Characteristics and prognosis of colorectal signet ring cell carcinoma in patients aged ≥ 65 years

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Research Article

Keywords: Signet ring cell carcinoma, colorectal, elderly, prognosis, SEER database.

DOI: https://doi.org/10.21203/rs.3.rs-200148/v1

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Abstract

Objective: To evaluate the prognostic value of age on colorectal signet ring cell carcinoma (SRCC) and identify the prognosis factors of patients aged ≥ 65 years.

Methods: Patients were recruited from the Surveillance, Epidemiology, and End Results (SEER) database. We ensured that all characteristics were well balanced through adopting the propensity score matching (PSM) method. In addition, the prognostic factors were evaluated by the Cox proportional hazardous model.

Results: Altogether 3305 cases were enrolled, including 1564 in elderly group (aged ≥65 years). As a result, more patients were female, unmarried, white, earlier AJCC stage, tumor size ≤5cm, grade III/IV and located in cecum–transverse colon in the elderly group; whereas significant fewer patients received chemotherapy and radiotherapy. After 1:1 PSM analysis, each group contained 1032 cases. As discovered by Kaplan-Meier analysis, the elderly group was associated with remarkably dismal survival compared with the younger group after PSM analysis (P=0.0091). Moreover, grade, primary site, AJCC stage, tumor size, surgery and chemotherapy were identified as the independent prognostic factors for the elderly patients.

Conclusion: The prognosis of colorectal SRCC aged ≥ 65 years was worse than the younger patients. We may need strengthen the chemotherapy of the elderly colorectal SRCC.

Introduction

In the USA, colorectal cancer (CRC) ranks the second place among the common causes of cancer-associated mortality, and it has became severe health threat in the world [1]. Of the diverse CRC subtypes, colorectal signet ring cell carcinoma (SRCC) arouses wide interests recently. Originally depicted by Laufman and Saphirin[2], SRCC is suggested to be mainly derived from undifferentiated colorectal mucosal stem cells; as a result, SRCC usually shows low differentiation, fast proliferation, high metastasis and diffuse infiltration[3, 4].

Many diverse clinicopathological features and prognostic outcomes have been reported for the elderly CRC cases in existing studies. It has been suggested that, the younger CRC cases showed unfavorable pathological characteristics and advanced stage relative to the elderly patients[5, 6]. However, other studies discover no difference in the pathological characteristics and tumor stage between the younger and elderly populations[7, 8]. But no specific data on the elderly patients with colorectal SRCC are available at present due to the rarity of this disease.

The aim of this study was to compare the clinicopathologic characteristics and survival of colorectal SRCC in two groups of patients (< 65 years and ≥65 years). We also aimed to identify the prognosis factors of patients aged ≥ 65 years.
Materials And Methods

Ethical statement

The Surveillance, Epidemiology, and End Results (SEER) database formulated by the National Cancer Institute, which is started in 1973 and updated every year, utilizes the population-based data for the development of all-sided sources[9]. This databases covers about 30% US population among different geographic areas[10]. To access the SEER database, we signed the SEER Research Data Agreement (reference number, 18753-Nov 2016). Related data were obtained according to the approved guidelines. The data analysis was considered by the Office for Human Research Protection to be non-human subjects who were researched by the United States Department of Health and Human Services, as they were publicly available and de-identified. Thus, it did not require approval by the institutional review board.

Study population

The eligible cases were screened by adopting the SEER*State v8.3.6 approach (released on August 8th, 2019). A total of 18 SEER areas were included from 2004 to 2015, including Arizona Indians, Alaska Native Tumor Registry, Connecticut, Cherokee Nation, Georgia Center for Cancer Statistics, Detroit, Greater California, Greater Bay Area Cancer Registry, Iowa, Hawaii, Los Angeles, Kentucky, New Jersey, Louisiana, Seattle-Puget Sound, Utah, and New Mexico. Patients conforming to the criteria below were included: (1) patients with primary colorectal SRCC; (2) the diagnosis of SRCC was made according to the third edition of the International Classification of Disease for Oncology (ICD-O-3, 8490/3). The exclusion criteria were listed as following: (1) those with multiple primary tumor; (2) those only with the clinical diagnosis, or those diagnosed based on autopsy or the death certificate; (3) those with no available information on AJCC stage; and (4) those with no data on prognosis. All the rest participants were included into the initial SEER cohort.

