Malays J Pathol 2022; 44(2): 285 – 290

CASE SERIES

Colorectal cancer in patient younger than 50-year-old in Kelantan: Two case reports

Nur Asyilla CHE JALIL[1,4]*, Nor Hayati OTHMAN[1,4], Wan Faiziah WAN ABDUL RAHMAN[1,4], Andee Dzulkarnaen ZAKARIA[2,4], Ahmad Hadif Zaidin SAMSUDIN[3,4], Siti Norasikin MOHD NAFI[1], Nur Ain Nabila MAZUKI[4]

[1]Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia; *[2]Department of Surgery, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia*; *[3]Department of Radiology, School of Medical Sciences, Universiti Sains Malaysia, Health Campus, Kubang Kerian, Kelantan, Malaysia*; *[4]Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia*

Abstract

Although young-onset colorectal cancer (CRC) is commonly linked to genetic predispositions such as Lynch syndrome, there has been an increasing trend in the prevalence of sporadic type young-onset CRC. We highlighted two cases of young patients diagnosed with CRC. Both patients came at the late stage of presentation with right sided colon tumour and local lymph nodes involvement. Loss of MLH1 expression with positive BRAF V600E was seen on immunohistochemistry staining. Additionally, they have no chronic disease or familial history of malignancy. The follow-up surveillance CT scan and the surveillance colonoscopy of case 1 showed no local recurrence and distant metastasis. However, another patient defaulted on the subsequent follow-up. In this report, we review the clinicopathological characteristics of these two cases and discuss the importance of the screening for the BRAF V600E and the four MMR proteins to characterise the sporadic and hereditary subgroups of young-onset CRC.

Keywords: young-onset, colorectal cancer, sporadic, BRAF V600E, MLH1

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide, mainly in older age groups. However, the disease's prevalence in patients less than 50 years old has steadily increased over recent years. They have a poorer prognosis as compared to the older age group. A young adult's definition varies, but most published articles define it as under 40 years old and others less than 50 years old. The Northern states in Malaysia showed the incidence rates of 25.2 cases per 100000 population.[1] Globally, the incidence rates were varies, in which in USA ranging from 9.5 to 15.1 cases (per 100000 population).[2] Whereas in Korea, China, Thailand and India showed the incidence rates of 12.9, 6.5, 5.4 and 3.5 cases per 100000 population respectively[3] (Table 1).

Recent studies have established several risk factors in young-onset CRC, such as inflammatory bowel disease, adenomatous polyps, and genetic predispositions such as Lynch syndrome. However, there has been an increasing trend in the prevalence of sporadic type young-onset CRC. The earliest presentation includes non-specific abdominal discomfort, which often leads to delayed diagnosis. There is no proper routine screening to subgroups the young-onset CRC into the sporadic and hereditary subgroups. Here we describe two cases of young-onset CRC in patients without risk factors or family histories of CRC. In this report, we review the clinicopathological characteristics of these two cases and discuss the importance of the screening for the BRAFV600E and the four MMR proteins to characterise the sporadic and hereditary subgroups of young-onset CRC.

**Address for correspondence:* Dr. Nur Asyilla Che Jalil, Address: Department of Pathology, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kota Bharu, Kelantan, Malaysia. Tel: +609-7676949. Email: *asyilla@usm.my*

Table 1: Comparison of incidence rates of colorectal cancer between countries

Country	Incidence rates (cases per 100000)
Malaysia (Northern regional)	25.2
USA	9.5 -15.1
Korea	12.9
China	6.4
Thailand	5.4
India	3.5

CASE PRESENTATION

CASE 1

A 23-year-old Malay man presented with worsening right-sided abdominal pain. The patient had a history of recurrent visits to a private clinic with similar complaints. In addition, the patient had experienced a low-grade fever, abdomen distension, and altered bowel habits over the previous two weeks. No significant past medical or family history of malignancy was noted. Other risk factors, such as inflammatory bowel disease or adenomatous polyp were absent. An abdominal examination revealed a distended abdomen with tenderness at the right iliac fossa. No mass was palpable on rectal examination. Abdominal radiograph (FIG. 1A) revealed dilated small and large bowels. The impression was small bowel obstruction, possibly due to perforated appendicitis with ileus. Emergency exploratory laparotomy was performed, revealing a cecal mass, dilated small bowel, and multiple mesenteric nodes. The appendix was normal. A right hemicolectomy was performed. Histopathological examination showed signet-ring carcinoma of the colon, which infiltrated up to the serosa layer with free proximal and distal margins (FIG. 3A). The tumour shows loss of MLH1 protein expression and positive for BRAF V600E by immunohistochemistry staining (FIG. 4). Out of 11 identified nodes, four harboured carcinoma cells. Computed tomography (CT) scan of the thorax, abdomen, and pelvis showed no distant metastasis. The patient was treated with adjuvant chemotherapy, FOLFOX (5-Fluorouracil, Leucovorin, and Oxaliplatin) for 12 cycles. The follow-up surveillance CT scan showed no local recurrence and distant metastasis; the surveillance colonoscopy showed no recurrence at the anastomotic site.

