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Right colon cancer: Left behind

P. Gervaz [a,*], M. Usel [b], E. Rapiti [b], P. Chappuis [c], I. Neyroud-Kaspar [b], C. Bouchardy [b]

[a] Division of Coloproctology, Clinique Hirslanden La Colline, Geneva, Switzerland
[b] Geneva Cancer Registry, Institute of Global Health, Geneva University of Medicine, Switzerland
[c] Division of Genetic Medicine, Geneva University Hospital, Geneva, Switzerland

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Abstract

Introduction: Prognosis of colon cancer (CC) has steadily improved during the past three decades. This trend, however, may vary according to proximal (right) or distal (left) tumor location. We studied if improvement in survival was greater for left than for right CC.
Methods: We included all CC recorded at the Geneva population-based registry between 1980 and 2006. We compared patients, tumor and treatment characteristics between left and right CC by logistic regression and compared CC specific survival by Cox models taking into account putative confounders. We also compared changes in survival between CC location in early and late years of observation.
Results: Among the 3396 CC patients, 1334 (39%) had right-sided and 2062 (61%) left-sided tumors. In the early 1980s, 5-year specific survival was identical for right and left CCs (49% *vs*. 48%). During the study period, a dramatic improvement in survival was observed for patients with left-sided cancers (Hazard ratio [HR]: 0.42, 95% confidence interval [CI]: 0.29–0.62, $p < 0.001$) but not for right CC patients (HR: 0.76, 95% CI: 0.50–1.14, $p = 0.69$). As a consequence, patients with distal CC have a better outcome than patients with proximal CC (HR for left *vs*. right CC: 0.81, 95% CI: 0.72–0.90, $p < 0.001$).
Conclusion: Our data indicate that, contrary to left CC, survival of patients with right CC did not improve since 1980. Of all colon cancer patients, those with right-sided lesions have by far the worse prognosis. Change of strategic management in this subgroup is warranted.
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Keywords: Colon cancer; Location; Survival; Cancer registry; Population-based study

Introduction

Clinical outcome of colon cancer (CC) is continuously improving in Europe,[1] North America,[2] and Asia.[3] Implementation of screening programmes,[4] facilitated access to colonoscopy,[5] and development of efficient chemotherapy regimen,[6] are factors which contributed to this process. In large descriptive data on cancer survival, the colon is considered as an organ *per se* and no distinction is made between CC sub-sites. Therefore, clinicians are likely to consider that improvement in survival encompasses all CC, irrespective of tumor location proximal or distal to the splenic flexure.

In fact, right- and left-sided CC may represent different embryological, epidemiological, physiological, pathological, genetic and clinical entities.[7] Relationship between CC location and survival has been recently investigated in several studies. In particular, two large population-based studies reported conflicting results, even though both queried the same (Surveillance, Epidemiology and End Results-SEER) database.[8,9] Most studies however, did not consider the evolution of prognosis over a long period of time. In addition, these studies are hampered by the fact that they do not report the cause of death and often fail to provide adequate information regarding adjuvant chemotherapy.[10,11] A recent meta-analysis concluded that the impact of tumor location on CC survival remains unclear.[12]

The objective of our study is to assess the differences of CC presentation and 5-year survival in Geneva between 1980 and 2006 according to tumor location. We postulated that better outcome was not homogenously distributed

* Corresponding author. Division of Coloproctology, Clinique Hirslanden La Colline, Avenue de la Roseraie 76A, 1205 Geneva, Switzerland. Tel.: +41 22 789 5050; fax: +41 22 789 0591.
E-mail address: pascalgervaz@gmail.com (P. Gervaz).

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among all CC patients, and hypothesized that, during this time period, improvement in survival was superior for left than for right colon carcinomas.

Patients and methods

Geneva Cancer Registry

We used data from the Geneva Cancer Registry, which records since 1970 all incident cancers occurring in the population of the county (approximately 450,000 inhabitants in 2010). All hospitals, pathology laboratories and practitioners are requested to report cancer cases. Recorded data include socio-demographic variables, tumor characteristics (coded according to the International Classification of Diseases for Oncology [ICD-O]), stage at diagnosis (coded according to the Tumor Node Metastasis [TNM] classification of malignant tumors), and treatment received within 6 months after diagnosis.

