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Influence of *KRAS* Mutation Status in Metachronous and Synchronous Metastatic Colorectal Adenocarcinoma

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Abstract

BACKGROUND—Mutations in the v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) are present in approximately 30% to 40% of colorectal adenocarcinomas. Wild-type (WT) *KRAS* mutation status is predictive of tumor response with epidermal growth factor receptor-directed therapies, but the results from studies evaluating the prognostic value of *KRAS* status in localized disease have been contradictory. The prognostic value of *KRAS* in metastatic disease, specifically according to whether patients have synchronous or metachronous disease at presentation, is less understood.

METHODS—One-hundred ten consecutive patients with metastatic colorectal adenocarcinoma underwent testing for *KRAS* exon 2 mutations by polymerase chain reaction amplification and direct nucleotide sequencing. The clinical characteristics, treatments, and outcomes of these patients were then analyzed retrospectively, stratified according to whether patients presented with synchronous or metachronous metastasis and according to *KRAS* mutation status (WT or mutated).

RESULTS—For the entire cohort, the median overall survival from the date of diagnosis of metastatic disease was 34.3 months (95% confidence interval, 28.3–49.4 months) for patients with WT *KRAS* (n = 70). The median overall survival for patients with mutated *KRAS* (n = 40) was 40.3 months (95% confidence interval, 27.9–51.1 months; log-rank $P = .91$). Kaplan-Meier survival analysis indicated that 3-year overall survival and 5-year overall survival were not statistically different. Within the subgroups of patients with synchronous and metachronous metastatic disease, no significant differences were observed in median overall survival, 3-year overall survival, or 5-year overall survival between the WT *KRAS* and mutated *KRAS* groups.

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CONFLICT OF INTEREST DISCLOSURES

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CONCLUSIONS—In this study, *KRAS* mutation status did not influence overall survival in either synchronous or metachronous metastatic colorectal adenocarcinoma and, as such, had no prognostic role in this disease setting.

Keywords

metastatic colorectal adenocarcinoma; KRAS; mutation; prognosis

INTRODUCTION

The development of colorectal adenocarcinoma is a multistep process characterized by an accumulation of genetic alterations.[1] The v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) belongs to a family of oncogenes that includes the v-Ha-ras Harvey rat sarcoma viral oncogene homolog (*HRAS*) and the neuroblastoma RAS viral oncogene homolog (*NRAS*). When mutated, these oncogenes have the ability to promote the malignant transformation of normal cells. Mutated *KRAS* is the most frequently encountered oncogene of the *RAS* family in colon cancer and is present in 30% to 40% of colorectal adenocarcinomas.[2,3] KRAS is a small G-protein with guanine diphosphate (GDP)-binding and guanine triphosphate (GTP)-binding abilities, with GDP binding in its inactive form and GTP binding when activated. In normal function, KRAS is activated transiently in response to extracellular signals, such as growth factors, cytokines, and hormones. Mutations in *KRAS* usually are point mutations on codons 12 and 13 (exon 2), codon 61 (exon 3),[4] and codon 146 (exon 4).[5] Mutations result in loss of its GTPase activity, leading to activation and unregulated proliferation of its downstream effects through signal-transduction pathways, including the Raf/mitogen-activated protein kinase/extracellular signal-regulated kinase (Raf/MEK/ERK) pathway and the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway, thereby promoting cell growth and survival in the absence of external signals.

Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor involved in the transmission of extracellular signals to KRAS. Ligands bind the extracellular domain with resultant autophosphorylation of the intracellular domain and downstream activation of KRAS. Inhibition of EGFR has become an important pharmacologic target in oncology. Two anti-EGFR monoclonal antibody therapies, panitumumab and cetuximab, are approved for use in metastatic colorectal cancers. Although initial studies of these agents demonstrated modest activity in unselected patients,[6,7] it has become clear that *KRAS* mutation status is predictive of tumor response.[8,9] Wild-type (WT) *KRAS* status is predictive of tumor response to the EGFR-directed antibodies and, conversely, mutated *KRAS* is negatively predictive of response. The American Society of Clinical Oncology recently released a provisional clinical opinion that patients with metastatic colorectal who harbor *KRAS* mutations should not receive EGFR-directed therapies.[10]

The presence of a *KRAS* mutation also may be prognostic, although studies have produced conflicting results.[11–23] Given the limited and conflicting data available on the outcome of metastatic colorectal cancer on the basis of *KRAS* mutation status, in the current study, we retrospectively analyzed the outcomes of patients with colorectal cancer in the metastatic setting. This was performed irrespective of whether EGFR-directed therapies were received, and we evaluated for the first time patients in both synchronous (metastatic at the time of diagnosis) and metachronous (metastases developing after initial diagnosis of localized disease) metastatic settings. The prognostic implication of the time to disease recurrence remains unclear in medically treated patients; modern chemotherapy trials have not addressed this issue and often exclude patients who develop recurrent disease within 6 to 12

months after completing adjuvant therapy. However, when considering metastatectomy, metachronous presentation of disease is associated with improved survival.[24]

MATERIALS AND METHODS

Study Design

Patients who had *KRAS* mutation testing for colorectal adenocarcinoma from a single tertiary care institution (The Ohio State University Medical Center) were included in this study. Only patients with documented metastatic disease were included. Synchronous was defined as metastatic disease at the time of the original colorectal cancer diagnosis. Metachronous was defined as the absence of metastatic disease at the time of initial diagnosis with metastatic disease developing later. Patients were excluded if they died in the immediate postoperative period before receipt of any systemic therapy (n = 3). *KRAS* testing could be performed at any time during the disease course.

