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ORIGINAL ARTICLE – COLORECTAL CANCER

Survival After Resection of Colorectal Cancer Based on Anatomical Segment of Involvement

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ABSTRACT

Purpose. To determine survival differences for patients undergoing colonic or rectal resection for cancer on the basis of the specific anatomical location of primary tumor.

Methods. A total of 143,747 patients undergoing segmental colectomy, hemicolectomy, anterior resection, or abdominoperineal resection (APER) for adenocarcinoma from 1995 to 2009 were identified from 13 Surveillance, Epidemiology, and End Results regions. The primary end point was overall survival determined by adjusted hazard ratios (HRs); the secondary end point was lymph node yield.

Results. Total lymph node yield significantly decreased from proximal to distal resected segment in stage 0–II cancer, but not in stage III cancer. Lymph node ratio increased from cecum to hepatic flexure and then decreased distally ($p < 0.001$). Adjusted HRs revealed that survival after right colonic resection for ascending hepatic flexure and transverse colon cancer was not significantly different from cecal cancer. Survival after left colonic resection for descending colon cancer was not different from splenic flexure cancer, but sigmoid colectomy carried improved survival (HR 0.95, $p = 0.027$). APER carried worse survival compared to anterior resection (HR 1.28, $p < 0.001$) or right colonic resection for cecal cancer (HR 1.61, $p < 0.001$).

Conclusions. Survival after resection from colorectal cancer depends on specific anatomical segment and not just the division between colon and rectum, or left and right colon. This may be related to inherent differences in the anatomical characteristics of the particular colorectal segment, with varying lymph node yields contributing to understaging. This supports an individualized approach to colorectal cancer, with particular attention to surgical technique, leading to survival improvement.

Colorectal cancer is increasingly recognized as representing a heterogenous group of tumors with distinct differences in presentation, genetic composition, and survival.[1–3] Right colonic cancer (compared to left) is more likely to present at an advanced stage and to have increased CpG island methylator phenotype (CIMP) and microsatellite instability (MSI), and it may have a worse survival.[1–5] A recent genetic analysis of specific colorectal cancer segments identified gradual genetic changes from the rectum to ascending colon, challenging previous assumptions of discrete differences between proximal and distal colorectal cancer.[2]

A corresponding population-level survival analysis is lacking. Current studies broadly consider left versus right-sided colonic cancer without specific colonic segmental stratification, and they do not compare rectal and colon cancer.[1,4–6] It may also be that certain anatomical locations lead to more challenging surgery, with correspondingly lower lymph node yields.[7,8]

High-quality data on survival differences based on the location of colorectal cancer within a specific anatomical segment carry important implications. First, it would help stratify patient entry into trials on the basis of equivalent risk. Second, it may allow for appropriate statistical

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adjustment during multivariable analyses. Third, it may allow for greater individualization of management, including pathological assessment, neoadjuvant and adjuvant therapies. Fourth, it would allow for increased prognostic detail for the individual patient, especially when combined with modern tumor molecular biology.[2] These implications will advance knowledge on the specific surgical challenges posed by the affected colorectal segment, with the ultimate aim of improving patient care by driving higher quality of standardized surgery.

The aim of this study was to determine population-level survival differences for patients undergoing resectional surgery for cancer of the colon and rectum on the basis of specific anatomical segment.

METHODS

Surveillance, Epidemiology, and End Results

Surveillance, Epidemiology, and End Results (SEER) collects data on incidence, prevalence, and survival from specific geographical regions representing approximately 28 % of the US population.[9] Anonymized patient-level data were extracted from the publicly available online SEER database for 13 regions.

Patient Selection

All adult patients (aged $\geq$18 years) with colorectal adenocarcinoma treated operatively from 1995 to 2009 (inclusive) were included. Only patients undergoing partial colectomy, hemicolectomy, Hartmann operation, anterior resection of rectum, or abdominoperineal excision of rectum (APER) were included. Those undergoing local resections, extended resections (i.e., those with removal of a contiguous organ), total colectomy, or an undefined procedure were excluded. This allowed a more controlled estimation of the influence of difficulty of resectional surgery for each segment. Patients who received radiotherapy for colonic cancer were excluded.

End Points

The primary end point was adjusted all-cause 10-year overall survival. The secondary end point was total lymph node yield, as a marker of surgical quality.

