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ORIGINAL RESEARCH

# Evaluating Treatment Patterns for Small Cell Carcinoma of the Colon Using the National Cancer Database (NCDB)

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## Abstract

**Objective(s)** The objective of this study was to characterize the clinicopathological prognostic factors and treatment patterns for small cell carcinoma (SCC) of the colon, a rare disease without standard treatment guidelines.

**Methods** We analyzed clinicopathological and treatment variables for 503 cases of histologically proven SCC colon entered into the National Cancer Database (NCDB) between 2004 and 2013. Survival curves were generated using Kaplan-Meier and compared by the log-rank test. Cox proportional hazard regression was used to control for covariates and evaluate the effect of different treatment modalities on overall survival.

**Results** Four hundred seventy-two (93.8%) patients had complete clinical staging information and were therefore included in our analysis. Of these patients, 149 (31.5%) had limited stage disease (LD) and 323 (68.4%) had extensive stage disease (ED) at presentation. Median overall survival (OS) for patients with ED was significantly lower than for those with LD (4.04 months vs. 21.82 months; $p < 0.001$). Multivariate Cox regression analysis showed administration of chemotherapy was associated with improved survival in patients with LD and ED ($p = 0.026$, $p < 0.001$) while surgery was not associated with improved survival in patients with LD or ED ($p = 0.943$, $p = 0.630$). Radiation therapy was associated with improved survival in patients with ED ($p = 0.044$).

**Conclusions** SCC of the colon carries a poor prognosis, especially in patients presenting with metastatic disease. Surgery and chemotherapy are administered more frequently than radiation, and chemotherapy is associated with improved survival, unlike surgery.

**Keywords** Extrapulmonary small cell carcinoma · Colon cancer · Radiation · Chemotherapy

## Introduction

High-grade neuroendocrine carcinomas (HGNEC) are poorly differentiated neoplasms that encompass large cell and small cell carcinoma variants. Typically, HGNEC have a poor prognosis due to its rapid and aggressive clinical course. These tumors are generally classified by their anatomic site of origin and most commonly arise from Kulchitsky cells or enterochromaffin-like cells usually found in the GI and pulmonary systems [1]. Small cell cancer (SCC) of the GI tract, a type of HGNEC, is a rare type of malignancy that is aggressive in nature. SCC of the GI tract shares many common features with SCC of the lung including sharing neuroendocrine features, having high metastatic potential, similar pattern of spread, poor prognosis, overall chemosensitivity, and prognostic impact of the extent of the disease and performance status [2]. However, SCC of the GI tract has its own unique features, such as affecting a smaller proportion of smokers, having a predisposing medical condition, higher percentage of locoregional disease at presentation, and larger proportion of long-term survivors following surgery. There is limited research on small cell cancer of the colon specifically, since occurrence in this region is rare. The SEER database from 1992 to 2010 of 243 cases reports an incidence of 0.4% colon and rectal SCC of all SCC and an incidence of 10.0% of colon and rectal SCC amongst all cases of extrapulmonary SCC [3]. Of the SCC cases of the GI tract, the esophagus seems to be the most common location. In this paper, we focus on the

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updated incidence of SCC in the colon, its prognostic implications, and the role of surgery, chemotherapy, and radiation as possible modalities of treatment for these patients.

## Materials and Methods

### Study Source

We used the National Cancer Data Base (NCDB) as our source of de-identified patient cases that have small cell cancer of the colon. The NCDB was created in 1989 as a joint program of the Commission on Cancer (CoC) of the American College of surgeons (ACoS) and the American Cancer Society (ACS). It contains almost 29 million records from hospital cancer registries across the USA. Since 1989, the database has captured clinicopathologic, treatment, and outcome information for approximately 70% of the diagnosed cancers in the USA. A waiver was obtained from the Baylor College of Medicine Institutional Review Board to utilize the NCDB database for research purposes.

### Study Cohort

The study cohort consisted of patients of any age who were diagnosed with SCC of the colon and rectosigmoid from the years 2004–2013. The patients diagnosed before 2004 have not been included in our study cohort because some crucial information has been left out or have been misinterpreted according to the disclosure statement we received upon receiving access to the NCDB. We included patients who had a diagnosis of small cell cancer of the colon and rectosigmoid and subsequently used CD 18.0–18.9, CD 19.9, and CD 20.9, which referred to "SCC," "oat cell carcinoma," and "combined SCC," respectively. The information we collected includes demographic variables, such as race and age, type of treatment received, if any, and staging of the cancer at diagnosis. Information regarding treatment was limited, however. The NCDB does not report the type of chemotherapy used, the number of agents used, the duration of treatment, the frequency of treatments, or the timing of chemotherapy treatments. Staging information was based on American Joint Committee on Cancer (AJCC) sixth/seventh edition of clinical staging system.

