The Oncologist®

Brief Communications

Another Chapter of the *Right Versus Left Story*: Is Primary Tumor Location a Prognostic Feature in *RAS* Mutant Metastatic Colorectal Cancer?

Fotios Loupakis,[a,†] Marta Schirripa,[a,†] Rossana Intini,[a] Francesca Bergamo,[a] Roberta Bertorelle,[b] Matteo Fassan,[c] Vincenzo Dadduzio,[a] Stefano Merigliano,[d] Pierluigi Pilati,[g] Emanuele Luca Damiano Urso,[e] Umberto Cillo,[f] Massimo Rugge,[c] Sara Lonardi,[a] Vittorina Zagonel[a]

Units of [a]Medical Oncology 1 and [b]Immunology and Oncological Molecular Diagnostics, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto, IRCCS, Padua, Italy; [c]Surgical Pathology Unit, Department of Medicine (DIMED); [d]UOC Clinica Chirurgica, Department of Surgical, Oncological and Gastroenterological Sciences; [e]Clinica Chirurgica I, Department of Surgical, Oncological and Gastroenterological Sciences; and [f]Hepatobiliary Surgery and Liver Transplant Center, Department of Surgery, University of Padua, Padua, Italy; [g]Chirurgia ULSS 16 Unità Locale Socio Sanitaria Padova, Ospedale Sant' Antonio, Padua, Italy

[†]Contributed equally

Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Background. The prognostic value of primary tumor location (PTL) in patients with metastatic colorectal cancer (mCRC) was reported by recent analyses in *RAS* wild-type patients. Here, we investigated the prognostic value of PTL in *RAS* mutated mCRC patients.

Materials and Methods. PTL was defined as left or right if distal or proximal to the splenic flexure. Primary endpoint was overall survival (OS) according to PTL. Subgroup analyses were conducted according to time to metastases and *RAS* mutation subtypes.

Results. Five hundred sixty-four patients were included. Left- and right-sided cases were 65% and 35%, respectively. No difference in OS was detected according to PTL (hazard ratio [HR] = 0.99, p = .964). No difference in OS was observed in right versus left when looking at synchronous (HR 0.92, p = .557) or metachronous (HR 1.07, p = .807) patients.

Conclusion. No OS difference was detected in *RAS* mutated mCRC. Molecular and clinical features able to improve prognosis and treatment strategies in this setting are needed. ***The Oncologist*** 2019;24:e77–e79

Introduction

In the last years, many data emerged leading to the identification of right- and left-sided colorectal cancer (CRC) as two distinct clinical, pathological, and molecular diseases [1].

Many post hoc analyses and recent metanalyses [2–5] deriving from randomized trials of molecularly selected patients showed a negative prognostic role and a negative predictive value to anti-epidermal growth factor receptor's response for right cancer (RC).

According to the most recent guidelines, primary tumor location (PTL) is a fundamental feature in the definition of patients' prognosis and therapeutic approaches. However, no specific data are available regarding the population of *RAS* mutated patients, as highlighted by a recent editorial by Ciombor et al. [6]. A major putative confounder in prognostic studies on PTL for metastatic CRC (mCRC) could theoretically be the later diagnosis occurring in RC, and a possible different impact on prognosis for different *RAS* mutation has been reported. On these bases we analyzed the prognostic impact of PTL in a population of *RAS* mutated mCRC patients, but also considering the time to metastases development and according to the specific *RAS* mutation subtype.

Materials and Methods

Clinical and molecular data of mCRC patients referred to Medical Oncology 1, Veneto Institute of Oncology from January 1, 2010, to December 31, 2016, were collected. Patients were evaluable for the present study if a *RAS* mutation (*KRAS* and *NRAS* exons 2, 3, and 4) was detected either on primary tumor and/or metastasis.

