KRAS and BRAF Mutations as survival prognostic factors for Metastatic Colorectal Cancer patients after Lung metastasectomy: A Systematic Review and Meta-Analysis

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Abstract

Introduction

While knowledge has grown extensively regarding the impact of mutations on colorectal cancer prognosis, their role in outcomes after pulmonary metastasectomy (PM) remains minimally understood. Therefore, in this paper, we conduct a systematic review and meta-analysis of retrospective and prospective studies to evaluate whether KRAS or BRAF mutation status can be independent predictors in colorectal cancer patients undergoing complete lung metastasis surgery.

Methods

A systematic literature review was performed to identify articles reporting overall survival (OS) of patients who underwent lung metastasectomy for colorectal cancer lung metastases (CRLM), stratified according to KRAS and BRAF mutational status. Hazard ratios (HRs) from multivariate analyses were pooled in the meta-analysis.

Results

9 studies, including 1833 patients, were eligible for the meta-analysis. Based on the random effect model, the total frequency of KRAS mutations in 1305 patients who had undergone the lung metastasectomy was 45% and the total 5-year OS in these patients was 55.7%. Five of them reported OS stratified according to KRAS mutation. The pooled analysis revealed that KRAS mutation was negatively associated with OS (HR, 1.674; 95% confidence interval [CI], 1.341-2.089; P < .001). The rate of KRAS mutations were lower in the studies with higher male to female ratio. There was statistically significant linear trend in univariate meta-regression to explain effect size variation by male to female ratio of study with coefficient = 0.47 (95% CI 0.03, 0.91), P = 0.03. Disease free survival (DFS), thoracic metastases and origin of primary tumor were significantly influenced by KRAS mutation status.
Conclusions

Our meta-analysis confirms the KRAS mutation as a strong and predictive biomarker which makes overall survival lower in patients with colorectal cancer undergoing pulmonary metastasis surgery. Certainly, this interesting evidence represents the first step towards a deeper understanding of the molecular mechanisms underlying tumor behavior and patient outcomes in a subgroup of clinically selected colorectal cancer patients. By considering tumor molecular characteristics and other clinical-pathological factors, our results confirm the use of new therapeutic models to predict outcomes of patients undergoing colorectal lung metastasis surgery and to isolate both systemic and loco-regional treatment strategies.

Introduction

Colorectal cancer is the third most common cancer and the second leading cause of cancer deaths in the world. Despite advances in its treatment, colorectal cancer is still one of the leading causes of cancer deaths (1). Reports show that in 25%-30% of patients with metastatic disease, the lung is the most common extra-abdominal metastatic site (2). Approximately 10%-20% of all patients with colorectal cancer develop pulmonary metastasis during the course of their disease (3, 4). Therefore, identifying high-risk patients with pulmonary metastasis is one of the current research areas (5–7). Pulmonary metastasectomy is an integral part of the interdisciplinary treatment of these patients. Although randomized, controlled trials on pulmonary metastasectomy have not been performed, resection of metastases via a multidisciplinary treatment program is crucial for selective patients (8, 9). Besides, the concept of repeated metastasectomy for recurrent disease leads to long-term treatment in metastatic colorectal cancer (10, 11). Predicting the outcome of treatment for patients with recurrent pulmonary metastasis is an obstacle in oncology surgery (12). Prior identification of patients at high risk of pulmonary...
recurrence may influence the treatment strategy. Therefore, the search for precise biomarkers in pulmonary metastasectomy is increasing (13). Numerous studies have used genetic, familial, and sporadic mutations in the pathogenesis of colorectal cancer. Besides, the association of these mutations with poorer prognosis has also been demonstrated. One study has found that mutations in RAS genes are independent predictors of overall survival and DFS in patients with colorectal cancer (14). Also, a comprehensive population-based study showed that mutations can increase the risk of mortality (15). Mutations in APC and TP53 tumors may be hereditary especially familial adenomatous polyposis and Li–Fraumeni syndrome but may represent a sporadic process in the development of colorectal cancer (16, 17). Like RAS, these two mutated genes are also used in the pathogenesis of colorectal cancer (18–20). Colorectal cancer patients with liver metastases who have a mutated KRAS gene have been shown to have lower overall survival (OS) and DFS (disease free survival) after liver metastasectomy (21). However, despite all available data from the assessment of the effect of genetic mutations on this disease, the role of these mutations after pulmonary metastasectomy for pulmonary metastases in colorectal cancer is not well understood. Little data are available about the role of KRAS mutations in predicting death after pulmonary metastases, but RAS family mutations have not been fully evaluated (22, 23). Therefore, in this paper, we conduct a systematic review and meta-analysis of retrospective and prospective studies to evaluate whether KRAS or BRAF mutation status can be independent predictors in colorectal cancer patients undergoing complete lung metastasis surgery.

