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ORIGINAL ARTICLE

The Prognostic Impact of *KRAS* Mutation in Patients Having Curative Resection of Synchronous Colorectal Liver Metastases

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Abstract

Background m-*KRAS* has been recently reported to be a significant prognostic factor in patients undergoing resection of colorectal liver metastases. This is due to the lack of response to monoclonal epithelial growth factor receptor antibodies, and potentially as a result of a more aggressive tumor biology.

Methods The National Cancer Database was queried to identify patients with known *KRAS* status presenting with colorectal cancer and liver metastases who underwent resection of the primary tumor and metastatic disease between 2010 and 2015.

Results A total of 2655 patients were identified of which 1116 (42%) had m-*KRAS*. Tumor size, lymph node involvement rates, and margin status of the primary tumor were similar between patients with m-*KRAS* and wild-type *KRAS* (wt-*KRAS*). In the multivariable analysis, African-American race and right-sided colon cancers were independently associated with m-KRAS (both $p < 0.001$). m-*KRAS* patients had a significantly lower overall survival (OS) than those with wt-*KRAS*, with a 3- and 5-year OS of 51 vs. 64% and 31 vs. 42%, respectively ($p < 0.001$). After adjustment for available prognostic confounders, factors independently associated with worse OS were increasing age, receipt of monoagent chemotherapy, tumor size, positive lymph node, and resection margin status of the primary tumor, right-sided cancers, and m-*KRAS*.

Conclusions m-*KRAS* is associated with worse OS in patients presenting with colorectal cancer and liver metastases undergoing resection of the primary tumor and metastatic disease. Right-sided lesions and African-American race were associated with m-*KRAS*. However, while right-sided remained an independent prognostic factor for OS, race did not.

Keywords Colorectal liver metastases · KRAS mutation

Introduction

Approximately, 15 to 25% of patients diagnosed with colorectal cancer have metastatic disease at presentation.[1] For these patients, oncologic surgical resection of the primary tumor and all metastatic disease remains the only chance of cure and long-term survival. Among patients with liver metastases alone, hepatic resection with multi-agent chemotherapy has been able to achieve 5-year overall survival (OS) rates of up to 50% in contemporary institutional studies.[2] Epidermal growth factor receptor (EGFR) inhibitors block cell growth and have been associated with a survival benefit when used in the treatment regimens of patients with metastatic colorectal cancer.[3] Currently, the mutation of the Kirsten Rat Sarcoma viral oncogene homolog (*KRAS*) gene is used as a biomarker of poor response to anti-EGFR antibodies (i.e., panitumumab and cetuximab).[4,5] Moreover, patients carrying m-*KRAS* have been found to have a higher cumulative incidence of metastases, possibly representing a more aggressive tumor biology.[6]

Over the past decade, m-*KRAS* have been reported to be a significant predictor of worse OS in patients undergoing resection of colorectal liver metastases.[7–10] Two recent meta-analyses investigating the survival impact of m-*KRAS* in this subset of stage IV colorectal patients have confirmed these observations.[1,6] These reviews analyzed institutional series published between 1995 and 2016 and, although the number of patients varied between 19 and 334 over almost two decades with variable follow up, both studies found m-*KRAS* to

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be significantly associated with decreased OS. This finding emphasizes the importance of *KRAS* testing in patients undergoing resection of colorectal liver metastases for preoperative evaluation and prognostication, assessment of surgical outcomes, and to guide follow-up strategies.

The aim of the current study was to validate the prognostic significance of m-*KRAS* in patients presenting with colorectal cancer and liver metastases who underwent surgical resection of both the primary and metastatic disease using the National Cancer Database. The secondary endpoint was to identify factors associated with m-*KRAS* within this cohort.

Patients and Methods

Data Sources and Study Subjects

The National Cancer Database (NCDB) is a joint program of the Commission on Cancer (CoC) of the American College of Surgeons and the American Cancer Society.[11] It is a nationwide oncology outcomes dataset, which collects data for over 70% of all newly diagnosed cancers in the USA. Data elements are collected and submitted to the NCDB from CoC-accredited cancer program registries using nationally standardized data item and coding definitions.

