Characteristics of primary signet ring cell carcinoma of colon and rectum: a case control study

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Abstract
Background: Primary signet ring cell carcinoma of the colon and rectum (PSRCCR) is rare, usually diagnosed at advanced stage with poor outcomes. We aimed to find possible diagnostic clues in order to help diagnosis.

Methods: A retrospective study of PSRCCR patients from 1993 to 2018 was reviewed at a single tertiary center. Colorectal adenocarcinoma patients as control group with 1:4 ratio was also enrolled.

Results: 18 patients with PSRCCR were identified. The prevalence rate was 0.16% (18 of 11,515). The mean age was 50.2 years-old in PSRCCR group and 63 years-old in non-SRCC colorectal cancer patients (p < 0.001). Diagnosis tool depends on colonoscopy were much less in PSRCCR group than control group (44.4% vs 93%, p < 0.001). SRCC patients had higher level of CEA (68.3 vs 17.7 ng/mL, p = 0.004) and lower level of Albumin (3.4 vs 4.3 g/dL, p < 0.001). The majority of PSRCCR tumor configuration was ulcerative and infiltrative. More PSRCCR pathology presented as high-grade carcinoma (66.7 vs 1.4%, p < 0.001) and lymphovascular invasion (77.8 vs 44.4%, p = 0.011) than control group. More PSRCCR patients were diagnosed at advanced stage (88.8 vs 40.3%, p = 0.001). Higher mortality was also noticed in PSRCCR group than control group (72.2 vs 20.8%, p < 0.001).

Conclusion: For young patients with long segment colonic stenosis and ulcerative/ infiltrative mucosa but endoscopic biopsy failed to identify malignant cells, earlier operation or non-colon site biopsy is suggested for diagnosing the PSRCCR.

Keywords: Colorectal cancer, Primary signet ring cell carcinoma, Young patients

Background
Primary signet ring cell carcinoma of the colon and rectum (PSRCCR) is a rare histologic subtype, accounting for approximately 0.6–2.7% of all adenocarcinomas of the colon [1, 2]. Signet ring cell carcinoma (SRCC) contains a large amount of mucin, which pushes the nucleus to the cell periphery. The World Health Organization has a specific criterion for diagnosing this subtype; that is, the presence of > 50% of signet cells [3]. The symptoms of PSRCCR include bloody stool, body weight loss, abdominal pain or bowel habit change and usually appear at late stage [4]. The symptoms are similar to those of colorectal cancer (CRC) [5], whereas the clinical behavior is more aggressive than colorectal cancer. Patient with colonic signet ring cell carcinoma were more frequently diagnosed at advanced stage (75.2–91%) [6–8] than patients with colon adenocarcinoma (43.6–48%). Less than 40% of cases have a change to receive curative operation [9]. Compared with non-SRCC colorectal cancer, PSRCCR
tends to occur at a younger age, presented as scirrhous appearance, with more lymphovascular and peritoneal involvement, and has a poorer prognosis [6, 10, 11].

As PSRCCR is a rare subtype and its characteristic is different from common colon adenocarcinoma. In this study, we aimed to compare the difference of clinical characteristics, pathologic features, diagnostic stage and outcome between patients with SRCC and non-SRCC colorectal cancer. Through this comparison, we also would like to find the possible diagnostic clues in order to help diagnosis.

**Methods**

**Data collections**

This is a retrospective study reviewed the colorectal cancer patients from October 1993 to June 2018 in National Taiwan University Hospital. In total, 11,515 colorectal cancer tissues were received and registered in the pathology databank. Clinical information including demographic data, laboratory, endoscopic and pathologic report, treatment regiments and the disease course were assessed. The pathological diagnosis of SRCC was confirmed through histological examination (using hematoxylin and eosin staining) which revealed the presence of signet ring cell was greater than 50%. Tumor configuration was classified into 3 types: exophytic, ulcerative and infiltrative. Exophytic is defined as an abnormal growth that sticks out from the surface of a tissue. Ulcerative is defined as the lesion is depressed than surrounding mucosa. Infiltrative is defined as the margin between cancerous tissue and surrounding non-cancerous tissue is poorly demarcated. In Crohn's disease, stricture is poorly demarcated. In Crohn's disease, stricture is defined as short stricture [12]. In this study, we defined wall thickening > 5 cm as long segment. Tumor stage was based on TNM staging system and American Joint Committee on Cancer, AJCC Cancer Staging Manual (8th edition, 2017). Stage I and II were defined as early stage and stage III and IV as advanced stage. The survival duration was based on the last outpatient department date or date of death. A retrospective computer-aided search generated 18 PSRCCR cases. In order to compare the stage, location of tumor, age, sex, also omitting the outcomes influenced by the treatment choices in different year, we match PSRCCR patients with non-PSRCCR colorectal cancer patients as a control group at a 1:4 ratio according to the year of patient diagnosed with colorectal cancer. This study was approved by the Ethics Review Board of National Taiwan University Hospital (IRB Number 201808070RINB). The Institutional Review Board of NTUH allowed to waive the informed consent because of the retrospective nature of the study and the analysis used anonymous clinical data.

