RESEARCH ARTICLE

Colorectal cancers metastases clinicopathology, and PET/CT

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Abstract

Objective: To investigate the difference in primary tumour locations according to the organs to which colorectal cancers metastasised.

Method: The retrospective study was conducted at the Health Sciences University, Gulhane Training and Research Hospital, Ankara, Turkiye, and comprised data from January 2011 to January 2021 of metastatic colorectal cancer patients. The data was divided into three groups based on their primary tumour locations as per the positron emission tomography and computed tomography images. The ascending colon and transverse colon were categorised as right-sided and placed in group 1, the descending colon and sigmoid colon were categorised as left-sided and placed in group 2, while rectal cancers were placed in group 3. The groups were compared in terms of the organs to which their cancer metastasised. Data was analysed using SPSS 15.

Results: Of the 83 patients, 52(62.6%) were males and 31(37.4%) were females. The overall mean age was 63.58±10.2 years (range: 34-87 years). There were 44(53%) patients in group 1, 22(26.5%) in group 2, and 17(20.5%) in group 3 (p=0.053). Liver alone encountered metastases in 48(57.8%) cases. The frequency of only lung metastasis, and only liver metastasis in group 1 was higher than the other groups (p=0.001). There was no significant difference among the groups in terms of synchronous metastatic spread of cancer to both the liver and the lungs (p=0.031).

Conclusion: The right-sided colon tumours had a higher potential to metastasise compared to the other colon cases.

Keywords: Colorectal cancer, Metastases physiology, PET, CT. (JPMA 76: 201; 2026)

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Introduction

Cancer is the second leading cause of death worldwide, and accounted for nearly 10 million deaths in 2020. Lung, prostate, colorectal, stomach and liver cancers are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid cancers are the most common among women.[1-3] Breast, lung and colorectal cancers (CRCs) have also been reported as common cancer types.[4-7] The likelihood of the success of curative surgical treatment in early-stage CRCs is >90%. In more advanced stages, the expectation of curative treatment and survival decreases. Metastases are present at the time of diagnosis in 25-30% of CRC patients, and their 5-year survival rate is <15%.[8,9] About 25-30% of stage-2 and stage-3 CRC cases who undergo surgical treatment progress to stage-4, with liver and/or lung metastases within the first5 years.[10-14] Until 40-50 years ago, surgical treatment was not indicated in metastatic CRCs (mCRCs), and only palliative care was provided. Today, as a result of advancements in radiological imaging methods, such as computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET), patients can be examined more accurately, while combined surgical treatments involving liver and lung resections can be performed with the help of developments in anaesthesiology and surgical techniques, leading to increase in the 5-year survival expectancy.

Studies, including large series regarding CRC metastases, have revealed different metastatic characteristics of tumours localised in the proximal and distal regions of the colon. In addition to the anatomical characteristics of the colon, this difference has been linked to biogenetic factors and embryological differences, such as the fact that the right colon originates from the midgut, while the left colon and the rectum originate from the hindgut.[15-19] CRCs usually metastasise to the liver first through the portal venous system, followed by the lungs, and other distant organs. The most significant known routes of metastasis are the lymphatic and haematogenous routes. The haematogenous route may also explain the distant organ metastasis of rectal cancers by skipping portal circulation and reaching systemic circulation through the middle and inferior rectal veins.[20-22] In contrast to liver metastases, lung metastases occur through the lymphatic route rather than the haematogenous route, and the rate of lung metastasis (lung-only) without liver metastasis in right-sided colon

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cancers has been reported higher in comparison to left-sided colon cancers and rectal cancers.[12,20,23] Some reasons for this have been listed as factors such as tumour physiopathology, antigenic structure, and tumour microenvironment-organ hosting, rather than the route of the spread.

