Clinical Outcome of Signet Ring Cell Carcinoma and Mucinous Adenocarcinoma of the Colon

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Background: The purpose of this study was to evaluate the clinicopathologic features and prognosis of signet ring cell carcinoma (SCC) and non-SCC mucinous adenocarcinoma (MC) and to compare them with those of nonmucinous adenocarcinoma (NMC) of the colon.

Methods: From January 1995 to December 2003, 45 patients with SCC and 332 with MC were identified from prospectively collected medical records. The clinical data and outcomes were compared with those of 2984 consecutive patients with NMC in the same period.

Results: The mean age at onset of SCC was 54.3 years. This was significantly lower than those for MC (mean 59.5 years, $p = 0.038$) and NMC (62.4 years, MC vs. NMC, $p < 0.01$). The rate of spread of tumors in TNM stage IV via hematogenous routes (liver, lung, bone, and brain) was significantly lower in SCC patients (5/28, 17.9%) than in MC (40/104, 38.5%) and in NMC patients (417/694, 60.1%). The rate of tumor spread via lymphatic drainage (systemic node) or seeding to the peritoneum was higher in SCC (23/28, 82.1%) and MC patients (79/104, 76.0%), than in NMC patients (343/694, 49.4%, $p < 0.001$). There was a higher proportion of poorly differ-entiated tumors in SCC (32/42, 71.1%) than in MC (26/332, 7.8%) and NMC (203/2984, 6.8%). The 1-, 2-, and 5-year overall survival rates of patients with SCC were 77.8%, 26.7%, and 11.9%, of those with MC, 81.6%, 65.9%, and 49.4% and of those with NMC, 84.1%, 73.3%, and 58.7%, respectively.

Conclusion: The prognosis of SCC is poorer than that of MC and NMC. SCC patients had more locally advanced and almost no early-detected tumors, less hematogenic spread, and very poor surgical outcomes. The role of resection for late stage SCC should be carefully evaluated.
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Specific histologic types of colorectal carcinoma such as mucinous carcinoma and signet ring cell carcinoma (SCC) have a poor prognosis.[1-5] SCC of the colon and rectum is a subtype of colorectal mucinous adenocarcinoma. It is characterized by cells with abundant mucin in the cytoplasm and nuclei

located at the cell periphery. The infiltrating cells may be arranged singly or in loose clusters, and they spread diffusely throughout the bowel wall.[6] According to Symonds et al, mucinous tumors located in the rectum, rather than in the colon, have different clinical outcomes than nonmucinous tumors.[7]

In a previous study,[8] we identified the distinct clinicopathologic features and clinical outcomes of patients with SCC of the rectum (lower margin of tumors located < 15 cm from the anal verge) and compared them with those of mucinous adenocarcinoma (MC) and non-mucinous adenocarcinoma (NMC) of the rectum. The clinical manifestations of mucinous tumors include diffusely infiltrating linitis plastica with mainly peritoneal dissemination,[2,9-11] lymphatic spread,[3,10,12] young age at presentation,[2,13,14] advanced stage at presentation,[2,3,9] low curative resection rates,[2] few liver metastases,[2,9,10,15] and poor prognosis.[1-5,10,11,15] However, mucinous tumors may be associated with a worse prognosis because of the advanced tumor stage rather than the histology. Thus, wider en bloc resection is recommended for cases that may be cured by the procedure. Compared with mucinous tumors in the rectum, those in the colon may have more advanced characteristics (cannot be detected by rectoscopy) but are more likely to be cured by resection (wider operative space). The focus of the present study is on the clinicopathological features and prognosis of SCC, non-SCC MC and NMC of the colon.

METHODS

From January 1995 to December 2003, 45 patients with SCC and 332 patients with MC were identified from prospectively designed medical records. The clinical data and outcomes were compared with those of 2984 consecutive patients with NMC during the same period. MC has been defined as a tumor which contains an amount of mucin of more than half its volume and has histological findings of pools of extracellular mucin that contain malignant epithelium with an acinar structure, strips of cells, or single cells.[16] SCC is diagnosed if more than 50% of tumor cells have prominent intracytoplasmic mucin.[9,16] The chi-square test was used to compare patient data, tumor characteristics, and tumor extension between the three groups. The Kaplan–Meier method was used to analyze the cumulative survival rates. Statistical analysis was performed using the SPSS package for Windows (Microsoft, Redmond, WA).

