Journal of Clinical and Investigative Surgery

https://doi.org/10.25083/2559-5555
https://proscholar.org/jcis/
ISSN: 2559-5555

Colorectal carcinoma incidence and association of preoperative carcinoembryonic antigen levels with staging and histological types in the Malabar region; A cross-sectional study

Bibin James[1], Edathikudi Manjush[2*]

[1]*Junior Resident, Department of General Surgery, Govt. Medical College, Kozhikode, Kerala, India*
[2]*Associate Professor, Department of General Surgery, Govt. Medical College, Kozhikode, Kerala, India*

ABSTRACT

Introduction. Colorectal carcinoma has a tendency to increase in recent times worldwide. Even though it is less prevalent in the developing world like India, Kerala has seen a sudden increase in incidence due to changing lifestyle and dietary habits. *Objectives*. The study aims to describe the epidemiological characteristics of colorectal cancer in adults from the Malabar region, and to find out the relationship between preoperative carcinoembryonic antigen (CEA) values with histological results and TNM staging. *Methods*. This is a descriptive cross-sectional study conducted at Government Medical College, Kozhikode over a period of 1 year and 6 months starting from July 2020. 168 adult patients aged above 30 years were included in the study. *Results*. 92 out of 168 patients included in the study (54.8%) were men, colorectal carcinoma being more common in the 50-70 age group. The most common histological variant was well-differentiated adenocarcinoma. 32.7% of the study population had higher CEA levels (>5 ng/ml). *Conclusion*. While CEA levels in 67.3% of study subjects were within normal limits, the obtained data showed that preoperative CEA levels had a statistically significant relationship only with TNM staging, and not with histological variants.

Category: Original Research Paper

Received: April 13, 2022
Accepted: June 29, 2022
Published: November 20, 2022

Keywords:

colorectal carcinoma, carcinoembryonic antigen, dietary factors, TNM staging

***Corresponding author:**

Edathikudi Manjush,

Associate Professor (CAP); Department of General Surgery, Govt. Medical College, Kozhikode, Kerala, India

E-mail: drmanjushe@gmail.com, manjush.e@rediffmail.com

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the fourth leading cause of cancer death globally, with steadily increasing mortality rates [1-3]. At the same time, CRC is third in terms of recognition/diagnosis (6.1%) and second in terms of mortality (9.2%). It is estimated that by 2035, the total number of deaths from rectal and colon cancer will increase by 60% and 71.5%, respectively [4-6].

As the incidence of CRC, it is the seventh most common cancer in India and the fourth most common in Kerala [7,8]. It is more common in developed countries than in developing countries. Even though the incidence in India is low, Kerala has shown an increase in incidence in recent times. Worldwide the prevalence of colorectal carcinoma is closely associated with the consumption of red meat and especially processed meat products. Therefore, there is a need to study the risk factors of colorectal cancer in Kerala, especially in the Malabar region, as there is a high intake of meat products in the region. Our institution is the largest tertiary care center for the four districts of the Malabar region. And the food habits of the people here are different from other parts, the food of Malabar being famous all over the world.

Lifestyle changes, including high-fat diet, lack of exercise and mental stress, have led to an increase in CRC cases. Radical surgery still remains the best therapeutic option for CRC patients [9,10]. Tumor biomarkers are widely used in the diagnosis, postoperative follow-up of tumor recurrence, prognosis and curative therapy of CRC cases [11-13].

Serum CEA is a universally used tumor marker for colorectal malignancies. Even so, the significance of pre- and post-operative CEA levels is still controversial [14]. The study by Hotta et al. reported that the pre- and post-operative CEA ratio is the prognostic predictor after surgery in stage III rectal cancer [15].

CRC tumor is evaluated by TNM staging for treatment purpose. There are different histological variants of CRC, as in any form of cancer. Forms such as adenocarcinoma (including well-differentiated, moderately differentiated

To cite this article: James B, Manjush E. Colorectal carcinoma incidence and association of preoperative carcinoembryonic antigen levels with staging and histological types in the Malabar region; A cross-sectional study. *J Clin Investig Surg*. 2022;7(2):185-190. doi: 10.25083/2559.5555/7.2.12

and poorly differentiated tumors), signet ring tumors, mucinous tumors, etc. have been described.

