Original Article

Clinicopathological Differences between Mucinous Adenocarcinoma and Signet-Ring Cell Carcinoma in the Colorectum

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Key Words
Colorectum;
Signet-ring cell carcinoma;
Mucinous adenocarcinoma

Purpose. This study aimed to evaluate the clinicopathological differences between signet-ring cell carcinoma and mucinous adenocarcinoma of the colon and rectum.
Methods. We prospectively reviewed the medical records between January 2000 and December 2007, and identified 19 patients with signet-ring cell carcinoma and 192 patients with mucinous adenocarcinoma. We examined the differences in age, tumor location, pathologic stage, pre-operative carcinoembryonic antigen level, microsatellite instability, and 5-year overall survival between each subtype.
Results. The patients with signet-ring-cell carcinoma (mean age, 60.4 years) were slightly younger than patients with mucinous adenocarcinoma (mean age, 65.6 years; $p = 0.001$). In addition, the incidence of mucinous adenocarcinoma and signet-ring cell carcinoma was higher in right-sided colon cancer (35.4% and 36.8%) than in other subtypes of colorectal cancer (25%). Further, no significant difference was observed in gender, preoperative carcinoembryonic antigen level, high probability of microsatellite instability, and tumor recurrence rate between the 2 subtypes. Signet-ring cell carcinoma was more likely to present at the later stages (stage III/IV, 100.0%) than mucinous adenocarcinoma (stage III/IV, 64.1%; $p < 0.001$). The 5-year overall survival rates of patients with signet-ring cell carcinoma were poorer than those of patients with mucinous adenocarcinoma (29.5% vs. 57.8%; $p < 0.001$). Patients with signet-ring cell carcinoma (17.6%) had significantly poorer cancer-specific survival than those with mucinous adenocarcinoma (51.1%; $p < 0.001$).
Conclusion. Colorectal signet-ring cell carcinoma patients had advanced disease and poorer outcome than mucinous adenocarcinoma patients. No significant difference was observed in microsatellite instability analyses between signet-ring cell carcinoma and mucinous adenocarcinoma.
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In Taiwan, the incidence of colorectal cancer (CRC) has increased steadily, and CRC is now the most common cancer in our country. Although colorectal adenocarcinoma has a relatively better prognosis than

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other gastrointestinal malignancies at the same stage, specific histological types of colorectal carcinoma such as mucinous adenocarcinoma (MA) and signet-ring cell carcinoma (SRC) have a poor prognosis.[1] The presence of mucin and signet-ring cells are recognized as subtypes of CRC by the World Health Organization (WHO).[2] These subtypes may have different biologic behaviors and confer variable prognostic outcomes. MA is a morphologic subtype of adenocarcinoma in which > 50% of the tumor is composed of mucin. These tumors, also known as colloid carcinomas, are characterized by large pools of extracellular mucin. The other variant, SRC, also produces abundant amounts of mucin that is intracytoplasmic rather than extracytoplasmic.[3,4] The incidence of MA in Western populations ranges from 9.6% to 25.4%,[4-8] while its incidence in Asian populations ranges from 3.9% to 11.7%.[8-13] Signet-ring cell lesions were first described by Laufman and Saphir,[14] and they predominantly occur in the stomach. Thus, the overall incidence of SRC in the colon and rectum is very low and ranges from 0.4% to 2.6%.[4,12,13,15-17] In addition, we believe that there are clinicopathological differences between MA and SRC, particularly in the aggressiveness of biological behavior. Colorectal SRC has an adverse prognostic significance independent of the stage at presentation.[4] Borger et al.[17] reported that the presence of signet-ring cells in MA was correlated with increased T-stage and poor prognosis. Both colorectal MA and SRC are associated with high-frequency microsatellite instability (MSI-H).[18-20] To assess the biological characteristics of colorectal SRC, we analyzed its clinicopathological features, MSI status, and survival outcomes and compared these with those of colorectal MA.

Materials and Methods

Patient population and clinical data

We enrolled 3941 patients with CRC who underwent surgery at Taipei Veterans General Hospital between January 2000 and December 2006. Our protocols were reviewed and approved by the institutional review board at our medical center. The preoperative surveillance was as follows. For non-obstructive cancer, complete colonoscopy was performed. For obstructive cancer, colonoscopy was performed 6 months after operation. The computed tomography (CT) examination was performed from the neck to the pelvis. For patients with symptomatic bone pain or a high carcinoembryonic antigen (CEA) level, a whole body bone scan was performed.

