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Original Articles

Colorectal carcinoma in pediatric patients: A comparison with adult tumors, treatment and outcomes from the National Cancer Database

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ABSTRACT

Background: Pediatric colorectal cancer (CRC) is rare. Comparison with adult CRC tumors, management, and outcomes may identify opportunities for improvement in pediatric CRC care.
Study Design: CRC patients in the National Cancer Data Base from 1998 to 2011, were grouped into Pediatric (≤21 years), early onset adult (22–50) and older adult (>50) patients. Groups were compared with χ^2 and survival analysis.
Results: A total of 918 pediatric (Ped), 157,779 early onset adult (EA), and 1,304,085 older adults (OA) were identified ($p < 0.01$ for all comparisons). Patients ≤50 presented more frequently with stage 3 and 4 disease (Ped: 62.0%, EA: 49.7%, OA: 37.3%) and rectal cancer (Ped: 23.6%, EA: 27.5%, OA: 19.2%). Pediatric histology was more likely signet ring, mucinous, and poorly differentiated. Initial treatment was usually surgery, but patients ≤50 were more likely to have radiation (Ped: 15.1%, EA: 18.6%, and OA: 9.2%) and chemotherapy (Ped: 42.0%, EA: 38.2%, and OA: 22.7%). Children and older adults showed poorer overall survival at 5 years when compared to early onset adults. Adjusting for covariates, age ≤21 was a significant predictor of mortality for colon and rectal cancers (colon HR: 1.22, rectal HR: 1.69).
Conclusions: This is the largest cohort of pediatric CRC patients, revealing more aggressive tumor histology and behavior in children, particularly in rectal cancer. Despite standard oncologic treatment, age ≤21 was a significant predictor of mortality. This is likely owing to worse tumor biology rather than treatment disparities and may signal the need for different therapeutic strategies.

Colorectal cancer (CRC) is the third most common cancer in adults and the second leading cause of cancer-related death in the United States. In contrast, colorectal adenocarcinoma is a rare pediatric tumor, representing only 1% of all pediatric malignancies, with an incidence of approximately 1 per million [1]. There is a robust body of evidence in adults, but studies of pediatric CRC have been limited by small numbers of patients, with no large institutional experience or prospective studies to guide treatment. The largest database study to date used the Surveillance, Epidemiology, and End Results Project (SEER) database, studying 159 patients, and the largest single center study reviewed 77 patients [2,3]. Despite small numbers, these studies demonstrated differences between pediatric and adults CRC patients, showing a significantly higher proportion of aggressive histology, particularly signet ring and mucinous and a higher proportion presenting with metastatic disease [2,4–7]. However, no studies specifically compare rectal cancer outcomes in children and adults.

Utilizing the National Cancer Database (NCDB) data, our study compares pediatric and adult CRC patients with regards to demographics, histology, and treatment regimens and survival outcomes. Comparison with adult patients may uncover unique features of pediatric CRC and suggest opportunities for improvements in pediatric CRC care.

1. Methods

Ethical approval for this study was granted by the Maine Medical Center Institutional Review Board. All patients with a histologic diagnosis of colorectal adenocarcinoma, using ICD-O-3 classification, diagnosed between years 1998 and 2011 were identified from the NCDB. The NCDB, a joint project of the American Cancer Society and the Commission

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on Cancer (CoC) of the American College of Surgeons, is a nationwide, facility-based, comprehensive clinical surveillance resource oncology data set that currently captures 70% of all newly diagnosed malignancies in the US annually [8].