Elevated preoperative CEA levels correlate with older age, circumferential tumors, large colon tumors, liver metastases, and high-stage tumors.

The objective of our study is to analyze the incidence of colorectal carcinoma in adults in Malabar region and also to find out the relationship between serum CEA with different histological tumor variants and its TNM staging.

Materials and Methods

Study design

This is a descriptive cross-sectional analysis of prospectively collected data from a single general surgery department. 168 patients operated on for colorectal adenocarcinoma over 1 year and 6 months at the Department of General Surgery, Government Medical College, Kozhikode.

Ethics statement

Ethics committee approval was received for this study from the ethics committee of the Government Medical College, Kozhikode, India. Written informed consent was obtained from patients participating in this study.

Study Population

Adult patients over 30 years who are diagnosed with colorectal carcinoma and operated on from the Department of General Surgery. All patients over 30 years of age newly diagnosed with colorectal carcinoma were also included in the study.

Exclusion criteria were patient age below 30 years, patients with other synchronous malignancies, patient with history of other malignancies or recurrences, patient with pre-malignant lesions, and patients with family history of colorectal carcinoma or premalignant lesions.

Sample size calculation

The number of enrolled patients was calculated using the formula [8,16]:

N = Z2P (1-P)/d2

Where N = minimum required sample size

Z = value of 1.96 for 95% confidence interval

P = highest prevalence of pregnancy induced-hypertension in India (10.3%).

d = absolute precision of 5% or 0.05.

N= 168.

Study variables

Independent variables such as demographics and dependent variables such as tumor site, presenting complaints, histopathology, serum CEA levels, and metastases were measured.

Statistics

The Statistical Package for Social Sciences software version 20.0 was used for data analysis (SPSS Inc. Chicago, IL, USA). The chi-square test was used to analyze the significance between categorical variables. The dependent variables were analyzed by the t-test. Spearman correlation analysis was performed to explain this relationship. A p value < 0.05 was considered as a statistically significant result.

Results

In the present study, data from 168 patients diagnosed with colorectal cancer over an 18-month period were evaluated.

The mean age was 59.6 years (range 33 to 85 years). The male: female ratio was 54.8:45.2. Most of the patients were in the age group of 50-70 years which measured 55.4% followed by 23.8% in 70-90 years and 20.8% in 30-50 years respectively.

The presenting complaints and dietary habits of the colorectal patients were described in Table 1. The histology, CEA levels and staging of the colorectal patients were detailed in Table 2

Table 1. Presenting complaints, religion, food habits and site of lesion

	frequency	percentage
Presenting complaints		
Bleeding PR	92	54.8
Abdominal pain	32	19.0
Constipation	2	1.2
Low	6	3.6
LOA	1	0.6
Obstruction	22	13.1
Altered bowel habits	3	1.8
Anemia	2	1.2
Incidental	2	1.2
Mass P/A	1	0.6
Religion		
Hindu	85	50.6
Muslim	77	45.8
Christian	6	3.6
Food habits		
Veg	14	8.3
Non veg	152	90.5
Total	166	98.8
Site of lesion		
Ascending colon	9	5.4
Transverse colon	8	4.8
Descending colon	11	6.5
Sigmoid	27	16.1
Rectosigmoid	23	13.7
Rectum	79	47.0
Caecum	11	6.5

When CEA levels were evaluated with tumor differentiation degrees, and found no statistically significant correlation was identified between the patients with CEA levels of ≤5 ng/mL and those with >5 ng/mL ($p>0.05$) (Table 3).

Table 2. Histology, CEA levels, and Staging

	frequency	percentage
Histology		
Adenocarcinoma		
well differentiated	72	42.9
moderately differentiated	57	33.9
poorly differentiated	13	7.7
Mucinous adenocarcinoma	17	10.1
Lymphoma	1	0.6
Net	2	1.2
CEA levels		
<5	113	67.3
>5	54	32.1
TNM Staging		
Stage 1	4	2.4
Stage 2	79	47.0
Stage 3	74	44.0
Stage 4	11	6.5