Covariates

The clinicopathological features of patients shown below were examined, including age, sex, race, marital status, insurance status, year of diagnosis, tumor size, primary site, AJCC stage, grade, lymph node dissection (LND), surgery, chemotherapy and radiotherapy.

In this study, the single (never married), widowed (having a domestic partner), separated and divorced cases were classified into unmarried category. With regard to primary tumor site, it was divided into cecum–transverse colon (like appendix, cecum, hepatic flexure, ascending colon, transverse colon), descending colon–sigmoid (like splenic flexure, descending colon, sigmoid colon), rectum, multiple or unknown[11]. As for the year of diagnosis, it was classified as 2004-2007, 2008-2011, 2012-2015, in accordance with previous studies[12, 13]. Additionally, and tumor size[14, 15] were also grouped in line with previous reports. Cancer stage was classified by the AJCC classification system (6th edition) adapting to SEER-derived patients diagnosed between 2004 and 2015[16]. In this study, we set cancer-
specific survival (CSS) as the endpoint, which referred to the duration between diagnosis and death because of colorectal SRCC.

**Propensity score matching (PSM)**

Selection bias was inevitable in the observational studies; as a result, confounding factors may be unequally distributed between the two groups. PSM refers to the process to assign conditional probabilities to the specific treatment based on diverse observed covariates\[^{17}\]. For reducing the selection bias and avoiding the unequal confounding factor distribution, we adopted PSM in the present study\[^{18}\]. In addition, the logistic regression model was utilized to predict the propensity score for each case using the SPSS plug-in PSM, including each survival-affecting covariate. Thereafter, PSM at the 1:1 nearest neighbor matching was carried out between the elderly and younger groups for all subgroups, and the caliper was set at 0.01 for the sake of accepting the matched pair.

**Statistical analysis**

All the categorical were expressed in the manner of number and percentage, while continuous variables were expressed as mean ±SD. Fisher's exact test and Pearson's chi-square test were used to compare clinicopathological features pre- and post-PSM. Meanwhile, the Kaplan–Meier method was utilized to estimate patients’ survival. Differences in patients’ survival between different groups were evaluated by log-rank test. Cox proportional hazards regression was adopted for assessing the relationships of different variables with survival. Later, significant variables obtained from univariate analysis (\(P < 0.05\)) or those identified to be prognostic factors before were enrolled in multivariate analysis. SPSS23.0 (SPSS Inc., Chicago, USA) was utilized for statistical analysis. A two-sided \(P < 0.05\) was considered as statistically significant.

**Results**

**Patient selection procedure and age distribution**

A total of 3305 patients met the inclusion criteria for analyzing characteristics. Figure 1 presents the patients selection procedure. Median age at diagnosis of all patients was 63 years (12-103 years). The age of patients is almost normal distribution, and the age group of 50-70 accounted for 43.4%. Figure 2 shows the age distribution. Besides, in line with previous\[^{19, 20}\], the enrolled patients were classified as two age groups, including the older (≥65 years, n=1564) and younger (<65 years, n=1741) groups.

**Patient features between two groups**

Table 1 presents the patient demographic, tumor feature and treatment data. Differences in sex, race, insurance status, marital status, tumor size, grade, primary site, AJCC stage, LND number, chemotherapy and radiotherapy were statistically significant between the two groups. There were more female (\(P < 0.001\)), unmarried (\(P < 0.001\)), white (\(P < 0.001\)), medicaid/insured (\(P = 0.023\)), earlier AJCC stage, tumor size ≤5cm, grade III/IV (\(P < 0.001\)) and cecum–transverse colon (\(P < 0.001\)) cancer patients in the
elderly group; whereas a lower proportion of these patients received chemotherapy ($P<0.001$) and radiotherapy ($P<0.001$) in comparison with those in the younger group. Meanwhile, difference in received surgery was not significant between the two groups ($P=0.065$).