Explanatory Variables

The main explanatory variable was specific anatomical segment of colon or rectum resection. For patients undergoing segmental resection of the colon, this was defined as partial colectomy or hemicolectomy for cancer at the cecum (C18.0), ascending colon (C18.2), hepatic flexure (C18.4), splenic flexure (C18.5), descending colon (C18.6), or sigmoid colon (C18.7). For the rectosigmoid (C19.9) and rectum (C20.9), cancer was classified as treated with anterior resection or APER (thus making an approximation of high and low rectal cancer). The following variables were also included: age, gender, race, marital status, year of diagnosis, American Joint Committee on Cancer stage, histological grade (well differentiated, moderately differentiated, poorly differentiated/undifferentiated/anaplastic), and number of lymph nodes retrieved. Lymph node ratio was calculated for stage III disease and was defined as the total number of positive lymph nodes divided by total number of lymph nodes retrieved. For the analysis of proctectomy for rectal cancer, additional adjustment was made for radiotherapy use (none, neoadjuvant [i.e., preoperative] or adjuvant [i.e., postoperative]). Data on patients received preoperative or postoperative chemotherapy are not collected in the SEER database, so no adjustment for it was possible.

Statistical Analysis

Total lymph node yield, positive lymph node yield, and lymph node ratio were categorized and considered for specific segment. Differences between demographic groups were tested by the χ^2 test. Kaplan–Meier survival curves were constructed, with differences between groups being detected by the log rank test. Cox's proportional hazard regression models were used to obtain adjusted hazard ratio (HR) and 95 % confidence interval (CI) for predictors of 10-year overall survival (death from any cause within 10 years of diagnosis). Forward stepwise selection was used to identify significant predictors, with variables entering models with a p value of <0.1 and remaining if p values were maintained at <0.05. For stage III disease, the number of positive nodes and lymph node ratio were included. For rectal cancer, use of radiotherapy was included. Year of diagnosis was considered as a continuous variable. The first survival models constructed used resection of cecal cancer as a reference and included all other segments. Subsequent models were constructed for right colonic resection (from cecum to transverse colon), left colonic resection (splenic flexure to sigmoid), and rectum (anterior resection and APER), in each case with the most proximal tumor segment used as a reference. For models relating to only the rectum, radiotherapy use was added as a stratification variable (none, neoadjuvant [i.e., preoperative] or adjuvant [i.e., postoperative]). Data were analyzed by SPSS 18.0 (SPSS, Chicago, IL).

RESULTS

Basic Cohort Demographics

A total of 143,747 patients were included, with 66,679 right colonic resections, 41,405 left colonic resection, and 35,663 rectal resections. Demographic differences between nine detailed colonic and rectal anatomical segments are shown in Table 1. With increasing distal location, patient age decreased, male proportion increased, and poor/anaplastic differentiation decreased until tumors were treated by anterior resection but then increased again for those undergoing APER. The proportion of stage III cancer was highest in patients treated by APER, followed by those treated with anterior resection, resection of splenic flexure cancer, and then cecal cancer. There were gradual declines

TABLE 1 Demographic differences for patient and tumor related factors by tumor location

