Point-by-point responses to Reviewers' comments

Responses to Reviewer-1

Definition dmGFRA1 using table
Response: Thank you for this suggestion. We described the definition of dmGFRA1-high and -low for different assay platforms in the supplemental Table S1.

Replaced "dmGFRA1" with GFRA1 demethylation in P.8, 2nd paragraph.
Response: Replaced.

Chi-square test and Fisher's exact test in table 1
Response: At least 5 cases should be enrolled into each group in a regular chi-square test. Because there was only one patient in the poorly differentiated colon cancer group, therefore, we had to use the Fisher's exact test.

P-values issues: p<0.001 for Age term
Response: The p-value is true. Comparison of 99.77% of dmGFRA1 in SMs from patient at age <60 yrs with 99.58% for patients at age ≥60 yrs is equal to comparison of **0.23%** of mGFRA1 with **0.42%** of mGFRA1 in SMs from two group patients.

P-values issues: p=0.039 in the result section and 0.06 in Table S2 between vessel embolus-positive and -negative patients
Response: Relative GFRA1 mRNA level in the vessel embolus-positive patients was significantly higher than that in the vessel embolus-negative patients (0.57 vs. 0.47, p=0.039). We mentioned the p-value 0.039 in both the result section and Table S2 footnote. To compare overall survival of cancer patients with different GFRA1 mRNA expression levels, these patients were subclassified into GFRA1 expression-high and -low groups using the median GFRA1 mRNA level as the cutoff value. The p-value 0.060 represents the statistic difference of proportion of GFRA1 expression-high between cancer patients with and without vessel embolus. We have modified the GFRA1-high and -low with GFRA1 expression-high and -low. We hope this modification could make the meaning more clear.

Responses to Reviewer-1

The gene name (GFRA1) is lacking.
Response: Thank you. Added.

The abbreviation "CC" should be mentioned in extenso at the beginning of the abstract.
Response: Modified.

The key words are lacking.
Response: They are under the abstract.

Bisulfite modification assay is not described.
Response: Added.

Limitation of Non-CpG methylation and three references
Response: Added into the discussion section.

Figure 1B and Figure S2
Response: We replaced the Figure 1B with high-resolution image. The sample codes were deleted in the revised Figure S2. [Clones without target GFRA1 DNA sequence (empty vectors) were not listed in the Figure S2.]

Informed consent
We obtained informed consent from every patients.