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ORIGINAL ARTICLE

Clinical impact of K-*ras* mutation in colorectal cancer patients treated with adjuvant FOLFOX

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Abstract
Background K-*ras* proto-oncogene is commonly mutated in colorectal cancer (CRC) and has been associated with predictive markers for anti-EGFR (epidermal growth factor receptor) therapy. However, the prognostic role of K-*ras* status is still unclear. The aim of this study was to evaluate the association between k-*ras* status and addition of oxaliplatin to fluorouracil plus leucovorin (FOLFOX) chemotherapy in CRC patients with curative surgical resection.
Methods Sixty-six patients with stage II or III CRC were treated with FOLFOX or fluorouracil plus leucovorin (FL) followed by curative surgery between January 2004 and October 2007. K-*ras* status was assessed by direct sequencing.
Results Fifteen patients (22.7%) had K-*ras* mutations of codon 12 (11/15) or codon 13 (4/15). There were no significant differences in clinicopathological parameters, such as age, sex, stage, or adjuvant regimen between the wild-type K-*ras* and mutant K-*ras*. With a median follow-up of 41.6 months (range 25.1–72.3 months), median disease-free survival (DFS) and overall survival (OS) were not reached. With regard to K-*ras* status, DFS and OS were not statistically different ($P = 0.269$ and $P = 0.917$, respectively). Even in the group treated with FOLFOX only, neither DFS ($P = 0.651$) nor OS ($P = 0.265$) was significantly different according to K-*ras* status. With the exception of tumor location in DFS and OS, no differences in other variables were observed. Proximal colon cancer patients had a longer DFS than distal CRC patients ($P = 0.079$); this trend was maintained only in the wild-type K-*ras* group ($P = 0.051$).
Conclusions These results showed that K-*ras* status was not associated with clinical outcome in patients treated with adjuvant FOLFOX.

Keywords K-*ras* · Colorectal cancer · Adjuvant chemotherapy · FOLFOX4

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Introduction

K-*ras* proto-oncogene is commonly mutated in colorectal cancer (CRC) and has been associated with predictive markers for anti-EGFR (epidermal growth factor receptor) therapy [1]. Findings from several studies have demonstrated that patients with K-*ras* wild-type only benefited from anti-EGFR therapy [2, 3]. This means that K-*ras*

mutational status has a clear predictive role in anti-EGFR therapy. However, it is controversial if K-*ras* status has prognostic value. A previous RASCAL study showed that K-*ras* mutation was significantly associated with decreased disease-free (DFS) and overall survival (OS) [4]. Conlin et al. showed that K-*ras* mutation was predictive of poor prognosis of CRC [5]. However, there is also evidence to show that it is not related to prognosis [6–8].

Although adjuvant chemotherapy has been widely used for a small percentage of stage II or III CRC with a combination of fluorouracil plus leucovorin (FL), 3-year DFS was just 70% [9]. Therefore, intense drugs or regimens are needed. Oxaliplatin in combination with FL (FOLFOX) has been shown to be highly active in an adjuvant setting as well as in metastatic disease [10]. Within MOSAIC study, FOLFOX was definitely superior to FL alone, which is different from an irinotecan combination [11]. Although patients with stage II did not have a definitive survival benefit with FOLFOX, National Cancer Comprehensive network (NCCN) has recommended adjuvant therapy in stage II patients with high-risk features, such as poorly differentiated histology, T4, perforation, and peritumoral lymphovascular involvement [12]. Since MOSAIC study, FOLFOX has been commonly used and has shown survival benefits compared to the LV regimen in patients with CRC followed by curative surgery in an adjuvant setting [13].

The role of k-*ras* status in an adjuvant setting, as well as in a metastatic setting, is still unclear. Ahnen et al. showed that patients with wild-type K-*ras* benefit from adjuvant 5-fluorouracil (5FU) plus levamizole, whereas those with the K-*ras* mutation do not [14]. Findings from another study demonstrated that K-*ras* status was not associated with prognosis in patients who were treated with a 5FU-based or 5FU and irinotecan (FOLFIRI) regimen [15, 16]. However, up to now, definite correlation between K-*ras* mutation and adjuvant FOLFOX therapy has not yet been fully established.

Thus, this study was conducted to evaluate the association between K-*ras* mutation and FOLFOX chemotherapy in CRC patients with curative surgical resection.

