Synchronous Colorectal Carcinoma: Three Cases Report and Literature Review

jingfeng chen
Lishui Municipal People Hospital: Lishui Central Hospital and Fifth Affiliated Hospital of Wenzhou Medical College

Yi-shuo Wang
Three Gorges University College of Medical Science

Chuan Cheng
Lishui Municipal People Hospital: Lishui Central Hospital and Fifth Affiliated Hospital of Wenzhou Medical College

Li-ping Yan
Lishui Municipal People Hospital: Lishui Central Hospital and Fifth Affiliated Hospital of Wenzhou Medical College

Peng Gao
Lishui Municipal People Hospital: Lishui Central Hospital and Fifth Affiliated Hospital of Wenzhou Medical College

Xin-wu Mao
Lishui Municipal People Hospital: Lishui Central Hospital and Fifth Affiliated Hospital of Wenzhou Medical College

Jian-ping Wang
Lishui Municipal People Hospital: Lishui Central Hospital and Fifth Affiliated Hospital of Wenzhou Medical College

Chu-xiao Shao
Lishui Municipal People Hospital: Lishui Central Hospital and Fifth Affiliated Hospital of Wenzhou Medical College

Jie Xu (15157819011@sina.cn)
The Fifth Affiliated Hospital of Wenzhou Medical University

Case report

Keywords: synchronous colorectal carcinoma (SC), isolate colorectal cancer, MSI, gene mutation.

Posted Date: July 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-581061/v1

Abstract

Background: Multiple primary colorectal cancers (MPCC) includes synchronous colorectal carcinoma (SC) and metachronous colorectal carcinoma (MC), which are defined as multiple malignant colorectal tumors that occur simultaneously or heterochrony. Comparing to isolate colorectal cancer, the incidence of SC is still rare. At present, there are few literatures describing the cases and reviews of SC.

Case presentation: Here, we present three cases of SC. The first patient was admitted to our hospital because of a 5-month history of abdominal pain associated with difficult defecation. PET-CT revealed that a mass lesion of the splenic flexure of colon and another mass in sigmoid. Colonoscopy demonstrated double lesions in splenic flexure and sigmoid. Then we performed traditional open subtotal colon resection. Postoperative pathology confirmed that there are malignant characteristics of the double lesions. Another patient was suffered from with dizziness and fatigue for more than 2 years. Abdominal contrast-enhanced CT shows irregular thickening of the ascending colon wall and colonoscopy reveals that there is a tumor in rectum and many polyps in sigmoid. Then we underwent radical resection of rectal cancer and right colon cancer in a laparoscopic operation. Postoperative pathology confirmed moderately differentiated adenocarcinoma of the rectum and ascending colon. The third patient had hematochezia for 1 year. Both rectal magnetic resonance imaging (MRI) and colonoscopy showed that there are two lesions in the rectum, and conventional laparoscopic APR surgery was performed. Postoperative pathology confirmed malignant tumors in the rectum respectively. The mini review summed up the main points about prevalence, clinical manifestation, diagnosis, pathological, treatment and molecular mechanism features of SC based on current literature, which probably has significant distinctions with solitary tumors.

Conclusions: Compared with isolated colorectal cancer, SC usually has a low stage□grade and incidence, but the age, sex and location is still a controversial issue. Colonoscopy and surgery are considered to be the best diagnosis and treatment method for SC. At present, serrated adenoma, hyperplastic polyp, ulcerative colitis and Crohn's disease are considered to be closely related to SC. MSI and gene mutation are two molecular mechanisms that lead to SC.

Background

The incidence of colorectal cancer (CRC) is increased over the years. However, multiple primary colorectal cancers (MPCC) are still rare. Research indicated that the incidence of MPCC between 1.1% and 8.1%, mostly less than 5%, but generally speaking, the occurrence rate is an upward trend [1]. MPCC includes synchronous colorectal carcinoma (SC) and metachronous colorectal carcinoma (MC), which is the occurrence of multiple mutually discontinuous primary malignant tumors in the colon and rectum in a patient. The diagnosis time of the second tumor of SC was less than 6 months from that of the first tumor. The time between the diagnosis of the second tumor of MC and the first tumor was more than 6 months [2, 3]. The clinical characteristics, diagnosis, treatment, prognosis, pathology and pathogenesis of

SC are different from those of isolated colorectal cancer. Here, we report three cases of SC and present an associated mini review on current research of SC.

Case Presentation

Case 1

The 77-year-old woman was presented in December 2020 to colorectal surgery department of the fifth affiliated hospital of Wenzhou medical university with abdominal pain and difficult defecation. She had a 5-months history of intermittent midriff pain and abdominal distension that progressively worsened and anus stops defecating 5 days ago. There was no history of diarrhea, hematochezia, chills, nausea, vomiting, headache, dizzy giddy and other systemic symptoms. She had a history of hypertension disease, and who had no family history of carcinoma or hereditary non-polyposis colorectal cancer (HNPCC). Physical examination revealed a soft tenderness in the middle quadrant of the abdomen and without rebound tenderness and have not any mass palpated, and stable vital signs. Digital rectal examination shows no abnormality. The general examination was unremarkable, and laboratory investigations demonstrated that the hemoglobin concentration is 11.3 g/dL, the white blood cell count is 103, 00 cells/μL, and the platelet count is 184,000 cells/μL, and the fecal occult blood test was positive as well. The liver function revealed albumin and pro-albumin are low level (34.8g/l and 127mg/l) respectively, and the renal function test was normal. Serum tumor markers were high level (CEA 118.9 ng/ml, CA125 38.1U/ml, CA50 31.71 IU/ml, NSE 22.1ng/ml) respectively. The Abdomen ultrasound (US) with liver, gallbladder and bile duct, pancreas, and spleen examination was unremarkable. Electrocardiogram (ECG) and echocardiographic examination were no abnormalities. Lung function test revealed that moderate decrease inpulmonary reserve function. Contrast-enhanced CT of the abdomen suggested that the splenic flexure of colon is thickening and incomplete obstruction (Fig. 1a). The PET-CT demonstrated that a mass lesion of the splenic flexure of colon with associated circumferential thickening and local infiltration, and the corresponding secondary obstruction of intestinal lumen (Fig. 1b). There is a mass in sigmoid, and showed increased FDG metabolism, considered to be malignant tumor (Fig. 1c). The left Supraclavicular lymph node enlargement (Fig. 1d), retroperitoneal lymph node metastasis is possible (Fig. 1e). No metastases were observed in lung, liver, bone or brain. The complete colonoscopy revealed a malignant tumor in hepatic flexure of colon and sigmoid.

