

# Patterns of practice with third-line anti-EGFR antibody for metastatic colorectal cancer

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## ABSTRACT

**Background** Therapy with anti-epidermal growth factor receptor (EGFR) monoclonal antibody improves outcomes for patients with metastatic colorectal cancer (mCRC) in the first-, second-, and third-line trial settings. In British Columbia, the use of EGFR inhibitors (EGFRIs) is confined to third-line therapy, which might lower the proportion of patients who receive this therapy. The objective of the present study was to describe EGFRi treatment patterns when those agents are limited to the third-line setting. The results will inform decisions about optimal use of EGFRi agents, including earlier in the course of therapy for metastatic disease.

**Methods** All patients with newly diagnosed mCRC who were referred to BC Cancer Agency clinics in 2009 were included in the study. Prognostic and treatment information was prospectively collected; *KRAS* test results were determined by chart review.

**Results** The study included 443 patients with a median age of 66 years. For the 321 patients who received systemic therapy, median survival was 22.3 months. Of the 117 patients who were treated with 5-fluorouracil, oxaliplatin, and irinotecan, and who were potentially eligible for EGFRi therapy, 90% (105 patients) were tested for *KRAS* status. Of the 60 patients with *KRAS* wild-type tumours, 82% (49 patients) received EGFRi therapy.

**Conclusions** When EGFRi therapy is limited to the third-line setting, only a small proportion of patients receive such therapy, with death and poor performance status preventing its use in the rest. Availability of EGFRi in earlier lines of therapy could increase the proportion of patients treated with all active systemic agents.

**Key Words** EGFR inhibitors, third-line therapy, metastatic colorectal cancer

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## INTRODUCTION

Colorectal cancer (CRC) is one of the most common and lethal cancers in the developed world, with approximately 24,400 new cases diagnosed and 4700 deaths in Canada annually<sup>1</sup>. Treatment for patients with metastatic CRC (mCRC) is generally palliative and consists of systemic therapy. An increase in the number of new agents since the early 2000s has significantly improved outcomes for patients with mCRC. In the population-based setting, the median overall survival (OS) for patients with unresectable mCRC treated with systemic therapy approaches 24 months, compared with 5–6 months for those who receive best supportive care alone<sup>2–5</sup>.

Systemic agents with significant antitumour activity in the mCRC context include chemotherapy agents and biologics. Chemotherapy agents with proven efficacy in mCRC include fluoropyrimidines [fluorouracil (5FU) and

capecitabine], irinotecan, and oxaliplatin. Biologics used in mCRC include monoclonal antibodies directed against the vascular endothelial growth factor (VEGF) (bevacizumab) and the epidermal growth factor receptor (EGFR) (cetuximab and panitumumab). The optimal combination and sequencing of those systemic agents is still being determined.

In Canada, the first-line therapy of choice for mCRC is an anti-VEGF (bevacizumab) in combination with 5FU-based therapy. The optimal clinical setting for EGFRi in the mCRC setting has not yet been established, but trial evidence supports their use in the first-, second-, and third-line settings<sup>2–9</sup>. Randomized trials in the first-line setting combining cetuximab with FOLFIRI (irinotecan–5FU–leucovorin) or FOLFOX (5FU–leucovorin–oxaliplatin)<sup>10,11</sup>, or panitumumab with FOLFOX<sup>12,13</sup>, compared with the chemotherapy alone demonstrated significant improvements in progression-free survival and OS. Studies comparing first-line EGFRi combination therapy with anti-VEGF

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combination therapy showed that first-line EGFRi therapy is associated with similar or superior outcomes in patients with *KRAS* wild-type (wt) tumours<sup>14–17</sup>.

As of 1 July 2009, cetuximab and panitumumab were approved only for patients with *KRAS* wt mCRC previously treated using 5FU or capecitabine, oxaliplatin, and irinotecan within the province of British Columbia. The objective of the present study was to describe the frequency and pattern of use of EGFRi in the third-line setting. Reasons for no use of EGFRi or performance of *KRAS* testing were ascertained on retrospective chart review. Results could inform decisions concerning the optimal use of the EGFRis, including use earlier in the course of therapy for metastatic disease.

## METHODS

All patients with a diagnosis of new or recurrent mCRC who were referred to the BC Cancer Agency (BCCA) from 1 January 2009 to 31 December 2009 were included. The BCCA has a mandate to fund all systemic therapies, and approximately 65% of CRC patients in British Columbia are referred to 1 of the 5 BCCA centres for therapy. Eligible patients were identified in the BCCA's Gastrointestinal Cancers Outcomes Unit, which prospectively collects patient, tumour, stage, and treatment data for all referred patients. Specific data collected include patient age, sex, histologic diagnosis, primary tumour site, clinical and pathologic stage at time of referral, surgery, date of the first cycle of chemotherapy, and outcome. Patients with appendiceal cancer, small-cell carcinoma, squamous cell carcinoma, carcinoid tumour, neuroendocrine carcinoma, gastrointestinal stromal tumour, pseudomyxoma, and prior or synchronous CRC (*in situ* or invasive) were excluded from the study. The study was conducted only after it had received full approval from the Research Ethics Board at the BCCA.

