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ORIGINAL CONTRIBUTION

The Impact of Chronic Kidney Disease in Patients With Locally Advanced Rectal Cancer Treated With Neoadjuvant Chemoradiation

Shaan Dudani, M.B. Ch.B.[1] • Horia Marginean, M.S., M.D.[1] • Joanna Gotfrit, M.D.[1]
Patricia A. Tang, M.D.[2] • Jose Gerard Monzon, M.D., Ph.D.[2] • Kristopher Dennis, M.D., Ph.D.[1]
Hagen F. Kennecke, M.D.[3] • Erin D. Powell, M.D.[4] • Sam Babak, M.D.[2]
Winson Y. Cheung, M.P.H., M.D.[3] • Michael M. Vickers, M.P.H., M.D.[1]

1 The Ottawa Hospital Cancer Centre/University of Ottawa, Ottawa, Ontario, Canada
2 Alberta Health Services/University of Calgary, Calgary, Alberta, Canada
3 British Columbia Cancer Agency, Vancouver, British Columbia, Canada
4 Dr. H Bliss Murphy Cancer Centre, St. John's, Newfoundland, Canada

See "Editorial" on page 1441.

BACKGROUND: Patients with chronic kidney disease are commonly excluded from clinical trials. The impact of chronic kidney disease on outcomes in patients with locally advanced rectal cancer has not been previously studied.

OBJECTIVE: This study aimed to investigate the impact of chronic kidney disease on outcomes in patients with locally advanced rectal cancer.

DESIGN: This is a multi-institutional, retrospective cohort study.

SETTINGS: This study was conducted at academic and community cancer centers participating in the Canadian Health Outcomes Research Database Consortium Rectal Cancer Database.

PATIENTS: Consecutive patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation before curative-intent surgery from 2005 to 2013 were selected.

MAIN OUTCOME MEASURES: Disease-free survival, overall survival, pathologic complete response, and neoadjuvant chemotherapy/radiotherapy completion rate were the primary outcomes measured.

RESULTS: A total of 1254 patients were included. Median age was 62, and 29%/69% had clinical stage II and III disease. Median estimated creatinine clearance was 93 mL/min, with 11% <60 mL/min (n = 136). There was no significant difference in the completion rate of neoadjuvant chemotherapy (82% vs 85%, $p = 0.36$) or radiotherapy (93% vs 95%, $p = 0.45$) between patients with and without chronic kidney disease. Patients with chronic kidney disease were less likely to receive adjuvant chemotherapy (63% vs 77%, $p < 0.01$). On multivariate analysis, patients with chronic kidney disease had decreased disease-free survival (HR, 1.37; 95% CI, 1.03–1.82; $p = 0.03$) but not overall survival (HR, 1.23; 95% CI, 0.88–1.75; $p = 0.23$) or pathologic complete response (OR, 0.83; 95% CI, 0.50–1.39; $p = 0.71$).

LIMITATIONS: This study was limited by its retrospective design and by limited events for overall survival analysis.

CONCLUSIONS: In patients with locally advanced rectal cancer undergoing neoadjuvant chemoradiation, baseline chronic kidney disease was associated with less use of adjuvant chemotherapy and decreased disease-free survival. Chronic kidney disease was not independently associated

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Ethics approval and consent to participate: This study was approved by the University of British Columbia BC Cancer Research Ethics Board, The University of Ottawa Research Ethics Board, and the Alberta Cancer Research Ethics committee (ACREC). For all jurisdictions, informed consent was waived by the respective research ethics boards.[11]

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Correspondence: Shaan Dudani, M.B.Ch.B., William Osler Health System – Brampton Civic Hospital, 2100 Bovaird Dr E, Brampton, Ontario L6R 3J7, Canada. E-mail: shaan.dudani@williamoslerhs.ca

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with neoadjuvant chemotherapy/radiotherapy completion rate, pathologic complete response, or overall survival. These data suggest that patients with locally advanced rectal cancer with chronic kidney disease may have distinct outcomes and, accordingly, the results of landmark clinical trials may not be generalizable to this population. See **Video Abstract** at http://links.lww.com/DCR/B694.

