# The prognostic value of KRAS mutation in locally advanced rectal cancer.

**Palash Asawa**
Allegheny General Hospital
**Veli Bakalov**
Allegheny General Hospital
**Pragnan Kancharla**
Allegheny General Hospital
**Stephen Abel**
Allegheny General Hospital
**Zena Chahine**
Markey Cancer Center
**Dulabh K. Monga**
Allegheny General Hospital
**Alexander V. Kirichenko**
Allegheny General Hospital
**Rodney E. Wegner** ( Rodney.wegner@ahn.org )
Allegheny General Hospital

**Research Article**

**Keywords:** Locally advanced rectal cancer, KRAS mutation, prognostic value, colorectal cancers, gene mutations

**Posted Date:** March 7th, 2022

**DOI:** https://doi.org/10.21203/rs.3.rs-1413877/v1

# Abstract

### Background

The prognostic value of the KRAS proto-oncogene mutation in colorectal cancer has been debated. Herein, we analyzed the National Cancer Database (NCDB) to assess the role of KRAS mutation as a prognostic marker in patients with locally advanced rectal cancer (LARC).

### Methods

We identified LARC patients treated with neoadjuvant chemoradiation from 2004-2015 excluding those with stage I/IV disease and unknown KRAS status. Multivariable logistic regression identified variables associated with KRAS positivity. Propensity adjusted univariable and multivariable analyses identified predictors of survival.

### Results

Of the 784 eligible patients, 506 were KRAS negative (KRAS-) and 278 were KRAS positive (KRAS+). Median survival was 63.6 months and 76.3 months for KRAS+ and KRAS- patients respectively, with propensity adjusted 3 and 5-year survival of 79.9% vs. 83.6% and 56.7% vs 61.9% respectively (HR 1.56, p 1.074-2.272). Male sex, no insurance, and KRAS+ disease was associated with poorer survival on unadjusted and propensity adjusted multivariable analyses.

### Conclusions

Our analysis of KRAS+ LARC suggest that KRAS+ disease is associated with poorer overall survival. Given the inherent limitations of retrospective data, prospective validation is warranted.


# Introduction

Colorectal cancers (CRC) are commonly occurring malignancies and are the fourth most common cancer worldwide. Treatment is directed after careful consideration of primary tumor, regional lymph node involvement, and the presence of distant metastasis. Surgery, radiotherapy, and chemotherapy are three major treatment options available for rectal cancer. Historically, neoadjuvant chemoradiotherapy (CRT) has been utilized in the neoadjuvant setting for locally advanced rectal cancer (LARC). Important prognostic factors for overall survival include the extent of the disease (TNM stage), lymphatic and vascular invasion, pathological grade, circumferential resection margin, and the type of surgery. [1]

The use of biomarkers to help more accurately prognosticate for patients with rectal cancer is gaining popularity. About 35–45% of patients diagnosed with LARC have an underlying KRAS mutation. [2,3] The KRAS protein is a member of the RAS family and is a membrane-anchored guanosine triphosphate/guanosine diphosphate (GTP/GDP)-binding protein. [4] The KRAS is responsible for intracellular signal transduction mainly from the epidermal growth factor receptor (EGFR). The transition

from inactive KRAS (GDP-bound) to the active state (GTP-bound) leads to downstream activations of more than 20 effectors, including Raf, phosphatidylinositol 3-kinase (PI3K), and Ral guanine nucleotide-dissociation stimulator (RALGDS), and regulates proliferation, survival, and differentiation. Mutations in KRAS result in persistent accumulation of the active GTP-bound KRAS protein and leads to activation of downstream pro-proliferative signaling pathways and associated with resistance to anti-EGFR therapy. [5]

The prognostic value of the KRAS proto-oncogene mutation in colorectal cancer has been debated. Herein, we analyzed the National Cancer Database (NCDB) to assess the role of KRAS mutation as a prognostic marker in patients with locally advanced rectal cancer (LARC).

# Methods

For our analysis, we used the National Cancer Database (NCDB). The database comprises approximately 70% of cancer cases in the United States from over 1500 hospitals accredited by the Commission on Cancer. [6] For our analysis we queried the database to identify rectal cancer patients diagnosed between the years 2004–2015. A complete CONSORT diagram is illustrated in Fig. 1. Patients with known KRAS status, stage II and III, known resection of the rectum, radiotherapy, chemotherapy, and patients with known pathological stage were included in our study.