Materials and methods

Patients and treatment

Between January 2004 and October 2007, 66 patients treated with FL or FOLFOX who also had adequate tissue samples for K-*ras* mutation test were analyzed. Following curative surgery, all patients were treated with either FL [17] or FOLFOX [11]. Rectal cancer patients who received adjuvant or neoadjuvant chemoradiotherapy (CCRT) were excluded. Patients were followed up every 3–6 months at the outpatient clinic. This analysis was approved by the St. Mary's Hospital institutional review board (SC10OISI0065).

Detection of K-*ras* mutation

Using the QIAamp DNA Mini kit, DNA was extracted from five paraffin sections of 10 μm thickness containing a representative portion of tumor tissue (Qiagen, Hilden, Germany). Fifty nanograms of DNA was amplified in a 20 μl reaction solution containing 10 μl of 2× concentrated HotStarTaq Master Mix (Qiagen, Hilden, Germany), including polymerase chain reaction (PCR) buffer with 3 mM $MgCl_2$, 400 μM each dNTP, and 0.3 μM of each primer pair (codon 12, 13, F: 5′-cgtctgcagtcaactggaat, R: 5′-gagaa tggtcctgcaccagtaa). Amplifications were performed using a 15-min initial denaturation at 95°C, followed by 35 cycles of 30 s at 94°C, 30 s at 59°C, and 30 s at 72°C, and a 10-min final extension at 72°C. PCR products were then 2% gel-purified using a QIAgen gel extraction kit (Qiagen).

DNA templates were processed for the DNA sequencing reaction using the ABI-PRISM BigDye Terminator version 3.1 (Applied Biosystems, Foster, CA) with both forward and reverse sequence-specific primers. Twenty nanograms of purified PCR products was used in a 10-μl sequencing reaction solution containing 1 μl of BigDye Terminator v3.1 and 0.1 μM of the same PCR primer. Sequencing reactions were performed using 25 cycles of 10 s at 96°C, 5 s at 50°C, and 4 min at 60°C. Sequence data were generated with the ABI PRISM 3100 DNA Analyzer (Applied Biosystems). Sequences were analyzed by sequencing analysis 5.1.1. software (Applied Biosystems) for comparison of variation.

Statistical analysis

Clinical and pathological variables were compared across groups using the sample *t* tests and χ^2 or Fisher's exact tests for continuous and categorical variables. Duration of OS was calculated from the day of surgery until the date of death, or the most recent documented follow-up. Disease-free survival was calculated from the day of surgery to the day when recurrence was recognized, or the day of the last follow-up visit. For DFS, patients who died without recurrence were censored. OS and DFS were estimated using the Kaplan–Meier method. Comparisons between groups were performed using the log-rank test for time-to-event variables. *P* values less than 0.05 were considered statistically significant. The Cox proportional hazard regression model with 95% confidence intervals (CIs) was used for calculation of the HR of events.

Results

Characteristics of the patients

The median age of the 66 patients was 61 years (range 36–75 years), and 40.9% were women. Stage II and stage III included 16 patients and 50 patients, respectively. Proximal colon, distal colon, and rectum were 24.2, 51.5, and 24.2%, respectively. Most histology showed adenocarcinoma (95.5%). FL and FOLFOX were administered in 20 patients and 46 patients, respectively (Table 1).

Table 1 Characteristics of patients

	No. of patients ($N = 66$) (%)
Median age (years)	61 (36–75)
Age, years	
<65	45 (68.2)
≥65	21 (31.8)
Gender	
Male	39 (59.1)
Female	27 (40.9)
Stage	
II	16 (24.2)
III	50 (75.8)
T stage	
T3	65 (98.5)
T4	1 (1.5)
N stage	
N0-1	47 (71.3)
N2	19 (28.8)
Primary site	
Proximal (right) colon	16 (24.2)
Distal (left) colon	34 (51.5)
Rectum	16 (24.2)
Pathology	
Adenocarcinoma	63 (95.5)
Mucious	3 (4.5)
Differentiation	
G1-2	62 (94)
G3-4	4 (6)
Adjuvant regimen	
FL	20 (30.3)
FOLFOX4	46 (69.7)
K-*ras*	
Wild	51 (77.3)
Mutant	15 (22.7)

FL 5-FU/leucovorin, *FOLFOX4* 5-FU/oxaliplatin/leucovorin

Treatment outcome

Most patients received 6 cycles of FL or 12 cycles of FOLFOX. One patient who received FL discontinued therapy after 1 cycle due to general weakness, and five patients discontinued FOLFOX due to neurotoxicity (3–7 cycles). Seventeen patients relapsed, and six patients (9.1%) died. Two patients died without relapse. With a median follow-up of 41.6 months (range 25.1–72.3 months), median DFS and OS were not reached.