The NCDB Participant User File was used to identify all patients diagnosed with colorectal adenocarcinomas from 2010 to 2015 (data regarding sites of metastases was only available beginning in 2010). The database utilizes the International Classification of Diseases for Oncology, Third Edition (ICD-O-3) for histology coding.[12] Patients were selected according to age greater than 18, stage IV disease with metastatic lesions to the liver only, and resection of the primary tumor and "resection of the distant site," which, in the setting of metastatic disease to the liver, represents hepatic metastasectomy (Fig. 1). Only patients who were alive at 90 days following resection of the primary tumor and received chemotherapy were included in the survival analyses. This was done in order to eliminate perioperative surgical mortality and lack of systemic therapy as possible confounders.

Demographic variables analyzed included patient gender, age at diagnosis, race, insurance status, annual income, education level, institution type, and year of diagnosis. Annual income and education level were estimated by matching the zip code of the patient recorded at the time of diagnosis against files derived from year 2000 US Census data per NCDB PUF.[11] Annual income was binary treated, as low (< $35,000) and high. Education level was recoded as low vs. high, with low representing a rate of adults < 14% in the patient's zip code who did not graduate from high school.

Clinical variables included surgery of the primary and metastatic site, chemotherapy, radiation, and Charlson/Deyo score to evaluate comorbidity. Surgery of the distant site included resection of metastatic disease only. Chemotherapy was analyzed as none, monoagent, and multi-agent.

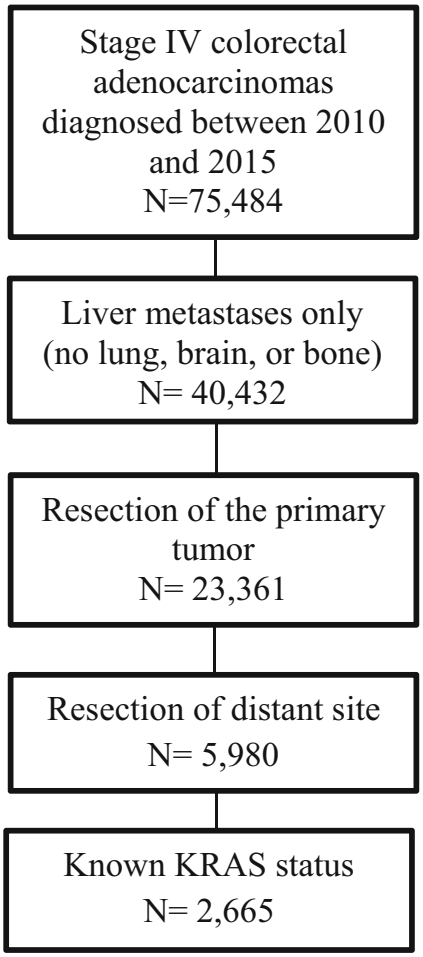

Fig. 1 Inclusion selection of the study patients from the National Cancer Database (NCDB)

Pathologic variables were location, size, lymph node involvement, margin status, and *KRAS* status of the primary tumor. Positive margin status included both microscopic and macroscopic positive margins. Tumors > 200 mm were excluded from our size analyses due to the possibility of coding errors. The location of lesion was coded as right sided (cecum to transverse colon) and left sided (splenic flexure to rectum). Lymph node status was recorded as positive and negative.

Statistical Analyses

Demographic, clinical, and pathologic data were analyzed using summary statistics; chi-square and Student's *t* test were used for categorical and continuous variable comparisons, respectively. Binary logistic regression was employed to identify factors independently associated with *KRAS* mutation based on their statistical significance in univariate analysis. The Kaplan-Meier method was used to determine overall survival, and the log-rank test to calculate statistical significance

of comparisons of survival. Cox proportional hazards regression was utilized for the multivariable model; hazard ratios and 95% confidence intervals were calculated for the strength of association between each variable and survival.

Data analyses were performed using Statistical Package for the Social Sciences (SPSS) software (version 23.0; SPSS Inc., Chicago, IL); all tests were two sided, and a p value < 0.05 was considered statistically significant. The NCDB database is publicly available and all patient information is de-identified; therefore, this study was exempted from institutional review board approval.

