THE MODELING OF RECURRENT AND METASTATIC COLORECTAL CANCER GROWTH KINETICS TO ASSESS CHEMOTHERAPEUTIC TREATMENT EFFICACY

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One of the major problems in drug therapy administration in cancer patients is the lack of information on sensitivity of tumor cells to chemotherapeutic agents (initial uncertainty). A dividing cancer cell is known to be the primary point of chemotherapeutic agent application. The authors have developed a mathematical model, where tumor growth is considered as a complex balance between cancer cell division and death. There have been studied the combinations of parameters of proliferative activity of cells and cell death, when it is possible to reach maximum effect in cytostatic treatment. The efficacy of adjuvant chemotherapy in the prevention of colorectal cancer recurrences and metastases has been analyzed.

Key words: recurrent and metastatic colorectal cancer; growth kinetics; modeling.

In evidentiary medicine, in order to determine the efficacy of chemotherapy and radiotherapy of malignancies, statistical methods are used. “The gold standard” among statistical techniques is Kaplan–Meier method [1–3], when recurrence-free survival curves of patients with different treatment modalities are compared [4, 5]. For example, two conditioned groups of patients have the same localization of tumors. Group 1 patients underwent surgical treatment and adjuvant chemotherapy, group 2 patients — surgical management only (Fig. 1).

The comparison and analysis of two mathematical relations (red and blue curves) clearly shows the advantage in the efficacy of treatment methods used in group 1. The gap in survival median in this case is 10 months, and five-year survival rate in group 1 is about 20% as high compared to group 2. At the first glance, the findings are impressive. However, the analysis shows that the treatment produced a long-term effect only in one of five cases. It is also obvious that when considering the problem of high-cost adjuvant therapy administration to a certain patient, this method cannot guarantee that group 1 patients will fall within these 20% survivals but not within those 70% patients with an unfavorable outcome or 10% survived patients who were not administered any additional treatment.

Parabolic character of Kaplan–Meier curve in most cases makes it impossible to analyze in detail the treatment efficacy. In other words, when studying statistical aggregates of two conditioned clinical groups, we cannot say if group 1 patient survived longer by clinical parameters than a similar patient in group 2, or there is certain percentage of patients sensitive to adjuvant treatment due to which there is difference in treatment results. If both variants described are possible, then the following question arises: to what extent each of these variants has an effect on survival rate increase of the whole statistical aggregate of group 1.

At first sight, to answer these questions we are to study and compare the data on group 1 and group 2 patients with favorable outcomes. The most studies in this field have been carried out in such a way [6, 7]. In our survey we intentionally examined the patients with unfavorable outcomes. We attempted to analyze the dynamics of tumor growth in patients with recurrent and metastatic tumors with or without treatment. Tumor recurrences and metastases, as a rule, result in an unfavorable outcome [8].

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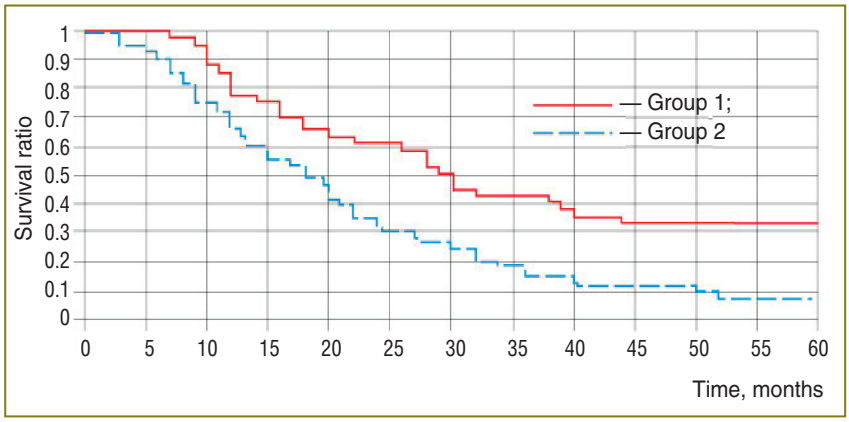

Fig. 1. Kaplan–Meier curve example

From a mathematical standpoint, a parabolic Kaplan–Meier curve is the derivative of the set of parabolic tumor growth curves of all members of a statistical group. Increasing in size exponentially at different rate due to the duplication of tumor cells, different tumors reach their critical mass at different time, the critical mass being fatal to the body. These time periods drawn successively in a diagram Y-direction top down form a survival curve of Kaplan–Meier.