Characteristics	Variables		Right colonic resection				Left colonic resection			Proctectomy		Total	*p*
			Cecum	Ascending	Hepatic flexure	Transverse	Splenic flexure	Descending	Sigmoid	AR	APER		
Age	<60 years	*n*	4001	3125	1023	1850	931	1580	7835	8991	2321	31657	
		%	14.7	14.4	15.3	16.7	21.9	24.2	25.6	32.0	30.5	22.0	
	60–79 years	*n*	14298	11429	3560	5735	2235	3452	16495	14586	4082	75872	
		%	52.4	52.8	53.4	51.7	52.5	52.8	53.9	52.0	53.6	52.8	
	≥80 years	*n*	8985	7076	2082	3515	1091	1508	6278	4477	1206	36218	
		%	32.9	32.7	31.2	31.7	25.6	23.1	20.5	16.0	15.8	25.2	<0.001
Gender	Male	*n*	11796	9636	3187	5112	2246	3444	16046	15897	4732	72096	
		%	43.2	44.5	47.8	46.1	52.8	52.7	52.4	56.7	62.2	50.2	
	Female	*n*	15488	11994	3478	5988	2011	3096	14562	12157	2877	71651	
		%	56.8	55.5	52.2	53.9	47.2	47.3	47.6	43.3	37.8	49.8	<0.001
Race	Non-African American	*n*	24477	19507	6102	10081	3688	5776	28189	26134	7067	131021	
		%	89.7	90.2	91.6	90.8	86.6	88.3	92.1	93.2	92.9	91.1	
	African American	*n*	2807	2123	563	1019	569	764	2419	1920	542	12726	
		%	10.3	9.8	8.4	9.2	13.4	11.7	7.9	6.8	7.1	8.9	<0.001
Married	Married/ previously married	*n*	24428	19473	6037	9987	3738	5723	27088	24778	6729	127981	
		%	89.5	90.0	90.6	90.0	87.8	87.5	88.5	88.3	88.4	89.0	
	Single	*n*	2856	2157	628	1113	519	817	3520	3276	880	15766	
		%	10.5	10.0	9.4	10.0	12.2	12.5	11.5	11.7	11.6	11.0	<0.001
Year	1995–1999	*n*	9215	6440	2322	3699	1500	2178	10474	9277	3296	48401	
		%	33.8	29.8	34.8	33.3	35.2	33.3	34.2	33.1	43.3	33.7	
	2000–2009	*n*	18069	15190	4343	7401	2757	4362	20134	18777	4313	95346	
		%	66.2	70.2	65.2	66.7	64.8	66.7	65.8	66.9	56.7	66.3	<0.001
Grade	Well	*n*	2646	2062	536	1029	398	680	3369	2319	536	13575	
		%	9.7	9.5	8.0	9.3	9.3	10.4	11.0	8.3	7.0	9.4	
	Moderate	*n*	18423	14613	4518	7804	3115	4907	23469	21587	5606	104042	
		%	67.5	67.6	67.8	70.3	73.2	75.0	76.7	76.9	73.7	72.4	
	Poor/ anaplastic	*n*	6215	4955	1611	2267	744	953	3770	4148	1467	26130	
		%	22.8	22.9	24.2	20.4	17.5	14.6	12.3	14.8	19.3	18.2	<0.001
Stage	0/I	*n*	7245	5824	1490	2718	804	1632	10129	9649	2123	41614	
		%	26.6	26.9	22.4	24.5	18.9	25.0	33.1	34.4	27.9	28.9	
	II	*n*	10524	8999	3113	5016	1913	2721	10423	8527	2522	53758	
		%	38.6	41.6	46.7	45.2	44.9	41.6	34.1	30.4	33.1	37.4	
	III	*n*	9515	6807	2062	3366	1540	2187	10056	9878	2964	48375	
		%	34.9	31.5	30.9	30.3	36.2	33.4	32.9	35.2	39.0	33.7	<0.001

p values relate to the changes in each explanatory variable across proximal (i.e., cecum) to distal (i.e., rectum) location, taking into account each specific affected segment

AR anterior resection, *APER* abdominoperineal resection

from cecum to hepatic flexure, and from splenic flexure to sigmoid colon.

Lymph Node Collection

For stages 0–II cancers, total lymph node collection increased slightly from those undergoing cecal resection to those undergoing resection of ascending colonic tumors, but then decreased to those undergoing anterior resection ($p < 0.001$; Fig. 1a). The highest proportion of patients with 0–3 lymph nodes collected were those undergoing APER. Although a similar pattern was observed with stage III cancer, the proportion of patients with lowest lymph node collection was similar throughout (Fig. 1b).

For stage III cancer, total positive lymph node collection changed in an inverted U shape; it increased from cecum to hepatic flexure, plateaued until sigmoid, and then decreased (Fig. 1c; $p < 0.001$); this result was nonsignificant after gamma correction ($p = 0.066$). For the proportion of patients with the lowest lymph node ratio, there was an increase from cecal resection to ascending colon/hepatic flexure resection, and then a linear decrease toward those undergoing APER ($p < 0.001$; Fig. 1d).