Results

Patient Characteristics Based on *KRAS* Status

A total of 2655 patients with colorectal adenocarcinomas and liver metastases with known *KRAS* status who underwent resection of both their primary tumor and metastatic disease were identified in the NCDB; 1116 (42%) had m-*KRAS*. As compared to wt-*KRAS*, m-*KRAS* was more commonly seen in females (49 vs. 44%, $p = 0.013$), older age (mean age at diagnosis 60.4 vs. 58.4 years, $p < 0.001$), and African-American race (18 vs. 11%, $p < 0.001$; Table 1). There were no differences between the two groups for other demographic characteristics, as well as for chemotherapy administration and comorbidity rates. Tumor size, lymph node involvement, 90-day mortality, and margin status of the primary tumor were also similar between the two patient groups. m-*KRAS* was significantly more common in right-sided cancers than in left-sided cancers (58 vs. 42%, $p < 0.001$; Table 1).

In the multivariable analysis, African-American race (OR 1.58, 95% CI 1.26–1.99) and right-sided cancers (OR 2.54, 95% CI 2.16–2.98) were independently associated with m-*KRAS* status (Table 2).

Survival Analyses

In a univariate analysis, m-*KRAS* patients had a significantly lower OS than those with wt-*KRAS*, with 3- and 5-year OS rates of 51 vs. 64% and 31 vs. 42%, respectively ($p < 0.001$; Fig. 2). Patients with right-sided tumors had a significantly worse 5-year OS compared to those with left-sided cancers; the magnitude of this difference was greater among the wt-*KRAS* than the m-*KRAS* cancers ($p < 0.001$ and $p = 0.025$, respectively; Fig. 3).

After adjustment for available prognostic confounders, factors independently associated with worse OS were increasing age, receiving monoagent chemotherapy, increasing primary tumor size, positive margin of the primary tumor and lymph node status, right-sided location, and m-*KRAS* (Table 3).

Discussion

The current study analyzed the impact of m-*KRAS* on overall survival in a nationally representative cohort of 2655 patients presenting with colorectal cancer and liver metastases who underwent resection of both the primary and metastatic disease. We observed that m-*KRAS* status was associated with a worse prognosis as compared to wt-*KRAS*. Additionally, we identified right-sided lesions and African-American race as independent factors associated with m-*KRAS*. However, while right-sided cancer remained an independent prognostic factor, race was not independently associated with worse overall survival.

In the meta-analysis by Brudvik et al.,[6] which included 14 studies with 1181 patients evaluating the association between *KRAS* status and outcomes after resection of colorectal liver metastases, eight studies reported overall survival. The results were generally consistent across studies and m-*KRAS* had an adverse association with OS. This observation was confirmed in the subsequent meta-analysis by Tosi et al.,[1] which excluded three studies from the previous meta-analysis and added three more recent series and included a total of 1369 patients with reported OS. The current analysis demonstrates a significantly lower OS that is of similar magnitude for patients with m-*KRAS* undergoing resection of colorectal liver metastases within the NCDB, validating the previously reported findings from institutional series. Although *KRAS* testing is already recommended by current guidelines in patients with stage IV disease[13,14] and liver resection remains their only curative option, our data underscores the importance of *KRAS* assessment in a multidisciplinary setting in order to guide surgical and nonsurgical management of colorectal liver metastases and to appropriately prognosticate outcomes.

In our cohort, 42% of patients carried m-*KRAS*, which is similar to the m-*KRAS* rates described in previous institutional series' of between 14 and 46%.[1,6] Charlton et al.[15] utilized the Surveillance, Epidemiology, and End Results (SEER) database to analyze 22,542 stage IV colorectal cancer patients diagnosed between 2010 and 2013, of which 6794 patients had a known *KRAS* status. They identified a mutation rate of 44% with 52% of those patients having a right-sided lesion, similar to our findings in the NCDB. The association of the m-*KRAS* with race and location of the primary tumor as well as its prognostic significance has not been clearly elucidated in patients undergoing surgical management of metastatic disease. In a recent meta-analysis of 20 studies reporting the incidence of m-*KRAS* and race by Staudacher et al.,[16] Caucasians were found to be 36% less likely to have m-*KRAS* than African-Americans among 4648 patients with sporadic colorectal cancers. In their analysis, this difference remained significant after adjustment with meta-regression of covariates such as age, gender, stage, and cancer site. However, no significant differences were observed in the