### Systemic Treatment

Treatment data were obtained from the BCCA Pharmacy Database. Standard mCRC chemotherapies included oxaliplatin and irinotecan in combination with bolus and infusional 5FU and leucovorin (FOLFOX and FOLFIRI respectively). Capecitabine was available as an option to replace 5FU in circumstances in which the placement of a central venous infusion device was not permitted because of patient preference or because of geographic considerations. Bevacizumab was approved for funding as standard therapy with 5FU-based chemotherapy (FOLFIRI or FOLFOX) in the first-line setting as of 1 January 2006. Cetuximab and panitumumab were approved for patients with *KRAS* wt mCRC, previously treated with 5FU or capecitabine, oxaliplatin, and irinotecan as of 1 July 2009. Because EGFRi therapy was limited to the third-line setting, it was assumed that all patients diagnosed with mCRC in 2009 would potentially be eligible for EGFRi treatment because of a requirement to initially receive first- and second-line chemotherapy.

### Surgical Therapy

In a detailed medical chart review, data for all patients—resection of the main tumour and ablation of hepatic

metastases, including pathology, operative, and treatment notes—were collected.

## Statistical Analyses

Baseline and prognostic variables were assessed using descriptive statistics. Overall survival was measured from date of diagnosis to date of death from any cause. Survival estimates were calculated using the Kaplan–Meier method, and patients who were alive at the last follow-up date were censored. All analyses were performed using the SPSS software application (version 15.0: SPSS, Chicago, IL, U.S.A.).

## RESULTS

### Patient Characteristics and Outcomes

The study included 443 patients (Table 1), whose median age at the time of diagnosis of mCRC (*de novo* or relapse) was 66 years. Most patients (82%, *n* = 363) had metastatic disease at presentation, and 31% of patients (*n* = 136) had

**TABLE 1** Baseline patient and disease characteristics

| Characteristic                                          | Value    |
|---------------------------------------------------------|----------|
| Patients ( <i>n</i> )                                   | 443      |
| Median age at diagnosis (years)                         | 66       |
| Sex [ <i>n</i> (%)]                                     |          |
| Men                                                     | 259 (58) |
| Women                                                   | 184 (42) |
| Primary site [ <i>n</i> (%)]                            |          |
| Colon                                                   | 307 (69) |
| Rectum                                                  | 136 (31) |
| Metastatic presentation [ <i>n</i> (%)]                 |          |
| At diagnosis                                            | 363 (82) |
| At relapse                                              | 80 (18)  |
| Site                                                    |          |
| Liver only                                              | 224 (51) |
| Lung only                                               | 30 (7)   |
| Distant nodal only                                      | 14 (3)   |
| Other single solitary                                   | 52 (12)  |
| >1 Distant site                                         | 123 (28) |
| Grade at initial diagnosis [ <i>n</i> (%)]              |          |
| I/II                                                    | 288 (65) |
| III                                                     | 84 (19)  |
| IV                                                      | 1 (0)    |
| Unknown                                                 | 70 (16)  |
| Primary resection [ <i>n</i> (%)]                       |          |
| Yes                                                     | 320 (72) |
| No                                                      | 123 (28) |
| Systemic therapy for metastatic disease [ <i>n</i> (%)] |          |
| Yes                                                     | 321 (72) |
| No                                                      | 122 (28) |
| Local therapy for hepatic metastases [ <i>n</i> (%)]    |          |
| Yes                                                     | 53 (12)  |
| Hepatic metastasectomy                                  | 45 (10)  |
| Ablation                                                | 8 (2)    |
| No                                                      | 390 (88) |