CASE 2

A 22-year-old Malay lady presented with worsening abdominal pain. Over the preceding four weeks, she had a history of recurrent right-sided abdominal pain associated with occasional loose stool, poor appetite, and rapid weight loss. She frequently visited a medical practitioner and was treated as gastritis. Patient had no history of fever, haematochezia, passing mucus stool, or altered bowel habits at earlier presentation. She also had no family history of colon cancer or malignancy. The abdominal examination showed epigastric tenderness with no palpable mass and rectal examination was unremarkable. The urine pregnancy test was negative, and serum amylase and urine diastase were normal. Abdominal radiograph showed dilatation of small bowel and ascending colon (FIG. 1B). CT scan was performed which revealed bowel thickening at the proximal transverse colon, proximal dilatation of the small bowel to the transverse colon, incompetent ileocecal valve, and ascites (FIG. 2). A colonoscopy was performed, revealing an intraluminal ulcerative mass at the hepatic flexure, which was friable and bled on contact. The patient underwent extended right hemicolectomy. Histopathological findings are consistent with mucinous adenocarcinoma (FIG. 3B). The mucinous adenocarcinoma exhibits loss of MLH1 & PMS2 protein expressions and positive BRAF V600E immunostains (FIG. 4). Four out of 24 identified nodes harboured metastatic carcinoma. However, the patient defaulted on subsequent follow-up.

DISCUSSION

Colorectal cancer is a disease that mainly affects older adults. However, recent studies show that young-onset colorectal cancer is on the rise.[4] In examining health data from 143.7 million European people aged 20–49, Vuik *et al.*[5] reported a 0.13% (187,918 people) prevalence

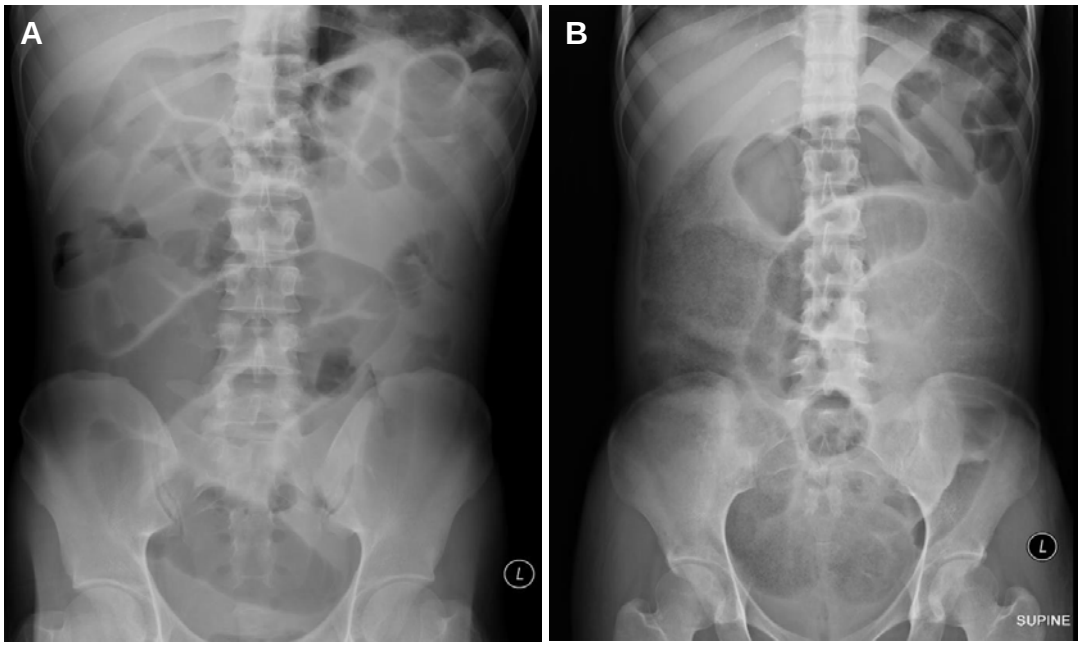

FIG. 1: Plain abdominal radiograph. A, dilated large and small bowel in Case 1. B, Case 2 shows similar findings as in Case 1.