LA REPERCUSIÓN DE LA ENFERMEDAD RENAL CRÓNICA EN PACIENTES CON CÁNCER DE RECTO LOCALMENTE AVANZADO TRATADOS CON QUIMIORRADIOTERAPIA NEOADYUVANTE

ANTECEDENTES: Los pacientes con enfermedad renal crónica generalmente se excluyen de los ensayos clínicos. La repercusión de la enfermedad renal crónica en el desenlace en pacientes con cáncer de recto localmente avanzado no se ha estudiado previamente.

OBJETIVO: Investigar la repercusión de la enfermedad renal crónica en los desenlaces en pacientes con cáncer de recto localmente avanzado.

DISEÑO: Estudio de cohorte retrospectivo multiinstitucional.

ESCENARIO: Centros oncológicos académicos y comunitarios que participan en la base de datos de cáncer rectal del consorcio CHORD.

PACIENTES: Pacientes consecutivos con cáncer de recto localmente avanzado, tratados con quimiorradioterapia neoadyuvante, previa a la cirugía con intención curativa del 2005 al 2013.

PRINCIPALES VARIABLES EVALUADAS: Sobrevida libre de enfermedad, sobrevida global, respuesta patológica completa, tasa de conclusión de quimioterapia / radioterapia neoadyuvante.

RESULTADOS: Se incluyeron 1254 pacientes. El promedio de edad fue de 62, y el 29% / 69% tenían enfermedad en estadio clínico II y III, respectivamente. El promedio de la depuración de creatinina estimada fue de 93 mililitros / minuto, con un 11% <60 mililitros / minuto (n = 136). No hubo diferencias significativas en la tasa de conclusión de la quimioterapia neoadyuvante (82% vs 85%, p = 0,36) o radioterapia (93% vs 95%, p = 0,45) entre pacientes con y sin enfermedad renal crónica. Los pacientes con enfermedad renal crónica tenían menos probabilidades de recibir quimioterapia adyuvante (63% contra el 77%, p <0,01). En el análisis multivariado, los pacientes con enfermedad renal crónica tenían una sobrevida libre de enfermedad menor (HR 1,37, IC 95% 1,03-1,82, p = 0,03) pero no en la sobrevida global (HR 1,23, IC 95% 0,88-1,75, p = 0,23) o respuesta patológica completa (OR 0,83, IC 95% 0,50-1,39, p = 0,71).

LIMITACIONES: Diseño retrospectivo y acontecimientos limitados para el análisis de sobrevida global.

CONCLUSIONES: En pacientes con cáncer de recto localmente avanzado tratados con quimiorradioterapia neoadyuvante, la enfermedad renal crónica de base se asoció con un menor uso de quimioterapia adyuvante y una menor sobrevida libre de enfermedad. La enfermedad renal crónica no se asoció de forma independiente con la tasa de conclusión de la quimioterapia / radioterapia neoadyuvante, la respuesta patológica completa o la sobrevida global. Estos datos sugieren que los pacientes con cáncer de recto localmente avanzado con enfermedad renal crónica pueden tener resultados distintos y, en consecuencia, los resultados de los ensayos clínicos de referencia pueden no ser generalizables a esta población. Consulte **Video Resumen** en http://links.lww.com/DCR/B694. *(Traducción—Dr. Lisbeth Alarcon-Bernes)*

KEY WORDS: Disease-free survival; Overall survival; Pathologic complete response; Renal impairment; Toxicity.

Chronic kidney disease (CKD) and cancer are common illnesses with advancing age, and a complex, bidirectional relationship exists between them. Chronic kidney disease, conventionally defined as having an estimated glomerular filtration rate (eGFR) of <60 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ and/or kidney damage for 3 or more months, affects approximately 50% of patients older than 70 years in the United States,[1,2] and has been reported to occur in 12% to 38% of patients with cancer.[3–7] Although most patients who have cancer with CKD have preexisting renal disease that develops independently of their neoplastic process, CKD can also occur in patients who have cancer as a direct result of their malignancy or indirectly through the adverse effects of therapies.[8] Conversely, CKD may be an independent risk factor for developing cancer, including colorectal cancer, and has also been demonstrated to be an independent prognostic factor in select cancers.[3,4,6,9] Finally, CKD is an important comorbidity and clinical consideration in most patients with cancer, because impaired renal function may influence drug tolerance and/or the efficacy of many cancer-directed and supportive therapies, and may also impair the diagnosis and monitoring of cancer.[9]