### Outcome

All-cause mortality served as the primary endpoint of the study, and follow-up time was calculated based on the month and year of the patient's initial diagnosis. We also analyzed the primary sites of metastasis.

### Statistical Analysis

We divided our patients into two groups. The limited stage disease (LD) group was defined as those patients with stage I–III disease. The extensive stage disease group (ED) was defined as those patients with stage IV disease. Although no consensus exists on the guidelines for this nomenclature, we have decided to follow the terminology from other extrapulmonary small cell cancer papers [4]. We used the Kaplan-Meier test to generate overall survival curves for patients with LD and ED, which were subsequently compared using the log-rank test. Univariable analyses were conducted to evaluate the influence of the covariates on survival. Multivariate analysis was conducted using the Cox proportional hazard method. This was done by initially including all covariates significant at the $p < 0.20$ level and removing them as necessary if non-significant on multivariable analyses, while evaluating the effect on the treatment variables of interest. If the covariate removal caused a large change in the hazard function of the treatment variables, they were kept in the model. We used age, sex, race, stage, and receipt of treatment (radiation vs. chemotherapy vs. surgery) as our covariates. Statistical analysis was performed using SPSS version 23.0 (SPSS Inc., Chicago, IL). Statistical significance was defined as a 2-sided $p$ value of 0.05 or less.

## Results

### Patient Characteristics and Treatment Selection

A total of 503 patients were identified with SCC of colon. 93.8% of (472) patients had complete staging information. Amongst these 472 patients, 31.5% (149) had limited stage disease (stage I, II, and III) (LD), and 68.4% (323) had extensive stage disease (ED) at presentation. Median age of our cohort was 65 years (24–90 years); 49.5% (249) were male; 82.7% (416) White, 10.7% (54) Black, 1.6% (8) Asian, 4.0% (20) Hispanic, and 1.0% (5) other. Further details regarding patient characteristics can be found in Table 1.

### Sites of Metastasis

Of the 323 patients who presented with metastatic disease, there was information on the location of the metastasis for 179 of these patients because the data is part of the Collaborative Stage Data Collection System, which was introduced in 2004. From the data that was available, the most common site of metastasis was the liver. About 71.5% of patients (128) had liver, but fewer, 2.8% (5) had brain as the metastatic site at presentation.

**Table 1** Patient characteristics

| | All patients | | LD | | ED | | *p* value |
|---|---|---|---|---|---|---|---|
| Sample size | 503 | | 149 | 29.6% | 323 | 64.2% | < 0.001 |
| Mean age (years) | 64.3 | | 66.5 | | 63.0 | | 0.013 |
| Age range (years) | 24–90 | | 32–90 | | 24–90 | | |
| Median survival (months) (95% CI) | 6.5 | (5.3–7.8) | 21.8 | (13.3–30.4) | 4.0 | (3.0–5.1) | < 0.001 |
| Sex | | | | | | | 0.521 |
| Male | 249 | 49.5% | 70 | 47.0% | 162 | 50.2% | |
| Female | 254 | 50.5% | 79 | 53.0% | 161 | 49.8% | |
| Race | | | | | | | 0.008 |
| White | 416 | 82.7% | 117 | 78.5% | 271 | 83.9% | |
| Black | 54 | 10.7% | 19 | 12.8% | 33 | 10.2% | |
| Asian | 8 | 1.6% | 0 | 0.0% | 8 | 2.5% | |
| Hispanic | 20 | 4.0% | 12 | 8.1% | 7 | 2.2% | |
| Other | 5 | 1.0% | 1 | 0.7% | 4 | 1.2% | |
| Insurance | | | | | | | 0.374 |
| None | 17 | 3.4% | 5 | 3.4% | 11 | 3.4% | |
| Private | 209 | 41.6% | 55 | 36.9% | 143 | 44.3% | |
| Medicaid | 4 | 0.8% | 8 | 5.4% | 16 | 5.0% | |
| Medicare | 241 | 47.9% | 79 | 53.0% | 143 | 44.3% | |
| Other | 12 | 2.4% | 2 | 1.3% | 10 | 3.1% | |
| Median income | | | | | | | 0.476 |
| < $38,000 | 82 | 16.3% | 24 | 16.1% | 54 | 16.7% | |
| $38,000–$47,999 | 123 | 24.5% | 30 | 20.1% | 83 | 25.7% | |
| $48,000–$62,999 | 126 | 25.0% | 44 | 29.5% | 78 | 24.1% | |
| > $63,000 | 159 | 31.6% | 47 | 31.5% | 100 | 31.0% | |
| Stage | | | | | | | |
| I | 37 | 7.4% | – | | – | | |
| II | 22 | 4.4% | – | | – | | |
| III | 90 | 17.9% | – | | – | | |
| IV | 323 | 64.2% | – | | – | | |
| Unknown | 31 | 6.2% | – | | – | | |
| Comorbidity index = 0 (%) | | | | | | | 0.768 |
| Index = 0 | 366 | 72.8% | 106 | 71.1% | 234 | 72.4% | |
| Index = 1 | 96 | 19.1% | 28 | 18.8% | 63 | 19.5% | |
| Index ≥ 2 | 41 | 8.2% | 15 | 10.1% | 26 | 8.0% | |
| Treatment as a component | | | | | | | |
| Chemotherapy | 261 | 51.9% | 73 | 49.0% | 178 | 55.1% | 0.216 |
| Radiation therapy | 37 | 7.4% | 13 | 8.7% | 23 | 7.1% | 0.542 |
| Surgery | 202 | 40.2% | 83 | 55.7% | 114 | 35.3% | < 0.001 |
| Specific treatment | | | | | | | < 0.001 |
| No treatment | 129 | 25.6% | 36 | 7.2% | 93 | 28.8% | |
| Surgery only | 90 | 17.9% | 40 | 8.0% | 46 | 14.2% | |
| Radiation therapy only | 5 | 1.0% | 0 | 0.0% | 5 | 1.5% | |
| Chemotherapy only | 131 | 26.0% | 23 | 15.4% | 100 | 31.0% | |
| Chemotherapy and radiation therapy | 19 | 3.8% | 7 | 4.7% | 11 | 3.4% | |
| Surgery and chemotherapy | 99 | 19.7% | 37 | 24.8% | 61 | 18.9% | |
| Surgery, chemotherapy, and radiation | 12 | 2.4% | 6 | 4.0% | 6 | 1.9% | |
| Dose to primary site (Gy) | | | | | | | |
| Mode | 45.0 | | 45.0 | | 8, 30, 37.5 | | |
| Mode number of total fractions | 28 | | 28 | | 10 | | |

