Original Article

Clinicopathological features and survival outcomes of primary signet ring cell and mucinous adenocarcinoma of colon: retrospective analysis of VACCR database

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Background: Signet ring cell carcinoma (SRCC) accounts for less than 1% of all colon cancers. We examined the clinicopathological features and prognosis of signet ring cell and mucinous adenocarcinoma (MCC) of colon.

Methods: A total of 206 patients diagnosed with SRCC from 1995 to 2009 were identified from the VA Central Cancer Registry (VACCR) database. Age, race, histology, grade, lymph node status, stage and type of treatment received data were collected.

Results: Out of 206 patients, 173 (84%) were white, 31 (15%) were black, and 2 patients were listed as unknown. Median age of diagnosis was 67 years as compared to 70 years for both mucinous cell (MCC) and non-mucinous adenocarcinoma (NMCC) of colon. Pathological T-stages were as follows: T1 =3%, T2 =5%, T3 =34%, T4 =26%, and unknown 32%. Of the total, 22.3% were located in cecum, 7.7% in appendix, 21.8% in ascending colon, 7.7% in hepatic flexure of colon, 11% in transverse colon, 2.9% in splenic flexure 4.4% in descending colon, and 15.5% in sigmoid colon. 46.5% were lymph node positive, 21% were lymph node negative, and 32.5% were unknown. SRCC were in general poorly differentiated tumors (57%), small proportion of patients included were well-differentiated tumors with focal signet ring cell pathology (10%) and in 33% grade was unknown. Among stage 3 patients, 34% patients received only surgery while 64% received surgery with adjuvant chemotherapy and 2% received chemotherapy alone. The stage specific 5-year survivals for SRCC, MCC and NMCC were--Stage I: 100%, 61%, and 41% respectively (P<0.0001); Stage II: 42%, 58% and 32% respectively (P<0.0001); Stage III: 19%, 41% and 47% respectively (P=0.0002); Stage IV: 1.5%, 7% and 31% respectively (P<0.0001). Median survival of SRCC compared to NMCC was 18.6 *vs*. 46 months (P<0.0001) and mucinous cell adenocarcinoma versus NMCC was 47.8 and 46 months (P=0.63) respectively.

Conclusions: SRCC of colon has poor survival rates compared to other histological subtypes. SRCC presents at an earlier age, has higher tumor grade and advanced stage at diagnosis when compared to mucinous and NMCC of colon. Due to rarity of this disease further prospective multi-institute studies are required for in-depth understanding of this disease.

Keywords: Signet ring cell carcinoma; colon; mucinous and non-mucinous adenocarcinoma

Submitted Sep 07, 2012. Accepted for publication Sep 27, 2013.
doi: 10.3978/j.issn.2078-6891.2013.051
Scan to your mobile device or view this article at: http://www.thejgo.org/article/view/1680/2662

Introduction

Signet ring cell carcinoma (SRCC) of colon and mucinous adenocarcinoma (MCC) of colon are rare histologic subtypes of adenocarcinoma of colon accounting for approximately 0.5-1 percent and 15-20 percent of all adenocarcinomas of colon respectively (1). Signet ring cell cancers are most commonly seen in the stomach (95%) and occasionally found in colon, rectum, ovary, peritoneum and

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gallbladder (2). It is characterized by specific morphologic appearance of abundant intracytoplasmic mucin pushing nucleus to the periphery giving it a signet ring cell appearance. SRCC is similar to MCC in possessing abundant mucin. The World Health Organization classification of tumors has a specific criteria for diagnosis of these sub types--SRCC is defined as presence of more than 50 percent of signet cells and MCC is defined as presence of more than 50 percent of mucin component (3).