KRAS Mutation Analysis

For *KRAS* mutation testing, genomic DNA was extracted from formalin-fixed, paraffin-embedded tumor tissue using the Qiagen DNA preparation kit (Qiagen, Valencia, Calif). The sequences containing the target mutations were amplified by polymerase chain reaction (PCR) with primers flanking exon 2 of the *KRAS* gene. This included the codons G12 and G13. The PCR products were purified and sequenced bidirectionally using the ABI3130xl DNA analyzer (Applied Biosystems, Foster City, Calif) at the Clinical Laboratory Improvement Act-certified and College of American Pathologists-accredited clinical molecular laboratory at the Pathology Core Facility of The Ohio State University Medical Center.

Statistical Analysis

The demographic and clinical characteristics of patients are summarized in Table 1, in which frequencies/percentages are used for categorical variables, and means, standard deviations, and ranges are used for continuous variables. The Kaplan-Meier method was used to estimate the median overall survival, the 3-year survival rate, and the 5-year survival rate for each patient group. Kaplan-Meier plots also were generated. The log-rank test was used to compare the survival of different patient groups. All *P* values were from 2-sided tests, and *P* values < .05 were considered statistically significant. Data analyses were conducted using SAS 9.1 statistical software (SAS Institute Inc., Cary. NC).

RESULTS

Demographics

Baseline characteristics of the study population are described in Table 1. In total, 110 patients were identified, of whom 40 had *KRAS* mutations (36%). This proportion of *KRAS*-mutant colorectal cancer is consistent with previously reported values.[2,3] Sixty four patients(58%) had synchronous metastatic disease, and the other 46 patients (42%) had with metachronousmetastatic disease. In the metachronous group, the diagnosis of metastatic disease occurred at a median of 20 months (range, 4–125 months) from the time of the original, localized diagnosis. Eighteen percent of *KRAS* mutant patients received EGFR-directed therapy, all of which was prescribed before knowledge that *KRAS*-mutant tumors do not respond to these agents.

Treatment Efficacy

Kaplan-Meier analyses of overall survival from the original date of colorectal cancer diagnosis for synchronous metastatic and metachronous metastatic disease, stratified by *KRAS* mutation status, are illustrated in Figure 1. The median overall survival (mOS), 3-year, and 5-year survival estimates are presented in Table 2. Analyses of these endpoints did not differ significantly when comparing patients with WT *KRAS* and mutant *KRAS* who had either synchronous or metachronous disease.

For the patients with synchronous disease, the mOS for the WT *KRAS* group was 36.3 months (95% confidence interval [CI], 21.8–58.3 months), and it was 40.3 months (95% CI, 27.3–51.0 months) for the mutant *KRAS* group (log-rank test; $P = .55$). Kaplan-Meier analysis indicated that patients with synchronous WT *KRAS* had a 3-year survival estimate of 0.51 (95% CI, 0.33–0.66) and a 5-year survival estimate of 0.28 (95% CI, 0.12–0.46). Patients with synchronous disease who had mutant *KRAS* had a 3-year survival estimate of 0.59 (95% CI, 0.36–0.77) and 5-year survival estimate of 0.16 (95% CI, 0.03–0.38).

For the patients with metachronous disease, the mOS for the WT *KRAS* group was 68.4 months (95% CI, 53.1–95.1 months), and it was 92.0 months (95% CI, 51.8 months to not applicable) for the mutant *KRAS* group (log-rank $P = .37$). Kaplan-Meier analysis indicated that patients with metachronous WT *KRAS* had a 3-year survival estimate of 0.83 (95% CI, 0.64–0.93) and a 5-year survival estimate of 0.65 (95% CI, 0.44–0.79). Patients with metachronous who had mutant *KRAS* had a 3-year survival estimate of 0.93 (95% CI, 0.61–0.99) and a 5-year survival estimate of 0.69 (95%CI, 0.37–0.87). Patients who were diagnosed with metachronous disease, as would be expected, had a prolonged mOS from the time of original diagnosis compared with those who were diagnosed with synchronous disease (log-rank $P = .015$ for *KRAS* WT and $P = .001$ for *KRAS* mutant).