Given the multitude of mechanisms in which CKD may affect the clinical course of patients with cancer, clinical trials often mandate an eGFR of ≥60 mL/min for inclusion.[7] As a result, patients with CKD, in general, are underrepresented and/or excluded from clinical trials, and it is unclear whether the results of such studies can be safely and validly extrapolated to this important and increasingly prevalent patient population. In light of the unique clinical considerations involved in treating patients with concomitant cancer and CKD, it is important to demonstrate

the tolerability and effectiveness of standard-of-care treatments in this population to provide data that may support or refute current practices.

Locally advanced rectal cancer is an example of a malignancy in which there are minimal data regarding outcomes of patients with concomitant CKD. In this setting, the landmark German Rectal Cancer Study that established neoadjuvant chemoradiation (nCRT) followed by total mesorectal excision (TME) as a standard of care excluded patients with any comorbidity that contraindicated the use of (neo)adjuvant chemoradiotherapy, including "kidney failure" (specific eGFR cutoff not reported).[10] To our knowledge, the impact of CKD on outcomes in this patient population has not previously been studied. We performed a multi-institution review of patients with locally advanced rectal cancer (LARC) treated with nCRT followed by TME to assess the incidence and effect of CKD on treatment tolerance, response, and outcomes in this population.

MATERIALS AND METHODS

Study Design and Patient Selection

Study design has been described in previous publications from the Canadian Health Outcomes Research Database (CHORD) Consortium and is included in Table 1.[11,12]

Table 1. Study design as described from the Canadian Health Outcomes Research Database (CHORD) Consortium with two exceptions for the present study.[11,12]

"Patients were identified and data were extracted from the CHORD Consortium's Rectal Cancer Database, which is a national, multi-institutional registry of consecutive locally advanced rectal cancer patients who have undergone nCRT followed by curative intent-surgery from five academic (British Columbia Cancer Agency, Cross Cancer Institute, Dr. H Bliss Murphy Cancer Centre, The Ottawa Hospital Cancer Centre, Tom Baker Cancer Centre) and four community (Central Alberta Cancer Centre, Grand Prairie Cancer Centre, Jack Ady Cancer Centre, Margery E. Yuill Cancer Centre) cancer centres in Canada.

Patients were eligible for inclusion if they had: pathologically-confirmed rectal adenocarcinoma; clinical stage II or III disease as per the seventh edition of the American Joint Commission on Cancer (AJCC) staging system[12]; underwent long-course nCRT followed by curative intent surgery between 2005-2013; baseline creatinine available; documented absence of metastases (confirmed by CT or MRI of the abdomen and either chest radiograph or CT thorax). Patients were excluded if they had prior treatments for rectal cancer, evidence of metastatic disease, did not receive surgery, or received neoadjuvant radiation alone."

Exceptions for the Present Study

In the present study, data from a fifth academic center in Canada were obtained (Dr. H Bliss Murphy Cancer Centre).

In the present study, baseline hematologic parameters were not required for inclusion. Instead, baseline creatinine measurement was part of the inclusion criteria."

nCRT = neoadjuvant chemoradiation.

For the purposes of this study, data regarding patient demographics, baseline characteristics, renal function, tumor/treatment details and outcomes were extracted from the database.

Renal Function

Baseline renal function was estimated using the Cockroft-Gault equation. This equation estimates creatinine clearance based on age, sex, body weight, and serum creatinine.[13] Chronic kidney disease was defined as estimated creatinine clearance (CrCl) <60 mL/min, because this is the most widely accepted cutoff value and has commonly been used to screen patients for eligibility in clinical trials.[1,7] All creatinine values were obtained within 4 weeks before and 2 weeks after initiating nCRT. Patients who developed renal dysfunction more than 2 weeks after initiating nCRT were not classified as having baseline CKD.

