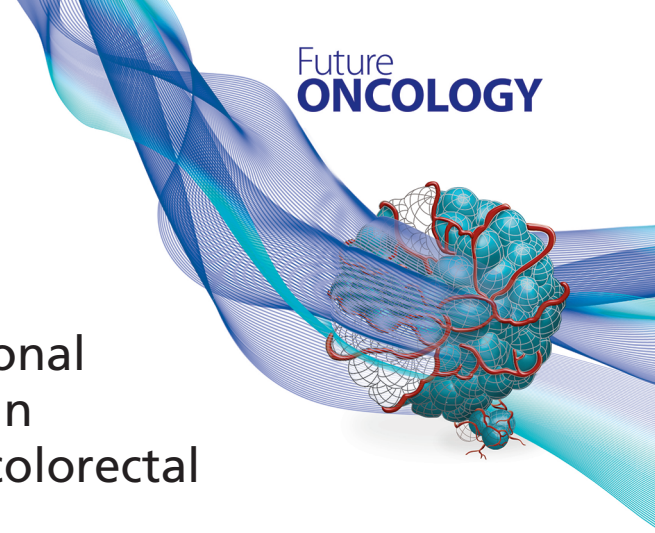
Research Article

*For reprint orders, please contact: reprints@futuremedicine.com*



# Prognostic impact of K-RAS mutational status and primary tumor location in patients undergoing resection for colorectal cancer liver metastases: an update

Juan M O´Connor*[,1], Fernando Sanchez Loria[2], Victoria Ardiles[3], Jorge Grondona[4], Pablo Sanchez[5], Oscar Andriani[6], Martin Fauda[7], Fernando Brancato[2], Eduardo Huertas[2], Fernando Alvarez[8] & Eduardo de Santibañes, on behalf of the METHEPAR Registry Group[9]

[1]GI Clinical Oncology, Instituto Alexander Fleming, Buenos Aires, Argentina
[2]Surgical Oncology Department, Instituto Alexander Fleming, Buenos Aires, Argentina
[3]Hepato-Pancreato-Biliary & Liver Transplant, General Surgery Service, Hospital Italiano de Buenos Aires, Argentina
[4]Hospital de San Isidro, Buenos Aires, Argentina
[5]Surgical Department, Instituto de Oncologia Angel Roffo, Buenos Aires, Argentina
[6]Hepato-Pancreato-Billiary Sections, Sanatorio Los Arcos, Buenos Aires, Argentina
[7]Hepato-Pancreato-Billiary Department, Hospital Universitario Austral, Pilar, Argentina
[8]Hepato-Pancreato-Biliary Surgery, Clinica Universitaria Reina Fabiola, Cordoba, Argentina
[9]FACS, Hepato-Pancreato-Biliary & Liver Transplant, General Surgery Service, Hospital Italiano de Buenos Aires, Argentina
*Author for correspondence: Tel.: +54 9 11 58097651; juanmanuel.oconnor@gmail.com

**Aim:** To determine the impact of KRAS mutation status on survival in patients undergoing surgery for colorectal liver metastases (CLM). **Patients & methods:** Patients with resected CLM and KRAS mutations. Survival was compared between mt-KRAS and wt-KRAS. **Results:** Of 662 patients, 174 (26.3%) were mt-KRAS and 488 (73.7%) wt-KRAS. mt-KRAS patients had significantly lower recurrence-free survival (HR: 1.42; 95% CI: 1.10–1.84). There were no differences between the groups for sidedness. Poorer survival was associated with mt-KRAS with positive lymph nodes, >1 metastases, tumors >5 cm, synchronous tumors and R1–R2. **Conclusion:** KRAS mutation status can help predict recurrence-free survival. Primary tumor location was not a prognostic factor after resection. KRAS mutation status can help design a multidisciplinary approach after curative resection of CLM.

First draft submitted: 2 April 2019; Accepted for publication: 12 July 2019; Published online: 20 August 2019

**Keywords:** Argentinian group • chemotherapy • KRAS • liver metastases • liver resection • molecular profiling • multidisciplinary • perioperative chemotherapy • reference centres

In most patients with colorectal cancer liver metastasis (CLM), the best outcomes are achieved by a combination of R0 surgery and systemic treatment. However, controversy still surrounds the appropriate timing of chemotherapy and the role of biological agents in the neoadjuvant treatment of resectable CLM. In conversion therapy [1,2], the combination of oxaliplatin or irinotecan-based chemotherapy with biological agents plays an important role for patients with potentially resectable CLM.

Various prognostic scores have been created to classify risk of recurrence after surgery. These prognostic scores are difficult to reproduce owing to the advent of new and more effective drugs and to better knowledge of tumor biology. Many predictors of recurrence-free survival (RFS) and overall survival (OS) in patients with CLM have been reported [3]. The rat sarcoma viral oncogene homolog (RAS) genotype is predictive of response to EGFR inhibitors, and is commonly used in clinical practice. Nevertheless, KRAS mutations have been associated with poor survival in recent years.

There is more evidence showing the prognostic impact of these mutations in patients with metastatic colon cancer [4–7]. Interest in the primary tumor location in advanced colorectal cancer (CRC) as a prognostic and

predictive factor has grown in recent years [8–11]. However, the impact of this variable in curative resection remains less clear.

