for personalized recommendations on the use of antitumor agents targeting cells in specific cell cycle phases.

Keywords: colorectal cancer, cell cycle, mitosis, G1 phase, S phase, tumor

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Особенности клеточного цикла у больных колоректальным раком

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РЕЗЮМЕ

Цель исследования. Оценка показателей клеточного цикла в клетках опухоли и условно интактной кишки (линии резекции) у больных колоректальным раком (КРР) обоих полов.
Пациенты и методы. Исследование фаз клеточного цикла проводили у 36 мужчин и 36 женщин больных КРР – прямой кишки, с правосторонней и левосторонней локализацией. Средний возраст пациентов составил 66 лет. Степень дифференцировки опухоли у всех больных соответствовала G2. Никто из больных до операции не получал неоадъювантного лечения. В 10 % гомогенатах опухоли и линии резекции определяли фазы клеточного цикла на флуоресцентном анализаторе клеток Adamii LS (Корея). Для определения клеточного цикла использовали пропидий йодид (PI), специально подготовленный для ADAMII LS, содержащий PI и RNase A, который используется путем прямого окрашивания клеток без прохождения дополнительного этапа фиксации. Точный анализ интенсивности реагента позволял прибору различать клетки в фазах G0/G1 (покоящиеся клетки (G0) и клетки в ранней фазе G1), S и G2/M. Статистический анализ результатов проводили с помощью пакета программ Statistica 10.0.
Результаты исследования. Количество живых и мертвых клеток в исследуемых образцах, в большинстве случаев, было однотипным: у мужчин живых клеток от 56,6 до 73,6 %; мертвых клеток от 26,4 до 43,4 %, у женщин живых клеток от 60,8 до 77,3 %; мертвых клеток от 22,7 до 39,2 %. У мужчин в образцах опухолей левостороннего КРР максимальных процент клеток находился в фазах S и G2, а в опухолях правосторонней локализации и прямой кишки в фазе G1. У женщин при левостороннем КРР максимальный процент клеток в образцах опухоли приходился на фазу G1, а образцы опухоли при правостороннем КРР и раке прямой кишки в S-фазе.
Заключение. Выявленные особенности клеточного цикла и гибели клеток опухолей у больных КРР, в зависимости от пола и локализации опухоли, описывают пролиферативный статус ткани и могут служить основой для персонализированных рекомендаций по применению противоопухолевых препаратов, действующих на клетки в определенной фазе.

Ключевые слова: колоректальный рак, клеточный цикл, митоз, фаза G1, фаза S, опухоль

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BACKGROUND

Colorectal cancer (CRC) is the third most common cancer in men and the second most common cancer in women worldwide and ranks second in cancer-related mortality [1]. The intestinal epithelium, consisting of a layer of epithelial cells grouped into the crypts of Lieberkühn, is a rapidly renewing tissue. The large intestine contains millions of crypts, each with more than 2,000 cells, which are replaced every 2–7 days. Renewal is carried out by colonic stem cells located at the base of the crypts [2]. There is a hypothesis that malignant cells of the large intestine originate from these stem cells. This hypothesis is supported by the fact that intestinal adenomas arise from stem cells [3].

The sequence of events occurring in a cell that leads to its division and duplication is known as the cell cycle [4]. The cell cycle consists of the G1 phase (presynthesis), S phase (DNA synthesis), G2 phase (late synthesis), and M phase (mitosis) [5]. During the G1 phase, the cell grows and prepares for DNA synthesis. In the S phase, DNA synthesis occurs, leading to the replication of genetic material [6]. In the G2 phase, the cell continues to grow and prepares for mitosis the stage of the cell cycle during which replicated DNA is distributed into two identical nuclei [7]. The cell cycle is strictly regulated by a complex network of proteins and signaling pathways. A failure in cell cycle control mechanisms can lead to various diseases, including cancer [8].