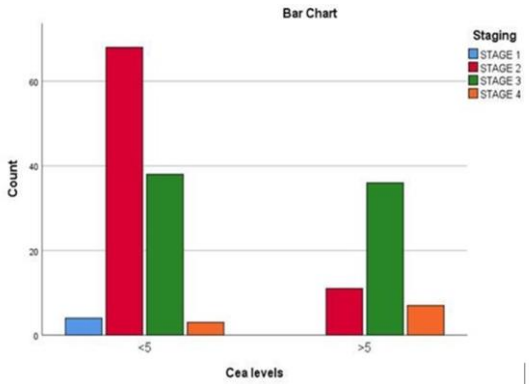

Figure 1. Association of CEA levels with different stages of CRC

When CEA levels were evaluated with tumor different stages of colorectal carcinoma, and found statistically significant correlation was identified between the patients with preoperative CEA levels ($p<0.05$) (Table 4) (Figure 1). The p value < 0.05 shows that there was a significant relationship between CEA levels and disease stage.

Table 3. CEA levels and histology

	Histology					
CEA levels	Adenocarcinoma well differentiated	Moderately differentiated	Poorly differentiated	Mucinous adenocarcinoma	Lymphoma	NET
<5	39	40	12	13	1	2
	36.4%	37.4%	11.2%	12.1%	0.9%	1.9%
<5	32	17	1	4	0	0
	59.3%	31.5%	1.9%	7.4%	0.0%	0.0%
Chi-Square Test	Value	df	Asymptotic significance (2-sided)			
Pearson Chi-Square	10.762[a]	5	0.056			
Likelihood Ratio	12.612	5	0.027			
Linear-by-Linear Association	8.070	1	0.005			
Number of Valid Cases	161					

[a]5 cells (41.7%) have expected count less than 5. The minimum expected count is 0.34

Table 4. CEA levels and staging

CEA levels	Staging			
	Stage 1	Stage 2	Stage 3	Stage 4
<5	4	68	38	3
	3.5%	60.2%	33.6%	2.7%
>5	0	11	36	7
	0.0%	20.4%	66.7%	13.0%
Chi-Square Tests				
	Value	df	Asymptotic Significance (2-sided)	
Pearson Chi-Square	29.635a	3	.000	
Likelihood Ratio	31.695	3	.000	
Linear-by-Linear Association	28.550	1	.000	
N of Valid Cases	167			

[a]3 cells (37.5%) have expected count less than 5. The minimum expected count is 1.29.

Discussion

In this study, most patients are in the age group of 50 to 70 years and the mean age of presentation is 59.6 years. There is a slight preponderance among male patients with colorectal carcinoma. 54.8% are male and the rest are female. According to Patil et al. study men were 65%, and according to Dakubo et al. study men were 53.5% [17,18].

The most common presenting complaint in this study is bleeding per rectum (54.8%), followed by abdominal pain (19.0%). Rectal bleeding (57%) was noticed as the most common presentation in Patil et al. study, followed by abdominal pain (44%). Dakubo et al. observed that 51.1% had rectal bleeding as presenting symptoms, followed by abdominal mass [17,18].

In the current study, rectum is the most common site of the lesion (47%), followed by sigmoid (16.1%). The study by Dakubo et al. also showed that the rectum was the main site of lesion, consisting of 46.8% cases. Similar results were observed in the study of Patil et al. (with rectum 49%).

In the current study, 90.5% of the study population consumes non-vegetarian diet. Similarly, studies show that vegetarian diets are associated with an overall lower incidence of colorectal cancer. Thus, vegetarians, pescetarians and 1 day/week meat eaters showed a non-significantly decreased risk of colorectal cancer compared to 6-7 day/week meat consumers, mainly due to differences in dietary pattern other than meat intake [19-21].

However, the relationship of vegetarian or non-vegetarian dietary patterns to colorectal cancer risk is not well established [22-24].

In the present study of all histological variants, well-differentiated adenocarcinoma was observed in most cases and represents 44.4%, followed by moderately differentiated adenocarcinoma. Whereas the study by Dakubo et al. showed that 62.5% is well differentiated and 25.6% is moderately differentiated adenocarcinoma [18].

CEA is a structural protein that regulates promoter functions in intracellular adhesion and aggregation. As a result, it is considered that CEA plays an important role in tumour invasion and metastasis. Filiz et al. reported in a study (published in 2009) performed on 151 colorectal cancer patients that 58.8% of patients had normal preoperative CEA levels [25].