Materials and Methods

Objectives

The purpose of this analysis was to evaluate the status of the KRAS and BRAF mutations in
retrospective and prospective studies on patients undergoing radical surgery for colorectal cancer lung metastases. The primary objective was to evaluate overall survival and the secondary objective was to determine the disease-free survival (DFS)

Data sources and search strategies

A systematic review of the literature was conducted in November 2019, and we reviewed MEDLINE/PubMed, the Cochrane Library, and ClinicalTrials.gov for further citations or experiments from January 2000 to November 2019. The search criteria were limited to human studies published in English. The medical terms for PubMed searches were ‘BRAF’ or ‘KRAS’; ‘colon cancer’ or ‘colorectal cancer’ or ‘rectal’ or ‘rectum’; ‘metastasis’ or ‘metastatic’ or ‘metastases’ or ‘metastasectomy’; and ‘lung’ or ‘pulmonary’.

Selection criteria

Selected articles had to meet the following selection criteria: (1) To address metastatic colorectal cancer patients undergoing complete lung metastatic resection surgery; (2) To report the results of genetic tests for KRAS or BRAF mutation status from CRLM(colorectal lung metastasectomy) specimens isolated from metastatic colorectal cancer; and (3) To report disease-free survival (DFS) and/or overall survival (OS)results according to the mutation status. This meta-analysis included studies published since 2000 to illustrate the results of recent surgical techniques. Duplicate articles or repeated articles that were selected based on the same patient group were not included in this meta-analysis: If another cohort article was identified, we would select one with the largest number of patients and if not specified, we would have chosen the older article. The exclusion criteria were: The article was not published in English; the initial cause was not colorectal cancer; and the initial site of metastasis was not lung (R2 resection).

Data extraction
The data were extracted independently and based on preferred reporting of cases for systematic reviews and meta-analyses. Two authors [FP] and [MS] selected studies according to the previously described selection criteria. After the first selection, another author [ISH] was consulted if necessary. A predefined protocol was used to extract the data from each study including the first author's name, year of publication, the name of journal, study period, sample size, research design, demographic characteristics, and BRAF and KRAS mutation status, overall and free-disease survival, and variables affecting the univariate and multivariate analysis. The overall survival and disease-free survival were categorized based on the mutation status in each cohort study. Besides, the relative hazard ratio (HR) was measured at a 95% confidence interval, and the Kaplan–Meier survival analysis was used in all articles.

Statistical analysis

This meta-analysis was performed using the inverse-variance method, in which the specific weight of each study was calculated as the standard error square among the studies reviewed. Heterogeneity among studies was assessed using Cochran Q and I² statistics. The fixed and random effects were reported.

Results

Literature Search Result

The electronic search provided a total of 1198 results. After screening, 257 were eliminated because they were not in English language and/or duplicates; 684 were excluded because they were reviews, editorial letters, case reports, no full text available or no quality. Further, we excluded 249 articles because they included liver metastases, more than 1 (lung) metastatic site, pathways other than KRAS and BRAF, or were not focused on the effect of KRAS and BRAF mutations after lung metastasectomy as the main
At the end of the review process, 9 studies were identified as meeting the inclusion criteria of this review. These articles constitute the study population (Fig. 1). Study characteristics are shown in Table 1. The Cochrane database of systematic review was then cross-checked to ensure that no similar systematic reviews had been undertaken.