Table 1 Demographic, clinical, and pathologic characteristics of patients with colorectal adenocarcinomas and liver metastases who underwent resection of primary tumor and metastatic disease by *KRAS* mutation status ($n = 2655$), NCDB 2010–2015

	Patient characteristics	*KRAS*		*p* value
		Wild type, % $n = 1539$	Mutated, % $n = 1116$	
Demographic	Gender			0.013
	Female	44.2	49.1	
	Age at diagnosis, years (mean ± SD)	58.4 ± 13.5	60.4 ± 12.8	< 0.001
	Race			< 0.001
	White	84.3	78.5	
	African-American	11.1	17.7	
	Others	4.6	3.8	
	Primary payer			0.063
	Not insured	3.4	2.9	
	Private	54.2	50.2	
	Government	42.4	46.9	
	Income			0.218
	Low	31.2	29.0	
	Education level			0.256
	Low	37.8	40.1	
	Type of county			0.355
	Metro	81.7	83.8	
	Urban	16.3	14.7	
	Rural	2.0	1.6	
	Institution			0.711
	Academic	45.5	45.6	
	Comprehensive	46.7	45.7	
	Community	7.8	8.7	
	Year of diagnosis*			0.312
	2010	54.9	45.1	
	2011	55.9	44.1	
	2012	57.1	42.9	
	2013	62.2	37.8	
	2014	58.4	41.6	
	2015	57.9	42.1	
Clinical	Radiation			0.898
	Yes	3.4	3.3	
	Chemotherapy			0.682
	None	8.4	9.0	
	Monoagent	5.4	6.0	
	Multi-agent	86.2	85.0	
	Charlson/Deyo score			0.283
	0	78.0	75.6	
	1	16.9	19.3	
	≥ 2	5.1	5.1	
Pathologic	Margin status of primary tumor			0.073
	Positive	15.7	13.2	
	Primary tumor size, mm (mean ± SD)	49.5 ± 22.8	51.3 ± 21.1	0.050
	Location of primary site			< 0.001
	Right	35.2	58.4	
	Lymph node involvement			0.965
	pN+	79.1	79.2	

Percentages have been rounded up so the total may not add up to 100%

*All percentages are vertical, except for year of diagnosis

incidence of other genes, such as *BRAF* and *PI3CA*. Our data confirmed these findings in a surgically managed cohort of patients presenting with colorectal cancer and liver metastases, with African-Americans having significantly higher rate of m-*KRAS* even after adjustment for age, gender, and cancer location. These data suggest that differences in tumor biology could be a significant contributory factor to previously observed racial disparities in colorectal cancer outcomes.[17,18] To some extent, this parallels what has been previously demonstrated for breast cancer, where African-American women have a higher incidence of triple-negative breast cancers and conversely a worse prognosis that is driven by biology.[19]

Right-sided colon cancer has been shown to be independently associated with a worse prognosis. Petrelli et al.[20]

Table 2 Multivariable analysis for factors associated with *KRAS* mutation among patients presenting with colorectal cancer and liver metastases who underwent resection of primary tumor and metastatic disease, NCDB 2010–2015 ($n = 2655$)

Characteristics	Stage IV colorectal cancer		
	OR	95% CI	*p* value
Race			
Caucasian	Reference		
African-American	1.58	1.26–1.99	< 0.001
Others	1.03	0.69–1.53	0.902
Location of primary site			
Left	Reference		
Right	2.54	2.16–2.98	< 0.001