Previous studies have shown that SRCC often presents at young age, in advanced stage, with more peritoneal involvement and has poor prognosis (4,5). However, majority of these studies are single institution based including small number of patients. Because of the rarity of the disease, clinico-pathological features and prognosis has not been well understood and there have been very few studies comparing SRCC with MCC and non-mucinous adenocarcinoma (NMCC) of colon. Hence we conducted a retrospective study on the large nationwide veteran population to understand the clinicopathological features and the survival outcomes of SRCC, MCC and NMCC.

Methods

Data source

The study was approved by the local Institutional Review Board. Data for this study was obtained by accessing the Veteran's Affairs Central Cancer Registry (VACCR) database. VACCR is a population-based registry sponsored by the Veteran's Affairs Healthcare system that contains information from patients diagnosed and/or treated at all 143 Veterans Affairs (VA) medical centers. Each case report adheres to the standards established by the American College of Surgeons' Commission on Cancer Facility Oncology Registry Data Standards for data collection and definitions and must pass North American Association of Central Cancer Registry electronic quality assurance edits before being merged/consolidated into the master database.

Study population

A total of 36,260 Veteran's diagnosed with colon cancer between January 1995 and December 2008 were identified from the VACCR database. Of which 26,669 were NMCC patients, 2,443 were MCC patients, and 206 were SRCC patients and 6,942 were other histology's. Colon cancer cases associated with other histology's, inflammatory bowel disease and familial polyposis syndromes were excluded from this study.

Patient characteristics and survival data

The variables recorded were patient age, gender, ethnicity, clinical stage, pathological stage, histology, grade, location of tumor, number of regional lymph nodes retrieved, number of positive lymph nodes, date of diagnosis, CEA, sites of metastases, type of surgery, surgical margins and treatment. Tumor histology was classified by using the International Classification of Histology (ICD-O-3) into NMCC [8,140, 8,243-8,245, 8,210, 8,211], MCC [8,470, 8,472, 8,480, and 8,481] and SRCC [8,490]. Tumor locations were divided into cecum, appendix, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon and overlapping tumors (NOS) based on the SEER Program Coding and Staging Manual 2007. Tumor stage was based on TNM staging system and American Joint Committee on Cancer, AJCC Cancer Staging Manual (6th edition, 2002). Tumor grade was further classified as well differentiated, moderately differentiated, poorly differentiated, undifferentiated or anaplastic tumors. Overall survival was calculated for patients not alive as total number of months from date of diagnosis to date of last contact and for those alive as total number of months from date of diagnosis to July 30, 2009 i.e., when the database was last updated.

Statistical analysis

Quantitative variables such as age and number of lymph nodes were summarized as mean and standard deviation. One-way ANOVA model was fitted to a continuous variable to examine if means of several groups are all equal. Univariate logistic regression analysis was performed to determine the factors significantly associated with various histologies. Chi-square analysis was used to compare differences between NMCC, MCC and SRCC. For all statistical tests, significance level is set at 0.05. Statistical analysis was carried out with SAS 9.2 (SAS Institute Inc., Cary NC).

Results

Demographics

Of 36,260 colon cancer patients, 26,669 (73.5 percent) were NMCC, 2,443 (7 percent) were MCC and 206 (0.6 percent)

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Table 1 Patient demographics

	SRCC	MCC	NMCC
No. of patients	206 (0.6%)	2,443 (7%)	26,669 (75.4%)
Age at diagnosis (years)	67	70	70
Gender			
Males	200 (97.1%)	2,375 (97.2%)	26,131 (98.0%)
Females	6 (2.9%)	68 (2.8%)	538 (2.0%)
Race			
Caucasians	173 (84.0%)	1,990 (81.4%)	20,961 (78.6%)
African American	31 (15.0%)	402 (16.4%)	5,047 (19.0%)
Others	0	23 (0.9%)	199 (0.7%)
Unknown	2 (1.0%)	28 (1.1%)	462 (1.7%)

were SRCC patients. Median age at diagnosis of SRCC was 67 years as compared to 70 years for both MCC and NMCC. Study patients were mainly males and caucasians. There were no significant gender differences noted among the three histological subtypes. However, African Americans were found to have less SRCC and MCC incidence as compared to NMCC (15%, 16.4% and 19%, respectively). Detailed demographic data is shown in *Table 1*.