We used a large national multicenter database to evaluate the potential impact of KRAS mutation status on the survival of patients with CLM who underwent surgical resection. We also evaluated the impact of primary tumor location in CLM patients.

## Patients & methods

### Study design & setting

The present study cohort is based on data from the Argentinian Registry of Hepatic Metastases from Colorectal Cancer (METHEPAR), a national web-based database that is prospectively and voluntarily updated in a decentralized way by each of the participating centers. The METHEPAR registry was set up in 20 medical centers. Completeness of data entry was monitored weekly by a central data administrator, who verified the completeness and coherence of the data entered and kept users notified of errors that needed to be corrected. Centers were encouraged to enter all cases and not to select patients on the basis of specific criteria, such as outcome. Access to data was protected and confidential. The present study was approved by the Scientific Committee of the METHEPAR Registry on 15 July 2015 (www.methepar.com). Informed consent was obtained from all patients before surgery, and the approval of the Institutional ethics committee was obtained.

### Study population & variables

All patients aged ≥18 years who underwent liver resection for CLM, and were entered by centers after the creation of the METHEPAR registry were eligible for this analysis. Patients were screened for inclusion in the study based on data completeness. The data extracted were patient demographics, primary tumor location and stage (Tumor, Node, Metastasis [TNM]), prior systemic therapy, characteristics of metastatic liver lesions (number, size and distribution), surgical details, histopathology, survival and recurrence. Mutational status was investigated by isolating genomic DNA from representative areas of either the primary tumor or liver metastases with an adequate ratio of neoplastic cells to nuclear cells. Exon 2 (codons 12 and 13), exon 3 (codon 61) and exon 4 (codons 117 and 146) were screened for KRAS mutations.

### Systemic treatment & surgical management

Pre- and postoperative systemic treatment was selected by a multidisciplinary team comprising surgeons, oncologists and radiologists. The definitions applied have been reported elsewhere [12]. Response to preoperative chemotherapy was determined according to the Response Evaluation Criteria in Solid Tumours (RECIST 1.1) [13]. The duration of follow-up was defined as the time from the initial liver resection to the date of death or, in cases where the patient did not die, to the most recent follow-up visit. The type of liver resection performed was defined using the Brisbane 2000 nomenclature [14]. Follow-up consisted of outpatient clinical evaluation, routine laboratory tests, tumor markers and imaging evaluation (CT or magnetic resonance scan) 1 month after surgery and every 3 or 4 months thereafter depending on local policy. Recurrences were managed with surgery in selected patients only when curative treatment was deemed possible, often in combination with chemotherapy.

### Statistical analyses

Categorical data are expressed as number and percentage. Continuous variables are expressed as mean and standard deviation in the case of normally distributed data and as median and interquartile ranges in the case of non-normally distributed data. The normality of the distribution was checked using the Shapiro–Wilk test and the visual exploration of q-q plots. For continuous variables, comparisons between groups were conducted using the t-test in the case of normally distributed data or the Mann–Whitney test in the case of non-normally distributed data. Categorical data were compared using the $\chi^2$ test or Fisher exact test, as appropriate. Cox proportional hazard models were used for the assessment of the independent value of KRAS to predict death or recurrence and for the analysis of predictors of events during follow-up. The Kaplan–Meier method was used to estimate OS and RFS. OS was defined as the time from surgery to death (all causes) or date of last follow-up. RFS was defined as the time from surgery to the first recorded evidence of recurrence on imaging (local or distant) or, in cases without recurrence, to the most recent follow-up visit or death (all causes). All analyses were two-tailed and a p-value $<0.05$ was considered statistically significant. Analyses were conducted using R version 3.3.2 for Mac OS X (R Foundation for Statistical Computing Platform, Vienna, Austria).

