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ORIGINAL ARTICLE – COLORECTAL CANCER

Oncologic Effects of Primary Tumor-Sidedness on Patients with Stages 1–3 Colon Cancer: A Meta-Analysis

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ABSTRACT

Background. Previous studies comparing the oncologic outcomes of primary tumor-sidedness for patients with colon cancer have reported a worse prognosis for those with right-sided tumors. However, most of these studies evaluated patients with metastatic disease.

Methods. PubMed, EMBASE, and the Cochrane Library were searched for studies that assessed the effects of primary tumor-sidedness on survival outcomes for patients with stages 1, 2, and 3 colon cancer. The hazard ratio (HR) for primary tumor location was estimated for overall survival (OS), cancer-specific survival (CSS) and disease-free survival (DFS).

Results. The inclusion criteria were met by 37 studies involving 581,542 patients. The patients with a right-sided tumor had better CSS (HR, 0.67; 95% confidence interval [CI], 0.56–0.80; $p < 0.0001$) among those with stage 1 cancer as well as better OS (HR, 0.89; 95% CI 0.86–0.92; $I^2 = 19\%$) and CSS (HR, 0.78; 95% CI 0.70–0.86; $I^2 = 78\%$) among those with stage 2 cancer. In contrast, among the patients with stage 3 cancer, those with a right-sided tumor had worse OS (HR, 1.12; 95% CI 1.04–1.20; $p = 0.002$), CSS (HR, 1.05; 95% CI 1.01–1.10; $p = 0.02$), and DFS (HR, 1.32; 95% CI 1.07–1.63; $p = 0.008$).

Conclusions. Primary tumor location may be a prognostic factor for patients with non-metastatic colon cancer. The prognosis for patients with right-sided tumor may be better for those with stage 1 or 2 cancer, but worse for those with stage 3 cancer.

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Recent studies have identified many prognostic factors for patients with colorectal cancer (CRC). Since the report of Venook et al.[1] at an American Society of Clinical Oncology meeting, researchers have increasingly focused on primary tumor location. Differences in clinical presentation, patient demographics, and tumor biology between right- and left-sided colon cancers may result in oncologic distinction.[2–5]

Many studies, including meta-analyses of colon cancer patients, have reported a worse prognosis for those with right-sided tumors. However, the influence of tumor side on prognosis has not been validated, and most recent studies assessing the prognostic relevance of tumor sidedness evaluated patients with metastatic colon cancer.

Therefore, because of our interest in understanding the oncologic impact of tumor location in non-metastatic colon cancer, we performed a meta-analysis of patients with stages 1, 2, and 3 colon cancer to evaluate the prognostic role of primary tumor-sidedness.

MATERIALS AND METHODS

This meta-analysis followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[6] Multiple comprehensive databases were searched for studies that assessed the effects of primary tumor-sidedness on oncologic outcome for patients with stages 1, 2, and 3 colon cancer. The study protocol used Cochrane Review Methods.[7]

Data Source and Literature Source

Studies were identified from PubMed (1 January 1976 to 1 October 2017), EMBASE (1 January 1985 to 1 October 2017), and the Cochrane Central Register of Controlled Trials (CENTRAL) (1 January 1987 to 1 October 2017). There were no restrictions on year of publication, and

articles in all languages were sought. The search terms were "colon cancer," "tumor sidedness," "tumor location," "prognosis," and "survival." After the initial electronic search, articles were manually searched to identify additional studies. All articles were assessed individually before inclusion in the study.

Study Selection and Data Extraction

Article titles and abstracts were screened, and full texts were reviewed independently by two reviewers (G.W.H. and M.R.L.) based on the selection criteria. Discrepancies were resolved by discussion between the reviewers.

The included studies assessed survival outcomes including overall survival (OS), cancer-specific survival (CSS), and disease-free survival (DFS) of patients with colon cancer according to the primary tumor location. Primary tumors originating in the cecum, ascending colon, hepatic flexure, or transverse colon were classified as right-sided cancers, and primary tumors originating in the splenic flexure, descending colon, sigmoid colon, or rectosigmoid colon were classified as left-sided cancers. Studies were excluded if they examined patients with stage 4 colon cancer, examined patients with rectal cancer, assessed patients whose tumor pathology was not adenocarcinoma, had no extractable data or authors who were unavailable to provide additional information (e.g., only an abstract was available), were case series with fewer than 10 patients.

All eligible studies were reviewed, and all relevant data were extracted independently by the two reviewers using a predefined data extraction form. The variables recorded were basic publication information including name of the first author, year of publication, and number of patients; demographic and clinical characteristics of all the patients; and outcome measures (OS, CSS, and DFS).