Descriptive statistics were reported for pertinent variables and Chi-square test was used to compare demographic, socioeconomic, clinical, and treatment characteristics between the KRAS positive and negative patients. A bivariate logistic regression model was used to determine the association between independent variables of interest and KRAS status. Overall survival (OS) was calculated from the date of diagnosis to the date of last contact or death using Kaplan Meier curves to present the cumulative probability of survival, and log-rank statistics to assess statistical significance between groups. Adjusted hazard ratios (HR) and 95% confidence interval (CI) are reported, with $\alpha = 0.05$ used to indicate statistical significance. Propensity score analysis was used to account for indication bias caused by a lack of randomization.[7] Propensity scores were calculated by multivariable logistic regression to provide a score reflecting the conditional probability for KRAS status and were used to create a pseudo population with the identical distribution of the confounding variables in each KRAS group. We used Cox proportional hazard model adjusting for propensity score. Statistical analysis was performed using SPSS version 23.

# Results

# Baseline characteristics

A total of 784 patients were selected for final analysis and among them, 506 (64.5%) were KRAS negative and the remaining KRAS positive. Baseline demographic characteristics are shown in Table 1. The median age of the patients was 56 with a male predominance (57.3). Most patients had poorly differentiated (70.3%) and clinical stage III (62.4%) disease. Most of the patients received radiation therapy with a dose between 50.4–54 Gy (62.8%). The KRAS mutation was more likely to be found in

patients treated at academic research programs (OR 1.510, 95% CI 1.1109 to 2.0770) (Table 2). Female gender was also associated with mildly increased risk of KRAS mutation; however, this association was not significant (OR 1.2897 95 CI 0.9603 to 1.7322).

Table 1
Baseline characteristics

| | Number of patients (%) | | |
|---|---|---|---|
| **All patients** | 784 | | |
| **Demographics** | | **Disease characteristics** | |
| **Sex** | | **Clinical T stage** | |
| Male | 449 (57.27) | T1/T2 | 49 (6.25) |
| Female | 335 (42.73) | T3 | 631 (80.48) |
| **Age** | | T4 | 90 (11.48) |
| **Median / Mean** | 56 / 56.20 | Unknown | 8 (1.0) |
| <60 | 454 (57.91) | **Clinical T size** | |
| >60 | 330 (42.09) | <2 cm | 113 (14.41) |
| **Race** | | 2–5 cm | 286 (36 .48) |
| White | 664 (84.69) | >5 cm | 293 (37.37) |
| African American | 78 (9.95) | Unknown | 92 (11.73) |
| Other/unknown | 42 (5.36) | **Clinical N stage** | |
| **Comorbidity score** | | N0 | 288 (36.73) |
| 0 | 612 (78.06) | N1 | 365 (46.56) |
| 1 | 136 (17.35) | N2 | 115 (14.67) |
| 2 | 36 (4.59) | Unknown | 16 (2.04) |
| **Insurance** | | **Clinical stage** | |
| Private | 434 (55.36) | Stage II | 295 (37.6) |
| Not insured | 46 (5.87) | Stage III | 489 (62.4) |
| Government | 294 (37.5) | **Grade** | |

| | Number of patients (%) | | |
|---|---|---|---|
| Other | 10 (1.28) | Well differentiated | 83 (10.59) |
| **Treatment facility type** | | Moderately differentiated | 64 (8.16) |
| Comprehensive cancer program/other | 298 (38.01) | Poorly differentiated | 549 (70.03) |
| Academic/research program | 443 (56.51) | Unknown/Other | 88 (11.22) |
| Community cancer program | 43 (5.48) | **Microsatellite instability** | |
| **Treatment facility location** | | Negative (stable) | 703 (89.67) |
| Metro counties | 587 (74.87) | Positive (instable) | 81 (10.33) |
| Urban counties | 150 (19.13) | **Pathologic Complete Response** | |
| Rural/other counties | 47 (5.99) | pCR negative | 740 (94.4) |
| **Income, US dollars** | | pCR positive | 44 (5.6) |
| <48,000 | 480 (63.2) | **Treatment characteristics** | |
| >48,000 | 279 (36.8) | **Radiation dose, Gy** | |
| **Distance to treatment facility, miles** | | Median Gy | 50.4 |
| <10 | 350 (44.64) | <50.4 | 249 (31.76) |
| >10 | 434 (55.36) | >50.4 and < 54 | 492 (62.76) |
| **Year of diagnosis** | | >54 | 43 (5.48) |
| 2010–2011 | 186 (23.72) | | |
| 2012–2013 | 277 (35.33) | | |
| 2014–2015 | 321 (40.94) | | |