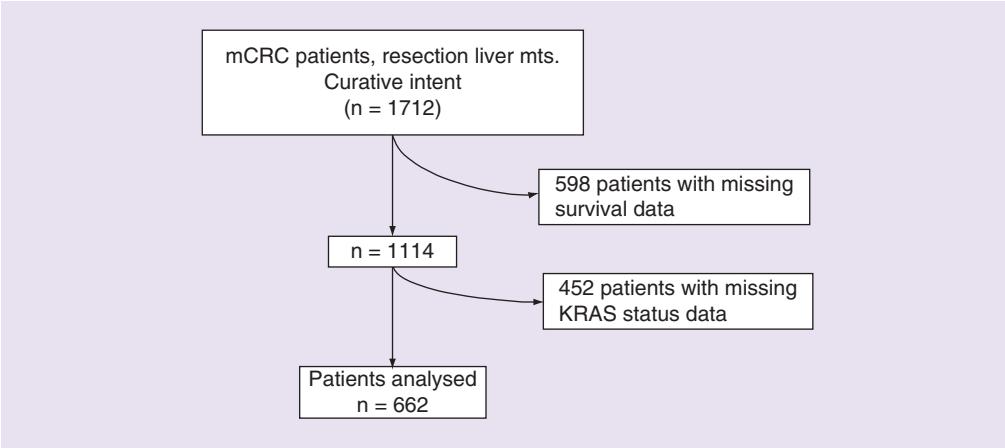



**Figure 1. Selection of the study population.**
mCRC: Metastatic colorectal cancer.

## Results

During the study period, 20 centers entered data on 1712 patients undergoing liver resection for CLM. Of these, 598 patients had to be excluded owing to missing information on survival status and 452 owing to missing data on KRAS mutation status (Figure 1). Of the 662 patients with complete data who were included in the present analysis, 174 patients (26.3%) were KRAS-mutated (mt-KRAS), while 488 (73.7%) were KRAS wild type (wt-KRAS). The clinicopathological characteristics of the overall study population according to KRAS mutation status are provided in Table 1. In total, 395 patients (59.7%) were men, and the mean age was 62.5 years. There were no significant differences in terms of preoperative clinicopathological characteristics between the mt-KRAS and the wt-KRAS groups, except for the median preoperative CEA level which was 68 (7–135) ng/ml in the mt-KRAS group, and 30.5 (6–122) ng/ml in wt-KRAS patients. Metachronous disease was recorded in 42.5% of patients (M0) in the mt-KRAS group and in 43% in the wt-KRAS patients ($p = 0.983$). Bilateral disease was observed in 64% of patients in the mt-KRAS group and in only 56.5% in the wt-KRAS group ($p = 0.108$). The median number of metastases was significantly higher in the mt-KRAS group ($p = 0.015$). Even though the maximum size of metastases tended to be greater in the mt-KRAS group, the difference was not statistically significant ($p = 0.127$).

As for operative variables (Table 2), parenchymal resections were R0 in 96.2% of cases, with no significant differences between groups. Simultaneous resections were performed in 20%. Extrahepatic disease was observed in 12.4% of cases. Only 6.4% of local procedures were performed without resection. With respect to chemotherapy, patients received a median of six cycles. Modern chemotherapy schedules with biological drugs were used in 60.8% of cases. EGFR inhibitors were applied in 43.4% of wt-KRAS patients. Bevacizumab was used in 40.5% (wt-KRAS and mt-KRAS); FOLFOXIRI was applied in only 1.5%.

With regard to the survival analysis, no significant differences in OS were observed between both groups (Figure 2). However, significant differences were observed in terms of RFS (Figure 3 & Table 3).

Analysis of the subgroup defined as conversion therapy revealed no differences in RFS or OS between groups (mt-KRAS vs wt-KRAS). The fact that the definition of conversion therapy and chemotherapy schedules varied between centers made analysis of these parameters unfeasible.

Multivariate analysis revealed that, with respect to death and survival, the only statistically significant variables were primary tumor with positive lymph nodes, presence of more than one liver metastasis in the initial diagnosis, maximum lesion diameter >50 mm and initially synchronous metastases ($p < 0.05$).

Conversely, when death or recurrence (extending the analysis to the RFS) were analyzed, the KRAS mutation acquired a prognostic role, together with positive lymph nodes, more than one metastasis, diameter >50 mm, initially synchronous metastasis, T3–T4 and R1–R2 liver resection (Table 4).

## Discussion

We analyzed the potential impact of KRAS in 662 prospectively included patients with long-term follow-up in the METHEPAR registry. Most had received at least first line of modern chemotherapy.

**Table 1. Characteristics of the study patients. comparisons according to KRAS mutation status.**

| Variables | All (n = 662) | KRAS-mutated (n = 174) | Non–KRAS-mutated (n = 488) | p-value |
|---|---|---|---|---|
| Age, mean (SD) | 62.5 (12.8) | 63.2 (12.7) | 62.2 (12.9) | 0.390 |
| Male sex, n (%) | 395 (59.7) | 104 (59.8) | 291 (59.6) | 0.974 |
| Year of diagnosis, n (%): | | | | 0.906 |
| – 2008 or before | 148 (22.4) | 34 (19.5) | 114 (23.4) | |
| – 2009 | 96 (14.5) | 25 (14.4) | 71 (14.5) | |
| – 2010 | 153 (23.1) | 42 (24.1) | 111 (22.7) | |
| – 2011 | 157 (23.7) | 45 (25.9) | 112 (23.0) | |
| – 2012 | 82 (12.4) | 22 (12.6) | 60 (12.3) | |
| – 2013 or after | 26 (3.9) | 6 (3.4) | 20 (4.1) | |
| Location, n (%): | | | | 0.508 |
| – Left | 483 (73.3) | 132 (75.9) | 351 (72.4) | |
| – Right | 168 (25.5) | 41 (23.6) | 127 (26.2) | |
| – Both | 8 (1.2) | 1 (0.6) | 7 (1.4) | |
| Colectomy performed, n (%) | 595 (90.0) | 154 (88.5) | 441 (90.6) | 0.531 |
| Number of resected lymph nodes, median (IQR) | 12.5 (9.0–18.0) | 12.0 (8.5–18.5) | 13.0 (9.0–18.0) | 0.386 |
| Tumor stage, n (%): | | | | 0.418 |
| – T0/T1 | 11 (2.0) | 3 (2.1) | 8 (1.9) | |
| – T2 | 70 (12.6) | 21 (14.5) | 49 (11.9) | |
| – T3 | 349 (62.8) | 83 (57.2) | 266 (64.7) | |
| – T4 | 126 (22.7) | 38 (26.2) | 88 (21.4) | |
| N stage, n (%): | | | | 0.382 |
| – N0 | 173 (31.7) | 47 (32.4) | 126 (31.5) | |
| – N1 | 193 (35.4) | 45 (31.0) | 148 (37.0) | |
| – N2 | 179 (32.8) | 53 (36.6) | 126 (31.5) | |
| M stage, n (%): | | | | 0.983 |
| – M0 metachronous | 241 (42.9) | 62 (42.5) | 179 (43.0) | |
| – M1 synchronous | 321 (57.1) | 84 (57.5) | 237 (57.0) | |
| Maximum diameter, median (IQR) | 35.0 (25.0–50.0) | 31.5 (22.0–47.8) | 36.0 (25.0–50.0) | 0.127 |
| Bilaterality, n (%) | 383 (58.5) | 110 (64.0) | 273 (56.5) | 0.108 |
| CEA, median (IQR) | 34.0 (7.0–135.0) | 68.0 (10.0–230.0) | 30.5 (6.0–122.0) | 0.016 |
| Ca-19.9, median (IQR) | 42.0 (15.0–181.0) | 49.0 (18.5–266.0) | 40.0 (15.0–152.5) | 0.217 |