The Registry regularly assesses survival. The index date refers to the date of confirmation of diagnosis (usually from the pathology report of the biopsy/operative specimen) or the date of hospitalization if it precedes the diagnosis. In addition to passive follow-up (routine examination of death certificates and hospital records), active follow-up is carried out yearly by linking the files of the Cantonal Population Office in charge of the registration of the resident population with the Registry database, using a personal identity number. The cause of death is established by consulting clinical records and/or by inquiring the patient's physician, and coded according to the international statistical classification of diseases and health-related problems established by the World Health Organization.

Patients

For the purpose of this study, we considered all invasive primary cancers of the colon occurring in the resident population diagnosed between 1980 and 2006. We excluded patients with previous malignant tumors other than basal cell skin carcinoma (n = 513), colonic tumors other than adenocarcinomas (lymphomas, sarcomas, n = 41), familial adenomatous polyposis, tumors of the appendix (ICD-O code 18.1, n = 58), and CC with undetermined location (ICD-O code 18.9, n = 37). We also excluded patients with cancer discovered at death or with less than 1 day of survival (n = 225). Finally, the study included a total of 3396 patients with sporadic adenocarcinomas of the colon. The Geneva Tumor Registry keeping all data strictly anonymous, and since the study did not require additional clinical information, approval of the Ethics Committee was not required.

We divided patients in 2 groups according to colonic tumor location. We considered that the frontier between right-sided and left-sided tumors was the splenic flexure: thus, right colon cancers included tumors occurring in the cecum, ascending colon, hepatic flexure, and transverse colon (ICD-O codes: C18.0, C18.2–18.4). Left-sided tumors included tumors located at the splenic flexure, descending colon, sigmoid, and recto-sigmoid junction (ICD-O codes: C18.5–18.7, 19.9). All patients were followed up for survival until 31 December 2011.

Variables

Variables of interest were: age at diagnosis (<65, 65–74, 75 years and more), year of diagnosis (3 years periods), social class based on patients' last occupation and for unemployed women, that of the spouse (high, medium, low, unknown), country of birth (Switzerland, other) and healthcare sector (public, private). The origin of diagnosis was considered in 4 groups: symptoms (tumor diagnosed following symptoms, fortuitous (tumor discovered during investigation of symptoms related to other pathology), screening (including test for fecal occult blood, sigmoidoscopy, or colonoscopy), and unknown. Tumor stage was coded according to TNM classification: we considered pathological classification and when missing clinical classification) and regrouped stage in 4 groups: I (T1, T2, N0, M0), II (T3, T4, N0, M0), III (Any T, N1, N2, M0), and IV (any T, any N, M1). We also considered pathological tumor size in mm, and tumor differentiation (well, moderate, poor, unknown). Treatment was considered in 5 groups: surgery alone, surgery with adjuvant chemotherapy, chemotherapy alone, other methods (radiation therapy, palliative measures), and no treatment.

Statistical analysis

We compared patients and tumor characteristics between left and right CC patients by chi-square test of heterogeneity. We calculated the effect of tumor location on 5-year specific survival (i.e. considering only death linked to CC) by Cox models. CC-specific survival time was measured from the date of confirmation of diagnosis to the date of death due to CC with times censored at last contact for patients who were lost to follow-up or who remained alive in December 2011, or at the date of death for those who died of causes other than CC. All other variables linked to 5-year CC mortality in monovariate Cox-model were considered as confounding variables and adjusted for when we estimated the independent effect of CC location on specific survival. Finally, 2 distinct adjusted models for right-sided and left-sided tumors were performed to study time trends in survival for each CC sub-sites. We considered differences to be statistically significant at p (two-sided test) value <0.05. We performed all analyses using SPSS software (Version 15; SPSS Inc., Chicago, IL, USA).

Results

Among the 3396 patients of the study, 1334 (39%) had right CC and 2062 (61%) left CC. Patients' and tumors