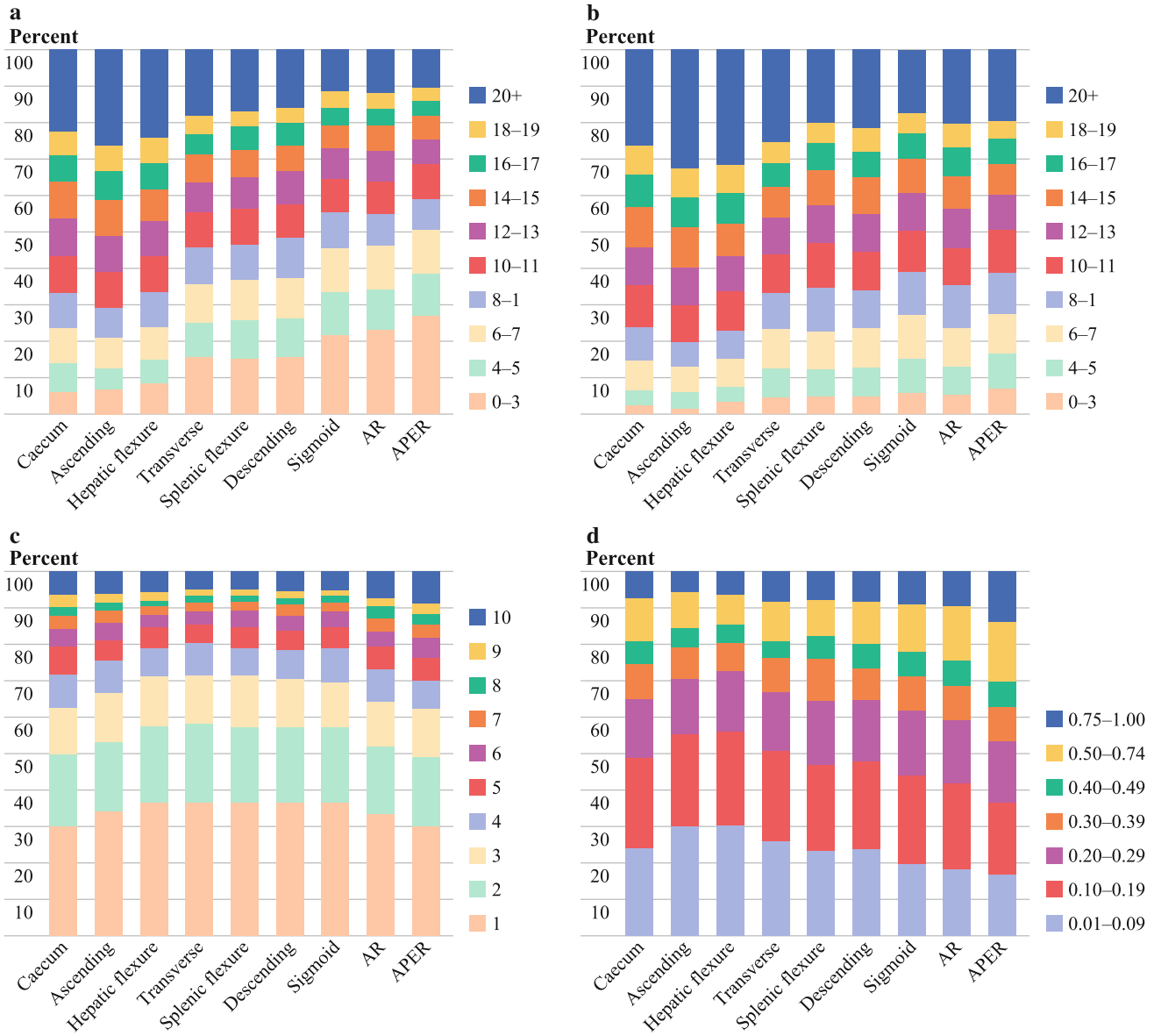

FIG. 1 Lymph node collection by tumor location. **a** Total number of lymph nodes collected for stages 0–II cancers ($p < 0.001$), **b** total number of lymph nodes collected for stage III cancers ($p < 0.001$), **c** positive nodes ($p < 0.001$; 0.066 with gamma correction), **d** lymph node ratio ($p < 0.001$). Lymph node ratio is the total number of positive lymph nodes divided by total number of lymph nodes retrieved

Unadjusted Survival by Segment

Kaplan–Meier survival curves revealed that those undergoing APER had the lowest overall survival from 5 years onward (Fig. 2a); those undergoing anterior resection consistently had the highest survival ($p < 0.001$). For right-sided cancer, transverse colonic tumor resection had the worst survival and ascending colonic tumor resection the highest, although differences were small (Fig. 2b; $p < 0.001$). For left-sided cancer, there were marked differences between resection for splenic flexure tumors (lowest) and sigmoid cancer (highest) (Fig. 2c; $p < 0.001$). For rectal cancer, those undergoing APER had a significantly worse survival than those undergoing anterior resection (Fig. 2d; $p < 0.001$).