Based on results of preoperative evaluation, the patient underwent total colectomy in a laparoscopic operation. However, due to the of the surgery technic because of the obstruction of the colon, the surgical method was changed the traditional open subtotal colon resection during the operation. Postoperative pathological analysis of two synchronous malignant lesions in colon, which demonstrated the following: Tumor A (white arrow) was an ulcerative mass in descending colon (Fig. 1f) with moderate differentiation adenocarcinoma, and it infiltrate into the subserosal layer (Fig. 1g). Tumor B (red arrow) was a bulging mass in sigmoid (Fig. 1f) with moderate differentiation adenocarcinoma (Fig. 1h). The pathology revealed that tumor cell had not metastasized to tumor around lymph nodes (0/4), ileum lymph nodes (0/9) and ileocecal lymph nodes (0/9), and lymph node around the colon (0/9). There are no residual

tumors and metastasis in incisal margins. After performed immunohistochemistry the cancer positive for MSH2, MSH6, MLH1, PMS2 and PMS2, approximately 85% of Ki-67, negative for CerB-2, CD31, D2-40 and S-100. No severe complications such as anastomotic leakage occurred during hospital stay post-operatively. The TNM pathological staging of this patient was mpT3N0M0 stage IIA, thus we performed 8 cycles of mFOLFOX6 regimen as adjuvant therapy.

Case 2

The 81-year-old woman was presented in October 2016 to hematology department of the sixth affiliated hospital of Wenzhou medical university with dizziness and fatigue for more than 2 years, aggravated for 2 months. She had a history of cerebral infarction 3 years ago, and Long-term use of aspirin and atorvastatin. The patient has a history of hypertension for more than 7 years and took medicine for hypotensor irregularly. There was no history of abdominal distension, diarrhea, hematochezia, chills, nausea, vomitingand other systemic symptoms, and who had no family history of carcinoma or hereditary non-polyposis colorectal cancer (HNPCC). Physical examination revealed a soft tenderness in the middle quadrant of the abdomen and without rebound tenderness and have not any mass palpated, and stable vital signs. Digital rectal examination shows no abnormality. The general examination was unremarkable, and laboratory investigations demonstrated that the hemoglobin concentration is 37g/dL, the white blood cell count is 4400 cells/μL, and the platelet count is 262, 000 cells/μL, and the fecal occult blood test was positive as well. The liver function revealed albumin and pro-albumin were low level (33.4g/l and 144mg/l) respectively, and the renal function test was normal. Serum tumor markers were in the normal range. CT scan of the head showed no obvious abnormality. Chest Computed Tomography (CT) examination revealed that there are some Solid nodules in right horizontal fissure and left upper lobe, and no lung metastasis. Abdominal contrast-enhanced CT shows irregular thickening of the ascending colon wall (Fig. 2a), and there was no liver metastasis. Colonoscopy reveals that there is a tumor in rectum and many polyps in sigmoid. Pathology examination revealed that there are rectal cancer and some low-grade intraepithelial neoplasia of sigmoid colon. No images were collected because the patient underwent colonoscopy in another hospital. Gastroscopy revealed gastro-horn ulcer and non-atrophic gastritis accompanied by erosion. Bone marrow biopsy revealed iron deficiency anemia. Electrocardiogram (ECG), echocardiographic and Lung function examination were no abnormalities.

Based on results of preoperative evaluation, the patient underwent radical resection of rectal cancer and right colon cancer in a laparoscopic operation. Postoperative histopathological analysis of dual synchronous malignant lesions in total colon, which demonstrated the following: tumor A (white arrow) was an ulcerative 2.3×2.0×1.0cm mass in rectum (Fig. 2b) with moderate differentiation and it infiltrate into the deep muscularis (Fig. 2c), and no metastases were found nine lymph nodes in paracolic. Tumor B (red arrow) was a carcinoma (5cm×4.5cm×1.1cm) in ascending colon (Fig. 2b) with moderate differentiation, and it infiltrate into the extrserosal adipose tissue (Fig. 2d), and no metastases were found two lymph nodes in meso-ileum, ten lymph nodes in paracolic, and ten lymph nodes in mesocolon. After performed immunohistochemistry, the tumor is positive for 70% of Ki-67, MSH2, MLH1, MSH6 and PMS2.

Postoperative pathology revealed that the tumor invaded the nerve (Fig. 2e). No severe complications occurred during hospital stay post-operatively, such as anastomotic leakage, postoperative bleeding and so on. The TNM pathological staging of this patient is mpT4aN0M0 II_B stage. Thus, we performed 8 cycles of single capecitabine as adjuvant therapy and the patient revealed good tolerance and compliance without tumor relapse.