Assessment of Methodologic Quality

The methodologic quality of the included studies was assessed using the Newcastle–Ottawa quality scale (NOS), which allocates a maximum of nine points to each study and classifies a study with a score of six or higher as "high quality."[8] The quality of the included studies was determined by examining three factors: patient selection, comparability of the study groups, and assessment of outcomes.

Statistical Analysis

The meta-analysis determined the hazard ratio (HR), variance, and 95% confidence interval (CI). The presence and extent of heterogeneity were assessed using the Q test and the I^2 index, respectively, and a p value lower than 0.1 was considered statistically significant[9] The DerSimonian–Laird random effects model (REM) was used to pool data in anticipation of cross-study heterogeneity[10] If sufficient data were available, planned subgroup analyses were performed. For these analyses, the long-term oncologic outcomes of tumor sidedness were separately determined for patients with stages 1, 2, and 3 colon cancer. Sensitivity analyses also were performed to assess the robustness of the meta-analysis findings[11,12] Analysis of the data was performed using the trim-and-fill method and an alternative statistical effects model.

An analysis excluding studies with large outlying effects was performed. Analyses of high-quality studies (NOS $\geq$ 6) and large database studies were performed. Publication bias was assessed using the Egger weighted linear regression test and visual inspection of funnel plots of the outcomes[13,14] All data analyses were performed using Review Manager software (version 5.3; London, UK) from the Cochrane Collaboration and Comprehensive Meta-Analysis software (version 3; Englewood, NJ, USA).

RESULTS

Description of Studies

The predefined search strategy and manual searching identified 25,470 potentially relevant articles. We excluded