Adjusted Survival by Segment

Adjusted HRs are shown in Table 2, with complete adjusted hazard models being available in Supplementary Table 1. Overall survival for all segments was initially compared to colonic resection of cecal cancer. Ascending colon resection had improved survival, hepatic to splenic flexure resections had similar survival, and anterior resection had improved survival, but those undergoing APER had significantly worse survival. Patients were then separated into right, left, and rectal groups, with the most proximal segment of each acting as reference (i.e., cecum, splenic flexure, and anterior resection, respectively). With these models, there were no significant differences in survival of segments from proximal colonic resections.

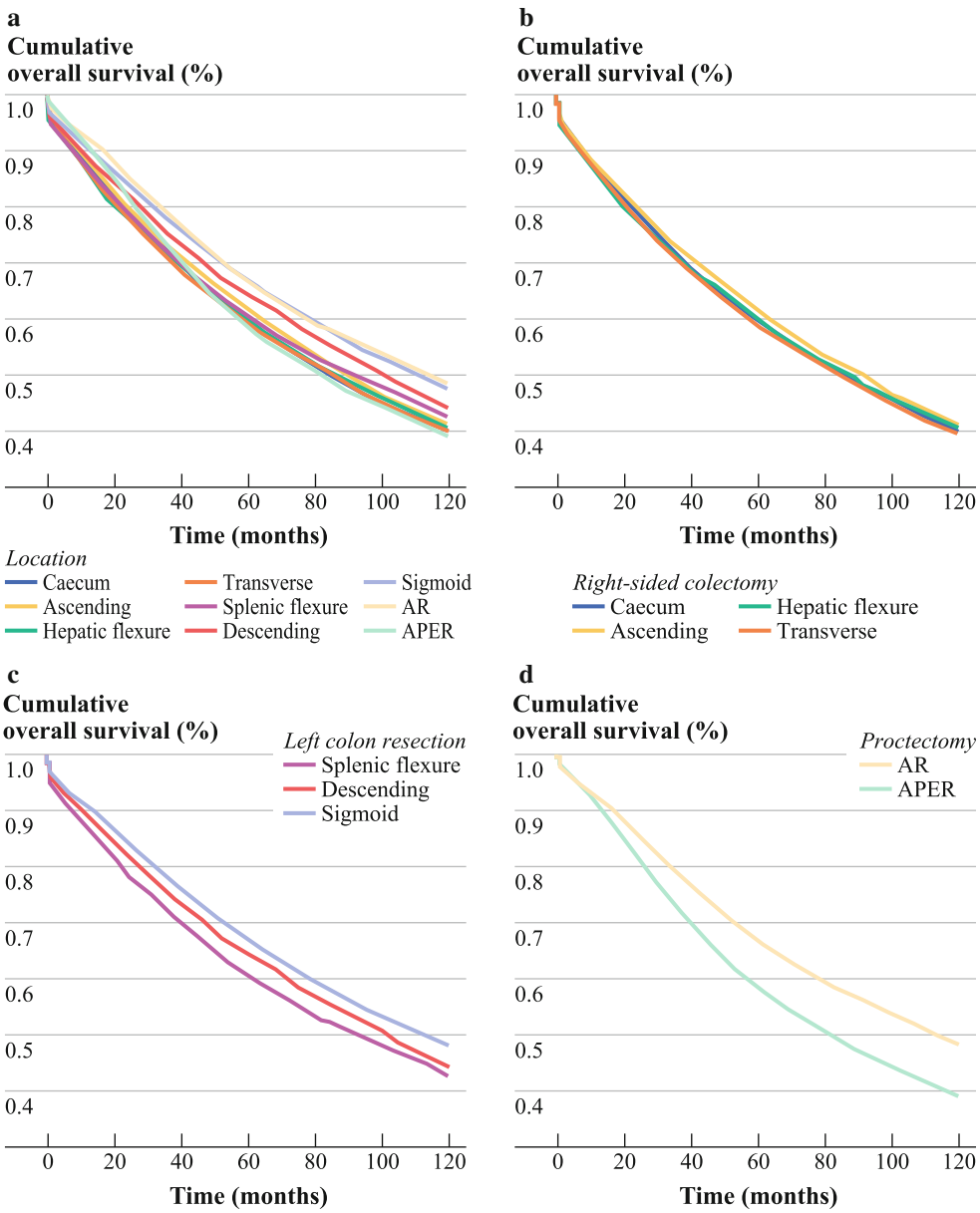

FIG. 2 Kaplan–Meier survival curves for segments of colorectal cancer. **a** Overall ($p < 0.001$), **b** right colon resection ($p = 0.001$), **c** left colon resection ($p < 0.001$), **d** proctectomy ($p < 0.001$)

TABLE 2 Adjusted HRs evaluating survival for anatomical segments based on references for right-sided colectomy, left-sided colectomy, and proctectomy

Colectomy/proctectomy	HR[a]	95 % CI		*p*
		Upper	Lower	
Overall				
Cecum	Ref.			
Ascending	0.972	0.946	0.999	0.042
Hepatic flexure	1.007	0.968	1.048	0.727
Transverse	1.012	0.979	1.046	0.472
Splenic flexure	0.972	0.926	1.021	0.261
Descending	0.952	0.912	0.993	0.022
Sigmoid	0.898	0.875	0.922	<0.001
AR	0.948	0.922	0.973	<0.001
APER	1.161	1.118	1.206	<0.001
Right colonic resection				
Cecum	Ref.			
Ascending	NE			
Hepatic flexure	NE			
Transverse	NE			
Left colonic resection				
Splenic flexure	Ref			
Descending	0.985	0.928	1.045	0.618
Sigmoid	0.946	0.901	0.994	0.027
Proctectomy				
Resection				
AR	Ref.			
APER	1.281	1.233	1.332	<0.001

Adjusted for age, gender, race, marital status, year of diagnosis, grade, stage, and number of lymph nodes collected

HR hazard ratio, *CI* confidence interval, *NE* not entered into final model, *AR* anterior resection, *APER* abdominoperineal resection

[a] A HR of <1 indicates improved survival compared to the reference group; >1 indicated worse survival

Patients undergoing sigmoid colectomy had improved survival compared to left-sided resection for splenic flexure tumor. Those undergoing APER had significantly worse survival compared to those undergoing anterior resection. In all models (i.e., overall, right colon, left colon, and rectum), increasing lymph node yield significantly improved survival in adjusted models (Supplemental Information).

