Prognostic factors of overall survival and cancer-specific survival in patients with resected early-stage rectal adenocarcinoma: a SEER-based study

Ko-Chao Lee,[1] Kuan-Chih Chung,[2] Hong-Hwa Chen,[1] Chia-Cheng Liu,[3] Chien-Chang Lu[1]

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jim-2017-000496).

[1]Division of Colorectal Surgery, Department of Surgery, Chang Gung Memorial Hospital - Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan
[2]Department of Anesthesiology, Chang Gung Memorial Hospital - Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan
[3]Department of Surgery, Pingtung Christian Hospital, Pingtung, Taiwan

Correspondence to
Dr Kuan-Chih Chung, Department of Anesthesiology, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung 83301, Taiwan; s21096@ms24.hinet.net

K-CL and K-CC contributed equally.

Accepted 16 June 2017

ABSTRACT

The benefits of radiotherapy for colorectal cancer are well documented, but the impact of adjuvant radiotherapy on early-stage rectal adenocarcinoma remains unclear. This study aimed to identify predictors of overall survival (OS) and cancer-specific survival (CSS) in patients with stage II rectal adenocarcinoma treated with preoperative or postoperative radiation therapy. Patients with early-stage rectal adenocarcinoma in the postoperative state were identified using the Surveillance, Epidemiology, and End Results database. The primary endpoints were OS and overall CSS. Stage IIA patients without radiotherapy had significantly lower OS and CSS compared with those who received radiation before or after surgery. Stage IIB patients with radiotherapy before surgery had significantly higher OS and CSS compared with patients in the postoperative or no radiotherapy groups. Patients with signet ring cell carcinoma had the poorest OS among all the groups. Multivariable analysis showed that ethnicity (HR, 0.388, p=0.006) and radiation before surgery (HR, 0.614, p=0.006) were favorable prognostic factors for OS, while age (HR, 1.064, p<0.001), race (HR, 1.599, p=0.041), stage IIB (HR, 3.011, p=0.011), and more than one tumor deposit (TD) (HR, 2.300, p=0.001) were unfavorable prognostic factors for OS. Old age (HR, 1.047, p<0.00 L), stage IIB (HR, 8.619, p=0.005), circumferential resection margin between 0.1 mm and 10 mm (HR, 1.529, p=0.039), and more than one TD (HR, 2.688, p=0.001) were unfavorable prognostic factors for CSS. This population-based study identified predictors of OS and CSS in patients with early-stage resected rectal adenocarcinoma, which may help to guide future management of this patient population.

Significance of this study

What is already known about this subject?

- Early detection of colorectal cancer through routine screening programs was significantly associated with reduced mortality.
- The addition of radiation therapy to surgical care was shown to improve local control as well as overall survival.
- Preoperative radiation therapy has been accepted as the standard of care in patients with stage II–III rectal cancer.

What are the new findings?

- Asian and Pacific Islander ethnicity was a positive predictor of overall survival for patients with early-stage resected rectal adenocarcinoma.
- Stage IIB and presence of more than one tumor deposit were unfavorable prognostic factors for overall survival and cancer-specific survival of patients with early-stage resected rectal adenocarcinoma.
- Stage IIB, circumferential resection margin between 0.1mm and 10mm, and number of tumor deposits were significant prognostic factors for cancer-specific survival of early-stage resected rectal adenocarcinoma.

How might these results change the focus of research or clinical practice?

- Our results from this study expand our understanding of the factors impacting therapeutic outcomes, and will help to guide future management of patients with early-stage resected rectal adenocarcinoma.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common malignancies diagnosed worldwide, with between one and two million new cases diagnosed annually.[1] Studies investigating the molecular pathogenesis of CRC have shown that CRC onset is associated with mutations in specific genes including APC, KRAS, TP53 and DCC.[2] Risk factors for CRC include age (>50 years old), history of CRC or inflammatory bowel disease, obesity, smoking and alcohol consumption.[3] Rectal cancer is the second leading cause of cancer-related deaths in the USA and constitutes approximately 28% of all large bowel carcinomas. Although rectal cancer is more commonly seen in elderly adults, recent studies have shown an increased incidence of rectal cancer in adults <40 years old.[4] A number

To cite: Lee K-C, Chung K-C, Chen H-H, *et al*. *J Investig Med* Published Online First: [*please include* Day Month Year]. doi:10.1136/jim-2017-000496

of clinical trials have reported that early detection of CRC through routine screening programs was significantly associated with reduced mortality.[5 6]