Case 3

The 68-year-old man was presented in January 2021 to colorectal surgery department of the fifth affiliated hospital of Wenzhou medical university with hematochezia for more than 1 year. He has a history of aortic valve replacement two years ago and taking aspirin for a long time. There was no history of stomachache and abdominal distension other systemic symptoms, and no history of hypertension and diabetes and who had no family history of carcinoma or hereditary non-polyposis colorectal cancer (HNPCC). Abdominal examination was soft without tenderness and rebound pain, and no mass was touched. Digital rectal examination touched a 3*2cm mass with hard texture and poor movement away from the anus about 7cm, and another mass about 3*3cm at a distance of 2cm from the anus. The mass was hard and poor in movement, occupying 1/3 of the circumference of the intestine, and the fingertip was stained with blood. The general examination was unremarkable, and laboratory investigations demonstrated that the hemoglobin concentration is 57g/dl, the white blood cell count is 4200 cells/μl, and the platelet count is 322, 000 cells/μl, and the fecal occult blood test was positive as well. The liver function revealed albumin and pro-albumin were low level (31g/l and 132mg/l) respectively, and the renal function test was normal. Serum tumor markers were in the normal range. CT scan of the chest showed no obvious abnormality. Electrocardiogram (ECG), echocardiographic and Lung function examination were no abnormalities. Contrast-enhanced CT of the abdomen showed that rectal wall away from 7cm the anus is thickening (Fig. 3a), and there was no liver metastasis. Rectum MRI showed that the first tumor is a median rectal cancer (Fig. 3b) and the clinical stage is cT3bN2Mx, the tumor is 6.0cm from the anal margin, the circumferential resection margin (CRM) was negative, the external wall vascular invasion (EVI) was negative, and the anal canal invasion was negative. Another tumor is a carcinoma at the rectum and anus junction (Fig. 3c) and the clinical stage is cT3bN2Mx, positive for CRM, negative for the external wall vascular invasion, positive invasion of anal canal. The colonoscopy showed that there are two tumors in the rectum (Fig. 3d) and junction of the rectum and anal canal (Fig. 3e).

Based on results of preoperative evaluation, the patient underwent abdominal perineal resection (APR) in a laparoscopic operation. Postoperative histopathological analysis of dual synchronous malignant lesions in rectum, which demonstrated the following: Tumor A (white arrow) was a moderately to poorly differentiated adenocarcinoma at the anorectal junction and the tumor size is about 3*3*1.5cm (Fig. 3f), with no vessel carcinoma embolus but nerve infiltration (Fig. 3g). What is more, it is infiltration into the anal external sphincter, and the anal subcutaneous tissue (Fig. 3h). The size of tumor B (red arrow) is about 4*2.5*2.5cm (Fig. 3f), and it is a medium-low differentiated adenocarcinoma at the lower margin of the rectum, infiltrating into the muscular layer (Fig. 3i), with vessel carcinoma embolus (Fig. 3j) and no

nerve infiltration. There are 11 positive lymph nodes around tumors, we selected one of the positive lymph node pathological image (Fig. 3k). After performed immunohistochemistry, which are positive for 80% of Ki-67, MSH2, MLH1, MSH6 and PMS2. No severe complications occurred during hospital stay post-operatively, such as anastomotic leakage, postoperative bleeding and so on. The TNM pathological staging of this patient is mpT3bN2bM0 IIIC stage. The patient was to be given 2 cycles of chemoradiotherapy and 6 cycles of mFOLFOX6 regimen after surgery.

Discussion

The conception of MPCC is reported by Warren S research in 1941, and studies have shown that the incidence of it is rare [2]. Now, we are does a miniature literature review of SC's clinical features, diagnosis, treatment, prognosis, pathology and pathogenic mechanism.

The manifestations of SC were similar to the isolated colorectal cancer. There are not obvious symptoms in the early stage [4]. However, there will be a lot of symptoms when cancer ruptures to form ulcers, infection or tumor obstruction. Firstly, the most important is rectal stimulation symptoms, which includes frequent bowel movements, changes in bowel habits, anus drop feeling, tenesmus and lower abdominal pain in tumor advanced-stage. Secondly, the symptom of intestinal lumen stenosis is very common. The tumor growing, infiltrate intestinal wall muscle layer and tumor ulceration lead to intestinal stenosis, which causes stool deformation, thinner. Next, patient will have symptoms of incomplete intestinal obstruction that includes abdominal pain, abdominal distension, hyperactive bowel sounds and so on when partial intestinal obstruction occurs. Next, there are symptoms of cancer infection, which mainly for stool surface with blood and mucus, even pus and blood stool. What's more, tumor invades prostate and bladder, which causes symptoms of urinary frequency, odynuria, hematuria. Severe and persistent sacrococcygeal pain occurred when the anterior sacral nerve was invaded [5]. There are corresponding clinical manifestations when liver, lung and bone have metastases. Finally, in addition to the clinical manifestations of the first primary cancer, the clinical symptoms of the second primary colorectal cancer mainly include change of stool habits, abdominal pain, anemia, bleeding (from anus or ostomy), ileus, and abdominal mass [6, 7].

Some studies suggested that compared with isolated colorectal cancer, SC usually has a low stage (I or II) and a low grade, and synchronous colorectal cancer has some different clinical characteristics [8]. At first, it has a lower incidence. Some research has shown that the incidence of synchronous colorectal cancer is between 1.1% and 8.1% of colorectal cancer [1]. Secondly, many studies have indicated that SC are significant gender differences. Men are more likely to have SC than women [9]. Next, compared with isolated colorectal cancer, there was no significant difference in the age group of SC [10]. What's more, several studies have reported that the most common sites of SC are sigmoid colon and rectum [1], but other research have reported that it is more likely to occur in the proximal colon, especially in the ascending colon [11]. Many studies have found that it tends to occur in the same or similar areas of the large intestine, but a large proportion of concurrent tumors occur in different areas of the large intestine

[12]. From these clinical feature we concluded that colonoscopy is very important for the diagnosis of colorectal cancer.

