Original Study

Lung Metastasis Predicts Better Prognosis in Metastatic Colorectal Cancer With Mutated *KRAS*

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Abstract

We used the National Cancer Database to identify 58,044 metastatic colorectal cancer (mCRC) patients with a synchronous single site of metastasis. We evaluated prognosis in these patients according to several clinical and genetic variables. Individuals with lung metastasis and mutant Kirsten ras (*KRAS*) had the best prognosis, followed by those with liver metastasis, whereas those with bone or brain metastasis had the worst prognosis. Single-site metastasis to the lungs was associated with better prognosis in patients with mCRC, specifically among those with *KRAS* mutant tumors.

Background: Previous studies have shown that prognosis in metastatic colorectal cancer (mCRC) might vary according to sites of metastasis. We evaluated prognosis in individuals with mCRC and single-site metastasis, according to several clinical and genetic variables. **Patients and Methods:** Using the National Cancer Database we identified 58,044 mCRC patients with a synchronous single site of metastasis. We first examined the effect of metastasis site on prognosis. In a secondary analysis, among individuals who had not undergone surgery or received radiotherapy, we examined the prognostic value of chemotherapy intensity, Kirsten ras (KRAS) status, primary tumor location and carcinoembryonic antigen (CEA) levels. **Results:** Individuals with lung metastasis had the best prognosis (hazard ratio [HR], 0.80; 95% confidence interval [CI], 0.77-0.83), followed by those with liver metastasis (HR, 1.11; 95% CI, 1.07-1.15), whereas those with bone or brain metastasis had the worse prognosis. In a subgroup analysis, we assessed prognosis among individuals who received multiagent chemotherapy and had not undergone surgery or received radiotherapy. Individuals with lung metastasis and mutant KRAS had better prognosis compared with those with liver metastasis (HR, 0.69; 95% CI, 0.54-0.88), regardless of primary tumor location or CEA levels. **Conclusion:** Single-site metastasis to the lungs is associated with better prognosis in mCRC, specifically among patients with *KRAS* mutant tumors.

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Introduction

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths in men and women combined in the United States,[1] with nearly 25% of patients diagnosed with metastatic disease (ie, stage IV). The most common site of metastatic spread is the liver, with the lungs being the next frequently involved site.[2-5] Less frequent metastatic sites are the peritoneum, bones, and brain, at varying degrees of frequencies, usually approximately 5% to 10%.[6-8]

The prognosis of individuals diagnosed with metastatic disease at presentation is approximately 29 to 30 months with the current standard of care treatment options,[9] with Kirsten ras (*KRAS*) mutations conferring worse prognosis.[10,11] Retrospective analyses of randomized trials from the Analysis and Research in Cancers of the

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Digestive System (ARCAD) database, as well as Dutch and Australian populations suggested that single-site metastasis to the lungs is associated with a better outcome compared with single-site metastasis to the liver, peritoneum, bone, or brain.[12-17] In these studies, the difference in median overall survival between individuals with lung versus liver metastasis was approximately 5, 8, and 9 to 18 months in favor of those with lung metastasis, in the ARCAD database, and Dutch and Australian populations, respectively.[12,13,15-17] Importantly, these studies had several limitations. First, the analyses included patients who had undergone surgery[13] or received radiotherapy[12-14] for their metastatic site, which are usually oligometastatic patients with better prognosis and do not represent the population of bona fide metastatic patients. Second, data reported on survival was not stratified according to chemotherapy intensity, tumor location, *KRAS* status or carcinoembryonic antigen (CEA) levels.[12-15]

Because the association between site of metastasis and outcome might have a profound effect on clinical decision-making, we performed an analysis using the National Cancer Database (NCDB), a large nationwide oncology outcomes database. Our aim was to further define subpopulations of individuals with single-site metastasis to the lungs that harbor favorable outcomes.

Patients and Methods

Data Source and Patient Population

Our cohort was derived from the NCDB, a hospital-based cancer registry, from 2010 to 2014. The NCDB captures data on 70% of cancer diagnoses in the United States from >1400 hospitals with cancer programs accredited by the American College of Surgeons' Commission on Cancer and American Cancer Society.[18]

All individuals with CRC who had synchronous metastasis at a single site at diagnosis were identified. All 4 metastasis sites defined in the NCDB were used for the analysis (ie, lung, liver, bone, and brain). Patients who had undergone surgery or received radiotherapy were excluded.