**PSM and CSS post-PSM**

PSM incorporated factors such as age, sex, race, insurance status, marital status, tumor size, grade, primary site, LND number, AJCC stage, chemotherapy, surgery and radiotherapy. After 1:1 PSM analysis, both groups contained 1032 cases, respectively. None of the variables showed significant difference after PSM (Table 2). In addition, according to Kaplan–Meier analysis, the elderly patients had markedly poorer survival compared with the younger patients after PSM ($P=0.0091$) (Figure 3).

**Survival and prognostic factors for the elderly group patients**

For the 1564 elderly cases, the survival time ranged from 0 to 155 (median, 13.0) months. The CSS rates at 1, 3 and 5 years were 57.25%, 37.66% and 33.64%. As revealed by univariate analysis, sex, tumor size, primary site, AJCC stage, grade, LND number, surgery and chemotherapy were identified as the predicting factors for CSS (all $P<0.05$). According to multivariate analysis, tumor size $\leq 5\text{cm}$, primary site at cecum–transverse colon, earlier AJCC stage and grade I/II were identified to be the favorable prognostic factors. Moreover, patients who received surgery or chemotherapy were associated with superior prognosis compared to those who did not [(HR:0.674, 95% CI: 0.498–0.912, $P=0.010$) and (HR:0.488, 95% CI: 0.424–0.562, $P<0.001$)] (Table 3).

**Discussion**

The present population-based, retrospective study was carried out to illustrate age distribution in colorectal SRCC and evaluate the significance of age in prognosis prediction. As far as we know, this study is the first large scale population-based study that utilizes PSM for assessing the significance of age in predicting colorectal SRCC prognosis. As a result, the age of colorectal SRCCs patients was almost distributed normally. Difference in survival was significant between patients of the two age groups. Moreover, tumor size, primary site, AJCC stage, grade, chemotherapy and surgery were identified to be the independent prognostic factors for the elderly patients.

Colorectal SRCC, an uncommon CRC histological subtype, is classified by the WHO classification of tumors to be the colorectal adenocarcinoma variant, where over 50% cancer cells have obvious intracytoplasmic mucin[21]. Such cancer is featured by different clinical presentations and prognostic outcomes[22]. SRCC shows dismal prognostic outcome and high malignancy grade relative to additional CRC subtypes[23, 24].

Due to the low prevalence of colorectal SRCC, little information is available regarding the role of age in predicting the colorectal SRCC prognosis. As discovered by Ping He, the elderly ($\geq 65$ years old) showed
dismal prognosis compared with the younger patients (≥ 65 years old)[19], which is conformed to our findings.

In addition, our study suggested that chemotherapy and surgery were the factors for the favorable prognosis among the elderly patients, indicating that the aggressive and effective treatment markedly decreased the colorectal SRCC-associated mortality among the elderly patients. Surgery exerts an important part in treating locoregional tumors[25]. The value of chemotherapy has also been affirmed by many studies[14, 19, 26]. Our results suggested that the proportions of the patients who received surgery were similar between the two age groups, while that of patients who received chemotherapy significantly decreased in the elderly group (39.0% vs. 74.8%). Such finding is commonly found among the elderly patients who receive anticancer treatment in other tumors[27-29]. Therefore, we should strengthen the treatment of elderly patients.

So far, the present study is the first large-scale retrospective analysis on the role of age in predicting colorectal SRCC prognosis. Our study assists the clinical workers in further understanding the clinicopathological characteristics and treatment for the elderly colorectal SRCC patients (≥65 years old). Nonetheless, certain limitations should be noted in the present study. First of all, selection bias was inevitable in the observational study. The application of PSM analysis could reduced the bias resulting from the unequal distribution of covariates measured, but bias induced by the unmeasured variables were inevitable. Secondly, we enrolled altogether 14 variables, but some variables still could not enrolled in the SEER database, like vascular invasion, status of surgical margin or the molecular-genetic profiles. Thirdly, detailed information about chemotherapy was not available. Therefore, we can not further explore which chemotherapy regimen is safe and effective for elderly patients. Our future work will focus on solving the above limitations.

**Conclusion**

In conclusion, the clinicopathological features were significantly different between younger and older group, and the prognosis of colorectal SRCC in aged ≥65 years patients was significantly worse than that in younger patients. Primary site, grade, tumor size, AJCC stage, surgery and chemotherapy were independent risk factors for the prognosis of elderly patients. Nevertheless, more studies are warranted to determine whether more intense treatment is necessary for colorectal SRCC patients if appropriate.