Table 2
Comparative Baseline Characteristics for KRAS Status

| | KRAS (-) | KRAS (+) | OR (95% CI) | *p* |
|---|---|---|---|---|
| **All patients** | 506 | 278 | | |
| **Demographics** | | | | |
| **Sex** | | | | |
| Male | 301 (59.49) | 148 (53.24) | 1 | |
| Female | 205 (40.51) | 130 (46.76) | 1.2897 (0.9603 to 1.7322) | 0.0909 |
| **Age** | | | | |
| **Median / Mean** | 58 / 51.01 | 55 / 54.71 | | |
| <60 | 295 (58.3) | 159 (57.19) | 1 | |
| >60 | 211 (41.70) | 119 (42.81) | 1.0464 (0.7782 to 1.4070) | 0.7641 |
| **Race** | | | | |
| White | 427 (84.39) | 237 (85.25) | 1 | |
| African American | 52 (10.28) | 26 (9.35) | 0.9008 (0.5481 to 1.4805) | 0.6804 |
| Other/unknown | 27 (5.34) | 15 (5.40) | 1.0009 (0.5221 to 1.9190) | 0.9977 |
| **Comorbidity score** | | | | |
| 0 | 394 (77.87) | 218 (78.42) | 1 | |
| 1 | 87 (17.19) | 49 (17.63) | 1.0179 (0.6911 to 1.4993) | 0.9283 |
| 2 | 25 (4.94) | 11 (3.96) | 0.7952 (0.3839 to 1.6472) | 0.5374 |
| **Insurance** | | | | |
| Private | 278 (54.94) | 156 (56.12) | 1 | |
| Not insured | 27 (5.34) | 19 (6.83) | 1.2540 (0.6754 to 2.3284) | 0.4734 |

| | KRAS (-) | KRAS (+) | OR (95% CI) | *p* |
|---|---|---|---|---|
| Government | 193 (38.14) | 101 (36.33) | 0.9326 (0.6837 to 1.2721) | 0.6594 |
| Other | 8 (1.58) | 2 (0.78) | 0.4455 (0.0934 to 2.1241) | 0.3103 |
| **Treatment facility type** | | | | |
| Comprehensive cancer program/other | 209 (41.3) | 89 (32.01) | 1 | |
| Academic/research program | 269 (53.16) | 174 (62.59) | 1.510 (1.1109 to 2.0770) | 0.008 |
| Community cancer program | 28 (5.53) | 15 (5.4) | 1.2580 (0.6409 to 2.4694) | 0.5047 |
| **Treatment facility location** | | | | |
| Metro counties | 388 (76.68) | 199 (71.58) | 1 | |
| Urban counties | 87 (17.19) | 63 (22.66) | 1.4119 (0.9786 to 2.0369) | 0.0651 |
| Rural/other counties | 31 (6.13) | 16 (5.76) | 1.0063 (0.5375 to 1.8840) | 0.9843 |
| **Income, US dollars** | | | | |
| <48,000 | 306 (62.57) | 174 (64.4) | 1 | |
| >48,000 | 183 (37.4) | 96 (35.6) | 0.9226 (0.6771 to 1.2569) | 0.6094 |
| **Distance to treatment facility, miles** | | | | |
| <10 | 233 (46.05) | 117 (42.09) | 1 | |
| >10 | 273 (53.95) | 161 (57.91) | 1.1744 (0.8741 to 1.5780) | 0.2860 |
| **Year of diagnosis** | | | | |
| 2010–2011 | 123 (24.31) | 63 (22.66) | 1 | |
| 2012–2013 | 182 (35.97) | 95 (34.17) | 1.0191 (0.6885 to 1.5084) | 0.9247 |
| 2014–2015 | 201 (39.72) | 120 (43.17) | 1.1656 (0.7982 to 1.7021) | 0.4276 |

| | KRAS (-) | KRAS (+) | OR (95% CI) | *p* |
|---|---|---|---|---|
| **Disease characteristics** | | | | |
| **Clinical T stage** | | | | |
| T1/T2 | 31 (6.13) | 18 (6.47) | 1 | |
| T3 | 412 (81.42) | 219 (78.78) | 0.9155 (0.5007 to 1.6739) | 0.7742 |
| T4 | 53 (10.47) | 37 (13.31) | 1.2023 (0.5872 to 2.4619) | 0.6144 |
| Unknown | 6 (1.2) | 2 (0.7) | 0.5741 (0.1046 to 3.1502) | 0.5229 |
| **Clinical T size** | | | | |
| <2 cm | 75 (14.82) | 38 (13.67) | 1 | |
| 2–5 cm | 187 (36.96) | 99 (35.61) | 1.0449 (0.6596 to 1.6553) | 0.8516 |
| >5 cm | 188 (37.15) | 105 (37.77) | 1.1023 (0.6976 to 1.7419) | 0.6764 |
| Unknown | 56 (11.07) | 36 (12.9) | 1.2688 (0.7158 to 2.2489) | 0.4150 |
| **Clinical N stage** | | | | |
| N0 | 192 (37.94) | 96 (34.53) | 1 | |
| N1 | 229 (45.26) | 136 (48.92) | 1.1878 (0.8590 to 1.6425) | 0.2981 |
| N2 | 77 (15.22) | 38 (13.67) | 0.9870 (0.6235 to 1.5625) | 0.9555 |
| Unknown | 7 (1.4) | 5 (1.8) | 1.4286 (0.4418 to 4.6191) | 0.5514 |
| **Clinical stage** | | | | |
| Stage II | 195 (38.5) | 100 (36.0) | 1 | |
| Stage III | 311 (61.5) | 178 (64.0) | 1.1161 (0.8240 to 1.5117) | 0.4780 |
| **Grade** | | | | |
| Well differentiated | 55 (10.87) | 28 (10.07) | 1 | |
| Moderately differentiated | 42 (8.3) | 22 (7.91) | 1.0289 (0.5172 to 2.0469) | 0.9353 |