### Table 1

| Author                  | Year  | Country  | Duration | Mean Age | Male to Female | Duration of follow-up (Months) | Molecular Analysis | HR | 5-year OS |
|-------------------------|-------|----------|----------|----------|----------------|------------------------------|-------------------|----|-----------|
| Zabala et al.           | 2014  | Spain    | 1998–2010| 65.7 (40–82) | 64/2          | 90                           | Retrospective     | 30 (0.33) | 84 (70.4–97.6) |
| Renaud et al.           | 2019  | Italy    | 2004–2014| 65       | 106/62        | 62                           | Retrospective     | 95 (0.56) | 101 (75.0–126.89) |
| Renaud et al.           | 2015  | France   | 1998–2011| -----     | 112/68        | 180                          | Retrospective     | 93 (0.52) | 98 (88.0–112.66) |
| Perera et al.           | 2015  | USA      | 2008–2010| 55 (25–85) | 291/203       | 26                           | Retrospective     | 202 (0.41) | 292 (0.52) |
| Corsini et al.          | 2019  | USA      | 2011–2017| 57 (41–73) | 70/60         | 36.2                         | Prospective       | 82 (0.63) | -----       |
| Ghidini et al.          | 2019  | Italy    | 1997–2009| 65.4 (33.4–80.1) | 27/4          | 82.9                         | Retrospective     | 27 (0.36) | 48 (0.64) |
| Schweiger et al.        | 2014  | Austria  | 2009–2012| 64 (37–79) | 20/19         | 27                           | Prospective       | 18 (0.46) | 21 (0.54) |
| Kim et al.              | 2017  | Korea    | 2005–2015| 56 (3–76) | 77/52         | 46.4                         | Retrospective     | 19 (0.15) | 31 (0.24) |
| Liang et al.            | 2018  | China    | 2011–2014| 57.2 ± 11.2 | 145/143       | 46.5                         | Retrospective     | 221 (0.54) | -----       |

**Case Volume, Mutational Status, and Clinical Characteristics**

The total number of patients included in these studies was 1726, of whom 41% (787 patients) were KRAS-mutated. The mutation rate of KRAS ranges from 15% to 63%. BRAF mutation was analyzed only in 3 of 9 studies and it occurred in 20 patients (5.7%); Table
1) All patients included underwent macroscopic complete lung metastases resection. **Kirsten Rat Sarcoma Viral Oncogene Homolog (KRAS) Mutational Status and OS**

Four of 9 studies reported OS after resection of CRC lung metastases, stratified according to KRAS mutation. One study did not perform the multivariate analysis because KRAS status was not significant in the univariate analysis. One study did not provide the OS stratified according to KRAS status, but the multivariate HR of OS according to KRAS status was available. The Three studies for which HRs were available were then pooled in the meta-analysis, which at the end with these constraints included 699 patients. The KRAS mutation rate was 41% (Figure 3). The pooled analysis, using a fixed effect model, revealed that KRAS mutation was negatively associated with OS (HR, 1.64; 95% CI, 1.12-2.16; P < .001)(Figure 2a). Similarly, using a random effect model, KRAS mutation was negatively associated with OS (HR, 1.64; 95% CI, 1.12-2.16; P < 0.24) (Figure 2a).

**B-Viral Oncogene Homolog B1 (BRAF) Mutational Status and OS:**

Only 3 of 9 studies analyzed OS stratified according to BRAF mutation. These studies have no provided the HR data of the multivariate analysis regarding OS according to BRAF mutational status. These 3 studies were pooled in a separate meta-analysis.

**META-ANALYSIS OF frequency of KRAS and BRAF mutations:**

Based on the random effect model, the total frequency of KRAS mutations in 1726 patients who had undergone the lung metastasectomy was 41% (95% confidence interval [CI]:39%-44%, I2 = 94.3%) (Table 1, Figure 3). BRAF mutation was analyzed only in 3 of 8 studies and it occurred in 20 patients (5.7%)(Table 1).

**META-ANALYSIS OF frequency of 5-year OS:**

Based on the random effect model, the total 5-year OS in patients who had undergone the lung metastasectomy was 55.7% (95% confidence interval [CI]:51.8%-59.5%, I2 = 89.9%). (Table 1)
**Meta-regression finding based on the mean of age and frequency of KRAS mutations:**

The studies’ meta-regression was according to the association between frequency of KRAS mutations and the mean age of study and the overall rate of KRAS mutations. There was no statistically significant linear trend in univariate meta-regression to explain effect size variation by mean of age of study with coefficient = 0.14 (95% CI -2.17, 2.46), $P = 0.88$ (Figure 4a).