The relationship between patients' CEA levels and the degree of differentiation of CRC was also investigated in other studies. CEA levels were high in tumors that were well and moderately differentiated, while they were low in tumors that were poorly and slightly differentiated [26-28].

This condition was thought to be caused by low CEA levels in patients with undifferentiated or poorly differentiated tumors at an advanced stage. When CEA levels and differentiation degrees of tumors were compared in the aforementioned study, it was discovered that tumour differentiation was mild or undifferentiated in patients with CEA levels > 5ng/mL, but generally well or moderate in cases with CEA levels < 5ng/mL. The observation, however, was not statistically significant [29,30].

Huh et al., investigated the correlation between CEA levels and TNM staging in 474 patients with colorectal cancer. Patients were divided into two groups according to CEA levels of above or below 5 ng/mL. In addition, only patients with non-metastatic colorectal cancer were included in the study. As result of the study, a statistically significant correlation between CEA levels and TNM staging of patients was established [31].

CEA levels were high in 32.1% of the study population in our study. Study by Topdagi et al. noted higher CEA levels in 47.8% of subjects [32].

In the current study, the association of CEA levels with different stages of colorectal carcinoma was investigated and association tested with chi-square test, which results in P value < 0.05, showing that there is significant association with stages of cancer and preoperative CEA levels.

In the study by Topdagi et al. it was observed that cases with CEA ≤ 5 ng/mL were majorly in Stage III, whereas those with CEA >5 ng/mL were predominantly in Stage IV. TNM stage, tumor sizes, and differentiation levels were defined, but no statistically significant relationship between these parameters and CEA levels was found.

In our study, an association was tested between the histologic variants and its association with CEA values, and chi-square test showed p>0.05, thus suggesting no significant association.

According to study of Topdagi et al., when CEA levels were evaluated with tumor differentiation degrees, no statistically significant correlation was identified between the patients with CEA ≤5 ng/mL and those with CEA >5 ng/mL (p>0.05) [32].

Conclusions

Colorectal cancer worldwide is associated with consumption of red meat and smoked products. In this study, we investigated various aspects of colorectal carcinoma, including epidemiology and relationship with dietary habits, as well as preoperative carcinoembryonic antigen (CEA) levels in relation to histological variants and TNM staging.

Most of the patients (90.2%) were non vegetarians. The most common presentation among the study population was rectal bleeding followed by abdominal pain, with rectum as the most common site of the cancer. Eating habits have a significant role in colorectal carcinoma; also, high preoperative CEA levels may suggest a possible advanced stage of the disease.

In conclusion, colorectal cancer is a malignancy in which more studies should be performed, as there appears to be a statistical association between CEA levels and TNM stages.

Acknowledgments

Authors acknowledge teaching and non-teaching staff of Surgery Department for their contribution.

Conflict of interest disclosure

There are no known conflicts of interest in the publication of this article. The manuscript was read and approved by all authors.

Compliance with ethical standards

Any aspect of the work covered in this manuscript has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.