| | KRAS (-) | KRAS (+) | OR (95% CI) | *p* |
|---|---|---|---|---|
| Poorly differentiated | 355 (70.16) | 194 (69.78) | 1.0734 (0.6593 to 1.7478) | 0.7757 |
| Unknown/Other | 54 (10.67) | 34 (12.23) | 1.2368 (0.6617 to 2.3116) | 0.5054 |
| **Microsatellite instability** | | | | |
| Negative (stable) | 454 (89.72) | 249 (89.57) | 1 | |
| Positive (instable) | 52 (10.28) | 29 (10.43) | 1.0168 (0.6293 to 1.6430) | 0.9456 |
| **Pathologic Complete Response** | | | | |
| pCR negative | 477 (94.3) | 263 (94.6) | 1 | |
| pCR positive | 29 (5.7) | 15 (5.4) | 0.9381 (0.4940 to 1.7814) | 0.8452 |
| **Treatment characteristics** | | | | |
| **Radiation dose, Gy** | | | | |
| Median Gy | 50.4 | 50.4 | | |
| <50.4 | 159 (31.42) | 90 (32.37) | 1 | |
| >50.4 and < 54 | 316 (62.45) | 176 (63.31) | 0.9840 (0.7163 to 1.3517) | 0.9205 |
| >54 | 31 (6.13) | 12 (4.32) | 0.6839 (0.3346 to 1.3976) | 0.2974 |

Survival analysis

Median survival for KRAS-positive patients was 63.6 months and 76.3 months for KRAS-negative patients (Fig. 2). On a propensity score, matched 3-year survival of KRAS negative patients was 83.6% and 79.9% for KRAS positive patients; 5-year survival of KRAS negative patients was 61.9% and 56.7% of KRAS negative patients (p = 0.0195). On multivariable analysis year of diagnosis of 2014–2015, KRAS positivity was associated with an increased risk of death, while female gender was associated with decreased risk of death. The significance of the above-mentioned variables was preserved after adjustment to propensity score. (Table 3)

Table 3
Multivariable Cox Proportional Hazards Models for Overall Survival.

| | Without Propensity Score | | Propensity Score Adjusted | |
|---|---|---|---|---|
| | **Hazard of death with 95.0% CI** | **p-value** | **Hazard of death with 95.0% CI** | **p-value** |
| **Gender** | | | | |
| Male | Reference | | Reference | |
| Female | 0.651 (0.458–0.927) | 0.017 | 0.627 (0.439–0.896) | 0.010 |
| **Insurance** | | | | |
| Private | Reference | | Reference | |
| Not insured | 0.494(0.262–0.934) | 0.030 | 0.475 (0.251–0.901) | 0.023 |
| Government | 0.843(0.433–1.641) | 0.614 | 0.923 (0.487–1.749) | 0.806 |
| **Year of diagnosis** | | | | |
| 2010–2011 | Reference | | Reference | |
| 2012–2013 | 1.056 (0.720–1.549) | 0.779 | 1.044 (0.719–1.516) | 0.822 |
| 2014–2015 | 2.133(1.225–3.713) | 0.007 | 1.845 (1.072–3.175) | 0.027 |
| **KRAS status** | | | | |
| KRAS negative | Reference | | Reference | |
| KRAS positive | 1.641(1.178–2.286) | 0.003 | 1.489 (1.078–2.058) | 0.016 |

# Discussion

In our study, we utilized the NCDB database to understand the role of KRAS mutation in 784 LARC patients. The KRAS mutation in LARC patients was associated with poorer median survival (63.6 months) as compared to wild-type KRAS (76.3 months). It was also associated with poorer 3 (79.9%) and 5-year (56.7%) survival as compared to KRAS negative LARC patients. Over 35–45% of patients diagnosed with LARC have an underlying KRAS mutation, which is like the representation of KRAS-positive patients in our analyzed population (35.5%). [2] The reported prognostic value of KRAS mutations in rectal cancer is conflicting. While several studies have indicated no association of KRAS mutations with treatment responsiveness and long-term survival [8–12], some studies have demonstrated that KRAS mutation is associated with an increased risk of relapse and death in patients with colorectal cancer and tend to have high rates of resistance to chemotherapy. [13,14]