Figure 2 illustrates the shows Kaplan-Meier analyses for overall survival from the date of diagnosis of metastatic disease for patients with synchronous and metachronous disease stratified according to *KRAS* mutation status. The mOS and the 3-year and 5-year survival estimates are presented in Table 3. No significant differences were observed in OS or in the 3-year or 5-year survival estimates between the WT *KRAS* group and the mutant *KRAS* group for those with either synchronous or metachronous disease. By definition, synchronous disease is metastatic at diagnosis; thus, the data in Table 3 are the same as the data from Table 2, described above, and are included in Table 3 for comparative purposes. The mOS for patients with WT *KRAS* and mutant *KRAS* from the date of diagnosis of metachronous disease was 33.2 months (95% CI, 28.3–49.4 months) and 53.0 months (95% CI, 26.7 months to not applicable; log-rank $P = .33$), respectively. In Kaplan-Meier analysis, patients with metachronous disease who had WT *KRAS* had a 3-year survival estimate of 0.43 (95%CI, 0.24–0.62) and a 5-year survival estimate of 0.27 (95% CI, 0.11–0.47). Patients with metachronous who had mutant *KRAS* had a 3-year survival estimate of 0.53 (95% CI, 0.23–0.76) and a 5-year survival estimate of 0.27 (95% CI, 0.02–0.65).

Figure 3 illustrates the Kaplan-Meier analyses of overall survival calculated from the date of diagnosis of metastatic disease for all patients (synchronous and metachronous) stratified according to *KRAS* mutation status. The mOS and the 3-year and 5-year survival estimates are presented in Table 3. Again, no differences in these endpoints were observed between patients with WT *KRAS* and patients with mutant *KRAS*. The mOS was 34.3 months (95% CI, 28.3–49.4 months) for patients with WT *KRAS* and 40.3 months (95% CI, 27.9–51.1 months) for patients with mutant *KRAS* (log-rank $P = .91$). In Kaplan-Meier analysis, patients with WT *KRAS* had a 3-year survival estimate of 0.50 (95% CI, 0.37–0.62) and a 5-year survival estimate of 0.28 (95% CI, 0.16–0.41), and patients with mutant *KRAS* had a 3-

year survival estimate of 0.53 (95% CI, 0.35–0.69) and a 5-year survival estimate of 0.17 (95% CI, 0.04–0.39).

Outcomes after the diagnosis of metastatic disease for all 110 patients who were included in this study are provided in Table 3. The mOS was 35.2 months (95% CI, 30.5–49.4), the 3-year survival estimate was 0.50 (95% CI, 0.39–0.60), and the 5-year survival estimate was 0.25 (95% CI, 0.15–0.37).

DISCUSSION

KRAS mutations are observed commonly in colorectal cancer, and WT status is predictive of response to EGFR-directed therapy. The prognostic implications of *KRAS* mutation status are less well defined, and various studies in both localized and metastatic disease have produced conflicting results. The current study demonstrates that, with modern chemotherapy regimens, patients who have metastatic colorectal cancer with mutant *KRAS* tumors have an overall survival similar to that of patients who have metastatic colorectal cancer with WT *KRAS* tumors. This finding was observed consistently in patients who were diagnosed with synchronous as well as metachronous metastatic disease.

Our findings are in overall concordance with other studies of metastatic disease. The recently published follow-up analysis of the phase 3 Australian Gastrointestinal Trials Group (AGITG) (the AGITG MAX trial[12]) assessed the predictive and prognostic value of *KRAS* and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF*) mutation status in patients who were receiving capecitabine with or without mitomycin and bevacizumab in the first-line setting. Mutation status was determined in 315 patients (67%) in the original study population, and *KRAS* mutations were observed in 28.8% of the population. *KRAS* was not prognostic of patient outcomes, and the mOS was 18.4 months in the mutant *KRAS* group compared with 20.0 months in the WT *KRAS* group ($P = .82$). Two other studies that assessed the efficacy of EGFR inhibitors added to chemotherapy and bevacizumab confirmed that *KRAS* mutation status had no prognostic significance. The Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) study assessed the efficacy of panitumumab added to first-line 5-fluorouracil–based doublet chemotherapy plus bevacizumab.[12] There was no difference in overall survival when patients were stratified according to *KRAS* mutation status. The second Capecitabine, Irinotecan, and Oxaliplatin (CAIRO2) study assessed the addition of cetuximab to capecitabine, oxaliplatin, and bevacizumab.[13] Seven hundred fifty-five patients were enrolled, and 520 underwent *KRAS* mutation assessment. Sixty percent of those patients had WT *KRAS*. There was no significant difference in overall survival when the patients were stratified according to the presence of *KRAS* mutation in either the control arm or the experimental arm, which was receiving cetuximab. An assessment of 394 specimens for *KRAS* mutation status in the CO. 17 trial confirmed the predictive role in WT *KRAS* tumors and response to cetuximab.[9] Despite its predictive value for cetuximab, *KRAS* mutation status lacked prognostic significance.