Besides these anatomical and embryological properties, cancer biology and tumour-suppressing genes, as well as genetic changes, such as oncogenes, and deoxyribonucleic acid (DNA) repair mechanisms also affect the form of metastasis.[24,25] According to genetic data that obtained about the development and progression of CRCs and oncogenic mutations that have been identified, it is accepted that 5% of CRCs are hereditary, 20-25% are familial, and 70-75% are sporadic.[17]

Quite a few studies have emphasised that right-sided CRCs metastasise more frequently, and show a poorer prognosis than left-sided CRCs and rectal cancers.[12,15,16,18-22] Knowing the organs to which CRCs are likely to metastasise, and the mechanisms of these metastases are important factors that affect the prognosis and treatment of the disease.

The current study was planned to investigate the difference in primary tumour locations according to the organs to which CRCs metastasised.

Materials and Methods

The retrospective study was conducted at the Health Sciences University, Gulhane Training and Research Hospital, Ankara, Turkiye, and comprised data from January 2011 to January 2021 of metastatic CRC patients. After approval from the institutional ethics review committee, all patients diagnosed with CRC who had been referred to the nuclear medicine clinic for PET/CT imaging and were found to be metastatic were evaluated. Patients diagnosed with colorectal cancer and referred to our nuclear medicine department for follow-up and PET/CT scans between 2011 and 2021 were included in the study. Inclusion criteria included having a primary colorectal cancer diagnosis and not being pregnant or breastfeeding, which would prevent radioactive injection. Patients who underwent PET/CT scans outside our hospital or whose follow-up was ongoing outside our hospital were excluded from the study. Patients who were diagnosed with a secondary malignancy during follow-up were excluded from the study.

A retrospective review of images from a total of 88 patients was conducted. A review of the medical histories of these patients revealed a history of squamous cell carcinoma of the skin in two patients, and one patient underwent surgery for basal cell carcinoma. Furthermore, one patient underwent surgery for renal cell carcinoma, and one underwent transurethral resection of the prostate without a known diagnosis. The imaging data of these patients were excluded from the study.

The study included patients diagnosed with colorectal cancer who presented to the nuclear medicine clinic for PET/CT and were followed up at our hospital.

Since the sensitivity of PET/CT imaging method in the mucinous pathology subtype is low, only lesions in the adenocarcinoma pathological subgroup were included. The sample was raised using consecutive simple sampling method. All patients diagnosed with metastatic CRC were included. Informed consent had been obtained from all the patients.

When the PET/CT images were examined, the location of the colonic segment where the CRC was diagnosed was noted, and the localisation of the spread of the tumour was evaluated. In all these patients, treatment was started according to the PET/CT imaging results performed for restaging purposes, and FDG PET/CT imaging was performed again after an appropriate time for response evaluation. On imaging, the spread of the primary tumour was metastatic, which was confirmed by the response to the treatment.

The data was divided into three groups based on their primary tumour locations as per the PET/CT images. The ascending colon and transverse colon were categorised as right-sided and placed in group 1, the descending colon and sigmoid colon were categorised as left-sided and placed in group 2, while rectal cancers were placed in group 3. The groups were compared in terms of the organs to which their cancer had metastasised (Figures 1-2). Data was analysed using SPSS 15. Data was expressed as frequencies and percentages, or as mean±standard

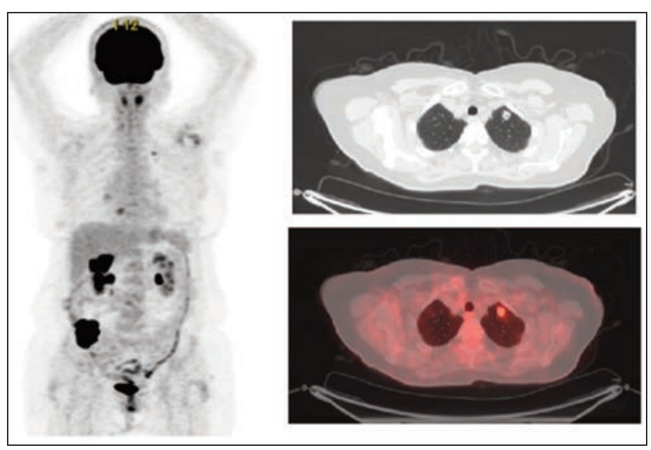

Figure-1: A 41-year-old female patient's fluorodeoxyglucose (FDG) positron emission tomography (PET) and computed tomography (CT) images showing right colonic primary lesion and multiple lung metastases.