Tumor growth dynamics is the result of a complex balance between cell division and cell death. We realize that in reality a tumor will never reach its calculated potential sizes; the reason is a cell loss factor [9].

We intentionally chose recurrent and metastatic tumors for study. The advantage of the choice is in the fact that we are aware of a real tumor growth rate at a certain time period. It enables to correct a potential tumor growth model and determine more precisely the balance between cell division and cell death. If we have quantitative data on medical pathomorphism of a tumor, by means of the present model one can assess the effect of chemotherapy on tumor growth.

The aim of the investigation was to determine in what morphological parameters of recurrent and metastatic tumors, medical treatment (chemotherapy, hormone therapy, radiotherapy) has a maximum effect on tumor growth, and reveal in what cases the expected effect of the treatment is close to zero.

Materials and Methods. 36 patients with recurrent and metastatic colorectal cancer were examined morphologically on the base of the Department of Pathological Anatomy, Nizhny Novgorod State Medical Academy. There were studied both completely removed tumors and biopsy material (in case the resection of a recurrent and metastatic tumor was impossible or unreasonable). In each case we determined the following parameters of tumor parenchyma:

percentage of mitotic cells;

percentage of pathological mitoses;

percentage of proliferatively active cancer cells — in these cells there are division preparative processes;

percentage of cancer cells in a resting phase, which are not going to divide in the nearest future;

percentage of cancer cells with irreversible changes.

In collaboration with the researchers of the Department of Mathematics, Lobachevsky State University, Nizhny Novgorod, we developed a recurrent

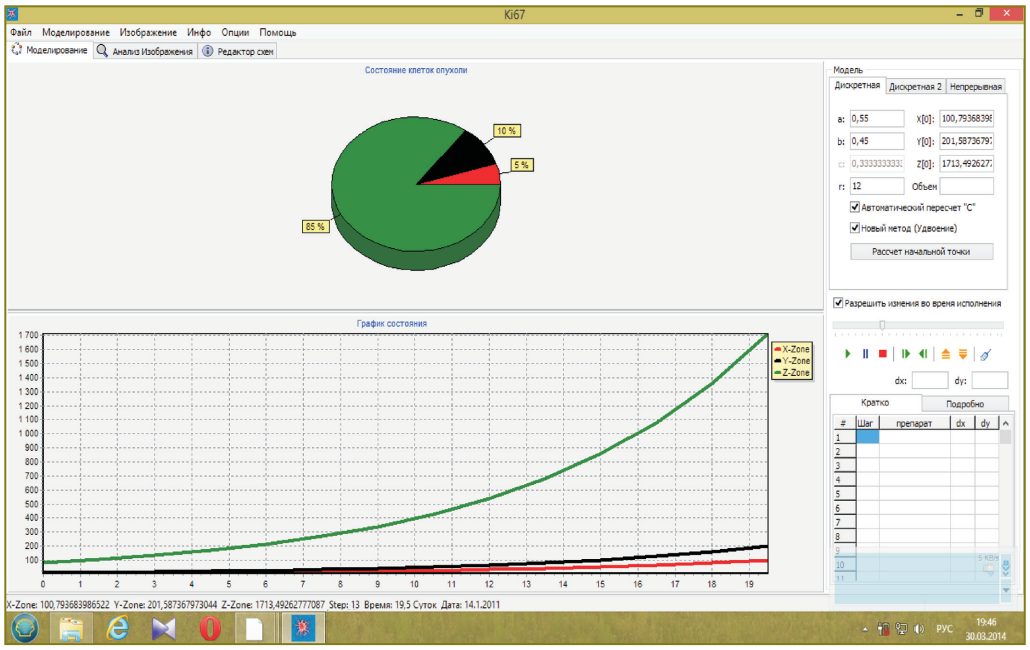

Fig. 2. Program interface

and metastatic tumor growth model. In the model we took into consideration a dynamic balance between dividing cells (the percentage of living cancer cells in mitosis) and dying cells (parameter part: the percentage of cells in apoptosis, the percentage of pathological — nonviable — mitoses, the percentage of cells with irreversible changes).

