KRAS Mutation Is Associated with Lung Metastasis in Patients with Curatively Resected Colorectal Cancer

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Abstract

**Purpose:** Oncogene mutations contribute to colorectal cancer development. We searched for differences in oncogene mutation profiles between colorectal cancer metastases from different sites and evaluated these as markers for site of relapse.

**Experimental Design:** One hundred colorectal cancer metastases were screened for mutations in 19 oncogenes, and further 61 metastases and 87 matched primary cancers were analyzed for genes with identified mutations. Mutation prevalence was compared between (a) metastases from liver (n = 65), lung (n = 50), and brain (n = 46), (b) metastases and matched primary cancers, and (c) metastases and an independent cohort of primary cancers (n = 604). Mutations differing between metastasis sites were evaluated as markers for site of relapse in 859 patients from the VICTOR trial.

**Results:** In colorectal cancer metastases, mutations were detected in 4 of 19 oncogenes: **BRAF** (3.1%), **KRAS** (48.4%), **NRAS** (6.2%), and **PIK3CA** (16.1%). **KRAS** mutation prevalence was significantly higher in lung (62.0%) and brain (56.5%) than in liver metastases (32.3%; P = 0.003). Mutation status was highly concordant between primary cancer and metastasis from the same individual. Compared with independent primary cancers, **KRAS** mutations were more common in lung and brain metastases (P < 0.005), but similar in liver metastases. Correspondingly, **KRAS** mutation was associated with lung relapse (HR = 2.1; 95% CI, 1.2 to 3.5, P = 0.007) but not liver relapse in patients from the VICTOR trial.

**Conclusions:** **KRAS** mutation seems to be associated with metastasis in specific sites, lung and brain, in colorectal cancer patients. Our data highlight the potential of somatic mutations for informing surveillance strategies. *Clin Cancer Res;* 17(5); 1122–30. ©2011 AACR.

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**Note:** Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-10-1720

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**Introduction**

Approximately 20% of colorectal cancer patients present with distant metastasis, and about one third of patients undergoing curative-intent surgery for primary cancer will relapse at distant sites (1). Relapse often occurs within 3 years, with distant recurrence commonly found in the liver, lung, and peritoneum (2–4). Given this pattern, surveillance of the abdomen and chest is recommended, though the optimal strategy remains uncertain (5, 6).

Activating mutations in oncogenes contribute to carcinogenesis, and more than 20 oncogenes have been identified in human solid malignancies (7). In colorectal cancer, oncogenic mutations are commonly found in the mitogen-activated kinase (MAPK) pathway members **BRAF** (~10%; refs. 8, 9), **KRAS** (~40%; refs. 10, 11), and **NRAS** (~3%; refs. 12, 13), and the phosphatidylinositol 3-kinase (**PI3K**) pathway member **PIK3CA** (~20%; refs. 14, 15). Recent studies have
showed that patients with metastatic colorectal cancer harboring KRAS mutation do not benefit from therapy with monoclonal antibodies against the epidermal growth factor receptor (EGFR; refs. 16–18), and BRAF and PIK3CA mutations may similarly confer resistance to such treatment (19–22), although this remains controversial (23).

Recurrence patterns are partly determined by patient characteristics such as primary tumor location (2–4), but whether the somatic mutation profile of the primary tumor influences site of relapse remains unknown. There is limited data suggesting that KRAS mutation prevalence may differ between colorectal cancer metastases from the liver (32%) and lung (58%), and between primary cancers from patients with synchronous or metachronous liver (35%) and lung metastases (57%; ref. 24). However, another study of resected liver and lung metastases reported similar KRAS mutation frequencies (50.0% vs. 43.5%; ref. 25).