**Declarations**

**Ethics approval**

Approval from the ethical board for this study was not required because of the public nature of all the data.

**Funding**
No funding.

Conflict of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

We thank the staff members of the National Cancer Institute and their colleagues across the United States and at Information Management Services, Inc., who have been involved with the Surveillance, Epidemiology, and End Results (SEER) Program.

Author contributions

Jian-dong Diao conceived the study. Di Zhou searched the database and literature. Di Zhou, Yong-jing Yang, Chun-cao Niu and Yong-jiang Yu discussed and analyzed the data. Di Zhou wrote the manuscript. Jian-dong Diao revised the manuscript. All authors reviewed the manuscript.

References

1. El-Shami K, Oeffinger KC, Erb NL, Willis A, Bretsch JK, Pratt-Chapman ML, Cannady RS, Wong SL, Rose J, Barbour AL, Stein KD, Sharpe KB, Brooks DD, et al. American Cancer Society Colorectal Cancer Survivorship Care Guidelines. CA Cancer J Clin. 2015; 65: 428-55.
2. Laufman H, Saphir O. Primary linitis plastica type of carcinoma of the colon. AMA Arch Surg. 1951; 62: 79-91.
3. Gopalan V, Smith RA, Ho YH, Lam AK. Signet-ring cell carcinoma of colorectum–current perspectives and molecular biology. Int J Colorectal Dis. 2011; 26: 127-33.
4. Hugen N, van de Velde CJH, de Wilt JHW, Nagtegaal ID. Metastatic pattern in colorectal cancer is strongly influenced by histological subtype. Ann Oncol. 2014; 25: 651-7.
5. Gallagher EG, Zeigler MG. Rectal carcinoma in patients in the second and third decades of life. Am J Surg. 1972; 124: 655-9.
6. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Ko CY. Are survival rates different for young and older patients with rectal cancer? Dis Colon Rectum. 2004; 47: 2064-9.
7. Isbister WH, Fraser J. Large-bowel cancer in the young: a national survival study. Dis Colon Rectum. 1990; 33: 363-6.
8. Mitry E, Benhamiche AM, Jouve JL, Clinard F, Finn-Faivre C, Faivre J. Colorectal adenocarcinoma in patients under 45 years of age: comparison with older patients in a well-defined French population. Dis Colon Rectum. 2001; 44: 380-7.
9. Yu JB, Gross CP, Wilson LD, Smith BD. NCI SEER public-use data: applications and limitations in oncology research. Oncology (Williston Park). 2009; 23: 288-95.
10. Cahill KS, Claus EB. Treatment and survival of patients with nonmalignant intracranial meningioma: results from the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Clinical article. J Neurosurg. 2011; 115: 259-67.

11. Nitsche U, Friess H, Agha A, Angele M, Eckel R, Heitland W, Jauch KW, Krenz D, Nussler NC, Rau HG, Ruppert R, Schubert-Fritschle G, Wilhelm D, et al. Prognosis of mucinous and signet-ring cell colorectal cancer in a population-based cohort. J Cancer Res Clin Oncol. 2016; 142: 2357-66.

12. Lv X, Yu H, Gao P, Song Y, Sun J, Chen X, Wang Y, Wang Z. A nomogram for predicting bowel obstruction in preoperative colorectal cancer patients with clinical characteristics. World J Surg Oncol. 2019; 17: 21.

13. Wu SG, Chen XT, Zhang WW, Sun JY, Li FY, He ZY, Pei XQ, Lin Q. Survival in signet ring cell carcinoma varies based on primary tumor location: a Surveillance, Epidemiology, and End Results database analysis. Expert Rev Gastroenterol Hepatol. 2018; 12: 209-14.

14. Shi T, Huang M, Han D, Tang X, Chen Y, Li Z, Liu C, Xiang D, Wang T, Chen Y, Wang R, Lei Z, Chu X. Chemotherapy is associated with increased survival from colorectal signet ring cell carcinoma with distant metastasis: A Surveillance, Epidemiology, and End Results database analysis. Cancer Med. 2019; 8: 1930-40.