**Statistical analyses**

Results are expressed as the mean and range. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were expressed as frequency (percentage). Student's t-test was used for quantitative variables and Chi-square statistic was used for categorical variables among the two cohorts. A p-value less than 0.05 was considered as statistically significant. The survival was calculated using the Kaplan–Meier method. Prognostic factors including age, sex, underlying disease, laboratory data, tumor subtype, pathological parameters, cancer stage were included in survival analyses. Parameters with p < 0.05 in univariable analyses were further checked by multivariable Cox proportional hazard model. These analyses were carried out with SPSS 11.0 program (SPSS, Paris, France).

**Results**

**Demographic and clinical characteristics of PSRCCR patients**

A total of 11,515 patients were diagnosed with colorectal cancer from the hospital database between 1993 and 2018. Among them, 18 were identified with PSRCCR. The incidence of PSRCCR was 0.16% in colorectal patients. A total of 72 patients with non-SRCC CRC were included as controls. PSRCCR patients was significant younger than non-SRCC CRC patients (mean age 50.2 vs 63 years-old, p < 0.001). In both the PSRCCR and non-SRCC groups, male predominance was noted (66.7% vs 62.5%, p = 0.74). The baseline hypertension (22.2% vs. 38.9%, p = 0.19), diabetes mellitus (5.6% vs. 16.7%, p = 0.23), hyperlipidemia (0% vs. 12.5%, p = 0.20), viral hepatitis (5.6% vs. 5.6%, p = 1), coronary artery disease (5.6% vs. 11.1%, p = 0.48) and chronic kidney disease (5.6% vs. 9.7%, p = 0.58), was comparable in these two groups. Most of the non-SRCC CRC patients were diagnosed by colonoscopy. In contrast, more than one-third PSRCCR patients were diagnosed by operation or non-colon site biopsy (p < 0.001). The PSRCCR group was associated with higher level of CEA (68.3 vs 17.7 ng/mL, p = 0.004), the albumin level was significantly lower in the PSRCCR group than in the non-SRCC group (3.4 vs 4.3 g/dL, p < 0.001). The clinical information of PSRCCR and non-SRCC CRC patients were summarized in Table 1. We further compared the CEA and Albumin level between tumor stage III and IV and noticed that the CEA level was significantly higher in stage IV than stage III (124.9 vs 7.66, p = 0.007). There was no significant difference of albumin level between stage IV and III (4.13 vs 4.3, p = 1).
Comparison of pathologic characteristics between PSRCCR and non-SRCC CRC patients

Majority of the tumor were located at left side in both groups (61.1% vs 68.1%, \( p = 0.59 \)). Most tumor configuration of PSRCCR patients were ulcerating or infiltrative, whereas those of non-SRCC patients were exophytic or ulcerating (\( p < 0.001 \)). The differentiation grade of PSRCCR group was significantly advanced than that of non-SRCC group (66.7% vs 1.4% high grade, \( p < 0.001 \)). PSRCCR patients also had more lymphovascular invasion than non-SRCC patients (77.8% vs 44.4%, \( p = 0.01 \)). The pathologic features were listed in Table 2.