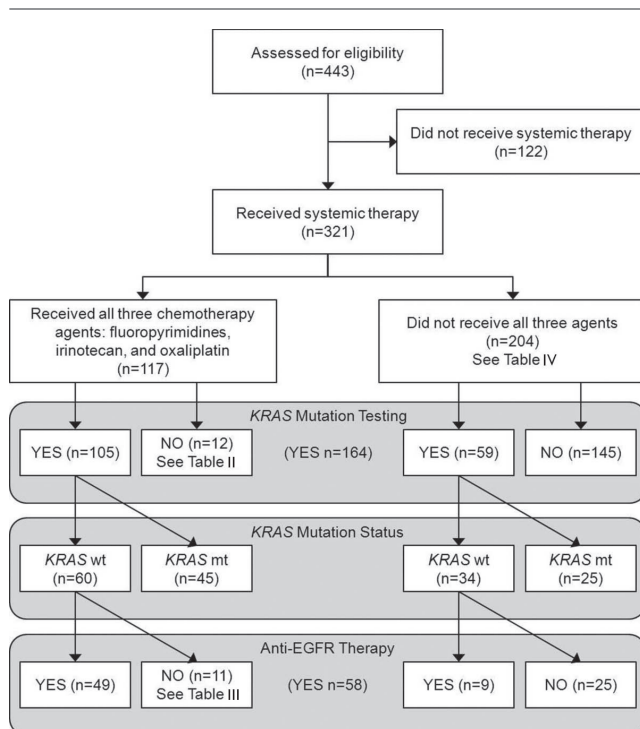
a rectal primary. Nearly three quarters of the patients underwent resection of the primary tumour (72%,  $n = 320$ ). Median os was 18.1 months for all patients; median os for the patients who received any systemic therapy ( $n = 321$ ) for advanced disease was 22.3 months (compared with 5.6 months for patients who received no systemic therapy,  $n = 122$ ).

### Systemic Therapy Received

Of the entire 2009 cohort, 73% ( $n = 321$ ) received systemic therapy for metastatic disease, but only 26.4% ( $n = 117$ ) received all 3 chemotherapy agents (irinotecan, oxaliplatin, and 5FU or capecitabine; Figure 1). Among the patients who received any systemic therapy, 57% ( $n = 184$ ) received bevacizumab, and only a subgroup of those patients ( $n = 58$ ) received EGFR-directed therapy within the study period.

### KRAS Testing and EGFR Therapy

Of the 117 patients who received all 3 chemotherapy agents and who were thereby potentially eligible for EGFR therapy, 90% ( $n = 105$ ) underwent KRAS testing (Figure 1). Among those tested, 57% ( $n = 60$ ) were KRAS wt. In the patients who were KRAS wt, 82% ( $n = 49$ ) received EGFR therapy. Of the 12 patients in the group who received all 3 chemotherapy agents, but who did not undergo KRAS testing, the most-cited reasons for that lack of testing were death ( $n = 6$ ), significant decline in performance status ( $n = 2$ ), and loss to follow-up ( $n = 2$ , Table II). The reasons documented for the 11 KRAS wt patients who did not receive EGFR therapy included significant decline in performance status ( $n = 5$ ) and death ( $n = 3$ , Figure 1, Table III).



**FIGURE 1** Patient flow diagram. In this retrospective study, 443 patients with metastatic colorectal cancer were analyzed for extent and timing of therapy and KRAS mutation testing.

Of the 204 patients who received systemic therapy, but who did not receive all 3 chemotherapy agents, 29% ( $n = 59$ ) underwent KRAS testing (Figure 1). Among the patients tested, 57% ( $n = 34$ ) were KRAS wt, a proportion equal to that in the 3-chemotherapies group; 9 received EGFR therapy (Figure 1).

A multivariate analysis for variables associated with not receiving all 3 active agents showed that an increase in age (odds ratio: 1.684; 95% confidence interval: 1.396 to 2.032) and relapsed compared with *de novo* disease (odds ratio: 5.229; 95% confidence interval: 2.165 to 12.632) increased the odds of not receiving all 3 active agents (Table IV). Sex ( $p = 0.7660$ ) and local therapy (ablation and hepatic metastasectomy,  $p = 0.499$ ) were found not to be statistically significant.

The numbers of patients receiving 1, 2, or 3 lines of systemic therapy were determined. Patients receiving first-line chemotherapy with 5FU and irinotecan numbered 184. However, only 120 patients were eligible to receive second-line chemotherapy with 5FU and oxaliplatin; 117 patients received all 3 chemotherapy agents (irinotecan, oxaliplatin, and 5FU or capecitabine).

## DISCUSSION

Since the late 1990s, mCRC treatment options have greatly expanded. For advances in drug therapies to translate into better results, patients with mCRC have to be able to access as many lines of therapy as possible. Our review of the 443 mCRC patients referred to the BCCA in 2009 found a difference in os between the patients who received any type

**TABLE II** Reasons for no KRAS test in the cohort of 117 patients receiving 5-fluorouracil–irinotecan–oxaliplatin

| Reason                                                    | n of 12 untreated |
|-----------------------------------------------------------|-------------------|
| Death                                                     | 6                 |
| Poor ECOG status                                          | 2                 |
| No evidence of active liver disease after liver resection | 1                 |
| Response to prior line of therapy                         | 1                 |
| Lost to follow-up                                         | 2                 |

ECOG = Eastern Cooperative Oncology Group.

