ORIGINAL RESEARCH ARTICLE

**KRAS as a prognostic marker for metastatic colorectal cancer: Qatar experience**

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**Abstract:** Colorectal cancer (CRC) is the third most common cancer worldwide and in Qatar. Kirsten Ras (*KRAS*) mutation occurs in 30%–50% of CRC cases in different geographical areas. A total of 104 metastatic CRC cases were tested for *KRAS* mutation from 2009–2013 at the National Center for Cancer Care and Research (NCCR), Qatar. The incidence of *KRAS* mutation was 42% versus that of the wild-type (58%). Wild-type *KRAS* metastatic CRC (mCRC) patients tend to have better survival and this was especially evident after they received anti-epithelial growth factor receptors targeted therapy. Meanwhile, mutant-type *KRAS* mCRC patients receiving anti-vascular endothelial growth factor were more inclined to have poor survival outcomes. To confirm the observation, more studies with larger sample populations and a longer follow-up duration are needed. To our best knowledge, this is the first known report of *KRAS* status and its impact on the prognosis of metastatic colorectal cancer.

**Keywords:** colorectal cancer; chemotherapy; *KRAS*; anti-EGFR; anti-VEGF

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**Introduction**

Colorectal cancer (CRC) is the third most common cancer worldwide and the disease incidence rates increase with industrialization and urbanization[1]. It is responsible for the second highest cancer-related death in USA and the European Union[2]. Meanwhile, the CRC incidence in Qatar is 15/100,000 per year (based on the 2014 Qatar National Cancer Registry). Although patients diagnosed at an early stage have high recovery rates, many cases were detected at later stages when the five-year survival rate is relatively poor[3].

CRC biology and carcinogenesis have recently been recognized as a multistep process that involves the accumulation of molecular alterations[4]. In addition, it has also been suggested that there is a potential association between many of these abnormalities with a patient’s survival rate[5,6]. Kirsten Ras (*KRAS*) is an epidermal growth factor proto-oncogene, encoding a small 21 kDa guanosine triphosphate/ guanosine diphosphate (GTP/GDP) binding protein, involved in the regulation of cellular responses and many extracellular stimuli[7]. Its major signal transduction pathway, including the Ras-Raf mitogen-activated protein kinase (MAPK), leads to the expression of proteins involved in cell proliferation, differentiation, and apoptosis[8,9].

*KRAS* mutation occurs in 30%–50% of CRC and is thought to be predictive of non-responsiveness to epithelial growth factor receptors (EGFR)-targeted monoclonal antibody therapy across all treatment lines, either as a single agent or in combination with chemotherapy[10,11]. The question of whether *KRAS* mutation in CRC has a prognostic role independent of anti-EGFR treatment has been controversial[12]. Reports on the prognostic value of *KRAS* mutation status in metastatic colorectal cancer (mCRC) have been conflicting[13]. The most

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studied biological targets are the EGFR, vascular endothelial growth factor (VEGF), and KRAS.

The aim of our study was to identify the KRAS status of patients diagnosed with mCRC in Qatar from 2009 to 2013. We also studied whether there was an association between KRAS status and treatment outcomes.

Cohort and methods

This is a retrospective study of mCRC patients that compares the survival rate of patients with wild-type versus mutant-type KRAS status. We included all patients above 18 year-old with histologically-proven metastatic adenocarcinoma of the colon and they were also KRAS-tested. The KRAS test was performed either in the UK or France. We retrieved a total of 104 medical records of all patients diagnosed with mCRC at our institute. The following data were obtained: age, gender, nationality (Qatari versus non-Qatari), date of diagnosis, cancer stage at diagnosis, date of diagnosis upon confirming disease metastasis, chemotherapy regimen, target therapy, and survival (in months) since diagnosis.

Treatment protocol

Surgery

All patients underwent surgical resection of the primary tumor at one point of their treatment. Eight patients underwent liver metastasectomy (six metachronous and two synchronous metastases).

Chemotherapy

All 104 patients were given fluorouracil (FU), a fluoropyrimidine-based chemotherapy. All mutant-type metastatic patients received oxaliplatin in addition to FU as a first line treatment. A total of 35 out of 44 mutant-type patients received bevacizumab, 45 wild-type metastatic patients received irinotecan in addition to FU, and 15 wild-type metastatic patients received oxaliplatin in addition to FU. Meanwhile, 42 out of 60 wild-type KRAS patients received targeted therapy (cetuximab, panitumumab or bevacizumab). There were 10 (out of 60) wild-type patients and 18 (out of 44) mutant-type patients who were initially diagnosed with stage IV metastasis.

Statistical analysis

Quantitative variable data (expressed as means), along with standard deviations and frequencies (percentages), were used to summarize the qualitative data. Medians and ranges were reported for skewed (non-normal) data. Univariate Kaplan-Meier survival analysis was performed to estimate the overall and group-wise median survival. Furthermore, a log-rank test was used to determine the statistical differences (if any) of median survival among the various subgroups. In addition, the Cox regression method was used to assess the significant effect of various prognostic factors on survival time outcomes. Statistically significant values were reported with their corresponding 95% confidence interval (CI) values, and \( p < 0.05 \) was considered statistically significant. Statistical analyses were performed using a statistical software package: Statistical Package for Social Sciences (SPSS, version 22.0, Chicago, IL).

Results

Table 1 shows the demographic data and KRAS status of all the patients included in the study. The incidences of KRAS versus wild-type mutations are 42% and 58%, respectively.