15. Wei F, Lyu H, Wang S, Chu Y, Chen F. Postoperative Radiotherapy Improves Survival in Gastric Signet-Ring Cell Carcinoma: a SEER Database Analysis. J Gastric Cancer. 2019; 19: 393-407.

16. Shi M, Zhou B, Yang SP. Nomograms for predicting overall survival and cancer-specific survival in young patients with pancreatic cancer in the US based on the SEER database. PeerJ. 2020; 8: e8958.

17. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. Annu Rev Public Health. 2000; 21: 121-45.

18. Pattanayak CW, Rubin DB, Zell ER. [Propensity score methods for creating covariate balance in observational studies]. Rev Esp Cardiol. 2011; 64: 897-903.

19. Yang LL, Wang M, He P. Clinicopathological characteristics and survival in colorectal signet ring cell carcinoma: a population-based study. Sci Rep. 2020; 10: 10460.

20. Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015; 21: 5167-75.

21. Tajiri K, Sudou T, Fujita F, Hisaka T, Kinugasa T, Akagi Y. Clinicopathological and Corresponding Genetic Features of Colorectal Signet Ring Cell Carcinoma. Anticancer Res. 2017; 37: 3817-23.

22. Nitsche U, Zimmermann A, Spath C, Muller T, Maak M, Schuster T, Slotta-Huspenina J, Kaser SA, Michalski CW, Janssen KP, Friess H, Rosenberg R, Bader FG. Mucinous and signet-ring cell colorectal cancers differ from classical adenocarcinomas in tumor biology and prognosis. Ann Surg. 2013; 258: 775-82; discussion 82-3.

23. Hartman DJ, Nikiforova MN, Chang DT, Chu E, Bahary N, Brand RE, Zureikat AH, Zeh HJ, Choudry H, Pai RK. Signet ring cell colorectal carcinoma: a distinct subset of mucin-poor microsatellite-stable signet ring cell carcinoma associated with dismal prognosis. Am J Surg Pathol. 2013; 37: 969-77.
24. Ling CR, Wang R, Wang MJ, Ping J, Zhuang W. Prognosis and value of preoperative radiotherapy in locally advanced rectal signet-ring cell carcinoma. Sci Rep. 2017; 7: 45334.

25. Arifi S, Elmesbahi O, Amarti Riffi A. Primary signet ring cell carcinoma of the colon and rectum. Bull Cancer. 2015; 102: 880-8.

26. Hugen N, Verhoeven RH, Lemmens VE, van Aart CJ, Elferink MA, Radema SA, Nagtegaal ID, de Wilt JH. Colorectal signet-ring cell carcinoma: benefit from adjuvant chemotherapy but a poor prognostic factor. Int J Cancer. 2015; 136: 333-9.

27. Fu J, Ruan H, Zheng H, Cai C, Zhou S, Wang Q, Chen W, Fu W, Du J. Impact of old age on resectable colorectal cancer outcomes. PeerJ. 2019; 7: e6350.

28. Krok-Schoen JL, Adams IK, Baltic RD, Fisher JL. Ethnic disparities in cancer incidence and survival among the oldest old in the United States. Ethn Health. 2020; 25: 79-92.

29. Cao L, Li ZW, Wang M, Zhang TT, Bao B, Liu YP. Clinicopathological characteristics, treatment and survival of pulmonary large cell neuroendocrine carcinoma: a SEER population-based study. PeerJ. 2019; 7: e6539.