The RASCAL study, a meta-analysis of 2721 patients with CRC found an association of KRAS mutations with increased risk of death. [14] Similarly, Lièvre et al. studied the effect of anti-EGFR targeted monoclonal antibody (cetuximab) on 30 mCRC patients screened for KRAS and found a significant association between a KRAS mutation and failure of response to the anti-EGFR treatment. Those who responded to the treatment had no KRAS mutation in their tumor. [15] In a larger series of 89 patients, Lièvre et al. again showed KRAS mutation had a statistically significant decrease in progression-free survival and overall survival in patients with metastatic CRC treated with Cetuximab. [16]

Peng et al. studied 70 LARC patients of which 25 had a documented KRAS mutation. Like our study, these patients all underwent preoperative irradiation of 50 Gy and had a total resection of their primary tumor. The study also looked at other oncogenic mutations such as PIK3CA, NRAS, and BRAF and showed patients with an oncogenic mutation had a statistically significantly worse 3-year disease-free survival, however, had similar OS. Those with KRAS mutation not only exhibited worse disease-free survival than patients with wild-type KRAS but also worse OS. [17]

Conflicting studies argue that while KRAS mutations confer resistance to targeted treatment and may thus affect tumor progression, it may not be a reliable prognostic factor. The CALGB randomized control trial studied 508 patients with stage III colon cancer for disease-free survival. Patients were divided into two treatment groups (5-fluorouracil, leucovorin with or without irinotecan) and were followed for 6 years. They found no significant difference in disease-free, recurrence-free, and overall survival between KRAS wild-type and KRAS-mutated patients. The authors believe that the results of previous trials showing a significant association between KRAS mutation and OS is likely because the studies included smaller patient populations and are therefore inaccurate. When the population is larger (such as their 508 patients), it becomes more difficult to prove a prognostic value of KRAS. [18] Similarly, Lee et al. retrospectively studied 108 patients with LARC treated with preoperative CRT and curative surgery with a follow-up time of 34 months. [19] They found no statistical significance in the recurrence-free survival and overall survival at 3 years between KRAS wild-type and KRAS-mutated patients. The authors attributed previous significant outcomes to patients being treated with anti-EGFR-targeted therapies. Patients in this study received leucovorin and 5-FU and thus KRAS mutation status is not a prognostic factor in their analysis. Differences inpatient population, treatment modality, and sample sizes may all be factors that explain the inconsistency between study data on whether KRAS is a good prognostic indicator.

Implications of KRAS as a prognostic value may play a role in improving treatment modalities. There is substantial evidence to support the predictive value of KRAS mutations in the setting of anti-EGFR treatment in metastatic CRC. This is seen in trials such as the PRIME, CRYSTAL, and OPUS experience where adding anti-EGFR medication showed improved outcomes with patients who have WT KRAS and no improvement of survival for those with a mutated KRAS. [20–22] However, studies to assess response to treatment of LARC are limited, and thus larger studies are warranted. Analyzing KRAS mutations may help identify high-risk patients who may require more aggressive therapeutic modalities. Moreover,

molecular testing of RAS mutations is essential to further tailor anti-EGFR therapy for patients with LARC being considered for anti-EGFR therapy.

The large population sample and robust statistical analysis confer high statistical power to this study; however, several factors limit the interpretation of the results. This includes the possibility of selection bias given the retrospective nature of the NCDB database. The NCDB database is based on diagnostic codes and thus there is a potential for incomplete or inaccurate coding. In addition, the NCDB database does not provide information on important aspects like ECOG status, smoking history, type of chemotherapy, number of cycles of chemotherapy provided, and dose-limiting toxicities, all of which could impact treatment response and survival.

# Conclusion

Our study validates the notion that KRAS is a good prognosticator in LARC patients through the NCDB database, which to our knowledge has not been done before. We focused on patients with LARC as data regarding the prognostic significance of KRAS is more limited in this population.

# Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

Conflict of Interest: No author present on this article has any conflicts of interest.