The OncoCarta Panel v1.0 from Sequenom allows for high-throughput screening of 238 pathogenic mutations in 19 oncogenes. We applied this technology to search for differences in oncogene mutation profiles between colorectal cancer metastases from different sites, we provide evidence that KRAS mutation in the primary tumor is associated with an increased risk of metastasis in the lung and brain, but does not modify the risk of metastasis in the liver. Our data highlight the potential of somatic mutations for informing surveillance strategies and has implications for understanding metastatic progression in colorectal cancer.
Statistical analysis

Statistical analyses were conducted using R software (28). Differences between groups were assessed using Fisher’s exact test for categorical variables and the Welch 2-sample t test for continuous variables. Multivariate logistic regression analysis was used to evaluate associations between mutation status and patient characteristics. For the analysis of liver or lung relapse as first site of recurrence, disease-free survival was defined as the time of surgery to the first confirmed relapse. Synchronous relapse in liver and lung was regarded as event in both analyses. Censoring was done when a patient died or was alive without recurrence at last contact, or when a patient recurred at a site other than the metastatic site under investigation. Cox proportional-hazards models were used to estimate survival distributions and HRs, and were adjusted for patient characteristics and MSI status as indicated. All statistical analyses were 2-sided and considered significant if $P < 0.05$.

Results

Oncogene mutation profile of colorectal cancer metastases (cohort A)

Oncogene mutations were surveyed in 161 metastases (65 liver, 50 lung, and 46 brain) from 148 colorectal cancer patients (cohort A, Table 1). Initially, a subset of 100 metastases was screened for 19 oncogenes using the OncoCarta Panel v1.0 from Sequenom (ABL, AKT1, AKT2, BRAF, CDK, EGFR, ERBB2, FGFR1, FGFR3, FLT3, HRAS, JAK2, KIT, KRAS, MET, NRAS, PDGFRA, PIK3CA, and RET). Seventy-two mutations were identified in 60 of 100 (60.0%) cases clustering in BRAF, KRAS, NRAS, and PIK3CA (Supplementary Table 2). A T992I variant in the MET gene, detected in two samples, was found to be a germline variant by sequencing of constitutional DNA. BRAF, KRAS, NRAS, and PIK3CA mutation screening was then extended to the remaining 61 metastases by direct DNA sequencing.

Overall, BRAF mutations were detected in 3.1% (5 of 161), KRAS mutations in 48.4% (78 of 161), NRAS mutations in 6.2% (10 of 161), and PIK3CA mutations in 16.1%
(26 of 161) of metastases (Supplementary Table 2). A total of 63.4% (102 of 161) of cases had mutation in at least one of these oncogenes and 11.2% (18 of 161) had mutations in more than one oncogene. Mutations in the MAPK pathway members KRAS, NRAS, and BRAF were mutually exclusive ($P < 0.001$, log-linear analysis). PIK3CA mutations coexisted with KRAS (15 cases) and NRAS (3 cases) mutations, but were not found with BRAF mutations; these findings were as expected from independent mutations ($P > 0.20$ for all pairwise comparisons, Fisher’s exact test). For the 12 persons for whom two or more metastases were tested, mutation status was concordant.

Differences in oncogene mutation spectra between colorectal cancer metastases from different sites (cohort A)

Frequencies of BRAF, KRAS, NRAS, and PIK3CA mutations were compared between metastases from the liver, lung, and brain (cohort A, Table 2). KRAS and PIK3CA mutation frequencies were found to vary significantly across these sites ($P = 0.003$ and $P = 0.044$, respectively; Fisher’s exact test). For both genes, mutation frequencies were higher in lung and brain metastases as compared with liver metastases [KRAS mutant: lung 62.0% (31 of 50), brain 56.3% (26 of 46), liver 32.3% (21 of 65); PIK3CA mutant: lung 20.0% (10 of 50), brain 23.9% (11 of 46), liver 7.7% (5 of 65)]. No associations were evident for BRAF and NRAS mutations with respect to metastasis site, although differences in oncogene mutation spectra between these sites ($P = 0.144$, Fisher’s exact test), liver (5.0%, 3 of 60), lung (18.5%, 5 of 27), and brain (10.0%, 1 of 10).

Concordance of oncogene mutation status between paired primary cancers and metastases (cohort A)

To assess whether oncogene mutations observed in metastases were acquired prior or post distant spread, we analyzed the matched primary cancers that were available for 87 of 148 patients (cohort A, Supplementary Table 3); 9 of these patients had multiple resected cancers to give 97 primary cancer-metastasis pairs. BRAF, KRAS, NRAS, and PIK3CA mutation status were concordant in 100% (97 of 97), 91.8% (89 of 97), 99.0% (96 of 97), and 95.9% (93 of 97) of paired specimens, respectively ($P < 0.001$ for each gene, Fisher’s exact test). Overall, 86 of 97 (88.7%) pairs showed concordant results across all 4 genes. Of the 11 pairs with discordant mutation status, 9 had mutations detected only in the metastasis (5xKRAS, 2xPIK3CA, 1xKRAS and PIK3CA, 1xNRAS and PIK3CA). These discordant samples represented all distant sites ($P = 0.144$, Fisher’s exact test), liver (5.0%, 3 of 60), lung (18.5%, 5 of 27), and brain (10.0%, 1 of 10).