PTL was defined as "right" or "left" if located proximally or distally to the splenic flexure. Time to metastasis was defined as "synchronous" if metastases appeared

Correspondence: Fotios Loupakis, M.D., Ph.D., Unit of Medical Oncology 1, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto, IRCCS, Via Gattamelata 64, 35128 Padua, Italy. Telephone: 390498215911; e-mail: fotios.loupakis@iov.veneto.it Received March 23, 2018; accepted for publication June 19, 2018; published Online First on August 17, 2018. http://dx.doi.org/10.1634/theoncologist.2018-0180

Table 1. Baseline patient characteristics

Characteristic	Total = 564, *n* (%)	Left-side = 365, *n* (%)	Right-side = 199, *n* (%)	*p* value
Sex				
Female	123 (39)	143 (39)	80 (40)	.858
Male	341 (61)	222 (61)	119 (60)	
Age, years				
Median (range)	63 (22–90)	63 (22–85)	63 (24–90)	—
Age, years (70 years cutoff)				
>70	178 (32)	109 (30)	69 (35)	.258
≤70	386 (68)	256 (70)	130 (65)	
Baseline ECOG PS				
≤1	452 (93)	286 (93)	166 (93)	1.000
≥2	33 (7)	21 (7)	12 (7)	
NA	79	58	21	
Primary tumor resected				
Yes	462 (82)	296 (81)	166 (84)	.495
No	102 (18)	69 (19)	33 (16)	
Presentation of mets				
Synchronous	393 (70)	243 (67)	150 (75)	.028[a]
Metachronous	171 (30)	122 (33)	49 (25)	
Sites of mets at diagnosis				
Liver	405 (72)	254 (70)	151 (77)	.017[a]
Lung	144 (25)	106 (29)	38 (19)	
Distant nodes	100 (18)	55 (15)	45 (23)	
Peritoneum	94 (17)	52 (14)	42 (21)	
Other	44 (8)	27 (7)	17 (9)	
Metastatic sites, *n*				
1	383 (68)	258 (71)	125 (63)	.073
≥2	181 (32)	107 (29)	74 (37)	
KRAS mutation				
Cod 12	340 (60)[b]	216 (59)	124 (62)	.937
Cod 13	86 (15)	57 (16)	29 (15)	
Other codons	56 (10)	35 (10)	21 (11)	
Double mutation	3 (1)	2 (1)	1 (1)	
Data not available	44 (8)	27 (7)	17 (8)	
No	35 (6)	28 (7)	7 (3)	
NRAS mutation				
Yes	36 (6)[b]	28 (8)	8 (4)	.238
No	528 (94)	337 (92)	191 (96)	

[a]Statistically significant.
[b]One patient had KRAS codon 12 mutation plus NRAS codon 61 mutation.
Abbreviations: —, no data; ECOG PS, Eastern Cooperative Oncology Group Performance Score; NA, not applicable.

within 6 months from primary tumor diagnosis or as "metachronous" if metastases appeared after 6 months.

Median overall survival (OS) and 95% confidence interval (CI) were calculated using Kaplan-Meier method. Cox proportional hazards regression analyses were used to estimate the association between PTL and survival according to time to metastases. Categorical clinical features were compared by means of chi-square test.

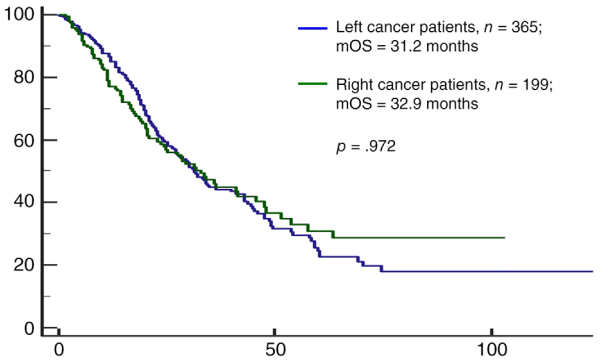

Figure 1. Median overall survival results according to primary tumor location.
Abbreviation: mOS, median overall survival.

Results

Clinical and molecular data were available from 1,319 patients referred to our institution in the prespecified time frame. The study population included 564 patients. Specific features were observed in LC (left cancer) compared with RC patients, as shown in Table 1.

Univariate analysis showed no difference in median OS (mOS) according to PTL (mOS was 31.2 months for RC vs .32.9 months for RC, hazard ratio [HR] = 1.00, 95% CI 0.77–1.29, p = .972; Fig. 1). In synchronous patients, mOS in LC and RC was 26.2 and 29.6 months, respectively (HR 0.92, p = .557). Among metachronous patients, mOS in LC and RC was 45.3 and 47.5 (HR 1.07, p = .807). No differences were observed when looking at specific *RAS* mutations subtypes (Table 2).