Statistical Analysis

Patient demographics and baseline characteristics are reported using proportions (%) for categorical variables and medians (range) for continuous variables. Outcomes of interest were disease-free survival (DFS), overall survival (OS), pathologic complete response (pCR) rate, and neoadjuvant chemotherapy (nCT)/radiotherapy (nRT) completion rate. Completion of nCT was defined as completing all planned cycles without dose reduction and/or delay. Completion of nRT was defined as having received the total planned radiation dosage. Receipt of adjuvant chemotherapy was defined as receiving one or more cycles of postoperative chemotherapy.

"DFS was defined as time from diagnosis to first event (local recurrence, distant recurrence, or death from any cause) or censored at the date of last follow-up. OS was defined as the time from diagnosis to death from any cause or censored at the date of last follow-up. pCR was defined as the absence of any residual tumour cells on post-operative histologic evaluation of the rectal surgical specimen."[11]

DFS and OS were evaluated using the Kaplan-Meier method. Univariate and multivariate logistic regression and Cox proportional hazard models were used to assess for an association between baseline variables (selected a priori) and outcomes of interest. Factors that were significant at the 0.2 level were retained for analysis in the multivariate model.

"Estimates (hazards ratios, odds ratios) are presented with 95% confidence intervals (95% CIs). We considered a p-value of <0.05 to be significant. All statistical analyses were performed using Stata® software, version 13.1 (Stata Corp LP, College Station, TX)."[11]

RESULTS

Patient and Tumor Characteristics

Of 1527 identified patients with stage II or III rectal cancer, 1254 (82%) met eligibility criteria and had sufficient data available to be included for analysis. Median age was 62 (range, 24–88), with 38% ≥65 years if age. Thirty percent

TABLE 2. Patient demographic and clinical characteristics by eGFR

Characteristic	Total (N = 1254)	eGFR > 60 (n = 1118, 89%)	eGFR < 60 (n = 136, 11%)	p value
Province, n (%)				
Alberta	490 (39)	446 (40)	44 (32)	0.27
British Columbia	214 (17)	186 (17)	28 (21)	
Newfoundland/Labrador	188 (15)	169 (15)	19 (14)	
Ontario	362 (29)	317 (28)	45 (33)	
Age, y				
Median (range)	62 (24–88)	60 (24–84)	73 (44–88)	<0.001
≥65, n (%)	474 (38)	367 (33)	107 (79)	<0.001
Female, n (%)	371 (30)	308 (28)	63 (46)	<0.001
BMI, kg/m^2 (n=1224)				
Median (range)	27 (13–71)	27 (15–71)	24 (13–36)	<0.001
≥ 25, n (%)	806 (64)	747 (67)	59 (43)	<0.001
ECOG PS, n (%)				
0	600 (48)	537 (48)	63 (46)	0.12
1	459 (37)	408 (36)	51 (38)	
2+	60 (5)	49 (4)	11 (7)	
Unknown	135 (11)	124 (11)	11 (8)	
Distance from anal verge, cm (n = 1169)				
Median (range)	6 (0–30)	6 (0–30)	6 (0–16)	0.93
<5, n (%)	414 (33)	366 (33)	48 (35)	0.57
5–10, n (%)	510 (41)	461 (41)	49 (36)	
>10, n (%)	245 (20)	218 (20)	27 (20)	
Unknown, n (%)	85 (7)	73 (7)	12 (9)	
Pretreatment CEA, ng/mL (n = 1130)				
Median (range)	4 (0–664)	3 (0–664)	5 (1–249)	0.68
<5, n (%)	686 (55)	624 (56)	62 (46)	0.60
≥5, n (%)	444 (35)	384 (34)	60 (44)	
Unknown, n (%)	124 (10)	110 (10)	14 (10)	
Clinical stage, n (%)				
II	367 (29)	316 (28)	51 (38)	0.08
III	862 (69)	780 (70)	82 (60)	
Unknown	25 (2)	22 (2)	3 (2)	
Hemoglobin, g/dL, median (range)	136 (68–183)	137 (68–183)	124 (75–178)	<0.001
eGFR, mL/min, median (range)	93 (23–353)			

ECOG PS = Eastern Cooperative Oncology Group performance status; eGFR = estimated glomerular filtration rate.

were women, and 85% had a performance status of 0-1. Body mass index was ≥25 in 64%. Median pretreatment CEA level was 4 (range, 0–664). Median CrCl was 93 mL/min (interquartile range, 74–114), with 11% of patients <60 mL/min (n = 136). Twenty-nine percent and 69% had clinical stage II and III disease. Patients with CKD were older, had lower median BMI and baseline hemoglobin, and were more likely to be a woman than those without CKD. Patient demographics and tumor characteristics are summarized in Table 2.

