

These results demonstrate that both pain interference score and pain intensity are significant predictors of overall survival in men with castrate-refractory prostate cancer. Furthermore, pain interference score and pain intensity are statistically significant predictors of overall survival even when adjusting for established prognostic factors. It is known that high levels of alkaline phosphatase, PSA, and lactate dehydrogenase; low levels of hemoglobin; and high Gleason scores are indicators of advanced progression and death. Thus, these findings support the hypothesis that pain intensity and pain interference score are validated measures of advanced disease in men with prostate cancer. We agree with Klepstad and Kaasa in that investigating the relationship between pain and clinical outcomes in cancer patients is a fruitful area of research.

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ACKNOWLEDGMENT

Supported in part by Grants No. DAMD 17-03-1-0112 and W81XWH-06-1-0032 from the Department of Defense and Grant No. CA 36601 from the National Cancer Institute, Bethesda, MD.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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DOI: 10.1200/JCO.2008.18.5496

Mutations of *KRAS* and *BRAF* in Primary and Matched Metastatic Sites of Colorectal Cancer

TO THE EDITOR: After the demonstration that *KRAS* or *BRAF* mutations in colorectal cancer (CRC) are associated with clinical resistance to treatment with the epidermal growth factor receptor (EGFR)-targeted monoclonal antibodies,¹⁻³ the clinical confirmation of these findings in independent retrospective reports^{4,5} as well as in a phase III trial recently published in *Journal of Clinical Oncology* has led the European Medicines Agency to license panitumumab and cetuximab only for patients with CRC without *KRAS* mutations.^{6,7} Nevertheless, among patients with wild-type *KRAS* CRC, the objective response rate is limited to 17% (*v* 0% in unselected patients) with panitumumab monotherapy⁸ and to 59% and 61% (*v* 43% and 33% in unselected patients) with cetuximab plus either irinotecan- or oxaliplatin-based chemotherapy, respectively.^{9,10} These data indicate that other mechanisms of resistance play a significant role. Moreover, evaluation of metastatic rather than primary sites could be of clinical relevance because occurrence of a mutation in the metastasis could, at least theoretically, explain resistance despite a wild-type primary tumor. Scarce and heterogeneous reports have evaluated whether *KRAS* status matches in primary tumor and metastatic site(s),¹¹⁻¹⁴ whereas *BRAF* remains unexplored. For these reasons, we elected to evaluate *KRAS* (exon 2) and *BRAF* (exon 15) by DNA sequencing in a cohort of 48 CRC patients (median age, 56 years; range, 37 to 79 years; 28 men and 20 women) in primary tumor (colon, *n* = 32; rectum, *n* = 7; and

sigma-rectum junction, *n* = 9) and matched metastases (liver, *n* = 39; ovary, *n* = 2; distant lymph nodes, *n* = 1; adrenal gland, *n* = 1; pancreas, *n* = 1; lung, *n* = 2; omentum, *n* = 1; and pelvic mass, *n* = 1). DNA sequencing showed a frequency of mutation in the primary tumor or metastases of 13 (27%) of 48 and two (4%) of 48 patients for *KRAS* and *BRAF*, respectively. None of the patients carried both mutations (in primary tumor or metastasis); the occurrence of the mutations was a mutually exclusive phenomenon, as expected by literature.¹⁵ We observed an overall concordance of *KRAS* and *BRAF* mutational status (ie, mutated or wild type) between primary tumor and metastasis in 44 (92%) of 48 patients. In patients carrying a *KRAS* mutation, concordance between primary tumor and secondary deposits was observed in 10 (77%) of 13 patients, all but one of whom presented with synchronous metastases (Table 1). Discordance of *KRAS* mutational status was detected in three (23%) of 13 patients with mutations, with one patient carrying *KRAS* mutation in the primary tumor only and two patients carrying the mutation in the metastatic site only (pancreas and adrenal gland). Notably, occurrence of *KRAS* mutations with wild-type primary tumor was detected in extrahepatic sites only. In the two patients carrying *BRAF* mutation, one patient presented the same mutation in both primary tumor and metastasis, whereas the other patient presented the mutation in the primary tumor site only.