CEA: Carcinoembryonic antigen.

**Table 2. Surgery and systemic treatment.**

| Variables | All (n = 662) | KRAS-mutated (n = 174) | Non–KRAS-mutated (n = 488) | p-value |
|---|---|---|---|---|
| Type of hepatic resection, n (%): | | | | |
| – R0 | 384 (96.2) | 99 (99.0) | 285 (95.3) | 0.326 |
| – R1 | 7 (1.8) | 0 (0.0) | 7 (2.3) | |
| – R2 | 8 (2.0) | 1 (1.0) | 7 (2.3) | |
| Extrahepatic metastases, n (%): | 54 (12.4) | 13 (12.3) | 41 (12.5) | 0.949 |
| Nonresective local treatment, n (%) | 28 (6.4) | 9 (8.4) | 19 (5.8) | 0.464 |
| Chemotherapy, n (%): | | | | |
| – Neoadjuvant | 104 (30.3) | 40 (40.4) | 64 (26.2) | 0.016 |
| – Adjuvant | 155 (45.2) | 34 (34.3) | 121 (49.6) | |
| – Conversion | 84 (24.5) | 25 (25.3) | 59 (24.2) | |
| Number of cycles, median (IQR) | 6.0 (3.0–6.0) | 6.0 (3.0–6.0) | 6.0 (3.0–6.0) | 0.974 |
| Monoclonal antibodies, n (%) | 262 (60.8) | 65 (54.6) | 197 (63.1) | 0.131 |
| Cetuximab, n (%) | 111 (33.3) | 2 (2.3) | 116 (43.4) | <0.001 |
| Bevacizumab, n (%) | 142 (40.5) | 61 (70.9) | 81 (30.6) | <0.001 |
| Regimen, n (%): | | | | |
| – 1† | 241 (87.6) | 67 (87.0) | 174 (87.9) | 0.095 |
| – 2‡ | 30 (10.9) | 7 (9.1) | 23 (11.6) | |
| – FOLFOXIRI | 4 (1.5) | 3 (3.9) | 1 (0.5) | |

†Chemotherapy regimen: BFOL, CAPOX, FLOX, FOLFOX.
‡Chemotherapy régimen: IFL, CAPIRI, FOLFIRI.
IQR: Interquartile range.