The standard of diagnosis for synchronous multiple primary carcinoma were proposed by Moertel. There are follow six requirements for diagnose it. (1). each tumor was pathologically confirmed as carcinoma. (2). It must be ruled out as the spread or metastasis of another cancer. (3). All tumors diagnosed at the same time or within 6 months are synchronous cracinoma (SC); if the tumor is diagnosed more than 6 months after the first tumor is found which defined as metachronous carcinoma (MC). (4). At the same time, two tumors must not be located in the same or adjacent intestinal segment. If they are located in the same intestinal segment, must be diagnosed with different pathologic types of tumors or between the normal bowel segments. (5). Metachronous tumor must be at least 5cm away from the anastomosis after resection of the first tumor, and the anastomosis should be normal. (6). Patients with ulcerative colitis or familial adenomatosis should be excluded [13]. The following points should be noted in MPCC diagnosis and treatment. (1). Preoperative examination of colorectal cancer should examine the whole large intestine to avoid the omission of the SC. Some studies reported that the detection rate of barium perfusion in MPCC was 50% and that in colonoscopy was only 76.7% [14]. This is due to a tumor of a certain size can cause intestinal cavity narrow. Therefore, barium meal and colonoscopy are difficult to enter, generally can only find the most distant cancer foci, proximal cancer foci difficult to find. (2). Regular colonoscopy should be performed after post-operation, especially appear diarrhea, abdominal distension, abdominal pain and bloody stool, in order to detect tumor recurrence or MPCC and Early treatment. (3). No matter SC or MC, or how many tumor foci there are, tumor growth is slow and metastases late. The prognosis is good, if early detection, diagnosis and treatment.

Surgery is considered to be the best treatment for MPCC. The choice of surgical method should be based on the location, spacing, range of the tumor and the patient's age, basic condition and other comprehensive considerations. At present, there are two kinds of surgical methods for SC: One is total colectomy, the other is radical resection of colon by segmental resection. There are four main types of extensive total colectomy. Firstly, total colectomy and permanent ileostomy, which has advantage of permanently avoiding postoperative colonic recurrence. However, it has many disadvantages, including poor postoperative intestinal function and complications, such as large trauma, slow postoperative recovery, postoperative diarrhea, electrolyte disorders, and low quality of life. Studies have shown that the surgical method apply to this cases that rectal cancer with low rectal carcinoma or ileorectal anastomosis after total colectomy. Secondly, total colon resection and rectal ileostomy. Many studies indicated that it applied for patient that has multiple tumor lesions in the colon but no lesions in the rectum. However, the disadvantage is that the retained rectum still has the possibility of tumor recurrence. Thirdly, subtotal resection of colon and anastomosis of ascending colon and rectum. The advantages of this operation are simple, safe and less complications, and it is beneficial to postoperative colonoscopy examination. What is more, the patient had good defecation function after operation. However, the disadvantage is that the number of times for defecation increased, and the retention of the rectum still has the possibility tumor recurrence. Finally, the method is total colectomy combination with rectal mucosal exfoliation combination with ileum bag anal anastomosis, which removes the entire large

intestine mucosa, preventing mucosa canceration while preserving the sphincter muscle function that controls defecation. However, the operation is difficult, low penetration rate, high incidence of complications, especially anastomotic fistula, pelvic infection, and poor postoperative intestinal function. Radical resection of colon is a combination of partial resection of colon [15, 16, 17]. There are four surgical methods of partial colon resection: (1) Right half colon resection; (2) Left semicolon resection; (3) Sigmoidectomy; (4) Complete rectal resection. These surgical methods can not only ensure the complete excision of the lesion, but also retain the function of the colon to the greatest extent, which with less complication and improves the quality of life [18, 19, 20]. Nevertheless, if we find lymph node or adjacent viscera metastasis during the operation, simultaneous lymph node dissection or resection of the metastases is necessary. At present, however, there is a little research on this field and lack of long-term postoperative follow-up data. As for the surgical treatment of MC, some studies suggest that the resection scope should be expand, especially for patients with positive family history of colorectal cancer and those with more than three tumor foci, especially hereditary non-polyposis colorectal cancer (HNPCC) patients should undergo subtotal colectomy [21]. Other research suggested that heterochronous segmental resection of colon, radical resection of colorectal cancer performed for each tumor foci and we should strengthen postoperative follow-up and radical resection should be performed when we found out that recurrence of the disease, should be performed for patient with MC [22]. Postoperative chemotherapy for MPCC includes mFOLFOX6, FOLFIRI, CapeOX, single capecitabine [23]. However, there is no evidence that postoperative chemotherapy can prolong its recurrence time and life.

The follow-up methods included colonoscopy, rectal examination and finger examination of ostomy, fecal occult blood, serum carcinoembryonic, CT, MRI and other imaging examinations[1]. However, it should be noted that the diagnosis of recurrence and MPCC at the same time, and must attention to the extra-intestinal multiple primary cancer. Many studies have shown that the prognosis of SC is better than that of isolated colorectal cancer [1]. However, Oya et al reported that there was no difference between the prognosis of SC and that of single carcinoma [9]. Wang et al indicated that the second primary cancer was better than the first primary cancer in neoplasm differentiation and staging [24].