Clinical data were prospectively recorded in detail and stored in computerized files. The data base includes: (1) name, gender, age, family history, and major medical problems of each patient; (2) location, size, gross appearance, stage, differentiation, and the important pathological prognostic features of the tumor; (3) type of operation, complications, recurrence, and follow-up conditions. Pathologic staging of the disease was performed according to the American Joint Committee on Cancer (AJCC) Staging Manual, sixth edition,[21] after surgical resection with review of the resected specimen and investigations of distant metastases. Pathologic examination and classification of the MA and SRC were performed in accordance with the WHO criteria.[2] SRC was defined by the presence of > 50% of tumor cells with a large amounts of intracytoplasmic mucin and MA was defined as a carcinoma with > 50% of the tumor volume with extracellular mucin.

After surgery, patients were monitored every 3 months for the first 2 years, and every 6 months thereafter. At each visit, a complete history was obtained and complete physical examination was performed. CEA levels were assayed, and imaging studies, including chest radiographs and abdominal ultrasound (US) or abdominopelvic CT were performed. Colonoscopy was performed within 6 months to 1 year after surgery and every 3 years thereafter. Unscheduled CT, whole-body bone scan, or positron emission tomography (PET) scans were performed in patients with increased serum CEA concentrations or in patients who were symptomatic. The serum level of CEA was measured by radioimmunoassay, which was performed in the Department of Nuclear Medicine in Taipei-Veterans General Hospital. CEA concentration > 6 ng/mL was defined as a high level of CEA.

In the case of 41 MA patients and 7 SRC patients, tumor and corresponding normal tissues were ob-

tained from the Residual Tissue Bank of Taipei-Veterans General Hospital. DNA extracted from the microdissected tissues was analyzed by polymerase chain reaction (PCR) at five microsatellite loci: BAT 25, BAT 26, D2S123, D5S346, and D17S250. We classified the tumors as MSI-positive when the PCR product of tumor DNA revealed at least one peak that was not visible in the PCR product of the corresponding normal tissue DNA (Fig. 1). We used the criteria of the National Cancer Institute Workshop to classify MSI and microsatellite stability using the five primers that are commonly accepted in estimating MSI status.[22] MSI is determined to be of high-frequency if two or more of the five markers exhibit instability and of low-frequency if only one of the five markers exhibits instability. A previous study indicated that microsatellite stability and low-frequency MSI tumors have a common molecular background;[23] therefore, tumors that showed MSI-H were classified as microsatellite instability and the others were classified as microsatellite stability.

Survival and statistical analysis

The statistical analyses were performed by using the SPSS package (version 16.0 for Windows, SPSS, Chicago, IL, USA). Group distribution for each clinicopathological trait was compared using the two-tailed Fisher's exact procedure and the chi-square test. Numerical values were compared using Student's-*t* test. Data are expressed as the mean ± standard deviation (SD).

Overall survival time was measured from the date of resection to the date of death due to any cause, with patients alive in September 2011 and those lost to follow-up being censored in survival analyses. Cancer-specific survival time was measured from the date of resection to the date of death due to CRC, with censoring as described above. In the analysis of disease-free survival, a patient was considered to have an event if