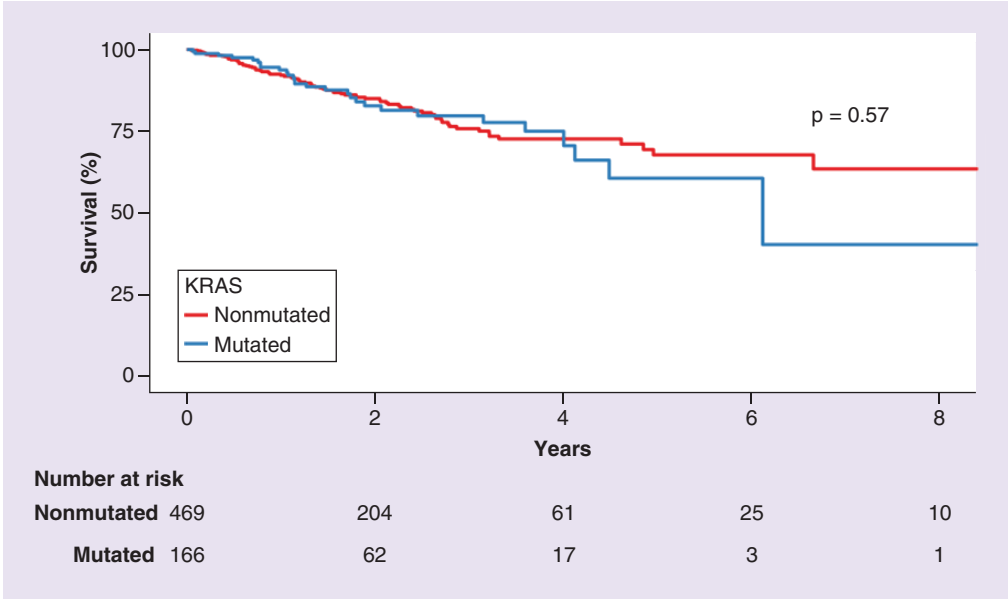



**Figure 2. Overall survival.**

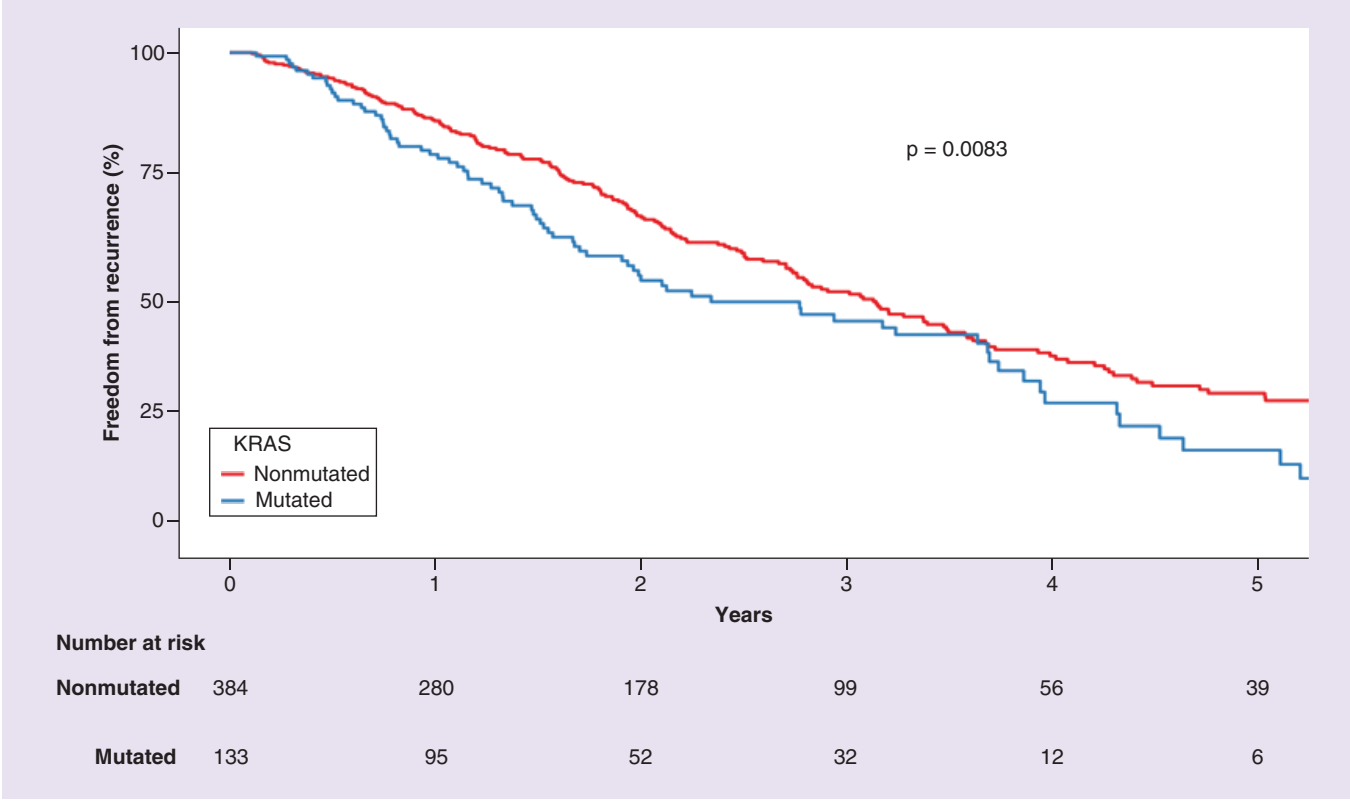



**Figure 3. Recurrence-free survival.**

Recent evidence indicates that the effect of the KRAS mutation and Ras on RFS and even on OS has become more pronounced [6]. In a Spanish study of 394 patients, the OS for wt-KRAS was 26.7 versus 18 months for the mutant group [5]. Other studies [6] have confirmed these data in patients with liver metastasis, mainly in RFS.

**Table 3. Survival analysis.**

| Event | Nonadjusted HR (95% CI) | p-value | Adjusted HR (95% CI)† | p-value |
|---|---|---|---|---|
| Death | 1.13 (0.74–1.72) | 0.573 | 1.11 (0.73–1.69) | 0.207 |
| Death or recurrence | 1.25 (1.00–1.56) | 0.048 | 1.26 (1.01–1.57) | 0.04 |
| Recurrence | 1.42 (1.10–1.84) | 0.009 | 1.42 (1.10–1.85) | 0.008 |

†Adjusted for age and sex.