In contrast, a retrospective analysis of the Medical Research Council (MRC) Fluorouracil, Oxaliplatin, and Irinotecan (FOCUS) trial evaluated several chemotherapy strategies in patients with previously untreated advanced colorectal cancers.[14] It is noteworthy that none of those patients received EGFR-directed therapies. A retrospective *KRAS* assessment of 711 tumor specimens identified mutations in codons 12 and 13 in 288 patients (40.5%) along with 3 patients (0.6%) who had an additional mutation in codon 61. Progression-free survival was comparable between the mutant *KRAS* and WT *KRAS* groups, but overall survival was shorter for patients with mutant *KRAS*, suggesting the possible prognostic relevance of the mutation.[14] The MRC COIN (COntinuous versus INtermittent

chemotherapy) trial assessed the benefit of adding cetuximab to oxaliplatin and 5-fluorouracil or capecitabine in 1650 patients with untreated, metastatic colon cancer.[15] Patients in that trial were not stratified according to *KRAS* mutation status before entry of the study. Eighty percent of the patients enrolled underwent *KRAS*, *NRAS*, and *BRAF* mutation assessment. Five hundred sixty-five patients (43%) in that study had a *KRAS* mutation, 50 patients (4%) had an *NRAS* mutation, and 102 patients (8%) had a *BRAF* mutation. In the patients with WT *KRAS* who received cetuximab, there was no improvement in overall survival compared with those who received chemotherapy alone. The prognostic value of *KRAS* also was assessed. Patients with any of the aforementioned 3 mutations had worse survival compared with patients who had WT *KRAS* (14.4 months vs 20.1 months for patients who did not receive cetuximab and 12.7 months vs 19.9 months for patients who did receive cetuximab). There was a strong prognostic effect for *KRAS*, *NRAS*, and *BRAF* mutation status independent of the receipt of cetuximab. Like what was observed in the third Pan-European Trial in Adjuvant Colon Cancer (PETACC-3) study,[16] patients who had *BRAF* mutations fared the poorest in this study. Finally, an updated analysis of the Cetuximab Combined With Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer (CRYS-TAL) study using combined folic acid, 5-fluorouracil, and irinotecan (FOLFIRI) with or without cetuximab examined the prognostic significance of *KRAS* mutations.[17] Of the initial intent-to-treat population of 1198, 1063 patients had tissue available for *KRAS* assessment. Six hundred sixty-six patients (62.7%) had WT *KRAS*, and 397 patients (37.3%) had mutant *KRAS* in codons 12 and 13. Patients with mutated *KRAS* appeared to have worse overall survival than those with WT tumors (16.7 months vs 20.0 months for who received FOLFIRI, respectively; and 16.2 months vs 23.5 months for those who received FOLFIRI plus cetuximab, respectively). Other studies, such as the German Association of Medical Oncology (AIO) study KRK-1014,[18] again suggested a prognostic role for the presence of *KRAS* mutations.

Studies evaluating the prognostic value of *KRAS* in earlier stage, resected disease also are conflicting. A large, retrospective analysis of 3439 patients from the KRAS Mutations in Colorectal Cancer Collaborative Group (RASCAL) II study identified 12 different mutations on codons 12 and 13.[19] Multivariate analyses identified only a glycine-to-valine substitution on codon 12 (identified in 8.6% of patients) that had a statistically significant impact on failure-free survival. There was a more pronounced influence in patients who had Duke C disease compared with patients who had Duke B disease. Drawbacks to that analysis included the absence of a microsatellite instability assessment as well heterogeneity in assay methodology, because it was not standardized.[19] The N0147 study, which evaluated the addition of cetuximab to 5-fluorouracil and oxaliplatin (FOLFOX) in patients with resected, stage III colon cancer, suggested a prognostic role for the mutation.[20] In the absence of cetuximab, patients with WT *KRAS* tumors who received FOLFOX had an improved prognosis with a 75.8% 3-year disease-free survival rate compared with 67.2% of patients who harbored a *KRAS* mutation. In contrast, investigators from PETACC-2 trial evaluated the prognostic role of *KRAS* and *BRAF* mutations in 493 patients with resected stage III colon cancer who received adjuvant 5-fluorouracil.[21] *KRAS* mutations were detected by direct sequencing. After 3 years, 63% of patients with mutant *KRAS*, 68% of patients with WT *KRAS/BRAF*, and 65% of patients with *BRAF* mutations were still alive, indicating no prognostic value of *KRAS/BRAF* status in that study. In addition, the PETACC-3 trial retrospectively analyzed archival tissue for multiple molecular markers, including *KRAS* mutations (exon 2, codons 12 and 13) in 1564 patients with resected, stage II and stage III disease.[16] *KRAS* mutations were identified in 36% of patients with stage II colon cancer and in 37% of patients with stage III colon cancers. Multivariate and univariate analyses, again, identified no clear association between *KRAS* mutation status and relapse-free survival or OS in either stage II or III cancers. In a retrospective analysis of 508 patients with stage III colon cancer who were treated on the Cancer and Leukemia Group B (CALGB) clinical trial

CALGB 89803, 35% had *KRAS* mutations identified. *KRAS* mutation status did not influence overall survival.[22]