Variables Definition

Covariates included chemotherapy regimen as first line, *KRAS* status, age, sex, race, patient comorbidities (Charlson-Deyo comorbidity condition; CDCC),[19,20] tumor location, tumor grade, and preoperative CEA levels. Chemotherapy regimen as first-line treatment was defined as either any (including multiagent chemotherapy, single-agent chemotherapy, and nontreated patients), multiagent chemotherapy or none, under the "chemotherapy" variable in the NCDB. *KRAS* status was defined as either wild type or mutant, and was evaluated only in individuals who received multiagent chemotherapy. Race and ethnicity were used to create a composite variable categorized as white, African American, or other/unknown. Tumor location was defined either as right colon, left colon, or rectum. Right colon tumors included International Classification of Diseases 10th Revision (ICD-10) codes C180 to 183, and left colon tumors included ICD-10 codes C185 to 187 and C199. Rectal tumors included ICD-10 code C209. Tumors located at the transverse colon were not designated as either right or left colon, and were not included in the analysis. Tumor grade was defined as either well differentiated, moderately differentiated, poorly differentiated, or undifferentiated.

Outcomes Definition

The primary outcome was overall survival measured from the time of cancer diagnosis until death from any cause or last follow-up.

Statistical Analysis

Patients were grouped according to site of metastasis. Baseline characteristics were compared using χ^2 test for categorical variables and *t* test for continuous variables. Differences in overall survival and median overall survival were compared between patients with either site of metastasis. Kaplan–Meier analyses, log rank tests, and Cox proportional hazards were used to assess this effect. The Cox model was adjusted for all of the mentioned covariates. In a secondary analysis, we excluded patients who had either undergone surgery or received radiotherapy, to eliminate any possible confounding effect of local treatment on prognosis. We then stratified the patients on the basis of their *KRAS* status and primary tumor location.

All statistical analyses were performed using Stata/IC software 14.0 (StataCorp, College Station, TX). A 2-sided P value $< .05$ was used to define significance.

Results

Patient Characteristics

We identified 501,022 individuals diagnosed with CRC during the years 2010 to 2014. In this cohort, 76,052 individuals had a metastatic disease upon diagnosis, of whom 58,044 had a synchronous single site of metastasis (ie, lung, liver, bone, or brain; see Supplemental Figure 1 in the online version). Patient characteristics are presented in Table 1. The median follow-up time was 14.9 months (interquartile range [IQR], 4.2-27.7). Of the 9993 patients who had not undergone surgery or received radiotherapy, and received multiagent chemotherapy as first-line therapy, *KRAS* status was documented for 39.7% (n = 3970), of whom 41.9% (1662/3970) and 58.1% (2308/3970) were *KRAS* mutant and wild type, respectively. KRAS mutant proportion was 48.7% and 41.2% for individuals with lung and liver metastasis, respectively.

Differences in Prognosis Among Individuals With a Single Site of Metastasis

Among individuals with single-site metastasis, those with lung metastasis had the best prognosis, followed by those with liver metastasis, whereas those with bone or brain metastasis had the worse prognosis. This effect was evident in individuals who received multiagent chemotherapy (Figure 1A and Table 2) as well as in those who did not receive chemotherapy (Figure 1B and Table 2). Median overall survival according to single-site metastasis and first-line chemotherapy regimen is summarized in Table 3.

Differences in Prognosis According to KRAS *Status*

In a subgroup analysis, we assessed prognosis among individuals with a documented *KRAS* status who received multiagent chemotherapy, and had not undergone surgery or received radiotherapy. Individuals with lung metastasis had better prognosis compared