Clinico-pathological characteristics

Location of tumor

SRCC and MCC were more common on the right side of the colon involving cecum and ascending colon (59.5%, 56.5% and 39%) while NMCC was most commonly found on the left side of the colon involving the sigmoid colon (23%, 29.5% and 46%). The individual distribution of SRCC, MCC and NMCC across various portions of the colon was shown in *Table 2*.

Grade

The percentage of SRCC, MCC and NMCC patients significantly varied across the grade distribution with SRCC often presented as high-grade tumors (poorly differentiated or undifferentiated: SRCC, 55.3%; MCC, 17%; NMCC, 11.4%) while MCC and NMCC presented as moderately differentiated tumors (SRCC, 7.3%; MCC, 60%; NMCC, 62%).

Tumor invasion

The majority of SRCC and MCC patients had diffuse colonic wall invasion at the time of presentation often involving sub serosa and serosal layers as represented by their T stage. Pathological T-stages at presentation among SRCC, MCC and NMCC were as follows: T3 + T4 were 60%, 63% and 45.2%; T1 + T2 were 8%, 18% and 25%, respectively.

Nodal involvement

The majority of SRCC had nodal involvement at the time of presentation unlike MCC and NMCC. The nodal status at the time of presentation among three histological subtypes is detailed in *Table 2*. Percentage of node negative disease among SRCC, MCC and NMCC was 21%, 48% and 44% respectively. We also noted no significant differences in number of lymph nodes retrieved among SRCC, MCC and NMCC (<12 nodes retrieved was 34%, 42% and 38%; >12 nodes examined was 33%, 43% and 31% respectively).

AJCC stage

In terms of stage, SRCC often presents as advanced stage (stage 3+4: SRCC, 61.2%; MCC, 44.6%; NMCC, 44.5%) while MCC and NMCC were early stage at presentation (stage 1+2: SRCC, 16.5%; MCC, 38.8%; NMCC, 23.5%). Percentages of unknowns: SRCC, 22.3%; MCC, 16%; NMCC, 32%.

Carcinoembryonic antigen (CEA) levels

CEA levels were not available for most of the patients (SRCC, 71.8%; MCC, 72.4%; NMCC, 73.8%). However, from the limited available data, majority of the SRCC and MCC patients had high CEA levels as compared to NMCC (SRCC, 50%; MCC, 48%; NMCC, 42%).

Treatment

A majority of stage III SRCC patients received adjuvant chemotherapy compared to MCC and NMCC. As

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Table 2 Clinico-pathological characteristics