of colorectal cancer in young age patients. Worldwide, CRC is the third most common cause of cancer-related death.[6] Previous studies showed increasing CRC trends in 20–35-year-old young adults.[7] Young adult definition varied with the majority of published articles defines it is as under 40 years old. However, others described it as less than 50 years old.[7,8] The worldwide prevalence of young-onset CRC is approximately 5.0%,[9] in Peninsular Malaysia, the prevalence is 1.0%.[10] According to the National Cancer Patient Registry-Colorectal Cancer (NCPRC) 2007–2008, 5.0% of the Malaysian population was diagnosed with young-onset CRC. From 2008 to 2013, the prevalence rose to 11.8%.[11] In Kelantan, colorectal cancer is one of the most common cancers, and the incidence has increased from 1987 to 2007.[12] Data from Hospital Universiti Sains Malaysia also increased in young-onset CRC from 2012–2015.[13]

In current cases, they are young, presented at the late stage of the disease, had no family

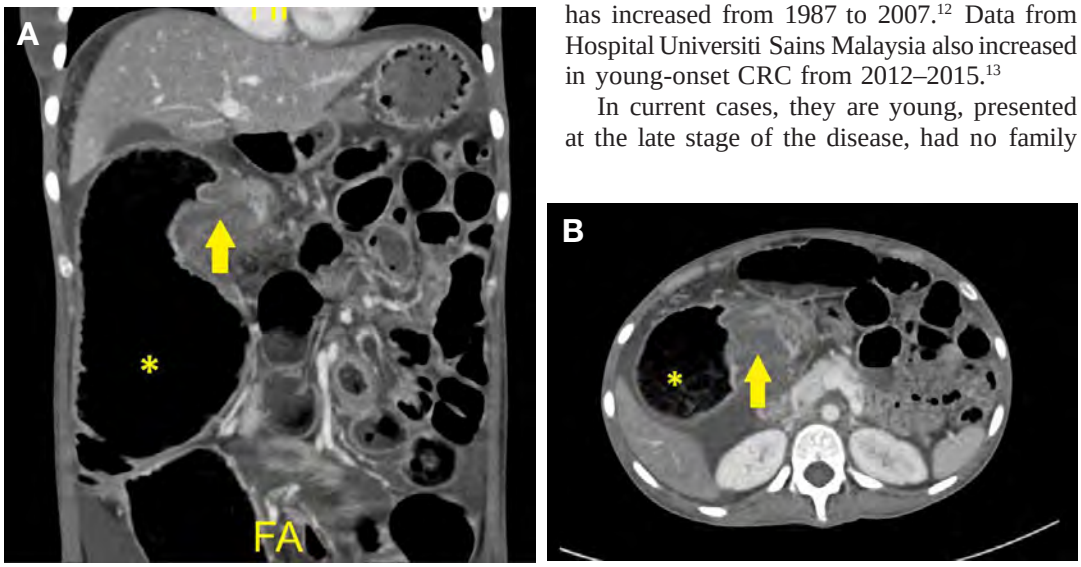

FIG. 2: Contrast enhanced CT scan of Case 2. A, a coronal view and B, an axial view showing circumferential bowel thickening at proximal transverse colon (arrow) causing dilatation of the ascending colon (*).