Table 1 Patient Characteristics

Characteristic	All Patients With a Single Site of Metastasis (n = 58,044)	Single Site of Metastasis			
		Lung (n = 5571)	Liver (n = 51,001)	Bone (n = 1088)	Brain (n = 384)
Median Age (IQR), Y	65 (55-75)	67 (57-78)	64 (54-75)	66 (56-77)	66 (57-76)
Male Sex, % (n)	54.5 (31,603)	49.8 (2776)	54.9 (27,991)	58.8 (640)	51.0 (196)
Race, % (n)					
White	80.0 (46,453)	80.8 (4500)	79.9 (40,747)	81.3 (884)	83.9 (322)
Black	15.1 (8769)	14.0 (780)	15.3 (7791)	14.2 (154)	11.5 (44)
Other	4.9 (2822)	5.2 (291)	4.8 (2463)	4.6 (50)	4.7 (18)
CDCC, % (n)					
0	74.1 (43,033)	71.1 (3960)	74.5 (38,008)	71.3 (776)	75.3 (289)
1	18.9 (10,981)	21.0 (1168)	18.7 (9535)	20.0 (218)	15.6 (60)
≥2	6.9 (4030)	8.0 (443)	6.8 (3458)	8.6 (94)	9.1 (35)
Primary Tumor Location, % (n)					
Right colon	37.4 (18,457)	25.7 (1229)	38.7 (16,804)	32.6 (289)	42.6 (135)
Left colon	41.1 (20,280)	35.4 (1690)	42.0 (18,239)	28.6 (254)	30.6 (297)
Rectum	21.6 (10,654)	38.9 (1858)	19.3 (8367)	38.8 (344)	26.8 (85)
Tumor Grade, % (n)					
Well	5.1 (2981)	5.7 (315)	5.1 (2621)	3.0 (33)	3.1 (12)
Moderate	48.8 (28,345)	50.6 (2818)	49.2 (25,082)	28.2 (307)	35.9 (138)
Poor	17.6 (10,187)	13.4 (746)	17.6 (8973)	33.4 (363)	27.3 (105)
Unknown	2.7 (1583)	2.1 (119)	2.8 (1405)	4.0 (43)	4.2 (16)
Other	25.8 (14,948)	28.2 (1573)	25.3 (12,920)	31.4 (342)	29.4 (113)

Abbreviation: Charlson-Deyo comorbidity condition.

with those with liver metastasis, with an adjusted hazard ratio (HR) of 0.82 (95% confidence interval [CI], 0.69-0.97; $P = .02$). This effect was confined to individuals with *KRAS* mutated tumors (adjusted HR, 0.69; 95% CI, 0.54-0.88; $P = .003$), whereas no difference in prognosis was noted for individuals with wild type *KRAS* (adjusted HR, 0.91; 95% CI, 0.72-1.15; $P = .43$; Figure 2). Median overall survival was improved by 5.2 months in individuals with mutant *KRAS* and lung metastasis compared with those with liver metastasis (19.7 months; IQR, 11.1-29.1) versus 14.5 months (IQR, 7.5-22.6), respectively). On the contrary, there was a minimal difference in median overall survival among individuals with wild type KRAS and lung metastasis compared with those with liver metastasis (17.8 months; IQR, 9.6-24.8 vs. 17.0 months; IQR, 9.5-26.4, respectively). Among individuals with liver metastasis, in a comparison of those with mutant *KRAS* with those with wild type *KRAS*, there was a statistically significant difference in overall survival in favor of wild type *KRAS* ($P < .001$). Median overall survival was accordingly improved by 2.5 months in the *KRAS* wild type versus the *KRAS* mutant group (17.0 vs. 14.5 months, respectively). However, there was no statistically significant difference among

Figure 1 Overall Survival Among Individuals With Single Site Metastasis, (A) Who Received Multiagent Chemotherapy or (B) Who Did Not Receive Chemotherapy