**Meta-regression finding based on the publication year and frequency of KRAS mutations:**

The studies’ meta-regression was according to the association between the publication year of study and the overall rate of KRAS mutations. It showed the overall rate of KRAS mutations was upper in newer studies than the older ones (Figure 4b). But there was no statistically significant linear trend in univariate meta-regression to explain effect size variation by publication year of study with coefficient = −35.63 (95% CI -171.21, 99.94), $P = 0.71$ (Figure 4b).

**Meta-regression finding based on the male to female ratio of study and frequency of KRAS mutations:**

The overall rate of KRAS mutations based on the female to male ratio of the studies is showed in (Figure 4-c), the rate of KRAS mutations was lower in studies with higher male to female ratio. There was statistically significant linear trend in univariate meta-regression to explain effect size variation by male to female ratio of study with coefficient = 0.47 (95% CI 0.03, 0.91), $P = 0.03$.

**Sub-group analysis**

**Comparison of the prevalence of other prognostic factors in WT and mKRAS patients:**
The overall prevalence of CEA≥5 based on four articles was 53%(95%CI:47%-58%, I²:92.2), 52%(95%CI:47%-58%, I²:92.2) for WT and mKRAS groups respectively. The overall prevalence of DFS<12 months based on four articles(24-26,32) was 18.5%(95%CI:12%-24%, I²:91), 36%(95%CI:29%-43%, I²:93) for WT and mKRAS groups respectively. The overall prevalence of liver metastases based on 7 articles(24-28,30,32) was 56%(95%CI:53%-59%, I²:98.7) and 54%(95%CI:55%-58%, I²:97.6) for WT and mKRAS groups respectively. The overall prevalence of thoracic metastases based on four articles (24,25,27,28) was 20%(95%CI:16%-24%, I²:80.7) and 22%(95%CI:18%-27%, I²:90) for WT and mKRAS groups respectively. The overall prevalence of rectum as the first origin of cancer based on 5 articles (24,26,28-30)was 32%(95%CI:28%-36%, I²:95), 29%(95%CI:24%-33%, I²:92) for WT and mKRAS group respectively.

Comparison of OS and DRS between WT and mKRAS patients

The mean overall survival time based on 7 articles (24-29,32) were 66 months in WT and 54 months in mKRAS colorectal cancer patients undergoing lung metastasectomy. The mean overall disease free survival time based on 3 articles (24,29,32) were 12 months in WT and 10.5 months in mKRAS colorectal cancer patients undergoing lung metastasectomy.

Publication bias:

Funnel plot in (Figure 4d) shows no indication of publication bias. It is shows in funnel plot symmetrically. Circles’ size shows the weight of studies (bigger circles shows more sample and smaller circles shows fewer sample).