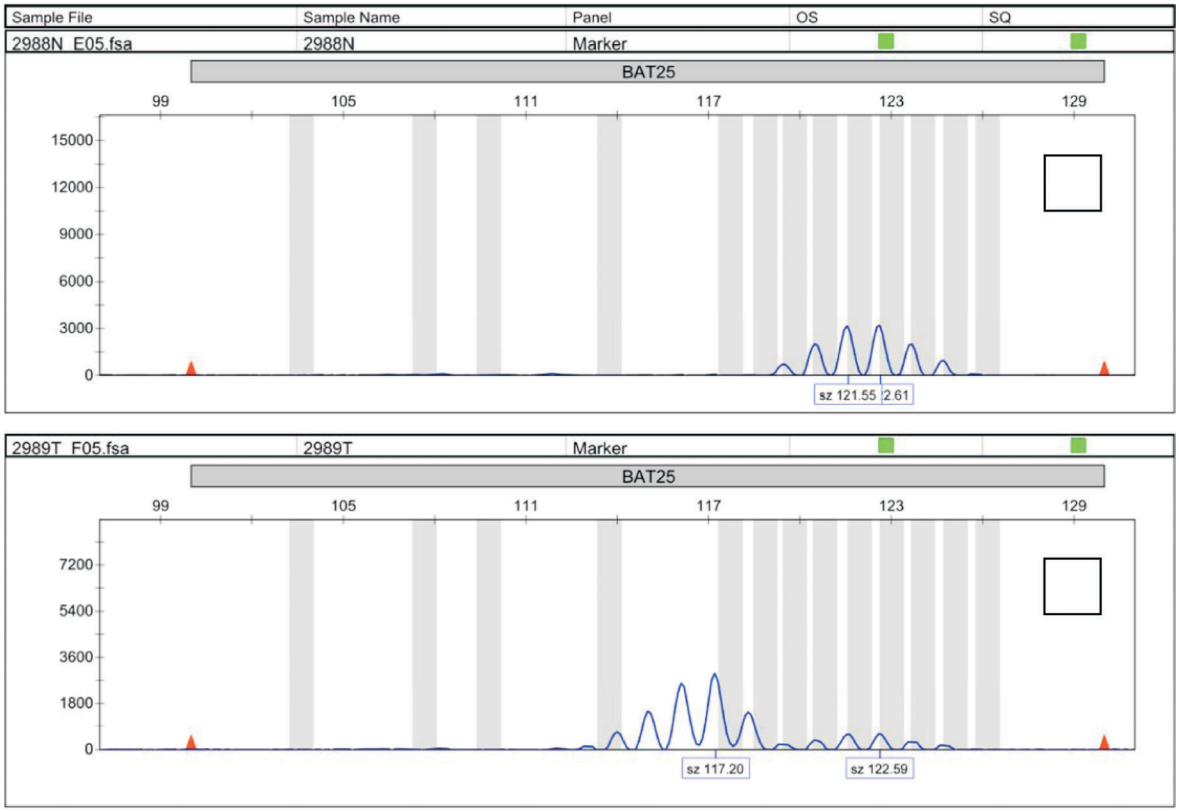

Fig. 1. Capillary electrophoresis of a microsatellite instability (MSI) cancer. Electropherograms and colorectal cancer tissue (T). Electropherograms can identify MSI by the appearance of new shorter peaks due to the shortening of the adenine repeats in cancer cells. The residual normal signal is under-represented compared with the new signal that demonstrates instability, as most of the analyzed tissue is composed of neoplastic cells.

there was local or systemic recurrence after the completion of primary treatment. Disease-free survival was calculated from the date of surgery till the date when a recurrence first occurred. Patients with no evidence of disease after treatment were censored at the date of last follow-up. The overall survival, cancer-specific survival, and disease-free survival curves were constructed using the Kaplan-Meier method, and comparisons between groups of clinical interest were made using the log-rank test. Finally, a multivariate Cox regression analysis was performed to evaluate the independent prognostic factors after adjustment for possible confounding factors. Statistical significance was defined as $p < 0.05$.

Results

Of the 3941 patients with CRC, 192 (4.87%) had MA and 19 (0.48%) had SRC. Patient and tumor characteristics are shown in Table 1. The SRC patients (mean age, 60.4 ± 18.0 years) were younger

Table 1. Comparison of clinicopathological features between mucinous adenocarcinoma (MA) and signet-ring cell carcinoma (SRC)

	Mucinous adenocarcinoma (n = 192) (4.87%)	Signet-ring cell carcinoma (n = 19) (0.48%)	*p* value
Gender			
Male	130 (67.7)	12 (63.2)	0.798
Female	62 (32.3)	7 (36.8)	
Age (years)			
Mean (years)	65.57 ± 15.09	60.44 ± 17.95	0.001
≤ 50	32 (16.7)	6 (31.6)	0.120
> 50	160 (83.3)	13 (68.4)	
Preoperative carcinoembryonic antigen (CEA) level[a]			
≤ 6	101 (53.7)	10 (55.6)	1.000
> 6	87 (46.3)	8 (44.4)	
Tumor location			
Right colon	68 (35.4)	7 (36.8)	0.558
Left colon	72 (37.5)	5 (26.3)	
Rectum	52 (27.1)	7 (36.8)	
Tumor differentiation			
Well	7 (3.6)	0 (0)	< 0.001
Moderately	146 (76.1)	0 (0)	
Poorly	39 (20.3)	19 (100)	
Lymphovascular invasion			
Yes	46 (24.0)	16 (84.2)	< 0.001
No	146 (76.0)	3 (15.8)	
T stage			
T1/T2	13 (6.8)	0 (0)	0.613
T3/T4	179 (93.2)	19 (100.0)	
N stage[b]			
N0	79 (41.6)	0 (0)	< 0.001
N1/N2	111 (58.4)	19 (100.0)	
M stage			
M0	138 (71.9)	11 (57.9)	0.289
M1	54 (28.1)	8 (42.1)	
AJCC stage			
I/II	69 (35.9)	0 (0)	< 0.001
III/IV	123 (64.1)	19 (100.0)	
Recurrence			
Yes	33 (17.2)	7 (36.8)	< 0.001
No	159 (82.8)	12 (63.2)	
Microsatellite analysis[c]			
Microsatellite instability	8 (19.5)	2 (28.6)	0.625
Microsatellite stability	33 (80.5)	5 (71.4)	