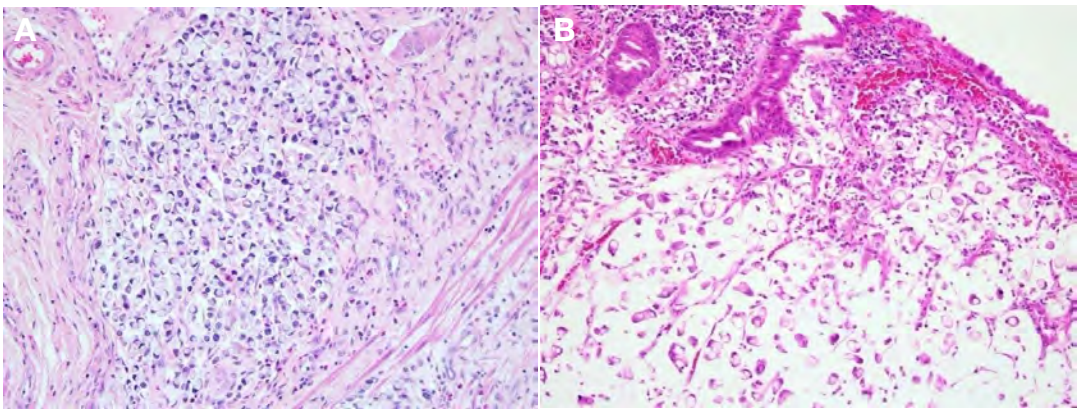

FIG. 3: Histopathological examination. A, signet ring cell carcinoma, invading the submucosa forming a cluster of tumour cells with prominent intracytoplasmic mucin and eccentrically located crescent shape hyperchromatic nuclei in Case 1 (H&E stain, 200X). B, Mucinous carcinoma exhibiting pools of acellular mucin with malignant cells floating in it in Case 2. (H&E stain, 200X)

history of malignancy or established risk factors. The tumour was on the right side of the colon, with both cases show loss of MLH1 and positive for BRAF V600E on immunohistochemistry staining. The most common CRC symptoms are rectal bleeding, abdominal pain, weight loss, and bowel habits changes, including constipation and diarrhoea.[14] The most common histological features of young-onset CRC include mucinous or poorly differentiated tumours, including signet-ring carcinoma. The majority of high-frequency microsatellite instability (MSI-H) carcinomas are of this histopathological type.[15]

It is common for young-onset CRC patient to present at a later stage than adult due to a delay in diagnosis.[16] The non-specific symptoms can also mimic other more common pathology such as gastritis and enteritis. Abdominal radiograph, GI fluoroscopy, and CT abdomen are the standard radiological workups in colorectal cancer patients. The decision to undergo such an investigation depends on the patient's first presentation. The role of fluorodeoxyglucose positron emission tomography (FDG-PET) is still unclear.[17] It is less helpful in detecting mucinous lesion, which is the predominant histological feature in the young age group.

In the young population, the disease's behaviour is typically aggressive and presented at a later stage than their older counterparts. However, if detected early, young patients have better overall five-year survival rates. However, early diagnosis of CRC in young patients is often challenging. Delay in diagnosis is attributed to late presentation, lack of access to the tertiary centre, or misdiagnosis.[18]

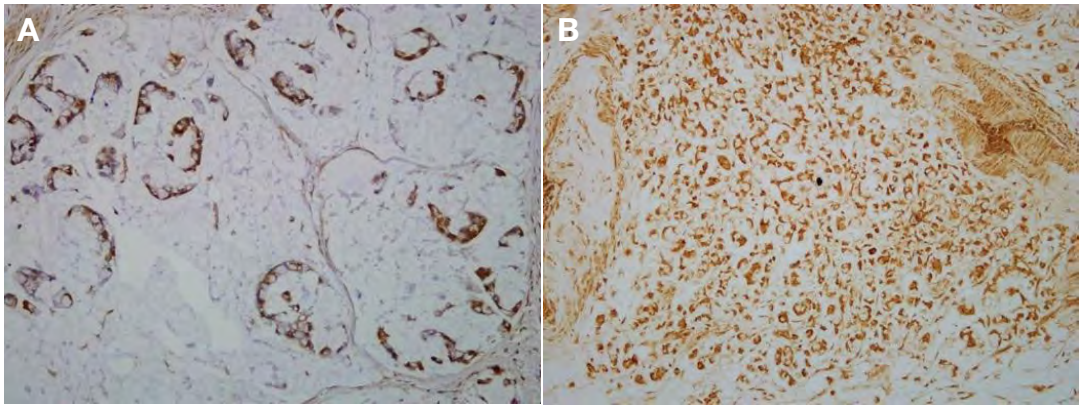

FIG. 4: Immunohistochemical staining for BRAF V600E. A, positivity in mucinous adenocarcinoma (200x). B, positivity in signet ring cell carcinoma (200x).