It is believed that any disruption of the stages of the cell cycle whether under the influence of genetic, carcinogenic, or infectious factors can result in uncontrolled cell proliferation and, ultimately, tumor formation [9]. Cancer is a disease characterized by uncontrolled cell growth and proliferation, which is the result of impaired regulation of normal cell cycle control mechanisms [10]. The development of cancer is often the result of mutations or changes in genes controlling the cell cycle, which disrupt the normal regulation of cell growth and division [11].

Dysregulation of the cell cycle is a common feature of cancer cells and plays a crucial role in their uncontrolled growth and proliferation. Understanding the mechanisms underlying cell cycle dysregulation in cancer cells is essential for the development of targeted therapies that can selectively suppress the growth of cancer cells while preserving normal cells [12].

Purpose of the study: to evaluate cell cycle indices in tumor cells and conditionally intact intestine (resection line) in patients with colorectal cancer of both sexes.

PATIENTS AND METHODS

The study included results obtained from 72 patients with colon cancer T2-3N0M0, comprising 36 women and 36 men, who underwent treatment at the Department of Abdominal Oncology, National Medical Research Centre for Oncology, during 2023–2024. The mean age of the patients was 66 (58–73) years. Groups were formed with 12 male and 12 female patients each diagnosed with left-sided CRC (sigmoid colon cancer), rectal cancer, and right-sided CRC (ascending colon cancer). The degree of tumor differentiation in all patients corresponded to G2. None of the patients received neoadjuvant therapy prior to surgery. A good performance status (ECOG 0 or 1) was observed in 98.5 % of the patients. All patients underwent surgical intervention.

During surgery, specimens of tumor tissue (1 cm from the visible tumor margin towards the center) and fragments of intestinal tissue at the resection line (proximal margin) were collected. On ice, 10 % homogenates were prepared in 0.1 M potassium phosphate buffer (pH 7.4), which were subsequently used for cell cycle analysis with the ADAMII LS fluorescent cell analyzer with image analysis capability (Korea). Cell viability was determined using a reagent designed for total cell count and viability assessment, consisting of a combination of acridine orange (AO), a cell-permeable DNA stain, and DAPI, a non-permeable DNA stain.

To determine the cell cycle, propidium iodide (PI), specially prepared for ADAMII LS and containing PI and RNaswA, was used for direct staining of cells without an additional fixation step. The instrument's precise reagent intensity analysis enabled the identification of cells in the G0/G1 phase (resting cells (G0) and cells in the early G1 phase), S phase, and G2/M phase.

Statistical analysis

Statistical analysis of the results was performed using the Statistica 10.0 software package. The Shapiro-Wilk test was used to assess the normality of distribution. The significance of statistical

differences between the studied parameters was determined using the Mann-Whitney U test. A value $p < 0.05$ was considered the threshold for statistical significance. Data in the tables are presented as the median and the 25th and 75th percentiles (Me (C25–C75)).

STUDY RESULTS

It was found that the number of living and dead cells in the studied samples was, in most cases, similar: in men, living cells ranged from 56.6 % to 73.6 %, and dead cells from 26.4 % to 43.4 %; in women, living cells ranged from 60.8 % to 77.3 %, and dead cells from 22.7 % to 39.2 %. The highest percentage of living cells was observed in the resection line of the rectum in men and in the resection line in left-sided CRC in women (73.6 % and 73.6 %, respectively). The highest percentage of dead cells was found in men in tumor samples of left-sided and right-sided CRC (41.1 % and 43.4 %, respectively) and in women in tumor samples of left-sided cancer and in the resection line of right-sided CRC (37.7 % and 39.2 %, respectively).

The study revealed differences in the percentage of cells in different phases of the cycle, depending on the sex of the patients and tumor location – rectum, left-sided, and right-sided colon tumors.

In men with rectal cancer, tumor samples were dominated by cells in the resting/synthetic phase (G0/G1), exceeding the levels in the S and G2/M phases by 1.8-fold and 1.9-fold, respectively (Table 1).