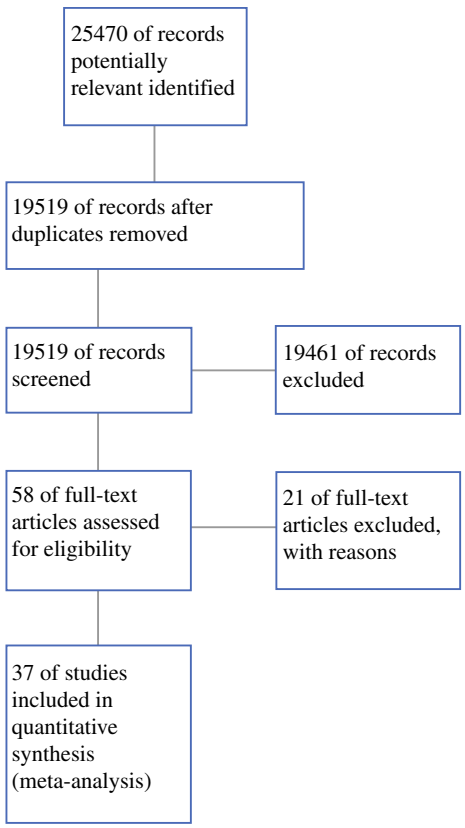


FIG. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram

TABLE 1 Characteristics of the included studies

Study	Design	Period	Country	Analysis method	Right-sided (*n*)	Left-sided (*n*)	Stage	Median follow-up period (months)	Outcome measures	NOS scale
Brungs et al.[15]	RCS, large database	2006–2013	Australia	Multivariate	5051	4458	1, 2, 3	46	OS, CSS	8
Karim et al.[16]	RCS, large database	2002–2008	Canada	Multivariate	3074	3291	1, 2, 3	NR	OS, CSS	6
Lim et al.[17]	RCS, single center	2000–2012	Korea	Multivariate	207	207	1, 2, 3	66.7	OS, DFS	7
Liu et al.[18]	RCS, single center	2008–2014	China	Multivariate	927	966	1, 2, 3	28.3	OS, DFS	6
Qin et al.[19]	RCS, single center	2005–2008	China	Multivariate	317	310	2, 3	66	OS, DFS	7
Wang et al.[43]	RCS, large database	2004–2008	USA	Multivariate	15,816	12,683	2	60	CSS	7
Zhong et al.[20]	RCS, single center	2005–2012	China	Multivariate	98	77	3	> 60	OS, DFS	8
Warschkow et al.[21]	RCS, large database	2004–2012	USA	Multivariate	51,937	39,479	1, 2, 3	38	OS, CSS	8
Ahmadi et al.[22]	RCS, large database	2000–2012	New Zealand	Multivariate	6710	5342	1, 2, 3	50.1	OS	8
André et al.[23]	RCS, multicenter	1998–2001	Multi nations	Multivariate	768	1235	2, 3	113.5	OS	9
Gilardoni et al.[24]	RCS, single center	2006–2009	Italy	Multivariate	100	96	1, 2	> 60	OS, DFS	6
Jeong et al.[48]	RCS, single center	2008–2010	Korea	Multivariate	56	39	2	31	DFS	7
Paquet et al.[25]	RCS, multicenter	2000–2002	Multi nations	Multivariate	359		3	66.3	OS, DFS	6
Pectasides et al.[26]	RCT, multicenter	2005–2008	Greece	Multivariate	122	173	2, 3	74.7	OS, DFS	8
Moritani et al.[49]	RCS, single center	1990–2006	Japan	Multivariate	399	421	1, 2, 3	55.8	DFS	8
Oue et al.[27]	RCS, single center	2005–2007	Germany	Multivariate	63	73	2	51.6	OS	6
Renfro et al.[28]	RCS, multicenter	1989–2002	USA	Multivariate	5415	7434	3	NR	OS, DFS	8
Bhangu et al.[29]	RCS, large database	1995–2009	USA	Multivariate	66,679	41,405	1, 2, 3	NR	OS	7
Gleisner et al.[30]	RCS, large database	1998–2007	USA	Multivariate	91,767	59,829	1, 2, 3	NR	OS	7
Lykke et al.[31]	PCS, large database	2003–2008	Denmark	Multivariate	4050	4533	1, 2, 3	NR	OS	6
Merok et al.[50]	RCS, single center	1993–2003	Norway	Multivariate	133	91	2	65	DFS	7
Ishihara et al.[44]	RCS, multicenter	1997–2000	Japan	Univariate	1219	1954	1, 2, 3	73.8	CSS	6
Kalady et al.[32]	RCS, single center	2000–2009	Canada	Multivariate	237	101	1, 2, 3	60	OS	8
Katkoori et al.[33]	RCS, single center	1986–2004	USA	Multivariate	69	40	3	130.8	OS	7
Powell et al.[45]	PCS, single center	1997–2008	UK	Univariate	134	125	1, 2, 3	94	CSS	7
van Steenbergen et al.[34]	RCS, large database	1997–2009	Netherlands	Multivariate	5218	2706	3	NR	OS	7
Katoh et al.[51]	RCS, single center	1991–2005	Japan	Multivariate	169	215	3	77	DFS	8
Weiss et al.[35]	RCS, large database	1992–2005	USA	Multivariate	36,066	17,735	1, 2, 3	NR	OS	6
Benedix et al.[36]	PCS, multicenter	2000–2004	Germany	Multivariate	9030		1, 2, 3	39	OS	8
Fariña-Sarasqueta et al.[37]	RCS, single center	1996–2004	Netherlands	Multivariate	206	150	2, 3	55, 46	OS, CSS, DFS	8
Roth et al.[38]	PCS, multicenter	NR	Multi nations	Multivariate	1404		2, 3	68	OS, DFS	8
Horst et al.[46]	RCS, single center	1994–2004	Germany	Multivariate	78	83	2	NR	CSS, DFS	6
Deschoolmeester et al.[39]	RCS, multicenter	1996–2000	Belgium	Multivariate	241		1, 2, 3	NR	OS, DFS	5
Meguid et al.[40]	RCS, large database	1988–2002	USA	Multivariate	38,619	28,719	1, 2, 3	NR	OS	8

TABLE 1 continued

Study	Design	Period	Country	Analysis method	Right-sided (*n*)	Left-sided (*n*)	Stage	Median follow-up period (months)	Outcome measures	NOS scale
Burton et al.[41]	RCS, single center	1999–2003	UK	Univariate	133	118	1, 2, 3	NR	OS	5
Sinicrope et al.[42]	RCS, multicenter	1979–1991	USA	Multivariate	286	242	2, 3	NR	OS, DFS	8
Bleeker et al.[47]	RCS, single center	1991–1993	Netherlands	Univariate	26	29	3	47	CSS	6

NOS Newcastle–Ottawa quality scale, *RCS* retrospective cohort study, *OS* overall survival; *CSS* cancer-specific survival. NR not reported, *DFS* disease-free survival *RCT* randomized controlled trial, *PCS* prospective cohort study