Young-onset CRC appears to have distinct clinical-pathological characteristics and molecular pathways compared to older-onset cases. There are two distinct subtypes in young-onset CRC: the sporadic subtype, in which the patient has no family history of CRC or malignancy, and the inherited subtype, characterised by the presence of hereditary syndromes. In particular, the sporadic subtype of the disease appears to be increasing in prevalence. Deen *et al.*[19] reported that only 16.0% of young-onset CRC patients had established genetic predisposition; while the remaining can be characterised as the sporadic subtype. Studies have been conducted to unravel the genetic basis of this group. A better understanding of the molecular entities and pathways responsible for sporadic young-onset CRC will help to tailor therapeutic management strategies specific to this group of patients.

Published data on the sporadic subtype of young-onset CRC is limited. Thus, exploring this group of patients' molecular signature is crucial to develop and provide the best treatment options in the future. At the earliest screening stage for young-onset CRC, exclusion of genetic predispositions such as Lynch syndrome is essential. The Amsterdam criteria are a means to identify patients likely to carry a mutation for Lynch syndrome. The Amsterdam criteria require young-onset CRC with a family history of three successive CRC cases in two subsequent generations. These criteria were modified to include the criterion of Lynch syndrome-associated malignancy and were called Amsterdam criteria II. Revised Bethesda Guidelines is to identify individuals who should be genetically tested for Lynch syndrome- related tumours, i.e., microsatellite instability.

Lynch syndrome is an autosomal dominant condition that exhibits an 80 per cent lifetime risk of getting colorectal cancer with 45 years mean age of diagnosis. This syndrome is commonly found in the proximal colon and happens due to DNA mismatch repair genes, mostly MLH1 and MSH2.[20] Those without hereditary syndrome usually presented with metastatic disease compared to those with a syndrome and positive family history of cancer, which are frequently detected at the initial stage. However, about 19 per cent of hereditary syndromes seen in patients who have a negative family history of the condition.[21] It becomes a significant challenge in dealing with young populations, particularly in differentiating sporadic CRC from the hereditary forms.[22] Prognosis of CRC with Lynch Syndrome was better and composed of discrete biologic characteristics compared to sporadic CRC. Sporadic CRC among young patients revealed more aggressive histologic differentiation with poorer outcomes than older patients.[23]

However, the more significant proportion of MSI-H tumours arises via DNA MMR impairment through hypermethylation of the MLH1 gene. MSI testing or immunohistochemistry polymerase chain reaction to assess protein expression is performed by screening for defective MMR DNA. Tumours with hypermethylation of MLH1 and the BRAF mutation nearly always represent sporadic CRC and are not associated with Lynch syndrome.[24] Genetic testing for the MLH1 gene and BRAF mutation is required.

Immunohistochemistry testing of MMR & BRAF proteins is an essential method for the initial screening of this particular young-onset CRC group. It is considered equally effective as MSI testing using PCR.[25] The majority of CRC patients with acquired MLH1 methylation also have the BRAF V600E mutation. Immunohistochemistry of the monoclonal BRAF V600E antibody has been developed using formalin-fixed CRC tissue specimens. BRAF V600E positivity is also a marker for poor CRC prognosis. Diagnostic pathology laboratories should routinely perform MMR & BRAF V600E immunohistochemistry staining in the future.

CONCLUSION

The proportion of young-onset CRC cases with no family history or predisposing risk factors is increasing. Early recognition of CRC in this group of patients is a challenge. Further investigation to exclude CRC for young patients with a recurrent history of abdominal pain is a must. Early screening with a panel of MMR proteins and BRAF V600E is crucial to scrutinise them into a sporadic or hereditary causative factor of young CRC that needs further genetic testing and family members screening for the later.

ACKNOWLEDGEMENTS

Ministry of Higher Education Malaysia for Fundamental Research Grant Scheme with Project Code: FRGS/1/2020/SKK0/USM/03/3 & USM: 203.PPSP.6171278.

Authors'contribution: NACJ, NHO, WFWAR, ADZ, NANM and AHZS conceived of the presented idea. NACJ wrote the manuscript with support from SNMN. All authors discussed the results and contributed to the final manuscript.

Conflict of interest: The authors declare no conflict of interest.