[a] Missing data 5; [b] 2 patients, no resection performed; [c] random analysis.

than the MA patients (mean age, 65.6 ± 15.1 years; $p < 0.001$). Our database consisting of nearly 4000 patients showed that 25% of the patients had right-sided colon cancer. MA and SRC were the subtypes that had a higher incidence of right-sided colon cancer than the other subtypes of CRC. Moreover, SRC was more likely to present at a later stage (stage III/IV, 100.0%) than MA (stage III/IV, 64.1%; $p < 0.001$). SRC (100.0%) presented with poorly differentiated lesions more often than MA (20.3%; $p < 0.001$). Additionally, SRC patients (84.2%) had a higher incidence of lymphovascular invasion than MA patients (24.0%; $p < 0.001$). The risk of recurrence was higher in SRC patients (36.8%) than in MA patients (17.2%; $p < 0.001$). No significant differences were observed in gender, preoperative CEA levels, and location between SRC and MA.

During the median follow-up period of 41.8 months (3-120 months), patients with SRC had significantly worse 5-year overall survival (29.5%) than patients with MA (57.8%, $p = 0.001$; Fig. 2). Similarly, SRC patients had significantly poorer cancer-specific survival (17.6%) than MA patients (51.1%, $p < 0.001$; Fig. 3). The statistical differences between disease-free survival were similar in both groups (SRC, 16.7%; MA, 46.5%; $p < 0.001$). To adjust the curves for any other factors that might have influenced overall survival of the cohort, we used Cox proportional hazards model to analyze covariates of gender, age, tumor location, pre-operative CEA level, tumor grade, histological subtype, lymphovascular invasion, and TNM stage. Our analysis showed that a high preoperative CEA > 6, signet-ring cell lesions, poorly differentiated tumor grade, lymphovascular invasion, and advanced nodal stage of disease were all significant factors that worsened survival. (Tables 2 and 3)

Discussion

Both SRC and MA of the colon and rectum are well-defined histopathological entities. They are rare types of colorectal adenocarcinoma. SRC of the colon and rectum have adverse prognostic significance independent of stage at presentation. Formation of signet-ring cells is associated with a poor prognosis. However, the mechanism underlying the formation of signet-ring cells is poorly understood.

In our study, SRC accounted for 0.48% of the 3941 CRC patients, a finding consistent with an incidence of 0.4%-2.6% described in the literature.[4,12,13,15-17] However, the incidence of MA in our study was 4.87%, similar to that of Asian populations 3.9%-11.7%,[8-13] but lower than that of Western populations 9.6%-25.4%.[4-8] We noted no statistical differences related to gender between patients with SRC and MA, which was similar to the findings reported in previous

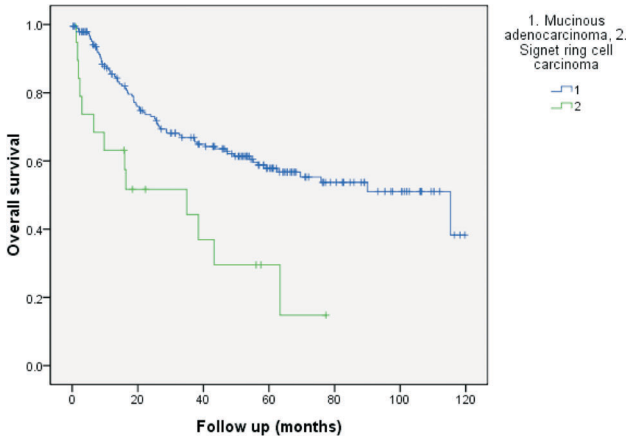

Fig. 2. Comparison of the overall survival between the two histological subtypes of colorectal cancer, mucinous adenocarcinoma and signet-ring cell carcinoma ($p < 0.001$).