5951 articles because they were duplicates and 19,461 articles because their titles and abstracts did not fulfill the selection criteria. After a full-text review of the remaining 58 articles, we excluded 21 articles because of the exclusion criteria they used. Therefore, the meta-analysis included 36 nonrandomized studies and 1 randomized study that examined 581,542 patients (Fig. 1). The studies assessing survival outcomes included 28 studies evaluating OS,[15] 9 studies evaluating CSS,[15,16,21,37,43] and 17 studies evaluating DFS.[17,24,28,37,42,46,48] In 18 studies, patients with stages 1, 2, and 3 colon cancer were examined,[15,21,22,29,35,36,39,44,45,49] and 6 studies provided a separate analysis of patients with stages 1, 2, and 3 colon cancer.[15,16,18,21,35,40] Six studies examined patients with stage 2 or 3 colon cancer,[19,23,26,37,38,42] and two studies separately analyzed patients with stage 2 or 3 colon cancer.[19,38] Five studies examined patients with stage 2 colon cancer only,[27,43,46,48,50] and seven studies examined patients with stage 3 colon cancer only.[20,25,28,33,34,47,51] Evaluation of methodologic quality showed that 35 studies scored high ($\geq$ 6) on the NOS. Table 1 summarizes the characteristics of all 37 included studies.

Outcome Measures

Analysis of the effects that tumor-sidedness has on oncologic outcomes for patients with stages 1, 2, and 3 colon cancer indicated that 27 studies (547,513 patients) reported data on OS. The patients with tumors on the left colon had worse survival than those with tumors on the right colon (HR, 1.07; 95% CI, 1.03–1.11; I^2 = 75%) (Fig. 2a). Nine studies (139,793 patients) reported data on CSS. Right- and left-sided tumors did not differ significantly (HR, 0.98; 95% CI, 0.87–1.10; I^2 = 93%) (Fig. 2b). In 17 studies (21,021 patients), data on DFS were reported. Right- and left-sided tumors showed no significant differences in survival (HR, 1.14; 95% CI, 1.00–1.32; I^2 = 60%) (Fig. 2c). Sensitivity analyses, performed using predefined methods, indicated that the results of these meta-analyses were robust.

Subgroup Analysis

The oncologic impacts of tumor-sidedness were determined for three subgroups according to the colon cancer staging. The analysis of the patients with stage 1 colon cancer (Fig. 3a) indicated that tumor-sidedness had no significant effect on OS (HR, 0.94; 95% CI, 0.89 to − 1.01; I^2 = 50%). The analysis of CSS indicated that the patients with tumors on the right colon had better outcomes (HR, 0.67; 95% CI 0.56–0.80; I^2 = 29%).

The analysis of the patients with stage 2 colon cancer (Fig. 3b) showed that the patients with tumor on the right

colon had better OS (HR, 0.89; 95% CI, 0.86–0.92; I^2 = 19%) and CSS (HR, 0.78; 95% CI, 0.70–0.86; I^2 = 78%). The analysis of DFS indicated no significant difference between those with tumor on the right side and those with tumors on the left side (HR, 0.95; 95% CI, 0.74–1.23; I^2 = 0%). The analysis of patients with stage 3 colon cancer (Fig. 4) indicated that those with tumor on the right colon had worse OS (HR, 1.12; 95% CI, 1.04–1.20; I^2 = 83%), worse CSS (HR, 1.05; 95% CI, 1.01–1.10; I^2 = 0%), and worse DFS (HR, 1.32; 95% CI, 1.08–1.63; I^2 = 71%).

Publication Bias

Publication bias was analyzed using the Egger weighted linear regression test, which assesses the asymmetry of funnel plots. The funnel plot for OS (p = 0.09) was found to be asymmetric, indicating the presence of publication bias. The funnel plot for DFS (p = 0.25) indicated no publication bias.

DISCUSSION

Since the reporting of Venook et al.[1] at the American Society of Clinical Oncology meeting in 2016[1] many studies have reported that colon cancer patients with right-sided tumor had worse survival outcomes than those with left-sided tumor. However, most of these studies, including several meta-analyses, evaluated patients with stage 4 disease. Our findings for the patients with stages 1, 2, and 3 colon cancer differ from the results of previous meta-analyses of patients with metastatic colon cancer, which reported worse oncologic outcomes for those with right-sided tumor.[52–54] To our knowledge, the current study is the first meta-analysis to assess the oncologic impact of tumor-sidedness on patients with stages 1, 2, and 3 colon cancer.

Although our primary analysis of patients indicated that those with tumors on the right colon had worse OS, we found no associations of tumor sidedness with CSS or DFS. In the subgroup analyses, we found oncologic differences between early (stages 1 and 2) and advanced (stage 3) colon cancers. Compared with patients who had tumors on the left colon, those with stage 1 or 2 tumor on the right colon had better CSS, and those with stage 2 tumor on the right colon had better OS. Although the analysis of the patients with stage 1 disease indicated no significant association of tumor-sidedness with OS, a trend for better survival among those with right-sided tumor was observed.