According to the model, all tumor parenchymal cells are studied in three states: mitosis, a resting phase, and preparation for mitosis. A tumor grows due to cell duplication and simultaneously diminishes due to cell loss (pathological mitoses, unviable cells with critical structure damages, cell apoptotic factor). In this case, proliferation processes are certain to prevail over cell death. Under these conditions only a tumor has growth potency. When cell death processes prevail, the tumor, generally, regresses at a preclinical stage and is unavailable for study. The exceptions to this rule are the tumors with a positive response to therapeutic treatment.

Based on the present model, we developed a computer program, which enables to plot an exponential tumor growth curve and calculate tumor growth rate (tumor doubling time), and cell loss factor (Fig. 2).

To our opinion, the main prognostic criterion is tumor growth rate (taking into account an exponential tumor growth curve due to cell duplication, it is calculated in the period of tumor volume duplication — in our study in days). It is evident that the higher the tumor growth rate (less number of days necessary for duplication), the worse the prognosis. Mathematically, in complete cure, tumor duplication time is to go to infinity. In our studies tumor duplication time was within the range from 1.5 days (fast-growing sarcomas, when after total tumor resection patients within 2 months complained again of tumor node, up to 15 cm in size) to 160 days (colorectal cancer metastases occurring 8 years after radical surgery). The analysis of nothing else but tumor parenchymal cell proliferation parameters provides no answer to the question: why in one case a tumor grows slowly, while in other cases it increases in size rapidly. Using the program, in each individual case we are to calculate cell loss factor (CLF). CLF in our survey is the percentage of cancer cells dying during the duplication cycle. It is just the parameter that mainly determines tumor growth rate (to a greater extent than proliferation indices). In fast-growing tumors CLF is 30–50%, the tumor volume doubling within 1.5–5 days.

The correlation of cytometric findings with the signs of tumor kinetic growth

Treatment schedules	Pathologic mitoses, %	Cells with irreversible changes, %	Tumor duplication time, days	Cell loss factor, %
Group 1				
Radiotherapy 40 Gy	40.00	6.00	12.57	76.71
Radiotherapy 40 Gy	45.00	19.00	33.17	78.96
Radiotherapy 40 Gy	7.00	4.00	30.56	61.96
9 FOLFOX	7.00	10.00	13.86	36.72
8 Mayo + 12 XELOX	19.00	13.00	31.83	93.15
8 CP	9.00	10.00	162.5	98.66
7 Mayo	25.00	16.00	38.98	91.07
6 Mayo	16.00	19.00	20.07	93.54
6 Mayo	2.00	10.00	46.16	91.62
6 FOLFOX	5.00	7.00	21.67	92.31
5 FOLFIRI	18.00	16.00	4.838	46.95
5 Mayo	1.00	14.00	22.75	53.40
4 Mayo	3.00	5.00	38.42	87.04
4 Mayo	23.00	8.00	9.161	78.57
4 Mayo	30.00	22.00	9.1	85.33
4 Mayo	61.00	10.00	74.29	99.04
4 FOLFOX + 8 FOLFIRI + 2 XELOX	23.00	15.00	41.14	99.83
12 XELOX	25.00	23.00	9.949	70.45
Group 2				
Radiotherapy 40 Gy	1.00	12.00	78.64	93.68
Radiotherapy 40 Gy	20.00	17.00	57.35	95.33
Radiotherapy 40 Gy	9.00	8.00	16.55	85.88
9 FOLFOX	4.00	10.00	7.82	49.64
8 Mayo + 12 XELOX	9.00	13.00	3.854	34.31
8 CP	25.00	16.00	7.65	53.65
7 Mayo	4.00	12.00	19.75	53.84
6 Mayo	16.00	16.00	18.43	78.90
6 Mayo	60.00	5.00	31.45	63.06
6 FOLFOX	24.00	14.00	24.08	91.47
5 FOLFIRI	10.00	19.00	17.26	77.38
5 Mayo	55.00	9.00	104	96.60
4 Mayo	45.00	11.00	88.17	96.71
4 Mayo	55.00	7.00	3.698	47.50
4 Mayo	40.00	10.00	9.087	28.00
4 Mayo	40.00	13.00	22.17	93.92
4 FOLFOX + 8 FOLFIRI + 2 XELOX	29.00	3.00	26.52	74.26
12 XELOX	6.00	5.00	31.92	63.60