Controversial and heterogeneous previous reports¹¹⁻¹⁴ demonstrated overall concordance between *KRAS* mutations in the primary tumor and secondary deposits in CRC, indicating that *KRAS* mutations are not essential for the attainment of metastatic capacity. In a previous study, Oudejans et al¹¹ evaluated 39 patients and found, in three patients, a *KRAS* point mutation in the metastasis with a

Table 1. Molecular and Clinical Characteristics of Patients With Colorectal Cancers Harboring *KRAS* or *BRAF* Mutations

Patient No.	Primary Tumor			First Metastatic Site			Other Metastatic Site		
	Tumor Site	<i>KRAS</i>	<i>BRAF</i>	Metastasis Site	<i>KRAS</i>	<i>BRAF</i>	Metastasis Site	<i>KRAS</i>	<i>BRAF</i>
1	Colon	G12S	NA	Liver	G12S	NA			
2	Colon	G12D	WT	Liver	G12D	WT			
3	Rectum	G12D	WT	Liver	G12D	WT	Liver	G12D	WT
4	Rectum	G12D	WT	Liver	G12D	WT			
5	Colon	G13D	WT	Liver	G13D	WT			
6	Sigma-rectum	G12S	WT	Liver	WT	WT			
7	Colon	G13D	WT	Liver	G13D	WT			
8	Colon	WT	V600E	Omentum	WT	V600E			
9	Sigma-rectum	G13D	WT	Liver	G13D	WT			
10	Colon	G12C	WT	Liver	G12C	WT			
11	Colon	G12V	WT	Ovary	G12V	WT			
12	Colon	G13D	WT	Liver	G13D	WT			
13	Colon	WT	V600E	Pelvis	WT	WT			
14	Colon	WT	WT	Pancreas	G12V	WT			
15	Rectum	WT	WT	Adrenal gland	G12V	WT	Kidney	G12V	WT

Abbreviations: NA, not assessable; WT, wild type.

wild-type primary tumor, whereas in a single patient, a point mutation was found in a primary tumor but was absent from the metastasis. Moreover, these investigators did not find differences in frequency of *KRAS* mutations between 23 patients with isolated lung metastases and 20 patients with liver metastases (57% and 50%, respectively), demonstrating that *KRAS* oncogene activation does not have a major role in determining the frequency of lung metastases versus liver metastases. Suchy et al¹² demonstrated the concordance of *KRAS* mutations in primary tumors and respective metastases in 15 patients, and the type of mutation was also identical in the instance of different metastases from the same primary tumor localized in different organs, indicating a stability of these mutations during metastatic progression. In a series from 1998, Al-Mulla et al¹³ reported that only two (8%) of 26 metastatic patients had a mutation in their primary carcinoma but none in liver metastases. In contrast with these data showing overall identity of *KRAS* mutations between primary tumor and matched metastatic deposits, Tórtola et al¹⁴ described discordance between *KRAS* mutation in bone marrow micrometastases and primary tumor. In particular, in six patients with primary tumor mutations, the pattern of *KRAS* mutation differed in three patients, and in one patient the same mutation plus a different one were found; moreover, in eight patients, there was a mutation in the primary tumor and none in bone marrow metastases. In the present cohort, we took into consideration *KRAS* and *BRAF* mutations because alterations of both of these cellular effectors can impair response to anti-EGFR therapy. For both genetic alterations, we observed overall concordance between primary tumor and metastasis in the vast majority of patients. Present findings represent additional knowledge supporting the notion that a concordance of *KRAS* and *BRAF* status is the most common feature in CRC. The clinical relevance of these data is that evaluation of the *KRAS* and *BRAF* mutations can be performed in either primary tumor or metastatic site(s) and that absence of such mutations could be enough to drive the selection of metastatic CRC patients who are candidates for anti-EGFR monoclonal antibody therapy.

