ORIGINAL RESEARCH

Objective Response Rate According to Response Evaluation Criteria in Solid Tumors in Patients with Metastatic Colorectal Cancer and Their Influence on Progression Free Survival and Overall Survival

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Abstract

Introduction. Colon cancer is one of the most common forms of cancer, affecting both sexes equally. The objective tumor response rate (ORR) is an important parameter that proves the effectiveness of treatment in oncology; one of the ways to evaluate ORR is the response evaluation criteria in solid tumors *Response evaluation criteria in solid tumors* (RECIST).

The aim of the research is to determine and compare the impact of the objective response rate in patients with metastatic colorectal cancer and the impact on *overall survival* (OS) and *progression-free survival* (PFS).

Methods. The work is based on a retrospective (2014-2020) clinical study, with follow-up of patients over a period of 5 years. The research included a total of n=101 patients diagnosed with colorectal cancer (stages II and III according to the *American Joint Committee of Cancer* -AJCC). Research included n=101 patients, 52% male, 48% female. The youngest patient is 18 years old, and the oldest patient is 80 years old.

Results. The average age is 59.69 years. The obtained data show that the largest percentage of *Colorectal Cancer*-CRC patients are in the third age. Adenocarcinoma is the most common pathohistological verification of colon cancer (77.23%). Overall survival and progression-free time in relation to objective response to therapy (ORR) according to RECIST criteria did not show statistical significance. One patient had a complete response (CR) to therapy, six patients (5.94%) had a partial response (PR) to therapy. Stable disease (SD) was verified in 32.67%, and disease progression (PD) was confirmed in 60.39% of subjects.

Conclusion. The extent of objective response to therapy has no influence on overall survival and survival without disease progression in patients with metastatic colorectal disease.

Key words: colorectal, cancer, response evaluation criteria in solid tumors.

INTRODUCTION

Objective response rate (ORR) refers to the percentage of individuals in a study or treatment group who exhibit a partial or complete response to the therapy within a specified timeframe (1, 2). A partial response refers to a decrease in tumor size or

the amount of cancer in the body, while a complete response means the total disappearance of all signs of cancer. In clinical trials, assessing the objective response rate helps evaluate the effectiveness of a new treatment (2). The Response Evaluation Criteria in Solid Tumors (RECIST) is a set of guidelines used to assess tumor response in cancer patients undergoing treatment. It defines whether tumors shrink, remain stable, or grow (progress) during therapy (1). Only patients with measurable disease at baseline should be included in studies where the primary endpoint is objective tumor response. These criteria are designed to evaluate tumor changes, not necessarily to assess overall patient improvement, as they focus on the tumor rather than the patient's overall condition (1, 2). Measurable disease is the presence of at least one measurable lesion. If measurable disease is limited to a solitary lesion, its neoplastic nature should be confirmed cytologically/histologically (1). Measurable lesions are lesions that can be accurately measured in at least one dimension with a longest diameter ≥20 mm using conventional techniques or ≥10 mm using helical computed tomography (CT), scanning (1).

Non-measurable lesions are all other lesions, including small lesions (longest diameter <20 mm with conventional techniques or <10 mm with helical CT scan) (1).

The theoretical basis for the RECIST criteria is that the sum of the longest diameters of individual tumors correlates more directly with the extent of cell death than the sum of two-dimensional measurements (4). According to the RECIST criteria, a partial response (PR) is defined as a reduction of at least 30% in the sum of the longest diameters of target lesions, while disease progression (PD) is defined as a 20% or greater increase in this sum. If tumors are assumed to be spherical, a 30% decrease in total diameter, which corresponds to a 65% reduction in tumor volume, is equivalent to a 50% reduction in the sum of the two-dimensional products (2, 3). Colorectal cancer originates from the epithelial cells lining the colon or rectum. It is primarily a disease of older adults, with colon cancer being one of the most common cancer types, affecting both men and women equally, and peaking in incidence during the seventh decade of life. Approximately 91% of new cases are diagnosed in individuals over 50 years old, with the average age at diagnosis ranging from 60 to 65 years. Colorectal cancer is relatively uncommon in younger individuals, with only about 9% of cases diagnosed before the age of 50, and 5-8% diagnosed before the age of 40 (4). Most colon cancers develop from malignant changes in colon polyps, with over 95% of cases arising from polyps, typically as adenocarcinomas (5). Over the past two decades, the incidence of colon cancer has been steadily and significantly increasing. In 2018, the global incidence of colorectal cancer was 19.7 per 100,000 people across all age groups and both sexes, according to GLOBOCAN (6). In Bosnia and Herzegovina, data from the International Agency for Research on Cancer (IARC) report approximately 663 new cases of colorectal cancer in women and 826 new cases in men annually, with 836 deaths expected each year from the disease (6).