Differences in KRAS mutation frequencies between colorectal cancer metastases (cohort A) and independent primary cancers (cohort B)

The association between KRAS mutation and metastasis site together with the high concordance of mutation status

<table>
<thead>
<tr>
<th>Oncogene</th>
<th>Site of colorectal cancer metastasis</th>
<th>Liver, n (%)</th>
<th>Lung, n (%)</th>
<th>Brain, n (%)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF</td>
<td>WT</td>
<td>63 (96.9)</td>
<td>50 (100)</td>
<td>43 (93.5)</td>
<td>0.184</td>
</tr>
<tr>
<td></td>
<td>Mut</td>
<td>2 (3.1)</td>
<td>0 (0)</td>
<td>3 (6.5)</td>
<td></td>
</tr>
<tr>
<td>KRAS</td>
<td>WT</td>
<td>44 (87.7)</td>
<td>19 (38.0)</td>
<td>20 (43.5)</td>
<td>0.003$^a$</td>
</tr>
<tr>
<td></td>
<td>Mut</td>
<td>21 (32.3)</td>
<td>31 (62.0)</td>
<td>26 (56.5)</td>
<td></td>
</tr>
<tr>
<td>NRAS</td>
<td>WT</td>
<td>60 (92.3)</td>
<td>47 (94.0)</td>
<td>44 (95.7)</td>
<td>0.917</td>
</tr>
<tr>
<td></td>
<td>Mut</td>
<td>5 (7.7)</td>
<td>3 (6.0)</td>
<td>2 (4.3)</td>
<td></td>
</tr>
<tr>
<td>PIK3CA</td>
<td>WT</td>
<td>60 (92.3)</td>
<td>40 (80.0)</td>
<td>35 (76.1)</td>
<td>0.044$^a$</td>
</tr>
<tr>
<td></td>
<td>Mut</td>
<td>5 (7.7)</td>
<td>10 (20.0)</td>
<td>11 (23.9)</td>
<td></td>
</tr>
</tbody>
</table>

$^aP < 0.05$.  
Abbreviation: Mut, mutant; WT, Wild type.
in primary and metastatic tumor indicate a potential for KRAS mutation in predicting site of relapse following surgery for primary cancer. To further investigate this suggestion, KRAS mutation frequencies in liver, lung, and brain metastases (cohort A) were compared with the baseline prevalence in 604 primary cancers from an independent, clinic-based patient cohort (cohort B, Table 1). Compared with a prevalence of 34.9% (211/604) in independent primary cancers, KRAS mutation frequency was similar in liver metastases (32.3%, P = 0.784, Fisher’s exact test), but significantly higher in lung (62.0%) and brain (56.5%) metastases (P < 0.001 and P = 0.004, respectively; Fisher’s exact test; Table 4). Taken together, these data suggest that KRAS mutation in the primary tumor may be associated with an increased risk of relapse in the lung or brain, but may not modify the risk of relapse in the liver.

**KRAS mutation status is associated with relapse in the lung (cohort C)**

To formally evaluate KRAS mutation status as a marker for specific sites of relapse, we analyzed primary colorectal cancers from 859 stage II and III patients participating in the VICTOR clinical trial (cohort C, Table 1). Patients in this study were followed up 3 and 6 months after study entry, then every 6 months up to 2 years, and annually thereafter. Radiological evidence or positive biopsy was required to show recurrence, and data on first site(s) of relapse were systematically recorded. The median follow-up time was 58.5 months (range, 4.8–100.0 months). Of 198 individuals who experienced disease recurrence, 68 had confirmed relapse in the liver and 55 confirmed relapse in the lung; 12 of these individuals relapsed in both sites. Relapse in the brain was not evaluated as cerebral imaging was not done as part of routine follow-up.