Gender and age were not significant

OR odds ratio, *CI* confidence interval

analyzed 66 studies from 1995 to 2016, including 1,437,846 patients with colorectal cancer to evaluate the prognostic significance of tumor location on OS. In their multivariable analysis, after adjusting for stage, race, adjuvant chemotherapy, year of study, number of participants, and quality of study, right-sided colon cancers were independently associated with a worse OS; this finding was even more pronounced for patients with stage IV cancer. The authors hypothesized a multifactorial etiology for this discordance, including a different embryological origin (midgut vs hindgut); differences in mucosal immunology (higher concentration of eosinophils and intraepithelial T cells in the proximal colon); gut microbiome distribution; a more standardized surgical technique for the left-sided cancers, consisting of total mesorectal excision; and a more aggressive biology characterizing right-sided lesions, including higher rates of microsatellite instability (MSI), CpG island methylation, and *BRAF* and *KRAS* mutations. This latter hypothesis was verified by Taieb et al., who performed a post hoc analysis on 2559 patients participating in the Pan-European Trials in Alimentary Tract Cancer (PETACC)-8 phase 3 randomized trial, which analyzed patients with stage III colon cancer receiving adjuvant treatment with FOLFOX with or without cetuximab.[21] The investigators found that patients with right-sided tumors were older and more likely to have poorly differentiated cancers with higher rates of lymphovascular invasion and MSI, *BRAF*, and *KRAS* mutations. Our survival analyses are in line with these data as both right-sided and m-*KRAS* tumors were independently associated with worse prognosis, suggesting that right-sided location could be a proxy for other genetic mutations not captured in the NCDB. We also observed that the difference in OS between right- and left-sided cancers was of greater magnitude for wt-*KRAS* than m-*KRAS* cancers, indicating that for metastatic m-*KRAS* colorectal cancers, location may not be as of a significant prognostic factor. Furthermore, race was found not to be an independent prognostic factor, which, together with its association with *KRAS* mutation, further validates the abovementioned biology-driven disparity in colorectal cancer outcomes.

Even though outside of the aims of this study, we identified an overall primary tumor positive margin rate of 14% that was associated with lower OS. This finding is of relevance in emphasizing the importance of surgical technique in achieving R0 resections at the primary site for metastatic colorectal cancers when technically feasible. Other well-established prognostic factors for outcomes after liver resection for colorectal