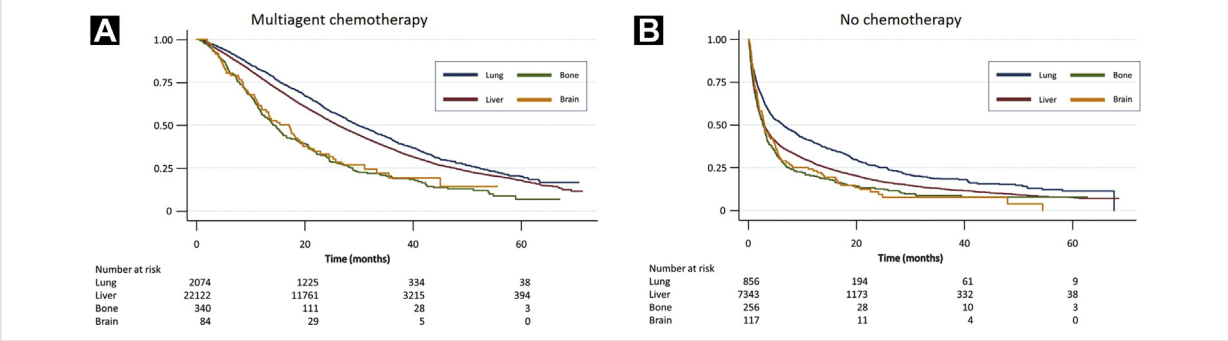


Table 2 Overall Survival of Individuals With Each Site of Single Metastasis Compared With All Other Sites of Metastasis, and According to First-Line Chemotherapy Regimen

Site of Metastasis	Chemotherapy Regimen as First-Line Treatment		
	Single/Multiagent or No Chemotherapy (n = 58,044)	Multiagent (n = 31,576)	No Chemotherapy (n = 10,539)
Lung, n (%)	5571 (10)	2689 (9)	1073 (10)
Unadjusted HR	0.86 (0.83-0.90), <.001	0.85 (0.80-0.90), <.001	0.74 (0.68-0.80), <.001
Adjusted HR[a]	0.80 (0.77-0.83), <.001	0.86 (0.80-0.91), <.001	0.69 (0.62-0.75), <.001
Liver, n (%)	51,001 (88)	28,351 (90)	9010 (85)
Unadjusted HR	1.1 (0.98-1.04), .59	1.04 (0.99-1.10), .15	1.19 (1.11-1.27), <.001
Adjusted HR[a]	1.11 (1.07-1.15), <.001	1.06 (1.00-1.12), .05	1.29 (1.19-1.39), <.001
Bone, n (%)	1088 (2)	423 (1)	311 (3)
Unadjusted HR	1.63 (1.51-1.76), <.001	1.79 (1.58-2.03), <.001	1.17 (1.02-1.33), .02
Adjusted HR[a]	1.41 (1.30-1.53), <.001	1.51 (1.32-1.73), <.001	1.07 (0.91-1.25), .41
Brain, n (%)	384 (0.7)	113 (0.4)	145 (1.4)
Unadjusted HR	1.76 (1.55-2.00), <.001	1.70 (1.33-2.19), <.001	1.14 (0.94-1.39), .19
Adjusted HR[a]	1.54 (1.34-1.77), <.001	1.42 (1.07-1.87), .01	1.14 (0.91-1.43), .25

Data for HR values are presented as HR (95% CI), *P*.
Abbreviations: CI = confidence interval; HR = hazard ratio.
[a]Adjusted for age at diagnosis, sex, race, Charlson-Deyo comorbidity condition, primary tumor location, and tumor grade.

individuals with lung metastasis according to *KRAS* status ($P = .7$), although median overall survival was numerically improved by 1.9 months in the *KRAS* mutant versus the *KRAS* wild type group (19.7 vs. 17.8 months, respectively).

Differences in Prognosis According to Primary Tumor Location

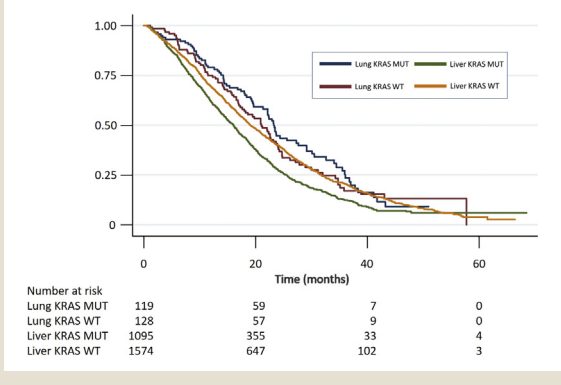
In a subgroup analysis, we assessed prognosis according to primary tumor location in individuals who had not undergone surgery or received radiotherapy (Table 4). Individuals with lung metastasis had better prognosis compared with those with liver metastasis regardless of primary tumor location within the colorectum. In individuals not treated with chemotherapy, a similar prognosis advantage was seen for those with lung metastasis, independent of primary tumor location. However, the differences in median overall survival between the groups did not exceed 1.5 months (Table 5).