**Table 4. Uni- and multivariate analysis of predicted factors of death or recurrence.**

| Event | Nonadjusted HR (95% CI) | p-value | Adjusted HR (95% CI)† | p-value |
|---|---|---|---|---|
| Age | 0.99 (0.98–1.00) | 0.086 | 1.00 (0.98–1.02) | 0.667 |
| Male | 1.08 (0.89–1.33) | 0.434 | – | – |
| Mutated KRAS‡ | 1.25 (1.00–1.56) | 0.048 | 1.41 (0.84–2.37) | 0.197 |
| Positive lymph node | 1.43 (1.11–1.84) | 0.005 | 0.69 (0.42–1.11) | 0.123 |
| Left location | 0.99 (0.80–1.24) | 0.957 | – | – |
| More than one liver metastasis | 2.37 (1.83–3.08) | <0.001 | 1.28 (0.77–2.15) | 0.346 |
| More than six chemotherapy cycles | 1.37 (1.01–1.86) | 0.042 | 1.89 (1.07–3.33) | 0.028 |
| Diameter >50 mm | 1.42 (1.11–1.81) | 0.005 | 0.79 (0.45–1.39) | 0.418 |
| Synchronous M1 tumor | 3.50 (2.75–4.45) | <0.001 | 3.35 (1.94–5.78) | <0.001 |
| T3/T4 tumor | 1.92 (1.32–2.79) | <0.001 | 1.84 (0.86–3.95) | 0.119 |
| R1/R2 resection of metastases | 6.69 (3.52–12.74) | <0.001 | 6.52 (2.78–15.28) | <0.001 |

†Based on 218 observations (444 had missing data).
‡Introduced in the multivariate model because it was of primary interest for the study.

The database of the Argentinian Register of Resected Hepatic Metastasis (METHEPAR) is a multi-institutional statistical instrument that prospectively registers data such as oncological records, surgery performed and postoperative course in major medical centers in Argentina. It covers liver surgery, surgical oncology and general surgery units.

The present analysis emerges from a specific evaluation of patients who underwent liver resection for metastasis, irrespective of whether they received or did not receive systemic treatment before or after surgery. Our main objective was to evaluate whether a molecular factor, such as KRAS, could play a role in surgical strategy and decision-making.

The somatic mutations of KRAS, NRAS [15–17], BRAF [18] and PIK3CA [17,18] have been the most widely studied mutations in primary CRC according to multiple recent reports. The KRAS mutation rate of 26.3% (174/662) in this series of patients who underwent surgery for hepatic metastasis was lower than the KRAS mutation rate of almost 40% reported in various series of patients with metastasis, including those for whom surgery was not indicated [19].

Our survival analysis showed that the KRAS mutation was an independent predictor of death or recurrence and of recurrence (local, hepatic, other organs), expressed as the RFS, which was 22% at 5 years for mt-KRAS and 33% for wt-KRAS (p = 0.0053; HR: 1.42), although it did not demonstrate that the mutation was predictive of OS (55 vs 63%, p = NS; HR: 1.13). We assume that subsequent lines of treatment could have masked the OS data.

A systematic review and meta-analysis [20] of KRAS mutations in patients who underwent resection owing to metastasis shows a mutation rate close to 27.6%, which is very similar to the rate we report (26.3%). We can assume that patients who undergo liver resection make up a different population with a different illness due to biological aggressiveness and with a lower mutation rate and better OS than those who do not undergo resection.

In this study, we analyzed the relationship between the KRAS mutation and recurrence and death. The survival analysis indicates that patients with mt-KRAS tumors had a significantly lower survival than patients with wt-KRAS tumors when the variable recurrence (no discrimination by site) and the combined variables of death and recurrence were analyzed (Table 3). This analysis suggests that mt-KRAS tumors tend to be recurrent and fatal in more patients than wt-KRAS tumors.

Consistent with previously published papers [21,22], we observed a tendency for mt-KRAS tumors to metastasize in different organs, mainly through hematogenous spread, although recurrence was not differentiated according to site or organ.

The differences in mutation rates between studies on metastatic CRC and our study, where all patients underwent surgery because of liver metastasis, suggest the biological versatility mt-KRAS tumors, which are widely distributed as a result of hematogenous spread. This is probably why many patients with mutated tumors did not undergo surgery and, therefore, were not included in this study population. As for sidedness of the primary tumor, current reports differ in how they see sidedness as a prognostic variable [23,24] and as a predictor of the response to anti-EGFR therapy [24]. In our series, the location of the primary tumor (right vs left) was not a significant variable. Our study focused on those patients who received only firstline of chemotherapy, either as primary adjuvant or neoadjuvant and/or conversion therapy for liver metastasis. Therefore, they comprise a group with a relatively favorable prognosis matched with a low mutation rate. The multivariable analysis showed that R1 and R2 liver resection were associated with poorer survival. *RAS* mutations indicate more aggressive tumor biology of CLM, and have been associated with more positive margins and poorer survival after resection. Consequently, anatomic resection and/or a wider surgical margin (e.g., >10 mm) may be indicated for patients with *RAS*-mutated CLM [25]. Margonis *et al.* published a meta-analysis, reporting on more than 11,000 patients from 34 studies highlighting the impact of margin width on survival following R0 hepatic resection for CLM [26].