RESULTS

The incidence of SCC was 1.34% (45/3361) and that of MC was 9.9% (332/3361). Patient and tumor characteristics are shown in Table 1.

The mean age of the SCC group was 54.3 years (range 15–88 years). Patients with SCC were younger than patients with MC and NMC, and the age difference was statistically significant. The proportions of male patients in the SCC, MC, and NMC groups were 60.0% (27/45), 47.6% (158/332), and 52.4% (1564/2984), respectively. There was no significant difference in gender between groups.

Tumor stages were classified according to the TNM system.[17] In the SCC group, there were 2 patients in stage I + II, 15 patients in stage III, and 28 patients in stage IV. The proportion of advanced stage tumors (TNM stage III + IV) was significantly higher in the SCC (95.6%) than in the MC (60.2%) and NMC (51.9%) groups ($p < 0.001$).

The colon was divided into the proximal (cecum, ascending, hepatic flexure, and transverse) and distal colon. In the SCC group, 28 patients (62%) had tumors in the proximal colon. There were 203 patients (61%) with MC and 1134 patients (38%) with NMC tumors in the proximal colon. There were significantly more tumors in the proximal colon in SCC and MC patients than in NMC patients (both $p < 0.001$).

The tumors in the SCC group (5.35 ± 2.40 cm, range 3.0–15.0 cm) and MC group (5.97 ± 2.53 cm, range 0.5–15.0 cm) were significantly larger than the tumors in the NMC group (4.49 ± 2.17 cm, range 0.5–24.0 cm) ($p < 0.001$).

In the SCC, MC, and NMC groups. 2, 110, and 542 patients, respectively, had well-differentiated tumors, 7, 186, and 2184 had moderately differentiated tumors, 32, 26, and 203 had poorly differentiated tumors, and 4, 10, and 55 had tumors that could not be classified. The proportion of poorly differentiated tumors was higher in SCC patients than in MC or NMC patients ($p < 0.001$).

Pre-operative CEA data were not available for 221 patients; thus, these patients were excluded from this analysis. In total, 54.5% (24/44) of patients with

Table 1. Clinical Data of Colon Adenocarcinoma

	SCC	MC	NMC	*p* value
Case number	45	332	2984	
Age (mean) in years	15-88 (54.3)	20-97 (59.5)	16-96 (62.4)	*p* 1 = 0.038, *p* 2 < 0.001, *p* 3 = n.s
Sex (M/F)	27/18	158/174	1564/1420	*p* 1, *p* 2, *p* 3 = n.s
Blood type (O/A/B/AB)	20/11/12/1	142/88/74/21	1302/819/656/170	*p* 1, *p* 2, *p* 3 = n.s
Tumor diameter (cm)	5.35 ± 2.40	5.97 ± 2.53	4.49 ± 2.17	*p* 1 = n.s, *p* 2, *p* 3 < 0.001
% with elevated preoperative CEA	54.5	51.6	44.7	*p* 1, *p* 2 = n.s, *p* 3 = 0.02
% of poorly differentiated	32/45 (71.1%)	26/332 (7.8%)	203/2984 (6.8%)	*p* 1, *p* 2 < 0.001, *p* 3 = n.s
Location in proximal colon*	28/45(62%)	203/332 (61%)	1134/2984 (38%)	*p* 1 = ns, *p* 2, *p* 3 < 0.001
TNM staging (I/II/III/IV), % of stage III + IV	0/2/15/28 95.6%	14/117/96/104 60.2%	361/1070/855/694 51.9%	*p* 1, *p* 2 < 0.001, *p* 3 = n.s

Abbreviations: SCC: signet ring cell carcinoma; MC: mucinous adenocarcinoma; NMC: nonmucinous adenocarcinomas; *p* 1: SCC vs MC; *p* 2: SCC vs NMC; *p* 3: MC vs. NMC; n.s: not significant; proximal colon *: cecum+ascending+transverse colon. Comparisons were performed with the chi-square test or independent *t*-test.