In 5-10% of cases, colorectal cancer has a hereditary component, with 3-4% of these cases linked to Hereditary Non-Polyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome, which is associated with microsatellite instability (MSI) in specific DNA regions. This includes conditions like familial adenomatous polyposis, non-polyposis colorectal cancer, familial colorectal cancer, and hereditary adenocarcinomatosis syndrome (7, 8). The majority of colon cancers result from mutations in the Wnt signaling pathway, leading to increased activation of this pathway (9).

The aim of this research is to determine and compare the impact of objective response rate (ORR) in patients with metastatic colorectal cancer and its influence on overall survival (OS) and progression-free survival (PFS).

METHODS

Patients and study design

This study is based on a retrospective clinical analysis conducted between 2014 and 2020, with a follow-up period of 5 years. It involved a total of 101 patients diagnosed with colorectal cancer (stages II and III according to the AJCC) who underwent surgery at the Clinical Center University of Sarajevo (CCUS) and subsequently received adjuvant chemotherapy.

Methods

After adjuvant chemotherapy, patients were followed. Those patients whose distant metastasis was verified during the follow-up period were included in the study. Some patients were surgically treated and for some patients, the diagnosis was made by biopsy. After adjuvant chemotherapy, patients were followed up. Those patients with verified distant metastasis during the follow-up period were included in the study.

Overall survival (OS) calculation was done from the operation (the appearance of metastases) until the end of the study, until the last written finding or until the death of the patient. PFS calculation was also done from the appearance of metastases to verified disease progression, which was established by radiological reevaluation. ORR in patients was verified on the basis of periodic oncological examinations, and on the basis of RECIST criteria. OS, PFS and ORR data were taken from patient medical histories at the Clinic of Oncology, CCUS.

Statistical Methods

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) software for Windows. The Mantel-Cox test was applied to compare observed survival times with the expected survival times, under the null hypothesis that the survival functions of the two groups are identical. The Kaplan-Meier method was used to estimate the probability of survival past a certain time point, accounting for censored data. Additionally, a t-test was conducted to compare the means of two groups and assess whether there were significant differences between them.

RESULTS

Overall survival and progression-free time in relation to objective response to therapy (ORR) according to RECIST criteria did not show statistical significance. Our research (Figure 1) shows a slightly higher percentage of patients with PD, and a smaller percentage of patients with SD.

One patient had a complete response to therapy (0.99%). Six patients (5.94%) had a partial response to therapy. Stable disease was verified in (n=33) patients or 32.67%, and disease progression was confirmed in (n=61) patients or 60.39%.

Figure 1. Objective response rate to therapy in the examined group of patients

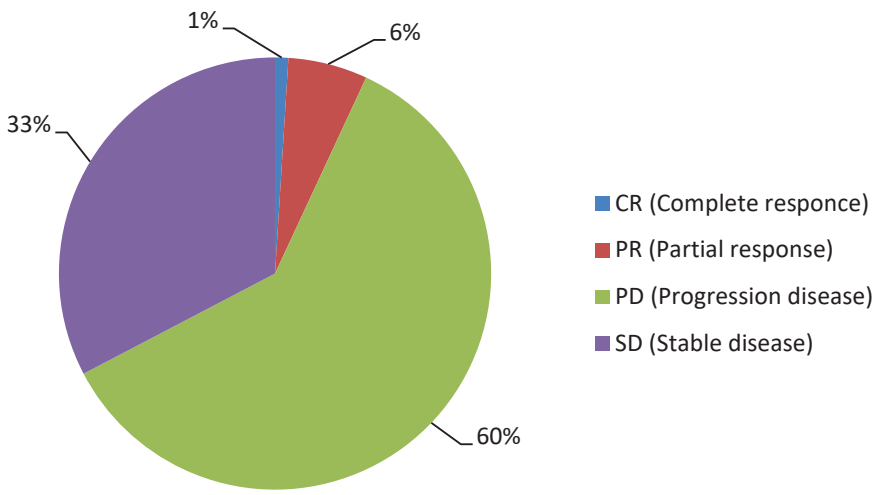

Table 1. Overall survival in relation to objective response to therapy

		t-test for equal means						
		t	df	Sig. (2-end)	Mean value t difference	Standard error of difference	95% Interval trust the difference	
							Lower	Top
In total	Probably	-	99	.066	-4.883	2.629	-10.100	.334
survival	equal variations	1.857						
(months)	Equal	-	72.613	.045	-4.883	2.393	-9.653	-.113
	variations are not likely	2.040						

df-degree of freedom; sig. - level of significance.