Tables

Table 1. Patient Demographic, Clinical, and Tumor Characteristics before PSM.
| Characteristic                  | All patients | <65 years | ≥65 years | P-value |
|--------------------------------|--------------|-----------|-----------|---------|
|                                | N=3305       | N=1741    | N=1564    |         |
| Sex                            |              |           |           | <0.001  |
| female                         | 1620 (49.0%) | 753 (43.3%) | 867 (55.4%) |         |
| male                           | 1685 (51.0%) | 988 (56.7%) | 697 (44.6%) |         |
| Race                           |              |           |           | <0.001  |
| black                          | 313 (9.47%)  | 204 (11.7%) | 109 (6.97%) |         |
| other                          | 282 (8.53%)  | 184 (10.6%) | 98 (6.27%)  |         |
| white                          | 2710 (82.0%) | 1353 (77.7%) | 1357 (86.8%) |         |
| Marital status                 |              |           |           | <0.001  |
| married                        | 1782 (53.9%) | 1012 (58.1%) | 770 (49.2%) |         |
| unmarried                      | 1523 (46.1%) | 729 (41.9%) | 794 (50.8%) |         |
| Insurance                      |              |           |           | 0.023   |
| any medicaid/insured           | 2268 (68.6%) | 1164 (66.9%) | 1104 (70.6%) |         |
| uninsured/unknown              | 1037 (31.4%) | 577 (33.1%) | 460 (29.4%) |         |
| Primary site                   |              |           |           | <0.001  |
| cecum–transverse colon         | 2002 (60.6%) | 919 (52.8%) | 1083 (69.2%) |         |
| descending colon–sigmoid       | 517 (15.6%)  | 323 (18.6%) | 194 (12.4%) |         |
| multiple                       | 50 (1.51%)   | 25 (1.44%)  | 25 (1.60%)  |         |
| rectum                         | 644 (19.5%)  | 425 (24.4%) | 219 (14.0%) |         |
| unknown                        | 92 (2.78%)   | 49 (2.81%)  | 43 (2.75%)  |         |
| Grade                          |              |           |           | 0.001   |
| grade I/II                     | 177 (5.36%)  | 90 (5.17%)  | 87 (5.56%)  |         |
| grade III/IV                   | 2537 (76.8%) | 1298 (74.6%) | 1239 (79.2%) |         |
| unknown                        | 591 (17.9%)  | 353 (20.3%) | 238 (15.2%) |         |
| Tumor size                     |              |           |           | <0.001  |
| >5cm                           | 1279 (38.7%) | 638 (36.6%) | 641 (41.0%) |         |
| ≤5cm                           | 1226 (37.1%) | 612 (35.2%) | 614 (39.3%) |         |
| unknown                        | 800 (24.2%)  | 491 (28.2%) | 309 (19.8%) |         |
| AJCC                           |              |           |           | <0.001  |
| I                              | 158 (4.78%)  | 69 (3.96%)  | 89 (5.69%)  |         |
| II                             | 465 (14.1%)  | 171 (9.82%) | 294 (18.8%) |         |
| Characteristic                        | All patients | <65 years | ≥65 years | P-value |
|--------------------------------------|--------------|-----------|-----------|---------|
|                                      | N=3305       | N=1741    | N=1564    |         |
| III                                  |              |           |           |         |
|                                      | 1227 (37.1%) | 615 (35.3%) | 612 (39.1%) |         |
| IV                                   | 1455 (44.0%) | 886 (50.9%) | 569 (36.4%) |         |
| Surgery                              |              |           |           | 0.065   |
| no                                   | 676 (20.5%)  | 378 (21.7%) | 298 (19.1%) |         |
| yes                                  | 2629 (79.5%) | 1363 (78.3%) | 1266 (80.9%) |         |
| Lymph node dissection                |              |           |           | 0.002   |
| 1 to 3                               | 87 (2.63%)   | 46 (2.64%)  | 41 (2.62%)  |         |
| ≥4                                   | 2325 (70.3%) | 1180 (67.8%) | 1145 (73.2%) |         |
| None or Biopsy                       | 893 (27.0%)  | 515 (29.6%)  | 378 (24.2%)  |         |
| Chemotherapy                         |              |           |           | <0.001  |
| no/unknown                           | 1393 (42.1%) | 439 (25.2%)  | 954 (61.0%)  |         |
| yes                                  | 1912 (57.9%) | 1302 (74.8%) | 610 (39.0%)  |         |
| Radiotherapy                         |              |           |           | <0.001  |
| no/unknown                           | 2868 (86.8%) | 1427 (82.0%) | 1441 (92.1%) |         |
| yes                                  | 437 (13.2%)  | 314 (18.0%)  | 123 (7.86%)  |         |
| Year of diagnosis                    |              |           |           | 0.567   |
| 2004-2007                            | 1120 (33.9%) | 580 (33.3%)  | 540 (34.5%)  |         |
| 2008-2011                            | 1069 (32.3%) | 577 (33.1%)  | 492 (31.5%)  |         |
| 2012-2015                            | 1116 (33.8%) | 584 (33.5%)  | 532 (34.0%)  |         |