In the resection line of rectal cancer, the distribution across cell cycle phases was uniform; the percentage of cells in each phase showed no significant differences from each other. In rectal tumor samples, the proportion of cells in the G0/G1 phase was 1.4 times higher compared to intestinal tissue at the resection line, whereas the S and G2/M phases had on average, 1.5 times fewer cells.

In women with rectal cancer, tumor samples contained, on average, twice as many cells in the G0/G1 and S phases compared to the G2/M phase. In the resection line of the rectum, the percentage of cells in the G2/M phase was, on average, 3.4 times lower than in the G0/G1 and S phases. At the same time, in women, tumor samples had 1.4 times more cells in the mitotic phase, whereas in the resection line the percentage of cells in the resting phase (G0/G1) was significantly 1.4 times higher.

In men with left-sided CRC, the percentage of cells in the G0/G1 phase in the tumor was, on average, two times lower than in the S and G2/M phases. In the resection line for left-sided CRC in men, the lowest percentage of cells was found in the G2/M phase – 1.8 times lower than in G0/G1 and 3.5 times lower than in the S phase. In addition, in resection line samples of left-sided CRC, the percentage of cells in the S phase exceeded that in the G0/G1 phase by 1.9 times. In tumor samples of left-sided CRC in men, compared to the resection line, the percentage of cells in the G2/M phase was twice as high, but in the G0/G1 and S phases it was, on average, 1.5 times lower.

In women with left-sided CRC, the percentage of cells in the resting phase (G0/G1) in tumor samples was, on average, twice as high as in the mitotic phase and the S phase. In the resection line for left-sided CRC, cells predominated in the G0/G1 and S phases, with the percentage in the mitotic phase being, on average, 2.6 times lower. Tumor samples of left-sided CRC in women differed significantly only in having a twofold lower percentage of cells in the S phase compared to the resection line.

In men with right-sided CRC, tumor samples had a percentage of cells in the G2/M phase that was, on average, 1.6 times lower than in other phases. Similarly, in the resection line, the G2/M phase had 2.6 times fewer cells than the G0/G1 phase and 3 times fewer than the S phase. At the same time, there was a 1.4-fold higher percentage of G2/M-phase cells in tumor samples compared to the resection line, while other phases showed no significant differences between tumor and resection line.

In women with right-sided CRC, tumor samples showed no statistically significant differences in the percentage of cells in different phases. However, in the resection line, the lowest percentage of cells was in the resting phase, being 4.4 times lower than in the S phase and 2.2 times lower than in the mitotic phase. The maximum percentage of cells in the resection line for right-sided CRC was in the S phase, which was twice as high as in the G2/M phase. In tumor samples of right-sided CRC in women, the percentage of cells in the G0/G1 phase was 2.4 times higher than in the resection line, while in the S phase it was 1.4 times lower; only the mitotic phase showed no significant differences between tumor and resection line samples.

As a result, in men, tumor samples of right-sided CRC differed from left-sided tumors by having a 1.7-fold higher percentage of cells in the resting phase and a 1.6-fold lower percentage in the G2/M phase. The resection line in right-sided CRC in men also contained 1.4 times more cells in the G0/G1 phase.

In women, tumor samples of right-sided CRC, on the contrary, differed from left-sided tumors by having a 1.6-fold lower percentage of cells in the G0/G1 phase, but a 1.4-fold higher percentage in the G2/M phase and a 1.5-fold higher percentage in the S phase. Similarly, in resection line samples from women with right-sided CRC, the percentage of cells in the resting phase was four times lower, and the percentage in the G2/M phase was 1.5 times higher.