KRAS mutations were identified in 290 of 859 (33.8%) primary cancers, and liver or lung relapse-free survival rates of patients were compared by mutation status (Fig. 1A and B). As anticipated from our comparison of KRAS mutation frequencies between metastases and independent primary cancers, the presence of KRAS mutation in patients from the VICTOR study was not associated with relapse in the liver (HR = 0.9; 95% CI, 0.6–1.6; P = 0.837, Wald test), but

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of patients</th>
<th>KRAS wild-type, n (%)</th>
<th>KRAS mutant, n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>PIK3CA wild-type, n (%)</th>
<th>PIK3CA mutant, n (%)</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastasis site</td>
<td>Liver</td>
<td>63</td>
<td>42 (66.7)</td>
<td>21 (33.3)</td>
<td>1 (Referent)</td>
<td>58 (92.1)</td>
<td>5 (7.9)</td>
<td>1 (Referent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brain</td>
<td>37</td>
<td>16 (43.2)</td>
<td>21 (56.8)</td>
<td>2.67 (1.13–6.31)</td>
<td>0.025</td>
<td>28 (75.7)</td>
<td>9 (24.3)</td>
<td>3.27 (0.95–11.29)</td>
</tr>
<tr>
<td></td>
<td>Lung</td>
<td>45</td>
<td>18 (40.0)</td>
<td>27 (60.0)</td>
<td>2.78 (1.23–6.26)</td>
<td>0.014</td>
<td>36 (80.0)</td>
<td>9 (20.0)</td>
<td>3.25 (0.95–11.12)</td>
</tr>
<tr>
<td>Age</td>
<td>Median</td>
<td>66.4</td>
<td>66.6</td>
<td>66.0</td>
<td>0.84 (0.57–1.24)</td>
<td>0.376</td>
<td>65.7</td>
<td>70.0</td>
<td>1.81 (0.98–3.36)</td>
</tr>
<tr>
<td>Gender</td>
<td>Female</td>
<td>51</td>
<td>27 (52.9)</td>
<td>24 (47.1)</td>
<td>1 (Referent)</td>
<td>49 (96.1)</td>
<td>2 (3.9)</td>
<td>1 (Referent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>94</td>
<td>49 (52.1)</td>
<td>45 (47.9)</td>
<td>1.06 (0.51–2.20)</td>
<td>0.884</td>
<td>73 (77.7)</td>
<td>21 (22.3)</td>
<td>6.13 (1.33–28.19)</td>
</tr>
<tr>
<td>Primary tumor site</td>
<td>Colon</td>
<td>88</td>
<td>50 (56.8)</td>
<td>38 (43.2)</td>
<td>1 (Referent)</td>
<td>75 (85.2)</td>
<td>13 (14.8)</td>
<td>1 (Referent)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rectum</td>
<td>57</td>
<td>26 (45.6)</td>
<td>31 (54.4)</td>
<td>1.23 (0.60–2.51)</td>
<td>0.574</td>
<td>47 (82.5)</td>
<td>10 (17.5)</td>
<td>1.02 (0.38–2.72)</td>
</tr>
</tbody>
</table>

*P < 0.05.

**Table 4. Prevalence of KRAS mutation is similar for independent primary colorectal cancers (cohort B) and liver metastases (cohort A), but differs significantly for lung and brain metastases (cohort A)**

<table>
<thead>
<tr>
<th>Colorectal cancer type</th>
<th>KRAS wild-type, n (%)</th>
<th>KRAS mutant, n (%)</th>
<th>P for difference between independent primary tumors and metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary tumor (cohort B)</td>
<td>393 (65.1)</td>
<td>211 (34.9)</td>
<td></td>
</tr>
<tr>
<td>Liver metastasis (cohort A)</td>
<td>44 (67.7)</td>
<td>21 (32.3)</td>
<td>0.784</td>
</tr>
<tr>
<td>Lung metastasis (cohort A)</td>
<td>19 (38.0)</td>
<td>31 (62.0)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Brain metastasis (cohort A)</td>
<td>20 (43.5)</td>
<td>26 (56.5)</td>
<td>0.004*</td>
</tr>
</tbody>
</table>

*P < 0.05.
was significantly associated with relapse in the lung with an estimated HR of 2.1 for individuals with KRAS mutant as compared with KRAS wild-type cancers (95% CI, 1.2–3.5; \( P = 0.007 \), Wald test). A similar result for lung relapse was obtained in multivariate analysis (Table 5), adjusting for patient age, gender, tumor stage, site, standard therapy, and rofecoxib treatment (HR = 1.9; 95% CI, 1.1–3.3; \( P = 0.017 \), Wald test). To exclude the possibility that the association of