## Treatment Modalities Used

Surgery, chemotherapy, and radiation were the three treatment options available for patients. 25.6% (129) of patients received no treatment. Of the patients that were treated, surgery was used in 55.7% patients with LD and 35.3% of patients with ED ($p < 0.001$), while radiation was used in 8.7% (13 pts) of patients with LD and 7.1% (23) of patients with ED ($p = 0.546$). Chemotherapy was used in 49% of patients with LD and 55.1% in patients with ED ($p = 0.036$) as any component of the oncological treatment. For LD and ED, the mode radiation dose was 45 Gy and 8, 30, and 37.5 Gy, respectively. The mode (median) number of treatments for LD and ED are 28 (28) and 10 (10), respectively. Radiation location for LD

(ED) patients includes 10 (4) patients receiving radiation to the pelvis, 2 (1) to the abdomen, and 2 (6) to the brain. Two patients with ED also received radiation to the liver, 3 to the spine, 2 to the pelvic bones, 1 to the spinal cord, and 1 to the whole body.

None of the patients we looked at received intraoperative radiation therapy (IORT). We further examined who received radiation therapy post-surgery. Patients who underwent surgery with no residual tumor received radiation more often than those who had positive tumor margins post-surgery (16 patients vs. 1 patient, $p = 0.085$); however, the $p$ value is not statistically significant. We also looked at clinical T staging and the receipt of radiation. Nine patients with stage cT3 received radiation and only two patients with cT4b received radiation ($p$ value = 0.06). Those with earlier stages of the disease did not receive radiation. Interestingly, more patients with stage III disease received radiation more often than those with stage IV disease. Of the 37 patients who received radiation, 14 patients received radiation to the pelvis, 8 to the brain, 3 to the abdomen, 4 to the spine, 2 to the liver, 2 to the pelvic bones, 1 to the whole body, and 1 to the spinal cord. This finding is interesting in that the location of radiation did not follow the same pattern of the most common sites of metastasis. Radiation is associated with a better survival in patients with metastatic disease.

### Indications for Chemotherapy

We looked at indications for chemotherapy, as it was associated with improved survival in both local and metastatic disease. The factors that we looked into include age, gender, stage, CD score, insurance, median income, ethnicity, facility type, and post-surgical margins. Stage and insurance were the two factors that seemed to impact the receipt of chemo. Patients with stage IV disease got chemotherapy more often than patients with stage I–III disease ($p$ value = 0). The receipt of chemo was affected by insurance status as well ($p$ value = 0). Those with private insurance were more likely to receive chemotherapy than those on Medicare.