Comparison of tumor stage between PSRCCR and non-SRCC CRC patients

Most of SRCC patients were diagnosed at stage T3 or T4 (94.4%) and N2 (77.8%). The distant metastasis rate was 50%. The only patient who was diagnosed with a tumor at an early stage, with carcinoma in situ, was due to a positive immunochemical fecal occult blood test during health examination. The number of the patients with initial AJCC stages 0 and 1, 2, 3, and 4 was 1 (5.6%) versus 0 (0%), 0 (0%) versus 23 (31.9%), 1 (5.6%) versus 20 (27.8%), 9 (50%) versus 18 (25%) and 7 (38.8%) versus 11 (15.3%) in the PSRCCR and non-SRCC groups, respectively (\( p = 0.001 \)). All these CRC patients underwent operation. As most PSRCCR patients were diagnosed at advanced stage, 88.9% of them also received chemotherapy or combine therapy. In contrast, a curative resection (R0 resection with related radical lymphatic dissection)
was performed in 37 (51.4%) non-SRCC patients. The PSRCCR group had shorter follow-up period than non-SRCC group (15 vs 94.5 months, \( p < 0.001 \)) (Table 3). The clinical characteristic, colonoscopic and histologic finding of the 18 PSRCCR patients were listed in Table 4. Typical endoscopical and CT images (case 18) was shown in Fig. 1. Seventeen PSRCCR patients with initial CT were reviewed. Most of the patients (13 of 17; 76.5%) presented with long segmental wall thickening and increased enhancement of the involved colon. The average length of the thickened wall was 6.6 cm (range 4.4–11.6 cm). Only 3 of the 15 (20%) patients presented with an intraluminal mass by colonoscopy. One patient (5.9%) had carcinoma in situ, which could not be identified on CT.

### Comparison of survival status between PSRCCR and non-SRCC CRC patients

The patients in the PSRCCR group had significantly poorer estimated overall survival than those in the Non-SRCC group (29.6 vs 162.7 months, log-rank \( p < 0.001 \), Fig. 2A). After stratification, the patients with PSRCCR still had significantly poorer estimated overall survival than did the patients with non-SRCC of early stage CRC (37 vs. 122.8 months, log-rank \( p < 0.001 \), Fig. 2B) and advanced stage CRC (18 vs. 140.7 months, log-rank \( p < 0.001 \), Fig. 2C). Since majority of the patients were diagnosed at advanced stage, most of them received chemotherapy and target therapy. Target therapy prescribed in this study included Cetuximab and Bevacizumab, and all non-SRCC CRC patients received Bevacizumab. Non-SRCC patients still had better prognosis than PSRCCR patients no matter which target therapy they used (Fig. 3A). Target therapy treated or not didn’t improve the overall survival of PSRCCR patients (Fig. 3B, C).

### Factors associated with overall survival

In the univariable analysis of overall survival in all CRC patients, poor differentiation grade, lymphovascular invasion, advanced cancer stage, high CEA level and histological SRCC subtype were associated with increased mortality rates (all \( p < 0.05 \), Table 5). Further multivariate analysis with adjusted Cox proportional hazard model revealed that the CEA level (HR, 1.003; 95% CI, 1.000–1.005; \( p = 0.03 \)) and histological SRCC subtype (HR, 8.333; 95% CI, 1.42–50; \( p = 0.005 \) were independent predictors of overall survival. The detail information of univariable and multivariate factor were listed in Table 5.

### Discussion

Primary signet ring cell carcinoma of colon and rectum is a rare variant of CRC. The frequency of SRCC was no difference between Western and Eastern Countries. In this study, 18 of the 11,515 CRC patients were diagnosed with PSRCCR. It accounted for 0.16% of all primary CRCs. The percentage of PSRCCR was even lower in our study than those of previous studies which indicated 0.6%–2.7% [1, 7, 10, 11, 13]. Compared to non-SRCC patients, PSRCCR patients were younger. In Wang’s study, they also reported PSRCCR is four times more prevalent among the young (ages <40 years) than older adults (>40 years) [14]. The underlying disease including hypertension, diabetes mellitus, viral hepatitis, coronary artery disease and chronic kidney disease were not significant different between PSRCCR and non-SRCC patients. Most (88.8%) PSRCCR patients were diagnosed at advanced stage as their initial presentations were non-specific such as abdominal fullness, pain and bowel habit change. The PSRCCR patients were also associated with low level of albumin and higher CEA level than non-SRCC patients. The high CEA level was related to 40% of SRCC patients diagnosed with stage IV.