In individuals treated with first-line multiagent chemotherapy, those with lung metastasis had better prognosis compared with those with liver metastasis, only in tumors located in the right colon and rectum, but not in tumors located in the left colon (Table 5 and Figure 3). Median overall survival difference between individuals with lung versus liver metastasis was 5.2 and 4.1 months for individuals with tumors located in the right colon and rectum, respectively (Table 5). Median overall survival was similar for individuals with either lung or liver metastasis with tumors located in the left colon, both approximately 16 months (Table 5). The proportion of individuals with mutated *KRAS* varied across groups according to primary tumor location. In individuals with right colon and rectal tumors, *KRAS* mutant was more frequent (56.6% versus 43.4% and 54.5% versus 44.5%, mutant versus wild type *KRAS*, respectively). On the contrary, in individuals with left colon tumors, *KRAS* wild type was more frequent (42.6% vs. 57.4%, mutant vs. wild type *KRAS*, respectively). In individuals with mutated *KRAS*, median overall

Table 3 Median Overall Survival According to Site of Metastasis and First-Line Chemotherapy Regimen

Survival According to Site of Metastasis	Chemotherapy Regimen as First Line Treatment		
	Any	Multiagent	None
Lung, mo (IQR)	17.2 (5.9-29.3)	23.2 (13.3-34.1)	4.8 (1.2-18.7)
Liver, mo (IQR)	15.0 (4.2-27.8)	21.2 (11.5-32.5)	2.5 (0.8-11.9)
Bone, mo (IQR)	6.7 (2.2-17.8)	13.2 (7.2-23.5)	2.6 (1.0-6.7)
Brain, mo (IQR)	5.5 (2.0-16.7)	14.3 (7.0-23.9)	2.7 (1.1-7.5)

Figure 2 Overall Survival Among Individuals With Lung Compared With Liver Single-Site Metastasis, With a Documented *KRAS* Status, Who Received Multiagent Chemotherapy, and Had Not Undergone Surgery or Received Radiotherapy



Abbreviations: MUT = mutant; WT = wild type.

Table 4 Overall Survival in Individuals With Lung Compared With Liver Metastasis, Who Had Not Undergone Surgery or Received Radiotherapy, According to First-Line Regimen

Primary Tumor Location	Chemotherapy Regimen as First-Line Therapy		
	Any	Multiagent	None
Right Colon (n = 6036)			
Unadjusted HR	0.86 (0.76-0.97), .01	0.78 (0.63-0.95), .02	0.72 (0.57-0.90), .004
Adjusted HR[a]	0.78 (0.69-0.88), <.001	0.74 (0.60-0.92), .005	0.71 (0.56-0.89), .003
Left Colon (n = 6643)			
Unadjusted HR	0.89 (0.79-0.99), .05	1.03 (0.86-1.23), .77	0.73 (0.57-0.92), .008
Adjusted HR[a]	0.75 (0.67-0.85), <.001	1.04 (0.87-1.24), .7	0.67 (0.52-0.85), .001
Rectum (n = 3940)			
Unadjusted HR	0.88 (0.78-0.98), .02	0.75 (0.63-0.88), .001	0.85 (0.67-1.07), .16
Adjusted HR[a]	0.82 (0.73-0.92), .001	0.74 (0.62-0.87), <.001	0.81 (0.64-1.02), .08

Data for HR values are presented as HR (95% CI), *P*.
Abbreviations: CI = confidence interval; HR = hazard ratio.
[a]Adjusted for age at diagnosis, sex, race, Charlson-Deyo comorbidity condition and tumor grade.

survival difference was evident in individuals with lung metastasis versus liver metastasis, regardless of primary tumor location, with a benefit in favor of lung metastasis ranging between 4.3 and 6.5 months (Table 6). In individuals with wild type *KRAS*, median overall survival was worse in individuals with lung metastasis compared with individuals with liver metastasis, in tumors located in the right or left colon (Table 6).