Treatments

Treatment details are summarized in Table 3. The median radiation dose delivered was 50 Gy (range, 20–80), with 97% receiving at least 45 Gy. Ninety-seven percent of patients received fluoropyrimidine-based nCT (44% capecitabine, 54% 5-fluorouracil). Patients with CKD were less likely to receive capecitabine for nCT (35% vs 45%, $p = 0.02$). Ninety-five percent completed nRT and 84% completed nCT. There was no significant difference in completion rate of neoadjuvant radiotherapy (93% vs 95%, $p = 0.45$) or neoadjuvant chemotherapy (82% vs 85%, $p = 0.36$) between the CKD and non-CKD groups. The majority (78%) underwent TME within 6 to 12 weeks of completion of nCRT. Adjuvant chemotherapy was used in 76% of patients, with 32% of the total group receiving oxaliplatin-based adjuvant chemotherapy. Patients with CKD were less likely to receive adjuvant chemotherapy (63% vs 77%, $p < 0.01$).

Clinical Outcomes

After a median follow-up time of 66 months, 8% developed local recurrence, 21% developed distant recurrence, and 22% had died. Median OS and DFS were not reached. Five-year OS and DFS rates were 78% (95% CI, 75%–81%) and 68% (95% CI, 65%–70%). The pCR rate in the entire cohort was 17%. Rates of OS and DFS at 5 years for each group are displayed in Figure 1.

TABLE 3. Treatment details

Characteristic	Total (N = 1254)	eGFR >60 (n = 1118, 89%)	eGFR <60 (n = 136, 11%)	p value
Neoadjuvant chemotherapy, n (%)				
5-Fluorouracil	675 (54)	591 (53)	84 (62)	0.02
Capecitabine	547 (44)	499 (45)	48 (35)	
Raltitrexed	16 (1)	16 (1)	0 (0)	
Unknown	16 (1)	12 (1)	4 (3)	
Radiotherapy dose, Gy (n = 1249)				
Median (range)	50 (20–80)	50 (20–74)	50 (22–80)	0.05
<45	42 (3)	36 (3)	6 (4)	0.64
≥45	1207 (96)	1077 (96)	130 (96)	
Unknown	5 (1)	5 (0)	0 (0)	
Time from nCRT completion to TME				
<6 wk	213 (17)	191 (17)	22 (16)	0.83
6–12 wk	984 (78)	878 (79)	106 (81)	
>12 wk	57 (5)	49 (4)	8 (6)	
Adjuvant chemotherapy, n (%)	948 (76)	863 (77)	85 (63)	<0.001
Adjuvant chemotherapy type, n (%)				
5-Fluorouracil	189 (15)	173 (15)	16 (12)	<0.001
Capecitabine	353 (28)	319 (29)	34 (25)	
5-Fluorouracil/oxaliplatin	321 (26)	295 (26)	26 (19)	
Capecitabine/oxaliplatin	63 (5)	60 (5)	3 (2)	
Other	22 (2)	16 (2)	6 (4)	
No adjuvant chemotherapy	306 (24)	255 (23)	51 (38)	
Completed treatment as planned, n (%)				
Neoadjuvant radiotherapy	1188 (95)	10,619 (95)	127 (93)	0.45
Neoadjuvant chemotherapy	1057 (84)	946 (85)	111 (82)	0.36

nCRT = neoadjuvant chemoradiotherapy; TME = total mesorectal excision.

Univariate and Multivariate Analyses

Factors included in univariate analyses were age, sex, province, year of diagnosis (pre-2010 vs post-2010), BMI, statin use, Eastern Cooperative Oncology Group performance status, pretreatment CEA, clinical stage, distance from anal verge, radiotherapy dose (<45 Gy vs ≥45 Gy), adjuvant chemotherapy use, and baseline renal function.