References

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, Jemal A, Yu XQ, He J. Cancer statistics in China, 2015. *CA Cancer J Clin*. 2016 Mar-Apr;66(2):115-32. doi: 10.3322/caac.21338
2. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, Jemal A. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. *J Natl Cancer Inst*. 2017;109(8):djw322. doi: 10.1093/jnci/djw322
3. Haggar FA, Boushey RP. Colorectal cancer epidemiology: incidence, mortality, survival, and risk factors. *Clin Colon Rectal Surg.* 2009 Nov;22(4):191-7. doi: 10.1055/s-0029-1242458
4. Douaiher J, Ravipati A, Grams B, Chowdhury S, Alatise O, Are C. Colorectal cancer-global burden, trends, and geographical variations. *J Surg Oncol*. 2017 Apr;115(5):619-630. doi: 10.1002/jso.24578
5. Guo H, Lin K, Yang K, Ma Z, Cao M, Hu Y, Yan Y. Trends of cancer incidence among Chinese older adults from 2005 to 2016: A log-linear regression and age-period-cohort analysis. *Front Public Health*. 2022 Oct 18;10:1023276. doi: 10.3389/fpubh.2022.1023276
6. Cabasag CJ, Vignat J, Ferlay J, Arndt V, Lemmens V, Praagman J, Bray F, Soerjomataram I. The preventability of cancer in Europe: A quantitative assessment of avoidable cancer cases across 17 cancer sites and 38 countries in 2020. *Eur J Cancer*. 2022 Oct 4;177:15-24. doi: 10.1016/j.ejca.2022.09.030
7. Ariyannur PS, Joy RA, Menon V, Paulose RR, Pavithran K, Vasudevan DM. Pilot Nanostring PanCancer pathway analysis of colon adenocarcinoma in a tertiary healthcare centre in Kerala, India. *Ecancermedicalscience*. 2021 Oct 12;15:1302. doi: 10.3332/ecancer.2021.1302
8. India State-Level Disease Burden Initiative Cancer Collaborators. The burden of cancers and their variations across the states of India: the Global Burden of Disease Study 1990-2016. *Lancet Oncol*. 2018 Oct;19(10): 1289-1306. doi: 10.1016/S1470-2045(18)30447-9
9. Vidigal VM, Silva TD, de Oliveira J, Pimenta CAM, Felipe AV, Forones NM. Genetic polymorphisms of vitamin D receptor (VDR), CYP27B1 and CYP24A1 genes and the risk of colorectal cancer. *Int J Biol Markers*. 2017 May 4;32(2):e224-e230. doi: 10.5301/jbm.5000248
10. Chow D, Stabile BE, Lee B. Efficacy of robotic-assisted surgery in colorectal cancer: A systematic review and meta-analysis. *J Clin Oncol*. 2011;29(15): e14125. doi: 10.1200/jco.2011.29.15_suppl.e14125
11. Zhang F, Zhang Y, Zhao W, Deng K, Wang Z, Yang C, Ma L, Openkova MS, Hou Y, Li K. Metabolomics for biomarker discovery in the diagnosis, prognosis, survival and recurrence of colorectal cancer: a systematic review. *Oncotarget*. 2017 May 23;8(21): 35460-35472. doi: 10.18632/oncotarget.16727
12. Meirovitz A, Baider L, Peretz T, Stephanos S, Barak V. PTX Treatment of Colon Cancer: Mode of Action Based on Tumor Marker and Cytokine Kinetics. *Anticancer Res*. 2022 Nov;42(11):5487-5496. doi: 10.21873/anticanres.16054
13. Keskin A, Karslioglu B. Did Covid-19 pandemic narrow the spectrum of surgical indications?. *J Clin Investig Surg*. 2021 May 25;6(1):58-63. doi: 10.25083/2559.5555/6.1.11
14. Zhou H, Wang S, Cai Z, Qiu E, Chen Q, Rao X, Han S, Li Z. Adjuvant chemotherapy benefits on patients with elevated carcinoembryonic antigen in stage IIA colon cancer: a SEER-based analysis. *Int J Colorectal Dis*. 2022 Nov 5. doi: 10.1007/s00384-022-04278-5
15. Hotta T, Takifuji K, Yokoyama S, Matsuda K, Oku Y, Nasu T, Ieda J, Yamamoto N, Iwamoto H, Takei Y, Mizumoto Y, Yamaue H. Impact of the post/preoperative serum CEA ratio on the survival of patients with rectal cancer. *Surg Today*. 2014 Nov; 44(11):2106-15. doi: 10.1007/s00595-014-0852-1
16. Mohandas KM. Colorectal cancer in India: controversies, enigmas and primary prevention. *Indian J Gastroenterol.* 2011;30(1):3-6. doi: 10.1007/s12664-010-0076-2
17. Patil PS, Saklani A, Gambhire P, Mehta S, Engineer R, De'Souza A, Chopra S, Bal M. Colorectal Cancer in India: An Audit from a Tertiary Center in a Low Prevalence Area. *Indian J Surg Oncol*. 2017 Dec;8(4): 484-490. doi: 10.1007/s13193-017-0655-0
18. Dakubo JC, Naaeder SB, Tettey Y, Gyasi RK. Colorectal carcinoma: an update of current trends in Accra. *West Afr J Med*. 2010 May-Jun;29(3):178-83. doi: 10.4314/wajm.v29i3.68218
19. Orlich MJ, Singh PN, Sabaté J, Fan J, Sveen L, Bennett H, Knutsen SF, Beeson WL, Jaceldo-Siegl K, Butler TL, Herring RP, Fraser GE. Vegetarian dietary patterns and the risk of colorectal cancers. *JAMA Intern Med*. 2015; 175(5):767-76. doi: 10.1001/jamainternmed.2015.59