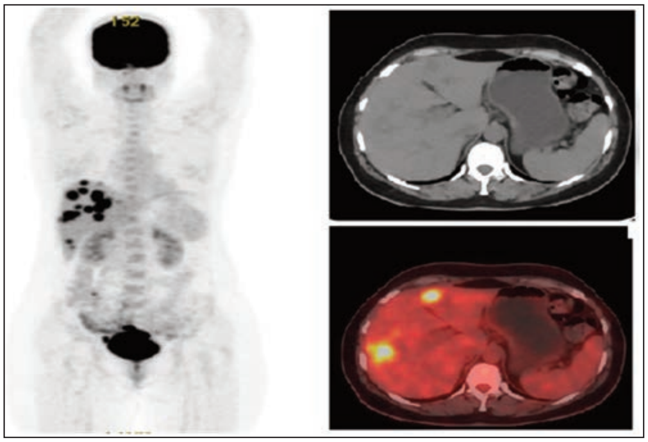

Figure-2: A 53-year-old female patient was operated for right colonic tumour. After 6 months of surgery, fluorodeoxyglucose (FDG) positron emission tomography (PET) and computed tomography (CT) showed multiple liver

deviation, as appropriate. Chi-square test and Fischer's exact tests were used for intergroup analyses. P<0.05 was considered statistically significant.

Results

Of the 83 patients, 52 (62.6%) were males and 31(37.4%) were females. The overall mean age was 63.58±10.2 years (range: 34-87 years). There were 44(53%) patients in group 1, 22(26.5%) in group 2, and 17(20.5%) in group 3 (p=0.053) (Table 1).

A retrospective analysis of this patient group revealed that two patients had a history of squamous cell carcinoma of the skin, and one patient had undergone surgery for basal cell carcinoma. Furthermore, one patient underwent surgery for renal cell carcinoma, and one patient underwent transurethral resection of the prostate gland without an known diagnosis. Imaging data from these patients were excluded from the study.

Liver-only metastasis was noted in 48(57.8%) cases, followed by lung-only 21(25.3%), while both lung and liver were involved in 14(16.7%) cases (Table 2). The frequency of lung-only metastasis, and liver-only metastasis in group 1 was higher than the other groups (p=0.001). There was no significant difference among the groups in terms of synchronous metastatic spread of cancer to both the liver

Table-1: Demographic characteristics of the patients.

Characteristics of the patients		**n (%)**
Mean Age (years)	63.58±10.2 (34–87)	
Gender		
Female		31 (37.4)
Male		52 (62.6)
Primary tumour localisation		
Right colon		44 (53)
Left colon		22 (26.5)
Rectum		7 (20.5)

Table-2: Metastatic regions in cases of different primary tumour locations.

Metastatic Regions	**Only Lung Met (± met to other organ(s) except the liver)** n (%)	**Only Liver Met (± met to other organ(s) except the lungs)** n (%)	**Liver + Lung Synchronous Met** n (%)
Right colon	12 (57.1)	27 (56.2)	6 (42.8)
Left colon	5 (23.8)	11 (23)	6 (42.8)
Rectum	4 (19.1)	10 (20.8)	2 (14.4)
Total	21	48	14

Met: Metastasis.

and the lungs (p=0.031). Besides the liver and lung metastases cases, 1(1.2%) patient had spleen metastasis, 1(1.2%) had adrenal gland metastasis, 1(1.2%) had brain metastasis, and 8(9.6%) had bone metastasis.