Many studies have shown that the association between SC and adenomas is stronger than that between isolated colorectal carcinoma. There is increasing evidence that serrate adenoma and hyperplastic polyp are closely related to synchronous colorectal cancer [25]. Many studies indicated that patients with serrated polyps are usually BRAF V600E positive and CIMP-H [26]. Other studies have indicated that the incidence of MPCC is higher in patients with ulcerative colitis, and significantly higher than that of crohn's disease [27]. There are two mechanisms of SC: MSI and gene mutation. Compared with isolated colorectal cancer, MSI-H is more significant in MPCC, especially in SSAs-induced MSI-H, and its overall survival (OS) rate is higher [12]. At present, there are two mechanisms lead to MSI-H. The one is mutation of mismatch repair genes. The other is methylation of mismatch repair genes, especially in BRAF-related methylation on MLH1 promoters is closely related to it. Some studies suggest that the SSA-related SC is more likely to occur in older women, and also presents MSI-H and BRAF V600E mutations. But its prognosis is good. Other research suggested that the SSA-related synchronous colorectal cancer always

expression loss of MSI-H, MLH1 and PMS2 and co-existence of SSA and BRAF V600E mutations, which usually occur in those patients that over the age of 65 and the tumor involved the right half of the colon [25, 28, 29, 30]. Other studies indicated that in addition to MSI, p-53, K-RAS and GSRM1 mutations are also correlated with it [31, 32, 33]. According to a retrospective case study, mucinous adenocarcinoma is more common in SC than in isolated colorectal cancer [19]. Some studies indicated that tumor stem cell markers CD44 and CD133 mRNA are highly expressed in synchronous colorectal cancer liver metastasis, but the expression of CD44 and CD133 mRNA in SC is rarely reported [34].

Conclusion

Nowadays, despite the rapid development of clinical diagnostic techniques, it is still difficult to completely diagnosis SC preoperatively. It is a distinct type of CRC and shows wide difference against solitary tumors with many probable clinical and molecular implications confirmed by current studies. More cases should be claimed in the literature to define the principle management in such challenging disease. Certainly, further understanding of the SC genesis and development will ultimately benefit molecular therapy and improve patient survival.

Declarations

Ethics approval and consent to participate

This study received the Lishui Central Hospital Ethics Committee Scientific Research Theory Group approval (202148)

Consent for publication

Written informed consent for publication was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

Availability of Data and Materials

All data generated or analysed during this study are included in this published article

Funding

This work was supported by Lishui City Key Discipline - General Surgery Program.

Author Contributions

JF.C. and J.X contributed the central idea, analysed most of the data, and wrote the initial draft of the paper. The remaining authors contributed to refining the ideas, carrying out additional analyses and

finalizing this paper.

Acknowledgements

First and foremost, I would like to show my deepest gratitude to my supervisor, Dr. Chen Bi Cheng, a respectable, responsible and resourceful scholar, who has provided me with valuable guidance in every stage of the writing of this thesis. Without his enlightening instruction, impressive kindness and patience, I could not have completed my thesis. His keen and vigorous academic observation enlightens me not only in this thesis but also in my future study. I shall extend my thanks to Dr. Huang Xin Ce and Dr. Gao Xiao Ming for all their kindness and help. I would also like to thank all my teachers who have helped me to develop the fundamental and essential academic competence.

References

1. Lam AK, Chan SS, Leung M. (2014) Synchronous colorectal cancer: clinical, pathological and molecular implications. *World journal of gastroenterology* 20(22):6815–6820.
2. Warren S, Gates O. (1941) Carcinoma of ceruminous gland. *The American journal of pathology* 17(6):821–826 823.
3. Yang J, Peng JY, Chen W. (2011) Synchronous colorectal cancers: a review of clinical features, diagnosis, treatment, and prognosis. *Digestive surgery* 28(5–6):379–385.
4. Soldatkina NV, Kit OI, Gevorkyan YA, Milakin AG. (2016) [Multiple primary colorectal cancer: Clinical aspects]. *Terapevticheskii arkhiv* 88(8):53–58.
5. Haraldsdottir S, Einarsdottir HM, Smaradottir A, Gunnlaugsson A, Halfdanarson TR. (2014) [Colorectal cancer - review]. *Laeknabladid* 100(2):75–82.
6. Cromheecke M, de Jong KP, Hoekstra HJ. (1999) Current treatment for colorectal cancer metastatic to the liver. *European journal of surgical oncology: the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology* 25(5):451–463.
7. Stewart CL, Warner S, Ito K, et al (2018) Cytoreduction for colorectal metastases: liver, lung, peritoneum, lymph nodes, bone, brain. When does it palliate, prolong survival, and potentially cure? *Current problems in surgery* 55(9):330–379.
8. Saito S, Hosoya Y, Togashi K, et al (2008) Prevalence of synchronous colorectal neoplasms detected by colonoscopy in patients with gastric cancer 38(1):20–25.
9. Oya M, Takahashi S, Okuyama T, Yamaguchi M, Ueda Y. (2003) Synchronous colorectal carcinoma: clinico-pathological features and prognosis. *Japanese journal of clinical oncology* 33(1):38–43.
10. Chen HS, Sheen-Chen SM. (2000) Synchronous and "early" metachronous colorectal adenocarcinoma: analysis of prognosis and current trends. *Diseases of the colon and rectum.* 43(8):1093–1099.
11. van Leersum NJ, Aalbers AG, Snijders HS, et al (2014) Synchronous colorectal carcinoma: a risk factor in colorectal cancer surgery. *Diseases of the colon and rectum* 57(4):460–466.