Overall, as discussed above, the data relating to the prognostic value of *KRAS* mutation status is conflicting across all stages in patients with colon cancer. In our study, the majority of patients with WT *KRAS* received anti-EGFR therapies, usually with irinotecan or FOLFIRI when combined with chemotherapy. In patients with metastatic disease, who were the focus of our current study, the receipt of anti-EGFR therapy may have affected the measured outcome. The most representative data set evaluating the influence of *KRAS* mutation status on prognosis in the metastatic setting ideally would exclude the use of EGFR-inhibitor therapy. For example, the MRC FOCUS study,[14] which included only 0.5% and 1.5% of patients in each respective arm received any EGFR-inhibitor therapy, suggested a prognostic role for *KRAS* mutation status. Whereas the CO.17 study demonstrated no difference in outcome between patients with WT and mutant *KRAS* in the best supportive care arm, suggesting a lack of prognostic significance for the mutation.[9]

To our knowledge, this is the first study to specifically investigate differential survival in patients with synchronous and metachronous metastatic colorectal cancer according to *KRAS* mutation status. Like all retrospective analyses, our study has several limitations. The sample size, although fairly representative, was relatively small. The *KRAS* testing performed in this study using PCR and direct nucleotide sequencing accounts only for mutations in codons 12 and 13, and not for less common mutations, like those in codons 61 and 146.[4,5] In addition, a breakdown of codon 12 mutations versus codon 13 mutations was not available. Mutations in *KRAS* codon 13 may have more prognostic significance than mutations in *KRAS* codon 12, although this remains somewhat controversial. [24,25] Finally, data on *BRAF* mutation status, which may be associated with a worse prognosis in colorectal cancer,[14–17,26,27] were not available in our study. Given the rarity of this mutation, this is unlikely to affect the outcome results of our study. One strength of our study is the availability of survival data from the date of first diagnosis for all included patients, allowing a more longitudinal analysis. In conclusion, our study suggests the absence of a prognostic role for KRAS mutation in colon cancer regardless of the presence of synchronous or metachronous metastatic disease.

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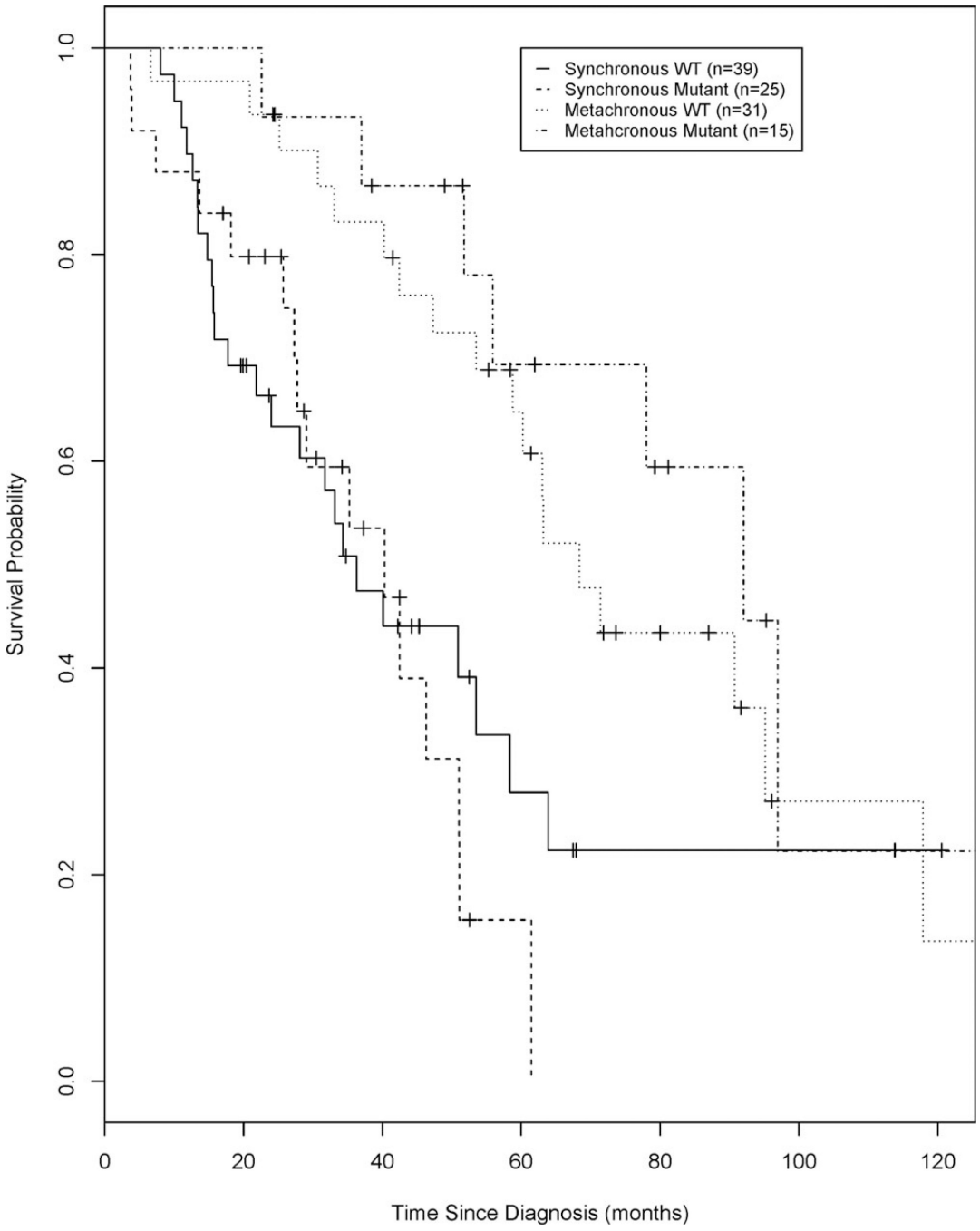

Figure 1.