Proportional hazards assumptions were checked graphically and by Schoenfeld residuals[14] for each variable individually before model fitting. Two factors, province and

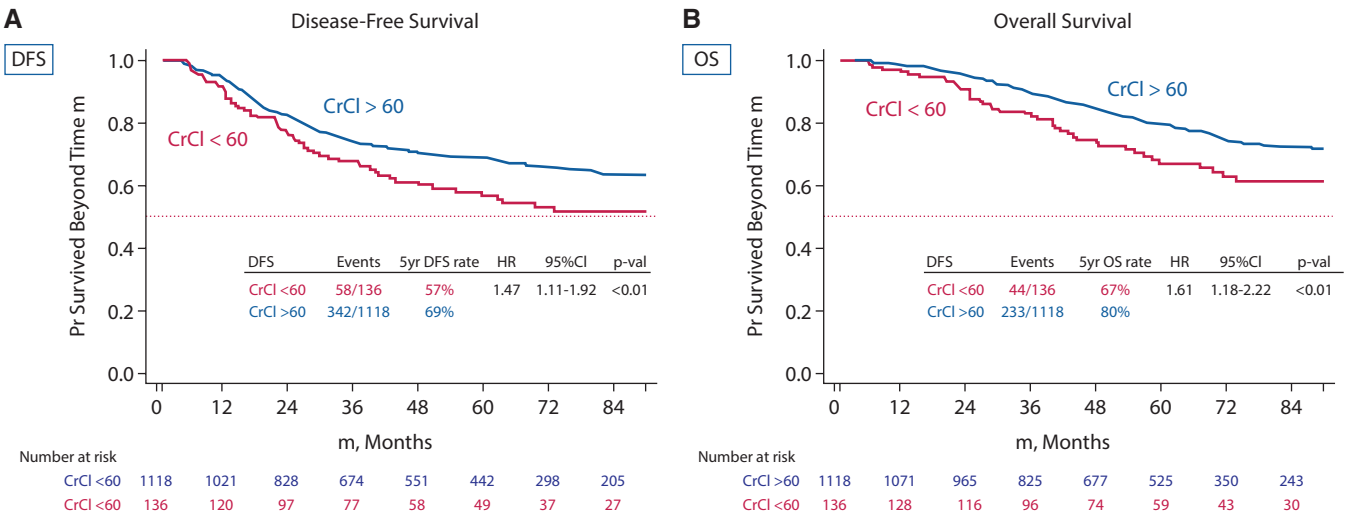

FIGURE 1. Disease-free survival (A) and overall survival (B) by baseline creatinine clearance. CrCl = creatinine clearance; DFS = disease-free survival; OS = overall survival; Pr = proportion.

TABLE 4. Univariate analyses: survival

Outcome	*5-year rate, %*	*HR (95% CI)*	*p value*
OS			
eGFR < 60	67	1.61 (1.18–2.22)	<0.01
eGFR ≥ 60	80	ref	
DFS			
eGFR <60	57	1.47 (1.11–1.92)	<0.01
eGFR ≥60	69	ref	

DFS = disease-free survival; eGFR = estimated glomerular filtration rate; OS = overall survival.

adjuvant chemotherapy, showed nonproportional hazards and therefore were set as strata for the multivariate analysis.

Results of univariate analyses are displayed in Tables 4 and 5. In these unadjusted models, CrCl <60 was associated with decreased DFS (5-year DFS 57% vs 69%; HR, 1.61; 95% CI, 1.18–2.22; $p < 0.01$) and OS (5-year OS 67% vs 80%; HR, 1.47; 95% CI, 1.11–1.92; $p < 0.01$). The pCR rates were not significantly different between those with versus without CKD (14% vs 18%; OR, 0.75; 95% CI, 0.45–1.25; $p = 0.27$).

On multivariate analysis, CKD remained an independent predictor of DFS (HR, 1.37; 95% CI, 1.03–1.82; $p = 0.03$). There was no independent association demonstrated between CKD and OS (HR, 1.23; 95% CI, 0.88–1.75; $p = 0.23$) or pCR (OR, 0.83; 95% CI, 0.50–1.39; $p = 0.71$). Multivariate analyses are summarized in Table 6 (DFS), Table 7 (OS), and Table 8 (pCR).