12. Hu H, Chang DT, Nikiforova MN, Kuan SF, Pai RK. (2013) Clinicopathologic features of synchronous colorectal carcinoma: A distinct subset arising from multiple sessile serrated adenomas and associated with high levels of microsatellite instability and favorable prognosis. *The American journal of surgical pathology* 37(11):1660–1670.
13. LI De-chuan LIU Yong (2009) Research Progress in Diagnosis and Treatment for Multiple Primary Colorectal Carcinoma. Journal of Oncology Vol.15,No.2.
14. Postic G, Lewin D, Bickerstaff C, Wallace MB. (2002) Colonoscopic miss rates determined by direct comparison of colonoscopy with colon resection specimens. *The American journal of gastroenterology* 97(12):3182–3185.
15. Slater G, Aufses AH Jr, Szporn A. (1990) Synchronous carcinoma of the colon and rectum. *Surgery, gynecology & obstetrics* 171(4):283–287.
16. Easson AM, Cotterchio M, Crosby JA, et al (2002) A population-based study of the extent of surgical resection of potentially curable colon cancer. *Annals of surgical oncology* 9(4):380–387.
17. Lillehei RC, Wangensteen OH. (1955) Bowel function after colectomy for cancer, polyps, and diverticulitis. *Journal of the American Medical Association* 159(3):163–170.
18. Arenas RB, Fichera A, Mhoon D, Michelassi F. (1997) Incidence and therapeutic implications of synchronous colonic pathology in colorectal adenocarcinoma. *Surgery* 122(4):706–709; discussion 709–710.
19. Adloff M, Arnaud JP, Bergamaschi R, Schloegel M. (1989) Synchronous carcinoma of the colon and rectum: prognostic and therapeutic implications. *American journal of surgery* 157(3):299–302.
20. Bardakcioglu O, Ahmed S. (2010) Single incision laparoscopic total abdominal colectomy with ileorectal anastomosis for synchronous colon cancer. *Techniques in coloproctology* 14(3):257–261.
21. Yurgelun MB, Hampel H. (2018) Recent Advances in Lynch Syndrome: Diagnosis, Treatment, and Cancer Prevention. *American Society of Clinical Oncology educational book. American Society of Clinical Oncology. Annual Meeting* 38:101–109.
22. Inada R, Yamamoto S, Takawa M, Fujita S, Akasu T. (2014) Laparoscopic resection of synchronous colorectal cancers in separate specimens. *Asian journal of endoscopic surgery* 7(3):227–231.
23. Bos A, Matthijsen RA, van Erning FN, van Oijen MGH, Rutten HJT, Lemmens V. (2018) Treatment and Outcome of Synchronous Colorectal Carcinomas: A Nationwide Study. *Annals of surgical oncology* 25(2):414–421.
24. Wang W, Zhou ZW, Wan DS, et al (2008) Clinical analyses of 70 cases of multiple primary colorectal carcinoma. *Ai zheng = Aizheng = Chinese journal of cancer* 27(5):505–509.
25. Pyleris E, Koutsounas IS, Karantanos P. (2014) Three Colon Adenocarcinomas Arising in a Patient with Serrated Polyposis Syndrome: Case Report and Review of the Literature. *Viszeralmedizin.* 30(2):136–139.
26. Rosty C, Walsh MD, Walters RJ, et al (2013) Multiplicity and Molecular Heterogeneity of Colorectal Carcinomas in Individuals With Serrated Polyposis. *The American journal of surgical pathology* 37(3):434–442.

27. Kiran RP, Khoury W, Church JM, Lavery IC, Fazio VW, Remzi FH. (2010) Colorectal cancer complicating inflammatory bowel disease: similarities and differences between Crohn's and ulcerative colitis based on three decades of experience. *Annals of surgery* 252(2):330–335.
28. Pakneshan S, Salajegheh A, Smith RA, Lam AK. (2013) Clinicopathological relevance of BRAF mutations in human cancer. *Pathology* 45(4):346–356.
29. Pritchard CC, Grady WM. (2011) Colorectal cancer molecular biology moves into clinical practice. *Gut* 60(1):116–129.
30. Ogino S, Goel A. (2008) Molecular classification and correlates in colorectal cancer. *The Journal of molecular diagnostics: JMD* 10(1):13–27.
31. Hayakumo T, Cho E, Nakajima M, Kato G, Kawai K, Azuma T. (1995) Point mutations in the c-K-ras 2 gene in multiple colorectal carcinomas. *Journal of gastroenterology and hepatology* 10(1):70–75.
32. Ueda E, Watanabe T, Umetani N, Ishigami H, Sasaki S, Nagawa H. (2002) Microsatellite instability of cancers and concomitant adenomas in synchronous multiple colorectal cancer patients. *Journal of experimental & clinical cancer research: CR* 21(2):149–154.
33. Koness RJ, King TC, Schechter S, McLean SF, Lodowsky C, Wanebo HJ. (1996) Synchronous colon carcinomas: molecular-genetic evidence for multicentricity. *Annals of surgical oncology* 3(2):136–143.
34. Jing F, Kim HJ, Kim CH, Kim YJ, Lee JH, Kim HR. (2015) Colon cancer stem cell markers CD44 and CD133 in patients with colorectal cancer and synchronous hepatic metastases. *International journal of oncology* 46(4):1582–1588.