SCC, 51.6% (159/308) of patients with MC and 44.7% (1246/2788) of patients with NMC had elevated pre-operative CEA levels. Patients with MC had a higher prevalence of elevated CEA than patients with NMC (*p* = 0.02).

The rate of spread of stage IV tumors via hematogenous routes (liver, lung, bone, and brain) was significantly lower among SCC patients (5/28, 17.9%) than among MC (40/104, 38.5%, *p* = 0.04) or NMC patients (417/694, 60.1%, *p* < 0.01). The rate of tumor spread via lymphatic drainage (systemic node) or seeding to the peritoneum was higher among patients with SCC (23/28, 82.1%) and MC (79/104, 76.0%) than among those with NMC (343/694, 49.4%, both *p* < 0.01).

In our hospital, postoperative adjuvant chemotherapy was administered to patients with T4 or stage III tumors, and high-dose 5-Fu/leucovorin (before and in year 2000) or 5-Fu/leucovorin combined with oxaliplatin or irinotecan (after 2000) was given for stage IV tumors. The overall survival (Fig. 1) of patients with SCC was poorer than those with MC (*p* < 0.001), and survival of MC patients was poorer than NMC patients (*p* = 0.002). The oncologic outcomes are described in Table 2. All patients with stage IV SCC died within 25 months. For stage

I + II tumors (Fig. 2), SCC was excluded because there were very few SCC cases to compare; there was no difference between the overall survival of patients with MC and NMC (*p* = 0.720). The same results were found for stage III tumors (*p* = 0.393). After adjustment for TNM stage, there was no difference in overall survival among patients with MC and NMC (Fig. 3).

DISCUSSION

Both signet ring cell carcinoma and mucinous adenocarcinoma are rare types of colorectal adenocarcinoma. The incidence of mucinous carcinomas in Europe and the United States is approximately 10%[6] and that in Japan is low, at 2.9% to 7.4%.[18] Mucinous carcinoma is characterized by the presence of extracellular mucin. Occasionally, mucin accumulates intracellularly in these tumors, which causes signet ring cell differentiation.[6] The incidence of SCC in the colorectum is 0.1%–2.4%.[1,9,12,19] In this study, the incidence of MC was 9.9%, while that of SCC was 1.34%. These results support the clinical features of SCC and mucinous adenocarcinoma of the colorectum described in other studies, including advanced stage at diagnosis, large tumor size, proxi-

mal location, young age, propensity for lymphovascular invasion, and peritoneal seeding.[2-4,11,19,20]

There are few studies that address the prevalence of elevated pre-operative CEA levels in mucinous colon cancer. Negri et al. reported no difference in pre-operative CEA levels between mucinous and non-mucinous tumors.[21] In the present study, more patients with MC than NMC had elevated CEA levels ($p = 0.02$).