Overall survival is illustrated from the original date of colorectal diagnosis for patients with synchronous metastatic and metachronous metastatic disease, stratified by v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation status. WT indicates wild type.

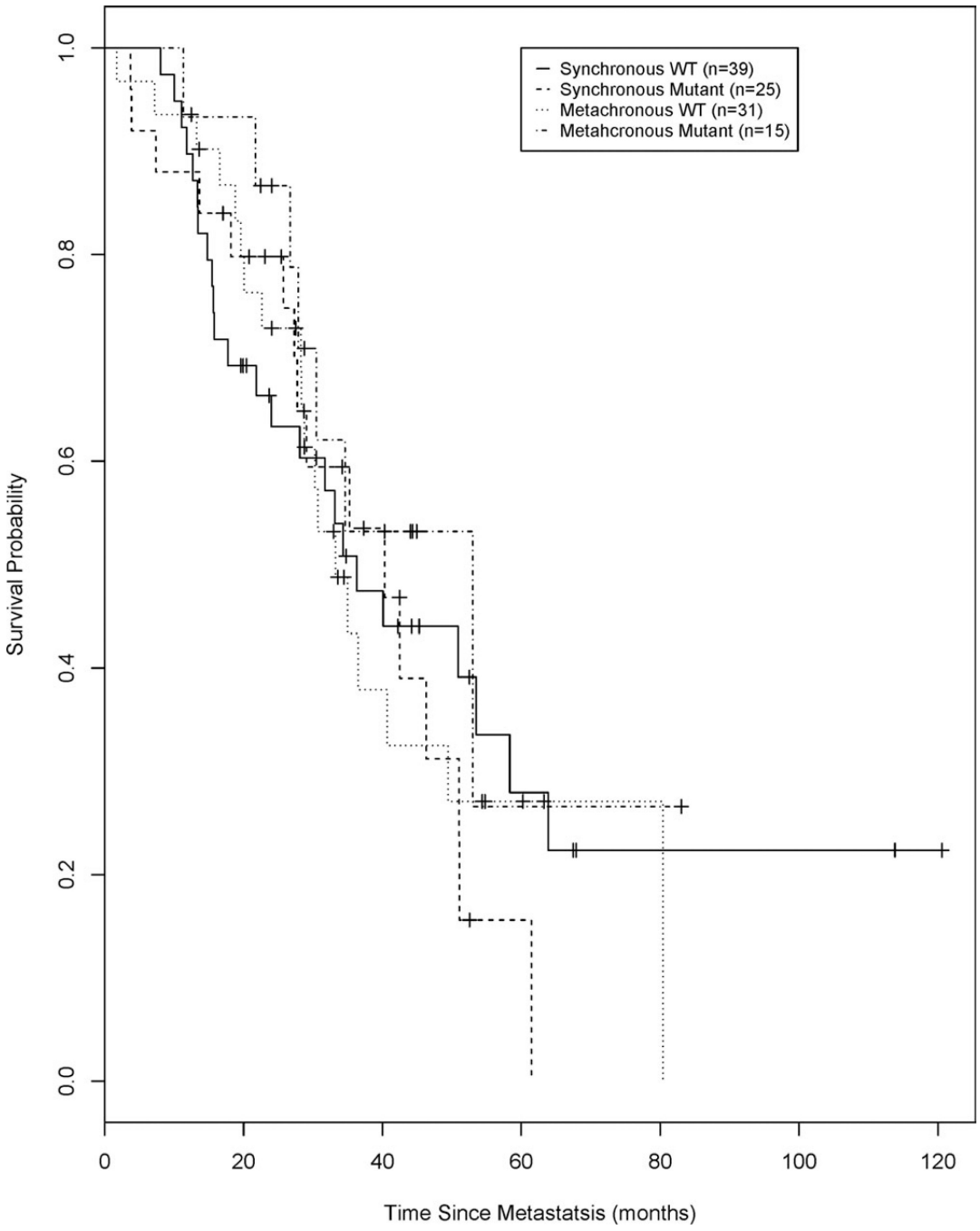

Figure 2.
Overall survival is illustrated from the date of diagnosis of metastatic disease for synchronous and metachronous disease, stratified by v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation status. WT indicates wild type.