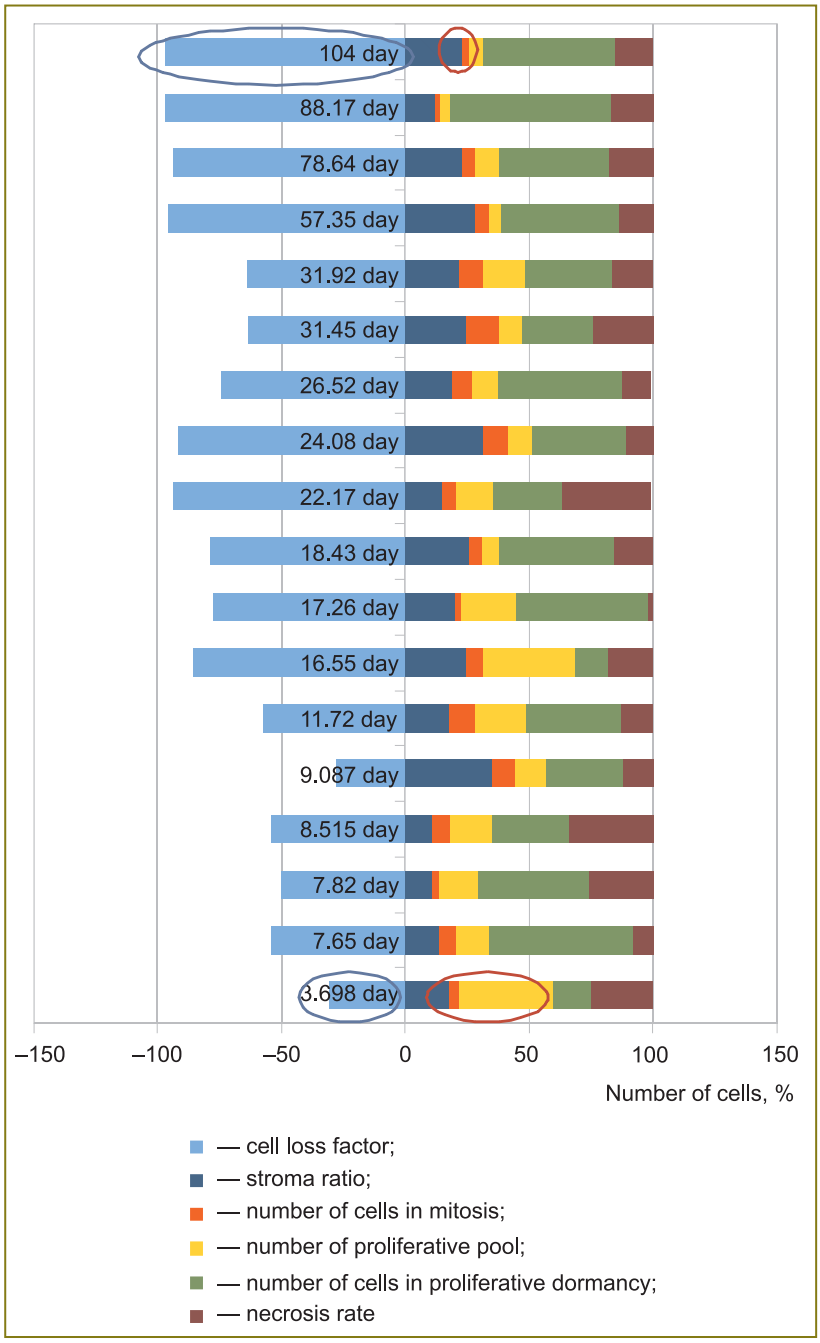

Fig. 3. Cytometric and kinetic tumor characteristics of patients with no additional treatment

In slow-growing tumors CLF is 95–99%. The rest 1–5% cancer cells (survived), as a rule, are enough to provide slow tumor growth. Recurrent tumor can be revealed clinically years after the first surgery.