Status of K-*ras* mutation

Among 66 patients, 15 patients (22.7%) had K-*ras* mutations of codon 12 (11/15) or codon 13 (4/15). Fifty-one patients (77.3%) had wild-type K-*ras*. Identified K-*ras* mutations were as follows: 6 cases with codon 12 GGT>GTT (p.G12V, c.35G>T); 4 cases with codon 13 GGC>GAC (p.G13D, c.38G>A); 3 with codon 12 GGT>GAT (p.G12D, c.35G>A); and 1 with codon 12 GGT>TGT (p.G12C, c.34G>T). There were no significant differences in clinicopathological parameters, such as sex, age, stage, or adjuvant regimen between the wild-type K-*ras* and the mutant. However, despite the fact that no statistical difference was observed ($P = 0.067$), the frequency of K-*ras* mutation in development of proximal colon cancer (43.8%, 7/16) showed a trend toward being higher than in distal colon (14.7%, 5/34) and rectal cancer (18.8%, 3/16) (Table 2).

Association of K-*ras* status with clinical outcome

According to clinicopathological variables including K-*ras* status, 3-year DFS and OS did not reach median value and showed no statistical difference ($P = 0.269$ and $P = 0.917$, respectively) (Fig. 1; Table 3). DFS and OS according to follow-up duration (1 and 3 year) were not also different ($P = 0.567$ and 100% survival in 1 year, $P = 1.000$ and $P = 0.767$ in 3 year, respectively). Also, analyzing with only

Table 2 Correlation of K-*ras* gene and primary site

	K-*ras*			*P*
	Wild type	Mutant type	Total	
Stage II				0.169
Proximal colon	2 (50%)	2 (50%)	4	
Distal colon	4 (66.7%)	2 (33.3%)	6	
Rectum	6 (100%)	0 (0%)	6	
Stage III				0.076
Proximal colon	7 (58.3%)	5 (41.7%)	12	
Distal colon	25 (89.3%)	3 (10.7%)	28	
Rectum	7 (70%)	3 (30%)	10	