REFERENCES

1. Wan Ibrahim N, Chan H, Soelar S, Azmi A, Mohd Said R, Abu Hassan M. Incidence, Clinico-demographic Profiles and Survival Rates of Colorectal Cancer in Northern Malaysia: Comparing Patients Above and Below 50 Years of Age. Asian PacJ Cancer Prev. 2020;21(4): 1057-61.
2. Stoffel EM, Murphy CC. Epidemiology and Mechanisms of the Increasing Incidence of Colon and Rectal Cancers in Young Adults. J Gastroenterol. 2020 Jan;158(2):341-53.
3. Siegel RL, Torre LA, Soerjomataram I, *et al*. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019;68(12):2179-85.
4. Saad El Din K, Loree JM, Sayre EC, *et al*. Trends in the epidemiology of young-onset colorectal cancer: a worldwide systematic review. BMC cancer. 2020 Dec;20:1-4.
5. Vuik FE, Nieuwenburg SA, Bardou M, *et al*. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut. 2019 Oct 1;68(10):1820-6.
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019 Jan;69(1):7-34.
7. Mauri G, Sartore-Bianchi A, Russo AG, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. Mol. Oncol. 2019 Feb;13(2):109-31.
8. O'Connell JB, Maggard MA, Livingston EH, Clifford KY. Colorectal cancer in the young. Am. J. Surg. 2004 Mar 1;187(3):343-8.
9. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int. J. Cancer Res. 2015 Mar 1;136(5):E359-86.
10. Omar ZA, Ali ZM, Tamin NSI. Malaysian cancer statistics–Data and figure Peninsular Malaysia 2006. National cancer registry, ministry of health Malaysia. 2006.
11. Wendy L, Radzi M. New Registry: National Cancer Patient Registry-Colorectal Cancer. Int. Med. J. Malays. 2008 Sep 1;63(suppl C):57-8.
12. Othman NH, Nor ZM, Biswal BM. Is Kelantan joining the global cancer epidemic?— Experience from hospital Universiti Sains Malaysia; 1987–2007. Asian Pac J Cancer Prev 2008 Jul 1;9(3):473-8.
13. Saizul Z, Ab Hamid Siti-Azrin AD, Zakaria AH, Rahman WFWA, Jalil NAC. BRAF V600E and Mismatch Repair Proteins Expression in Sporadic Young-onset Colorectal Cancer in Kelantan, Malaysia. Oman Med. J., 2021; 36(4): p.e284.
14. Gul A, Alam SI, Alam I. Clinical presentations of colorectal carcinoma in patients below 40 years of age presenting to a tertiary care level hospital. J. Med. Sci. 2012 Jun 1;20(2):67-70.
15. Nitsche U, Zimmermann A, Späth C, *et al*. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann. Surg. 2013 Nov;258(5):775.
16. Poles GC, Clark DE, Mayo SW, *et al*. Colorectal carcinoma in pediatric patients: a comparison with adult tumors, treatment and outcomes from the National Cancer Database. J. Pediatr. Surg.2016 Jul 1;51(7):1061-6.
17. Goldberg J, Furman WL. Management of colorectal carcinoma in children and young adults. Pediatr. Hematol. Oncol. J. 2012 May 1;34:S76-9.
18. De Sousa JB, Souza CS, Fernandes MB, *et al*. Do young patients have different clinical presentation of colorectal cancer causing delay in diagnosis?. Int. J. Colorectal Dis 2014 Apr;29(4):519-27.
19. Deen KI, Silva H, Deen R, Chandrasinghe PC. Colorectal cancer in the young, many questions, few answers. World J. Gastrointest. Oncol.2016 Jun 15;8(6):481.
20. S. Williams N, J.K. Bullstrode C, O'Connell P. Bailey & Love's Short Practice of Surgery 26E. 26th ed. CRC Press; 2013. 1162 p.
21. Mork ME, You YN, Ying J, *et al*. High prevalence of hereditary cancer syndromes in adolescents and young adults with colorectal cancer. Am. J. Clin. Oncol.2015 Nov 1;33(31):3544.
22. Campos FG. Colorectal cancer in young adults: A difficult challenge. World J. Gastroenterol.2017 Jul 28;23(28):5041.
23. Kim TJ, Kim ER, Hong SN, Chang DK, Kim YH. Long-term outcome and prognostic factors of sporadic colorectal cancer in young patients: a large institutional-based retrospective study. J. Med. 2016 May;95(19).
24. Boland CR, Goel A. Microsatellite instability in colorectal cancer. J. Gastroenterol 2010 May 1;138(6):2073-87.
25. Toon CW, Walsh MJ, Chou A, *et al*. BRAFV600E immunohistochemistry facilitates universal screening of colorectal cancers for Lynch syndrome. Am. J. Surg.2013 Oct;37(10):1592.