![Figure 1](https://www.aacrjournals.org/doi/10.1158/1078-0432.CCR-10-1720)

Figure 1. Relapse-free survival rates for colorectal cancer patients participating in the VICTOR clinical trial estimated using Kaplan-Meier analysis (n = 859, cohort C). A, liver relapse by KRAS mutation status of the primary cancer. B, lung relapse by KRAS mutation status of the primary cancer. C, liver and lung relapse for patients with KRAS wild-type (w.t.) cancers. D, liver and lung relapse for patients with KRAS mutant (mut.) cancers.

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Liver relapse</th>
<th>Lung relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>( P )</td>
</tr>
<tr>
<td>KRAS status (mutant vs. wild-type)</td>
<td>0.90 (0.54–1.50)</td>
<td>0.690</td>
</tr>
<tr>
<td>Age (decades)</td>
<td>0.91 (0.71–1.17)</td>
<td>0.470</td>
</tr>
<tr>
<td>Gender (male vs. female)</td>
<td>1.35 (0.80–2.28)</td>
<td>0.260</td>
</tr>
<tr>
<td>Tumor stage (III vs. II)</td>
<td>2.49 (1.21–5.10)</td>
<td>0.013*</td>
</tr>
<tr>
<td>Tumor site (rectum vs. colon)</td>
<td>0.68 (0.38–1.24)</td>
<td>0.210</td>
</tr>
<tr>
<td>Chemotherapy/radiotherapy (yes vs. no)</td>
<td>0.95 (0.43–2.09)</td>
<td>0.900</td>
</tr>
<tr>
<td>Rofecoxib (yes vs. no)</td>
<td>0.67 (0.41–1.08)</td>
<td>0.100</td>
</tr>
</tbody>
</table>

*\( P < 0.05 \).
KRAS mutation status and lung relapse was confounded by the MSI status of the primary tumor (MSI positive: 12.2%, 103 of 845), a known marker of outcome (29), this was included in multivariate analyses with similar results (Supplementary Table 4).

The differential impact of KRAS mutation on site-specific relapse was further evident when comparing lung and liver relapse-free survival for patients stratified by mutation status (Fig. 1C and D). Although patients with KRAS wild-type cancers exhibited a significantly lower risk of lung relapse as compared with liver relapse (HR = 0.59, 95% CI, 0.37–0.94, P = 0.028, Wald test), the risk of lung relapse was increased to mirror that of liver relapse for patients with KRAS mutant cancers (HR = 1.27, 95% CI, 0.73–2.22, P = 0.397, Wald test).

Discussion

This study presents a comprehensive survey and comparison of oncogene mutation profiles between primary colorectal cancers and metastases from commonly resected distant sites, including the liver, lung, and brain. Consistent with oncogene profiling studies in primary colorectal cancers, BRAF, KRAS, NRAS, and PIK3CA were identified as the main mutation targets in metastases, and somatic changes in the MAPK pathway members BRAF, KRAS, and NRAS were mutually exclusive (30, 31). Overall oncogene mutation status was greater than 88% concordant between primary cancer and distant metastasis from the same patient, suggesting that these activating mutations are generally acquired prior to metastatic spread. Our data are consistent with the high level of concordance between primary colorectal cancers and distant secondary deposits previously reported for KRAS and BRAF mutations (32–35), confirming that mutation testing of primary tumor is a reasonable surrogate for treatment decisions in metastatic disease.

In our comparison of oncogene mutation profiles between colorectal cancer metastases from different sites, KRAS mutations were significantly more common in lung (62%) and brain metastases (56%) as compared with liver metastases (32%), adjusting for patient clinicopathologic characteristics. A similar trend for PIK3CA mutation status did not reach statistical significance in multivariate analysis. The prevalence of KRAS mutations in our resected liver metastases was consistent with the 27% to 39% reported in previous series of between 62 and 188 patients (32, 35, 36). Less robust data are available for lung metastases, with KRAS mutation frequencies of 44% and 59% for two small cohorts of 23 and 17 cases, respectively (24, 25). To our knowledge, this study is the first to report comprehensive oncogene mutation data for colorectal cancer metastases to the brain.