Discussion

CRCs constitute a group of diseases that are characterised by specific molecular, morphological and phenotypic changes. Several studies have emphasised the differences between right-sided and left-sided CRC cases, and some studies have reported differences in pathogenesis, biogenetic and bio-molecular pathways, and metastatic characteristics based on primary tumour locations.[26-30]

As the diameter of the right colon is larger than that of the left colon, clinical symptoms emerge later, and the diagnosis may be delayed. Thus, right colon cancers are more likely to be detected in the metastasis stage compared to left colon and rectal cancers. As opposed to the case in other CRCs, rectal cancers can metastasise through the haematogenous route through the middle and inferior haemorrhoidal veins outside the portal venous system, and lung metastases without the presence of liver metastasis can be observed. Nevertheless, besides these anatomical and clinical characteristics, there are also studies arguing that bio-molecular and biogenetic factors, like genetic mutations, play a significant role in the emergence and clinical characteristics of cancers.[11,24,30]

The results obtained in studies in recent years on tumour biology and tumour genetics have shown that more comprehensive studies need to be conducted for a complete understanding of the development and metastatic behaviours of CRCs. Some biogenetics-based studies have defined three different pathways in the onset and development of CRCs; chromosomal instability (CIN), microsatellite instability (MSI) and the cytosine-phosphate-guanine (CpG) island methylation phenotype (CIMP). CIN is the most common (85%) genetic mechanism in CRC.[25,29] Nonetheless, these pathways are far from explaining the differences in the mechanisms of metastasis. So far, 59 different gene expressions associated with liver metastasis, 90 gene expressions associated with lung metastasis, and 45 gene expressions associated with both liver and lung metastases in CRCs have been identified along with seven different types of genes that affect both liver and lung metastases.[25] There is a need for more advanced studies to precisely determine to which organ metastasis will take place in which patient.

Serine/threonine-protein kinase B-Raf (BRAF) and Kristen Rat Sarcoma Viral oncogene homologue (KRAS) mutations provide information about the prognosis of the disease. As the stage advances in CRCs, the incidence of BRAF mutations increases, and this situation is accepted as an indicator of poor prognosis. Cancers localised in the right colon show a worse prognosis in comparison to left colon cancers, and KRAS wild-type and BRAF mutations are encountered more frequently in right colon cancers.[11,17,24,29.30] Studies on the biogenetics of cancer continue to be conducted at a fast pace, and in the light of the obtained data, clinical experimental studies have been initiated to prevent the development of cancer or stop its progression. The messenger ribonucleic acid (mRNA) vaccine, called BioNTech-122 (BNT122) (RO7198457), was administered to 108 mCRC patients in phase-Ib, and because T-cell immune responses were observed in 77% of the patients, the phase-II study was started in October 2020.[30]

Classifying tumours according to the particular mutations present is necessary in determining the treatment regimen to be offered. A combination of either 5-fluorouracil or capecitabine is usually offered as the main line of treatment. Targetted therapies, such as vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors, have recently been found effective as both first and second lines of treatment in CRC. However, evidence suggests that targetted therapy, like anti-EGFR treatment, is effective only in tumours lacking codon 12 and 13 mutations in KRAS. The treatment may even be detrimental when used with oxaliplatin in patients with KRAS-mutated tumours.[30] The BRAF mutation correlated with poor disease specific survival also confers resistance to anti-EGFR therapies even in the presence of wild-type KRAS. Similarly, the presence of microsatellite instability has been shown to be predictive of failure of the standard, first-line 5-fluorouracil treatment.[31]

In the light of the current findings, in isolated metastases to the liver, or the lungs, right colon tumours should be suspected first, while, on the other hand, in synchronous metastases to the liver and the lungs, the location of the primary tumour is not expected to indicate a difference. Considering all-organ metastases, mCRCs mostly originate from the right colon. Conducting further studies on the biogenetics and clinical behaviours of cancers may result in significant development in protection from CRCs, and their treatment.

Limitation: The sample size was not calculated which could influence the generalisability of the study.

Conclusion

The right-sided colon tumours had a higher potential to metastasise compared to the other colon cases.

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Author Contribution:

AC: Data analysis, interpretation, drafting and revision.

DC: Final approval and agreement to be accountable for all aspects of the work.