Radical resection including low anterior and abdominoperineal resection was shown to be associated with urinary and sexual dysfunction, low anterior syndrome and the need for a permanent colostomy.[7] The introduction of multimodal treatment approaches and addition of radiation therapy to surgical care were shown to improve local control as well as overall survival (OS).[8 9] Radiotherapy along with concurrent chemotherapy has been used for curative or palliative reasons to treat patients who are medically unfit for surgery, have unresectable tumors, or who may refuse surgery.[10 11] Preoperative radiation therapy has been accepted as the standard of care, and patients with stage II–III rectal cancer are typically treated with neoadjuvant chemoradiation followed by surgical resection with total mesorectal excision and adjuvant chemotherapy.[9 12 13] However, although the benefits of radiotherapy for CRC are well documented, the impact of adjuvant radiotherapy on early-stage CRC remains unclear.[14]

The Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute (NCI) provides information on cancer incidence and survival in the USA. The data are collected from population-based registries that cover approximately 28% of the US population and include patient demographics, primary tumor site, tumor morphology, stage at diagnosis, treatment and follow-up status.[15] The database is also linked to information on Medicare enrollment and Medicare claims along with healthcare utilization and cost information for beneficiaries with cancer in the USA. The SEER database provides an excellent data source for population-level analysis and minimizes discrepancies and biases.[16]

Understanding factors that predict treatment outcomes is a complex and important goal for optimal management of patients with rectal cancer. Our present study aimed to identify predictors of OS and cancer-specific survival (CSS) specifically in patients with stage II rectal adenocarcinoma treated with preoperative or postoperative radiation therapy.

METHODS

Data source

Data for this study were obtained from the SEER Program (www.seer.cancer.gov) research data (1973–2013), NCI, Division of Cancer Control and Population Sciences (DCCPS), Surveillance Research Program, Surveillance Systems Branch, released in April 2016, based on the November 2015 submission.

All of the SEER data are de-identified, and analysis of the data does not require institutional review board approval or informed consent by the study subjects. We obtained permission to access the research data files of the SEER Program from NCI, USA (reference number 15092-Nov2015).

Study population

We accessed data of patients with rectal cancer diagnosed based on specific International Classification of Diseases for Oncology, Third Revision codes of primary site tumors (C20.9). A majority of the tumors were adenocarcinomas, and early stages of rectal adenocarcinoma, denoted as stage 0–II, were separated between January 1, 2010 and December 31, 2013 in the SEER 18 registry. All patients selected were in the postoperative state.

Study variables

The primary endpoints of the present study were OS and overall cancer-specific mortality. OS was defined as the duration from the day of diagnosis until the date of death from any cause. CSS was defined as the duration from the day of diagnosis until the date of cancer-specific death, which was indicated as 'Vital Status' in the SEER database.

Independent variables for comparison included patient demographics (age at diagnosis, sex, race/ethnicity), clinical characteristics of the malignancy (histology, carcinoembryonic antigen (CEA), tumor deposits (TD), circumferential resection margin (CRM), perineural invasion), and treatment modalities (radiotherapy and its sequence relative to surgery).

Statistical analysis

Continuous variables were represented as mean and SD, and categorical data were represented by number (n) and percentage (%). The Kaplan-Meier method with log-rank test was used to compare OS and CSS among groups. A Cox proportional hazard regression model was built to analyze prognostic factors for survival outcomes in patients with early-stage rectal cancer. Variables having a p value <0.05 in the univariate analysis were selected and evaluated by multivariate analysis with stepwise selection. All p values were two-sided and $p<0.05$ was considered statistically significant. All statistical analyses were performed using the statistical software package SPSS V.22.

RESULTS

This study accessed data from the SEER 18 population-based registries for a total of 9757 patients with early-stage resected rectal cancer diagnosed during the years 2010~2013. Histology results showed that a total of 8847 patients (90.7%) had adenocarcinomas, while 328 patients (3.4%) had carcinoid tumors, 18 patients (0.2%) had signet cell carcinoma, and 75 patients (0.8%) had squamous cell carcinomas. This study focused on patients with resected early-stage rectal adenocarcinoma, and the clinical characteristics of this subpopulation are described in table 1. The majority of these patients (80.8%) were white, and 10.1% were Asian/Pacific Islander. The majority of these patients (76.4%) had rectal adenocarcinoma, while 3.3% had mucinous adenocarcinoma and 3% had papillary adenocarcinoma. More than half the patients (52%) had stage I, while 36.3% had stage IIA and 3.6% had stage IIB. Evaluation of CEA levels showed that 67.5% had negative/normal levels of CEA, while 32% had elevated CEA levels. Among the patients who received radiation therapy, 35.2% received preoperative radiation, while 8.6% received radiation after surgery. A total of 1586 patients (17.9%) had more than one TD.