Discussion

Pulmonary metastasectomy for colorectal cancer is well accepted in the field of thoracic surgery, although due to the lack of comparative data between simple follow-up and
surgery, it is still a subject of discussion. Because lung parenchymal resection can cause complications and alter respiratory function, surgery should be avoided at high risk. To help evaluate patients for metastasectomy, several studies have attempted to identify prognostic factors such as high preoperative CEA level, short-term disease-free survival (DFS), presence of liver and thoracic metastases, incomplete resection, or LNI (33-36). However, in spite of these predictive biomarkers, in some patients thoracic surgery is useless, leading to the search for other predictive markers. Over the past few years, the identification of molecular changes in tumors has led to better patient management and the identification of subgroups of patients with different responses to different drugs or predictors, such as EGFR-activating mutations in non-small cell lung cancer (37). In patients with colorectal cancer, two biomarkers have been considered: the KRAS 12/13 codon mutation and the V600E mutation from BRAF gene. The role of molecular biomarkers, such as KRAS and BRAF, in advanced and non-surgical disease is well established. However, its potential use in patients with colorectal cancer with pulmonary metastasis undergone surgery has not yet been known. Most published papers have reported a prevalence of KRAS mutation in local and metastatic colorectal cancer ranging from 35 to 55%. In this meta-analysis, the prevalence of KRAS mutation was 41% and the prevalence of BRAF mutation in patients with colorectal cancer after lung metastasectomy was 5.7%. We considered the results of 9 studies on the relationship between KRAS and BRAF mutation status and overall survival or disease-free survival (DFS) in patients with colorectal cancer undergoing pulmonary metastatic surgery. These studies evaluated overall survival and disease-free survival for patients undergoing colorectal cancer metastasectomy classified by BRAF and KRAS mutation status and showed that overall KRAS mutation is lower compared to the wild type (WT) population. There is lots of evidence that RAS mutation has a negative predictive role in patients with metastatic
colorectal cancer (39, 40). In fact, the KRAS mutation has weaker biology and faster onset, and aggressive metastasis, especially in the lungs and bones that challenges clinical decision making (41–46). In this meta-analysis, we found that in patients whose tumors had a KRAS mutation, overall survival and disease-free survival were lower, with an average KRAS mutation of 41%. Besides, the estimated overall survival was 54 months for the mKRAS (KRAS mutation) patients compared to 66 months for the non-mutated variant. Also, in line with other studies, the HR was 1.64 (95% confidence interval) and equal to 1.12–2.16 for mKRAS (p < 0.24) which is considered as a negative predictor. However, Zabaleta et al. concluded that the presence of a K-RAS mutation in lung metastases did not affect overall survival, but was associated with a higher rate of pulmonary recurrence (34). Our findings are consistent with two recent meta-analyses. In their meta-analysis, Tosi et al. stated that KRAS mutation had a negative relationship with overall survival and disease-free survival in patients undergoing complete liver surgery for colorectal cancer metastases. Passiglia et al. showed that KRAS mutation decreases the overall survival (HR = 1.65 and 1.23–2.21 at 95% confidence interval) and disease-free survival (HR = 1.86% and 1.51–2.30 at a 95% confidence interval) in patients undergoing liver metastasis resection for colorectal cancer (48). Some studies have shown a higher prevalence of pulmonary metastasis/recurrence in patients with KRAS mutation (17,18). In this meta-analysis, the incidence of KRAS mutation in patients undergoing lung metastasectomy was 41%. Our results are consistent with two previous studies that reported a higher rate of mKRAS in lung metastases than in liver metastases in patients with primary colorectal cancer. In fact, Tie et al. (49) reported 62% mKRAS in lung metastases versus 32.3% in liver metastases. Besides, Cejas et al. reported 57% mKRAS in lung metastases versus 35% in liver metastases. The prevalence of BRAF mutation in patients with colorectal cancer after lung metastasectomy was only 5.7% and there was not sufficient data to
evaluate the overall survival of mBRAF patients, so we cannot consider mBRAF as a negative predictor. Nevertheless, this low percentage may be related to the low number of studies (as the BRAF mutation was evaluated in only 3 of the 8 selected studies).

However, both studies mentioned above reported the BRAF mutation as a negative predictor. Concerning BRAF mutation, even in a small subset of patients, most of the published studies have identified BRAF mutations from early tumor specimens as a strong negative predictive marker in metastatic colorectal cancer (51) which has proven to be more aggressive and chemically refractory than malignant tumors (52). The prevalence of BRAF mutation in patients with colorectal cancer after pulmonary metastasectomy was 5.7% in our study, which is consistent with previous studies [5-10%] (53). The low percentage of BRAF mutations in this group of colorectal cancer patients may limit its clinical use as a predictive biomarker for routine use but does not affect its scientific significance as well as its potential consequences for patients. We also performed a subgroup meta-analysis to evaluate the prevalence of other predictive factors such as high preoperative CEA level (CEA ≥ 5), low disease-free survival (less than 12 months), presence of hepatic metastases, number of thoracic metastases (> 1), and the origin of the primary tumor in MKRAS and WT metastatic pulmonary patients to assess significant differences. We found that disease-free survival, thoracic metastases, and primary tumor origin were affected by KRAS mutation status, with disease-free survival being significantly lower and the number of thoracic metastases significantly greater in mKRAS patients. The origin of most mKRAS tumors was colon (71%) and the rectum in 32% of WT was the primary tumor origin.