Compared with the baseline KRAS mutation prevalence of 35% observed in a large cohort of independent primary cancers, KRAS mutations were significantly more common in lung and brain metastases, but similar in liver metastases. As anticipated from this data, the presence of KRAS mutation was found to be significantly associated with lung relapse, but not liver relapse, in patients from the VICTOR trial in both univariate and multivariate analyses. Our findings are supported by a recent report from Cejas and colleagues, who observed a significantly higher prevalence of KRAS mutation in primary colorectal cancers from patients with synchronous or metachronous lung metastases (57%) as compared with primary colorectal cancers from patients with liver metastases (35%; ref. 24). This metastasis site-specific association of KRAS may partly explain the heterogeneity seen in previous studies analyzing KRAS mutation status and survival in colorectal cancer patients (37–40).

Intensive surveillance has been shown to improve patient survival following surgery for primary colorectal cancer in meta-analyses of randomized clinical trials (41–43), with long-term survival achievable in individuals in whom resection of isolated liver, lung, or brain metastases is possible (44, 45). For patients treated with curative-intent surgery for primary colorectal cancer, American Society of Clinical Oncology (5) and European Society for Medical Oncology (6) guidelines recommend annual computerized tomography (CT) scanning of both abdomen and chest for 3 years. However, some controversy remains about the level of evidence supporting inclusion and interval of CT surveillance of the chest (3). In this study, we found that KRAS mutant tumor was associated with an increased risk of lung relapse compared with KRAS wild-type tumor in colorectal cancer patients from the VICTOR clinical trial. With the majority of lung recurrences (72.7%, 40 of 55) occurring within 3 years of surgery, the 3-year lung relapse-free rate was 90.9% (95% CI, 87.5–94.6%) for individuals with KRAS mutant tumors and 96.7% (95% CI, 95.1–98.2%) for individuals with KRAS wild-type tumors. In patients with KRAS mutant tumors, the risk of lung relapse was increased to mirror that of liver relapse. These data support the existing surveillance guidelines for equal importance of abdominal and chest imaging, in particular for patients with resected KRAS mutant tumors. Further evaluation of KRAS mutation as a predictor for lung relapse seems warranted to determine whether mutation status could be used to refine the optimal use of chest imaging.

Brain metastases are uncommon in colorectal cancer, and brain imaging is not routinely undertaken in initial staging or surveillance. Surgical resection of oligometastatic disease may produce survival benefits in suitable candidates (46–48). Our data suggest that KRAS mutation status may identify patients at increased risk of recurrence in the brain, but studies on larger patient cohorts will be required to formally show this association.

In conclusion, our findings provide evidence that recurrence patterns in colorectal cancer patients are partly determined by the somatic mutation profile of the primary tumor. This data has implications for understanding metastatic progression in colorectal cancer, and may help inform surveillance strategies for patients undergoing surgery with curative intent.
Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank Stephen Bell, Damien Tange, Bhadu Kavar, Suzanne Kosmider, Kathryn Firlik, Ian Jones, Steven McLaughlin, and Phillip Antippa for assistance in recruitment of patients for this study.

Grant Support

This work was supported by the Jeanakk M. Littlefield-AACR Grant in metastatic Colon Cancer Research (L. Lipton, P. Gibbs, O.M. Sieber), the Hilton Ludwig Cancer Metastasis Initiative (L. Lipton, P. Gibbs, O.M. Sieber), the CSIRO Preventive Health Flagship (L. Lipton, P. Gibbs, O.M. Sieber), the NHMRC through a Medical and Dental Postgraduate Research Scholarship (Application ID 487929), the Victorian Government through a Victorian Cancer Agency Clinical Researcher Fellowship (L. Lipton), the Cancer Council Victoria through a Postgraduate Cancer Research Scholarship (M. Christie), the Operational Infrastructure Support Program (P. Gibbs, O.M. Sieber), Victorian Cancer Agency Translational Cancer Research Fund (Application ID 10099_32; P. Gibbs), and the Oxford Comprehensive Biomedical Research Centre (E. Domingo, I. P.M. Tomlinson).

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Received June 30, 2010; revised November 1, 2010; accepted December 1, 2010; published OnlineFirst January 14, 2011.

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Clinical Cancer Research

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