The demographics and clinicopathological characteristics of the entire study population are summarized in online supplementary file 1.

Table 1 Patient demographics and basic clinical characteristics of patients with resected early-stage rectal adenocarcinoma

	n=8847
Age (years)	62.84±12.63
Gender, n (%)	
Male	5171 (58.4%)
Female	3676 (41.6%)
Race, n (%)	
White	7065 (80.8%)
Black	730 (8.3%)
American Indian/Alaska Native	68 (0.8%)
Asian or Pacific Islander	882 (10.1%)
Histology, n (%)	
Adenocarcinoma	6756 (76.4%)
Mucinous adenocarcinoma	288 (3.3%)
Papillary adenocarcinoma	288 (3.0%)
AJCC stage, n (%)	
Stage 0	718 (8.1%)
Stage I	4602 (52.0%)
Stage IIA	3212 (36.3%)
Stage IIB	315 (3.6%)
CEA, n (%)	
Positive/elevated	1474 (32.0%)
Negative/normal	310 (67.5%)
Borderline; undetermined if positive or negative	24 (0.3%)
CRM, n (%)	
Negative	3671 (64.2%)
0.1~10 mm	1594 (27.9%)
10.1~20 mm	245 (4.3%)
20.1~50 mm	174 (3.0%)
>50 mm	36 (0.6%)
Perineural invasion, n (%)	
No perineural invasion present	6982 (95.7%)
Perineural invasion present	316 (4.3%)
Tumor deposits, n (%)	
0	7261 (82.1%)
1+	1586 (17.9%)
Radiation sequence with surgery, n (%)	
No radiation	4888 (55.3%)
Radiation before surgery	3113 (35.2%)
Radiation after surgery	762 (8.6%)
Radiation both before and after surgery	84 (0.9%)

Age is presented as mean and SD, and data are presented as n (%).
AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CRM, circumferential resection margin.

There was a total of 766 deaths (8%) over the course of the study period, and the mean OS was 43 months. There were significant differences in OS (log-rank test, p<0.001) between patients with different types of histology who received different radiation treatment regimens (online supplementary file 2). Patients with stage IIA rectal cancer who did not receive radiation treatment had significantly lower OS and CSS compared with patients who received radiation before surgery, radiation after surgery, and radiation both before and after surgery (figure 1A,C). Patients with stage IIB disease who received radiation before surgery had significantly higher OS and CSS compared with (1) patients who received no radiation therapy, (2) patients who received radiation after surgery and (3) those who received radiation both before and after surgery (figure 1B,D).

The 1-year and 3-year survival rates were 95.7% and 88.2%, respectively, for patients with adenocarcinoma; 99.1% and 92.3%, respectively, for patients with carcinoid tumors; 92.3% and 48.1%, respectively, for patients with signet ring cell carcinoma; 94.5% and 86.3%, respectively, for patients with squamous cell carcinoma; and 94.3% and 86.2%, respectively, for other histological subtypes. Patients with signet ring cell carcinoma had the poorest OS among all the groups, with a median survival of 32 months (online supplementary file 2).

Univariate analysis showed that age, histological classification, American Joint Committee on Cancer (AJCC) stage, CEA levels, CRM, perineural invasion, TD and radiation sequence with surgery were significant prognostic factors for OS and CSS among patients with early-stage rectal adenocarcinoma (p<0.05) (table 2). Multivariate analysis with Cox proportional hazard model showed that age, ethnicity, stage, number of TDs and radiation sequence were independent prognostic factors for OS. Asian or Pacific Islander ethnicity (HR, 0.388, p=0.006) and radiation before surgery (HR, 0.614, p=0.006) were favorable prognostic factors for OS, while age (HR, 1.064, p<0.001), race (HR, 1.599, p=0.041), stage IIB (HR, 3.011, p=0.011), and more than one TD (HR, 2.300, p=0.001) were unfavorable prognostic factors for OS. Old age (HR, 1.047, p<0.00 L), stage IIB (HR, 8.619, p=0.005), CRM between 0.1 mm and 10 mm (HR, 1.529, p=0.039), and more than one TD (2.688, p=0.001) were unfavorable prognostic factors for CSS (table 3).