Table 2. Baseline characteristics after propensity score matching.
| Characteristic          | All patients | <65 years | ≥65 years | P-value |
|-------------------------|--------------|-----------|-----------|---------|
|                         | N=2064       | N=1032    | N=1032    |         |
| Sex:                    |              |           |           | 0.792   |
| female                  | 997 (48.3%)  | 495 (48.0%) | 502 (48.6%) |         |
| male                    | 1067 (51.7%) | 537 (52.0%) | 530 (51.4%) |         |
| Race:                   |              |           |           | 0.985   |
| black                   | 189 (9.16%)  | 95 (9.21%) | 94 (9.11%) |         |
| other                   | 168 (8.14%)  | 83 (8.04%) | 85 (8.24%) |         |
| white                   | 1707 (82.7%) | 854 (82.8%) | 853 (82.7%) |         |
| Marital_status:         |              |           |           | 0.566   |
| married                 | 1096 (53.1%) | 555 (53.8%) | 541 (52.4%) |         |
| unmarried               | 968 (46.9%)  | 477 (46.2%) | 491 (47.6%) |         |
| Insurance:              |              |           |           | 0.771   |
| any medicaid/insured    | 1465 (71.0%) | 729 (70.6%) | 736 (71.3%) |         |
| uninsured/unknown       | 599 (29.0%)  | 303 (29.4%) | 296 (28.7%) |         |
| Primary_site:           |              |           |           | 0.705   |
| cecum–transverse colon  | 1257 (60.9%) | 639 (61.9%) | 618 (59.9%) |         |
| descending colon–sigmoid| 311 (15.1%)  | 151 (14.6%) | 160 (15.5%) |         |
| multiple                | 41 (1.99%)   | 18 (1.74%) | 23 (2.23%) |         |
| rectum                  | 387 (18.8%)  | 194 (18.8%) | 193 (18.7%) |         |
| unknown                 | 68 (3.29%)   | 30 (2.91%) | 38 (3.68%) |         |
| Grade:                  |              |           |           | 0.691   |
| grade I/II              | 115 (5.57%)  | 54 (5.23%) | 61 (5.91%) |         |
| grade III/IV            | 1569 (76.0%) | 792 (76.7%) | 777 (75.3%) |         |
| unknown                 | 380 (18.4%)  | 186 (18.0%) | 194 (18.8%) |         |
| Tumor size:             |              |           |           | 0.998   |
| >5cm                    | 780 (37.8%)  | 390 (37.8%) | 390 (37.8%) |         |
| ≤5cm                    | 787 (38.1%)  | 394 (38.2%) | 393 (38.1%) |         |
| unknown                 | 497 (24.1%)  | 248 (24.0%) | 249 (24.1%) |         |
| AJCC:                   |              |           |           | 0.732   |
| I                       | 116 (5.62%)  | 53 (5.14%) | 63 (6.10%) |         |
| II                      | 262 (12.7%)  | 130 (12.6%) | 132 (12.8%) |         |
| III                     | 794 (38.5%)  | 394 (38.2%) | 400 (38.8%) |         |
| Characteristic         | All patients N=2064 | <65 years N=1032 | ≥65 years N=1032 | P-value |
|------------------------|---------------------|------------------|------------------|---------|
| IV                     | 892 (43.2%)         | 455 (44.1%)      | 437 (42.3%)      |         |
| Surgery:               |                     |                  |                  | 0.392   |
| no/unknown             | 445 (21.6%)         | 214 (20.7%)      | 231 (22.4%)      |         |
| yes                    | 1619 (78.4%)        | 818 (79.3%)      | 801 (77.6%)      |         |
| Reg_LN_Sur:            |                     |                  |                  | 0.166   |
| 1 to 3                 | 57 (2.76%)          | 23 (2.23%)       | 34 (3.29%)       |         |
| ≥4                     | 1420 (68.8%)        | 726 (70.3%)      | 694 (67.2%)      |         |
| None or Biopsy         | 587 (28.4%)         | 283 (27.4%)      | 304 (29.5%)      |         |
| Chemotherapy:          |                     |                  |                  | 0.349   |
| no/unknown             | 866 (42.0%)         | 422 (40.9%)      | 444 (43.0%)      |         |
| yes                    | 1198 (58.0%)        | 610 (59.1%)      | 588 (57.0%)      |         |
| Radiotherapy:          |                     |                  |                  | 0.836   |
| no/unknown             | 1826 (88.5%)        | 911 (88.3%)      | 915 (88.7%)      |         |
| yes                    | 238 (11.5%)         | 121 (11.7%)      | 117 (11.3%)      |         |
| Year_of_diagnosis:     |                     |                  |                  | 0.774   |
| 2004-2007              | 660 (32.0%)         | 323 (31.3%)      | 337 (32.7%)      |         |
| 2008-2011              | 716 (34.7%)         | 359 (34.8%)      | 357 (34.6%)      |         |
| 2012-2015              | 688 (33.3%)         | 350 (33.9%)      | 338 (32.8%)      |         |