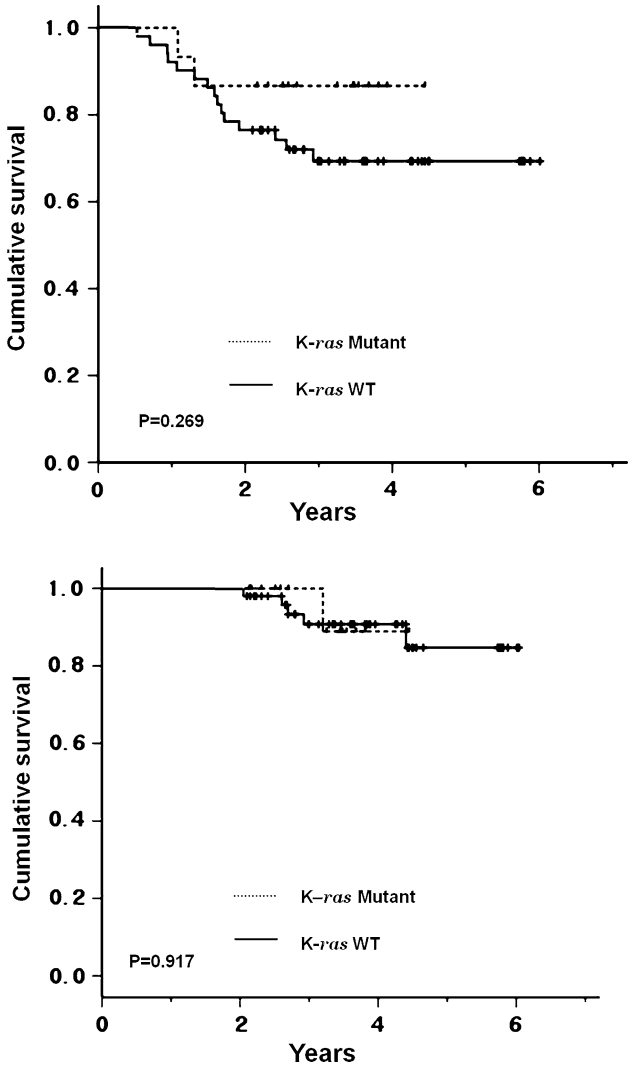

Fig. 1 DFS and OS by K-*ras* status

K-*ras* status and chemotherapeutic regimen, DFS and OS did not show difference (Tables 4, 5). With the exception of tumor location in DFS and OS, other variables also showed no difference. Proximal colon cancer patients had a longer DFS than distal CRC patients ($P = 0.079$); this trend was maintained only in the wild-type K-*ras* group ($P = 0.051$) (Fig. 2). Despite no statistical significance, mutant K-*ras* patients treated with FL showed a trend toward higher DFS compared with patients with wild-type K-*ras* ($P = 0.470$), and groups treated with FOLFOX appeared to be slightly superior to those treated with FL in wild-type K-*ras* compared to those in mutant K-*ras* group ($P = 0.287$) (Fig. 3).

Discussion

In this study, 22.7% (15/66) of CRC patients were positive for K-*ras* mutation. In spite of no statistical correlation, frequent K-*ras* mutation was found in the proximal colon of 43.8% (7/16) compared to the distal colon of 14.7% (5/34), and rectum of 18.8% (3/16). K-*ras* status had no influence on outcome with adjuvant FOLFOX therapy, as with metastatic patients [18]. However, in the wild-type K-*ras* subgroup, proximal colon cancer patients had a longer DFS than distal CRC patients ($P = 0.051$). Also, despite no statistical significance, FL treatment showed a trend toward better DFS in mutant K-*ras* patients ($P = 0.470$), and FOLFOX treatment appeared to be slightly superior in wild-type K-*ras* ($P = 0.287$).

Population-based studies have reported that 30–45% of patients with CRC in Western countries have K-*ras* mutation [16, 19, 20]. In contrast, Korean data showed a slightly lower frequency, as with our results (22–29%) [21, 22]. It is possible to explain that different techniques were used for detection of mutations, which means different sensitivity and specificity [23]. Also, as with an epidermal growth factor receptor mutation in non-small cell lung cancer, the difference may be ethnic [24].

The prognostic role of K-*ras* status is controversial. Anwar et al. showed that negative results were obtained for a specific disease stage, whereas those with positive results frequently included a mix of Dukes' A-D tumors [23]. In addition, the role of K-*ras* would be more complex if K-*ras* status is combined with chemotherapeutic agents. It is not known to correlate with K-*ras* status, and oxaliplatin, even in vitro, as well as in vivo, unlike K-*ras* status, influenced irinotecan sensitivity or 5-FU-induced apoptosis [25, 26]. Further study is needed on this subject.

K-*ras* status is generally known no correlation with tumor location [16, 27, 28]. However, some researchers have reported that frequency of K-*ras* mutation of the proximal colon is higher than with distal and rectal cancer [22, 29, 30]. Initially, the proximal colon and distal colon have been developed from different embryologic origins. In addition, there is also different expression of several antigens, metabolism of glucose, polyamines, and butyric acid, as well as in bile acid concentrations, and composition and density of the bacterial populations [31]. Also, Calcagno et al. suggested that K-*ras* mutation promoted early carcinogenesis in the mouse proximal colon, not the distal colon [32]. These differences may influence the region-specific effects of K-*ras* mutation.

In the wild-type only K-*ras* group, our result showed that proximal colon cancers have a better DFS trend than distal CRCs ($P = 0.051$). One possible explanation is the correlation between microsatellite instability (MSI) and K-*ras* mutation [19, 33]. Patients with MSI tend to have more poorly differentiated, mucin-producing tumors, which are more often found in proximal tumors [33]. However, they revealed longer overall survival than stage-matched

Table 3 Univariate analyses for DFS and OS in different variables

Feature	*N* = 66	3-year DFS (%)	*P*	HR, (95% CI)	3-year OS (%)	*P*	HR, (95% CI)
Age, years			0.160			0.938	
<65	45	67.6		0.41 (0.12–1.42)	92.2		0.94 (0.17–5.14)
≥65	21	84.8			86.7		
Gender			0.261			0.264	
Male	39	68.6		0.55 (0.19–1.56)	88.2		0.02 (0-18.38)
Female	27	79.5			100		
Stage			0.872			0.441	
II	16	75		0.91 (0.30–2.80)	92.9		0.43 (0.05–3.71)
III	50	72.1			89.8		
N stage			0.448			0.178	
N0-1	47	76.5		0.68 (0.25–1.84)	94.8		0.33 (0.07–1.65)
N2	19	74.7			78.8		
Primary site			0.065			0.288	
Proximal colon	16	93.8		0.52 (0.26–1.04)	100		0.50 (0.14–1.79)
Distal colon	34	68.9			86.1		
Rectum	16	62.5			100		
Pathology			0.064			0.710	
Adenocarcinoma	63	75		0.25 (0.06–1.08)	92.1		0.05 (0–542,426)
Mucious	3	33.3			100		
Differentiation			0.106			0.701	
G1-2	62	76.2		0.29 (0.07–1.30)	92		0.05 (0–307,648)
G3-4	4	33.3			100		
Adjuvant regimen			0.386			0.481	
FL	20	65		0.65 (0.25–1.72)	100		0.52 (0.09–3.20)
FOLFOX4	46	80.4			88		
K-*ras*			0.269			0.917	
Wild	51	69.3		0.44 (0.10–1.91)	90.8		0.89 (0.10–7.78)
Mutant	15	86.7			100		