Differences in Prognosis According to CEA Levels

We next assessed the possible prognostic value of CEA levels among individuals who had not undergone surgery or received radiotherapy. The mean CEA levels for mutated and wild type *KRAS* were 275 ng/mL and 246 ng/mL, respectively. Although this difference was statistically significant ($P = .007$), there was no association between CEA levels and prognosis (HR, 1.00; 95% CI, 0.99-1.00; $P = .15$), irrespective of chemotherapy administration, site of metastasis, or primary tumor location. HR was calculated per 10 ng/mL increase in CEA levels.

Discussion

In the current study, we showed that single-site metastasis to the lungs is associated with better prognosis in metastatic CRC (mCRC), as suggested by previous studies,[12-16] regardless of primary tumor location and CEA levels. Importantly, among individuals who received multiagent chemotherapy, and had not undergone surgery or received radiotherapy in our analysis, this effect was confined to patients with mutated *KRAS* tumors.

Of note, the difference in overall survival in favor of individuals with lung metastasis versus those with liver metastasis among *KRAS* mutated tumors was mainly because of a statistically significant detrimental effect of *KRAS* mutation in individuals with liver metastasis. This effect was observed regardless of primary tumor location. Although not statistically significant, there was an increase in median overall survival in individuals with lung metastasis and mutated *KRAS*.

Preoperative CEA levels were previously shown to be associated with poor prognosis in CRC, independent of tumor stage,[21,22] mainly using a cutoff level of ≥5 ng/mL. In our analysis, CEA levels, measured as a continuous variable, were not associated with survival, regardless of chemotherapy administration, *KRAS* status, site of metastasis, and primary tumor location.

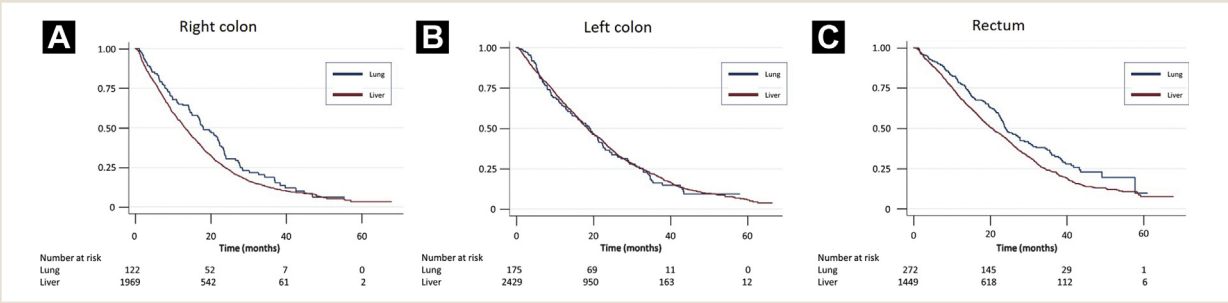
The main strength of this study was use of the NCDB, a large cohort of a hospital-based cancer registry, which captures data on 70% of cancer diagnoses in the United States. This database

Table 5 Median Overall Survival in Individuals With Lung Compared With Liver Metastasis, Who Had Not Undergone Surgery or Received Radiotherapy, According to Primary Tumor Location

Primary Tumor Location	Site of Metastasis	Chemotherapy Regimen as First-Line Therapy		
		Any	Multiagent	None
Right Colon	Lung, mo (IQR)	5.9 (1.9-18.6)	17.1 (7.8-24.1)	2.6 (0.7-5.1)
	Liver, mo (IQR)	4.9 (1.3-14.4)	11.9 (5.5-20.9)	1.2 (0.5-3.7)
Left Colon	Lung, mo (IQR)	9.1 (3.4-21.1)	16.0 (7.1-25.4)	3.0 (0.8-10.6)
	Liver, mo (IQR)	8.6 (2.1-20.2)	16.2 (7.7-25.7)	1.5 (0.5-5.1)
Rectum	Lung, mo (IQR)	12.6 (3.9-24.2)	21.6 (11.2-30.1)	3.4 (1.1-13.1)
	Liver, mo (IQR)	11.7 (3.4-24.0)	17.5 (8.6-27.7)	2.6 (0.7-9.4)

Abbreviation: IQR = interquartile range.