20. Gilsing AM, Schouten LJ, Goldbohm RA, et al. Vegetarianism, low meat consumption and the risk of colorectal cancer in a population based cohort study. *Sci Rep*. 2015;5:13484. doi: 10.1038/srep13484
21. Orlov-Slavu C, Parosanu A, Olaru M, Serban D, Paunica I, Nitipir C. How opportune is multigene testing in metastatic colorectal cancer? A review. *J Mind Med Sci*. 2021;8(2):215-220. doi: 10.22543/7674.82.P215220
22. Sinha R, Doval DC, Hussain S, Kumar K, Singh S, Basir SF, Bharadwaj M. Lifestyle and Sporadic Colorectal Cancer in India. *Asian Pac J Cancer Prev*. 2015; 16(17):7683-8. doi: 10.7314/apjcp.2015.16.17.7683
23. Lee CG, Hahn SJ, Song MK, et al. Vegetarianism as a protective factor for colorectal adenoma and advanced adenoma in Asians. *Dig Dis Sci*. 2014 May;59(5): 1025-35. doi: 10.1007/s10620-013-2974-5
24. Dumitru FA, Micu SI, Popoiag RE, Musat M, Caloian AD, Calu V, Constantin VD, Balan DG, Nitipir C, Enache F. Intestinal dysbiosis – a new treatment target in the prevention of colorectal cancer. *J Mind Med Sci*. 2021;8(2):221-228. doi: 10.22543/7674.82.P221228
25. Filiz AI, Sucullu I, Kurt Y, Karakas DO, Gulec B, Akin ML. Persistent high postoperative carcinoembryonic antigen in colorectal cancer patients--is it important? *Clinics (Sao Paulo)*. 2009;64(4):287-94. doi: 10.1590/s1807-59322009000400004
26. Ma Y, Zhang Y, Bi Y, He L, Li D, Wang D, Wang M, Wang X. Diagnostic value of carcinoembryonic antigen combined with cytokines in serum of patients with colorectal cancer. *Medicine (Baltimore)*. 2022;101(37): e30787. doi: 10.1097/MD.0000000000030787
27. Zhou S, Sheng N, Ren J, He Q, Zhang Y, Gong J, Wang Z. Clinical Significance of and Predictive Risk Factors for the Postoperative Elevation of Carcinoembryonic Antigen in Patients With Non-Metastatic Colorectal Cancer. *Front Oncol*. 2021 Oct 7;11:741309. doi: 10.3389/fonc.2021.741309
28. Popescu B, Oașă ID, Bertesteanu Serban VG, Balalau C, Scaunasu RV, Manole F, Domuta M, Oancea AL. Emergency tracheostomy protocols in Coltea Clinical Hospital in patients with SARS-CoV-2 infection. *J Clin Investig Surg*. 2020 May 25;5(1):34-38. doi: 10.25083/2559.5555/5.1/34.38
29. Rao H, Wu H, Huang Q, Yu Z, Zhong Z. Clinical Value of Serum CEA, CA24-2 and CA19-9 in Patients with Colorectal Cancer. *Clin Lab*. 2021 Apr 1;67(4). doi: 10.7754/Clin.Lab.2020.200828
30. You W, Yan L, Cai Z, Xie L, Sheng N, Wang G, Wu X, Wang Z. Clinical Significances of Positive Postoperative Serum CEA and Post-preoperative CEA Increment in Stage II and III Colorectal Cancer: A Multicenter Retrospective Study. *Front Oncol*. 2020 May 20;10:671. doi: 10.3389/fonc.2020.00671
31. Huh JW, Oh BR, Kim HR, Kim YJ. Preoperative carcinoembryonic antigen level as an independent prognostic factor in potentially curative colon cancer. *J Surg Oncol*. 2010 Apr 1;101(5):396-400. doi: 10.1002/jso.21495
32. Topdagi O, Timuroglu A. Evaluation of the Relationship between Carcinoembryonic Antigen and TNM Stage in Colorectal Cancer. *Eurasian J Med*. 2018; 50(2):96-98. doi: 10.5152/eurasianjmed.2018.17093