Discussion

For the first time, our analysis evaluated the prognostic value of PTL in patients with *RAS* mutated mCRC. This study showed that in *RAS* mutant patients, tumor location does not affect prognosis. The same results were observed when looking at synchronous and metachronous mCRC patients separately and looking at *RAS* subtypes.

Interestingly, Taieb et al. evaluated the prognostic role of PTL in stage III CRC patients, and no differences were identified in the subgroup of *RAS* mutant patients in terms of OS, but also in *RAS* and *BRAF* wild-type patients [7].

Our findings underline the need of accurate and wide large study populations and subgroup analyses in the evaluation of potential prognostic clinical and molecular features in order to avoid misleading conclusions. Due to the exploratory nature of our work, the present results might be further validated in modern clinical trials of mCRC patients receiving first-line chemotherapy with known RAS status and PTL.

From a practical point of view, PTL has been proposed as a stratification factor for future clinical trials and as a driver of therapeutic choices in mCRC; however, in the *RAS*

Table 2. Univariate analyses according to primary tumor side looking at time to metastases and specific RAS mutation

Time to metastases	Primary tumor side	*n* (%)	Median OS, months	Overall survival		
				HR	95% CI	*p* value
Overall	Left	365 (65)	31.2	1	—	—
	Right	199 (35)	32.9	1.00	0.77–1.29	.972
Synchronous	Left	243 (62)	26.2	1	—	—
	Right	150 (38)	29.6	0.92	0.68–1.23	.557
Metachronous	Left	122 (71)	45.3	1	—	—
	Right	49 (29)	47.5	1.07	0.63–1.82	.807
KRAS mut						
Cod 12	Left	216 (64)	31.9	1	—	—
	Right	124 (36)	31.6	1.07	0.77–1.48	.700
Cod 13	Left	57 (66)	22.7	1	—	—
	Right	29 (34)	45.5	0.68	0.32–1.43	.313
Other codons	Left	35 (63)	23.7	1	—	—
	Right	21 (37)	NR	0.76	0.32–1.80	.528
NRAS mut						
All codons	Left	28 (78)	45.3	1	—	—
	Right	8 (22)	47.9	0.84	0.27–2.65	.769

Abbreviations: —, no data; CI, confidence interval; HR, hazard ratio; NR, not reached; OS, overall survival.

mutant population, features other than PTL should be identified and considered in the future. Moreover, our results suggest the need for a constant and careful integration of new clinical prognostic markers with known molecular determinants and vice versa.

Conclusion

Extensive and modern clinical and molecular characterization is key to understanding both *RAS* wild-type and mutant CRC biology and clinical behavior and to identifying new prognostic determinants and targeted treatment strategies. In particular, we can indirectly hypothesize that still-unrevealed molecular drivers other than *RAS* and *BRAF* mutations might be responsible for the prognostic impact of PTL in *RAS* wild-type patients.

Acknowledgments

This study was approved by the Ethics Committee of Istituto Oncologico Veneto and was conducted according to ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was funded by Regione Veneto – RP-2014-00000395.

Disclosures

The authors indicated no financial relationships.

References

1. Missiaglia E, Jacobs B, D'Ario G et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol 2014;25:1995–2001.

2. Loupakis F, Yang D, Yau L et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 2015; 107:1–9.

3. Petrelli F, Tomasello G, Borgonovo K et al. Prognostic survival associated with left-sided vs right-sided colon cancer: A systematic review and meta-analysis. JAMA Oncol 2016 [Epub ahead of print].

4. Tejpar S, Stintzing S, Ciardiello F et al. Prognostic and predictive relevance of primary tumor location in patients with *RAS* wild type metastatic colorectal cancer: Retrospective analyses of CRYSTAL and FIRE-3 trials. JAMA Oncol 2016 [Epub ahead of print].

5. Arnold D, Lueza B, Douillard JY et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol 2017;28:1713–1729.

6. Ciombor KK, Goldberg RM. Primary tumor sidedness as prognostic and predictive biomarker in metastatic colorectal cancer: Further validation of a potentially practice-changing variable. JAMA Oncol 2016 [Epub ahead of print].

7. Taieb J, Kourie HR, Emile JF et al. Association of prognostic value of primary tumor location in stage III colon cancer with *RAS* and *BRAF* mutational status. JAMA Oncol 2017 [Epub ahead of print].