Characteristic	NMCC	MCC	SRCC
Grade			
Well differentiated	2,997 (11.2%)	238 (9.7%)	5 (2.4%)
Mod differentiated	16,197 (62.0%)	1,268 (60.0%)	15 (7.3%)
Poorly differentiated	3,030 (11.4%)	407 (17.0%)	114 (55.3%)
Anaplastic	110 (0.4%)	13 (0.5%)	4 (2.0%)
Unknown	433 (16.2%)	517 (21.0%)	68 (33.0%)
Location			
Cecum	4,613 (17.0%)	607 (25.0%)	46 (22.3%)
Appendix	90 (0.3%)	59 (2.5%)	16 (7.7%)
Ascending colon	4,498 (17.0%)	578 (24.0%)	45 (21.8%)
Hepatic flexure	1,247 (4.7%)	131 (5.0%)	16 (7.7%)
Trans colon	2,320 (9.0%)	229 (9.0%)	23 (11.0%)
Splenic flexure	809 (3.0%)	84 (3.5%)	6 (2.9%)
Descending colon	1,825 (7.0%)	117 (5.0%)	9 (4.4%)
Sigmoid colon	9,567 (36.0%)	512 (21.0%)	32 (15.5%)
NOS	1,700 (6.0%)	126 (5.0%)	13 (6.3%)
Node positive			
None	11,741 (44.0%)	1,163 (48.0%)	43 (21.0%)
1-3 nodes	4,550 (17.0%)	517 (21.0%)	34 (16.5%)
≥4 nodes	2,624 (10.0%)	412 (17.0%)	62 (30.0%)
Unknown	7,754 (29.0%)	351 (14.0%)	67 (32.5%)
Nodes examined			
None	7,098 (26.6%)	310 (12.7%)	55 (27.0%)
≤12 nodes	10,150 (38.0%)	1,017 (41.6%)	70 (34.0%)
>12 nodes	8,377 (31.4%)	1,046 (42.7%)	69 (33.0%)
Unknown	1,044 (4.0%)	70 (3.0%)	12 (6.0%)
T stage (Depth of invasion)			
1+2	6,738 (25.0%)	531 (18.0%)	17 (8.0%)
3+4	12,076 (45.2%)	1,544 (63.0%)	123 (60.0%)
Unknown	7,855 (30.0%)	467 (19.0%)	66 (32.0%)
Characteristic	NMCC	MCC	SRCC
1	8,647 (32.4%)	489 (20.0%)	70 (34.0%)
Unknown	1,926 (7.3%)	169 (7.0%)	22 (10.7%)
Stage			
1	2,424 (9.0%)	288 (11.8%)	7 (3.5%)
2	3,859 (14.5%)	661 (27.0%)	27 (13.0%)
3	3,250 (12.0%)	602 (24.6%)	56 (27.2%)
4	8,647 (32.5%)	489 (20.0%)	70 (34.0%)
Unknown	8,489 (32.0%)	403 (16.0%)	46 (22.3%)
Treatment (stage III only)	N=3,250	N=602	N=56
None	38 (1.1%)	10 (1.5%)	0
Surgery alone	1,292 (40.0%)	223 (37.0%)	19 (34.0%)
Adjuvant chemotherapy	1,892 (58.0%)	360 (6.0%)	36 (64.0%)
Chemotherapy alone	28 (0.9%)	9 (1.5%)	1 (2.0%)

Table 2 (*continued*)

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Table 2 (*continued*)

Characteristic	NMCC	MCC	SRCC
Surgery type			
Local excision	2,241 (8.4%)	46 (1.9%)	5 (2.4%)
Partial colectomy	6,298 (23.6%)	0	28 (13.6%)
Subtotal colectomy/Hemicolectomy	11,789 (44.2%)	1,966 (80.5%)	107 (52.0%)
Total colectomy	659 (2.5%)	70 (2.9%)	3 (1.4%)
Total proctocolectomy	118 (0.4%)	10 (0.4%)	0
Colectomy with resection of adjacent organ	207 (0.7%)	34 (1.4%)	5 (2.4%)
Colectomy NOS	398 (1.4%)	28 (1.1%)	2 (1.0%)
Unknown	663 (2.5%)	31 (1.3 %)	5 (2.4%)
Surgical margins			
Negative	16,657 (62.4%)	1,624 (66.5%)	108 (52.4%)
Positive	865 (3.24%)	138 (5.6%)	23 (11.2%)
Unknown	4,880 (18.4%)	423 (17.3%)	23 (11.2%)
CEA levels	N=6,987	N=678	N=58
Positive	2,928 (42.0%)	323 (48.0%)	29 (50.0%)
Negative	4,059 (58.0%)	355 (52.0%)	29 (50.0%)
Unknown	19,682 (73.8%)	1,765 (72.4%)	148 (71.8%)

Table 3 Stage specific five-year survival among SRCC, MCC and NMCC

Stage	SRCC (%)	MCC (%)	NMCC (%)	P value
1	100	61	41	<0.0001
2	42	58	32	<0.0001
3	19	41	47	0.0002
4	1.5	7	31	<0.0001

treatment is mainly stage specific we included only stage III patients while analyzing for adjuvant chemotherapy (64%, 60% and 58%).