DISCUSSION

This retrospective study accessed data from the SEER 18 population-based registries for 9757 patients with early-stage resected rectal cancer to evaluate the effect of postoperative radiation therapy for early-stage rectal adenocarcinoma. Our data showed that older age, Asian and Pacific Islander ethnicity, stage IIB, and number of TDs were significant prognostic factors of OS in these patients, while older age, stage IIB, CRM between 0.1 mm and 10 mm, and number of TDs were significant prognostic factors for CSS.

Preoperative short course radiation therapy has been shown to be safe and effective, and has now been included in the recent updates to the national guidelines as a treatment option for rectal cancer.[17] Radiation therapy has been shown to confer a survival advantage in patients with rectal small cell carcinoma,[16] and neoadjuvant radiotherapy with either short-course or long-course radiotherapy was superior to adjuvant radiotherapy for stage II/III rectal cancer.[9] A recent population-based study of 6752 patients with rectal adenocarcinoma reported that the 5-year OS in patients who received radiation therapy only was 56%, while the 5-year OS in patients who received radiation therapy followed by surgery was 80%.[18] Preoperative radiotherapy has been used to downstage locally advanced rectal tumors.[19] Interestingly, a recent study showed that elimination of neoadjuvant radiation therapy for select patients with stage II and stage II rectal adenocarcinomas was significantly associated