On the other hand, the analysis of the patients with stage 3 colon cancer showed results similar to previous findings for patients with stage 4 cancer. We found that patients with stage 3 colon cancer had worse survival outcomes when the tumor was on the right colon rather than the left colon.

These results may be explained by the presence of clinical and molecular differences in the characteristics of colon cancer on the right and left sides. The right-sided colon derives from the embryonic midgut, whereas the left-sided colon derives from the embryonic hindgut. In addition, tumors on the right side more frequently have BRAF mutations, microsatellite instability (MSI), hypermutation, activity of the serrated pathway, and mucinous histology. Tumors on the left side more frequently have a gene expression profile indicating activation of the EGFR receptor pathway and classical chromosomal instability.[2]

It is unclear whether the biologic differences between left- and right-sided tumors were responsible for the clinical differences in survival outcomes. The reasons for the inconsistent relationships between tumor-sidedness and survival by stage in our study also are not clear. Several studies have reported that trends for better survival outcomes of patients with stage 1 or 2 disease are related to tumor biology, especially MSI.[16,35,44] These findings are consistent with the observation that the MSI-positive tumor predominantly seen in right-sided colon[5] have a better overall prognosis and a more favorable stage profile.[55–57]

Previous studies of colon cancer patients have reported that 20% to 25% of stage 2 right-sided cancers are MSI-positive, but that fewer than 15% of stage 3 cancers on the right colon are MSI-positive, and even fewer stage 4 cancers on the right colon are MSI-positive.[57,58] Part of the reason for the poorer survival of patients with tumors on the right side is that many of these patients have stage 3 or 4 colon cancer. Patients with advanced cancers (e.g., stage 3) are more likely to relapse than those with early-stage cancers (stage 1 or 2). Once recurrent or metastatic colon cancer is established, recurrence arising from right-sided tumors may have a more aggressive phenotype or greater resistance to current therapeutic agents than recurrence arising from left-sided tumors.[59–61]

Another possible explanation for the survival differences we have identified in this report is that patients with fewer comorbidities and less frailty may be more likely to receive colonoscopy. Although colonoscopy is the gold standard for investigation of the colon, sigmoidoscopy is more common, and a complete colonoscopy is sometimes not possible. Examination of the entire colon may be technically difficult and might be prevented due to the poor general condition of the patient. In addition, patients with right-sided cancer are less likely to receive colonoscopy because they are more likely to lack specific symptoms. Therefore, healthier patients may receive colonoscopy in regular health checkups, and colonoscopy is more likely to