Table 4 Cox regression analysis of the correlation between chemotherapeutic regimen and survival in different K-*ras* gene status

	DFS	OS
	HR	
K-*ras* (−)	*P* = 0.293	*P* = 0.174
FL	1	1
FOLFOX	0.58 (0.21–1.60)	5.41 (0.48–61.67)
K-*ras* (+)	*P* = 0.654	*P* = 0.582
FL	1	1
FOLFOX	28.82 (0–68, 809, 166)	0.006 (0–500,061.29)

Table 5 Cox regression analysis of the correlation between K-*ras* gene status and survival in different chemotherapeutic regimen

	DFS	OS
	HR	
FL	*P* = 0.437	*P* = 0.788
K-*ras* (−)	1	1
K-*ras* (+)	0.04 (0–155.30)	5,863.56 (0–)
FOLFOX	*P* = 0.652	*P* = 0.495
K-*ras* (−)	1	1
K-*ras* (+)	0.7 (0.15–3.30)	0.03 (0–614.53)

patients with tumors exhibiting chromosomal instability [34]. MSI status may need to be checked in order to confirm prognosis of proximal cancer in our study.

According to our results, FOLFOX therapy that included platinum demonstrated a better DFS in wild-type K-*ras* only. Although the molecular mechanism has not been fully established, accumulated evidence has suggested that activated *ras* may contribute to platinum resistance through stimulation of DNA repair activity [35–37]. This finding indicates that K-*ras* mutation would be associated with efficacy of oxaliplatin. However, due to the retrospective nature of the analysis, the results should be cautiously interpreted and need to be validated in prospective studies with large numbers of patients.