Adjusted Survival by Segment and Stage

Figure 3 shows adjusted survival by colon or rectum segment and stage. Patients undergoing APER consistently had the worst overall survival, although for stage III disease, this was not significantly different from cecal cancer. In stage I cancer, sigmoid colectomy and anterior resection had improved survival compared to right-sided resection for cecal cancer. In stage II cancer, there were no significant differences from ascending colon resection to anterior resection of rectum; APER carried the worse survival. In stage III, survival improved from resection of descending colon to anterior resection compared to resection of cecal cancer.

DISCUSSION

This study has provided the most detailed population level survival analysis of the importance of specific colorectal segment for patients undergoing resection of colon and rectal cancer, and has several important implications. First, survival of colorectal cancer varies by specific site, which should be used as a stratification variable for entry into clinical trials and act as an adjustment factor in multivariable analyses. Second, lymph node yields are dependent on colorectal segment and in addition to lymph node distribution probably reflect difficulty and/or quality of surgery, which is an additional factor that affects survival. Third, there are gradual changes in clinicopathological variables from proximal to distal, without discrete cutoffs between left colon, right colon, and rectum. These findings improve knowledge of factors relating to survival of the individual patient and further indicate the specific areas where improvement in surgical quality should be focused.

This study was limited to patients who underwent resectional surgery, which remains among the most common surgical procedures used to treat colorectal cancer. Lymph node yield was used as a surrogate marker of both quality and technical challenge.[10] If these factors were even, then nodal yields would be expected to be the same across all locations. Thus, the greatest surgical challenge (indicated by lowest lymph node yields) arose from tumors involving the rectum, with the lowest yields and survival related to APER.