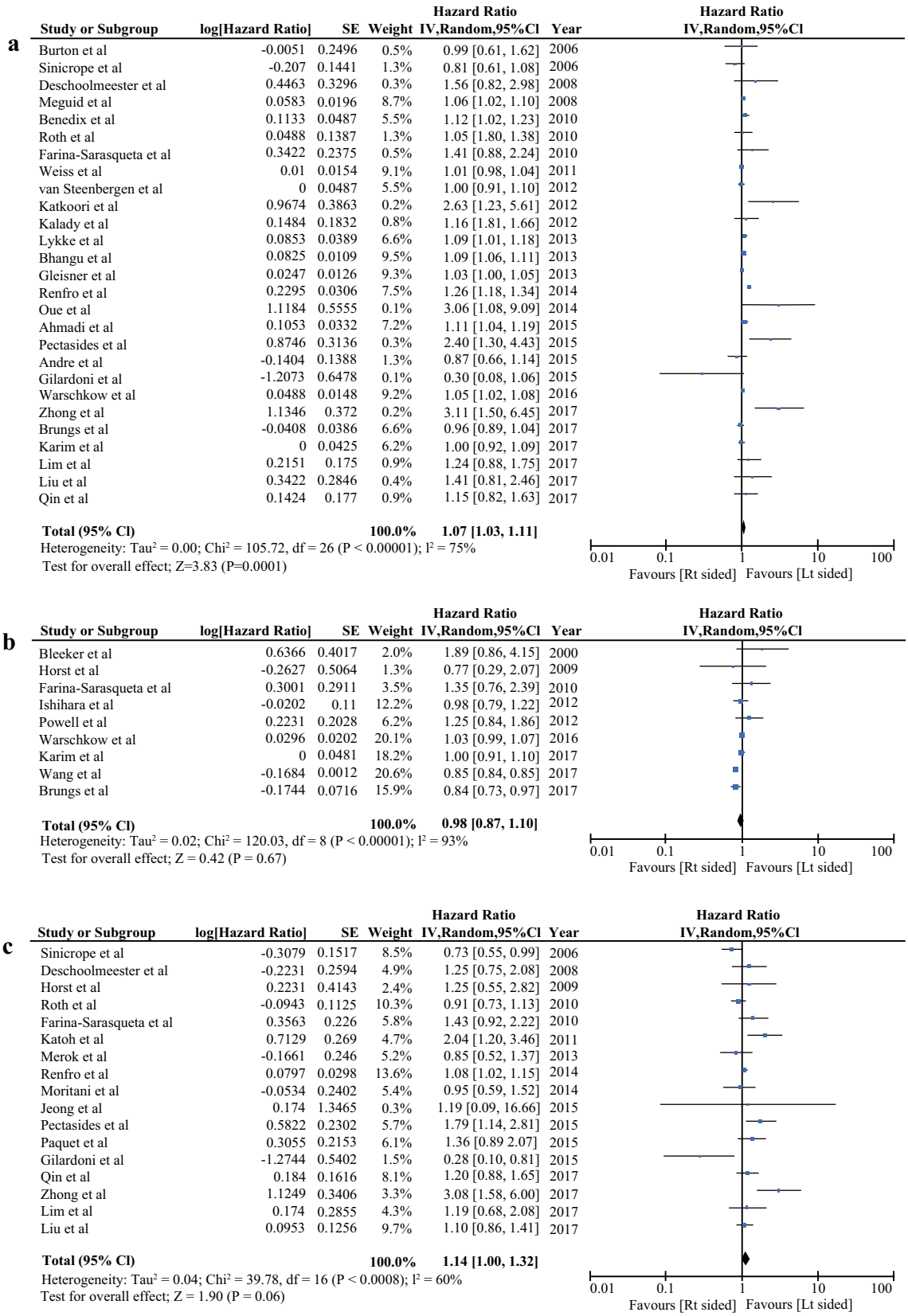
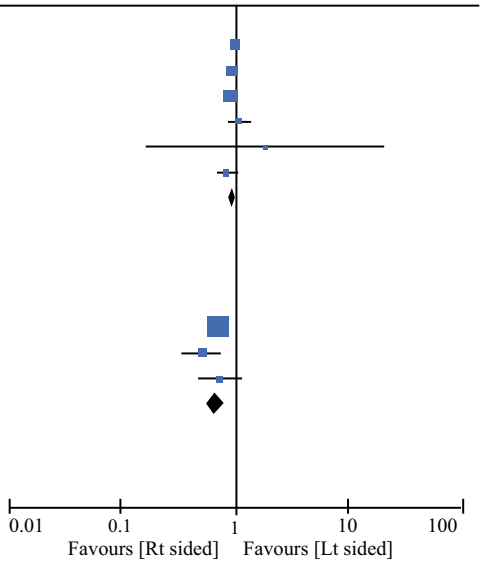


FIG. 2 Meta-analysis of oncologic effects of tumor-sidedness on patients with stages 1–3 colon cancer. **a** Overall survival. **b** Cancer-specific survival. **c** Disease-free survival

a

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV,Random, 95% CI	Year
1.1.1 OS					
Meguid et al	0.0022	0.0381	26.5%	1.00 [0.93, 1.08]	2008
Weiss et al	-0.0513	0.0391	26.0%	0.95 [0.88, 1.03]	2011
Warschkow et al	-0.1165	0.0295	30.8%	0.89 [0.84, 0.94]	2016
Karim et al	0.0953	0.1139	7.0%	1.10 [0.88, 1.38]	2017
Liu et al	0.6313	1.2262	0.1%	1.88 [0.17, 20.79]	2017
Brungs et al	-0.1744	0.093	9.7%	0.84 [0.70, 1.01]	2017
Subtotal (95% CI)			**100.0%**	**0.94 [0.88, 1.01]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 9.96$, df= 5 (P = 0.08); $I^2 = 50\%$					
Test for overall effect: Z = 1.76 (P = 0.08)					
1.1.2 CSS					
Warschkow et al	-0.3425	0.053	67.8%	0.71 [0.64, 0.79]	2016
Brungs et al	-0.6733	0.1921	17.5%	0.51 [0.35, 0.74]	2017
Karim et al	-0.3147	0.2139	14.7%	0.73 [0.48, 1.11]	2017
Subtotal (95%CI)			**100.0%**	**0.67 [0.56, 0.80]**	
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 2.81$, df= 2 (P = 0.25); $I^2 = 29\%$					
Test for overall effect: Z = 4.41 (P < 0.0001)					