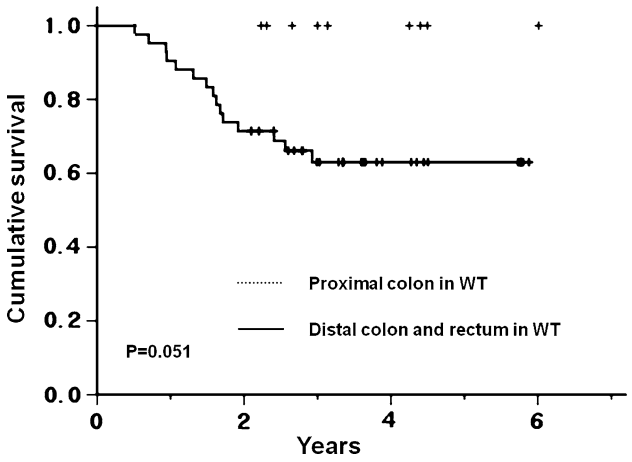

Fig. 2 DFS by location in wild-type K-*ras*

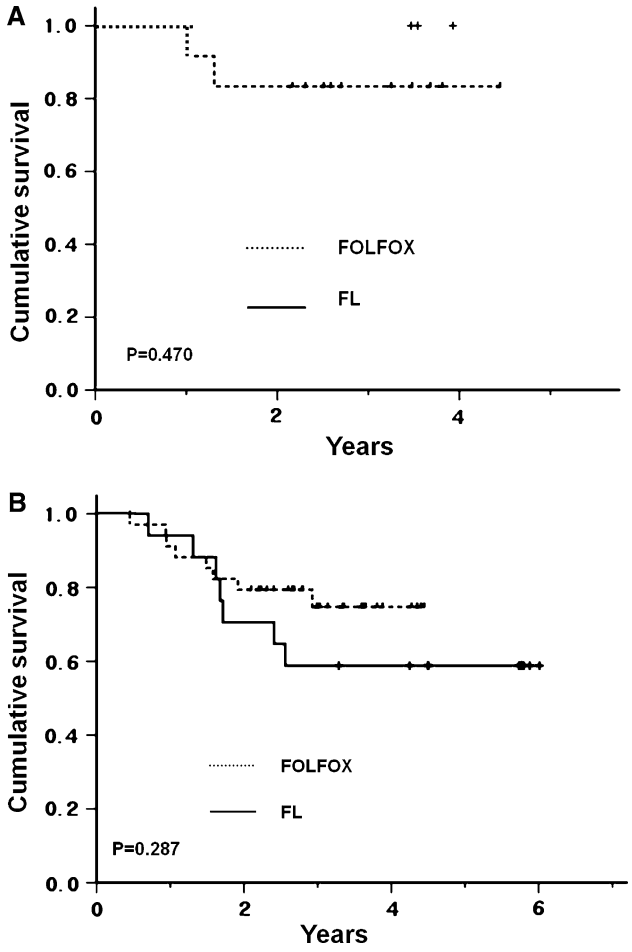

Fig. 3 **a** DFS by chemotherapy in mutant-type K-*ras*. **b** DFS by chemotherapy in wild-type K-*ras*

To the best of our knowledge, this is the first study to correlate prognosis and K-*ras* in CRC patients treated with an adjuvant FOLFOX regimen. This study has several limitations. First, although more than 5 years of follow-up are required for reliable evaluation of the potential survival benefit in adjuvant studies of colon cancer [13], this study had a short-term follow-up duration of 3.5 years. Second, although clinical outcomes, such as DFS or OS, were not significantly different in patients with mutant K-*ras* compared to those with wild-type K-*ras*, the statistical power is too weak to generate any conclusion due to the small number of cases in this study. Finally, given that the heterogeneous group of patients was retrospectively analyzed, caution should be exercised in drawing any firm conclusions from the present study. Thus, further prospective study with larger numbers of patients will be needed for validation of the role of FOLFOX in mutant K-*ras* patients.

In conclusion, this study shows that K-*ras* status was not associated with clinical outcome in patients treated with adjuvant FOLFOX.

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References

1. Jiang Y, Kimchi ET, Staveley-O'Carroll KF, Cheng H, Ajani JA (2009) Assessment of K-*ras* mutation: a step toward personalized medicine for patients with colorectal cancer. Cancer 115:3609–3617
2. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ, Zalcberg JR (2008) K-*ras* mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 359:1757–1765
3. Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, Patterson SD, Chang DD (2008) Wild-type K*RAS* is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 26:1626–1634
4. Andreyev HJ, Norman AR, Cunningham D, Oates J, Dix BR, Iacopetta BJ, Young J, Walsh T, Ward R, Hawkins N, Beranek M, Jandik P, Benamouzig R, Jullian E, Laurent-Puig P, Olschwang S, Muller O, Hoffmann I, Rabes HM, Zietz C, Troungos C, Valavanis C, Yuen ST, Ho JW, Croke CT, O'Donoghue DP, Giaretti W, Rapallo A, Russo A, Bazan V, Tanaka M, Omura K, Azuma T, Ohkusa T, Fujimori T, Ono Y, Pauly M, Faber C, Glaesener R, de Goeij AF, Arends JW, Andersen SN, Lovig T, Breivik J, Gaudernack G, Clausen OP, De Angelis PD, Meling GI, Rognum TO, Smith R, Goh HS, Font A, Rosell R, Sun XF, Zhang H, Benhattar J, Losi L, Lee JQ, Wang ST, Clarke PA, Bell S, Quirke P, Bubb VJ, Piris J, Cruickshank NR, Morton D, Fox JC, Al-Mulla F, Lees N, Hall CN, Snary D, Wilkinson K, Dillon D, Costa J, Pricolo VE, Finkelstein SD, Thebo JS, Senagore AJ, Halter SA, Wadler S, Malik S, Krtolica K, Urosevic N (2001) Kirsten *ras* mutations in patients with colorectal cancer: the 'RASCAL II' study. Br J Cancer 85:692–696
5. Conlin A, Smith G, Carey FA, Wolf CR, Steele RJ (2005) The prognostic significance of K-*ras*, p53, and APC mutations in colorectal carcinoma. Gut 54:1283–1286
6. Markowitz S, Hines JD, Lutterbaugh J, Myeroff L, Mackay W, Gordon N, Rustum Y, Luna E, Kleinerman J (1995) Mutant K-*ras* oncogenes in colon cancers Do not predict Patient's chemotherapy response or survival. Clin Cancer Res 1:441–445