### Clinicopathological Prognostic Factors

Univariate analysis revealed advancing age ($p < 0.001$), CD > 1 ($p = 0.001$), no insurance ($p = 0.006$), stage III and IV disease ($p = 0.002$ and $p < 0.001$, respectively) as poor prognostic factors for survival, but receipt of chemotherapy ($p < 0.001$), receipt of radiation therapy ($p = 0.032$), receipt of surgery ($p = 0.03$), and Hispanic race ($p = 0.019$) were associated with improved survival. Multivariate Cox regression modeling showed Medicare insurance (HR = 0.488, $p = 0.029$), private insurance (HR = 0.385, $p = 0.002$), Black race (HR = 0.666, $p = 0.025$), Hispanic race (HR = 0.504, $p = 0.040$), and receipt of chemotherapy (HR = 0.413, $p < 0.001$) were associated with improved survival, but CD = 1 (HR = 1.354, $p = 0.040$) and CD ≥ 2 (HR = 2.023, $p < 0.001$) were associated with poorer survival. See Table 2.

### 30-Day Readmission and 30-Day Mortality After Surgery

Since surgery did not seem to be associated with improved survival in both LD and ED, outcomes of surgery, specifically 30-day readmission and mortality rates were analyzed. Of those who received surgery, 7.4% (11) of patients with LD and 6.5% (21) of patients with ED had unplanned readmission within 30 days of discharge. In patients who underwent surgery, 1.3% (2) of patients with LD and 2.8% (9) of patients ED had planned readmission within 30 days of discharge. Zero percent of patients with LD and 0.3% (1) of patients with ED had both planned and unplanned readmission. After surgery was performed, 68.4% (102) of patients with LD and 36.8% (119) of patients with ED did not die within the 30-day mark. 7.4% (11) of patients with LD and 10.8% (35) of patients with ED died < 30 days after surgery was performed.

### Overall Survival

Median overall survival (OS) for patients with ED was significantly lower than for those with LD (4.04 months vs. 21.82 months; $p < 0.001$) see Table 3 and Fig. 1. Multivariate Cox regression analysis showed administration of chemotherapy was associated with improved survival in patients with LD and ED ($p = 0.026$, $p < 0.001$) while surgery was not associated with improved survival in patients with LD or ED ($p = 0.943$, $p = 0.630$). Radiation therapy was associated with improved survival in patients with ED ($p = 0.044$) see Table 4 and Fig. 2.

## Discussion

Small cell carcinoma of the colon is a rare disease, thus lending to a difficulty in finding specific information on the colon alone. Many studies combine both colon and rectum together or group all GI neuroendocrine tumors as one [3]. We have identified 503 patients with SCC of colon from the National Cancer Database (NCDB), making this the largest study available on this topic.

Extrapulmonary small cell carcinoma became increasingly recognized as a separate entity distinct from small cell lung cancer around the 1950s [5]. In 1950, Dukes described an anaplastic type of carcinoma in the rectum composed of polygonal or spheroidal cells devoid of glandular arrangement and mucin production [6]. This may have been the first description of a small cell carcinoma of the colorectal region. At the time, other clinicians had reported a case series