Chemotherapy regimen and neoadjuvant and/or conversion criteria were similar in both patient groups (mt-KRAS and wt-KRAS), suggesting that preoperative chemotherapy does not induce changes in KRAS or its mutation rate.

Our study is limited by the fact that it is a retrospective analysis of prospectively collected data. In addition, the fact that many data were missing indicates that the reader should be cautious when interpreting the results of multivariate analyses. The data tables for the analysis were generated based on the retrospective evaluation. Nevertheless, the study population is relatively homogeneous with respect to clinicopathological features, and the KRAS analysis was centralized in a single laboratory, thus ensuring that variables were standardized and the analysis more consistent.

## Conclusion

The data we provide, combined with evidence from the literature, enable us to conclude that the mutation status of KRAS is a good predictor of RFS. However, our data do not allow us to confirm the same about OS.

The genetic profile in CRC is useful for the selection of patients for surgical resection, and is beginning to take on a key role in predicting the outcome of cancer in this population.

### Added value of this study

METHEPAR was a multicenter observational study performed in liver surgery reference centers in Argentina.

Our study adds relevant data regarding the role of KRAS as a prognostic factor in metastatic colorectal cancer. In recent years, there has been increasing evidence of sidedness/location of the primary tumor as a prognostic factor.

While there is information on the role of sidedness as a prognostic factor in advanced colon cancer, this issue has been less studied in the scenario of resected hepatic metastasis. In the present series, we did not find a relationship between the location of the primary tumor and prognosis in the resection of liver metastasis. Furthermore, we analyzed KRAS as a prognostic factor in both KRAS MUT and KRAS WT in resection of liver metastasis.

Finally, we highlight the importance of reporting local data both from Argentina in particular and from Latin America in general with respect to liver metastasis in patients with CRC. This is the first multicenter study conducted in Argentina with data obtained from daily clinical practice. The use of real-world data overcomes the limitations of data from randomized trials.

#### Financial & competing interests disclosure

Merck S.A. provided support for maintenance of the database and editorial assistance. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

The authors thank Content Ed Net (Madrid, Spain) for editing the manuscript and editorial assistance.

## Summary points

- The appropriate timing of chemotherapy and the role of biological agents in the neoadjuvant treatment of resectable colorectal liver metastases remains controversial.
- The rat sarcoma viral oncogene homolog (RAS) genotype is predictive of response to epidermal growth factor receptor (EGFR) inhibitors and is commonly used in clinical practice, although KRAS mutations have been associated with poor survival.
- Analysis of recurrence and the combined variables of death and recurrence shows that survival is significantly poorer in patients with mt-KRAS tumors than in patients with wt-KRAS tumors.
- mt-KRAS tumors tend to metastasize in different organs, mainly through hematogenous spread, although recurrence is not differentiated according to site or organ.
- Sidedness of the primary tumor (right vs left) is not a significant variable.
- The fact that chemotherapy regimen and neoadjuvant and/or conversion criteria were similar in both patient groups (mt-KRAS and wt-KRAS) suggests that preoperative chemotherapy does not induce changes in KRAS or its mutation rate.
- The mutation status of KRAS is a good predictor of recurrence-free survival.
- The genetic profile in colorectal cancer is useful for the selection of patients for surgical resection and is beginning to take on a key role in predicting the outcome of cancer in this population.

## References

Papers of special note have been highlighted as: • of interest; •• of considerable interest


1. Kopetz S, Chang GJ, Overmann MJ *et al.* Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J. Clin. Oncol.* 27, 3677–3683 (2009).
2. Folprecht G, Gruenberger T, Bechstein W *et al.* Survival of patients with initially unresectable colorectal liver metastases treated with FOLFOX/cetuximab or FOLFIRI/cetuximab in a multidisciplinary concept (CELIM study). *Ann. Oncol.* 25, 1018–1025 (2014).

•• **Favorable long-term survival in patients with initially suboptimal or unresectable colorectal liver metastases (CLM) treated with conversion therapy (FOLFOX/FOLFIRI + cetuximab).**

3. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. *Ann. Surg.* 230(3), 309–318 (1999).
4. Kemeny NE, Chou JF, Capanu M *et al.* KRAS mutation influences recurrence patterns in patients undergoing hepatic resection of colorectal metastases. *Cancer* 120, 3965–3971 (2014).
5. Diaz-Rubio E, Gómez-España A, Massutí B *et al.* Role of Kras status in patients with metastatic colorectal cancer receiving first-line chemotherapy plus bevacizumab: a TTD group cooperative study. *PLoS ONE* 7(10), e47345 (2012).

•• **Data from the MACRO Study show KRAS status had a prognostic role in patients with metastatic colorectal cancer treated with XELOX + bevacizumab and that it was and independent factor for progression-free survival and overall survival.**

6. Karagkounis G, Torbenson MS, Daniel HD *et al.* Incidence and prognostic impact of KRAS and BRAF mutation in patients undergoing liver surgery for colorectal metastases. *Cancer* 119, 4137–4144 (2013).