DISCUSSION

The presence of CKD may negatively impact the diagnosis, treatment, and monitoring of patients with cancer in a variety of ways, and prior data suggest that outcomes in this group may be distinct from patients with cancer and preserved renal function.[3,4,9] In addition, this cohort is typically excluded from clinical trials and has been poorly studied in the context of LARC. Our study aimed to describe the baseline features of this population and characterize their clinical outcomes relative to patients without CKD. To our knowledge, these are the first data specifically addressing this patient population in LARC.

In our cohort, approximately 1 in 10 patients with LARC who received nCRT before TME had CKD, conventionally defined as an eGFR <60 mL/min (grade ≥3 CKD).[1,2] This proportion is in line with previously published data reporting the rate of CKD among patients with general cancer,[4–6] and slightly less than the rate reported in a specific cohort of patients with colorectal cancer (25%).[7] Patients with CKD were older and more likely to be women than those without CKD, but baseline tumor characteristics were not significantly different between groups (eg, clinical stage, distance from anal verge, baseline CEA).

We found that patients with CKD had a 47% relative increase in the risk of recurrence or death compared with those without CKD. We did not demonstrate any independent association between baseline renal function and OS, pCR, or neoadjuvant treatment completion rate.

We considered neoadjuvant treatment completion rate as a real-world surrogate end point for treatment tolerance. It is notable that patients with CKD were able to complete nRT and nCT as planned at rates similar to those with preserved renal function. Of note, patients with CKD were more likely to receive 5-fluorouracil instead of

TABLE 5. Univariate analyses: pCR

Outcome	*Frequency, %*	*OR (95% CI)*	*p value*
pCR			
eGFR <60	14	0.75 (0.45–1.25)	0.27
eGFR ≥60	18	ref	

pCR = pathologic complete response; eGFR = estimated glomerular filtration rate.

TABLE 6. Adjusted Cox proportional hazards model of overall survival

	OS		
Covariate	*HR*	*95% CI*	*p value*
eGFR, mL/min			
>60	ref		
<60	1.23	0.88–1.75	0.23
Age at diagnosis			
<65 y	ref		0.004
≥65 y	1.45	1.13–1.87	
ECOG PS			
0	ref		0.004
1	1.41	1.05–1.88	
2+	2.32	1.47–3.69	
Unknown	1.11	0.74–1.66	
Pretreatment CEA			
<5	ref		0.001
≥5	1.65	1.28–2.13	
Unknown	2.11	1.42–3.15	

Stratified on province and adjuvant chemotherapy.
ECOG PS = Eastern Cooperative Oncology Group performance status; eGFR = estimated glomerular filtration rate.

TABLE 7. Adjusted Cox proportional hazards model of disease-free survival

	DFS		
Covariate	*HR*	*95% CI*	*p value*
eGFR, mL/min			
>60	ref		
<60	1.37	1.03–1.82	0.03
Pretreatment CEA			
<5	ref		<0.001
≥5	1.61	1.30–1.99	
Unknown	1.94	1.39–2.69	
Clinical stage			
II	ref		0.06
III	1.28	1.01–1.63	
Unknown	1.88	0.92–3.83	

Stratified on province and adjuvant chemotherapy.
eGFR = estimated glomerular filtration rate.

TABLE 8. Adjusted logistic regression model of pCR

	pCR		
Covariate	*OR*	*95% CI*	*p value*
eGFR, mL/min			
>60	ref		
<60	0.83	0.50–1.39	0.71
ECOG PS			
0	ref		0.05
1	0.75	0.54–1.04	
2+	0.24	0.07–0.79	
Not reported	0.94	0.57–1.53	
Pretreatment CEA			
<5	ref		<0.001
≥5	0.47	0.33–0.66	
Unknown	0.85	0.52–1.40	

ECOG PS = Eastern Cooperative Oncology Group performance status; pCR = pathologic complete response.

capecitabine for nCT, because capecitabine is primarily renally cleared and not recommended for use in advanced CKD. Total radiation dose received was also not different between groups. Together, these data suggest that neoadjuvant treatment tolerance is not affected by the presence of CKD and supports current practices whereby patients with CKD do not receive dose-adjusted neoadjuvant treatment approaches to improve tolerability.