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### Table 3 Treatment and tumor stage of colorectal cancer patients

| Treatment       | SRCC (n = 18) | Non-SRCC (n = 72) | p-value |
|-----------------|--------------|------------------|---------|
| Operation       | 2 (11.1)     | 37 (51.4)        | 0.001   |
| Op + C/T        | 4 (22.2)     | 20 (27.8)        |         |
| Op + C/T + Target | 10 (55.6)   | 11 (15.3)        |         |
| Op + CCRT       | 2 (11.1)     | 4 (5.6)          |         |
| Tis             | 1 (5.6)      | 0                | 0.002   |
| 1               | 0            | 4 (5.6)          |         |
| 2               | 0            | 22 (30.5)        |         |
| 3               | 8 (44.4)     | 36 (50)          |         |
| 4               | 9 (50)       | 10 (13.9)        |         |
| N               |              |                  | <0.001  |
| 0               | 2 (11.1)     | 44 (61.1)        |         |
| 1               | 2 (11.1)     | 21 (29.2)        |         |
| 2               | 14 (77.8)    | 7 (9.7)          |         |
| M               |              |                  | 0.002   |
| 0               | 9 (50)       | 62 (86.1)        |         |
| 1               | 9 (50)       | 10 (13.9)        |         |
| Stage           |              |                  | 0.001   |
| 0               | 1 (5.6)      | 0                |         |
| 1               | 0            | 23 (31.9)        |         |
| 2               | 1 (5.6)      | 20 (27.8)        |         |
| 3               | 9 (50)       | 18 (25)          |         |
| 4               | 7 (38.8)     | 11 (15.3)        |         |
| Follow-up duration, mean (months) | 15 | 94.5 | <0.001 |

Chi-square statistic was used for categorical variables among the two cohorts. Op, operation; CT, Chemotherapy; CCRT, concurrent chemoradiotherapy.
| No | Age | Sex | Symptoms                  | CT Findings                                  | Colonoscopic finding                               | Histology configuration | Diagnosis tool         | Cancer stage | FU (m) | Survival |
|----|-----|-----|---------------------------|----------------------------------------------|--------------------------------------------------|--------------------------|-------------------------|--------------|--------|----------|
| 1  | 36  | M   | Abdominal fullness        | Bowel wall thickening Length: from transverse to ascending colon | Incomplete study due to patient intolerance       | not mentioned            | Colonoscopy             | T4bN2bM1c    | 9      | Loss FU  |
| 2  | 74  | M   | Bloody stool              | Bowel wall thickening with serosal invasion Length: 5.8 cm | A cauliflower-like tumor with central ulceration at ascending colon | Infiltrative Colonoscopy | T4aN2bM1c              | 23           | no     |          |
| 3  | 86  | F   | Colon obstruction         | Bowel wall thickening Length: 6 cm           | A cauliflower-like tumor at cecum                | Ulcerative Colonoscopy  | T4aN2bM1a              | 1            | Loss FU |          |
| 4  | 28  | F   | Bloody stool              | Not performed                                | An ulcerative tumor with easily bleeding at sigmoid colon | Ulcerative Colonoscopy  | T3N2bM0              | 13           | no     |          |
| 5  | 45  | F   | Noted during hemorrhoidectomy | Semi-circumferential mass                      | Not performed                                    | Ulcerative Operation    | T4N2bM0              | 19           | Loss FU |          |
| 6  | 14  | M   | Chronic diarrhea          | Bowel wall thickening and ascites Length: 11.6 cm | Colon ulcers with lumen stenosis at sigmoid colon | Ulcerative Colonoscopy  | T4bN2bM1c              | 17           | no     |          |
| 7  | 17  | M   | Bloody stool              | Bowel wall thickening Length: 7 cm            | Erosive and fragile mucosa with luminal stenosis at sigmoid colon | Infiltrative Skin biopsy | T3N2bM1b              | 14           | no     |          |
| 8  | 76  | M   | Bloody stool              | Bowel wall thickening Length: 5.2 cm          | Infiltrative tumor at rectum                     | Infiltrative Operation  | T3N0M0              | 37           | no     |          |
| 9  | 61  | M   | Positive stool occult blood | Negative finding                               | A semi-annular tumor at sigmoid colon            | Ulcerative Colonoscopy  | TisN0M0              | 100          | yes    |          |
| 10 | 31  | M   | Abdominal fullness        | Bowel wall thickening Length: 5.5 cm          | Infiltrative tumor with lumen stenosis at descending colon | Infiltrative Operation  | T4aN2bM1c              | 44           | Loss FU |          |
| 11 | 76  | M   | Right lower limb edema    | Bowel wall thickening Length: 5.2 cm          | A circular ulcerative tumor at S-D junction     | Exophytic Abdominal LN biopsy | T3N2bM0              | 15           | no     |          |
| 12 | 78  | M   | Constipation              | Bowel wall thickening Length: 6 cm            | An ulcerative tumor with luminal stenosis at sigmoid colon | Ulcerative Colonoscopy  | T3N2bM0              | 8            | no     |          |
| 13 | 40  | F   | Abdominal fullness        | Bowel wall thickening and regional LAP Length: 8.2 cm | A cauliflower like tumor with luminal obstruction at splenic flexure | Exophytic Colonoscopy  | T4bN2bM1c              | 10           | no     |          |
| 14 | 39  | M   | Anemia                    | Bowel wall thickening Length: 6.9 cm          | Chicken skin change and congestion of mucosa at hepatic flexure | Infiltrative Peritoneal biopsy | T3N2aM1C              | 14           | no     |          |
| 15 | 57  | F   | Anemia                    | Bowel wall thickening and regional LAP Length: 7.4 cm | Multiple lobulated tumors at sigmoid colon       | Infiltrative Colonoscopy  | T3N2bM0              | 17           | no     |          |
Table 4 (continued)