**TABLE III** Reasons for no anti-EGFR therapy in a cohort of 60 patients with KRAS wild-type metastatic colorectal cancer receiving 5-fluorouracil–irinotecan–oxaliplatin

| Reason                      | n of 11 untreated |
|-----------------------------|-------------------|
| Poor ECOG status            | 5                 |
| Death                       | 3                 |
| Lost to follow-up           | 2                 |
| Remission after hepatectomy | 1                 |

EGFR = epidermal growth factor receptor; ECOG = Eastern Cooperative Oncology Group.

**TABLE IV** Multivariate analysis of factors contributing to patients not receiving all three active chemotherapy agents

| Factor           | Comparator                        | p Value | Multivariate analysis |               |
|------------------|-----------------------------------|---------|-----------------------|---------------|
|                  |                                   |         | Estimated OR          | 95% CL        |
| Age at diagnosis | Per 10-year increase              | <0.0001 | 1.684                 | 1.396, 2.032  |
| Relapse          | <i>De novo</i> metastatic disease | 0.0002  | 5.229                 | 2.165, 12.632 |
| Women            | Men                               | 0.766   | 0.933                 | 0.590, 1.475  |
| No local therapy | Local therapy used                | 0.499   | 1.271                 | 0.634, 2.546  |

OR = odds ratio; CL = confidence limits.

of systemic therapy and those who did not (22.3 months vs. 5.6 months). The apparent difference in outcome was likely related to significant variation in patient- and disease-related factors between the two treatment groups. Our study found that, of 117 patients who received all 3 chemotherapy agents, 90% ( $n = 105$ ) underwent *KRAS* mutation testing (Figure 1). However, only 82% ( $n = 49$ ) of those with *KRAS* wt tumours received an EGFRi agent (cetuximab or panitumumab). Overall, of the 321 patients who received palliative systemic therapy, only 18% ( $n = 58$ ) received EGFR-directed therapy. Delays in timely initiation of *KRAS* testing, possibly as a result of the time required to obtain archival or new tissue, might have led to a decrease in the number of patients eligible for EGFRi therapy because of death or deterioration in Eastern Cooperative Oncology Group performance status.

Although our study did not compare the os for patients who received 1, 2, or 3 lines of therapy, mCRC patients who receive the greatest number of chemotherapy lines experience the longest os. Indeed, studies have shown that the sequence of 5FU or capecitabine, irinotecan, and oxaliplatin is less important<sup>9</sup> than exposure to all 3 agents<sup>6–8</sup>. Randomized studies comparing sequential single-agent therapy with combination chemotherapy show that the proportion of patients who receive second-line chemotherapy declines<sup>6</sup>. Furthermore, studies show that only a subgroup of patients with *KRAS* wt tumours randomized to either anti-VEGF or EGFRi combination chemotherapy as first-line therapy receive the other biologic in subsequent therapy<sup>18,19</sup>. Those observations are consistent with findings in our study, in which we observed a decline of 35% in the number of patients from receipt of first-line therapy to receipt of second-line therapy.

Our results suggest that advanced age and relapsed compared with *de novo* mCRC lowered the odds of a patient receiving all 3 chemotherapeutic agents in the metastatic setting. The finding that elderly patients were less likely to receive chemotherapy is consistent with results from prior studies demonstrating that because of toxicity concerns such as diarrhea and neutropenia, irinotecan, oxaliplatin, and bevacizumab are less often given to elderly patients than to their younger counterparts<sup>20,21</sup>. As well, older patients are more likely to experience age-related organ function decline and medical comorbidity that

can increase the perceived risks of chemotherapy<sup>22–24</sup>. Patients who present with relapsed mCRC are more likely to have previously been treated with oxaliplatin in the adjuvant setting, which can preclude its use in the metastatic setting.

## CONCLUSIONS

In this B.C. study, we found that EGFR-directed therapies are given to mCRC patients infrequently and late in their treatment timeline. Limitations to the study include its retrospective nature and the fact that relevant patient factors such as comorbidities were not captured. The strength of the study is its population-based analysis in a single-payer universal health care system in which all patients have equal access to health care services and cancer treatments. Our findings suggest that poor performance status and death were the predominant reasons that *KRAS* wt patients did not receive EGFRi therapy. Those results support an earlier introduction of EGFRi for *KRAS* wt mCRC, as supported by recent phase III clinical trials.

## Clinical Practice Points

- Clinical trials support the use of EGFRi therapy for patients with mCRC in the first-, second-, and third-line settings.
- In assessing the treatment patterns of EGFRis when those agents are available only in the third-line setting, we found that only a limited proportion of patients received such therapy.
- The main reasons that *KRAS* wt patients did not receive EGFRi therapy were poor performance status and death.
- Earlier introduction of EGFRis for *KRAS* wt mCRC might increase the proportion of patients treated with all active systemic agents.

## CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

## AUTHOR AFFILIATIONS

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