Figure 3 Overall Survival Among Individuals With Lung Compared With Liver Single-Site Metastasis, Who Received Multiagent Chemotherapy, and Had Not Undergone Surgery or Received Radiotherapy, According to Primary Tumor Location Within the Colorectum: (A) Right Colon; (B) Left Colon; and (C) Rectum



includes information regarding chemotherapy intensity, *KRAS* status, primary tumor location, and CEA levels. Analysis of individuals who did not receive any chemotherapy treatment enabled us to better assess the natural history of individuals on the basis of site of metastasis. Because *KRAS* status was previously reported to predict lung metastasis,[23-25] our analysis, which included data on site of metastasis and *KRAS* status, enabled us to separately evaluate the effect of each variable on prognosis.

This study had several important limitations. First, the NCDB lacks cancer recurrence and cancer-specific survival data. However, the NCDB includes overall survival data, which is a more clinically relevant parameter. Second, because of the small sample size of individuals with single-site lung metastasis, we were not able to evaluate the effect of *KRAS* status per primary tumor location. However, we were able to assess the effect of *KRAS* irrespective of primary tumor location. Third, the NCDB lacks data regarding the specific *KRAS* exons analyzed, BRAF mutation status, use of biologic agents, and the specific type of chemotherapy used. Fourth, in our main comparison between individuals with either lung or liver metastasis, baseline characteristics differed in age, CDCC score, primary tumor location, and *KRAS* status. Individuals with lung metastasis were older and with more comorbidities. However, these differences are expected to negatively affect prognosis, and therefore bias the results in favor of the null hypothesis. Fifth, the NCDB lacks data on microsatellite instability status and specific type of chemotherapy. However, according to current guidelines, these parameters should not be influenced by site of metastasis. Sixth, the NCDB details the site of metastasis only at diagnosis. Therefore, we were unable to include patients with metachronous metastasis. Seventh, a possibility exists for exclusion of rectal cancer patients who received pelvic radiation as palliation, and not for oligometastatic disease.

Table 6 Median OS in Individuals With Either Lung or Liver Metastasis, Who Had Received Multiagent Chemotherapy Regimen as First-Line Treatment, and Had Not Undergone Surgery or Received Radiotherapy, According to Primary Tumor Location and *KRAS* Status

Primary Tumor Location	*KRAS*	Site of Metastasis	Median OS, Months (IQR)
Right Colon	MUT	Lung	19.7 (10.0-23.5)
		Liver	13.2 (6.8-21.5)
	WT	Lung	9.3 (6.3-22.1)
		Liver	13.2 (7.1-22.0)
Left Colon	MUT	Lung	19.5 (11.2-29.1)
		Liver	15.2 (7.6-22.6)
	WT	Lung	15.5 (8.1-26.6)
		Liver	18.9 (10.6-27.8)
Rectum	MUT	Lung	23.1 (12.7-30.1)
		Liver	18.5 (10.9-25.9)
	WT	Lung	21.6 (15.0-30.0)
		Liver	19.6 (11.5-28.9)

Abbreviations: IQR = interquartile range; MUT = mutant; OS = overall survival; WT = wild type.

Conclusion

The current study suggests that lung metastasis predicts better prognosis in mCRC patients with mutated *KRAS*. Future clinical trials should accordingly take into account site of metastasis and *KRAS* status during patient randomization, to avoid bias.

Clinical Practice Points

- Previous studies have shown that prognosis in patients with mCRC might vary according to sites of metastasis.
- We used the NCDB to identify 58,044 mCRC patients with a synchronous single site of metastasis.
- We evaluated prognosis in these patients according to several clinical and genetic variables.
- Individuals with lung metastasis and mutant *KRAS* had the best prognosis, followed by those with liver metastasis, whereas those with bone or brain metastasis had the worse prognosis.
- Single-site metastasis to the lungs was associated with better prognosis in patients with mCRC, specifically among those with *KRAS* mutant tumors.

Disclosure

The authors have stated that they have no conflicts of interest.

Supplemental Data

The supplemental figure accompanying this article can be found in the online version at https://doi.org/10.1016/j.clcc.2019.06.001.

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Supplemental Figure 1 Patient Selection Flow Chart