7. Bouzourene H, Gervaz P, Cerottini JP, Benhattar J, Chaubert P, Saraga E, Pampallona S, Bosman FT, Givel JC (2000) p53 and Ki-*ras* as prognostic factors for Dukes' stage B colorectal cancer. Eur J Cancer 36:1008–1015
8. Tang R, Wang JY, Fan CW, Tsao KC, Chen HH, Wu CM, Chen JS, Changchien CR, Hsieh LL (2004) p53 is an independent pretreatment markers for long-term survival in stage II and III colorectal cancers: an analysis of interaction between genetic markers and fluorouracil-based adjuvant therapy. Cancer Lett 210:101–109
9. Andre T, Colin P, Louvet C, Gamelin E, Bouche O, Achille E, Colbert N, Boaziz C, Piedbois P, Tubiana-Mathieu N, Boutan-Laroze A, Flesch M, Buyse M, de Gramont A (2003) Semimonthly versus monthly regimen of fluorouracil and leucovorin administered for 24 or 36 weeks as adjuvant therapy in stage II and III colon cancer: results of a randomized trial. J Clin Oncol 21:2896–2903
10. Comella P, Casaretti R, Sandomenico C, Avallone A, Franco L (2009) Role of oxaliplatin in the treatment of colorectal cancer. Ther Clin Risk Manag 5:229–238
11. Andre T, Boni C, Navarro M, Tabernero J, Hickish T, Topham C, Bonetti A, Clingan P, Bridgewater J, Rivera F, de Gramont A (2009) Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol 27:3109–3116
12. Colon Cancer (2010) NCCN Clinical Practice Guidelines in Oncology
13. O'Connell MJ (2009) Oxaliplatin or irinotecan as adjuvant therapy for colon cancer: the results are in. J Clin Oncol 27:3082–3084
14. Ahnen DJ, Feigl P, Quan G, Fenoglio-Preiser C, Lovato LC, Bunn PA Jr, Stemmerman G, Wells JD, Macdonald JS, Meyskens FL Jr (1998) Ki-*ras* mutation and p53 overexpression predict the clinical behavior of colorectal cancer: a Southwest Oncology Group study. Cancer Res 58:1149–1158
15. Bleeker WA, Hayes VM, Karrenbeld A, Hofstra RM, Verlind E, Hermans J, Poppema S, Buys CH, Plukker JT (2001) Prognostic significance of K-*ras* and TP53 mutations in the role of adjuvant chemotherapy on survival in patients with Dukes C colon cancer. Dis Colon Rectum 44:358–363
16. Ogino S, Meyerhardt JA, Irahara N, Niedzwiecki D, Hollis D, Saltz LB, Mayer RJ, Schaefer P, Whittom R, Hantel A, Benson AB 3rd, Goldberg RM, Bertagnolli MM, Fuchs CS (2009) K*RAS* mutation in stage III colon cancer and clinical outcome following intergroup trial CALGB 89803. Clin Cancer Res 15:7322–7329
17. Moore HC, Haller DG (1999) Adjuvant therapy of colon cancer. Semin Oncol 26:545–555
18. Richman SD, Seymour MT, Chambers P, Elliott F, Daly CL, Meade AM, Taylor G, Barrett JH, Quirke P (2009) KRAS and BRAF mutations in advanced colorectal cancer are associated with poor prognosis but do not preclude benefit from oxaliplatin or irinotecan: results from the MRC FOCUS trial. J Clin Oncol 27:5931–5937
19. Nash GM, Gimbel M, Cohen AM, Zeng ZS, Ndubuisi MI, Nathanson DR, Ott J, Barany F, Paty PB (2009) K*ras* mutation and microsatellite instability: two genetic markers of early tumor development that influence the prognosis of colorectal cancer. Ann Surg Oncol 8:8
20. Bazan V, Migliavacca M, Zanna I, Tubiolo C, Grassi N, Latteri MA, La Farina M, Albanese I, Dardanoni G, Salerno S, Tomasino RM, Labianca R, Gebbia N, Russo A (2002) Specific codon 13 K-*ras* mutations are predictive of clinical outcome in colorectal cancer patients, whereas codon 12 K-*ras* mutations are associated with mucinous histotype. Ann Oncol 13:1438–1446
21. Oh HE, Cho SJ, Won NH, Lee D, Kim I, Yeom BW (2001) K-*ras* gene mutations and expression of K-*ras*, p16, Cyclin D1 and p53 in synchronous lesions of the colon adenoma carcinoma sequences. The Korean Journal of Pathology 35:291–298