In our study, baseline CKD was independently associated with decreased DFS. This is a key finding because it suggests that the presence of CKD may result in inferior clinical outcomes. These results may have important implications for patient counseling, prognostication, and treatment selection for this understudied patient cohort. In addition, these data suggest that the results of randomized trials that have excluded this population may not be applicable to them.

Consistent with previous studies in a range of patients with cancer,[3,4,6,9] our study found that the presence of CKD was associated with inferior OS. However, this OS difference may in part be explained by a higher average age among patients with CKD (median 73 vs 60 years of age), as seen in the multivariable analysis. We did not demonstrate any independent association between CKD and OS in our cohort. This result may also be impacted by having less mature OS data. Despite the 66-month median follow-up in our cohort, only 22% of patients had died at the time of analysis. These data highlight the relatively good outcomes of patients with LARC treated with contemporary approaches and are consistent with data from long-term results from landmark clinical trials.[15,16] We note that the point estimates of the effect sizes for DFS and OS were similar and had overlapping 95% CIs, and thus await data with further follow-up to report on more mature OS outcomes.

A noteworthy finding from our study was that patients with CKD were significantly less likely to receive adjuvant chemotherapy following TME. Patients and clinicians may have been more reluctant to pursue adjuvant systemic therapy given that its benefits after nCRT in LARC are controversial, in addition to a perceived increased risk of toxicity and/or reduced efficacy in those with impaired renal function.[17] In addition, differences in baseline characteristics between the CKD and non-CKD groups (eg, age) may have also contributed to this finding. The decreased use of adjuvant chemotherapy in the CKD cohort may have contributed to the inferior DFS noted in this group, although prospective randomized data suggest that adjuvant chemotherapy after nCRT may be associated neither with improved DFS nor with OS.[18]

We chose to estimate glomerular filtration rate using the Cockroft-Gault equation because this formula is commonly used in clinical trials.[7] Other methods to estimate creatinine clearance exist and have been considered by some to be more accurate than the traditional Cockroft-Gault formula, including the Modified Diet in Renal Disease equation and the more recently developed Chronic Kidney Disease Epidemiology equation.[19] However, several studies have shown comparable performance of these models in patients with cancer.[20,21] Furthermore, recent American Society of Clinical Oncology recommendations endorse the use of either the Cockroft-Gault or Modified Diet in Renal Disease formula for calculating renal function.[7]

Several limitations of the present study should be noted. First, the retrospective study design introduces the potential for confounding and selection bias. Indeed, only patients who were started on curative-intent nCRT followed by TME were included in our cohort. Thus, there may be a select group of patients with severe baseline renal dysfunction who were not believed to be fit for nCRT and/or could not have surgery and therefore were not captured in our database. Our data may also not be generalizable to older patients or those with poor performance status. Second, detailed data pertaining to adverse events, patient-reported outcomes, and postoperative complications were not available. Instead, we incorporated alternate end points including nCT and nRT treatment completion rate as surrogates for treatment tolerability. We did not have any data available to assess tolerance of adjuvant chemotherapy (including dose reductions and dose delays). Third, despite greater than 5 years of median follow-up, there were a limited number of events for the OS analysis. However, we did include DFS as an end point, which has been validated as a reliable surrogate for OS in the context of nonmetastatic colon cancer.[22] Finally, we were unable to control for other potential confounding variables such as comorbid illnesses and important surgical considerations such as the type of surgery performed and circumferential resection margin involvement.

Strengths of our study include the large sample size, long follow-up time, and the multi-institutional nature of our data. In addition, the baseline characteristics and observed outcomes of our cohort are consistent with data

from previously reported prospective, randomized studies.[15,23,24] Furthermore, only patients with LARC who underwent nCRT were included in this study. Thus, in contrast to observational studies published from large administrative databases, many potential confounders such as disparities in socioeconomic factors, health care access, and treatment selection were less likely to influence the results of our study.

CONCLUSION

A significant proportion of patients with LARC undergoing nCRT followed by TME had baseline CKD. These patients were able to complete nCT and nRT at high rates with no significant reduction in the rate of pCR noted in our study. However, their survival outcomes may be inferior compared to those with preserved renal function, and, therefore, the results of landmark clinical trials may not be generalizable to this population. Greater representation of patients with CKD in future prospective studies is warranted, because these patients represent a growing subgroup with distinct clinical challenges and outcomes.

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