Limitations

This meta-analysis was conducted with several limitations. First, although the reviewed studies were limited to those conducted on patients with pulmonary metastasis who had
undergone pulmonary metastasectomy and included studies from 2000 to recent studies, 9 selected studies differed in sample size and other criteria for patient selection, which was reflected as heterogeneity in Cochran Q and I² statistics. Also, this meta-analysis did not consider possible differences between different variants of KRAS mutations because KRAS mutations were not distinguished in the existing studies and therefore no information was extracted for analysis.

Conclusion

Our meta-analysis confirms the KRAS mutation as a strong and predictive biomarker which makes overall survival lower in patients with colorectal cancer undergoing pulmonary metastasis surgery. Certainly, this interesting evidence represents the first step towards a deeper understanding of the molecular mechanisms underlying tumor behavior and patient outcomes in a subgroup of clinically selected colorectal cancer patients. By considering tumor molecular characteristics and other clinical-pathological factors, our results confirm the use of new therapeutic models to predict outcomes of patients undergoing colorectal lung metastasis surgery and to isolate both systemic and loco-regional treatment strategies.

Abbreviations

Overall survival (OS), Colorectal cancer (CRC), Kirsten rat sarcoma viral oncogene homolog (KRAS), v-raf murine sarcoma b-viral oncogene homolog B1 (BRAF), WT: wild-type, OS indicates overall survival. HR: hazard ratio; CI: confidence intervals; N.A: not available

Declarations

Ethics Approval and Consent to Participate: not applicable.

Consent for publication: not applicable
Availability of data and supporting materials section: Please contact author for data requests

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Author contribution:
ISH participated in Conception and design of the study, library searches and assembling relevant literature, critical review of the paper, supervising writing of the paper, Database management. MS and FP participated in Data collection, library searches and assembling relevant literature, writing the paper, and critical review of the paper. ISH participated in Data collection, library searches and assembling relevant literature, writing the paper, analysis of the data and critical review of the paper. All authors read and approved the final manuscript.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Figures
Figure 1

PRISMA flow chart describing the selection process.
Figure 1

PRISMA flow chart describing the selection process.
Forest plot of hazard ratio between KRAS mutations and OS(a) after complete resection colorectal lung metastases. Forest plot of OS (b) and its 95% interval for the studied cases based on the model of the random effects model. The midpoint of each section of the line estimates the % value and the length of the lines showing the 95% confidence interval in each study. The oval sign shows overall mean of OS.
Forest plot of hazard ratio between KRAS mutations and OS (a) after complete resection colorectal lung metastases. Forest plot of OS (b) and its 95% interval for the studied cases based on the model of the random effects model. The midpoint of each section of the line estimates the % value and the length of the lines showing the 95% confidence interval in each study. The oval sign shows overall mean of OS.
The frequency of KRAS mutations and its 95% interval for the studied cases according to the year and the country where the study was conducted based on the model of the random effects model. The midpoint of each section of the line estimates the % value and the length of the lines showing the 95% confidence interval in each study. The oval sign shows overall of frequency of KRAS mutations.
Figure 3

frequency of KRAS mutations and its 95% interval for the studied cases according to the year and the country where the study was conducted based on the model of the random effects model. The midpoint of each section of the line estimates the % value and the length of the lines showing the 95% confidence interval in each study. The oval sign shows overall of frequency of KRAS mutations.
Figure 4

Meta-regression between mean age (a), publication year of study(b), male to female ratio(c) and frequency of KRAS mutations. Funnel plot of publication bias(d) shown in symmetrically. Circles’ size shows the weight of studies (bigger circles show more samples and smaller circles show fewer samples).
Figure 4

Meta-regression between mean age (a), publication year of study (b), male to female ratio (c) and frequency of KRAS mutations. Funnel plot of publication bias (d) shown in symmetrically. Circles’ size shows the weight of studies (bigger circles show more samples and smaller circles show fewer samples).
Figure 5

Frequency of KRAS mutations and OS based on the country