Patients were grouped based on age — pediatric (≤21 years), young adults (22–50) and older adults (>50). The dataset was queried using tumor histology codes from the International Classification of Disease for Oncology 3rd Edition (ICD-O-3) for all colorectal adenocarcinoma codes, including in situ disease, and classified as 1) adenocarcinoma (codes 8050–8052, 8140–8148, 8210–8231, 8255–8263, 8510, and 8560–8576), 2) signet ring cell carcinoma (code 8490), and 3) mucinous adenocarcinoma (codes 8480–8481). Non-adenocarcinoma histologies were excluded including carcinoid, sarcomas, GISTs, and lymphomas. Familial adenomatous polyposis (FAP) was identified by pathology (codes 8220–8221). Tumor location from cecum to rectosigmoid was classified as "colon"; tumors located distal to this were classified "rectal". Only cases for which this cancer was either the first or the only cancer diagnosis in their lifetime, and those diagnosed or treated at the reporting facility, were included. Demographic variables, pathology, as well as surgical, chemotherapy and radiation treatments were compared between groups. Charlson Deyo score was used as a measure of patient comorbidities [9]. TNM staging based on pathology was used preferentially owing to less change between years with new editions of the TNM staging system. If TNM stage was unavailable, owing to missing histologic stage, clinical stage was used. Groups were compared with chi-squared analysis for demographic data, histology, stage, surgical and adjuvant therapy, and outcomes. Patients with missing data were excluded from the univariate analysis. Factors found to be significant in a univariate analysis were then entered into a multivariate analysis using the Cox proportional hazards model, which was limited to patients ≤50 years of age owing to difficulty interpreting all-cause mortality in the oldest age group (age >50). Appropriateness of a proportional hazards model was investigated to determine graphically whether the hazards for subjects with and without a given covariate were approximately proportional over time. Hazard ratios for colon and rectal cancers were examined separately. Potential effect modification was explored by including interaction terms for each combination of covariates. In addition to the variables included in the reported models, preliminary models considered other racial categories and comorbidities, none of which were independently significant ($p > .05$). After considering interactions between age group and sex, race, stage, pathologic characteristics, and colon/rectal location, only the last of these appeared significant, which was most easily expressed by reporting separate models for colon and rectal locations.

Concordance probability estimates using the method of Gönen and Heller were performed for each model [10].

Five and ten year overall survival was estimated using the Kaplan–Meier method. Survival was calculated from the time of the initial diagnosis to the date of death, with survival curves for each stage for colon and rectal location of presenting tumor separately. Those excluded from the survival analysis were patients who were lost to follow up, those who had more than one cancer diagnosis, and those diagnosed in 2007 or later as they would not have had the 5 years of follow up required by NCDB. Data analysis was conducted using the statistical program Stata (Version 13.0, StataCorp, College Station, Texas).

2. Results

2.1. Demographics (Table 1)

A total of 918 pediatric (Ped), 157, 577 early onset adult (EA), and 1,303,655 older adult (OA) patients were identified (Fig. 1). There were no significant differences in gender or race among the 3 age groups. Comorbidities, as measured by the Charlson Deyo score, increased with increasing age. Significant differences exist in presenting location of tumor, with older adults presenting with a higher proportion of right colon cancer (Ped: 23.7%, EA: 22.9%, OA: 35.8%, $p < 0.001$) whereas the early onset adults had a slightly higher proportion of left colon cancer (including splenic flexure, descending, sigmoid and rectosigmoid) as

Table 1
Patient demographics.