characteristics according to CC location are summarized in Table 1. Compared with left CC patients, those with right CC were older (mean age at diagnosis: 71.9 *vs*. 68.4 years, $p < 0.001$), more likely to be women (55% *vs*. 47%, $p < 0.001$), and born in Switzerland (48% *vs*. 35%, $p = 0.002$). Throughout the study period, repartition of CC by subsite remained relatively stable. Right CCs were more often discovered fortuitously (16% *vs*. 10%, $p < 0.001$) while the proportion of CC discovered by screening was low (around 55%) but similar according to subsite. Right CC patients presented more frequently with advanced stage at diagnosis (proportion of stage I: 11% *vs*. 19%, $p < 0.001$), with poorly differentiated tumors (21% *vs*. 9%, $p < 0.001$), and were less frequently treated in the private sector (28% *vs*. 35%, $p < 0.001$). Treatment approaches did not differ significantly between right and left CCs; a similar percentage of patients in both groups underwent adjuvant chemotherapy (16.3% *vs*. 17.1%, respectively). Fig. 1 illustrates Kaplan–Meier survival for the whole population, over the entire period 1980–2006; 5-year specific survival was significantly poorer for patients with right-sided (52.8%; 95% CI 50.1%–55.5%) than for patients with left-sided (60.1%; 95% CI 57.9%–62.3%) tumors (log-rank test, $p > 0.001$).

All patients had at least 5 years of follow-up. The median follow-up of CC patients was 49 months. At the time of the last follow-up (31-12-2011), 1650 (49%) patients were alive, 1368 (40%) died from CC, and 378 (11%) died from other causes. Table 2 presents the effect of patients and tumor characteristics on CC specific mortality when both CC sub-sites are considered together. Risk of specific mortality are presented as crude Hazard ratio [HR] derived for univariate Cox models and as adjusted HR [$HR_{adjusted}$] derived from multivariate Cox analyses. Age, country of birth, socioeconomic status, sector of care, origin of diagnosis, stage, histologic differentiation, treatment and period of diagnosis were significantly correlated with CC prognosis in univariate analysis. These 6 variables were adjusted for in multivariate models. There was a 52% reduction in the risk of CC mortality between patients diagnosed in the years 1980–82 and those diagnosed in 2004–2006 (HR 0.48, 95% confidence interval [CI]: 0.38–0.61, $HR_{adjusted}$: 0.56, 95% CI: 0.44–0.68). Also, patients with right CC had 30% over-mortality in comparison with left CC patients (HR: 1.30, 95% CI: 1.17–1.45). In multivariate analysis, this over-mortality associated with right-sided CC was slightly reduced to 25% ($HR_{adjusted}$: 1.25, 95% CI: 1.12–1.39).

Table 3 presents 5-year specific survival and adjusted specific CC mortality by time period for left and right colon cancers. Fig. 2 displays the evolution of observed 5-year CC specific survival for left and right CC and Fig. 3 summarizes the trend of specific CC mortality as derived from analyses adjusted for other prognostic factors for all CCs (panel A), for left CCs (panel B) and right CCs (panel C). Overall, the risk of dying from CC decreased by 52% in Geneva County during the study period (Fig. 2). However, trends in CC survival strongly differed according to tumor location (Table 3 and Fig. 1). In adjusted Cox model, we observed a 58% decrease of risk of left CC specific

Table 1
Patient and tumor characteristics according to tumor location among colon cancer patients.

	Left colon (N = 2062) N (%)	Right colon (N = 1334) N (%)	Chi-square p value[a]
Gender			<0.001
Male	1096 (53.2)	596 (44.7)	
Female	966 (46.8)	738 (55.3)	
Age in years			<0.001
≤64	732 (35.5)	364 (27.3)	
65–74	605 (29.3)	328 (24.6)	
≥75	725 (35.2)	642 (48.1)	
Mean (±SD)	68.4 (±12.3)	71.9 (±12.7)	<0.001[b]
Country of birth			0.002
Switzerland	1285 (62.3)	900 (67.5)	
Others	777 (37.7)	434 (32.5)	
Socioeconomic status			0.251
Middle/Low	1424 (80.5)	893 (82.2)	
High	345 (19.5)	193 (17.8)	
Unknown	293	248	
Sector of care			<0.001
Private	713 (34.6)	372 (27.9)	
Public	1349 (65.4)	962 (72.1)	
Period of diagnosis			0.459
1980–82	211 (10.2)	121 (9.1)	
1983–85	218 (10.6)	124 (9.3)	
1986–88	249 (12.1)	148 (11.1)	
1989–91	202 (9.8)	144 (10.8)	
1992–94	245 (11.9)	148 (11.1)	
1995–97	236 (11.4)	159 (11.9)	
1998–00	211 (10.2)	158 (11.8)	
2001–03	260 (12.6)	165 (12.4)	
2004–06	230 (11.2)	167 (12.5)	
Origin of diagnosis			<0.001
Symptoms	1694 (85.1)	1010 (78.0)	
Fortuitous	194 (9.7)	212 (16.4)	
Screening	102 (5.1)	73 (5.6)	
Unknown	72	39	
Stage[c]			<0.001
I	318 (18.8)	130 (11.3)	
II	515 (30.5)	386 (33.5)	
III	365 (21.6)	273 (23.7)	
IV	492 (29.1)	364 (31.6)	
Unknown	372	181	
Differentiation			<0.001
Well	591 (35.4)	309 (27.8)	
Moderate	926 (55.4)	569 (51.3)	
Poor	154 (9.2)	232 (20.9)	
Unknown	391	224	
Treatment			<0.001
Surgery alone	1367 (66.3)	936 (70.2)	
Surgery + Chemotherapy	353 (17.1)	218 (16.3)	
Chemotherapy alone	30 (1.5)	31 (2.3)	
Other	145 (7.0)	30 (2.2)	
None	167 (8.1)	119 (8.9)	