Prior presentations: The abstract was published online by ASCO as part of the proceedings of the annual ASCO meeting, 2019

Ethical approval: Institutional review board approval was obtained for the study

Authors Contributions:

Palash Asawa: Conceptualization, Methodology, Writing - Original Draft

Veli Bakalov: Conceptualization, Methodology, Formal analysis, Investigation, Writing – Original Draft, Review and Editing, Visualization

Zena Chahine: Conceptualization, Methodology, Writing - Review and Editing

Stephen Abel: Conceptualization, Methodology, Writing - Review and Editing

Pragnan Kancharla: Conceptualization, Methodology, Writing - Review and Editing

Dulabh K. Monga: Conceptualization, Methodology, Writing - Review and Editing

Alexander V. Kirichenko: Conceptualization, Methodology, Writing - Review and Editing

Rodney Wegner: Conceptualization, Methodology, Formal analysis, Investigation, Software Resources, Writing – Original Draft, Review and Editing, Visualization, Project Administration

Acknowledgements: None

Data Statement: Authors VB and RW had full access to all the data in the study. We take full responsibility for the integrity of the data and the accuracy of the analysis as well as sharing the data with any interested investigators.

# References

1. Li Y, Wang J, Ma X, et al. A Review of Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer. Int J Biol Sci 2016;12(8):1022–31. (In eng). DOI: 10.7150/ijbs.15438.
2. von Moos R, Koeberle D, Schacher S, et al. Neoadjuvant radiotherapy combined with capecitabine and sorafenib in patients with advanced KRAS-mutated rectal cancer: A phase I/II trial (SAKK 41/08). Eur J Cancer 2018;89:82–89. (In eng). DOI: 10.1016/j.ejca.2017.11.005.
3. Abdul-Jalil KI, Sheehan KM, Toomey S, et al. The frequencies and clinical implications of mutations in 33 kinase-related genes in locally advanced rectal cancer: a pilot study. Ann Surg Oncol 2014;21(8):2642–9. (In eng). DOI: 10.1245/s10434-014-3658-x.
4. Malumbres M, Barbacid M. RAS oncogenes: the first 30 years. Nat Rev Cancer 2003;3(6):459–65. (In eng). DOI: 10.1038/nrc1097.
5. Schubbert S, Shannon K, Bollag G. Hyperactive Ras in developmental disorders and cancer. Nat Rev Cancer 2007;7(4):295–308. (In eng). DOI: 10.1038/nrc2109.
6. Winchester DP, Stewart AK, Bura C, Jones RS. The National Cancer Data Base: a clinical surveillance and quality improvement tool. J Surg Oncol 2004;85(1):1–3. (In eng). DOI: 10.1002/jso.10320.
7. D'Agostino RB, Jr. Propensity score methods for bias reduction in the comparison of a treatment to a non-randomized control group. Stat Med 1998;17(19):2265–81. (In eng). DOI: 10.1002/(sici)1097-0258(19981015)17:19<2265::aid-sim918>3.0.co;2-b.
8. Bengala C, Bettelli S, Bertolini F, et al. Prognostic role of EGFR gene copy number and KRAS mutation in patients with locally advanced rectal cancer treated with preoperative chemoradiotherapy. Br J Cancer 2010;103(7):1019–24. (In eng). DOI: 10.1038/sj.bjc.6605853.
9. Garcia-Aguilar J, Chen Z, Smith DD, et al. Identification of a biomarker profile associated with resistance to neoadjuvant chemoradiation therapy in rectal cancer. Ann Surg 2011;254(3):486–92; discussion 492-3. (In eng). DOI: 10.1097/SLA.0b013e31822b8cfa.
10. Kim SY, Hong YS, Kim DY, et al. Preoperative chemoradiation with cetuximab, irinotecan, and capecitabine in patients with locally advanced resectable rectal cancer: a multicenter Phase II study. Int J Radiat Oncol Biol Phys 2011;81(3):677–83. (In eng). DOI: 10.1016/j.ijrobp.2010.06.035.

