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Pseudoprogression; discussion of the concept of pseudoprogression on the characteristics of tomographic changes in liver metastases of colorectal cancer patients receiving bevacizumab therapy

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Abstract

In this study, we aimed to investigate the concept of pseudoprogression in colorectal cancer patients with liver metastases receiving bevacizumab treatment by considering the changes in the shape, size, and density of liver metastases by abdominal Computed Tomography (CT) scans taken before and after treatment. This study is a retrospective evaluation of 16 patients with metastatic colorectal cancer treated with 5-fluorouracil, leucovorin, irinotecan and bevacizumab and is based on computed tissue analysis of the dominant liver lesion at baseline and 2 months after chemotherapy. The borders of all metastatic lesions observed in the livers of patients treated with bevacizumab after adjuvant chemotherapy were sharpened, the size of some lesions remained the same while others increased, and the density of most metastatic lesions decreased. In our study, we concluded that the evaluation of response to treatment based only on size and number should be avoided by noting a pseudoprogression in liver metastases that shows an increase in size but no progression on clinical/laboratory and follow-up images.

Keywords: Bevacizumab, colon cancer, pseudoprogression, metastasis

Introduction

Colorectal cancer is the third most common solid cancer in the world. In terms of gender predominance, it is more common in men and is more prevalent in developed countries [1]. Furthermore, approximately 45% of patients with colon cancer develop liver metastases and colorectal liver metastases have heterogeneous histopathologic and immunohistochemical phenotypes that produce variable responses to treatment. According to world cancer statistics, the liver is one of the most common metastasis sites for all tumor types and liver metastases are more common than primary liver cancers. Approximately 15% of patients are diagnosed with synchronous liver metastases at initial diagnosis, and up to half of the remaining patients are diagnosed with liver metastases later in life. Considering that liver metastases are an important cause of death in colorectal cancer patients, therapeutic research is an important goal in order to plan the treatment of liver metastases in colorectal cancers correctly and to make the right decisions. [2,3].

Material and Methods

Patients who were admitted to SBU Dr. Abdurahman Yurtaslan Ankara Oncology Training and Research Hospital between 2015 and 2017, diagnosed with colorectal cancer, referred to the Radiology Clinic for metastasis screening, received

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5-fluorouracil, leucovorin, irinotecan and bevacizumab treatment for the presence of liver metastases, and responded to treatment clinically and laboratorially were included in the study. In this study, we retrospectively evaluated the morphologic changes and density changes in the target metastatic lesions of 16 consecutive patients in whom we obtained abdominal Computed Tomography (CT) control imaging before and 2 months after treatment by selecting the largest lesion in liver metastases as the target metastatic lesion in our patient series. Approval for our study was obtained from the clinical studies ethics committee of our hospital dated 21.12.2022 and numbered 2022-12/5.

Results

Of the patients included in the study, 4 (25%) were female patients and 12 (75%) were male patients. The age range of the patients included in the study was 42 to 77 years with a mean age of 66 years. When we looked at the tumor subtypes, only one of them had mucinous adenocarcinoma subtype, while the others were adenocarcinomas.

When we evaluated the control CT scans taken before and 2 months after bevacizumab treatment after adjuvant chemotherapy, we found that the perilesional borders of all target metastatic lesions in the liver were sharpened in the control abdominal CT scans of 16 patients. Our other findings were as follows; the intensity of only 2 (13%) target metastatic lesions remained the same after treatment, while the intensity of 14 lesions (87%) decreased. The range of change in density ranged from 3 HU to 27 HU and the mean decrease in density was 12 HU. Furthermore, the largest diameter of the target lesion remained the same in 3 patients (19%) and increased in 12 patients (81%) after treatment. The mean increase in the diameter of the target metastatic lesions after treatment was 14 mm, with a 270% increase in the diameter of the lesion with the largest diameter increase (Table 1).

Table 1. Demographic data of the participants and changes in diameter and density of the lesions

Age	Gender	Subtype	Before-after diameter mm	Increase mm	Before-after density HU	Decrease HU
62	M	Mucinous CA	17-22	5	21-18	3
55	M	Adeno CA	42-55	13	56-46	10
72	F	Adeno CA	40-44	4	40-40	-
74	M	Adeno CA	25-32	7	52-45	7
60	M	Adeno CA	35-44	9	52-44	8
73	M	Adeno CA	48-68	20	48-48	-
55	F	Adeno CA	156-164	8	66-48	18
51	M	Adeno CA	75-91	16	28-20	8
54	M	Adeno CA	21-21	-	35-35	-
54	M	Adeno CA	28-28	-	52-46	6
70	M	Adeno CA	34-92	58	55-32	13
42	F	Adeno CA	52-65	13	78-51	27
77	F	Adeno CA	28-38	10	42-28	14
74	M	Adeno CA	18-18	-	76-60	16
63	M	Adeno CA	33-44	11	36-28	8
67	M	Adeno CA	21-27	6		

Discussion

According to world cancer statistics, the liver is one of the most common sites of metastasis for all tumor types and liver metastases are more common than primary liver cancers [4,5]. Tumors of the gastrointestinal tract, genitourinary system, gynecologic system, neuroendocrine system and soft tissue sarcomas; melanomas; and lymphoma tend to metastasize to the liver [6].When we look at the metastasis orientation of colorectal cancers, the liver again stands out as the most common metastasis site and this order continues as lungs, lymph nodes and peritoneum [1].