[a] After exclusion of unknown cases.
[b] p Value for t-test.
[c] According to pathological TNM and when missing clinical TNM.

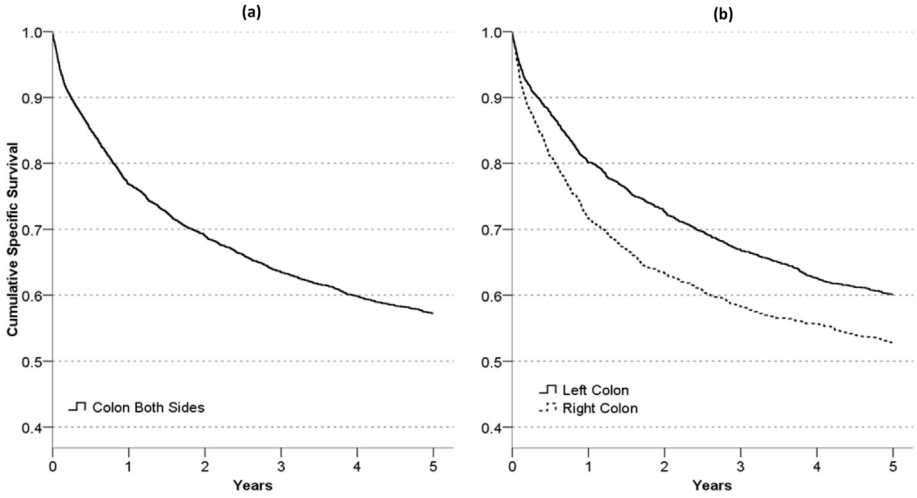

Figure 1. Kaplan–Meier 5-year specific survival for the whole population (1980–2006); All tumors (a); right-*vs*. left-sided CCs (b).

mortality in the years 2004–6 *vs*. 1980–82 ($HR_{adjusted}$: 0.42, 95% CI: 0.29–0.62). For right CC, the decrease of CC specific mortality was 24% only, with corresponding $HR_{adjusted}$ for the period 2004–6 *vs*. 1980–82 of 0.76, 95% CI: 0.50–1.14 (Table 3 and Fig. 2). As a consequence, patients with left CC have in 2004–2006 a better outcome than patients with proximal CC (HR for left *vs*. right CC: 0.81, 95% CI: 0.72–0.90, $p < 0.001$).

Discussion

Between 1980 and 2006, the risk of dying from CC decreased by 52% in Geneva County. However, our data clearly demonstrate that the increase of survival is mainly limited to patients with left-sided tumors. By contrast, there was no significant improvement of survival for patients with right CC. In 1980–1982, right-sided and left-sided tumors had similar 5-year survival rates (49% *vs*. 47%, respectively). In 2004–2006, the situation had dramatically changed; 5-year CC survival was 75% for left-sided *vs*. 60% for right-sided tumors. Since treatment does not vary according to cancer site within the colon (surgery with or without adjuvant chemotherapy), it is crucial to understand why this dichotomy occurred during this time period.