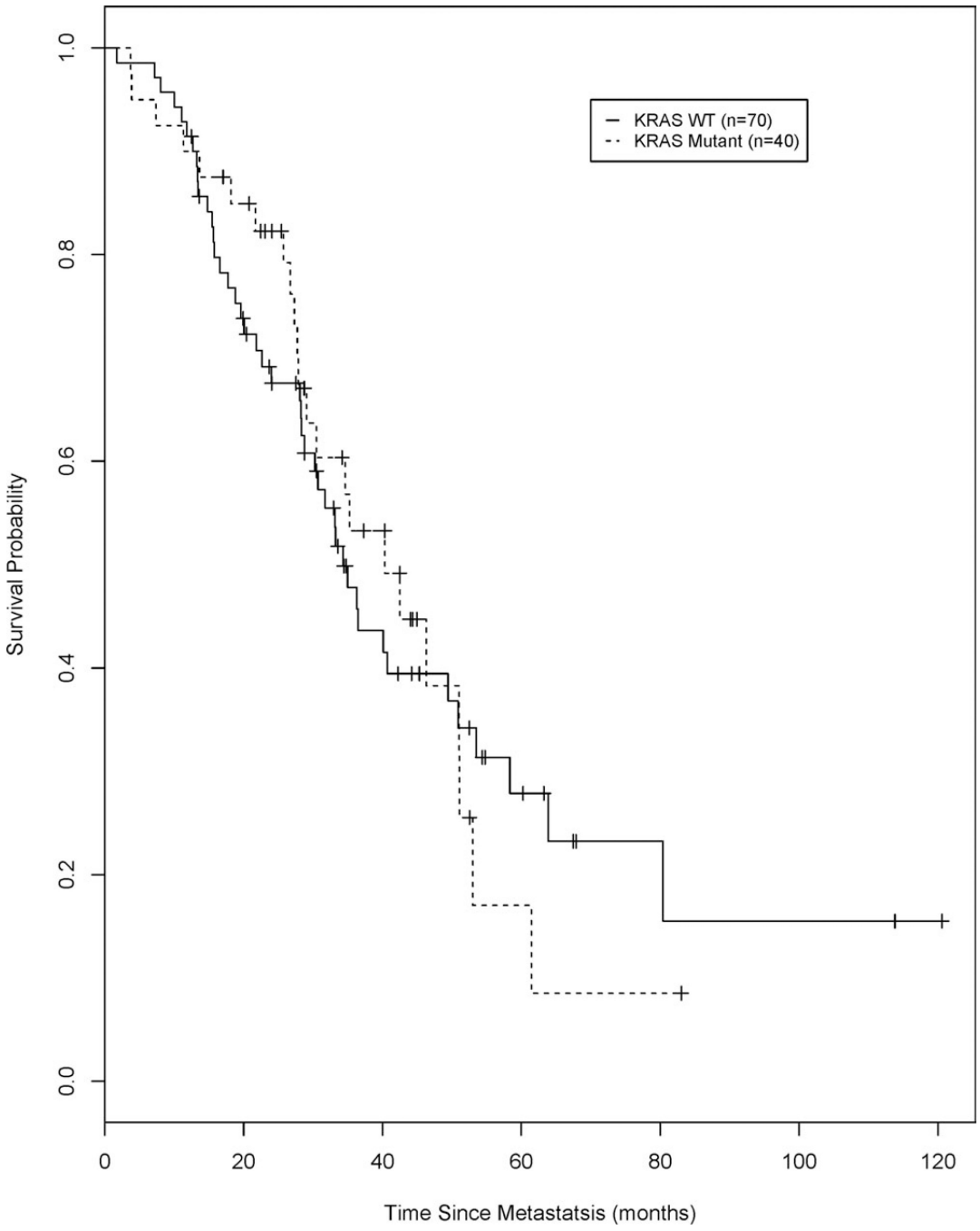

Figure 3.
Overall survival is illustrated from the date of diagnosis of metastatic disease for all patients (synchronous and metachronous), stratified by v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog (*KRAS*) mutation status. WT indicates wild type.