**Table 2** Univariate and multivariate Cox proportional hazard model predicting correlates of overall survival

| Variable | Univariate | | | | Multivariable | | | |
|---|---|---|---|---|---|---|---|---|
| | *p* value | HR | CI low | CI high | *p* value | HR | CI low | CI high |
| Advancing age | < 0.001 | 1.014 | 1.006 | 1.022 | 0.178 | 1.009 | 0.996 | 1.021 |
| Sex | 0.093 | | | | 0.239 | | | |
| Male (ref.) | – | – | – | – | – | – | – | – |
| Female | 0.093 | 0.841 | 0.687 | 1.029 | 0.239 | 0.879 | 0.710 | 1.089 |
| Race | 0.084 | | | | 0.046 | | | |
| White (ref.) | – | – | – | – | – | – | – | – |
| Black | 0.657 | 0.930 | 0.676 | 1.280 | 0.025 | 0.666 | 0.467 | 0.949 |
| Asian | 0.145 | 1.688 | 0.835 | 3.412 | 0.364 | 1.433 | 0.659 | 3.117 |
| Hispanic | 0.019 | 0.486 | 0.266 | 0.888 | 0.040 | 0.504 | 0.262 | 0.969 |
| Other | 0.579 | 0.756 | 0.282 | 2.028 | 0.722 | 0.831 | 0.300 | 2.304 |
| Insurance | 0.006 | | | | 0.012 | | | |
| None (ref.) | – | – | – | – | – | – | – | – |
| Private | 0.092 | 0.624 | 0.361 | 1.080 | 0.002 | 0.385 | 0.212 | 0.700 |
| Medicaid | 0.325 | 0.701 | 0.345 | 1.423 | 0.066 | 0.492 | 0.231 | 1.047 |
| Medicare | 0.721 | 0.906 | 0.526 | 1.560 | 0.029 | 0.488 | 0.256 | 0.930 |
| Other govt | 0.698 | 1.174 | 0.521 | 2.647 | 0.451 | 0.719 | 0.305 | 1.694 |
| Median income | 0.241 | | | | 0.893 | | | |
| < $38,000 (ref.) | – | – | – | – | – | – | – | – |
| $38,000–$47,999 | 0.839 | 0.968 | 0.706 | 1.326 | 0.694 | 0.934 | 0.665 | 1.312 |
| $48,000–$62,999 | 0.261 | 0.833 | 0.606 | 1.145 | 0.522 | 0.892 | 0.629 | 1.265 |
| > $63,000 | 0.093 | 0.77 | 0.567 | 1.045 | 0.468 | 0.885 | 0.636 | 1.231 |
| Comorbidity index | 0.001 | | | | 0.001 | | | |
| Index = 0 (ref.) | – | – | – | – | – | – | – | – |
| Index = 1 | 0.012 | 1.393 | 1.076 | 1.803 | 0.040 | 1.354 | 1.014 | 1.807 |
| Index ≥ 2 | 0.002 | 1.718 | 1.212 | 2.435 | <0.001 | 2.023 | 1.378 | 2.968 |
| Stage | < 0.001 | | | | <0.001 | | | |
| I (ref.) | – | – | – | – | – | – | – | – |
| II | 0.718 | 0.859 | 0.376 | 1.962 | 0.547 | 1.295 | 0.558 | 3.003 |
| III | 0.002 | 2.500 | 1.417 | 4.411 | < 0.001 | 4.065 | 2.248 | 7.352 |
| IV | < 0.001 | 5.791 | 3.407 | 9.841 | < 0.001 | 11.159 | 6.315 | 19.717 |
| Unknown | < 0.008 | 2.456 | 1.265 | 4.771 | 0.004 | 2.747 | 1.375 | 5.487 |
| Components of oncologic therapy | < 0.001 | | | | < 0.001 | | | |
| No treatment (ref.) | – | – | – | – | – | – | – | – |
| Chemotherapy | < 0.001 | 0.558 | 0.439 | 0.710 | < 0.001 | 0.413 | 0.315 | 0.541 |
| Radiation therapy | < 0.001 | 0.436 | 0.282 | 0.674 | < 0.001 | 0.347 | 0.216 | 0.555 |
| Surgery | 0.032 | 0.72 | 0.533 | 0.972 | 0.924 | 1.016 | 0.725 | 1.425 |

with 27 patients diagnosed with small cell carcinoma of the colon and rectum. Their case series suggested that early-stage small cell carcinoma of the colon and rectum treated with surgical resection offered the best long-term survival and cure [7].

In another study, patients with extrapulmonary small cell carcinoma were evaluated from 1974 to 1994. Out of 29 GI cases, 13 patients had small cell colorectal carcinoma. Five patients underwent surgery, and the median time to recurrence after surgical resection was 5 months for those with SCC of colon. Combined cisplatin-based chemotherapy and radiation therapy were used for only one patient with SCC of the rectum. Chemotherapy alone was not evaluated in this study. Radiation therapy was not used for SCC of the colorectum [8]. Since then, 650 cases of SCC of the GI tract have been reported in the literature. Fifty percent of cases occurred in the esophagus and 25% in the large bowel, and the rest in other locations [9].

**Table 3** Kaplan-Meier prediction of overall median survival

| Variable | Univariate | | | |
|---|---|---|---|---|
| | *p* value | OS (months) | 95% CI low | 95% CI high |
| Advancing age | < 0.001 | 1.014 | 1.006 | 1.022 |
| Sex | 0.092 | | | |
| Male | | 6.080 | 4.393 | 7.767 |
| Female | | 7.720 | 5.193 | 10.247 |
| Race | 0.072 | | | |
| White | | 6.310 | 4.884 | 7.736 |
| Black | | 7.030 | 3.381 | 10.679 |
| Hispanic | | 2.630 | 0.000 | 6.552 |
| Asian | | 14.750 | 9.048 | 20.452 |
| Other | | 6.280 | 1.900 | 10.660 |
| Insurance | 0.006 | | | |
| None | | 3.290 | 2.075 | 4.505 |
| Private | | 8.840 | 7.019 | 10.661 |
| Medicaid | | 8.770 | 4.796 | 12.744 |
| Medicare | | 3.810 | 2.834 | 4.786 |
| Other govt | | 2.170 | 0.000 | 8.266 |
| Median Income | 0.238 | | | |
| < $38,000 | | 4.010 | 1.697 | 6.323 |
| $38,000–$47,999 | | 5.880 | 3.293 | 8.467 |
| $48,000–$62,999 | | 6.970 | 4.849 | 9.091 |
| > $63,000 | | 7.200 | 5.401 | 8.999 |
| Comorbidity index | 0.001 | | | |
| Index = 0 | | 7.690 | 6.611 | 8.769 |
| Index = 1 | | 3.090 | 1.622 | 4.558 |
| Index ≥ 2 | | 2.660 | 0.485 | 4.835 |
| Stage | < 0.001 | | | |
| I | | 77.770 | 13.122 | 142.418 |
| II | | 72.180 | – | – |
| III | | 11.010 | 8.696 | 13.324 |
| IV | | 4.040 | 2.967 | 5.113 |
| Unknown | | 9.360 | 0.000 | 19.406 |
| Stage | < 0.001 | | | |
| Local disease | | 21.820 | 13.253 | 30.387 |
| Extensive disease | | 4.040 | 2.967 | 5.113 |
| Unknown | | 9.360 | 0.000 | 19.406 |
| Treatment as a component | | | | |
| Chemotherapy | < 0.001 | 9.360 | 8.466 | 10.254 |
| Radiation therapy | 0.030 | 11.790 | 8.809 | 14.771 |
| Surgery | 0.029 | 7.360 | 5.174 | 9.546 |
| Treatment | < 0.001 | | | |
| No treatment | | 1.350 | 0.733 | 1.967 |
| Chemotherapy only | | 8.380 | 6.907 | 9.853 |
| Radiation therapy only | | 1.450 | 0.000 | 3.290 |
| Surgery only | | 2.400 | 1.261 | 3.539 |
| Surgery and chemotherapy | | 9.890 | 7.887 | 15.053 |
| Chemotherapy and radiation therapy | | 11.470 | 8.522 | 11.258 |
| Surgery, chemotherapy, and radiation | | 18.300 | 0.000 | 36.949 |