In our population, like in others,[13,14] differences exist in patients and tumor presentation between left and right CC: patients with right-sided tumors are more often females, slightly older, and present more often with advanced (T3/T4) tumors. However, these differences do not explain our findings, since we adjusted CC specific mortality on those variables. Our hypothesis is that patients with right-sided CC, contrary to left CC, did not benefit from advances in surgical treatment that occurred during the study period. For example, widespread adoption of total mesorectal excision (TME) has permitted reducing local recurrences rates by 50% after surgery for rectal cancer.[15] By comparison, surgical strategies for colon cancer have remained unchanged, and in many European countries prognosis for rectal cancer is currently better than for colon cancer.[16–18] Surgical management of CC is poorly standardized in Western countries, where institutional guidelines are restricted to a couple of basic recommendations.[19] The authors of the CLASICC trial reported unacceptably high (15%) local recurrence rates after right colectomy.[20] The role of an extensive lymphadenectomy for T3/T4 tumors, as recommended for rectal cancers, is often neglected in right CC. Japanese surgeons, by contrast, consider that right colectomy for cancer is a complex procedure, which requires extensive dissection of the superior mesenteric vessels and its branches, including middle colic vessels.[21,22] This surgical approach (complete mesocolic excision plus central vascular ligation) has recently been popularized in a few European specialized centers,[23] but was not performed in Geneva during the study period. By contrast, in the early 1990s, Geneva surgeons enthusiastically adopted the techniques of total mesorectum excision and proximal ligation of the inferior mesenteric vessels for left-sided and rectal cancers, with subsequent dramatic improvement in survival. Thus, sub-optimal surgical care in this time period may be responsible for poor prognosis of right colon cancers. Our data suggest that complete mesocolic excision with central vascular ligation should be routinely implemented for locally advanced (stages II–III) right colon cancers.

Another hypothesis is the sub-optimal use of adjuvant chemotherapy for lymph node positive (stage III) CC in particular for patients affected by right colon cancer. Such adjuvant treatment increases the survival rates by approximately 30%.[24] In a previous study, we reported an underuse of such therapy in daily practice, in particular for right CC.[6] This could also contribute to discrepancies in survival

Table 2
Effect of patient and tumor characteristics on 5-year colon cancer specific mortality.

	Univariate models			Multivariate model[a]		
	HR	(95% CI)	p Value	HR	(95% CI)	p Value
Gender						
Male	1.00			1.00		
Female	1.05	(0.94–1.17)	0.371	0.89	(0.80–1.00)	0.057
Age in years						
≤64 y.	1.00		<0.001			<0.001
65–74 y.	1.18	(1.02–1.37)	0.026	1.20	(1.03–1.39)	0.022
≥75 y.	1.87	(1.64–2.13)	<0.001	1.67	(1.43–1.94)	<0.001
Country of birth						
Switzerland	1.00			1.00		
Others	0.78	(0.70–0.87)	<0.001	0.96	(0.85–1.09)	0.538
Socioeconomic status						
Medium–Low	1.00		<0.001	1.00		0.426
High	0.75	(0.64–0.88)	<0.001	0.92	(0.78–1.09)	0.319
Unknown	1.13	(0.98–1.30)	0.095	0.93	(0.79–1.09)	0.345
Sector of care						
Private	1.00			1.00		
Public	1.67	(1.48–1.89)	<0.001	1.25	(1.09–1.43)	0.001
Period of diagnosis						
1980–82	1.00		<0.001	1.00		<0.001
1983–85	0.98	(0.79–1.22)	0.868	1.14	(0.91–1.43)	0.250
1986–88	0.95	(0.77–1.16)	0.592	1.18	(0.95–1.47)	0.135
1989–91	0.80	(0.64–0.99)	0.042	1.02	(0.80–0.30)	0.857
1992–94	0.76	(0.61–0.94)	0.013	0.87	(0.68–1.10)	0.240
1995–97	0.73	(0.59–0.91)	0.005	0.84	(0.66–1.07)	0.159
1998–00	0.60	(0.48–0.76)	<0.001	0.67	(0.51–0.86)	0.002
2001–03	0.55	(0.44–0.69)	<0.001	0.62	(0.48–0.80)	<0.001
2004–06	0.48	(0.38–0.61)	<0.001	0.56	(0.42–0.73)	<0.001
Origin of diagnosis						
Fortuitous	0.84	(0.71–1.00)	0.048	0.95	(0.79–1.14)	0.590
Symptoms	1.00		<0.001	1.00		0.158
Screening	0.31	(0.21–0.45)	<0.001	0.65	(0.45–0.95)	0.026
Unknown	0.84	(0.62–1.14)	0.258	0.94	(0.68–1.29)	0.694
Stage[b]						
I	1.00		<0.001	1.00		<0.001
II	5.70	(3.46–9.37)	<0.001	4.55	(2.75–7.51)	<0.001
III	12.5	(7.64–20.4)	<0.001	11.5	(7.02–19.0)	<0.001
IV	60.3	(37.2–97.7)	<0.001	48.2	(29.5–79.0)	<0.001
Unknown	12.87	(7.84–21.11)	<0.001	8.16	(4.92–13.5)	<0.001
Differentiation						
Well	1.00		<0.001	1.00		<0.001
Moderate	1.04	(0.91–1.19)	0.585	1.13	(0.97–1.32)	0.124
Poor	2.17	(1.83–2.57)	<0.001	2.04	(1.69–2.45)	<0.001
Unknown	1.47	(1.25–1.73)	<0.001	1.09	(0.91–1.29)	0.344
Treatment						
Surgery alone	1.00		<0.001	1.00		<0.001
Surgery + Chemotherapy	1.53	(1.33–1.77)	<0.001	0.82	(0.69–0.97)	0.022
Chemotherapy alone	6.32	(4.82–8.30)	<0.001	1.97	(1.45–2.68)	<0.001
Others	1.53	(1.21–1.92)	<0.001	1.01	(0.78–1.29)	0.969
None	8.64	(7.42–10.05)	<0.001	3.57	(3.00–4.24)	<0.001
Tumor location						
Left	1.00			1.00		
Right	1.30	(1.17–1.45)	<0.001	1.25	(1.12–1.39)	<0.001

