Re: Microsatellite Instability and BRAF Mutation Testing in Colorectal Cancer Prognostication

Lochhead et al. recently reported the combined prognostic role of BRAFV600E mutation and microsatellite instability (MSI) in 1253 colorectal cancer patients with a median follow-up of 8.2 years (1). In their stage-stratified multivariable analyses that included age, year of diagnosis, body mass index (BMI), tumor differentiation, and LINE-1 methylation as additional covariables, they found that, compared with the microsatellite stable (MSS)/BRAF-wild-type group, MSS/BRAF-mutant, MSI-high/BRAF-mutant, and MSI-high/BRAF-wild-type groups showed colorectal cancer-specific mortality hazard ratios (HR) of 1.60 (95% confidence interval [CI] = 1.12 to 2.28, \( P = .009 \)), 0.48 (95% CI = 0.27 to 0.87, \( P = .02 \)), and 0.25 (95% CI = 0.12 to 0.52, \( P < .001 \)), respectively. It should be noted that adjustment (stratification) for stage at presentation means that any effect of MSI or BRAF on survival that is mediated by their effect on stage at presentation is lost.

We investigated the combined effect of MSI/BRAF V600E mutation in 747 patients (48.3% women) from the Melbourne Collaborative Cohort Study diagnosed with an incident colorectal carcinoma at mean ± SD age 68.2 ± 8.1 years (range = 42 to 85 years), and with available MSI and BRAF V600E mutation status (2). There were 588 MSS/BRAF-wild-type (78.7%), 72 MSS/BRAF-mutant (9.6%), 50 MSI-high/BRAF-mutant (6.7%), and 37 MSI-high/BRAF-wild-type (5.0%) tumors. During a median follow-up of 7.8 years after diagnosis (interquartile range = 2.9 to 12.2 years), we observed 377 deaths, including 236 from colorectal cancer. We performed Cox regression using Stata version 11.1 (College Station, TX: StataCorp LP). In multivariable models, these variables were initially included: age at diagnosis (continuous), sex, AJCC stage, tumor grade (high/low), year of diagnosis (continuous), BMI (≥30 vs <30 kg/m²), CIMP (high vs low/negative), mutation status of BRAF, KRAS and PIK3CA (present vs absent), and MSI (high vs low/MSS) (3, 4). We then eliminated variables that did not improve the fit of the model. The final multivariable colorectal cancer-specific and overall survival models were stratified by AJCC stage and adjusted for age at diagnosis, sex, and tumor grade.

Our results were similar to those of Lochhead et al. In multivariable analyses, BRAF mutation was associated with higher colorectal cancer-specific mortality (multivariable HR = 1.61, 95% CI = 1.13 to 2.31, \( P = .009 \)), and MSI-high was associated with lower colorectal cancer-specific mortality (multivariable HR = 0.40, 95% CI = 0.22 to 0.75, \( P = .004 \)). Table 1 shows the mortality for both models according to combined MSI/BRAF. There was no evidence of an interaction between BRAF and MSI in these two models (\( P = .913 \) and \( P = .310 \) in the model with only BRAF and MSI, and \( P = .433 \) and \( P = .786 \) in the multivariable model for colorectal cancer-specific/overall mortality, respectively). Models unadjusted for AJCC stage showed some evidence of non-proportionality of hazards, with MSI and BRAF hazard ratios diminishing over time. However, for comparison with Lochhead et al., we presented Cox models assuming proportionality (1).

In addition to other recent studies, our findings confirm the important combined role of MSI/BRAF mutation status in colorectal cancer prognostication (5). A newly available immunohistochemistry test for the BRAFV600E mutation now enables pathologists to offer affordable, parallel, and effective universal immunohistochemistry testing for both the mismatch repair proteins and the BRAFV600E mutation in colorectal cancer, thus providing information on prognosis as well as identifying Lynch syndrome (6).

Table 1. Hazard ratios for colorectal cancer-specific and overall mortality associated with BRAF mutation and microsatellite instability status

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>MSS/BRAF wild-type</th>
<th>MSS/BRAF-mutant</th>
<th>MSI-high/BRAF-mutant</th>
<th>MSI-high/BRAF-wild-type</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of events</td>
<td>588</td>
<td>38</td>
<td>72</td>
<td>50</td>
</tr>
<tr>
<td>Adjusted HR (95% CI)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
<td>1.00 (Referent)</td>
</tr>
</tbody>
</table>

* Adjusted for age at diagnosis (continuous), sex, grade (low/mixed), stratified by AJCC stage. CI = confidence interval; HR = hazard ratio; MSI = microsatellite instability; MSS = microsatellite stable.

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Notes
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