Figures

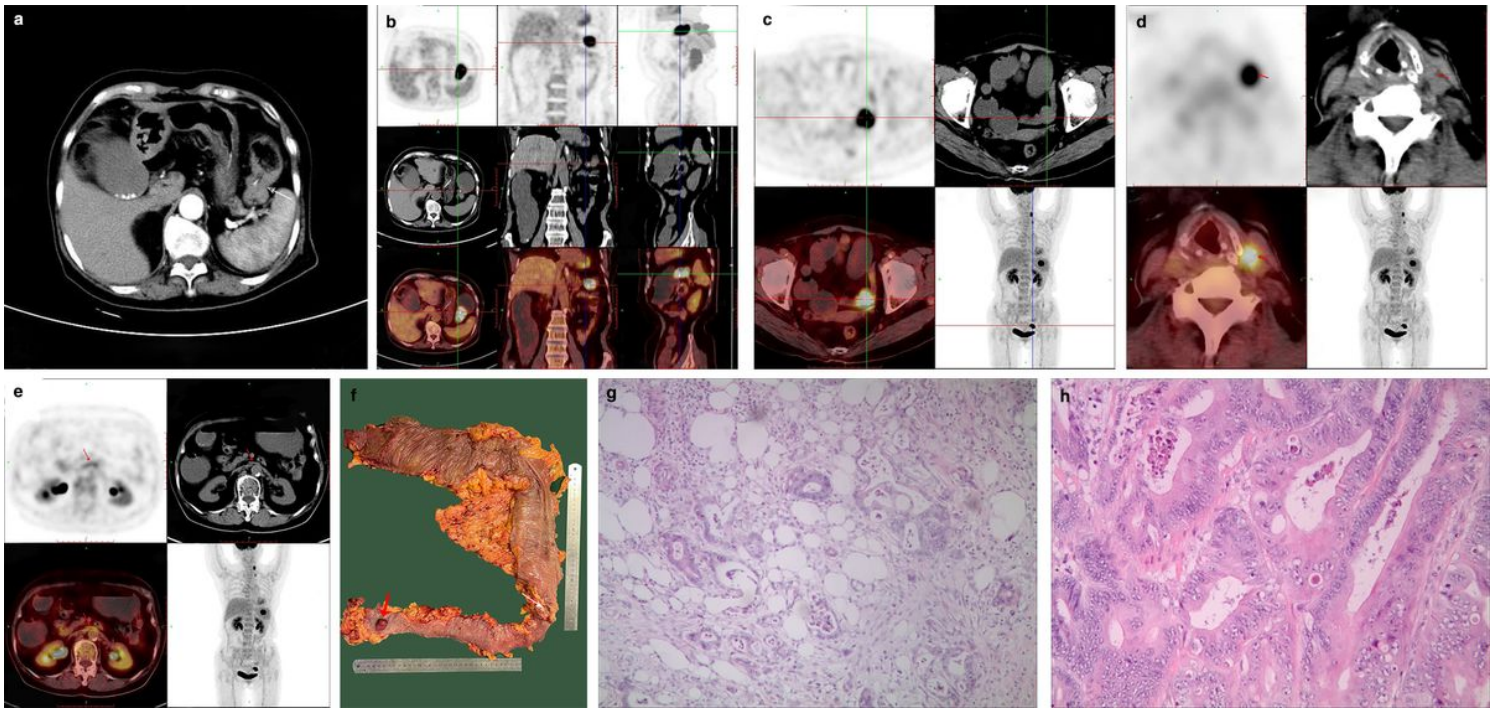

Figure 1

a: The white arrow indicates thickening of the splenic curvature of the colon and the red arrow indicates incomplete obstruction of the colon. b: In this PET-CT image, the intersection of the two lines represents a mass in the splenic curvature of the colon. c: This PET-CT image demonstrates a sigmoid mass at the intersection of two lines with increased FDG metabolism. d: This image shows that the patient has left supraclavicular lymph node enlargement. e: This image shows that the patient with possible retroperitoneal lymph node metastasis. f: Tumor A (white arrow) is an ulcerative mass in descending colon and tumor B (red arrow) is a bulging mass in sigmoid. g: H&E staining revealed that the tumor is a moderately differentiated adenocarcinoma and it was infiltrating into the subserosal layer. h: The tumor is a moderately differentiation adenocarcinoma were found by H&E staining.