Because of differences in the aggressiveness of the tumors, the prognosis is different for patients with SCC, MC, and NMC. SCC patients show worse clinical outcomes than MC or NMC patients. Messerini et al reported the overall 5-year survival rate of those with SCC of the colorectum was 9.1% and survival was influenced significantly by tumor stage.[3] In this study, for mucinous tumors, the overall 1-, 2-, and 5-year survival rates of patients with SCC were 77.8%, 26.7%, and 11.9%, respectively. These rates were significantly lower than those for MC and NMC patients. The relationship between
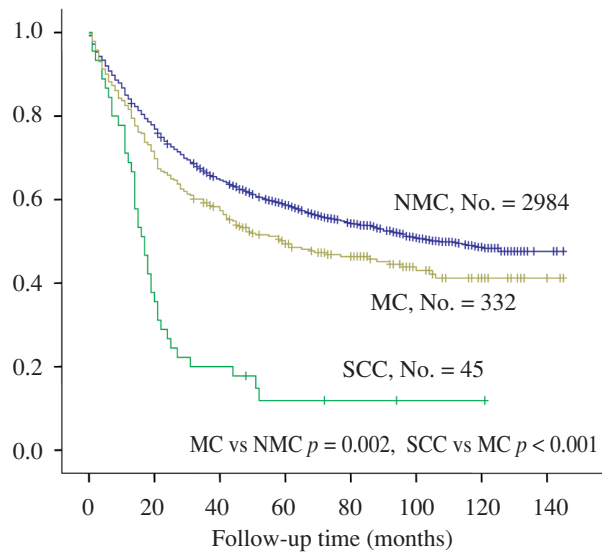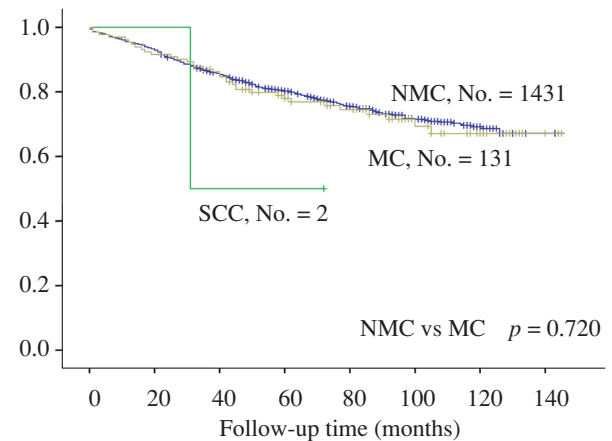

Fig. 1 Overall Survival of SCC, MC and NMC. Abbreviations used: SCC: signet ring cell carcinoma; MC: mucinous adenocarcinoma; NMC: nonmucinous adenocarcinomas.

Fig. 2 Overall Survival of Stage I + II Tumors. Abbreviations used: SCC: signet ring cell carcinoma; MC: mucinous adenocarcinoma; NMC: nonmucinous adenocarcinomas.

Table 2. Oncologic Outcomes of Colon Adenocarcinoma according to TNM Stage

	SCC	MC	NMC	*p* value
Stage (I + II/ III/ IV)	2/15/28	131/96/104	1431/855/694	
1,2,5 year overall survival for all tumors	77.8%, 26.7%, 11.9%	81.6%, 65.9%, 49.4%	84.1%, 73.3%, 58.7%	p 1, p 2 < 0.001 p 3 = 0.002
Follow-up period (months)	24.6 ± 24.0	52.5 ± 40.0	57.0 ± 38.3	
1,2,5 year overall survival for stage I + II tumors*	100%, 100%, 50.0%	95.4%, 84.7%, 76.9%	95.4%, 90.6%, 80.2%	p 3 = 0.720
1,2,5 year overall survival for stage III tumors*	93.3%, 60.0%, 28.0%	93.8%, 79.2%, 54.2%	91.1%, 81.9%, 62.0%	p 3 = 0.393

Abbreviations: SCC: signet ring cell carcinoma; MC: mucinous adenocarcinoma; NMC: nonmucinous adenocarcinomas; p 1: SCC vs MC; p 2: SCC vs NMC; p 3: MC vs. NMC; n.s: not significant; *: the number of SCC cases was too small to compare.
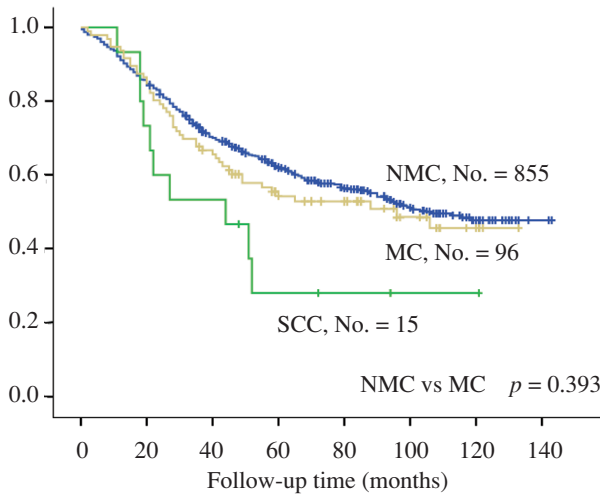
Fig. 3 Overall Survival of Stage III Tumors. Abbreviations used: SCC: signet ring cell carcinoma; MC: mucinous adenocarcinoma; NMC: nonmucinous adenocarcinomas.