**Table 3** Univariate and multivariate analyses of cancer-specific survival (CSS) for patients with colorectal SRCC aged ≥ 65.
| Characteristic                | Univariate analysis | Multivariate analysis |
|------------------------------|---------------------|-----------------------|
|                              | P-value             | HR(95%CI)             |
|                              |                     | P-value               |
| Year at diagnosis            | 0.761               |                       |
| 2004-2007                    |                     |                       |
| 2008-2011                    |                     |                       |
| 2012-2015                    |                     |                       |
| Sex                          | 0.049               | 0.317                 |
| Female                       | Reference           |                       |
| male                         | 1.069(0.938,1.219)  |                       |
| Race                         | 0.596               |                       |
| black                        | NI                  |                       |
| white                        |                     |                       |
| other                        |                     |                       |
| Marital status               | 0.374               |                       |
| unmarried                    | Reference           |                       |
| married                      |                     |                       |
| Insurance                    | 0.284               |                       |
| uninsured/unknown            | Reference           |                       |
| any medicaid/insured         |                     |                       |
| Primary Site                 | <0.001              | 0.026                 |
| cecum–transverse colon       | Reference           |                       |
| descending colon–sigmoid     | 1.150(0.947,1.396)  | 0.158                 |
| multiple                     | 1.361(0.865,2.140)  | 0.182                 |
| rectum                       | 1.369(1.101,1.702)  | 0.005                 |
| unknown                      | 1.374(0.962,1.962)  | 0.080                 |
| Grade                        | <0.001              | <0.001                |
| grade I/II                   | Reference           |                       |
| grade III/IV                 | 1.932(1.387,2.693)  | <0.001                |
| unknown                      | 2.071(1.446,2.968)  | <0.001                |
| Tumor size                   | <0.001              | 0.001                 |
| ≤5cm                         | Reference           |                       |
| >5cm                         | 1.200(1.031,1.395)  | 0.018                 |
| unknown                      | 1.456(1.180,1.796)  | <0.001                |
| AJCC stage                   | <0.001              | <0.001                |
| I                            | Reference           |                       |
| II                           | 1.419(0.889,2.267)  | 0.143                 |
| III                          | 4.765(3.088,7.354)  | <0.001                |
| IV                           | 11.678(7.543,18.079)| <0.001                |
| Surgery                      | <0.001              | 0.010                 |
| no surgery                   | Reference           |                       |
| yes                          | 0.674(0.498,0.912)  |                       |
| Dissected lymph node         | <0.001              | 0.480                 |
| none or biopsy               | Reference           |                       |
| 1 - 3                        | 1.118(0.700,1.785)  | 0.642                 |
| ≥4                           | 0.899(0.673,1.202)  | 0.473                 |
| Chemotherapy                 | 0.028               | <0.001                |
| no/unknown                   | Reference           |                       |
| yes                          | 0.488(0.424,0.562)  |                       |
| Radiotherapy                 | 0.960               | 0.731                 |
| no/unknown                   | Reference           |                       |
| yes                          | 1.049(0.800,1.375)  |                       |

**Abbreviation:** NI, not included in the multivariate survival analysis;