| No | Age | Sex | Symptoms               | CT Findings                                         | Colonoscopic finding                      | Histology configuration | Diagnosis tool | Cancer stage   | FU (m) | Survival |
|----|-----|-----|------------------------|-----------------------------------------------------|-------------------------------------------|----------------------------|------------------|----------------|--------|----------|
| 16 | 85  | M   | Colon perforation      | Bowel wall thickening and pneumoperitoneum Length 4.4 cm | Not performed. Ascending colon perforation | Ulcerative                | Operation       | T4aN1bM0       | 2      | no       |
| 17 | 43  | M   | Incidental finding by CT | Intraluminal mass                                   | Not performed                           | Exophytic                | Operation       | T3N1bM0        | 28     | no       |
| 18 | 18  | F   | Colon obstruction      | Bowel wall thickening and abscess Length 6.8 cm     | Erosive and fragile mucosa with lumen stenosis at transverse colon | Infiltrative              | Operation       | T4aN2bM1c       | 15     | no       |

CT, Computed Tomography; LA P, Lymphadenopathy; FU, follow-up; m, month
Most of our patients’ CT finding (76.5%) presented with long segmental wall thickening rather than an intraluminal mass. In Kim’s study, they also reported the CT features of PSRCCR was long segmental (> 5 cm) concentric bowel wall thickening without an intraluminal mass, which resembles the inflammatory process [2]. 82.4% of tumor configuration were ulcerative or infiltrative type and only 17.6% were exophytic type in the PSRCCR group. However, in non-SRCC CRC group, infiltrative type only accounted for 4.2% and exophytic type for 47.2%. This is compatible with Messerini study [7] that revealed that infiltrative type was predominant in PSRCCR tumors (70.6% infiltrative type and 29.4% exophytic type). Most colorectal cancer cases (93.1%) were diagnosed by colonoscopic biopsy in control group, whereas 4 of SRCC patients (22.2%) ever received colonoscopic biopsy but failed to identify malignant cells. As 82% of PSRCCR were infiltrative or ulcerative type, it increased the difficulty to identify cancer cell by endoscopic biopsy and led to delay diagnosis. This also explained the reason that half of PSRCCR patients were diagnosed depended on direct operation for colon obstruction, bloody stool or malignant cells identified at non-colon site. Long segment colonic stenosis in young patients, also leading to the possibility of inflammatory bowel disease. Indeed, at least one of this PSRCCR cohort was treated as Crohn’s disease initially. Therefore, close monitoring the treatment effect and get histology diagnosis are important in the differential diagnosis.