SCC tumor histology and poor prognosis is still unclear because the number of cases was small and many patients were at an advanced stage and had poor differentiation.

Even after exclusion of SCC most published studies suggest that MC is associated with poor outcomes. However, contradictory reports suggest that the clinical relevance of the histology of SCC tumors in this patient population is unclear. Symonds et al[7] reported no significant differences in the 5-year survival rate of patients with mucinous and non-mucinous carcinomas in the cecum, ascending and transverse colon, and descending and sigmoid segments. Other investigators have reported that the mucinous histological type is an independent factor for poor prognosis in patients undergoing curative surgery.[18,22] In the present study, there was no difference in the overall survival of patients with stage I + II and stage III MC compared with that of patients with NMC ($p = 0.720$, $p = 0.393$) (Fig. 2 and 3). This suggests that the mucinous histological type is not an independent factor for poor prognosis. One possible explanation for the contradictory evidence is that there may be 2 different subtypes of mucinous carcinoma with different prognoses. Goi et al reported 2 subtypes (papillotubular type and mucocellular type) in 20 cases of mucinous colorectal carcinoma.[23] The mucocellular type showed higher rates of venous invasion, lymph node metastasis, liver metastasis, and peritoneal dissemination, and higher frequencies of TNM stage III and IV cancers than the papillotubular type. Further, patients with the mucocellular type had a significantly poorer 3-year survival rate (27%) than those with the papillotubular type (60%). You et al. also found a difference of more than 50% in the 5-year cancer-specific survival rates of hereditary nonpolyposis colorectal cancer (HNPCC) and sporadic-mucinous groups (92% vs. 31%, $p = 0.0003$).[24] Kakar et al. reported that the outcomes of microsatellite-unstable mucinous carcinoma were better than that of microsatellite-stable mucinous carcinoma; however, microsatellite instability is not an independent predictor of survival.[25] Further histological and molecular classification of mucinous tumors may be needed to clarify the factors that predict their poor clinical outcome.

Conclusion

More MC patients than NMC patients had elevated preoperative CEA levels. SCC tumors were more locally advanced. Fewer SCC tumors showed hematogenic spread, and they were not detected at an early stage. SCC tumors were also associated with poor surgical outcomes. The role of resection for patients with late stage SCC should be carefully evaluated.

Although the prognosis for patients with MC was poorer than for those with NMC, this outcome has no significant difference because of the higher proportion of advanced stage tumors rather than the histology.

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大腸指環細胞癌及黏液癌之預後分析

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背 景： 大腸癌之病理分類上，大於 50% 之細胞內黏液沈積非常少見，稱爲指環細胞癌，而大於 50% 之細胞外黏液沈積較爲常見，稱爲黏液癌，黏液對大腸癌預後之影響，尚未被清楚釐清。

方 法： 從 1995 年元月至 2003 年 12 月的前瞻性大腸癌資料庫中，收錄了 45 位大腸指環細胞癌及 332 位黏液癌的病人，其臨床特徵及手術預後與同期 2984 位非黏液大腸癌作比較。

結 果： 指環細胞癌非常少見，佔全部大腸癌之 1.34%，1，2，5 年存活率分別爲 77.8%，26.7%，11.9%。而黏液癌及非黏液癌之 1，2，5 年存活率分別爲 81.6%，65.9%，49.4% 及 84.1%，73.3%，58.7%。指環細胞癌好發於較年輕之病患，期別較嚴重，較少血行 (肝、肺) 轉移，分化也較差，其預後極差，僅 5 人存活超過 5 年。黏液癌比起非黏液癌也有較年輕及少血行轉移及較嚴重期別之趨勢，但是將期別分層比較，其預後並不會比非黏液癌差。

結 論： 黏液沈積有使預後變差，但是似乎主因爲發現時期別較嚴重，而非黏液本身使然。指環細胞癌預後極差，對於晚期指環細胞癌是否以手術作治療應再評估。
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關鍵詞： 指環細胞癌，黏液癌，大腸癌，大腸