Yamauchi et al.[2] hypothesized that genetic and epigenetic features of colorectal cancer would gradually change along bowel segment, rather than change abruptly at the splenic flexure. They found gradual linear increases in CIMP-high, MSI-high, and BRAF mutations from rectum to ascending colon, with no abrupt change at the splenic flexure. In a previous study, Birkenkamp-Demtroder et al.[11] analyzed gene expression differences between patients with adenocarcinoma of the cecum compared to sigmoid and rectosigmoid. They identified differences in gene expression in both normal mucosa and cancerous tissue between cecal and sigmoid/rectosigmoid locations. In our study, cecal cancer had worse survival than ascending colon cancer and a lower lymph node yield, further identifying the potentially unique nature of these cancers.

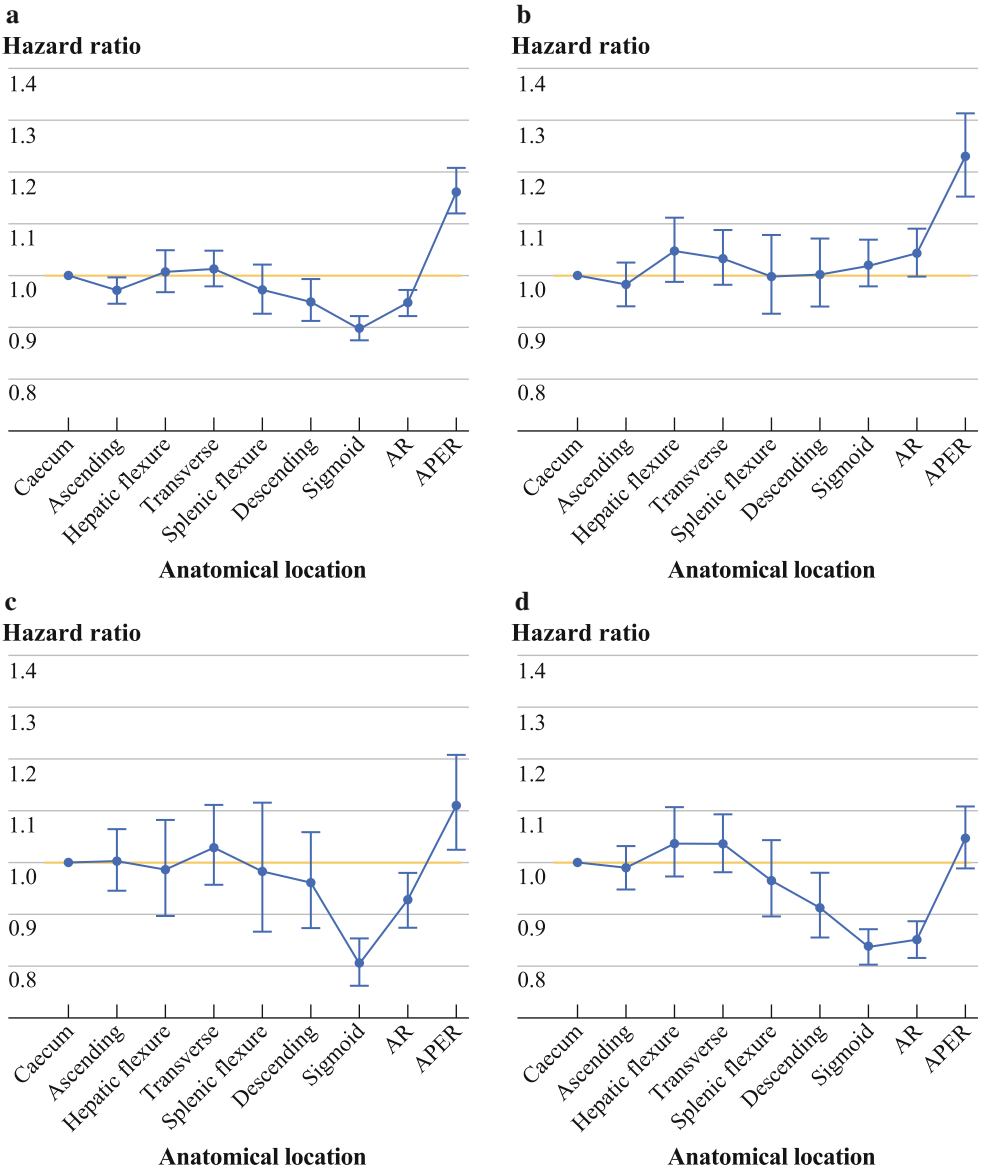

FIG. 3 Clinicopathologic adjusted HRs for 10-year overall survival, split by stage. A HR of <1 indicates improved survival compared to the reference group; >1 indicated worse survival. 95 % CIs are shown by the *tails*; if these cross the HR of 1.0 (indicated by the *horizontal line*), the effect is not significant