• **KRAS status was an independent predictor of overall and recurrence-free survival and may help to refine the assessment of patients undergoing surgery for CLM.**

7. Margonis GA, Buettner S, Andreatos N *et al.* Anatomical resections improve disease-free survival in patients with KRAS-mutated colorectal liver metastases. *Ann. Surg.* 266(4), 641–649 (2017).
8. Pugh SA, Shinkins B, Fuller A, Mellor J, Mant D, Primrose JN. Site and stage of colorectal cancer influence the likelihood and distribution of disease recurrence and postrecurrence survival: data from the FACS randomized controlled trial. *Ann. Surg.* 263, 1143–1147 (2016).
9. Loupakis F, Yang D, Yau L *et al.* Primary tumor location as a prognostic factor in metastatic colorectal cancer. *J. Natl Cancer Inst.* 107, pii:dju427 (2015).
10. Arnold D, Lueza B, Douillard JY *et al.* Prognostic and predictive value of primary tumor side in patients with *RAS* wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. *Ann. Oncol.* 28, 1713–1729 (2017)
11. Petrelli F, Tomasello G, Borgonovo K *et al.* Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. *JAMA Oncol.* 3(2), 211–219 (2017).
12. Adam R, De Gramont A, Figueras J *et al.* The oncosurgery approach to managing liver metastases from colorectal cancer: a multidisciplinary international consensus. *Oncologist* 17, 1225–1239 (2012).
13. Eisenhauer EA, Therasse P, Bogaerts J *et al.* New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer* 45, 228–247 (2009).
14. Strasberg SM. Nomenclature of hepatic anatomy and resections: a review of the Brisbane 2000 system. *J. Hepatobiliary Pancreat. Surg.* 12, 351–355 (2005).

15. Cercek A, Braghiroli MI, Chou JF *et al.* Clinical features and outcomes of patients with colorectal cancers harboring NRAS mutations. *Clin. Cancer Res.* 23, 4753–4760 (2017)

16. Jones RP, Brudvik KW, Franklin JM, Poston GJ. Precision surgery for colorectal liver metastases: opportunities and challenges of omics-based decision making. *Eur. J. Surg. Oncol.* 43(5), 875–883 (2017).

17. Nakayama I, Shinozaki E, Matsushima T *et al.* Retrospective study of RAS/PIK3CA/BRAF tumor mutations as predictors of response to first-line chemotherapy with bevacizumab in metastatic colorectal cancer patients. *BMC Cancer* 17(1), 38 (2017).

- **Selecting patients based on RAS/PIK3CA/BRAF mutations can identify those who will achieve a better response to bevacizumab.**

18. De Roock W, Claes B, Bernasconi D *et al.* Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol.* 11, 753–762 (2010).

19. Peeters M, Kafatos G, Taylor A *et al.* Prevalence of RAS mutations and individual variation patterns among patients with metastatic colorectal cancer: a pooled analysis of randomised controlled trials. *Eur. J. Cancer* 51(13), 1704–1713 (2015).

20. Brudvik KW, Kopetz SE, Li L, Conrad C, Aloia TA, Vauthey JN. Meta-analysis of *KRAS* mutations and survival after resection of colorectal liver metastases. *Br. J. Surg.* 102, 1175–1183 (2015).

- **KRAS mutation status is a prognostic factor in surgery for CLM and should be used in the evaluation of patients undergoing liver resection.**

21. Vauthey JN, Zimmitti G, Kopetz SE *et al.* RAS mutation status predicts survival and patterns of recurrence in patients undergoing hepatectomy for colorectal liver metastases. *Ann. Surg.* 258(4), 619–626, discussion 626–627 (2013).

- **RAS mutation can predict early lung recurrence and poorer survival after curative resection of CLM and can be used to tailor treatment and follow-up strategies.**

22. Passot G, Kim BJ, Glehen O *et al.* Impact of RAS mutations in metastatic colorectal cancer after potentially curative resection: does site of metastases matter? *Ann. Surg. Oncol.* 25(1), 179–187 (2018).

- **The prognostic significance of RAS mutations after resection of metastatic colorectal cancer depends on the site of the metastasis.**

23. Ciombor K, Goldberg R. Viewpoint. Highlights in gastrointestinal (colorectal) cancer treatment: the primary tumor sidedness debate and advances in immunotherapy. *JAMA Oncol.* 2, 1537–1538 (2016).

24. Holch JW, Ricard I, Stintzing S, Modest DP, Heinemann V. The relevance of primary tumour location in patients with metastatic colorectal cancer: a meta-analysis of first-line clinical trials. *Eur. J. Cancer* 70, 87–98 (2017).

25. Brudvik KW, Mise Y, Chung MH *et al.* RAS mutation predicts positive resection margins and narrower resection margins in patients undergoing resection of colorectal liver metastases. *Ann. Surg. Oncol.* 23(8), 2635–2643 (2016).

- **RAS mutations are associated with positive margins in resection of CLM and should prompt careful efforts to achieve negative resection margins.**

26. Margonis G, Sergentanis N, Stathopoulos I *et al.* Impact of surgical margin width on recurrence and overall survival following R0 hepatic resection of colorectal metastases. a systematic review and meta-analysis. *Ann. Surg.* 267, 1047–1055 (2018).