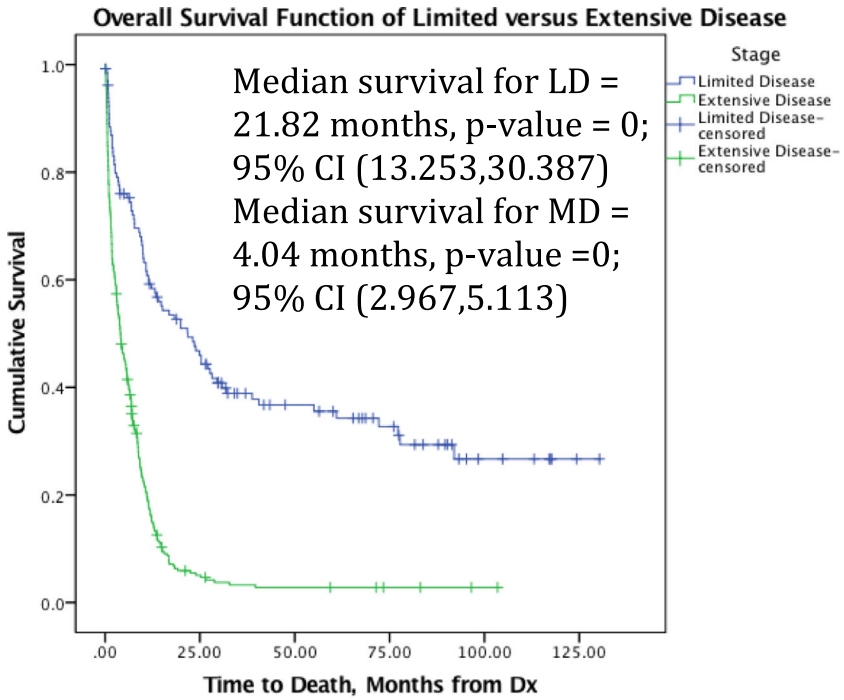


**Fig. 1** Survival curve comparing patients with limited stage disease and extensive stage disease. Median survival was higher in patients with limited stage disease than extensive stage disease

In a review of 75 cases, it was found that the most common site of SCC origin in the colon was the rectum, followed by the cecum, sigmoid colon, transverse colon, and ascending colon (38, 27,17, 12 and 6%, respectively) [10]. More recent studies from MD Anderson have looked at 100 cases of high-grade neuroendocrine tumors in the colorectum and have reported the most common site to be the rectum (40%), followed by the cecum (17%), ascending colon (17%), and rectosigmoid (8%) [11]. This study also reported 89% of the cases to be small cell in histology. Gastrointestinal HGNEC (high-grade neuroendocrine carcinoma) with Ki-67 > 20% is typically treated with surgery and/or chemoradiation when localized and with palliative platinum-based cytotoxic chemotherapy when metastatic.