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ACKNOWLEDGMENT

Supported in part by research grants from Oncologia Ca' Granda Onlus Fondazione; and Associazione Italiana per la Ricerca sul Cancro, Milan, Italy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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DOI: 10.1200/JCO.2008.18.7286

Detailed Analysis of Visitors to Cancer-Related Web Sites

TO THE EDITOR: Web sites are a valuable source of information for cancer patients.¹ Patients are seeking information necessary for their own treatment, as well as general cancer information. To satisfy such needs of cancer patients, it is necessary to build Web sites that are conducive to patients' individual needs, as well as to have organic linkage between a wide variety of sites. Although achieving this end requires sufficient study of the characteristics of cancer-related Web site users, there is little research on the topic, leaving an unclear picture of the actual state of cancer-related Web site users. Therefore, in this study, we conducted an access analysis

of cancer-related Web sites to shed light on the characteristics of their visitors, which is information necessary for improving the user friendliness of such Web sites.

Using Keyword Advice Tool (Overture KK, Tokyo, Japan),² we first selected 96 keywords pertaining to cancer that have been used in more than 3,000 searches per month on Yahoo! as of September 2006. Next, we used the 96 selected keywords to conduct Yahoo! searches,³ and then selected 2,000 Web sites that came up in these searches. We then used Keyword Advice Tool to obtain the number of searches performed with each keyword and ranked the Web sites proportionate to the number of searches. Then we computed a ranking score by giving the *n*th-ranking keyword of the converted ranking a $1/n$ value (eg, the first-ranking site gets 1,000 points, the second-ranking site half of that, and so on). We

Table 1. Web Sites Analyzed

Classification	Name of Web Site	Aggregation Period	No. of Visitors (daily average)	No. of Page Views (daily average)
Cancer center	Cancer center Web site A	September 1, 2006 to November 30, 2006	—	42,663
Cancer center	Cancer center Web site B	October 1, 2006 to November 30, 2006	—	62,181
Hospital	Hospital Web site C	August 1, 2006 to November 30, 2006	8026	—
Hospital	Cancer center Web site D	March 26, 2006 to November 18, 2006; October 15, 2006 to January 13, 2007	—	—
Hospital	Hospital Web site D	October 1, 2006 to December 31, 2006	—	421
Hospital	Hospital Web site E	November 1, 2006 to December 31, 2006	—	—
Pharmaceutical company	Pharmaceutical company Web site A	November 1, 2006 to December 31, 2006	—	—
Pharmaceutical company	Pharmaceutical company Web site B	November 1, 2006 to December 31, 2006	—	—
Pharmaceutical company	Pharmaceutical company Web site C	November 1, 2006 to December 31, 2006	—	—
Pharmaceutical company	Pharmaceutical company Web site D	November 1, 2006 to December 31, 2006	—	—
Pharmaceutical company	Pharmaceutical company Web site E	November 1, 2006 to December 31, 2006	—	—
Individual	Individual antiaging Web site A	December 1, 2006 to December 31, 2006	—	—
Cancer patient	Cancer blog B	October 1, 2006 to December 31, 2006	—	—
Cancer patient	Cancer blog C	October 1, 2006 to December 31, 2006	—	—
Cancer patient	Cancer blog D	December 2, 2006 to January 12, 2007	—	—
Cancer patient	Pediatric cancer blog E	December 10, 2006 to January 27, 2007	—	—
Cancer patient	Pediatric cancer blog F	December 10, 2006 to January 27, 2007	—	—
Cancer patient	Childhood leukemia blog G	December 10, 2006 to January 27, 2007	—	—
Cancer patient	Leukemia blog H	October 8, 2006 to January 8, 2007	—	—
Cancer patient	Leukemia blog I	October 6, 2006 to January 5, 2007	—	—
Cancer patient	Breast cancer blog J	January 1, 2007 to February 28, 2007	198	—
Cancer patient	Breast cancer blog K	January 1, 2007 to February 28, 2007	161	—
Cancer patient	Leukemia blog L	January 1, 2007 to February 28, 2007	173	—
Cancer patient	Ureteral cancer blog M	January 1, 2007 to February 28, 2007	51	—
Cancer patient	Individual cancer link site N	January 1, 2007 to February 28, 2007	—	—