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Wild-type</th>
<th>Mutant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>60 (58%)</td>
<td>44 (42%)</td>
</tr>
<tr>
<td>Age (Mean ± standard deviation)</td>
<td>51 ± 12</td>
<td>55 ± 12</td>
</tr>
<tr>
<td>Male</td>
<td>40 (66.7%)</td>
<td>25 (56.8%)</td>
</tr>
<tr>
<td>Female</td>
<td>20 (33.3%)</td>
<td>19 (43.2%)</td>
</tr>
<tr>
<td>Qatari</td>
<td>13 (21.7%)</td>
<td>7 (15.9%)</td>
</tr>
<tr>
<td>Non-Qatari</td>
<td>47 (78.3%)</td>
<td>37 (84.1%)</td>
</tr>
</tbody>
</table>

The median survival for KRAS mutants was observed to be 48 months (95% CI: 27.8, 68.2) and 72 months in wild-type KRAS patients (95% CI: 52.5, 91.5; \( p = 0.523 \)), as shown in Figure 1. In other words, wild-type KRAS patients are likely to have better survival compared to KRAS mutants (Hazard ratio = 1.39; 95% CI: 0.66, 2.91). However, the difference is not statistically significant \( (p = 0.386) \).

Targeted therapy apparently leads to different outcomes when given to patients with mutant versus wild-type KRAS. Our study showed a trend towards survival benefit in KRAS mutants who did not receive anti-VEGF targeted therapy (bevacizumab), with a median survival of 60 months (95% CI: 46.5, 74.0), when compared to KRAS mutants receiving the same treatment, whose median survival was 48 months (95% CI: 33.5, 62.5). However, the difference is not statistically significant \( (p = 0.326) \) (Figure 2).
We found that patients with wild-type KRAS who received EGFR-inhibitor targeted therapy such as cetuximab or panitumumab showed improved survival as reflected by their median survival of 72 months (95% CI: 52.2, 91.8). In contrast, wild-type KRAS patients who did not receive the anti-EGFR therapy recorded a median survival of >60 months. However, the difference is not statistically significant ($p = 0.499$) (Figure 3).

With regard to age as a prognostic factor, our study showed that among patients with a stage IV disease, the median survival for those who were $\leq 55$ years old was 72 months (95% CI: 55.03, 88.97), which is higher than that of patients in the age group of $>55$ years old (60 months, 95% CI: 43.98, 76.02). Nevertheless, this difference is not statistically significant ($p = 0.272$) (Figure 4). Evidently, younger wild-type KRAS patients did better regardless of the treatment they received.

**Discussion**

Our patient cohort constitutes of 58% wild-type and 42% mutant KRAS patients, which agree with the percentage
reported in the literature[14]. There were no significant differences in age distribution. On the other hand, gender distribution showed male dominance in both groups, which probably reflects the demography of the country since Qatar has a large proportion of young male labor force living without their families.

We were interested in identifying the nationality of the patients in order to establish a cancer database for the local Qatari population, who makes up ~20% of the total population. We showed that both wild-type and mutant KRAS patients who were <55 years old had better median survival compared to older patients (>55 years old). We could not determine the exact median survival for both wild-type KRAS patients who were >55 years old and KRAS mutants who were <55 years old owing to a small number of samples and the short duration of follow-up. Significant improvements have been made in the last decade regarding CRC treatments in terms of response rates (RR), progression-free survival (PFS), and overall survival (OS)[15–18]. These significant improvements are mainly from the development of a combination of standard chemotherapy using fluorouracil, irinotecan, and oxaliplatin, and therapeutic agents that target molecular events involved in colorectal carcinogenesis, with EGFR inhibitors being the most effective[19–20].

Our data demonstrated that wild-type KRAS patients have better overall survival trend compared to KRAS mutants. This finding was in agreement with two previous studies, which found that there was an absolute difference observed between treatments with and without anti-EGFR therapy, in terms of higher RR and PFS in wild-type KRAS cohorts[20–21]. Data from both studies showed a benefit in terms of the median OS time for wild-type KRAS patients who had undergone anti-EGFR therapy. However, the prognosis value of KRAS mutation remains questionable and independent of anti-EGFR therapy[20–21].

We also found a good survival outcome for wild-type KRAS patients who received EGFR antibody therapy even though the exact median survival for those who did not receive the EGFR antibody therapy was not reported in this retrospective study, as no information was available after 60 months owing to the short duration of follow-up. Similar observations had been reported in previous studies[21–22]. In addition, our study suggests that KRAS mutant patients who did not receive bevacizumab have better survival in comparison to KRAS mutants who received anti-VEGF antibody therapy. This was in accordance with most of the previous studies of bevacizumab (Avastin®)[19,23,24]. This observation could be affected by a small number of events affecting patients who did not receive targeted therapy. To establish a firm conclusion, we need to have a larger number of patients and a longer duration of follow-ups.

**Limitations**

As with all retrospective studies, some of the data were deficient. It was also very difficult to identify an accurate disease staging. If the number of patients studied was larger, along with a longer duration of follow-ups, our results would have been more robust.

**Conclusion**

Based on our study, metastasis CRC patients with wild-type KRAS status have better survival and this is more evident if they had undergone anti-EGFR targeted therapy. In contrast, KRAS mutants who skipped the anti-EGFR therapy tend to have a poor survival outcome. More studies with a larger population and longer duration of follow-ups are needed to confirm our observation.

**Conflict of interest**

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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