From our analysis of treatment regimens for patients, surgery and chemotherapy were more often used than radiation therapy. However, chemotherapy seemed to offer improved survival as opposed to surgery. When looking at the data, many of the stage IV patients received surgery and chemotherapy. We found that patients with stage IV disease have a higher comorbidity index than other patients (26 patients with CD score of 2 or above in stage IV disease vs. 15 patients with CD score of 2 or above in stages I, II, and III combined). Since surgery did not appear to be associated with increased

**Table 4** Treatment vs. LD/ED

| | LD | | | | ED | | | |
|---|---|---|---|---|---|---|---|---|
| Variables | *p* value | CI low | CI high | Median survival numbers | *p* value | CI low | CI high | Median survival numbers |
| Received CT | **0.026** | 5.582 | 44.218 | 24.9 | **0** | 6.179 | 8.541 | 7.36 |
| Received RT | 0.1 | 0 | 215.82 | 91.99 | **0.044** | 2.684 | 14.736 | 8.71 |
| Received Surgery | 0.943 | 12.077 | 35.763 | 23.92 | 0.63 | 2.579 | 6.301 | 4.44 |
| Chemo only | 0.207 | 0 | 162.097 | 77.17 | **0.001** | 5.693 | 8.167 | 6.93 |
| Radiation only | – | – | – | – | 0.745 | 0 | 3.29 | 1.45 |
| Surgery only | 0.491 | 4.598 | 49.802 | 27.2 | **0** | 1.164 | 1.856 | 1.51 |
| Chemoradiation | 0.157 | – | – | – | 0.193 | 4.865 | 14.575 | 2.477 |
| Surgeryradiation | – | – | – | – | 0.416 | – | – | 1.94 |
| Chemosurgery | 0.854 | 3.102 | 30.598 | 16.85 | **0.002** | 6.3 | 10.78 | 8.54 |
| No. treatment | **0.027** | 0 | 23.609 | 8.94 | 0 | 0.692 | 1.208 | 0.95 |
| Triple treatment | 0.408 | 0 | 195.967 | 91.99 | 0.084 | 1.291 | 22.289 | 11.79 |