It is known that patients with liver metastases have a worse prognosis than those without, and the majority of colon cancer patients die from progression of metastatic disease rather than primary tumors [7,8].Today, with the introduction of best practices in cancer treatment management, mortality rates in colorectal cancers, as in many cancers, are gradually decreasing [1]. One of these therapies, bevacizumab, a monoclonal antibody targeting vascular endothelial growth factor (VEGF), has an important role in the treatment of metastatic colorectal cancer [9]. VEGF is a glycoprotein that is an important regulator of physiological and pathological angiogenesis [10].

Bevacizumab is known to inhibit tumor growth by inhibiting the effect of VEGF on vascular structures, reducing tumor vascularization and preventing the development of new blood vessels [9]. Bevacizumab offers highly successful treatment results when used in combination with cytotoxic chemotherapy in colorectal cancer patients with liver metastases [11,12].

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The Response Evaluation Criteria in Solid Tumors (RECIST) criteria were developed to evaluate the reduction in tumor size after cytotoxic chemotherapy [11]. However, it is now accepted that the classical RECIST criteria used to evaluate tumor response to treatment are inadequate for evaluating cancer treatment with immunomodulatory agents [11]. Morphological response criteria based on CT scanning have been shown to have a statistically significant relationship with pathological response and overall survival and have much more correlated results compared to classical RECIST response criteria. In addition, there are studies presenting data suggesting that RECIST criteria only capture volumetric changes and may misinterpret patients who actually respond to treatment as having disease progression after bevacizumab therapy [13-15]. Indeed, in our patients, the diameter of metastatic lesions in the liver remained the same after bevacizumab treatment in only 3 patients, while in the remaining patients the lesion diameters increased after treatment. According to the classical RECIST criteria, since the diameter of these lesions increased, this could be considered in favour of progression, but there was no clinical or laboratory evidence in favour of progression in our patients.

A study by Hodi et al. compared patterns of response to treatment during PD-1 inhibitor therapy using RECIST1.1 criteria and immune-related response criteria (irRC) to better standardize immune-related response criteria [16]. This study demonstrated that traditional RECIST assessment alone may underestimate the benefit of PD-1 inhibitor therapy and reiterated the need to rely on these immune-related response assessment criteria [17].

In non-contrast CT series, the attenuation of lesions varies according to the proportions of areas containing mucin, fibrosis, calcification, and tumor cells, and the lowest attenuation is seen in the center of the tumor, while usually, the center of the tumor is surrounded by an irregular, often nodular rim of tissue with relatively higher attenuation [11]. Rarely, pretreatment colorectal liver metastases have homogeneous low attenuation [11]. And also the interface between the metastatic lesion and the perilesional tissue is usually obscured before any treatment. In our study, under bevacizumab treatment, only two target metastatic lesions had a density of less than 30 HU and appeared more hypoattenuated, while the others were heterogeneous high-density masses and the interface between the perilesional area and target metastatic lesions was faint. After treatment, only 2 target metastatic lesions remained unchanged in density, while 14 lesions decreased in density. The range of change in density ranged from 3 HU to 27 HU and the mean decrease in densities was 12 HU. After treatment, the largest diameter of 3 target metastatic lesions remained the same, while the diameter of 13 target metastatic lesions increased. The mean diameter increase in target metastatic lesions after treatment was 14 mm, and the diameter of the lesion with the largest diameter increase was 270%. In addition, the borders of all target metastatic lesions evaluated after treatment were sharpened. As our study demonstrated, in patients with metastatic colorectal cancer treated with adjuvant chemotherapy plus bevacizumab, the change in metastases from heterogeneous masses with indistinct borders revealed by imaging methods to homogeneous hypo-atenuated lesions with sharp borders is actually a morphologic type of response revealed by CT findings.

These different patterns of response to treatment highlight the importance of accurate radiological interpretation in patients receiving immunotherapy, which requires special attention and knowledge, Pseudoprogression actually describes one of the patterns of response of the tumor under treatment. The rate of pseudoprogression varies between 4.5% and 8% in different tumor subgroups receiving different treatments, and in some meta-analyses this rate has been reported to be 6% on average [18,19].

Conclusions

In the oncologic patient group, the decision to give the right and adequate treatment or to terminate ongoing treatment is of vital importance for patient survival. Many studies have shown that combined treatments with bevacizumab prolong the average overall survival and progression-free survival [9,11].Therefore, pseudoprogression should be taken into consideration when making the decision of no response to treatment and radiologic morphologic response should be evaluated for a pseudo type of progression that only shows an increase in size or number but does not show progression on clinical/laboratory and follow-up images. This evaluation is important in terms of the risk of early termination of treatment and large series studies should be continued in this regard.

Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical Approval
Ethics committee approval was obtained from the clinical studies ethics committee with the date 21.12.2022 and number 2022-12/5.

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