Half of non-SRCC CRC patients underwent curative operation and had good prognosis. Most of PSRCCR patients were diagnosed at advanced stage and received combination therapy, whereas chemotherapy or target therapy both failed to improve survival. We also stratified and analyzed the treatment efficacy of bevacizumab or Cetuximab and showed poorer response in SRCC patients. Previously, SRCC has been shown to have fair response to chemotherapy and our results also confirmed this result. Furthermore, we showed that even with current available target therapy (anti-VEGF and/or anti-EGFR), the survival still could not be improved. Novel therapy, either chemotherapy or target therapy for PSRCCR patients, remains as an unmet need.

The estimated overall survival time of the PSRCCR patients (26.9 months) was much shorter than that of non-SRCC patients (162.7 months). SRCC subtype and elevated CEA were independent predictors of overall survival by using Cox proportional hazard regression model. Compared with non-SRCC patients, PSRCCR patients had higher risk of lymphovascular invasion, poor-differentiated carcinoma, visceral peritoneum invasion, lymph node and distant metastasis. This also indicated that the behavior of PSRCCR was more aggressive. According to Huang et al. [15] study, patients aged < 35 years had shorter cancer-specific survival compared with those aged > 35 years, and the 5-year cancer-specific survival rates were 31.1% and 54.9% in patients aged < 35 and > 35 years, respectively. Five of the 18 patients in our series were aged < 35 years. The mean survival time was 20.6 months in this group. The survival time was not significantly different between these two groups. However, the results should be interpreted cautiously because of relatively few cases.

![Fig. 1 Typical endoscopic and CT image of SRCC. A The colonoscopy revealed edematous fragile mucosa with ulcer that led to lumen stenosis at transverse colon. B Abdominal computer tomography (CT) showed segmental wall-thickening of transverse colon with increased enhancement and prominent adjacent fat-stranding (arrow)](image)
There were still limitations of this study. First, this was a retrospective observable study in single referral center. Second, the case number was small. As the PSRCCR is a very rare disease, it is difficult to collect many patients or perform a prospective study.

**Conclusion**

Primary signet ring cell carcinoma of colon and rectum usually present as infiltrative or ulcerative configuration and is associated with poor differentiation, higher lymphovascular invasion and distant metastasis. Signet ring cell carcinoma is a strong predictor of poor overall survival. For young patients with colonic long segment stenosis and ulcerative/ infiltrative mucosa but endoscopic biopsy failed to identify malignant cells, PSRCC should be considered. Even with the progress in current chemotherapy and target therapy, they seemed to be with limited effect in improving the survival of PSRCCR patients and we still need to work out the novel therapy in order to improve the outcomes of these patients.

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**Fig. 2** Kaplan–Meier estimated overall survival curves. **A** Overall survival of all patients with SRCC and Non-SRCC CRC. SRCC is associated with poor overall survival (log-rank \( p < 0.001 \)). **B** Overall survival of patients with early stage SRCC and Non-SRCC CRC (log-rank \( p < 0.001 \)). **C** Overall survival of patients with advanced stage SRCC and Non-SRCC CRC. (log-rank \( p < 0.001 \))
Fig. 3 Kaplan–Meier estimated overall survival curves. A Overall survival of target therapy treated CRC patients. B Overall survival of SRCC patients received Cetuximab or not. C Overall survival of SRCC patients received Bevacizumab or not.

Table 5 Univariable and Multivariable Analysis of Overall Survival in colorectal cancer patients

|                      | Univariable Analysis | Multivariable Analysis |
|----------------------|----------------------|------------------------|
|                      | HR (95% CI)          | P value                | HR (95% CI)          | P value                |
| Age                  | 0.993 (0.969–1.018)  | 0.574                  |                       |                        |
| Sex (male vs female) | 1.091 (0.49–2.428)   | 0.832                  |                       |                        |
| Grade (low vs high)  | 0.131 (0.057 vs 0.301) | < 0.001               | 0.998 (0.184–5.4)    | 0.998                  |
| Location (right vs left) | 0.606 (0.281–1.306) | 0.201                  |                       |                        |
| Lymphovascular invasion (no vs yes) | 0.265 (0.112–0.631) | 0.003                  | 0.359 (0.109–1.186)  | 0.093                  |
| Stage (early vs advanced) | 0.194 (0.078–0.484) | < 0.001               | 0.599 (0.184–1.947)  | 0.394                  |
| CEA (ng/mL)          | 1.003 (1.002–1.005)  | < 0.001               | 1.003 (1.000–1.005)  | 0.03                   |
| Subtype (SRCC vs non-SRCC) | 10.64 (4.74–23.8)   | < 0.001               | 8.333 (1.42–50)      | 0.005                  |

The multivariate analysis only included the variables which P value < 0.05 in univariate analysis
HR, Hazard ratio, CI, confidence interval
Abbreviations
CD: Crohn’s disease; CRC: Colorectal cancer; IBD: Inflammatory bowel disease; NTUH: National Taiwan University Hospital; PSRCCR: Primary signet ring cell carcinoma of the colon and rectum; SRCC: Signet ring cell carcinoma; UC: Ulcerative colitis.