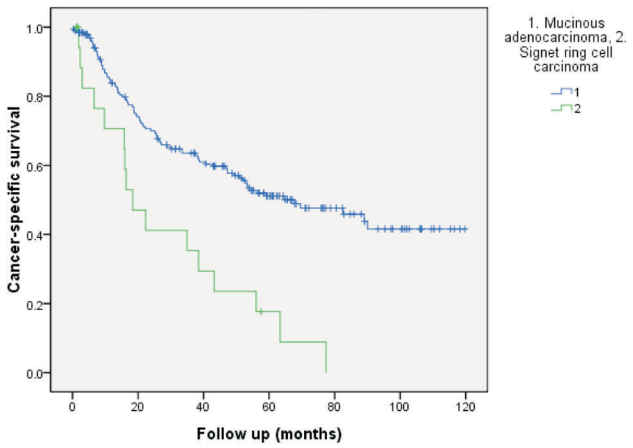

Fig. 3. Comparison of the cancer-specific survival between the two histological subtypes of colorectal cancer, mucinous adenocarcinoma and signet-ring cell carcinoma ($p < 0.001$).

Table 2. Univariate analysis of patient and tumor factors influencing cancer-specific survival

Variable	Cancer-specific survival	
	Hazard ratio (95% confidence interval)	*p* value
Gender		
Male	1.0	0.372
Female	0.82 (0.54-1.26)	
Age		
≤ 50	1.0	0.806
> 50	1.06 (0.65-1.75)	
Preoperative carcinoembryonic antigen (CEA) level[a]		
≤ 6	1.0	< 0.001
> 6	2.04 (1.38-3.02)	
Tumor location		
Right	1.0	0.037
Left	1.53 (1.03-2.29)	
Histological subtype		
Mucinous adenocarcinoma	1.0	< 0.001
Signet ring cell carcinoma	2.82 (1.65-4.82)	
Tumor differentiation		
Well/moderately	1.0	0.005
Poorly	1.79 (1.20-2.68)	
Lymphovascular invasion		
No	1.0	< 0.001
Yes	2.79 (1.89-4.12)	
T stage		
T1/T2	1.0	0.058
T3/T4	1.84 (0.96-2.59)	
N stage[b]		
N0	1.0	< 0.001
N1/N2	2.29 (1.47-3.58)	
AJCC stage		
I	1.0	
II	1.50 (0.46-6.56)	0.226
III	2.47 (1.21-6.68)	0.045
IV	2.78 (1.43-5.39)	0.003

[a] Missing data 5; [b] 2 patients, no resection performed.

studies.[5-10] In our study, patients with SRC were younger than those with MA. The incidence of SRC and MA located in the right-sided colon cancer tended to be higher (34.5%-44.2%) than colorectal adenocarcinoma (8.0%-17.9%), similar to that reported in the majority of the studies.[5,7,10,11,16] Our results also showed that SRC and MA had a higher incidence in the right-sided colon (MA, 35.4% and SRC, 36.8% vs. CRC, 25%). No significant difference was observed among SRC and MA groups in our study.

We observed that the 5-year cancer-specific survival of SRC patients (17.6%) was poorer than that of MA patients (51.1%). The poor clinical prognosis of SRC in our study may be because of the large number of patients with advanced tumor stage (stage III/IV, 100.0%) and higher rates of metastasis (42.1%) as well as higher recurrence rates (36.8%). This aggressive tumor behavior has been hypothesized to be because of a higher incidence of lymphovascular invasion.[16] In our study, SRC patients had a higher incidence of lymphovascular invasion (84.2%) than MA patients (24.0%, $p < 0.001$). The possible hypothesis is the decreased expression of cell adhesion molecules (E-cadherin and β-catenin) with a resultant disruption of adhesion complex and thus increased risk of invasion and metastasis.[17]

Table 3. Multivariate analysis of patient and tumor factors influencing cancer-specific survival