Results and Discussion. The Table presents the statistical analysis of cytometric findings of 36 patients with recurrent and metastatic colorectal cancer. 18 patients (group 1) received medical treatment after surgery (15 subjects — different chemotherapy schedules, 3 — radiotherapy), 18 patients (group 2) received no treatment during the period after a radical operation before the recurrence or tumor metastases were detected.

The comparison of tumor pathomorphism indices (the percentage of pathological mitoses plus the percentage of tumor parenchymal cells with irreversible changes) of the patients of both groups, the efficacy of the medical treatment provided is not evident. Arithmetic mean of pathological mitoses of group 1 patients (19.94%) was even lower than the same parameter of group 2 (25.11%). Arithmetic mean of the number of cells with irreversible changes in clinical groups was statistically equal — 12.16% (group 1) and 11.11% (group 2).

However, mean tumor growth rate in patients, who underwent medical treatment, was lower (mean tumor duplication time — 37.38 days) than in group 2 patients (mean tumor duplication time — 31.27 days).

Mean cell loss factor in group 1 was 80.94%, in group 2 — 72.44%.

Based on the above mentioned, it may be preliminary concluded that chemotherapy or radiotherapy in a postoperative period in patients with colorectal cancer improves the prognosis to a certain degree.

To answer the primal question of the study — to determine in what morphological parameters of recurrent and metastatic tumors medical treatment has its maximum effect on tumor growth — we are first to study the tumor growth balance in group 2 (Fig. 3).

Figure 3 demonstrates 18 clinical cases in the form of diagrams showing both: tumor growth and cell loss indices for patients with no medical effect on tumor after surgery. All cases are bottom-up arranged in the order of tumor duplication time increase. The right part of each diagram (over 0) consists of the sum of tumor parenchyma morphological parameters (such as the percentage of mitoses, the percentage of proliferatively active cancer cells, the percentage of resting cells, etc.) and characterizes how a tumor increases during each cycle. The left part of each diagram (a blue sector) — cell loss factor below zero — in the similar fashion characterizes how a tumor diminishes during each cycle. Lowest diagrams were plotted to describe the patients with fast-growing tumors. Tumor duplication time was up to 10 days. The diagrams show these tumors to have high proliferative

activity (the combination of mitotic index and proliferation index — red and yellow sectors encircled by a red oval). Moreover, relatively low CLF indices call attention. In such cases the balance is shifted towards proliferation, and a tumor grows rapidly. Upper diagrams represent the patients with slow-growing tumors. The combination of low proliferation indices with high CLF parameters (up to 98–99%) significantly inhibits tumor growth. Tumor duplication time in 4 upper diagrams is from 57 to 104 days.

Now let us consider the combination of similar diagrams of group 1 (Fig. 4).

The diagrams are also bottom-up arranged in the order of tumor growth rate decrease. In addition to tumor duplication time, medical treatment schedules are designated. The diagrams demonstrate that the best results (maximum tumor duplication time — 162 days), when chemotherapy and radiotherapy were administered, were shown in the cases when relatively high tumor proliferation activity (mitosis rate — 10%, there were many target cells for cytostatics or ionizing radiation) was combined with high CLF indices (97–99%). The main difference from group 2 diagrams is in the fact that in group 2 low proliferative active tumors occupy upper lines.

Treatment efficacy starts decreasing markedly from the top downwards if CLF declines. Lower lines are occupied by relatively low-active tumors — there are less target cells to provide treatment (the exception is the second-from-the-bottom line).

The group 2 diagrams show the most fast-growing tumors — the cells with high proliferation indices and low CLF.