Table 1

Patient Characteristics

	No. of Patients (%)[a]					
	Synchronous Group		Metachronous Group		Total	
	***KRAS* WT**	***KRAS* Mutant**	***KRAS* WT**	***KRAS* Mutant**	***KRAS* WT**	***KRAS* Mutant**
Total no. of patients	39	25	31	15	70	40
Men	17 (44)	7 (28)	19 (61)	9 (60)	36 (51)	16 (40)
Age: Median [range], yr	60.2 [22.8–79.1]	54.6 [32.8–76.6]	56.0 [33.7–76.6]	58.1 [45.4–81.1]	59.6 [22.8–79.1]	55.4 [32.8–81.1]
Primary location						
Colon	34 (87)	21 (84)	24 (77)	11 (73)	58 (83)	32 (80)
Rectum	5 (13)	4 (16)	7 (23)	4 (27)	12 (17)	8 (20)
Neoadjuvant chemoradiotherapy with 5-FU or capecitabine	1 (3)	2 (8)	5 (16)	1 (7)	6 (9)	3 (8)
Adjuvant chemotherapy, any	NA	NA	27 (87)	8 (53)[b]	NA	NA
5-FU/leucovorin/oxaliplatin	NA	NA	13 (42)	3 (20)	NA	NA
5-FU/leucovorin/irinotecan	NA	NA	1 (3)	0 (0)	NA	NA
5-FU or capecitabine alone	NA	NA	13 (42)	5 (33)	NA	NA
Stage at diagnosis						
I	NA	NA	2 (6)	0 (0)	NA	0 (0)
II	NA	NA	6 (19)	7 (47)	NA	7 (47)
III	NA	NA	23 (74)	8 (53)	NA	8 (53)
IV	39 (100)	25 (100)	NA	NA	NA	NA
Initial liver metastasis alone	21 (54)	12 (48)	10 (32)	1 (7)	31 (44)	13 (33)
Metastatectomy or RFA	12 (31)	3 (12)	3 (10)	1 (7)	15 (21)	4 (10)
Receipt of each fluoropyrimidine, irinotecan, and oxaliplatin	26 (67)	20 (80)	24 (77)	11 (73)	50 (71)	31 (78)
Receipt of EGFR-directed therapy	25 (64)	5 (20)[b]	20 (65)	2 (13)[b]	45 (64)	7 (18)[b]
Receipt of bevacizumab	32 (82)	23 (92)	26 (84)	14 (93)	58 (83)	37 (93)
Median follow-up from original diagnosis [range], mo	30.5 [8.0–120.6]	28.7 [3.7–61.4]	60.2 [6.6–156.1]	62.0 [22.6–152.7]	29.1 [1.8–120.6]	28.5 [3.7–83.1]
Median follow-up from metastatic diagnosis [range], mo	30.5 [8.0–120.6]	28.7 [3.7–61.4]	28.8 [1.8–80.4]	30.5 [11.3–83.1]	29.1 [1.8–120.6]	28.5 [3.7–83.1]

Abbreviations: 5-FU, 5-fluorouracil; EGFR, epidermal growth factor receptor; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NA, not applicable; RFA, radiofrequency ablation; WT. wild-type.

[a]Patients in the synchronous group had metastatic disease at the time of diagnosis; patients in the metachronous group developed metastases after their initial diagnosis of localized disease.

[b] $P < .05$ (Fisher exact test) compared with *KRAS* WT in the synchronous, metachronous, or combined groups.

Table 2

Analysis of Overall Survival Defined From the Date of Original Diagnosis of Colorectal Cancer

KRAS Status[a]	No. of Patients	Median OS (95% CI), mo	3-Year Survival Estimate (95% CI)	5-Year Survival Estimate (95% CI)	*p*[b]
Synchronous group					
WT	39	36.3 (21.8–58.3)	0.51 (0.33–0.66)	0.28 (0.12–0.46)	.55
Mutant	25	40.3 (27.3–51.0)	0.59 (0.36–0.77)	0.16 (0.03–0.38)	
Metachronous group					
WT	31	68.4 (53.5–95.1)	0.83 (0.64–0.93)	0.65 (0.44–0.79)	.37
Mutant	15	92.0 (51.8 to NA)	0.93 (0.61–0.99)	0.69 (0.37–0.87)	

Abbreviations: CI, confidence interval; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NA, not applicable; OS, overall survival; WT, wild type.

[a]Patients in the synchronous group had metastatic disease at the time of diagnosis; patients in the metachronous group developed metastases after their initial diagnosis of localized disease.

[b]*P* values for OS were calculated with the log-rank test.

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Table 3

Analysis of Overall Survival Defined From the Date of Diagnosis of Metastatic Disease

KRAS Status[a]	No. of Patients	Median OS (95% CI), mo	3-Year Survival Estimate (95% CI)	5-Year Survival Estimate (95% CI)	*p*[b]
Synchronous group					
WT	39	36.3 (21.8–58.3)	0.51 (0.33–0.66)	0.28 (0.12–0.46)	.55
Mutant	25	40.3 (27.3–51.0)	0.59 (0.36–0.77)	0.16 (0.03–0.38)	
Metachronous group					
WT	31	33.2 (28.3–49.4)	0.43 (0.24–0.62)	0.27 (0.11–0.47)	.33
Mutant	15	53.0 (26.7 to NA)	0.53 (0.23–0.76)	0.27 (0.02–0.65)	
Combined group[c]					
WT	70	34.3 (28.3–49.4)	0.50 (0.37–0.62)	0.28 (0.16–0.41)	.91
Mutant	40	40.3 (27.9–51.1)	0.53 (0.35–0.69)	0.17 (0.04–0.39)	
Total					
WT and mutant	110	35.2 (30.5–49.4)	0.50 (0.39–0.60)	0.25 (0.15–0.37)	

Abbreviations: CI, confidence interval; *KRAS*, v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog; NA, not applicable; OS, overall survival; WT, wild type.

[a] Patients in the synchronous group had metastatic disease at the time of diagnosis; patients in the metachronous group developed metastases after their initial diagnosis of localized disease.

[b] *P* values for OS were calculated with the log-rank test.

[c] The synchronous and metachronous groups combined.