DISCUSSION

The location of malignant tumors of the colon and rectum can have a significant impact on clinical outcomes and response to drug therapy [13]. This is attributed to the fact that the colon and rectum are distinct anatomical tissues of the gastrointestinal tract [14]. Tumors located in the right colon (ascending colon and cecum) are more often diagnosed at later stages, exhibit high microsatellite instability, and tend to metastasize more frequently compared to tumors of the left colon (descending colon, sigmoid colon) [15]. This difference can be explained by their distinct embryological origins (midgut and hindgut, respectively), different genetic and epigen-

Table 1. Cell cycle in tumor and resection line in patients with colorectal cancer (% of living cells) (Me (Q25–Q75))

	Cell cycle phases		
	G0/G1	S	G2/M
Males			
Rectal cancer	32.56 (28.6; 35.9)[2,4]	18.63 (13.97; 20.14)[1,4]	16.8 (14.9; 18.8)[1,4]
Resection line, rectum	22.63 (19; 26.06)	27.06 (18.18; 28.71)	22.48 (19.45; 26.8)
Left-sided CRC tumor	12.43 (9.27; 12.75)[2,3,4]	27.84 (20.11; 31.56)[1]	21.37 (18.85; 23.54)[3,4]
Resection line, left-sided CRC	18.81 (15.05; 22.15)[2]	37.35 (35.38; 44.07)[1]	9.84 (7.79; 11.34)[1,2]
Right-sided CRC tumor	22.34 (16.44; 26.6)	21.64 (21.26; 22.9)	12.74 (11.12; 15.71)[1,2,4]
Resection line, right-sided CRC	25.57 (21.2; 29.7)	31.7 (22.07; 37.36)	8.45 (7.03; 12.58)[1,2]
Females			
Rectal cancer	25.44 (23.55; 27.42)[4]	27.56 (24.04; 29.5)	12.0 (10.24; 14)[1,2,4]
Resection line, rectum	36.12 (26.37; 38.35)	27.9 (25.33; 30.44)	7.94 (6.46; 9.53)[1,2]
Left-sided CRC tumor	31.2 (29.1; 34.2)[2,3]	15.07 (12.97; 20.2)[1,3,4]	14.6 (12.2; 16.9)[1,3]
Resection line, left-sided CRC	33.89 (23.36; 37.86)	33.99 (25.52; 40.55)	11.56 (9.9; 13.9)[1,2]
Right-sided CRC tumor	19.64 (18.9; 20.5)[4]	24.65 (20.58; 29.55)[4]	19.05 (18.1; 23.1)
Resection line, right-sided CRC	8.09 (7.35; 8.54)[2]	36.9 (27.27; 42.84)[1]	17.34 (16.5; 18.5)[1,2]

Note: Statistically significant differences compared with: [1] – G0/G1 phase; [2] – S phase; [3] – differences between the corresponding samples of right-sided CRC; [4] – differences compared with the corresponding resection line ($p < 0.05$)

etic profiles, as well as differences in microbiome composition and the immune environment of the mucosa [16].

It is known that the duration of the mitotic phase constitutes only a small fraction of the entire cell cycle, while the total time of the S, G2, and M phases is relatively constant. Therefore, the duration of the cell cycle depends mainly on the G0/G1 phase. The resting phase G0 is thought to predominate in most highly differentiated cells performing their specific functions [17]. In our study, colorectal cancer (CRC) patients' resection line samples did not demonstrate a predominance of cells in the resting phase, which may indicate impaired functional activity of colon cells in CRC patients.

We hypothesize that the predominance of a particular cell cycle phase in tumor samples of right-sided CRC, left-sided CRC, and rectal cancer may be associated with the aforementioned differences and may determine the biological aggressiveness of the neoplasm.

In men, the highest percentage of cells in the G0/G1 phase was observed in rectal cancer and right-sided CRC, and the lowest in left-sided tumors. In women, conversely, the highest percentage of cells in the G0/G1 phase was found in left-sided CRC and rectal cancer, and the lowest in right-sided tumors. It is known that the cell cycle is tightly regulated by a number of regulatory proteins and checkpoints [18]. The G1 checkpoint is a critical stage in the cell cycle, regulated by a complex network of proteins and signaling pathways, including CDKs and tumor suppressor proteins, ensuring that the cell possesses the necessary resources such as nutrients and growth factors to proceed through the cycle and that no DNA damage is present that could be passed on to daughter cells [19]. Blockade of the p53-dependent G1 checkpoint can persist for long periods until it is stimulated by external signals (growth factors) to re-enter the cell cycle [20]. One of the clear effects of prolonged G0/G1 arrest is cell enlargement, as total cellular protein and RNA content continues to increase. Oncogenic signals, in turn, cause excessive cell growth, which soon becomes toxic [21].