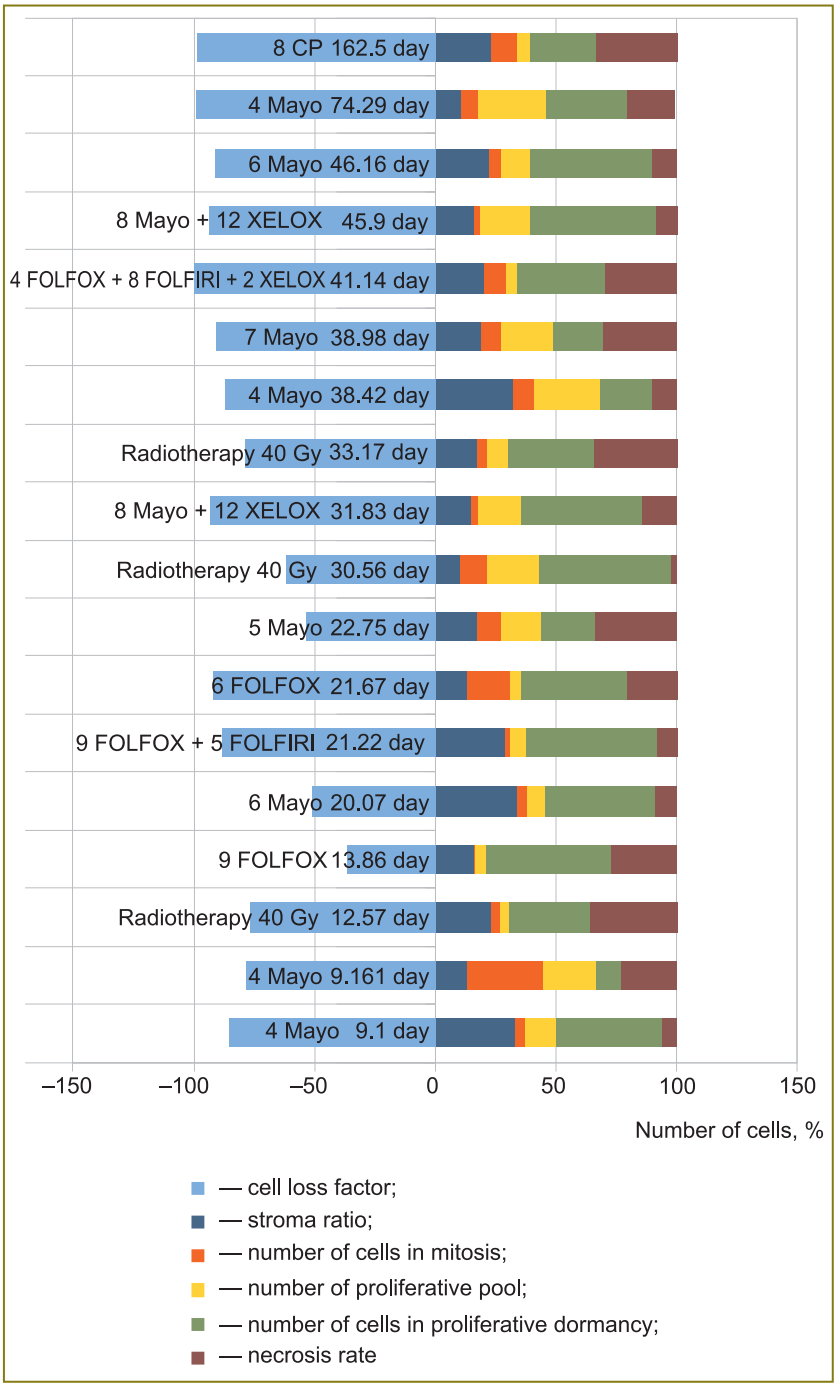

Fig. 4. Cytometric and kinetic characteristics of patients with additional therapy

In should be noted that there was no dependence of treatment efficacy on chemotherapy schedule used and the number of chemotherapy courses. So, the patients, who received the most common Mayo chemotherapy, rank not only two last positions but also the 2nd and the 3rd top lines. The patients with radiotherapy also hold different lines. According to our findings, there was no distinctive progress when high-cost treatment schedules were administered (FOLFOX, FOLFIRI, XELOX).

Conclusion. The developed model to assess adjuvant therapy efficacy has clearly shown that tumor growth rate and sensitivity to chemotherapy depend on the balance of tumor proliferative activity and cell loss factor. Maximum effect of adjuvant chemotherapy and postoperative radiotherapy can be achieved in case relatively high tumor mitotic activity indices are combined with high cell loss factor parameters. In all other cases the success of preventive medical treatment after radical surgery is disputable.

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