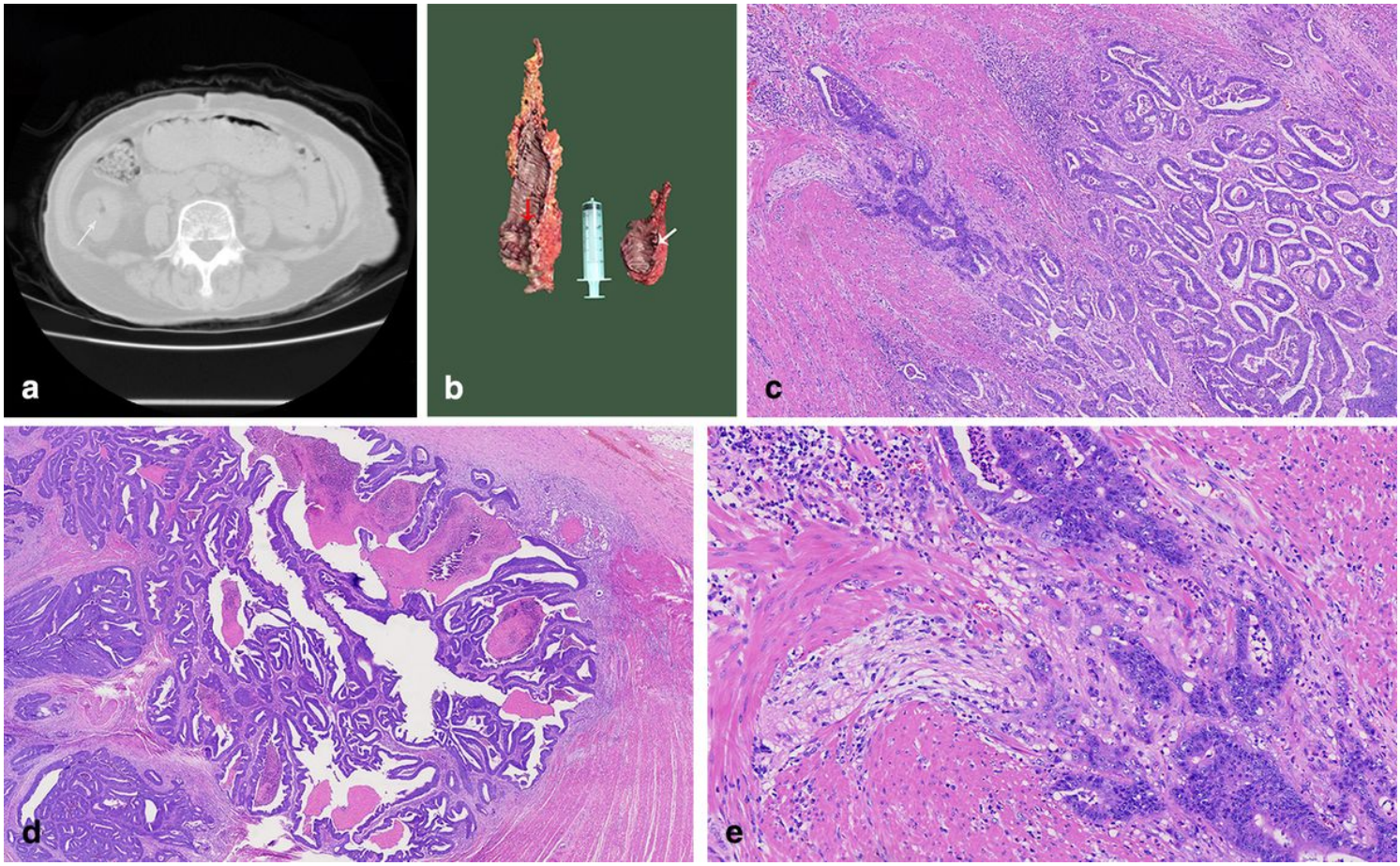

Figure 2

a: The white arrow shows irregular thickening of the ascending colon wall in abdominal contrast-enhanced CT. b: The tumor A (white arrow) points to an ulcerative mass (2.3cm×2.0cm×1.0cm) in the rectum, and the tumor B (red arrow) points to another ulcerative mass (5cm×4.5cm×1.1cm) in ascending colon. c: H&E staining revealed that the tumor is moderate differentiation adenocarcinoma and it infiltrates into the deep muscularis. d: The tumor is a moderately differentiation adenocarcinoma and it infiltrates into the extrserosal adipose tissue were found by H&E staining. e: H&E staining revealed that the tumor invaded the nerve.

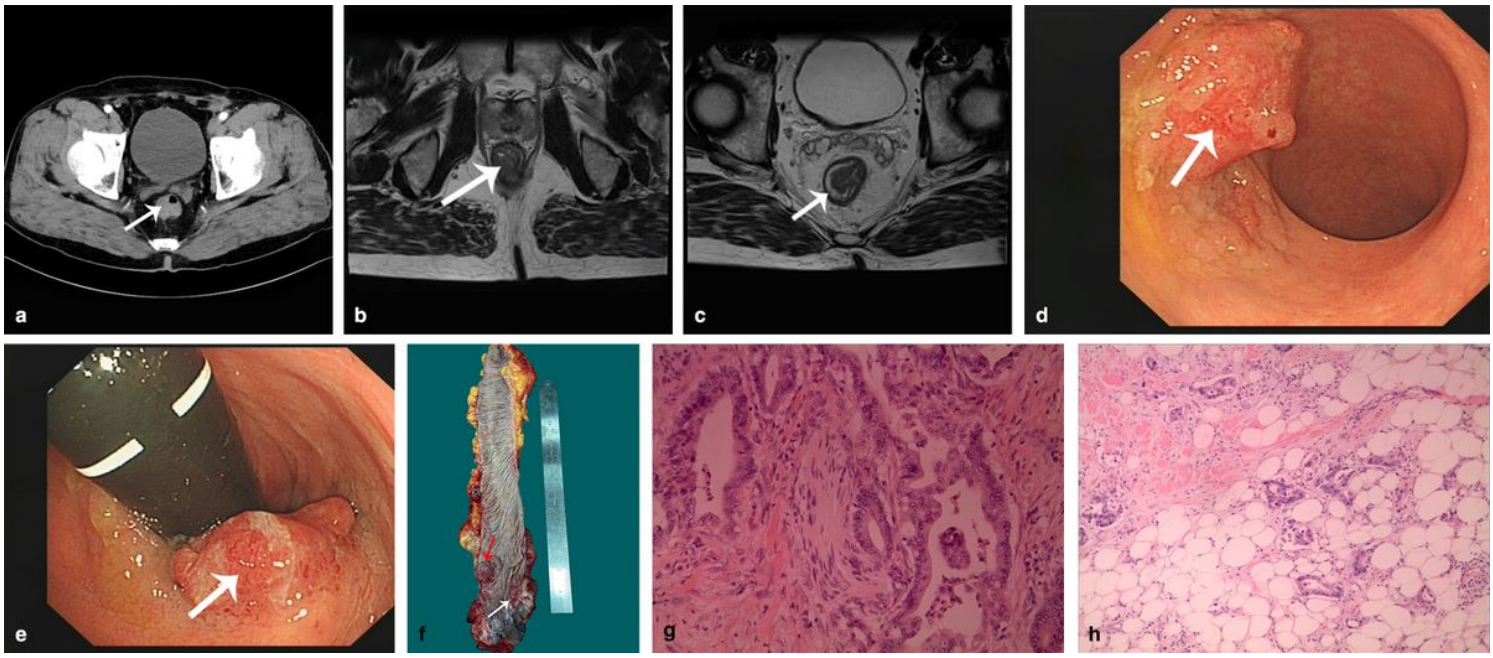

Figure 3

a: The thickening of the rectum wall is shown by the white arrow in this contrast-enhanced CT of the abdomen. b: The white arrows in this rectum MRI shows a neoplasm in the middle rectum. c: The white arrows in this rectum MRI shows the other carcinoma at the junction of the anal canal of the rectum. d: The white arrows in the colonoscopy image indicate that there is a tumor in the rectum. e: The white arrows in the colonoscopy image indicate that there is another tumor at the junction of the rectum and anal canal. f: The white arrow (tumor A) points to an ulcerative mass (3cm×3cm×1.5cm) at the junction of the rectum and anal canal and the red arrow (tumor B) points to the other ulcerative mass (5cm×4.5cm×1.1cm) in rectum. g: H&E staining revealed that the tumor invaded the nerve. h: H&E staining revealed that the tumor invaded the anal subcutaneous tissue. i: H&E staining revealed that the tumor is a medium-low differentiated adenocarcinoma and it infiltrates into the muscular layer. j: H&E staining revealed that carcinoma invasion of vessels k: H&E staining revealed that lymph nodes metastasis.