HR: Hazard Ratio, CI: Confidence Interval.
[a] Adjusted for all variables with significant effect in monovariate analysis i.e. gender, age, country of birth, socioeconomic status, sector of care, period, origin of diagnosis, stage, differentiation, and treatment.
[b] According to pathological TNM and if missing clinical TNM.

progress between CC locations. Another intriguing hypothesis is that right-sided tumors are biologically different, and might be less responsive to 5-fluorouracile and/or oxaliplatin-based current chemotherapy.

We are aware of the limitations of our study, related to its observational nature. We considered numerous variables to decrease possible biases, which could at least in part explain the differences of survival between CC sub-sites.

Table 3
Evolution of 5-year colon cancer survival and risk of specific colon cancer mortality according to colon cancer site and period.

Period of diagnosis	Colon cancer sub site							
	Left				Right			
	5-Year specific survival	$HR_{adjusted}$[a]	(95% CI)	p Value	5-year specific survival	$HR_{adjusted}$[a]	(95% CI)	p Value
1980–82	47%	1.00		<0.001	49%	1.00		P = 0.43
1983–85	51%	1.07	(0.80–1.43)		48%	1.33	(0.92–1.92)	
1986–88	51%	1.07	(0.81–1.43)		47%	1.36	(0.94–1.95)	
1989–91	55%	0.94	(0.68–1.28)		53%	1.12	(0.76–1.65)	
1992–94	59%	0.77	(0.56–1.05)		51%	0.98	(0.66–1.44)	
1995–97	62%	0.70	(0.50–0.97)		51%	1.02	(0.69–1.51)	
1998–00	67%	0.55	(0.39–0.78)		58%	0.87	(0.58–1.28)	
2001–03	71%	0.48	(0.34–0.69)		56%	0.82	(0.55–1.21)	
2004–06	75%	0.42	(0.29–0.62)		60%	0.76	(0.50–1.14)	

HR: Hazard Ratio, CI: Confidence Interval.
[a] Adjusted for gender, age, country of birth, socioeconomic status, sector of care, origin of diagnosis, stage, differentiation, and treatment.