Type of surgery and surgical margins

The number of patients who underwent subtotal colectomy and/or hemicolectomy were 107 (52%), 1,966 (80.5%) and 11,789 (44.2%) in SRCC, MCC and NMCC groups respectively. The surgical margins were positive in 11.2% of SRCC patients, 5.6% of MCC patients and 3.2% of NMCC patients.

Survival analysis

SRCC has worse overall survival compared to MCC and NMCC. The median survival of SRCC as compared to NMCC was 18.6 and 46 months respectively (P<0.0001), and MCC as compared to NMCC was 47.8 and 46 months respectively (P=0.63). The stage specific average five-year survivals were shown in *Table 3*. In our study early stage SRCC and MCC had better five-year survival compared to NMCC while advanced stage SRCC and MCC had worse survival compared to NMCC (Stage I: SRCC, 100%; MCC, 61%; NMCC, 41%; P<0.0001. Stage II: SRCC, 42%; MCC, 58%; NMCC, 32%; P<0.0001. Stage III: SRCC, 19%; MCC, 41%; NMCC, 47%; P=0.0002. Stage IV: SRCC, 1.5%; MCC, 7%; NMCC, 31%; P<0.0001). The small number of patients with early stage SRCC could have affected the survival. Stage specific and overall survival of SRCC, MCC and NMCC are shown in *Table 3*, *Figures 1,2*.

Discussion

SRCC and MCC are well recognized subtypes of colorectal carcinoma but are uncommon in occurrence. The frequencies of SRCC and MCC in our study are 0.6% and 7% respectively and our study is one of the largest series reported so far. These incidence rates are similar to that mentioned in other studies (1,4,6) with an incidence rate of nearly 1% for SRCC and 5-15% for MCC.

SRCC occurs at younger age compared to MCC and NMCC. Median age of diagnosis is 67 years in our study, which is higher than that mentioned in few single institution studies (50.8 years) (7). However it is very similar to those mentioned in other large population based studies (4). The difference in age at presentation is likely due to the bias

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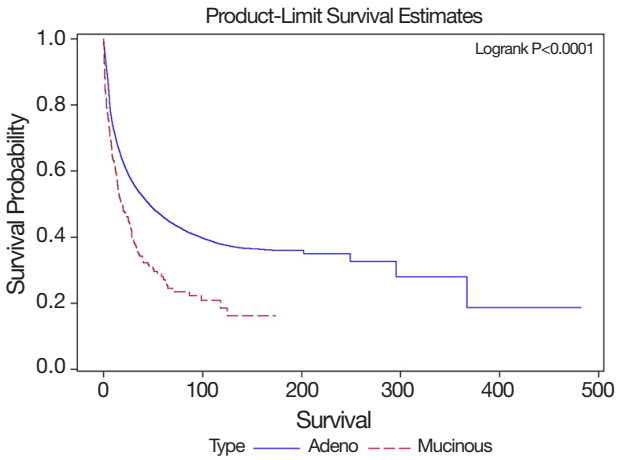

Figure 1 K-M curves for SRCC and NMCC (18.6 *vs.* 46 months)

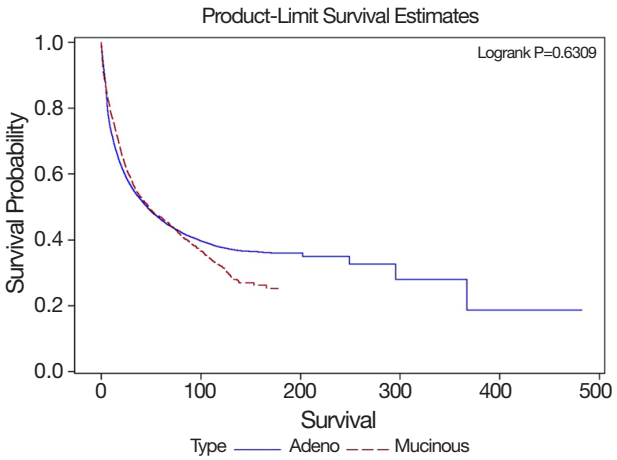

Figure 2 K-M curves for MCC and NMCC (47.8 *vs.* 46 months)