Variable	Age ≤ 21 % (No)	Age 22–50 % (No.)	Age >50 % (No.)	P-value
Sex				
Male	54.6 (502)	52.8 (83,248)	50.6 (659,718)	p < 0.001
Female	45.3 (416)	47.1 (74,329)	49.3 (643,937)	
Race				
White	78.2 (718)	78.7 (124,043)	85.7 (1,118,166)	p < 0.001
Black	14.4 (133)	15.0 (23,711)	10.3 (134,402)	
Asian	3.2 (30)	3.4 (5491)	2.1 (28,207)	
Other	4.0 (37)	2.7 (4332)	1.7 (22,880)	
Charlson Deyo Score				
0	94.4 (578)	88.7 (93,519)	69.9 (565,629)	p < 0.001
1	4.7 (29)	9.3 (9876)	21.9 (177,406)	
2	0.8 (5)	1.8 (1952)	8.1 (65,501)	
Site				
Right Colon	23.7 (218)	22.9 (36,212)	35.8 (466,723)	p < 0.001
Transverse Colon	8.3 (77)	5.0 (7892)	6.7 (88,337)	
Left Colon	34.8 (320)	40.6 (64,016)	34.6 (451,234)	
Rectum	23.6 (217)	27.5 (43,373)	19.2 (250,508)	
Large intestine, NOS	9.3 (86)	3.8 (6084)	3.6 (46,853)	
Histology				
Adenocarcinoma	66.9 (615)	88.2 (139,094)	90.2 (1,176,551)	p < 0.001
Mucinous Adeno	17.5 (161)	9.7 (15,304)	8.7 (114,256)	
Signet Ring	15.4 (142)	2.0 (3179)	0.9 (12,848)	
FAP (pathologic diagnosis)	2.6 (24)	0.2 (318)	0.03 (427)	P < 0.001
Microsatellite instability (MSI)				
No MSI (stable)	58.7 (27)	76.1 (4184)	73.3 (16,369)	P < 0.001
MSI (unstable)	41.3 (19)	23.9 (1313)	26.7 (5967)	
Grade				
Well differentiated	7.8 (72)	8.6 (13,546)	9.7 (126,753)	p < 0.001
Mod. differentiated	39.5 (363)	57.7 (90,961)	58.5 (762,809)	
Poorly differentiated	29.5 (271)	16.9 (26,726)	15.3 (200,673)	
Undifferentiated	3.3 (31)	1.2 (1977)	1.1 (14,651)	
Unknown	19.7 (181)	15.4 (24,367)	15.2 (198,769)	
TNM Stage (combined)				
0	5.2 (48)	6.1 (9611)	7.2 (93,895)	p < 0.001
1	8.3 (77)	17.2 (27,137)	22.4 (292,285)	
2	14.2 (131)	19.7 (31,120)	24.3 (318,015)	
3	32.7 (301)	28.0 (44,166)	22.4 (292,508)	
4	29.3 (269)	21.7 (34,213)	14.9 (195,088)	
Unknown	10.0 (92)	7.1 (11,330)	8.5 (111,864)	
Treatment Started after diagnosis				
Within 1 month	88.1 (743)	84.5 (122,973)	83.2 (968,069)	p < 0.001
1–3 months	10.2 (86)	14.1 (20,546)	15.2 (177,269)	
3–6 months	0.3 (3)	0.6 (978)	0.8 (9523)	
6 months–1 year	1.1 (10)	0.5 (855)	0.6 (7734)	
>1 year	0.1 (1)	0.08 (115)	0.06 (663)	
Surgery				
No excision/ unknown	17.4 (160)	11.4 (17,991)	12.2 (159,920)	p < 0.001
Local excision	3.5 (33)	7.5 (11,962)	8.2 (107,830)	
Segmental resection	54.1 (497)	68.1 (107,321)	71.5 (933,231)	
Total colectomy, proctectomy, or proctocolectomy	22.3 (205)	11.1 (88,432)	6.7 (88,432)	
Surgery, NOS	2.5 (23)	1.7 (2804)	1.0 (14,242)	
Lymph Nodes Removed				
<12	17.39 (160)	27.29 (43,063)	35.29 (460,282)	p < 0.001
≥12 nodes	53.59 (493)	47.85 (75,503)	39.35 (513,153)	
Unknown or none	29.01 (267)	24.85 (39,213)	25.36 (330,750)	
Chemotherapy				
Yes	70.1 (644)	59.7 (94,167)	32.6 (426,084)	p < 0.001
No or unknown	29.6 (274)	40.2 (63,410)	67.2 (877,571)	
Radiation				
Yes	19.5 (179)	22.9 (36,180)	12.2 (160,014)	p < 0.001
No	79.0 (726)	75.8 (119,536)	86.7 (1,130,225)	
Unknown	1.4 (13)	1.1 (1861)	1.0 (13,416)	