b

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV,Random, 95% CI	Year
1.2.1 OS					
Meguid et al	-0.0943	0.0171	39.5%	0.91 [0.88, 0.94]	2008
Roth et al	-0.4155	0.3694	0.2%	0.66 [0.32, 1.36]	2010
Weiss et al	-0.0834	0.0285	22.0%	0.92 [0.87, 0.97]	2011
Warschkow et al	-0.1625	0.0246	26.7%	0.85 [0.81, 0.89]	2016
Liu et al	0.239	0.3577	0.2%	1.27 [0.63, 2.56]	2017
Brungs et al	-0.1625	0.0639	5.8%	0.85 [0.75, 0.96]	2017
Qin et al	-0.1834	0.3491	0.2%	0.83 [0.42, 1.65]	2017
Karim et al	-0.1165	0.0673	5.3%	0.89 [0.78, 1.02]	2017
Subtotal (95% CI)			**100.0%**	**0.89 [0.86, 0.92]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 8.60$, df= 7 (P = 0.28); $I^2 = 19\%$					
Test for overall effect: Z = 7.18 (P < 0.00001)					
1.2.2 CSS					
Horst et al	-0.2552	0.5014	1.1%	0.77 [0.29, 2.07]	2009
Warschkow et al	-0.2877	0.0352	32.8%	0.75 [0.70, 0.80]	2016
Brungs et al	-0.5276	0.1382	10.6%	0.59 [0.45, 0.77]	2017
Wang et al	-0.1684	0.003	38.3%	0.85 [0.84, 0.85]	2017
Karim et al	-0.1863	0.0943	17.3%	0.83 [0.69, 1.00]	2017
Subtotal (95% CI)			**100.0%**	**0.78 [0.70, 0.86]**	
Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 18.19$, df= 4 (P = 0.001); $I^2 = 78\%$					
Test for overall effect: Z = 4.71 (P < 0.00001)					
1.2.3 DFS					
Horst et al	0.2194	0.417	9.5%	1.25 [0.55, 2.82]	2009
Roth et al	-0.2231	0.2936	19.2%	0.80 [0.45, 1.42]	2010
Merok et al	-0.1661	0.246	27.3%	0.85 [0.52, 1.37]	2013
Jeong et al	0.174	1.3465	0.9%	1.19 [0.09, 16.66]	2015
Qin et al	0.0198	0.3023	18.1%	1.02 [0.56, 1.84]	2017
Liu et al	0.0583	0.2574	25.0%	1.06 [0.64, 1.76]	2017
Subtotal (95% CI)			**100.0%**	**0.95 [0.74, 1.23]**	
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.25$, df= 5 (P = 0.94); $I^2 = 0\%$					
Test for overall effect: Z = 0.37 (P = 0.71)					

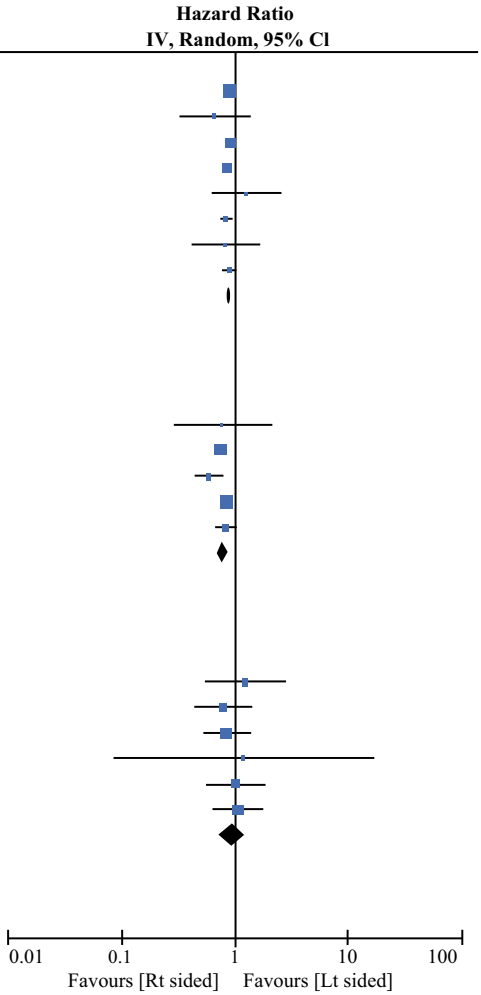


FIG. 3 Meta-analysis of oncologic effects of tumor-sidedness on patients with stage 1 or 2 colon cancer. **a** Stage 1. **b** Stage 2