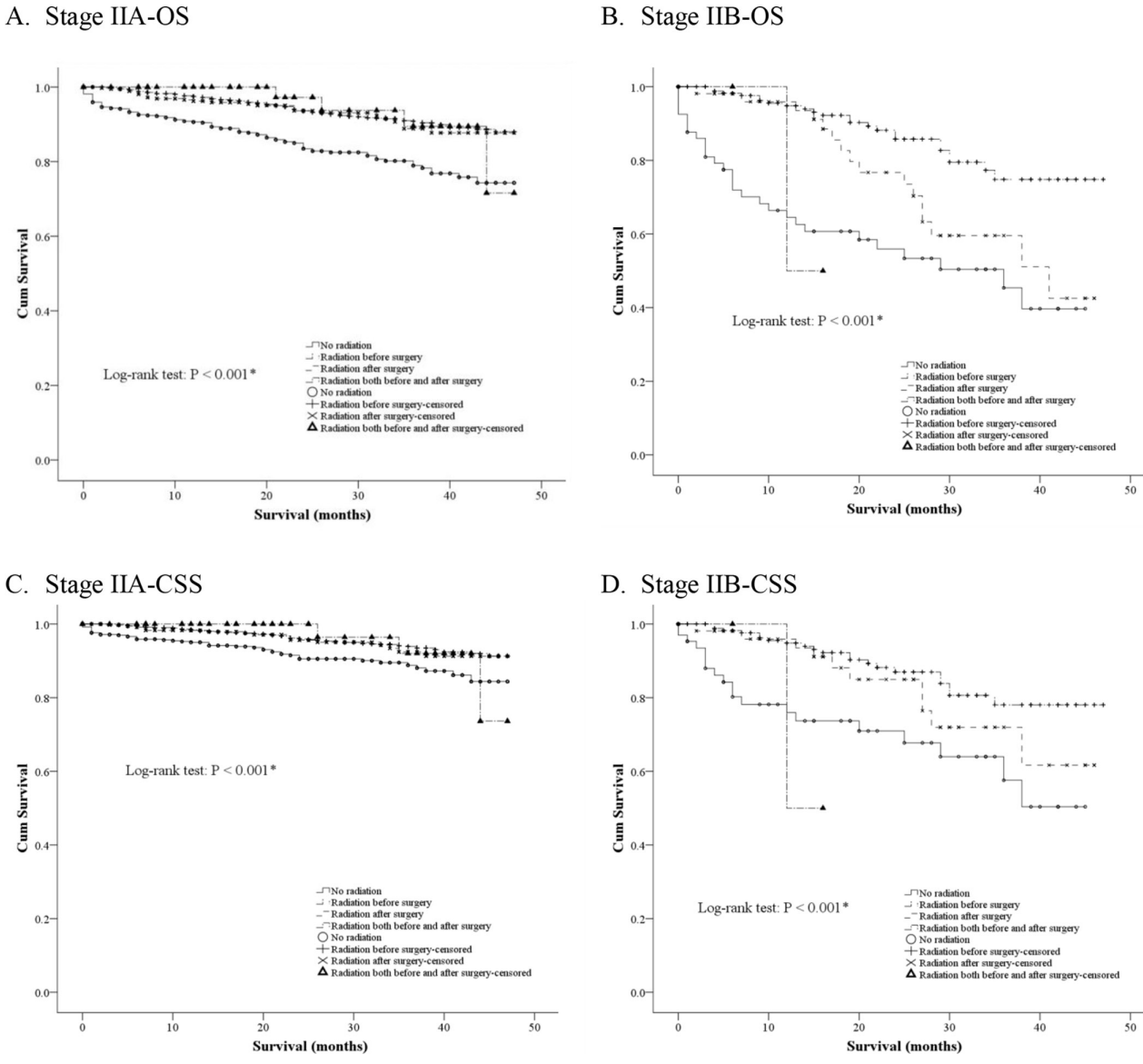

Figure 1 Kaplan-Meier curves for OS and CSS of patients with AJCC stage IIA and IIB rectal adenocarcinoma with or without radiotherapy (n=8847). AJCC, American Joint Committee on Cancer; CSS, cancer-specific survival; OS, overall survival.

with worse outcomes.[20] A meta-analysis of 22 randomized trials that compared preoperative, postoperative, and no radiotherapy in 8507 patients with rectal cancer showed a significantly reduced risk of local recurrence, and improved OS with both preoperative as well as postoperative radiotherapy, although the effect was greater with preoperative radiotherapy.[14] Our present study was consistent with these data, and showed that patients with stage IIA rectal cancer who received no radiation treatment had significantly lower OS and CSS compared with patients who received preoperative radiation, postoperative radiation, or both. Additionally, stage IIB patients who received radiation preoperative radiation had significantly higher OS and CSS compared with patients who received no radiation therapy, patients who received postoperative radiation, and those who received both preoperative and postoperative radiation. Our multivariate analysis showed that radiation therapy administered before surgery was a significant positive predictor of OS in patients with early-stage rectal adenocarcinoma. It will be interesting to further investigate the impact of tumor stage on treatment outcome after neoadjuvant radiation therapy.

A number of studies have reported an increasing incidence of CRC among patients <40 years old, who are typically below the age of routine screening.[4] While the risk of lymph node metastasis was shown to decrease with increasing age,[21 22] younger patients had more biologically aggressive tumors including more signet cell differentiation and perineural invasion.[22 23] Increasing age was also shown to be associated with higher 1-year overall as well as cancer-specific mortality.[24] In contrast, other data showed that CRC patients >65 years old had increased length of hospital stay and mortality compared with patients <65 years old.[25] Our present data showed that older age was an independent negative predictor of OS as well as CSS in patients with early-stage rectal adenocarcinoma.

Table 2 Univariate Cox proportional hazard model for survival outcomes in patients with early-stage rectal adenocarcinoma (n=8847)

	OS		CSS	
	Crude HR (95% CI)	p Value	Crude HR (95% CI)	p Value
Diagnostic age	1.068 (1.061 to 1.075)	**<0.001***	1.048 (1.039 to 1.058)	**<0.001***
Gender				
Female versus male	0.934 (0.802 to 1.088)	0.378	0.889 (0.713 to 1.109)	0.296
Race				
Black versus white	1.400 (1.101 to 1.779)	**0.006***	1.362 (0.957 to 1.938)	0.086
American Indian/Alaska Native versus white	0.937 (0.389 to 2.260)	0.885	1.968 (0.812 to 4.769)	0.134
Asian or Pacific Islander versus white	0.767 (0.577 to 1.019)	0.067	0.870 (0.589 to 1.285)	0.484
Histological classification				
Mucinous adenocarcinoma versus adenocarcinoma	1.805 (1.309 to 2.490)	**<0.001***	2.718 (1.851 to 3.991)	**<0.001***
Papillary adenocarcinoma versus adenocarcinoma	0.871 (0.715 to 1.060)	0.168	0.709 (0.521 to 0.965)	**0.029***
AJCC stage				
Stage I versus stage 0	1.220 (0.885 to 1.683)	0.226	1.281 (0.735 to 2.233)	0.382
Stage IIA versus stage 0	1.352 (0.975 to 1.873)	0.070	2.449 (1.417 to 4.233)	**0.001***
Stage IIB versus stage 0	4.317 (2.942 to 6.337)	**<0.001***	9.648 (5.340 to 17.431)	**<0.001***
CEA				
Negative/normal versus positive/elevated	0.661 (0.535 to 0.815)	**<0.001***	0.573 (0.430 to 0.765)	**<0.001***
Borderline versus positive/elevated	0.640 (0.159 to 2.583)	0.531	1.120 (0.275 to 4.553)	0.874
CRM				
0.1~10 mm versus negative	1.593 (1.307 to 1.941)	**<0.001***	1.910 (1.439 to 2.535)	**<0.001***
10.1~20 mm versus negative	0.540 (0.267 to 1.092)	0.087	0.616 (0.227 to 1.672)	0.341
20.1~50 mm versus negative	0.678 (0.320 to 1.438)	0.312	0.664 (0.211 to 2.092)	0.484
>50 mm versus negative	0.395 (0.055 to 2.817)	0.354	0.897 (0.125 to 6.429)	0.914
Perineural invasion				
No perineural invasion present versus perineural invasion	1.639 (1.169 to 2.298)	**0.004***	2.595 (1.730 to 3.892)	**<0.001***
Tumor deposits				
1+ versus 0	1.456 (1.222 to 1.735)	**<0.001***	1.731 (1.359 to 2.205)	**<0.001***
Radiation sequence with surgery				
Radiation before surgery versus no radiation	0.656 (0.553 to 0.779)	**<0.001***	1.185 (0.937 to 1.498)	0.156
Radiation after surgery versus no radiation	0.959 (0.741 to 1.241)	0.752	1.668 (1.191 to 2.338)	**0.003***
Radiation both before and after surgery versus no radiation	0.833 (0.395 to 1.758)	0.632	1.925 (0.852 to 4.351)	0.115