The present study suggests that there are important additional factors apart from genetic and molecular changes affecting observed survival rates, including varying lymph node yields and the influence of operation type. The introduction of total mesorectal excision has helped to improve surgical standards for excision of rectal cancer. Similar standardization of surgical technique may improve survival for colonic resections. The results of this study support this notion because the largest variation in lymph node yields was observed in stages 0–II cancer, suggesting significant understaging. Transverse colon cancer represents a significant surgical challenge, as the regional lymph node drainage is centered around the middle colic artery, making surgical dissection difficult. The resultant lower lymph node yields may thus account for the lack of survival differences seen when compared to cecal resection, despite a reduction in the proportion of stage III cancer. Complete mesocolic excision may be a method to ensure dissection in the mesocolic plane and ensure optimum lymph node yield.[12]

In the rectum, anterior resection had improved survival compared to right-sided resection for cecal cancer, but APER had worse survival compared to both anterior resection and cecum. Early data have indicated that low rectal cancer treated with neoadjuvant therapy may be subject to reduced lymph node counts, although further evidence is required.[13–15] Stage III cancer treated with APER also had the highest rate of positive lymph node collection and high lymph node ratios. It may be that patients requiring APER benefit from surgical

subspecialization to minimize margin positive resection rates and maximize lymph node collection; this may lead to better outcomes for the individual patient.

Using SEER data, Meguid et al.[4] previously reported that right-sided cancer had an overall reduced survival compared to left-sided cancer on multivariable analysis. They found no mortality difference between left- and right-sided cancer for stage I (HR 1.003, $p = 0.93$) but reduced mortality for right-sided cancer in stage II disease (HR 0.91, $p < 0.001$). Similar to the present study, theirs was based on a pure SEER data set that was unable to adjust for chemotherapy use. Weiss et al. subsequently compared stage-stratified left versus right colon cancer survival from a SEER–Medicare data set. Overall, they also found no difference (HR 1.01, 95 % CI 0.98–1.04). However, when stratified by stage, stage II right-sided cancer had lower mortality than left-sided cancer (HR 0.92, 95 % CI 0.87–0.97), while stage III right-sided cancer had higher mortality (HR 1.12, 95 % CI 1.06–1.18). Although their data set was able to adjust for chemotherapy use, it only included those aged 65 years or older and should be considered a subset analysis. There were further differences in inclusion criteria limiting these studies compared to the present study: Meguid et al.[4] included patients with stage IV cancer and excluded those who died within 60 days of surgery; Weiss et al.[1] included only patients aged 65 years or older and excluded those dying within 30 days of surgery.

Benedix et al.[5] analyzed right- versus left-sided colon cancer survival from 17,641 German patients from a multicenter observational study, and by including all ages and stages I–III disease and by not excluding postoperative moralities, they approximated a closer group to the present study. Their overall adjusted analysis found that right colon cancer had a worse survival compared to left (HR 1.12, 95 % CI 1.02–1.23), and their unadjusted stage-by-stage analysis found reduced right-sided survival for stage I cancer (78 vs. 84 %, $p = 0.01$) and stage III cancer (55 vs. 60 %, $p < 0.01$), but not for stage II cancer (74 vs. 72 %); these findings are more in keeping with those from the present study.

In conclusion, this study has demonstrated that survival differences for colon and rectal cancer depend on the specific segment and operation performed. It is likely that combining this information with molecular features distinct to specific tumor locations will form the most accurate prognoses; stratifying by colon versus rectum, or left versus right colon is less accurate. Cancer of some segments poses the greatest surgical challenge, with APER patients experiencing higher-stage tumors, the lowest overall lymph node yields, and the worst survival. Focus on quality improvements in these areas may further improve patient outcomes.

DISCLOSURES The authors declare no conflict of interest.

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