11. Erben P, Ströbel P, Horisberger K, et al. KRAS and BRAF mutations and PTEN expression do not predict efficacy of cetuximab-based chemoradiotherapy in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2011;81(4):1032–8. (In eng). DOI: 10.1016/j.ijrobp.2010.06.043.
12. Hu-Lieskovan S, Vallbohmer D, Zhang W, et al. EGF61 polymorphism predicts complete pathologic response to cetuximab-based chemoradiation independent of KRAS status in locally advanced rectal cancer patients. Clin Cancer Res 2011;17(15):5161–9. (In eng). DOI: 10.1158/1078-0432.Ccr-10-2666.
13. Andreyev HJ, Norman AR, Cunningham D, Oates JR, Clarke PA. Kirsten ras mutations in patients with colorectal cancer: the multicenter "RASCAL" study. J Natl Cancer Inst 1998;90(9):675–84. (In eng). DOI: 10.1093/jnci/90.9.675.
14. Andreyev HJ, Norman AR, Cunningham D, et al. Kirsten ras mutations in patients with colorectal cancer: the 'RASCAL II' study. Br J Cancer 2001;85(5):692–6. (In eng). DOI: 10.1054/bjoc.2001.1964.
15. Lièvre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 2006;66(8):3992–5. (In eng). DOI: 10.1158/0008-5472.Can-06-0191.
16. Lièvre A, Bachet JB, Boige V, et al. KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol 2008;26(3):374–9. (In eng). DOI: 10.1200/jco.2007.12.5906.
17. Peng J, Lin J, Qiu M, et al. Oncogene mutation profile predicts tumor regression and survival in locally advanced rectal cancer patients treated with preoperative chemoradiotherapy and radical surgery. Tumour Biol 2017;39(7):1010428317709638. (In eng). DOI: 10.1177/1010428317709638.
18. Ogino S, Meyerhardt JA, Irahara N, et al. KRAS mutation in stage III colon cancer and clinical outcome following intergroup trial CALGB 89803. Clin Cancer Res 2009;15(23):7322–9. (In eng). DOI: 10.1158/1078-0432.Ccr-09-1570.
19. Lee JW, Lee JH, Shim BY, et al. KRAS Mutation Status Is Not a Predictor for Tumor Response and Survival in Rectal Cancer Patients Who Received Preoperative Radiotherapy With 5-Fluoropyrimidine Followed by Curative Surgery. Medicine (Baltimore) 2015;94(31):e1284. (In eng). DOI: 10.1097/md.0000000000001284.
20. Douillard JY, Siena S, Cassidy J, et al. Final results from PRIME: randomized phase III study of panitumumab with FOLFOX4 for first-line treatment of metastatic colorectal cancer. Ann Oncol 2014;25(7):1346–1355. (In eng). DOI: 10.1093/annonc/mdu141.
21. Köhne CH, Poston G, Folprecht G, et al. FOLFIRI plus cetuximab in patients with liver-limited or non-liver-limited RAS wild-type metastatic colorectal cancer: A retrospective subgroup analysis of the CRYSTAL study. Eur J Surg Oncol 2016;42(10):1540–7. (In eng). DOI: 10.1016/j.ejso.2016.05.038.
22. Bokemeyer C, Bondarenko I, Hartmann JT, et al. Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. Ann Oncol 2011;22(7):1535–1546. (In eng). DOI: 10.1093/annonc/mdq632.