*Indicates statistical significance, p<0.05.
AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CRM, circumferential resection margin; CSS, cancer-specific survival; OS, overall survival.

Population-based data extracted from the SEER database showed large disparities in CRC incidence among racial minorities/ethnic groups compared with non-Hispanic whites in the USA, and that the incidence of CRC was significantly higher among the minority groups <50 years old.[26] Race has also been shown to impact OS in patients with CRC, and African–Americans have been shown to have poorer OS rates as well as treatment efficacy compared with non-African–Americans.[27 28] Our present data indicated that race was an important prognostic factor, and Asian and Pacific Islander ethnicity was a positive predictor of OS in our study population.

The AJCC Staging Manual (7th Edition) defines TDs as isolated tumor foci in the pericolic or perirectal fat or in the adjacent mesentery away from the leading edge of the tumor and with no evidence of residual lymph node tissue. The presence of TDs and perineural invasion was shown to be associated with poorer OS and disease-free outcomes and increased recurrence rates.[29 30] Although our present analysis indicated that perineural invasion did not significantly impact outcomes, we showed that the presence of more than one TD was an unfavorable prognostic factor for OS as well as CSS in patients with early-stage rectal adenocarcinoma.

Data from a large population-based study showed that patients with CRC with elevated baseline CEA levels had an increased risk of CRC-specific death compared with patients without elevated baseline CEA levels.[31] In our present study, although low CEA levels were a favorable prognostic factor for OS as well as CSS by univariate analysis, this was not the case in our multivariate analysis.

Signet ring cell adenocarcinoma is characterized by prominent intracytoplasmic mucin accumulation in >50% of the tumor cells, along with a deficiency of cell-to-cell adhesion molecules.[32] It has been reported that signet cell histology was significantly associated with worse outcomes.[33] These data were consistent with our present analysis, which showed that patients with signet cell adenocarcinoma had the poorest survival among all the subgroups, with a 3-year survival of only 48.1%.

Successful clinical management of patients with rectal cancer is dependent on appropriate selection of patients based on predictors of treatment response. Our present study identified a number of factors that were positive

Table 3 Multivariate Cox proportional hazard model for survival outcomes in patients with early-stage rectal adenocarcinoma (n=8847)