22. Jeon CH, Lee HI, Shin IH, Park JW (2008) Genetic alterations of APC, K-*ras*, p53, MSI, and MAGE in Korean colorectal cancer patients. Int J Colorectal Dis 23:29–35
23. Anwar S, Frayling IM, Scott NA, Carlson GL (2004) Systematic review of genetic influences on the prognosis of colorectal cancer. Br J Surg 91:1275–1291
24. Ahn MJ, Park BB, Ahn JS, Kim SW, Kim HT, Lee JS, Kang JH, Cho JY, Song HS, Park SH, Sohn CH, Shin SW, Choi JH, Ki CS, Park CK, Holmes AJ, Janne PA, Park K (2008) Are there any ethnic differences in molecular predictors of erlotinib efficacy in advanced non-small cell lung cancer? Clin Cancer Res 14:3860–3866
25. Klampfer L, Swaby LA, Huang J, Sasazuki T, Shirasawa S, Augenlicht L (2005) Oncogenic *Ras* increases sensitivity of colon cancer cells to 5-FU-induced apoptosis. Oncogene 24:3932–3941
26. Nemunaitis J, Cox J, Meyer W, Courtney A, Mues G (1997) Irinotecan hydrochloride (CPT-11) resistance identified by K-*ras* mutation in patients with progressive colon cancer after treatment with 5-fluorouracil (5-FU). Am J Clin Oncol 20:527–529
27. Smith G, Carey FA, Beattie J, Wilkie MJ, Lightfoot TJ, Coxhead J, Garner RC, Steele RJ, Wolf CR (2002) Mutations in APC, Kirsten-*ras*, and p53-alternative genetic pathways to colorectal cancer. Proc Natl Acad Sci USA 99:9433–9438
28. Gnanasampanthan G, Elsaleh H, McCaul K, Iacopetta B (2001) Ki-*ras* mutation type and the survival benefit from adjuvant chemotherapy in Dukes' C colorectal cancer. J Pathol 195:543–548
29. Harada K, Hiraoka S, Kato J, Horii J, Fujita H, Sakaguchi K, Shiratori Y (2007) Genetic and epigenetic alterations of *Ras* signalling pathway in colorectal neoplasia: analysis based on tumour clinicopathological features. Br J Cancer 97:1425–1431
30. Miranda E, Destro A, Malesci A, Balladore E, Bianchi P, Baryshnikova E, Franchi G, Morenghi E, Laghi L, Gennari L, Roncalli M (2006) Genetic and epigenetic changes in primary metastatic and nonmetastatic colorectal cancer. Br J Cancer 95:1101–1107
31. Glebov OK, Rodriguez LM, Nakahara K, Jenkins J, Cliatt J, Humbyrd CJ, DeNobile J, Soballe P, Simon R, Wright G, Lynch P, Patterson S, Lynch H, Gallinger S, Buchbinder A, Gordon G, Hawk E, Kirsch IR (2003) Distinguishing right from left colon by the pattern of gene expression. Cancer Epidemiol Biomarkers Prev 12:755–762
32. Calcagno SR, Li S, Colon M, Kreinest PA, Thompson EA, Fields AP, Murray NR (2008) Oncogenic K-*ras* promotes early carcinogenesis in the mouse proximal colon. Int J Cancer 122:2462–2470
33. Turaga K, Shibata D (2009) K-*Ras* and MSI: potential markers of both patient prognosis and treatment efficacy. Ann Surg Oncol 20:20
34. Popat S, Hubner R, Houlston RS (2005) Systematic review of microsatellite instability and colorectal cancer prognosis. J Clin Oncol 23:609–618
35. Dempke W, Voigt W, Grothey A, Hill BT, Schmoll HJ (2000) Cisplatin resistance and oncogenes—a review. Anticancer Drugs 11:225–236
36. Levy E, Baroche C, Barret JM, Alapetite C, Salles B, Averbeck D, Moustacchi E (1994) Activated *ras* oncogene and specifically acquired resistance to cisplatin in human mammary epithelial cells: induction of DNA cross-links and their repair. Carcinogenesis 15:845–850
37. Youn CK, Kim MH, Cho HJ, Kim HB, Chang IY, Chung MH, You HJ (2004) Oncogenic H-*Ras* up-regulates expression of ERCC1 to protect cells from platinum-based anticancer agents. Cancer Res 64:4849–4857