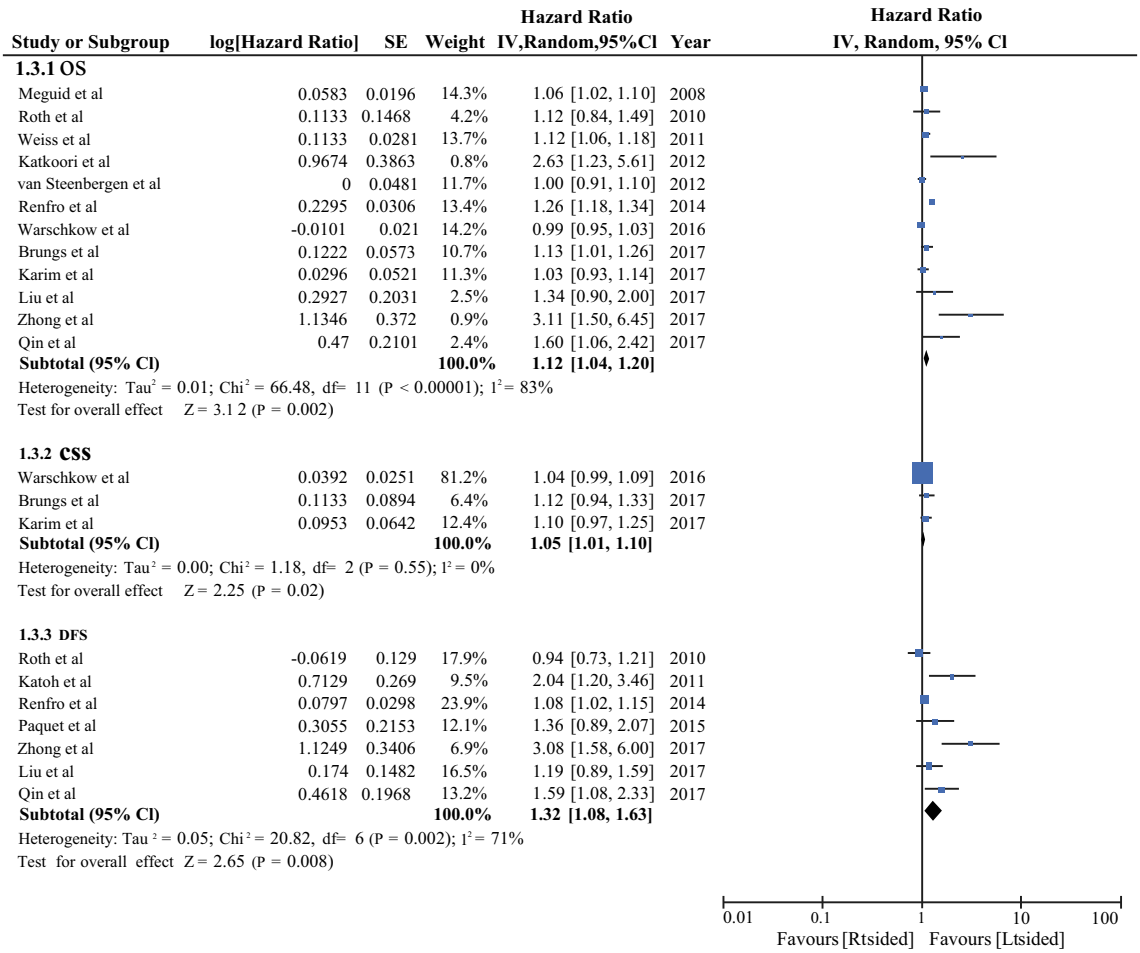


FIG. 4 Meta-analysis of oncologic effects of tumor-sidedness on patients with stage 3 colon cancer

find early-stage cancers on the right colon. This may partly explain why these patients have better survival outcomes than those with the same stage of cancer on the left colon.

Our study had several limitations. First, MSI tumor status was not available, and this prevented direct testing of the hypothesis that MSI status affects the survival of patients with stage 1 or 2 colon cancers on the right colon. Second, the included studies may have had imbalances in certain baseline characteristics of patients with tumors on the left and right sides because they were nonrandomized studies. Third, some heterogeneity may have remained among the included studies despite our performance of subgroup and sensitivity analyses.

CONCLUSIONS

Among the patients with stage 1 or 2 colon cancer, those with right-sided tumor appeared to have better survival outcomes. In contrast, the patients with left-sided tumor appeared to show better survival outcomes for stage 3 colon cancer. Further studies of the molecular biology, such as MSI status, are needed to identify the biologic reasons for the difference in oncologic outcomes between patients with right- and left-sided colon cancers.

DISCLOSURE There are no conflicts of interest.

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