If oncogenes make tumor cells more vulnerable to G1 arrest, effective blockade of all G1 cells for certain periods of time may lead to cancer-specific overgrowth, DNA damage, and senescence [21]. Therefore, a high proportion of cells in the resting phase (G0/G1) in tumor samples may be a cause of low sensitivity to anticancer therapy.

Several researchers have demonstrated gender differences in markers of proliferation and neoangiogenesis in both tumor samples and resection line tissues in CRC patients, particularly in rectal cancer. Furthermore, identification of different molecular-biological subtypes of CRC may also influence the predominance of specific cell cycle phases in both tumor and resection line tissues [22].

In our study, the percentage of G0/G1-phase cells in resection line samples from men was approximately the same, regardless of tumor location, whereas in women, right-sided CRC resection lines stood out, with an extremely low proportion of resting-phase cells. In women with right-sided CRC, resection line samples were dominated by cells in the synthetic (S) phase, which may be one of the reasons for the unfavorable course of right-sided CRC. It is known that progression through the G1 checkpoint is determined by the balance of G1 activators and inhibitors, and this balance shifts toward activators as cells grow. This ability to "break through" G1 arrest is thought to underlie the cell-size checkpoint, ensuring that cells reach an optimal size before entering the S phase [21, 23–26]. Overall, in CRC patients, cells in the S phase were either predominant or comparable in percentage to those in G0/G1, with the only exceptions being male rectal tumor samples and female left-sided CRC tumor samples.

Progression through the S phase is believed to be modulated mainly by cellular levels of certain proteins. Excessive expression of cyclin A promotes cancer progression, while suppression of cyclin A blocks cell cycle progression and induces arrest in the S phase [27]. From a therapeutic perspective, cells in the S phase are generally more radioresistant than those in other phases [20]. However, pharmaceutical companies are developing drugs, such as DNA topoisomerase I inhibitors, targeting the DNA synthesis elongation stage to arrest tumor cells in the S phase and subsequently induce apoptosis [28]. Thus, determining the predominant cell cycle phase in a tumor may help guide an appropriate personalized anticancer therapy strategy.

In male patients with left-sided CRC, the proportion of cells in the G2/M phase was significantly higher than in rectal cancer and right-sided CRC.

In contrast, in women, the proportion of G2/M-phase cells in right-sided CRC was significantly higher than in left-sided CRC and rectal cancer. In the resection line, the situation was somewhat different: the percentage of cells in the G2/M phase was significantly higher in rectal cancer in men and in right-sided CRC in women compared to other locations.

A high proportion of cells in the G2/M phase may indicate high proliferative activity of tumors at this location in men. There is evidence that mutations in tumor suppressor genes, such as p53, may prevent cells from halting the cell cycle upon detecting DNA damage or other abnormalities, allowing damaged cells to continue dividing and accumulate further mutations [29]. In addition, various enzymes, including the protein kinases Chk1 and Chk2, are activated in the G2 phase [30].

It should be noted that all studies were conducted in patients of both sexes without metastases, and the obtained results demonstrate sex- and location-specific differences, highlighting the substantial heterogeneity of colorectal cancer. Further studies of the cell cycle in metastatic CRC patients are warranted.

CONCLUSION

Therefore, in CRC patients, cell cycle characteristics were found to vary depending on sex and tumor location. In male patients, tumor samples from left-sided CRC showed the highest percentage of cells in the S-G2 phases, whereas in right-sided CRC and rectal cancer the majority of cells were in the G1 phase. In female patients, left-sided CRC tumors had the highest proportion of cells in the G1 phase, while in right-sided CRC and rectal cancer the predominant proportion of cells was in the S phase. These findings may serve as a basis for personalized recommendations regarding the use of anticancer drugs targeting cells in specific phases of the cell cycle.

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