# Figures

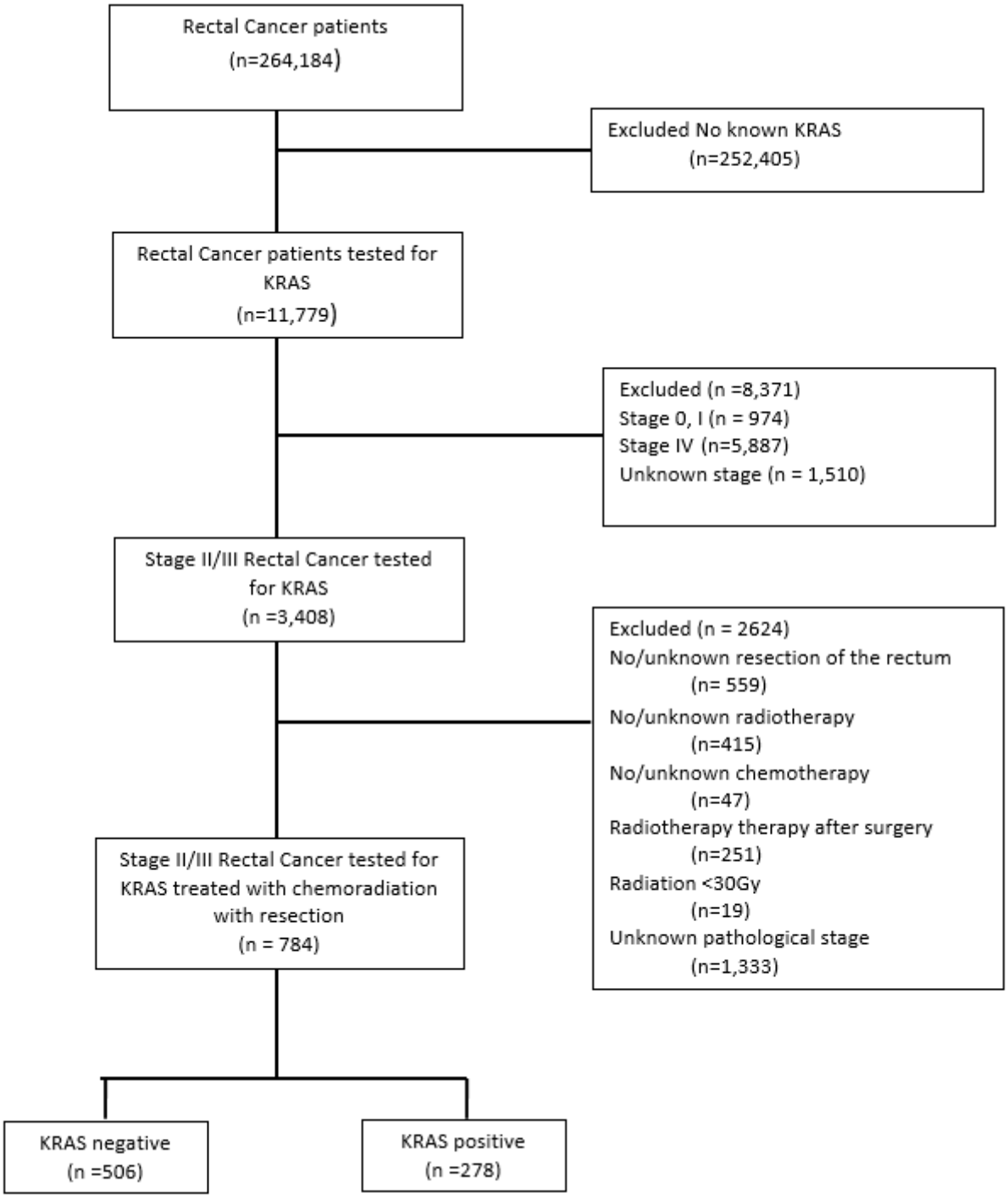
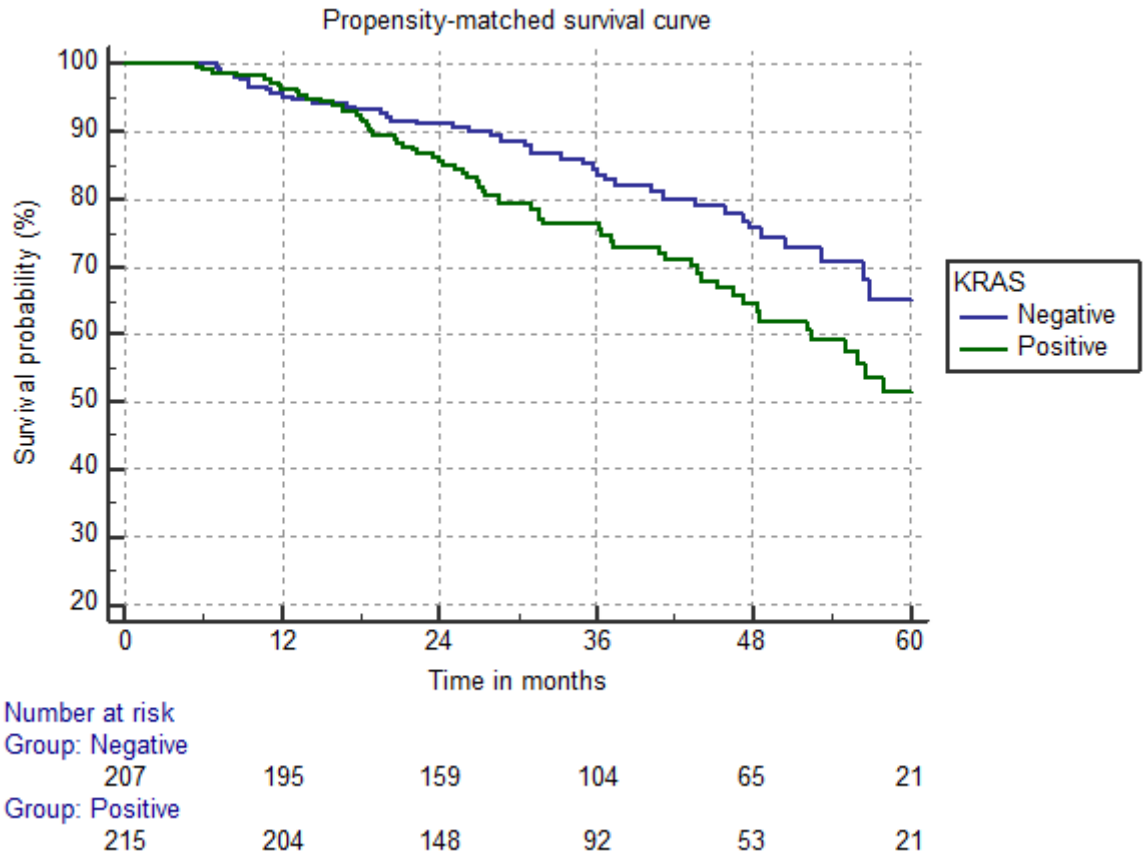



**Figure 1**

CONSORT diagram




## Figure 2

*Survival by KRAS status*