Items in bold are significant at the $p<.05$ level

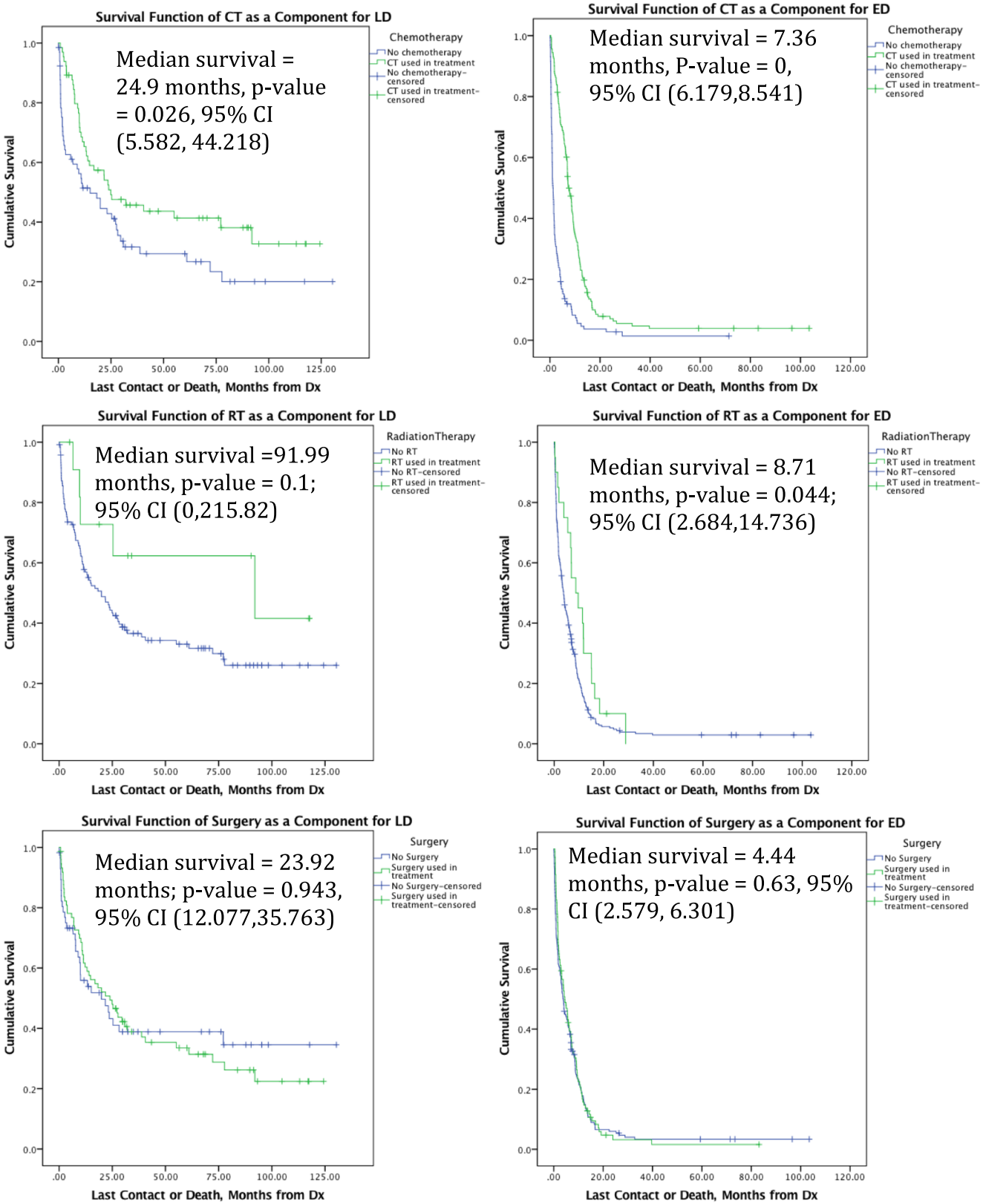


**Fig. 2** Survival curves comparing different treatment modalities to patients with limited stage (LD) vs. extensive stage disease (ED). Chemotherapy (CT) was significant for LD and ED. Radiation (RT) trends towards significance for ED. Surgery was not significant for LD or ED.

survival, we looked into 30-day readmission and mortality rates. Readmission rates within 30 days of surgical procedure were much higher in stage IV patients than the other stages. 6.5% of patients with stage IV disease had unplanned readmission within 30 days of discharge, but only 7.4% of patients with stage I, II, and III disease combined had unplanned readmission upon discharge. Of those who received surgery, 45.1% of patients were alive or died > 30 days after surgery was performed, whereas only 9.3% of patients died less than 30 days after surgery was performed.

In our study, the 30-day readmission rate for our patients was 7.4% in patients with LD and 6.5% in patients with ED ($p$ value = 0.638). The 30-day mortality in our study for patients with LD and ED were 7.4 and 10.8%, respectively ($p$ value = 0.072). The utility of surgery is not clear in patients with ED, so to evaluate, we looked at national standards of 30-day readmission and mortality rates for colon cancer. According to one study, which looked at 149,622 patients with colorectal cancer who underwent colectomy between 1986 and 2005, 30-day morbidity and mortality were 36.5% and 4.2%, respectively. Thirty-day readmission rates increased (1986 to 1990, 10.2%; 1991 to 1995, 10.9%; 1996 to 2000, 12.4%; 2001 to 2005, 13.7%; $p < 0.001$) [12]. In our study, 30-day mortality and 30-day readmissions were not higher than national standards, which possibly may indicate that patients with ED are not having worse outcomes from getting surgery in the first place.

Although only 179 patients out of the 323 patients with ED had data, we found that a large number of patients had metastasis to the liver (71.5%, 128). This was congruent with the findings from other large population-based studies [3, 11]. Therefore, we suggest that it is possible there is utility for a staging CT abdomen/pelvis to include the liver, since many patients are presenting with metastatic disease. Prophylactic cranial irradiation (PCI) is commonly used in managing pulmonary SCC for asymptomatic brain metastasis [13]. However, in our study, we found that only 2.8% of patients with metastatic disease had metastasis to the brain at presentation; therefore, the role of PCI is uncertain.

We evaluated several clinicopathological prognostic factors in this study and found that older age, stage III and IV disease, and having no insurance were associated with reduced survival according to univariate Cox regression analysis. On the other hand, Medicare and private insurance, receipt of chemotherapy in LD and ED, receipt of radiation in ED, and Hispanic race, were better prognostic factors that were associated with increased survival in patients. Most of these findings are congruent with previous studies.

Although our study includes the largest number of SCC colon cases, there are many limitations we encountered. For example, we are not provided with the specific chemotherapy agents used. We further cannot comment on epidemiological factors, symptoms, or the staging workup performed. Also, we are unaware of any biases involved in determining which patients will receive radiation, surgery, or chemotherapy. Additionally, we are not able to evaluate the causes of the unplanned admissions in our study. There are limitations to our interpretations of metastasis as well. The low percentage of brain metastasis could be a result of only a few people receiving MRI imaging of the brain. Alternatively, this data could have been gathered at the time of presentation, and therefore, it is a possibility that some of the patients could have developed brain metastasis later on. Hence, the role of PCI is unclear. One of the limitations to interpreting the receipt of radiation is that the NCDB only records the primary course/round of radiation. Lastly, none of the patients we looked at received intraoperative radiation therapy (IORT). This may be because NCDB was not recording patients who received IORT, or patients with this particular type of colon cancer may not benefit from IORT.

## Conclusions

Our large population-based study confirms many of the findings reported from previous literature. SCC of the colon is an aggressive malignancy with a poor prognosis. Aggressive treatment in the early stage of the disease provides the best chances for improved long-term survival in selected patients. Chemotherapy was associated with improved survival, while surgery was not. With regard to the best strategy for treatment, further studies should be conducted to assess the role of surgery, radiation therapy, and chemotherapy in the treatment of these patients. Novel treatment options like immunotherapy can be further explored upon evaluating the molecular and biological characteristics of the disease.

### Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflicts of interest.

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