Variable	Cancer-specific survival	
	Hazard ratio (95% confidence interval)	*p* value
Preoperative carcinoembryonic antigen (CEA) level[a]		
≤ 6	1.0	< 0.001
> 6	2.07 (1.20-3.42)	
Tumor location		
Right	1.0	0.061
Left	1.38 (0.98-2.18)	
Histological subtype		
Mucinous adenocarcinoma	1.0	< 0.001
Signet ring cell carcinoma	2.51 (1.51-4.11)	
Tumor differentiation		
Well/moderately	1.0	0.033
Poorly	1.62 (1.05-3.22)	
Lymphovascular invasion		
No	1.0	< 0.001
Yes	2.40 (1.47-3.90)	
T stage		
T1/T2	1.0	0.109
T3/T4	1.11 (0.50-2.92)	
N stage[b]		
N0	1.0	< 0.001
N1/N2	2.27 (1.37-3.48)	

[a] Missing data 5; [b] 2 patients, no resection performed.

The current literature thus suggests that MA and SRC are distinct biological entities and are independent from the outcomes of ordinary colorectal adenocarcinomas. Molecular biology analysis has suggested that the expression of p53 proteins is low (19%-49%) and the frequency of p16 expression is high (78%) in MA patients.[24] Loss of p53 and p16 tumor suppressor genes that regulate cell proliferation is shown to lead to uncontrolled tissue growth and subsequently more aggressive tumors. These molecular markers may be future prognostic predictors in patients with MA.

Leopoldo et al.[25] reported 2 subtypes of MA, which were MAs with and without MSI. They showed that MA with MSI was observed more frequently in the proximal part of the colon, and the expression of hM1h1 was markedly altered. SRC has been analyzed for MSI, which is present in approximately 30% of tumors.[26] In our study, the proportion of SRC patients with MSI was 28.6% compared to 19.5% in MA patients ($p = 0.625$). Katar et al.[27] reported that the outcomes of MA with MSI were better than those of MA with microsatellite stability. However, MSI is not an independent predictor of survival. On the basis of our observations, we recommend that pathologists report the percentage of signet-ring cell component in colorectal MA. Further histological and molecular classification of mucinous tumors may be useful in predicting the poor clinical outcome of these tumors.

Conclusion

Primary colorectal signet-ring cell carcinoma has distinctive clinicopathological features and is associated with a poorer prognosis than mucinous adenocarcinoma. However, our literature review indicated that the incidence of mucinous adenocarcinoma in our study was lower than that in Western populations. No significant difference was observed in microsatellite instability analyses between signet-ring cell carcinoma and mucinous adenocarcinoma.

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原　著

大腸直腸黏液性腺癌和戒環細胞癌的臨床病理表現之差異

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目的　本研究的目的是評估大腸直腸戒環細胞癌和黏液性腺癌的臨床病理表現之間的差異。

方法　從 2000 年 1 月至 2007 年 12 月，共 19 位大腸直腸戒環細胞癌和 192 位黏液性腺癌病人，針對年齡的差異，腫瘤部位，病理分期，術前腫瘤胚胎抗原指標，微衛星不穩定性，和五年整體存活率等，做了完整的病歷分析。

結果　大腸直腸戒環細胞癌患者的平均年齡為 60.4 歲，MA 患者的平均年齡為 65.6 歲 ($p = 0.001$)。比起其他大腸腺癌病人 (25%)，我們注意到黏液性腺癌和戒環細胞癌患者右結腸分布的比例較高 (35.4% 和 36.8%)。此外，病人性別、術前腫瘤胚胎抗原指數偏高、微衛星不穩定性高表現的族群、和兩個亞型之間的腫瘤復發率無顯著差異。相對於黏液性腺癌患者 (III/IV 期，64.1%)，戒環細胞癌病患大多為較晚的腫瘤分期 (III/IV 期，100.0% ; $p < 0.001$)。戒環細胞癌患者 5 年存活率比黏液性腺癌患者差 (29.5% 和 57.8%；$p < 0.001$)。戒環細胞癌病人 (17.6%) 與黏液性腺癌 (51.1%) 相比有顯著較差的癌症特異性生存率 ($p < 0.001$)。

結論　大腸直腸戒環細胞癌患者比黏液性腺癌患者有較晚的腫瘤期別和預後較差的結果。大腸直腸戒環細胞癌和黏液性腺癌之間的微衛星不穩定性分析沒有顯著性差異。

關鍵詞　大腸直腸、戒環細胞癌、黏液性腺癌。