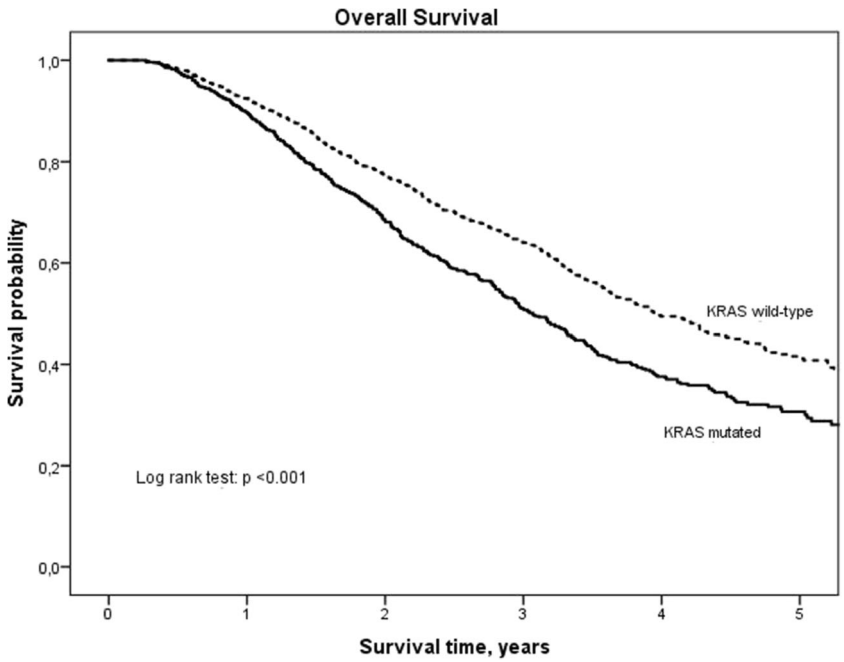

Fig. 2 Overall survival by KRAS mutation

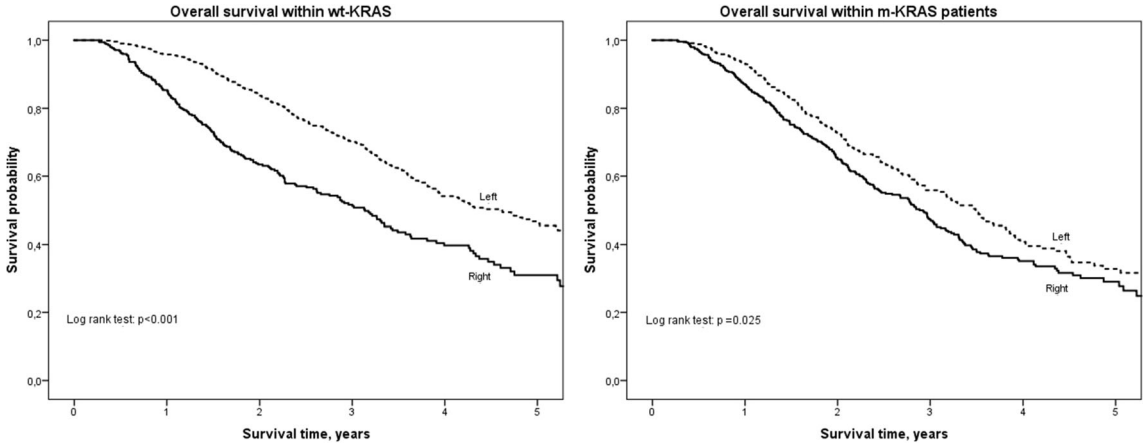

Fig. 3 Comparison of overall survival between right- and left-sided primary cancers by *KRAS* mutation status

metastases such as age, monoagent chemotherapy, tumor size, and positive lymph node status of the primary tumor were all independently associated with worse OS in our cohort.

This study has several limitations, particularly those inherent to retrospectively using large databases, such as coding errors. Nevertheless, the NCDB has been well validated for oncologic studies.[22,23] Certain variables that could significantly impact OS, including metastatic burden, rates and site of recurrence, reoperations, metastatic resection margin status, additional distant site therapies, including chemoembolization and radiofrequency ablation, and *BRAF* status could not be evaluated because they are not collected in the NCDB. Also, the NCDB does not define the extent or the quality of the liver resection including margin status, therefore possibly introducing an unaccounted bias. Finally, the NCDB lacks details on the chemotherapy regimen utilized in the neoadjuvant and/or adjuvant setting, hence it could be theoretically possible that the observed increased survival of the wt-*KRAS* patients was due to their responsiveness to EGFR inhibitors. Nonetheless, the initial reports of worse survival in m-*KRAS* tumors included patients treated prior to the Food and Drug administration (FDA) approval of cetuximab and panitumumab in 2004 and 2006, respectively, suggesting the importance of tumor biology in the prognosis of these patients.[6]

Table 3 Multivariable analysis for prognostic factors among patients presenting with colorectal cancer and liver metastases who underwent resection of primary tumor and metastatic disease, NCDB 2010–2015

Characteristics	Stage IV colorectal cancer		
	HR	95% CI	*p* value
Patient age, years	1.02	1.01–1.02	< 0.001
Monoagent chemotherapy	1.43	1.09–1.87	0.010
Positive primary tumor margins	1.83	1.53–2.18	< 0.001
Primary tumor size, mm	1.01	1.00–1.01	0.024
Right-sided primary tumor	1.45	1.25–1.68	< 0.001
Node-negative primary	0.63	0.52–0.77	< 0.001
KRAS mutated	1.21	1.04–1.39	0.012

Gender, race, and comorbidities were not significant

HR hazard ratio, *CI* confidence interval

References: chemotherapy, multi-agent chemotherapy; margins, negative; site of primary tumor, left colon; lymph node status, negative; KRAS status, wild type

Conclusion

In conclusion, the current study validates the prognostic significance of m-*KRAS* in patients presenting with colorectal cancer and liver metastases who underwent resection of both the primary tumor and metastatic disease within a large, nationally representative cohort. These data confirm that the genetic profile of the tumor should be taken into account in the multidisciplinary management of colorectal liver metastases. Moreover, our data demonstrate African-American race to be significantly associated with m-*KRAS* but not independently associated with lower survival, suggesting that historical data regarding a worse prognosis for colorectal cancer in African-American patients may be driven by a higher incidence of a worse biologic disease.

Author Contribution Each author provided substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; drafted/revised the work critically for important intellectual content; approved the version to be published; and agrees to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Disclaimer The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or

statistical methodology employed, or the conclusions drawn from these data by the investigator.

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