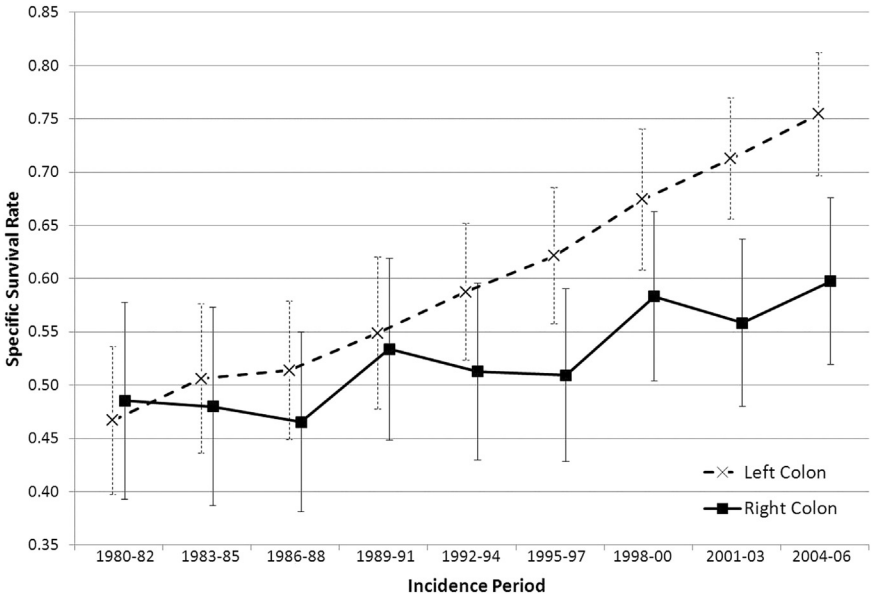

Figure 2. 5-Year observed specific colon cancer survival according to tumor location and incidence period.

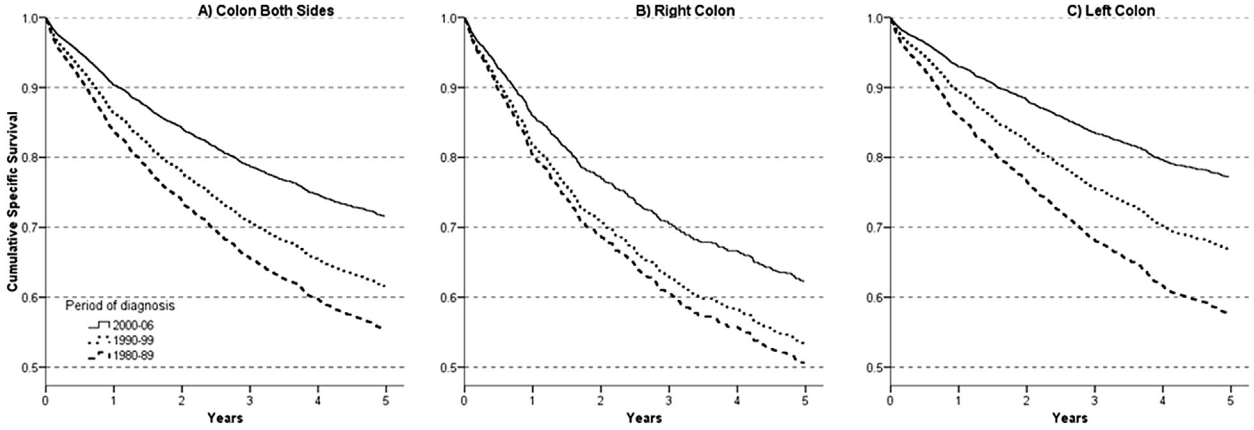

Figure 3. Cox multi-adjusted five-year specific survival for all (a) right (b), and left (c) colon cancer according to three time period of diagnosis (1980–89, 1990–99, and 2000–06).

However, other putative confounding factors such as the presence of co-morbidities, the timing of surgery (emergency procedures related to occlusion or perforation), surgical techniques and the surgeon's experience, are not recorded in our population-based data set. In summary, our results indicate that, of all Geneva colorectal cancer patients, those with right-sided tumors have by far the worse prognosis. This dichotomy was not present in the 1980s. At that time, prognosis was identical irrespective of CC location proximal or distal to the splenic flexure. Our data clearly demonstrates the huge progresses made in the management of left-sided colon carcinomas – for these patients survival increased by 58% over a 25-year period of time. This improvement in survival, for some reason, was not mirrored in patients with right-sided tumors, who were left behind. This subgroup should be considered the next target for implementing improved surgical strategies, such as right mesocolic dissection with D3 lymphadenectomy for T3/T4. Finally, our results also support the new paradigm, which considers left and right colon cancer as distinct clinical entities[25]; when performing international comparisons on cancer treatment and survival, results for CC should be stratified according to tumor location proximal or distal to the splenic flexure.

Conflict of interest

No.

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