The t-test of independent samples did not reveal a statistically significant difference in the length of overall survival (OS) between patients with stable (9.77±10.15) and progressive disease (PD) (14.66±12.98), t=-1.86, p=0.66, (95% CI: -10.10-0.33). The average difference in OS length by group was 4.88 days.

The t-test of independent samples did not establish a statistically significant difference in the length of survival without disease progression (PFS) between patients with stable (SD) (8.45±7.43) and progressive disease (PD) (9.61±7.18), t=- 0.742, p=0.46, (95% CI: -4.27-1.94). The average difference in the length of PFS by groups was 1.16 days.

Discussion

The study included n=101 patients, of which n=53 or 52% were male, and n=48 or 48% were female (10,11). The largest number of patients are in their third age. Looking at the age structure, we notice that the largest proportion of patients (n=86) or 85.15% are over 50 years of age, while younger patients (up to 50 years of age) make up only 14.85% (n=15) and of these, only n=2 patients or 1.98% are under 30 years of age. The obtained data on the sex structure correspond to the data from the literature (10).

By reviewing the age structure, we can see that the largest proportion of patients (n=86) or 85.15% are over 50 years of age, while younger patients (up to 50 years of age) make only 14.85% (n=15) (10), and of these younger than 30 years only n=2 patients or 1.98%. The youngest patient included in the research is 18 years old, and the oldest patient is 80 years old. American Cancer Society research from 2020 shows that patients under the age of 50 make 12% of patients. The obtained data correspond to the data of the consulted literature, which supports the fact that the largest percentage is made up of patients in their third age (12, 13).

Overall survival and progression-free time in relation to objective response to therapy (ORR) according to RECIST criteria did not show statistical significance. *Lucidarma O. et al.* in their prospective two-month study had 57% of patients with stable disease (SD) and 43% with progressive disease (PD) (14). Our research shows a slightly higher percentage of patients with PD and a smaller percentage of patients with SD.

Table 2. Survival without disease progression in relation to the objective response to therapy

		t-test for equal means						
		t	df	Sig. (2-end)	Mean value t difference	Standard error of difference	95% Interval trust the difference	
							Lower	Top
Progression free survival	Likely equal variances	- .742	99	.460	-1.163	1.566	-4.270	1.945
	Equal variations are not likely	- .733	55.783	.467	-1.163	1.587	-4.342	2.017

df-degree of freedom; sig. - level of significance.

Of the total number of patients with metastatic colorectal cancer included in the study, n=62 or 61.39% survived to the end of the study. Five-year survival ranges from 50 to 59% for patients with colorectal cancer in many countries (7). Patients with liver metastases have a median survival of 5 to 20 months without treatment (15). *Valderama et al.* state that in 14–18% of patients, metastases are recorded at the first examination, 10–25% of patients have liver metastases during the first operation, and the incidence of liver metastases additionally "jumps" after the use of *Computed Tomography Scan* (CT) diagnostics. The mentioned research says that even about 70% of patients with colorectal cancer will develop liver metastases (15).

Shahab D. et al. indicate in their research that in locally advanced colon cancer, 15–20% of patients are treated with neoadjuvant chemoradiotherapy, achieving a pathologically complete response to therapy (16, 17). The benefit of adjuvant chemotherapy is controversial in patients with rectal cancer. An eight-year study by *Shahab D et al.* shows a difference in 5-year OS for patients who received neoadjuvant chemoradiotherapy plus adjuvant (94%) and patients who received only neoadjuvant chemoradiotherapy (84%) (16, 17).

Conclusion

The extent of objective response to therapy has no influence on overall survival and survival without disease progression.

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Declaration of Patient Consent: Written, informed consent was obtained from all volunteers in the study.

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Conflict of Interest: None.

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