	OS		CSS	
	Adjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Diagnostic age	1.064 (1.051 to 1.077)	<0.001*	1.047 (1.030 to 1.065)	<0.001*
Gender				
Female versus male				
Race				
Black versus white	1.599 (1.019 to 2.510)	0.041*		
American Indian/Alaska Native versus white	1.614 (0.510 to 5.107)	0.415		
Asian or Pacific Islander versus white	0.388 (0.198 to 0.760)	0.006*		
Histological classification				
Mucinous adenocarcinoma versus adenocarcinoma	0.952 (0.481 to 1.884)	0.888	0.882 (0.352 to 2.208)	0.788
Papillary adenocarcinoma versus adenocarcinoma	1.073 (0.699 to 1.648)	0.746	1.081 (0.561 to 2.085)	0.816
AJCC stage				
Stage I versus stage 0	0.877 (0.420 to 1.834)	0.728	1.093 (0.257 to 4.652)	0.904
Stage IIA versus stage 0	0.978 (0.453 to 2.112)	0.955	2.013 (0.465 to 8.715)	0.349
Stage IIB versus stage 0	3.011 (1.288 to 7.039)	0.011*	8.619 (1.897 to 39.153)	0.005*
CEA				
Negative/normal versus positive/elevated	0.792 (0.595 to 1.054)	0.110	0.743 (0.500 to 1.103)	0.140
Borderline versus positive/elevated	0.767 (0.106 to 5.552)	0.793	1.189 (0.162 to 8.741)	0.865
CRM				
0.1~10 mm versus negative	1.325 (0.994 to 1.766)	0.055	1.529 (1.022 to 2.286)	0.039*
10.1~20 mm versus negative	0.821 (0.398 to 1.694)	0.593	0.768 (0.274 to 2.152)	0.616
20.1~50 mm versus negative	0.541 (0.171 to 1.715)	0.297	0.370 (0.051 to 2.695)	0.327
>50 mm versus negative	1.132 (0.157 to 8.180)	0.902	2.542 (0.347 to 18.624)	0.358
Perineural invasion				
No perineural invasion present versus perineural invasion	1.465 (0.871 to 2.465)	0.150	1.878 (0.993 to 3.552)	0.053
Tumor deposits				
1+ versus 0	2.300 (1.474 to 3.591)	<0.001*	2.688 (1.510 to 4.786)	0.001*
Radiation sequence with surgery				
Radiation before surgery versus no radiation	0.614 (0.435 to 0.868)	0.006*	0.637 (0.396 to 1.025)	0.063
Radiation after surgery versus no radiation	0.860 (0.522 to 1.417)	0.554	0.707 (0.349 to 1.429)	0.334
Radiation both before and after surgery versus no radiation	1.573 (0.487 to 5.078)	0.449	2.593 (0.775 to 8.677)	0.122

*Indicates statistical significance, p<0.05.
AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CRM, circumferential resection margin; CSS, cancer-specific survival; OS, overall survival.

and negative predictors of OS and CSS in a large sample size of patients with early-stage resected rectal adenocarcinoma. The most important limitation of this study was that the SEER database did not include chemotherapy records or information about evaluations after initial therapy. However, our results from this study expand our understanding of the factors impacting therapeutic outcomes and will help to guide future management of this patient population.

Acknowledgements The authors acknowledge the efforts of the Surveillance, Epidemiology, and End Results (SEER) Program Tumor Registries in the creation of the SEER database. The interpretation and reporting of these data are the sole responsibility of the authors.

Contributors K-CL: guarantor of integrity of the entire study, study concepts, study design, definition of intellectual content, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review. K-CC: guarantor of integrity of the entire study, study concepts, study design, definition of intellectual content, clinical studies, experimental studies, data acquisition, data analysis, statistical analysis, manuscript preparation, manuscript editing, manuscript review. H-HC: literature research, clinical studies, experimental studies, data analysis, statistical analysis, manuscript preparation, manuscript editing. Chia-CL: literature research, clinical studies, data analysis, statistical analysis, manuscript review. Chie-CL: literature research, clinical studies, data analysis, statistical analysis, manuscript review.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Brody H. Colorectal cancer. *Nature* 2015;521:S1.
2 Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. *Cell* 1990;61:759–67.
3 Mármol I, Sánchez-de-Diego C, Pradilla Dieste A, *et al*. Colorectal Carcinoma: A General Overview and Future Perspectives in Colorectal Cancer. *Int J Mol Sci* 2017;18:197.
4 Meyer JE, Narang T, Schnoll-Sussman FH, *et al*. Increasing incidence of rectal cancer in patients aged younger than 40 years: an analysis of the surveillance, epidemiology, and end results database. *Cancer* 2010;116:4354–9.
5 Hardcastle JD, Chamberlain JO, Robinson MH, *et al*. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472–7.
6 Kronborg O, Fenger C, Olsen J, *et al*. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996;348:1467–71.
7 Bleier JI, Maykel JA. Outcomes following proctectomy. *Surg Clin North Am* 2013;93:89–106.

