CORRESPONDENCE

RE: Primary Tumor Location as a Prognostic Factor in Metastatic Colorectal Cancer

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With interest we read the paper by Loupakis et al. (1), in which the prognostic impact of primary tumor location in metastatic colorectal cancer (CRC) was investigated. They found that patients with left-sided tumors had a lower risk of death and progression as compared with patients with right-sided tumors. We repeated the analyses for metastatic CRC patients and additionally investigated whether survival outcomes are also more favorable for patients with left-sided tumors as compared with right-sided tumors in case of nonmetastatic CRC.

Data were retrieved from the Netherlands Cancer Registry. All CRC patients diagnosed in the Netherlands between 2003 and 2008 with stage I to IV and who underwent resection were included. In line with Loupakis et al. (1), we classified tumors proximal to the splenic flexure as right sided and tumors distal to the splenic flexure as left sided. Crude five-year overall survival (OS) was calculated using Kaplan-Meier curves. OS was defined as the time from diagnosis to death or last follow-up date. Multivariable Cox regression was used to discriminate independent risk factors for death. Additionally, we analyzed recurrence-free survival (RFS) for a subgroup of nonmetastatic CRC patients diagnosed in the southern Netherlands for whom data on diagnosis of distant recurrences were retrospectively collected in 2010 and 2011. RFS was defined as the time from diagnosis to recurrence or death, whichever occurred first, or last follow-up date for patients without recurrence or death.

We identified 7104 patients with metastatic CRC, of whom 4158 (58.5%) had a left-sided tumor. In line with Loupakis et al. (1), we found that patients with left-sided tumors had favorable OS as compared with patients with right-sided tumors (crude 5-year OS 16% vs 10%, adjusted hazard ratio [HR] = 0.80, 95% confidence interval [CI] = 0.76 to 0.84, $P < .0001$).

We also included 43 482 patients with nonmetastatic CRC, of whom 28 131 (64.7%) had a left-sided tumor. The subgroup

consisted of 5457 patients, of whom 3572 (65.5%) had a left-sided tumor. As shown in Table 1, demographic and clinical characteristics differed by tumor location. Table 2 shows the survival outcomes. For the total nonmetastatic CRC population, crude five-year OS was higher for patients with left-sided tumors than for patients with right-sided tumors. However, in multivariable analysis, patients with left-sided tumors had a similar risk of death as compared with patients with right-sided tumors. In the subgroup of patients with data on distant recurrences, crude five-year OS was again higher for patients with left-sided tumors than for patients with right-sided tumors, but crude five-year RFS did not differ between patients with left-sided and right-sided tumors. In multivariable analyses, a trend was observed towards inferior OS for patients with left-sided tumors as compared with patients with right-sided tumors. RFS was inferior for patients with left-sided tumors as compared with patients with right-sided tumors.

Contrary to the findings for patients with metastatic CRC, we found on a population-based level that for patients with non-metastatic CRC left-sided tumor location showed similar OS and unfavorable RFS as compared with right-sided tumor location, even after adjustment for differences in demographic and clinical characteristics between both tumor locations.

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Reference

1. Loupakis F, Yang D, Yau L, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J Natl Cancer Inst*. 2015;107(3):dju427 doi:10.1093/jnci/dju427.

Table 1. Demographic and clinical characteristics of M0 patients by primary tumor location*

Characteristic	National level		Regional level with data on distant recurrences	
	Patients with right-sided tumors (n = 15 351) No. (%)	Patients with left-sided tumors (n = 28 131) No. (%)	Patients with right-sided tumors (n = 1885) No. (%)	Patients with left-sided tumors (n = 3572) No. (%)
Sex				
Male	6795 (44.3)	16 230 (57.7)	841 (44.6)	2063 (57.8)
Female	8556 (55.7)	11 901 (42.3)	1044 (55.4)	1509 (42.2)
P	<.0001		<.0001	
Age, y				
≤50	672 (4.4)	1899 (6.8)	87 (4.6)	233 (6.5)
51–65	3218 (21.0)	9146 (32.5)	413 (21.9)	1206 (33.8)
>65	11 461 (74.6)	17 086 (60.7)	1385 (73.5)	2133 (59.7)
P	<.0001		<.0001	
Comorbidity				
None	not available	not available	513 (27.2)	1203 (33.7)
1			523 (27.8)	1044 (29.2)
≥2			733 (38.9)	1115 (31.2)
Unknown			116 (6.1)	210 (5.9)
P			<.0001	
Stage at diagnosis				
I	2334 (15.2)	8164 (29.0)	275 (14.6)	1074 (30.1)
II	7471 (48.7)	10 097 (35.9)	938 (49.8)	1313 (36.7)
III	5546 (36.1)	9870 (35.1)	672 (35.6)	1185 (33.2)
P	<.0001		<.0001	
Mucinous histology				
Yes	3356 (21.9)	2566 (9.1)	352 (18.7)	286 (8.0)
No	11 995 (78.1)	25 565 (90.9)	1533 (81.3)	3286 (92.0)
P	<.0001		<.0001	
Differentiation grade				
Well/moderate	10 538 (68.6)	19 770 (70.3)	1292 (68.6)	2534 (70.9)
Poor/undifferentiated	3435 (22.4)	2774 (9.9)	451 (23.9)	336 (9.4)
Unknown	1378 (9.0)	5587 (19.8)	142 (7.5)	702 (19.7)
P	<.0001		<.0001	
Adjuvant chemotherapy				
Yes	3345 (21.8)	5075 (18.0)	403 (21.4)	570 (16.0)
No	12 006 (78.2)	23 056 (82.0)	1482 (78.6)	3002 (84.0)
P	<.0001		<.0001	
Neo-adjuvant radiotherapy				
Yes	10 (0.1)	8226 (29.2)	3 (0.2)	1184 (33.2)
No	15 341 (99.9)	19 905 (70.8)	1882 (99.8)	2388 (66.8)
P	<.0001		<.0001	
Neo-adjuvant chemoradiation				
Yes	6 (0.1)	1933 (6.9)	3 (0.2)	282 (7.9)
No	15 345 (99.9)	26 198 (93.1)	1882 (99.8)	3290 (92.1)
P	<.0001		<.0001	
Period of diagnosis				
2003–2005	7255 (47.3)	13 426 (47.7)	862 (45.7)	1738 (48.7)
2006–2008	8096 (52.7)	14 705 (52.3)	1023 (54.3)	1834 (51.3)
P	.3525		.0395	

* P values were based on χ^2 tests.

Table 2. Overall and recurrence-free survival outcomes of M0 patients by primary tumor location

Demographic level	Overall survival			Recurrence-free survival		
	Crude 5-y percentage	Hazard ratio (95% CI)	P	Crude 5-y percentage	Hazard ratio (95% CI)	P
National level*						
Tumor location						
Right-sided	61	1.00 (reference)	.4179	N/A	N/A	N/A
Left-sided	68	0.99 (0.95 to 1.02)				
Regional level†						
Tumor location						
Right-sided	64	1.00 (reference)	.0508	61	1.00 (reference)	.0111
Left-sided	68	1.11 (1.00 to 1.23)		61	1.14 (1.03 to 1.27)	

* Hazard ratio adjusted for sex, age, stage at diagnosis, mucinous histology, differentiation grade, adjuvant chemotherapy, neo-adjuvant radiotherapy, neo-adjuvant chemoradiation, and period of diagnosis. P value indicates significance of the hazard ratios. CI = confidence interval; N/A = not available.

† Hazard ratios adjusted for all variables listed under * and additionally for comorbidity.