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Author contributions
MTW, KHC, and ILS: drafting of the manuscript; CCT, CTS and SCW: analysis and interpretation of the data; KHC and HCC, and BRL: acquisition of the data; MTW, JMW, and SCW: critical revision of the manuscript for important intellectual content and study supervision; and SCW and JMW: study concept and design. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The institutional review board of the National Taiwan University Hospital (NTUH) ethics committee has approved this study. ID of the approval: 201808070RINB. The informed consent was waived by NTUH IRB. All methods were performed in accordance with the Declaration of Helsinki.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References
1. Thota R, Fang X, Subbiah S. Clinicopathological features and survival outcomes of primary signet ring cell and mucinous adenocarcinoma of colon: retrospective analysis of VACCRC database. J Gastrointest Oncol. 2014;5:18–24.
2. Kim HJ, Ha HK, Cho KS, et al. CT features of primary colorectal signet-ring cell carcinoma. J Comput Assist Tomogr. 2001;25:225–30.
3. SR, H LA. World Health Organization classification of tumours. Pathology and Genetics of Tumours of the digestive system. IARC Press, 2000.
4. Tung SY, Wu CS, Chen PC. Primary signet ring cell carcinoma of colorectum: an age- and sex-matched controlled study. Am J Gastroenterol. 1996;91:2195–9.
5. Fantiar FA, Sabbagh H, Andi T, Fakhruddin N, Farhat F. Signet ring cell carcinoma of the colon in young adults: a case report and literature review. Case Rep Oncol Med. 2019;2019:3092674.
6. Nitsche U, Zimmermann A, Spath C, et al. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surg. 2013;258:775–82 (discussion 782–773).
7. Belli S, Aytaç HO, Karagülle E, Yabanoglu H, Kayaselcuk F, Yıldırım S. Outcomes of surgical treatment of primary signet ring cell carcinoma of the colon and rectum. 22 cases reviewed with literature. Int Surg. 2014;99:691–8.
8. Hugen N, Verhoeven RH, Lemmens VE, et al. Colorectal signet-ring cell carcinoma: benefit from adjuvant chemotherapy but a poor prognostic factor. Int J Cancer. 2015;136:333–9.
9. Radhakrishnan CN, Bruce J. Colorectal cancers in children without any predisposing factors. A report of eight cases and review of the literature. Eur J Pediatr Surg. 2003;13:66–8.
10. Kang H, O’Connell JB, Maggard MA, Sack J, Ko CY. A 10-year outcomes of mucinous and signet-ring cell carcinoma of the colon and rectum. Dis Colon Rectum. 2005;48:1161–8.
11. Sasaki S, Masaki T, Umetani N, Futakawa N, Ando H, Muto T. Characteristics in primary signet-ring cell carcinoma of the colorectum, from clinicopathological observations. Jpn J Clin Oncol. 1998;28:202–6.
12. Rieder F, Letella G, Magro F, et al. European Crohn’s and colitis organisation topical review on prediction, diagnosis and management of fibrosteosing Crohn’s disease. J Crohns Colitis. 2016;10:873–85.
13. Messerini L, Palomba A, Zampi G. Primary signet-ring cell carcinoma of the colon and rectum: 22 cases reviewed with literature. Int Surg. 1995;80:189–92.
14. Wang R, Wang MJ, Ping J. Clinicopathological features and survival outcomes of colorectal cancer in young versus elderly: a population-based cohort study of SEER 9 Registries Data (1988–2011). Medicine (Baltimore). 2015;94:e1402.
15. Huang B, Ni M, Chen C, Feng Y, Cai S. Younger age is associated with poorer survival in patients with signet-ring cell carcinoma of the colon without distant metastasis. Gastroenterol Res Pract. 2016;2016:2913493.

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