8 Folkesson J, Birgisson H, Pahlman L, *et al*. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005;23:5644–50.
9 Häfner MF, Debus J. Radiotherapy for Colorectal Cancer: Current Standards and Future Perspectives. *Visc Med* 2016;32:172–7.
10 Tchelebi L, Guirguis A, Ashamalla H. Rectal melanoma: epidemiology, prognosis, and role of adjuvant radiation therapy. *J Cancer Res Clin Oncol* 2016;142:2569–75.
11 Wang Y, Cummings B, Catton P, *et al*. Primary radical external beam radiotherapy of rectal adenocarcinoma: long term outcome of 271 patients. *Radiother Oncol* 2005;77:126–32.
12 Network NCC. Rectal cancer. 2016. http://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf (accessed 20 Feb 2017).
13 Fleming M, Ravula S, Tatishchev SF, *et al*. Colorectal carcinoma: Pathologic aspects. *J Gastrointest Oncol* 2012;3:153–73.
14 Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001;358:1291–304.
15 Surveillance EaERS. Overview of the SEER program. https://seer.cancer.gov/about/overview.html (accessed 16 Feb 2017).
16 Modrek AS, Hsu HC, Leichman CG, *et al*. Radiation therapy improves survival in rectal small cell cancer - Analysis of Surveillance Epidemiology and End Results (SEER) data. *Radiat Oncol* 2015;10:101.
17 Roy A, Mahasittiwat P, Weiner AA, *et al*. Preoperative short-course radiation therapy for rectal cancer provides excellent disease control and toxicity: Results from a single US institution. *Pract Radiat Oncol* 2017;7:e51–8.
18 Abrams MJ, Koffer PP, Leonard KL. The Emerging Non-operative Management of Non-metastatic Rectal Cancer: A Population Analysis. *Anticancer Res* 2016;36:1699–702.
19 Rega D, Pecori B, Scala D, *et al*. Evaluation of Tumor Response after Short-Course Radiotherapy and Delayed Surgery for Rectal Cancer. *PLoS One* 2016;11:e0160732.
20 Cassidy RJ, Liu Y, Patel K, *et al*. Can we eliminate neoadjuvant chemoradiotherapy in favor of neoadjuvant multiagent chemotherapy for select stage II/III rectal adenocarcinomas: Analysis of the National Cancer Data base. *Cancer* 2017;123:783–93.
21 Brunner W, Widmann B, Marti L, *et al*. Predictors for regional lymph node metastasis in T1 rectal cancer: a population-based SEER analysis. *Surg Endosc* 2016;30:4405–15.
22 Meyer JE, Cohen SJ, Ruth KJ, *et al*. Young Age Increases Risk of Lymph Node Positivity in Early-Stage Rectal Cancer. *J Natl Cancer Inst* 2016;108:djv284.
23 Tawadros PS, Paquette IM, Hanly AM, *et al*. Adenocarcinoma of the rectum in patients under age 40 is increasing: impact of signet-ring cell histology. *Dis Colon Rectum* 2015;58:474–8.
24 Aquina CT, Mohile SG, Tejani MA, *et al*. The impact of age on complications, survival, and cause of death following colon cancer surgery. *Br J Cancer* 2017;116:389–97.
25 Caglar Bilgin B, Kahramanca S, Akin T, *et al*. Factors influencing cost, length of hospital stay and mortality in colorectal Cancer. *J Buon* 2015;20:1023–9.
26 Rahman R, Schmaltz C, Jackson CS, *et al*. Increased risk for colorectal cancer under age 50 in racial and ethnic minorities living in the United States. *Cancer Med* 2015;4:1863–70.
27 Wallace K, Hill EG, Lewin DN, *et al*. Racial disparities in advanced-stage colorectal cancer survival. *Cancer Causes Control* 2013;24:463–71.
28 Sanoff HK, Sargent DJ, Green EM, *et al*. Racial differences in advanced colorectal cancer outcomes and pharmacogenetics: a subgroup analysis of a large randomized clinical trial. *J Clin Oncol* 2009;27:4109–15.
29 Nagtegaal ID, Quirke P. Colorectal tumour deposits in the mesorectum and pericolon; a critical review. *Histopathology* 2007;51:141–9.
30 Mayo E, Llanos AA, Yi X, *et al*. Prognostic value of tumour deposit and perineural invasion status in colorectal cancer patients: a SEER-based population study. *Histopathology* 2016;69:230–8.
31 Dawood S, Sirohi B, Shrikhande SV, *et al*. Potential Prognostic Impact of Baseline CEA Level and Surgery of Primary Tumor Among Patients with Synchronous Stage IV Colorectal Cancer: A Large Population Based Study. *Indian J Surg Oncol* 2015;6:198–206.
32 Sung CO, Seo JW, Kim KM, *et al*. Clinical significance of signet-ring cells in colorectal mucinous adenocarcinoma. *Mod Pathol* 2008;21:1533–41.
33 Pande R, Sunga A, Levea C, *et al*. Significance of signet-ring cells in patients with colorectal cancer. *Dis Colon Rectum* 2008;51:50–5.