associated with single institution studies. In our series we found SRCC patients to have significantly higher incidence of poorly differentiated tumors, larger tumor size, proximal colonic tumor location and higher CEA levels. In addition, we found both mucinous and signet-ring cell type tumors were more likely to have lymph node involvement and organ infiltration. These findings are consistent with prior studies (5,8).

SRCC has poor survival rates compared to MCC and NMCC. The survival rates of MCC are similar compared to NMCC, which is consistent with few other studies (4,9,10), especially after adjusting for stage (11). SRCC's poor outcomes might be related to higher tumor stage and grade, propensity for nodal as well as peritoneal involvement however the reasons for these features are not well understood. SRCC is considered as a tumor arising in flat colonic mucosa and not following the adenoma-carcinoma sequence (12). This probably explains the reason for fewer patients being diagnosed in early stages. This also has implications in colon cancer screening with colonoscopy where these tumors are not easily visualized. A DNA based stool testing might overcome this issue in future (13).

Molecular mechanisms underlying the pathogenesis of SRCC have been evaluated to better understand the aggressive nature of this disease. Several candidate genes based on gene expression analysis have been studied however the exact molecular mechanisms are not well understood. Colon cancers with high-frequency microsatellite instability (MSI) have in general better survival outcomes. However, both SRCC and NMCC, inspite of increased rates of high-frequency MSI the prognosis is poor suggesting varied carcinogenesis in these tumors (14,15). SRCC are also found to have low rates of K-ras mutations and higher B-raf mutations compared to NMCC (16,17). B-raf mutations are considered an independent poor prognostic factor in colorectal cancer (18,19). Park *et al.* has shown higher expression of mucin regulating genes such as HATH1, MUC2 and SOX215 and Sentani *et al.* also reported high expression of MUC2, MUC5, Reg IV and Claudin 18 in SRCC (20,21). Overexpression of these genes leads to large amounts of intracellular mucin production, eventually forming clusters of cells, which disrupt the E-cadherin/β-catenin complex and cell-cell adhesions facilitating diffuse spread of the tumor. Ogni *et al.* has proposed that higher frequency of the CpG island methylator phenotype (CIMP) in SRCC leads to aberrant hyper methylation and reduced expression of E-cadherin (17). Others have hypothesized that the mucopolysaccharide of colloid-type carcinomas jams discrimination of host immunocytes from tumor cells, thus these colloid-secreting carcinomas easily invade peri-intestinal tissue resulting in infiltration into lymphatic vessels and nodes (12).

The main limitation of our study is lack of central pathology review. Retrospective nature, predominant male population and lack of information regarding patient preferences, performance status and physician biases are other limitations of the study. Despite these limitations, our study represents one of the largest retrospective studies of SRCC of colon.

Conclusions

In conclusion, mucinous and SRCCs have unique

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clinicopathological features and are more aggressive in biologic behavior than the common NMCC. SRCC is a poor individual prognostic factor. Because of the rarity of the tumor, prospective multi-institute studies with a special focus on gene expression, may lead to development of targeted therapies and improved survival outcomes of these patients.

Acknowledgements

Disclosure: The authors declare no conflict of interest.

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Cite this article as: Thota R, Fang X, Subbiah S. Clinicopathological features and survival outcomes of primary signet ring cell and mucinous adenocarcinoma of colon: retrospective analysis of VACCR database. J Gastrointest Oncol 2014;5(1):18-24. doi: 10.3978/j.issn.2078-6891.2013.051

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